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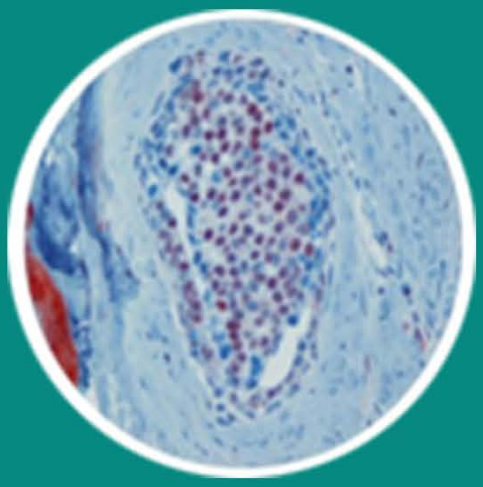

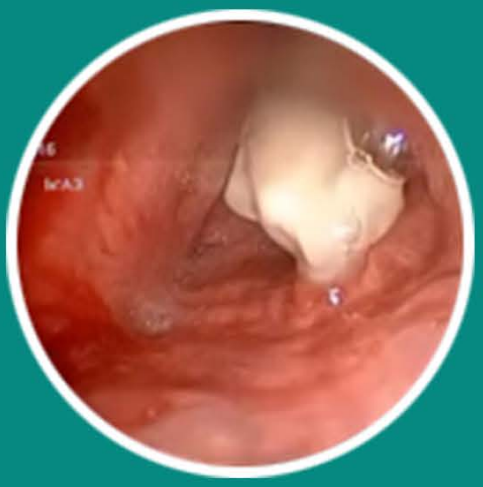

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Editorial Board

INTERNATIONAL EDITORIAL BOARD MEMBERS

Table of Contents

Original Articles

Case Report

Letter to the Editor

The European Research Journal 2019;5(5):722-728 ORIGINAL ARTICLE

Effect of urinary excretion on radiation dose in patients having PET/CT scans

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ABSTRACT

Objectives: ^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/ computed tomography (PET/CT) is commonly used for diagnosis, staging and re-staging of cancers and for determining the effectiveness of treatment. Because of renal, ureteral and urinary involvement of ^{18}F-FDG radiopharmaceutical after its injection, patients subject to radioactivity during its effective half-life. The aim of the present study was to determine the degree of association between effective dose levels of patients and bladder emptying of patients having PET/CT scans.

Methods: The present retrospective study included 108 patients (43 females and 65 males, average age: 60.9 ± 12.7 years). Effective dose level as mSv/h was determined from a distance of 1 m in all patients before and after bladder emptying at the first hour following ^{18}F-FDG injection. Radioactivity excretion amounts were compared based on gender, age, body mass index, fasting blood sugar level and clinical diagnosis.

Results: Amount of radioactivity decreased by 22.75% ± 14.77% after bladder emptying. No association was found between urinary excretion level and age, gender, fasting blood sugar and body mass index ($p > 0.05$).

Conclusions: Active emptying of bladder in patients having PET/CT scans where ^{18}F-FDG radiopharmaceutical is involved is an effective method for the radiation safety of both health workers and patients.

Keywords: ^{18}Fluorine-fluorodeoxyglucose, positron emission tomography, computed tomography, urinary excretion, effective dose

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Nuclear medicine imaging procedures has been increasingly used over the past 20 years, and theyprovided considerable reductions in morbidity and increases in longevity [1]. ^{18}Fluorine-fluorodeoxyglucose (18F-FDG) positron emission tomography/ computed tomography (PET/CT) is a molecular imaging technique used to differentiate tumor cells from normal cells. It is especially useful for pre- and post-treatment evaluation of oncology patients [2, 3]. PET radiopharmaceuticals are positron emitting agents which emit 511 keV annihilation photons [4]. PET imaging commonly uses maximum standardized uptake value (SUV) as a criterion for malignancy in clinical practice [5].

PET/CT has proven useful in management of several tumors. Since urinary excretion of ^{18}F-FDG radiotracer masks the presence of lesions, diagnostic power of PET/CT scanning is lower in urologic tract tumors and prostate cancer [6]. It was reported that PET/CT scanning has a high frequency of false-negatives in

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urologic tumors [7]. Absorption of ^{18}F-FDG in both benign and malignant lesions may often result in misinterpretation. A glucose analogue, ^{18}F-FDG accumulates in malignant lesions because of their elevated glucose metabolism. Nevertheless, ^{18}F-FDG can also accumulate in normal tissues, benign tumors of the pelvic area and other non-neoplastic occurrences of pelvis. ^{18}F-FDG is commonly excreted into urinary system and diagnostic evaluation may difficult in the bladder, prostate, uterus and ovarian cancer. ^{18}F-FDG accumulation in the urinary tract can be lowered by administration of diuretics, and patients are requested to empty their bladder completely before PET/CT imaging [8].

There is an increasing movement to minimize exposure to ionizing radiation especially from medical imaging involving X-rays and from internal radiation due to the use of radionuclides. Radiation from PET radiopharmaceuticals originates from positron and annihilation photons. General principles of radiation protection from the hazard of ionizing radiation are summarized as three key words; justification, optimization, and dose limit. Because medical exposure of radiation has unique considerations, diagnostic reference level is generally used as a reference value, instead of dose limits. The principle of justification and optimization are source-related and apply in all exposure situations. The principle of application of dose limits is individual-related and applies in planned exposure situations [9].

Patients are exposed to radioactivity due to physiological involvement of ^{18}F-FDG in kidneys, ureter and bladder during its effective half-life after injection. Health care workers andpatients are exposed to radiation during the PET/CT scan.The aim of the present study was to determine the association between urinary excretion and total effective dose level of ^{18}F-FDG in patients receiving PET/CT scans.

METHODS

This retrospective study included 108 patients. The patients had been referred to nuclear medicine department for staging of previously diagnosed cancer using ^{18}F-FDG PET/CT imaging. Forty-three patients were females (40%) and 65 males (60%), and average age was 60.9 ± 12.7 years. Patients who had histories of bladder operation, kidney failure, urethra stenosis, urinary incontinence and hyper-dynamic bladder were excluded. PET imaging was performed prior to any treatment and images were obtained using a combined PET/CT scanner (Biograph 2, USA). Each patient had fasted for at least six hours before imaging. After blood glucose level dropped below 170 mg/dl, 370 MBq ^{18}F-FDG was administered intravenously, patients were rested and image was taken one hour after injection. PET images were attenuation-corrected using CT images (70 mA, 120 kV, axial slice thickness of 3.75 mm).

All patients were given oral hydration with 800-1,000 ml of water. One hour after ^{18}F-FDG injection, effective dose levels (millisievert/hour, mSv/h) were determined at a distance of 1 meter in each patient before and after emptying bladder using aradiation survey meter (Dose-Rate Meter NEB.211, ÇNAEM, Turkey). Radioactivity excretion percentage was calculated using the formula *"[Full Bladder (mSv/h) – Empty Bladder (mSv/h) / Full Bladder (mSv/h)] x 100"* Radioactive excretion percentages of gender, age, body mass index, fasting blood sugar level and clinical diagnosis groups were compared.

Statistical Analysis

Data were analyzed using SPSS software (version 14.0; SPSS Inc.) and expressed as mean ± standard deviation. Statistical significance of the parameters was evaluated based on frequencies test. Pre-urinary and post-urinary excretion values were compared through paired t-test. Correlations of total effective dose with gender, age, body mass index, fasting blood sugar level and clinical diagnosis groups were studied using Mann-Whitney U test and Pearson correlation test. Significance levels were presented as *p* values. $P < 0.05$ was considered statistically significant.

RESULTS

Cancer diagnoses of 108 patients who had ^{18}F-FDG PET/CT scans were as follows: lung (26.8%), colorectal (16.6%), breast (12.9%), head and neck (8.3%), lymphoma (8.3%), male genitalia (5.5%), endometrium (2.7%), liver and bile ducts (2.7%), malignant melanoma (2.7%), stomach (2.7%), gastrointestinal stromal (1.8%), mediastinum and

Table 1. Total effective dose classification of study patients (n = 108)

Type of cancer	n	Radioactivity excretion (%)
Lung	29	18.9 ± 13.1
Colorectal	18	29.2 ± 18.1
Breast	14	17.4 ± 10.6
Head and neck	9	26.2 ± 17.2
Lymphoma	9	23.2 ± 18.6
Male genitalia	6	13.9 ± 4.9
Endometrium	3	28.9 ± 11.1
Liver and bile ducts	3	37.2 ± 12.3
Malignant melanoma	3	20.8 ± 5.3
Stomach	3	21.6 ± 12.6
Gastrointestinal stromal	2	27.3 ± 5.7
Mediastinum and thymus	2	15.4 ± 0.7
Ovarian	2	44.5 ± 22.5
Brain	1	19.1
Esophagus	1	10.4
Pancreas	1	46.4
Unknown primary	1	14.5
Sarcoma	1	14.9

thymus (1.8%), ovarian (1.8%) and others (5.4%). Cancer type and urinary excretion values of all patients were given in Table 1.

Effective dose levels of patients as mSv/h were measured at a distance of 1 m before and after bladder emptying. Comparisons were made between gender, age, body mass index and clinical diagnosis groups. Results showed that bladder emptying decreased radioactivity level by 22.75% ± 14.77%.

When the age groups were compared, the percentage of radioactivity excretion was higher in 41-60 years age group compared to 20-40 and over 61 age

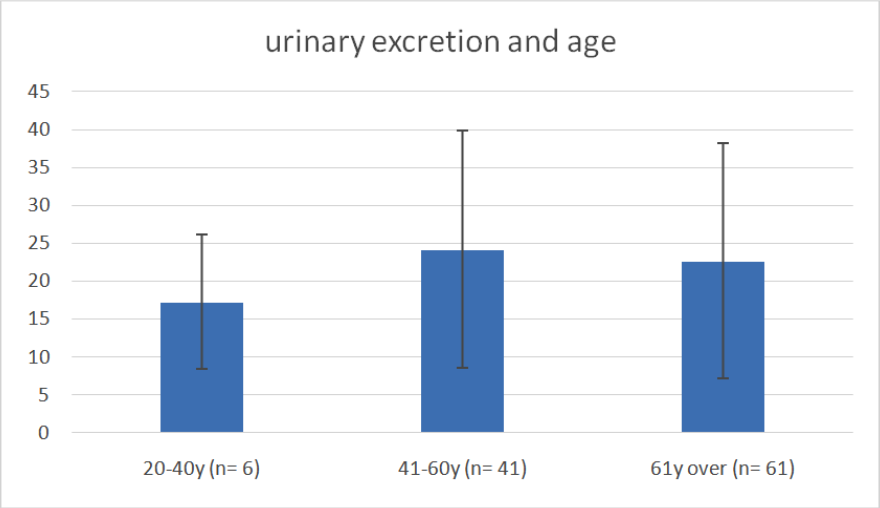

Figure 1. Urinary excretion of radioactivity in different age groups.

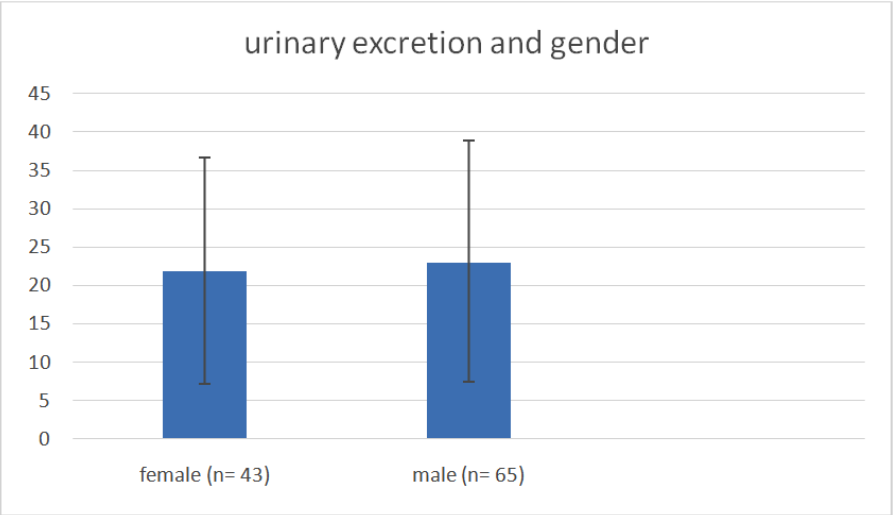

Figure 2. Urinary excretion of radioactivity in different gender groups.

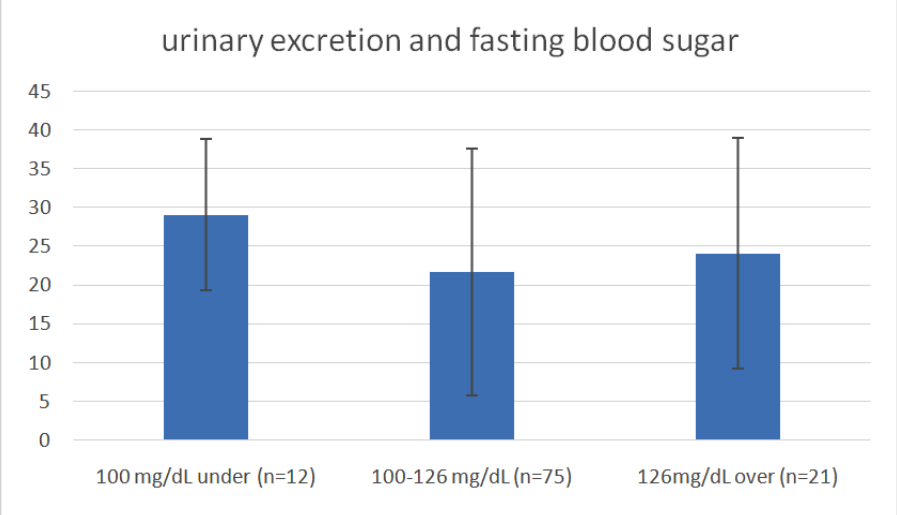

Figure 3. Urinary excretion of radioactivity in different fasting blood sugar groups.

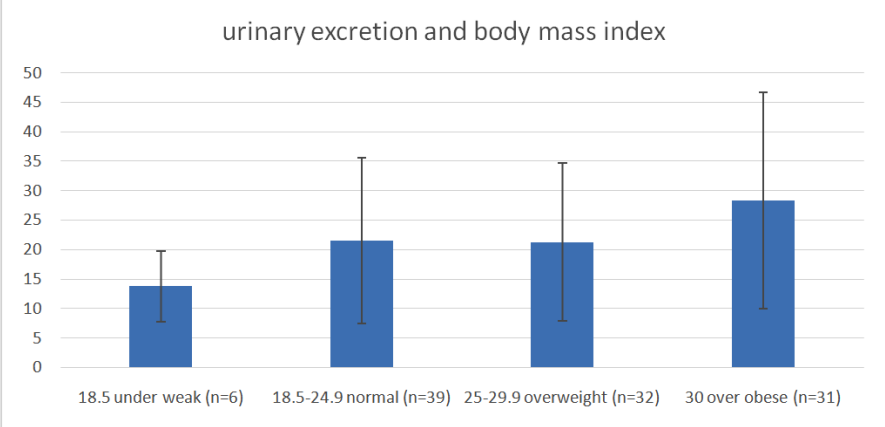

Figure 4. Urinary excretion of radioactivity in body mass index groups.

groups (Figure 1), but the difference was not significant ($p = 0.123$).

In terms of gender, urinary excretion was higher in male group compared to female group, but the difference was not significant ($p = 0.578$) (Figure 2). Radioactivity excretion did not change in different fasting blood sugar groups, despite a slight, but not significant, increase in group with less than 100 mg/dl ($p = 0.534$) (Figure 3).

In spite of a small increase in > 30 body mass index group, radioactivity excretion was not significantly different in body mass index groups ($p = 0.069$) (Figure 4).

^{18}F-FDG PET/CT images of a patient with lung cancer diagnosis were shown in Figure 5. Decrease change was observed in the amount of 18F-FDG radiopharmaceutical in the bladder before and after urinary excretion.

DISCUSSION

^{18}F-FDG PET/CT is widely used throughout the world for primary diagnosis, staging, restaging, evaluation of treatment effectiveness and radiotherapy planning in lung cancer [10]. PET/CT has the power to differentiate tumor and non-malignant tissue [11]. Maximum standardized uptake value is a commonly used malignancy criterion in clinical practice and is defined as ratio of activity in tissue per milliliter to the activity in the injected dose per kilogram body weight [12]. The present study was conducted to determine the effect of urinary excretion on total effective dose level in patients having PET/CT scans.

^{18}F-FDG in circulation undergoes glomerular filtration and is not reabsorbed as glucose. Thus, it is predominantly excreted in urine, which results in a problem in imaging of renal, ureteral, bladder, and prostate tumors. Poor ^{18}F-FDG uptake by some malignant neoplasms such as renal, prostate, and hepatocellular carcinomas is another drawback of ^{18}F-FDG. Therefore, ^{18}F-FDG PET has been considered useless to detect bladder cancer and perivesical lymph nodes [13]. In pelvis, increased physiological ^{18}F-FDG uptake may occur in bowel, uterus, ovary, bone marrow, bone, and urinary system [8].

PET/CT is typically acquired in the caudal to cranial direction to further reduce urinary bladder ^{18}F-FDG accumulation. Bladder catheterization or continuous bladder irrigation may also be used to reduce bladder radiopharmaceutical activity in patients who cannot urinate well [14]. Delayed ^{18}F-FDG PET/CT scans after a diuretic and oral hydration can dramatically improve detection of local recurrent or residual bladder tumors [13, 15]. In the present study, effective radiation level was lowered by 22.7% through urinary secretion in patients having ^{18}F-FDG PET/CT.

FDG is an^{18}F radionuclide-labelled analogue of glucose. It is the most widely used radiopharmaceutical in PET/CT technique. FDG is a typical short-lived radionuclide and has a half-life of 1.8 hours [16]. Studies have shown that ^{18}F-FDG urine excretion is highly variable. The results of the present study showed that FDG excretion varied between 5% and 15% during the hour between FDG administration and imaging in patients with normal kidney function and blood glucose levels for performing PET. Urinary FDG excretion was between 5.7% and 15.2% of decay-corrected injected dose. This variation is another problem for the accuracy of SUV. Urinary excretion relies upon hydration of patients along with various other factors influencing standardized uptake value. FDG excreted through kidneys is not absorbed by cells and is not accumulated intracellularly [17]. It was observed in the present study that age, gender, fasting blood sugar and body mass index did not affect urinary excretion of FDG.

Several strategies have been introduced to reduce radiation level exposed by patients and health care providers. The first and foremost strategy is proper use of ionizing radiation based on ALARA (As Low As Reasonably Achievable) principle. This principle aims to reduce exposed radiation level through reducing exposure time and using correct distance management (source-patient-detector, and source-patient-healthcare staff distances) and appropriate shielding. It was shown that adherence to this principle reduces radiation exposure. These precautions to reduce radiation exposure can compromise the efficiency and reliability of the procedure itself. Image fusion technology, for example, can further reduce radiation exposure [18]. Based on ALARA principle, the present study investigated minimal radioactivity level and corresponding imaging time required for reliable semi-quantification in PET/CT imaging [19]. The

cumulative 18F-FDG dose was calculated in milli-Curies during treatment and surveillance of all patients who received PET/CT scans. Calculated 18F-FDG PET/CT dose was converted to effective dose from milli-Curies to Becquerels and then from Becquerels to milli-Sieverts using a conversion factor of 0.019 mSv/MBq [20].

It is hypothesized that patients with renal failure may require a greater uptake time during an 18F-FDG PET/CT scan than patients with normal kidney function due to the impaired distribution and clearance of ^{18}F-FDG. Since urine production has such a drastic impact on the amount of dosage excreted, it can be associated with the rates of delayed urine production between renal failure [21]. It is may be decreased radioactivity dose in patients with renal failure during PET/CT scan.

Pain, loss of appetite, nausea, vomiting, cachexia, fatigue, dyspnea, acidity, liquid and electrolyte imbalances, anxiety, agitation, delirium and confusion are among the most common findings and symptoms in oncology patients [22, 23]. These patients frequently visit emergency services with these complaints. Therefore, emergency service employees are under a continuous radiation exposure risk. In addition to radiation protection measures for patients having PET/CT, effective urinary excretion practice would contribute to radiation safety of patients and emergency service workers. In the present study, it was shown that removal of ^{18}F-FDG from bladder through urinary excretion after PET/CT scan could protect patients and health care providers.

CONCLUSION

Active emptying of bladder, physiological area of involvement for ^{18}F-FDG, is an effective method in radiation safety of health care providers and patients in PET/CT use. Especially in cases where functional capacity of bladder is impaired, urinary catheter use could lower radiation exposure level.

Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The author disclosed that they did not receive any grant during conduction or writing of this study.

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The European Research Journal 2019;5(5):729-733 ORIGINAL ARTICLE

Fibromyalgia syndrome in chronic hemodialysis patients is associated with depression, hypoalbuminemia and inflammation

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ABSTRACT

Objectives: Fibromyalgia syndrome (FMS) is an entity that presents with wide-spread chronic pain in musculoskeletal system, disturbed sleep, reduced mental functioning and depressed mood. We aimed to determine the incidence of FMS in our hemodialysis patients and to evaluate the association between FMS, depression and inflammation in patients ongoing hemodialysis.

Methods: Among 169 patients, 140 patients were enrolled into our study. Twenty-nine patients were excluded according to exclusion criteria. Demographic characteristics including age, sex, body mass index, duration of dialysis, the etiology of end stage renal disease, the dialysis adequacy (Kt/V) were also recorded. All patients were evaluated through 2010 ACR preliminary diagnostic criteria including widespread pain index (WPI) and total symptom severity. All subjects completed Beck depression inventory (BDI) to determine psychological status.

Results: Among 140 hemodialysis patients, 76 (54.2%) patients presented chronic widespread pain and 20 patients (14.2%) met the 2010 ACR criteria for FMS. Patients were divided into FMS (n = 20; 14.2%) and non-FMS (n = 120; 85.8%) groups. FMS group had significantly higher serum C-reactive protein levels and lower serum albumin levels when compared to non-FMS group. BDI (31.4 ± 1.4 vs 14.8 ± 0.6, $p < 0.005$), WPI (11.2 ± 0.7 vs 2.8± 0.2, $p = 0.002$) and symptom severity (7.3 ± 0.3 vs 3.7 ± 0.1, $p < 0.005$) scores were significantly higher in FMS group.

Conclusions: The FMS itself and the related symptoms were correlated with depression in maintenance hemodialysis patients. Besides, inflammation and perhaps malnutrition-inflammation sydrome may trigger FMS in this population.

Keywords: Fibromyalgia, hemodialysis, depression

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Fibromyalgia is an idiopathic, chronic, nonarticular pain syndrome with generalized tender points. It is a multisystem disease characterized by sleep disturbance, fatigue, headache, morning stiffness, paresthesias, and anxiety. Fibromyalgia syndrome (FMS) is an entity that presents with widespread chronic pain in musculoskeletal system, disturbed sleep, reduced mental functioning and depressed mood [1, 2]. The prevalence of FMS in the general population has been estimated between 2.9%-

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5% [3]. Up to now, the classification criteria suggested by the American College of Rheumatology (ACR) in 1990 had been used in the diagnosis of fibromyalgia. According to this classification, there has to be left, right, top, bottom of body and axial skeletal chronic whole body pain for at least 3 months, and 11 or more tender points from the pre-defined 18 tender points for patient to be diagnosed as fibromyalgia [1]. However there are also some cases where 11 or more tender point criteria is not fulfilled so there are limitations in objectivity and usefulness of this diagnostic criteria [4]. Because of the kind of patient existing classification criteria, ACR suggested a new classification criteria in 2010 that diagnoses fibromyalgia as the sum of widespread pain index (WPI) and total symptom severity being more than a certain score, continuing symptoms for more than 3 months, and all three criteria without disease related to symptoms being satisfied [5]. The WPI is a measure of the number of painful body legions from a defined list of 19 areas. The symptom severity score includes an estimate of the degree of fatigue, waking unrefreshed, and cognitive symptoms and a number of somatic symptoms in general. The symptom severity scale may also be used for the assessment of patients with current and previous fibromyalgia or for longitudinal evaluation.

FMS is relatively frequent in the general population and affects females more often than males. Its prevalence is reported to increase with age [6]. Although FMS etiology and pathophysiology are still unclear, the current hypotheses focus on the central mechanisms of pain modulation and amplification in the genesis of FMS. Because musculoskeletal pain is regarded as the most prevalent form of chronic pain in end stage renal disease, a differential diagnosis of FMS should be considered in that group of patients. It may be difficult to determine if symptoms are related to FMS or the associated illness. Inflammatory rheumatic diseases, non-inflammatory musculoskeletal disorders, functional somatic syndromes, localized pain syndromes and anxiety disorders may coexist with FMS in end stage renal disease patients.

In our study, we aimed to determine the incidence of FMS in our hemodialysis patients and to evaluate the association between FMS, depression and inflammation in patients ongoing maintenance hemodialysis.

METHODS

Among 169 patients (male 63.3%) with end stage renal disease who received 4 hours 3 sessions/week, maintenance hemodialysis in Başkent University Hospital hemodialysis centre, 140 patients were enrolled into our study. Patients having unregulated diabetic disease, thyroid disorders, chronic rheumatic diseases and neuropathic diseases, co-existing liver disease, solid organ or hematological malignancy, immobilization, overt cardiovascular disease were excluded from the study. Twenty-nine patients were excluded according to exclusion criteria. We have received a consent form from all the patients. Demographic characteristics including age, sex, body mass index (BMI; kg/m^2), duration of dialysis, the etiology of end stage renal disease, the dialysis adequacy (Kt/V) were recorded. All patients were evaluated through 2010 ACR preliminary diagnostic criteria including WPI and symptom severity scale [5]. Subjects were asked if they had experienced chronic widespread pain for at least 3 months. Each subject was also examined for tenderness at 18 tender points by digital palpation. One score point was assigned for each tender point noted; thus, each individual's tender point score was between 0 and 18.

Patients were divided into FMS (n = 20; 14.2%) and non-FMS) (n = 120; 85.8%) groups. All subjects in FMS and non-FMS groups completed Beck depression inventory (BDI) to determine psychological status [7]. The BDI is a 21-question multi-choice self-report inventory that is one of the most widely used instruments for measuring the severity of depression. It is composed of items relating to depression symptoms such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex. It measures depression through scores, which can range from 0 to 63. The higher score is associated with the higher severity of depression. At the diagnosis of FMS in the current study, no patients were using specific medications for FMS, such as opioid analgesics or anti-depressants. As part of our quality assurance programme, all maintenance hemodialysis patients complete blood count and biochemical parameters were checked during monthly clinic visit within this

period. In all participants, a venous blood sample was collected after an overnight fast to measure the concentration of the following biochemical variables using standard laboratory techniques: calcium, phosphorus, albumin, C-reactive protein (CRP), parathyroid hormone (PTH) levels. (iPTH; by chemiluminescence immunoassay (Cobast®, Roche Diagnostics GmbH) levels. Body weight and BMI were taken after dialysis session. Height was obtained from the patient's chart.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS, version 15.0, SPSS Inc., Chicago, IL) was used to process and statistical analyses of all data. The results of monthly laboratory tests were reviewed and mean values of the tests were used for statistical correlation analyses. Data are presented as mean ± SD and as percentages when expressing frequency. The comparison between FMS and non-FMS patients were evaluated by student's t test for independent samples. Relationships between FMS and non-FMS or any parameters from the questionnaires were evaluated by Fisher's exact test. Pearson and Spearman rank tests were used to assess correlations between measurable variables, according to their parametric distribution, respectively. A p value < 0.05 was considered statistically significant.

RESULTS

Among 140 hemodialysis patients, 76 (44.9 %) patients presented chronic widespread pain and 20 patients (14.2%) met the 2010 ACR criteria for FMS. Patients were divided into FMS (n = 20; 14.2%) and non-FMS (n = 120; 85.8%) groups. Mean age of FMS and non-FMS groups were 55.2 ± 8.3 years and 54.5± 13.9 years, respectively (p = 0.520. No difference was obtained between FMS and NFMS patients according to their age, dialysis adequacy, duration of dialysis or marital status. In FMS and non-FMS groups, mean serum calcium levels were 9.1 ± 0.5 mg/dL and 9.0 ± 0.6 mg/dL, respectively (p = 0.649); mean serum phosphorus levels were 4.9 ± 0.9 mg/dL and 4.9 ± 1 mg/dL, respectively (p = 0.832); mean serum PTH levels were 439.5 ± 32.4 mg/dL and 481.3 ± 46.5 pg/dL, respectively (p = 0.180). FMS group had

Table 1. The clinical and biochemical findings of study population

	FMS Group (n = 20)	**Non-FMS Group (n = 120)**	***p* value**
Age (years)	55.2 ± 8.3	54.5 ± 13.9	0.520
Male gender, n (%)	12 (60)	78 (65)	0.623
Chronic kidney disease etiology			0.814
Diabetes Mellitus, n (%)	10 (50.0)	61 (50.8)	
Hypertension, n (%)	6 (30.0)	14 (11.6)	
Glomerulonephritis, n (%)	2 (10.0)	6 (5.0)	
Polycyctic kidney disease, n (%)	1 (5.0)	2 (1.6)	
Others, n (%)	1 (5.0)	4 (3.3)	
Duration of dialysis (years)	9.3 ± 0.8	10.7 ±0.4	0.516
Fasting glucose (mg/dL)	96.4 ± 2,6	98.6 ± 1.8	0.514
Calcium (mg/dL)	9.1 ± 0.5	9.0 ±0.6	0.649
Phosphorus (mg/dL)	4.9 ± 0.9	4.9 ± 1.0	0.832
PTH (pg/mL)	493.5 ± 32.4	481.0 ± 46.5	0.180
Albumin (g/dL)	3.1 ± 0.2	3.9 ± 0.3	**0.001**
CRP (mg/L)	13.8 ± 15.1	8.1 ± 13	**0.001**
Hemoglobin (g/dL)	10.6 ±1.2	11.3 ± 1.2	0.418
BMI (kg/m^2)	21.4 ±1.7	24.2 ± 2.1	0.316
WPI	11.2 ±0.7	2.8 ± 0.2	**0.002**
SS	7.3 ±0.3	3.7 ± 0.1	**0.005**
BDI	34.1 ±1.4	14.8 ± 0.6	**0.002**

Data are shown as mean ± standard deviation or number (%). BDI = Beck depression inventory, BMI = body mass index, CRP = C-recative protein, FMS = fibromyalgia, PTH = parathyroid hormone, SS = symptom severity, WPI = widespread pain index

significantly higher serum CRP (13.8 ± 15.1 vs 8.1 ± 13 mg/L, p = 0.01) whereas lower serum albumin levels (3.1 ± 0.2 g/L and 3.9 ± 0.3 g/L, p = 0.001) when compared to non-FMS group. Hemoglobin levels were similar between FMS and non-FMS groups (10.6 ± 1.2 g/dL and 11.3 ± 1.2 g/dL, respectively). BDI (31.4 ± 1.4 vs 14.8 ± 0.6, p < 0.005), WPI (11.2 ± 0.7 vs 2.8± 0.2, p = 0.002) and symptom severity (7.3 ± 0.3 vs 3.7 ± 0.1, p < 0.005) scores were significantly higher in FMS group (Table 1).

DISCUSSION

To our knowledge, present study is the first in the literature regarding clinical and laboratory outcomes of fibromyalgia in addition to impact on depression in maintenance hemodialysis patients. Fibromyalgia is usually considered as a disorder of females 20 to 50 years of age; however, it also has been observed in males, children, adolescents, and older persons [8, 9]. A study by Wolfe *et al*. [6] with screening of 3006 adults revealed FMS prevalence rates as 3.4% in female and 0.5% in male. The recent study in the literature about fibromyalgia in maintenance hemodialysis patients reported that the prevalence rates in the maintenance hemodialysis and control groups were statistically similar to work by Wolf *et al*. [6]. In accord with the literature, present study had similar prevalence rates in hemodialysis and control groups; however the overall rate of fibromyalgia was higher when compared to other studies. We can explain this higher prevalence with the 2010 preliminary classification criteria according to American College of Rheumatology (ACR) that we used for the FMS diagnosis, whereas the recent studies were diagnosing FMS with ACR classification criteria of 1990. Yuceturk et. al. [10] reported that FMS was more frequent in females, with rates of 10.4% in women and 1.9% in men. In contrast to the most studies FMS was more common in men, in current study. This conflicting result was not surprising because the percentage of men in the study was 63%. Fibromyalgia is a neurogenic inflammatory response to allergens, infectious agents, chemicals or emotional stress; however the sources of inflammation triggering the fibromyaigia syndrome remain to be unknown [11]. In our study, mean serum CRP levels were significantly higher in fibromyagia group, as expected. Although we didn't evaluate other inflammation markers as TNF-α, IL-6 and IL-8 as a limitation of this study. High levels of serum CRP reflects the importance to take into account the inflammation in patients with fibromyalgia to project the therapeutic approach. The index for dialysis adequacy (Kt/V) and nutritional status are known to be determinants for health status in the hemodialysis patients and affect their quality of life (QOL). In present study, while there was no significant difference for dialysis adequacy between two groups, hypoalbuminemia that is a major marker for malnutrition and a well-known negative acute phase reactant was significantly lower in FMS patients when compared to non-FMS patients in our study. This finding may be a result of malnutrition-inflammation syndrome that can trigger FMS in maintenance hemodialysis patients. We also couldn't detect an association between FMS and serum levels of PTH, alkaline phosphatase, calcium or phosphorus. Although this result was similar to the literature, we wonder for we anticipate high levels of parathormone and phosphorus levels that were well-known musculoskeletal pain causes in hemodialysis patients.

Chronic pain has been reported as a leading cause of insomnia in any medical illness where most studies have focused on rheumatic disorders for these symptoms [12]. Sleep difficulties and related symptoms as fatigue, paraesthesia and morning stiffness have been reported in >75% of patients with fibromyalgia [13]. In Yuceturk *et al*.'s study [10], the prevalence of fatigue, sleep disturbances and restless leg syndrome were higher in maintenance hemodialysis patients than in control subjects, regardless of whether or not the individual was diagnosed as having FMS. However all these entities were more common but not statistically significant in maintenance hemodialysis patients with proven FMS in current study.

Finally, we focused on depression which characteristically presents in FMS patients. The percentage of depressive symptoms is high in patients with FMS, ranging from 40% to 80% [14, 15].

Thus, similar to previous studies we showed the negative impact of fibromyalgia on quality of life by chronic pain and related symptoms, we observed

significantly higher BDI, WPI and symptom severity scores in FMS patients, as expected and then referred patients to psychiatry department. In conclusion, although several studies have evaluated the coexistence of FMS and psychiatric disorders, data about the fibromyalgia and depression in hemodialysis patients is limited and need further studies with higher number of subjects.

Limitations

There were several limitations of current study: 1)- The study especially FMS group have small sample size. 2)- We assess the relation between FMS and inflammation only with serum CRP and albumin levels, we may invigorate with evaluating other inflammation markers as IL-6, IL-8 and TNF-alpha. 3)- We didn't evaluate the questionnaires for assessing the quality of life and sleep disturbance.

CONCLUSION

In present study the prevalence of FMS in hemodialysis patients was 11.8%. The FMS itself and the related symptoms were correlated with depression. Moreover, inflammation and perhaps malnutrition-inflammation syndrome may trigger FMS. Thus patients with FMS and ongoing maintenance hemodialysis should be followed closely for inflammation and mood disorders.

Conflict of interest

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The European Research Journal 2019;5(5):734-739 ORIGINAL ARTICLE

Factor VII-401 and -402 polymorphisms and acute myocardial infarction in southern Turkey population

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ABSTRACT

Objectives: Factor VII has a crucial role in the extrinsic coagulation pathway and initiates the thrombus formation. Some studies showed that high plasma factor VII level was related to increased acute myocardial infarction (AMI) risk. But, some studies were reported opposite findings. Some polymorphisms can change the factor VII level. There is limited information about factor VII polymorphisms in southern Turkey population. Our aim was to determine the frequencies of Factor VII-401 and -402 polymorphisms and their relation to AMI in southern Turkey area.

Methods: We enrolled 83 patients with AMI and 71 healthy subjects. Routine laboratory tests and factor VII-401 and -402 polymorphisms were determined from blood samples. Factor VII -401 and -402 polymorphisms were analyzed by LightCycler device using Real-Time PCR technique.

Results: Family history of coronary artery disease and smoking frequencies were higher in patients group ($p < 0.001$ and $p = 0.013$, respectively). Patients had higher LDL cholesterol ($p = 0.011$) level, and lower HDL cholesterol ($p = 0.025$) level compared to healthy subjects. Factor VII-401 and -402 polymorphism genotypes were not significantly different in both groups. Also allele frequencies were similar in both groups.

Conclusion: Factor VII-401 and -402 polymorphisms do not seem to increase AMI risk in southern Turkey.

Keywords: Acute myocardial infarction, factor VII-401 and -402 polymorphisms

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Intracoronary thrombus is one of the reasons of acute myocardial infarction (AMI). It occurs via combination of circulating factor VII and tissue factor exposure after plaque rupture [1]. In clinical practice, it is observed that some patients with serious coronary artery disease (CAD) do not have any AMI. On the contrary, some patients without serious coronary artery lesions suffer from AMI. These facts have led the investigators to look for other abnormal thrombosis developing reasons. Some investigators focused mainly to the blood coagulation system. Increased plasma fibrinogen level was determined as a cardiovascular risk factor [2]. Factor VII is also a vitamin K dependent coagulation factor circulating as an inactive zymogen in blood. It has a crucial role in the extrinsic coagulation pathway and synthesized by liver [3]. There are some controversial reports in the literature about high plasma factor VII level's relation to increased AMI risk [4-7]. Factor VII level can be altered via genetic and environmental factors [8]. Guanine to

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thymine (G/T) base substitution at the -401st position of factor VII gene's promoter leads a decreased gene transcription and lower plasma factor VII level. Guanine to adenine (G/A) base substitution at the -402nd position of the same area increases the gene transcription and the factor VII level. Together both polymorphisms are responsible for 18% and 28% of the variation in the plasma concentrations of total factor VII and activated factor VII molecules, respectively. Both factor VII-401 and factor VII-402 polymorphism frequencies were reported as low [9]. There is limited information about factor VII polymorphisms in general Turkish population. The aim of this study was to determine the frequencies of these polymorphisms and their relation to AMI in southern Turkey population.

METHODS

We enrolled 83 patients who admitted with AMI to our coronary intensive care unit and 71 healthy subjects. Local Ethics Committee of Çukurova University was approved the study. Written informed consent was collected from all subjects. Diagnosis of AMI was based on typical chest pain, ST segment elevation in the admission electrocardiogram, and cardiac enzyme increase criteria. All patients were recruited consecutively, and all patients had their first myocardial infarction. Control subjects were selected randomly from healthy individualswho admitted for an examination to our polyclinic unit. None of these controls had any cardiovascular and valvular diseases. All the patients and control subjects were from southern Turkey. Diabetes mellitus (DM) was considered as a risk factor for atherosclerosis development [10]. Therefore, we excluded patients with DM. All patients and controls were questioned about age, gender, hypertension, smoking, hyperlipidemia, and family history. Body mass indexes were recorded. Complete blood count, glucose, lipid levels, and renal functions were recorded from routinely taken blood samples.

DNA isolation

2 cc of K3 EDTA anticoagulated venous blood sampleswere collected from all subjects for DNA analysis. DNA samples were isolated from whole blood with the aid of MagNa Pure LC DNA Isolation Kit I by MagNa Pure LC Automated DNA isolation instrument (Roche Applied Sciences). DNA samples were stored at –20 ºC until mutations were investigated.

Real-Time PCR

Primer and hybridization probes for the factor VII –401 G/T and -402 G/A polymorphisms were designed and synthesized by OlfertLandt (Tib-Molbiol, Germany). All polymorphism-related gene regions were amplified in 20 µl PCR capillary tubes. Amplification process was established using LightCycler FastStart DNA Master Hybridization Probes (Roche Applied Science). After preparation of primers, probes and kit mixtures, 18 µl of the reaction mixture and 2 µl (~40 ng) genomic DNA were added in each LightCycler capillary tube. Water was used as negative control. Capillary tubes were sealed and briefly centrifuged in a microcentrifuge and then placed into the LightCycler carousel. The PCR products were detected by using 3'- fluorescein (FLU) labelled probe and 5'- Red 640 labelled probe. When both probes hybridize in close proximity, fluorescence resonance energy transfer (FRET) occurs, producing a specific fluorescence emission of LC-Red as a result of FLU excitation. Fluorescence intensity depends on the amount of specific PCR products. Amplification was monitored on-line per cycle via LightCycler device. At the end of the amplification, LightCycler device increased the temperature and measured the fluorescence same time. Temperature / fluorescence curve (melting curve) was obtained this way and polymorphisms were determined with the analysis of this curve.

Statistical Analysis

The variables were divided into two groups as categorical and continuous. Categorical data were expressed as numbers and percentages, and compared with the chi-square test. Kolmogorov-Smirnov test was used to determine whether continuous variables had normal distribution or not. Normal distributed continuous variables were compared with the independent samples t-test. Not normal distributed variables were compared with Mann-Whitney U Test. Binominal logistic regression analysis was performed with significant variables. Independent predictors were found for AMI. Statisticalanalyses were

Table 1. Comparison of demographic findings

	Patients (n = 83)	Controls (n = 71)	*p* value
Age (years)	47.5 ± 7.5	45.6 ± 5.7	0.068
Male gender, n (%)	46 (55.4)	33 (46.5)	0.268
Systolic blood pressure (mmHg)	119.6 ± 17.0	122.7 ± 16.5	0.284
Diastolic blood pressure (mmHg)	70.2 ± 11.5	71.4 ± 11.2	0.508
Pulse (beat/minute)	81.7 ± 8.7	80.7 ± 8.1	0.489
BMI (kg/m^2)	24.5± 2.1	24.2± 2.1	0.394
Smoking, n (%)	56 (67.5)	34 (47.9)	**0.013**
Family history of CAD, n (%)	37 (44.6)	11 (15.5)	**< 0.001**
Hypertension, n (%)	65 (78.3)	56 (78.9)	0.933
Hyperlipidemia, n (%)	38 (45.8)	21 (29.6)	**0.039**

Data are shown mean ± standard deviation or number (%). BMI = Body mass index, CAD = Coronary artery disease

calculated with SPSS 20.0 (SPSS Inc., Chicago, IL, United States). A *P* value < 0.05 was considered to be statistically significant.

RESULTS

Demographic comparison was presented in the Table 1. Family history of CAD ($p < 0.001$), smoking ($p = 0.013$), and hyperlipidemia ($p = 0.039$) were significantly higher in patient group ($p < 0.05$). All other variables were similar between two groups. Low density lipoprotein cholesterol (LDL-C) levels were higher ($p = 0.011$) and high density lipoprotein cholesterol (HDL-C) levels were lower ($p = 0.025$) in patient group ($p < 0.05$). Other laboratory parameters were similar (Table 2). Factor VII-401 and -402 polymorphism genotype frequencies were similar between two groups (Table 3). It was determined that both polymorphisms were suitable to the Hardy-Weinberg equation. Factor VII-401 G/T allele frequencies were 0.59/0.41 and 0.51/0.49 in patients

Table 2. Comparison of laboratory findings

	Patients (n = 83)	Controls (n = 71)	*p* value
Glucose (mg/dl)	123.2 ± 82.5	100.7 ± 7.0	0.723
WBC (uL)	7.1 ± 1.5	6.8 ± 1.8	0.261
Hb (mg/dl)	12.1 ± 1.3	12.1 ± 1.5	0.979
BUN (mg/dL)	41.8 ± 4.6	41.1 ± 4.5	0.492
Cr (mg/dL)	0.9 ± 0.2	0.9 ± 0.1	0.95
Na (mmol/L)	137.7 ± 2.6	137.8± 3.6	0.94
K (mmol/L)	4.1 ± 0.3	4.1 ± 0.1	0.992
LDL-C (mg/dl)	128.7 ± 39.2	113.5 ± 31.3	**0.011**
HDL-C (mg/dl)	41.5 ± 8.7	44.9 ± 9.1	**0.025**
Triglyceride (mg/dl)	191.9 ± 102.8	183.5 ± 137.7	0.675
Total cholesterol (mg/dl)	202.0 ± 47.0	194.6 ± 35.4	0.284

Data are shown mean ± standard deviation. WBC = White blood cells, Hb = Hemoglobin, BUN = Blood urea nitrogen, Cr = Creatinine, LDL-C = Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol

Table 3. Genotype distributions of patients and control subjects

	Patients (n = 83)	Controls (n = 71)	*p* value
Factor VII -401 G/T			
Homozygous G, n (%)	33 (39.8)	24 (33.8)	
Heterozygous, n (%)	32 (38.6)	24 (33.8)	0.324
Homozygous T, n (%)	18 (21.7)	23 (32.4)	
Factor VII -402 G/A			
Homozygous G, n (%)	38 (45.8)	28 (39.4)	
Heterozygous, n (%)	25 (30.1)	18 (25.4)	0.318
Homozygous A, n (%)	20 (24.1)	25 (35.2)	
Allele distributions			
Factor VII -401 G/T, n	0.59/0.41	0.51/0.49	0.3
Factor VII -402 G/A, n	0.61/0.39	0.52/0.48	0.31

and controls, respectively. Factor VII-402 G/A allele frequencies were 0.61/0.39 in patients and 0.52/0.48 in control subjects. Both groups had similar allele frequencies (Table 3). Binominal logistic regression analysis was performed with statistically significant variables. Family history of CAD (OR: 5.101, 95% CI: 2.200 - 11.825, $p < 0.001$), LDL-C (OR: 1.018, 95% CI: 1.006 -1.031, $p = 0.003$), and HDL-C (OR: 0.938, 95% CI: 0.896 - 0.982, $p = 0.006$) were determined as independent predictors for AMI (Table 4).

Table 4. Independent predictors for acute myocardial infarction

	Odds ratio	CI (95%)	*p*
Family history of CAD	5.101	2.200-11.825	**< 0.001**
Hyperlipidemia	1.182	0.472-2.958	0.722
Smoking	0.553	0.248-1.229	0.146
LDL-C	1.018	1.006-1.031	**0.003**
HDL-C	0.938	0.896-0.982	**0.006**

CAD = Coronary artery disease, LDL-C = Low density lipoprotein cholesterol, HDL-C = High density lipoprotein cholesterol

DISCUSSION

The main finding of our study was that this was the first study which investigated the relation between factor VII-401 and -402 polymorphisms and AMI in factor VII southern Turkey population. Classic CAD risk factors were significantly higher in patients. There was no association between these polymorphisms and AMI in this population.

It was thought that increased plasma factor VII levelcould affect the formation speed and growth of thrombus. These facts can play an important role in acute coronary syndromes. The studies whichaimed to investigate this hypothesis had controversial results in factor VII the literature [11].

Seven factor VII gene related polymorphisms have been identified. These are A/G base substitution at the 353rd codon in exon 8, hyper variable region 4 (HVR4) polymorphism of intron 7, decanucleotide insertion at positions -323, -401G/T, -402G/A, -59T/G, and -32A/C[12].

There were conflicting results in studies that

investigated the relation between CAD and first two polymorphisms [13-16]. It was reported that -323rd nucleotide polymorphism in promoter has no biological activity [9]. Effects of the -401 G/T and -402 G/A polymorphisms over CAD and cerebrovascular diseasewere investigated in limited number of studies [17-20].

Kang *et al.* [17] reported that activated factor VII (FVIIa) level and factor VII coagulant activity (FVIIc) were higher in the AMI patients. But, CAD patients without AMI had similar FVIIa, FVIIc, and factor VII antigen (FVIIag) levels compared to control subjects. Their study population consisted of 60 CAD patients (33 of these patients had AMI) and 149 control subjects. Factor VII-401 and -402 polymorphism genotype and allele distributions were not different between groups. Same investigators showed that FVIIa, FVIIc, and FVIIag levels were higher in 62 cerebral infarction patients compared to the 149 healthy subjects [18]. They also reported that polymorphism genotype and allele distributions were similar in both groups.

Evangelista *et al.* [19] investigated the effect of factor VII-401 and -402 polymorphisms in arterial and venous thrombotic events. Their patient group consisted of 104 participants and control group had 106 healthy subjects. They showed that there was no significant difference about these polymorphisms between patients and controls. Likewise, Ramzi *et al.* [20] reported a similar result in their study. They tried to identify the role of factor VII-401 G/T and HVR4 polymorphisms in CAD. They enrolled 110 patients and 110 control subjects. They found no association between these polymorphisms and CAD. There were no genotype distribution and allele frequency difference between our groups. Our results were compatible with these studies.

Allele distributions can vary significantly in different populations. Kang *et al.* [17] found allele frequencies 0.03/0.97 for factor VII-401 G/T and 0.48/0.52 for -402 G/A in patients. We found -401 G/T allele frequency 0.59/0.41 and -402 G/A allele frequency 0.61/0.39 in our patient group. Van't Hooft *et al.* [9] found -401 G/T and -402 G/A allele frequency 0.91/0.09 and 0.71/0.29 respectively in healthy European subjects. Kang *et al.* [17] found allele frequencies for -401 G/T and -402 G/A polymorphisms in healthy Chinese subjects 0.97/0.03 and 0.52/0.48, respectively. In our control group, -401 G/T allele frequency was 0.51/0.49 and -402 G/A allele frequency was 0.52/0.48. There was a noticeable difference in the factor VII-401 G/T allele frequency between our population and their populations.

Limitations

Factor VII-401 and -402 polymorphism's effects on the factor VII level have been identified before. Some of the studies did not include measurements of factor VII [21]. We also did not measure factor VII level for this reason. But, this is an important limitation for us. Also, our small sample size is another limitation.

Age, lipid levels, obesity, andsmoking can alter factor VII level [22]. When all the environmental and genetic risk factors taken into account, we still have limited information about which factor how much strongly affects factor VII level. Further studies are needed to clarify role of factor VII gene polymorphism over arterial thrombosis development.

CONCLUSION

There is an association between classic CAD risk factors and AMI, butfactor VII-401 and -402 polymorphisms do not seem to increase risk of AMI in southern Turkey population.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2019;5(5):740-744 ORIGINAL ARTICLE

Dynamic thiol-disulphide homeostasis in grade 3-4 gonarthrosis

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ABSTRACT

Objectives: We aimed to determine thiol-disulphide homeostasis, which plays a vital role and to investigate the relationship among homeostatic parameters and disease.

Methods: In this prospective study, we enrolled 38 patients with osteoarthritis (31 females and 7 males) and 38 healthy controls (30 females, 8 males volunteers). Diagnosis of osteoarthritis was made according to the American College of Rheumatology Criteria. The severity of osteoarthritis was assessed and classified according to the Kellgren-Lawrence grading scale.

Results: The mean age was 63.8 (range; 53-74) years in the osteoarthritis group and 65.6 (range; 55-75) years in the control group. There were no significant differences between the patients and controls in respect to age, gender and body mass index ($p > 0.05$). Serum albumin ($p = 0.605$) and total protein levels ($p = 0.605$) between patients and controls were similar. In the osteoarthritis group disulphide/ native thiol percent ratios and disulphide/ total thiol percent ratios were found to be statistically higher ($p = 0.002$ and $p = 0.002$; respectively) and native/ total thiol percent ratios were significantly lower than that of the control group ($p = 0.002$).

Conclusions: Thiol-disulphide homeostasis is weakened in osteoarthritis, and the balance shifts to the disulphide bond formation side. Substitution of thiol deficiency and correction of thioldisulphide imbalance may be beneficial in the managing treatment of the disease. Further studies may be needed for evaluating articular fluid thiol-disulphide homeostasis.

Keywords: Oxidative stress, osteoarthritis, thiol-disulphide homeostasis

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Osteoarthritis is a chronic, progressive disorder of thesynovial joints, characterized by focal loss of cartilage and changes in subchondral and marginal bone, synovium, and peri-articular structures [1]. Osteoarthritis of the knee is a relatively common condition that affects approximately 10% of the general population above the age of 55 years [2]. Radiographic appearance and clinical features are still often used for diagnosis of the disease. However, the etiology of osteoarthritis is not fully understood, although mechanical, biochemical, and genetic factors are accepted to play roles [3, 4].

One possible cause of osteoarthritis is oxidative stress. There is some evidence of the relationship be-

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tween knee osteoarthritis and oxidative stress [3, 5, 6]. The levels of pro-inflammatory mediators, such as reactive oxygen species (ROS), are elevated in osteoarthritis [7, 8]. Thus, the increased levels of these reactive species with oxidative activity mediate the effects of many pro-inflammatory cytokines, such as interleukin (IL)-1 and tumor necrosis factor (TNF)-α [7-9]. IL-1 and TNF-α may play a crucial role in cartilage matrix degradation by stimulating matrix metalloproteinase (MMP) expression in patients with osteoarthritis [8, 9].

It is known that free radicals cause oxidation of –SH groups in sulfur-containing amino acids of proteins and this is the earliest observable signs of protein oxidation [10]. To protect cells against oxidative stress, certain low molecular weight antioxidant molecules, either water-soluble (e.g., ascorbic acid) or lipid-soluble (e.g., vitamin E), are present in extracellular fluids [11]. Thiols are in interaction with almost all physiological oxidants. And they are mentioned as essential antioxidant buffers. Thiols, also known as mercaptans, which consist of a sulfur atom and a hydrogen atom bound to a carbon atom, are functional sulfhydryl groups [12]. A very large part of the blood plasma thiol pools consist mainly of albumin and other proteins such as glutathione, thioredoxin, cysteine and homocysteine [13]. Thiol groups of proteins are oxidized by oxygen molecules present in the medium and are reversibly converted to disulphide bonds. Formed disulphide bonds can be reduced to thiol groups again. Thus the thiol-disulphide balance is maintained [14]. Dynamic thiol-disulphide homeostasis plays a critical role in antioxidant defense, detoxification, apoptosis, regulation of enzyme activity, transcription and cellular signal transduction mechanisms [15, 16]. Only a single side of this double-sided balance has been measured since 1979 [17]. Both variable levels are measured one by one and cumulatively with a novel and automated method [18].

We aimed to determine thiol-disulphide homeostasis, which plays a vital roleoa and to investigate the relationship among homeostatic parameters and disease.

METHODS

In this prospective study, we enrolled 38 patients with osteoarthritis (31 females and 7 males) and 38 healthy controls (30 females, 8 males volunteers). Diagnosis of osteoarthritis was made according to the American College of Rheumatology Criteria [19]. The severity of osteoarthritis was assessed and classified according to the Kellgren-Lawrence grading scale [20]. Grade 0 was accepted as normal, grade 1 as possible osteophytes only, grade 2 as absolute osteophytes and possible joint space narrowing, grade 3 as moderate osteophytes and/or absolute joint space narrowing, and grade 4 as large osteophytes, severe joint space narrowing, and/or bony sclerosis. All patients had grade III-IV knee osteoarthritis according to the radiological classification and clinical findings. Exclusion criteria included use of supplemental vitamins, smoking, diabetes mellitus, coronary artery disease, acute/chronic liver diseases, inflammatory rheumatic disease, clinically unstable medical illness, or the use of any medication within 4 weeks prior to initiation of the study.

All subjects were informed. Written consents were obtained and the study was approved by the local ethics committee. Patient and healthy groups were matched in terms of osteoarthritis grade and age.

Tablo1. Demographic characteristics of patients and controls

	Osteoarthritis group	Control group	*p* value
Age (years) Mean (range)	63.8 (53-74)	65.6 (55-75)	
Gender, n (male/female)	7/31	8/30	0.759
BMI (kg/m^2) Mean (range)	26.74 (25.5-31.75)	27.30 (24.8-32.63)	

BMI = body mass index

Venous blood samples were collected from the subjects and centrifuged at 2300 x g for 10min. Serum samples were separated and stored at -80 °C until analysis. Serum thiol -disulphide homeostasis was determined with a recently developed a novel and automatic measurement method by using an automated clinical chemistry analyser (Roche, cobas 501, Mannheim, Germany) [18]. Native thiol (-SH) and total thiol (-SH + -S-S-) were measured directly, and -S-S-/-SH, -S-S-/-SH + -S-S-, -SH/-SH + -S-S- results were obtained with calculation.

Statistical Analysis

All analyses were conducted using the SPSS software (version 22; IBM SPSS Inc., Chicago, IL, USA). The normality of distributions was evaluated using the one-sample Kolmogorov – Smirnov test, revealing a uniform distribution. Mann Whitney U test was used to analyze the numerical variables. p-values of less than 0.05 were regarded as significant.

RESULTS

The mean age was 63.8 (range; 53-74) years in the osteoarthritis group and 65.6 (range; 55-75) years in the control group. Demographic characteristics of patients with knee osteoarthritis and controls are shown in Table 1. There were no significant differences between the patients and controls in respect to age, gender and body mass index (BMI). Serum albumin and total protein levels of the between patients and controls were similar ($p = 0.605$ and $p = 0.652$; respectively).

There is no difference in native thiol levels and total thiol levels between the groups ($p = 0.06$ and $p = 0.07$; respectively). In addition there is no diffference in disulphide values between the groups ($p = 0.07$). In the osteoarthritis group disulphide/ native thiol percent ratios and disulphide/ total thiol percent ratios were found to be statistically higher ($p = 0.002$ and $p = 0.002$; respectively) and native/ total thiol percent ratios were significantly lower than that of the control group ($p = 0.002$) (Table 2).

DISCUSSION

Thiol groups have a significant role in the cell by minimizing the toxic effects of oxygenactivation processes. Fundamentally sulfhydryl groups are associated with proteins. So, when thiol levels decreases in serum its antioxidant power will decrease too. Because reactive species organized near the sides of their formation, increases in the expression of protein levels of thiol-disulphide will protect the tissular oxidative damage and cannot prevent the oxidation of thiol groups in serum [10-14].

Dynamic thiol-disulphide homeostasis has a critical role in the organism. Changes in the thiol-disulphide balance serve as components for antioxidant protection, detoxification, regulation of enzymatic activity and cellular signaling mechanisms [16, 21]. Changes in thioldisulphide homeostasis have been associated with various diseases such as diabetes mellitus, cancer, chronic kidney disease, liver disorders and chronic obstructive pulmonary disease [22-24].

Osteoarthritis is a process of progressive deterioration of articular cartilage and formation of osteophyte at the joint surface. Osteoarthritis is often associated with significant disability and an impaired

Table 2. Thiol-disulphide profiles of subjects

Parameter	Osteoarthritis group	Control group	*p* value
-SH (µmol/L)	375.07 ± 34.512	407.66 ± 48.99	0.603
-S-S- (µmol/L)	15.50 ± 4.507	18.76 ± 4.59	**0.003**
-SH + -S-S (µmol/L)	405.992 ± 37.493	407.66 ± 48.99	0.0712
-S-S- /-SH + -S-S- (%)	3.806 ± 1.030	4.61 ± 1.090	**0.002**
-SH/-SH + -S-S- (%)	92.407 ± 2.006	90.80 ± 2.21	**0.002**
-S-S- / -SH (%)	4.145 ± 1.217	5.11 ± 1.093	**0.002**

-SH = native thiol, -S-S- = disulphide, (-SH + -S-S- = total thiol

quality of life. Pathologically, the disease is characterized by fissuring and focal erosive cartilage lesions, as well as cartilage loss and destruction [5]. Oxidative stress leads to increased risk for osteoarthritis but the precise mechanism remains unclear. Studies suggested that oxidative stress causes chondrocyte senescence and cartilage ageing [24, 25].

Soran *et al*. [5] and Altindag *et al*. [6] found that oxidative stress extremely increased in osteoarthritis, which may be responsible for the ethiopathogenesis of the disease). In our study, we observed decreased antioxidant parameters in subjects with knee osteoarthritis compared to the controls. These results confirmed the presence of oxidative stress.

CONCLUSION

In conclusion, thiol-disulphide homeostasis is weakened in osteoarthritis, and the balance shifts to the disulphide bond formation side. Substitution of thiol deficiency and correction of thioldisulphide imbalance may be beneficial in the managing treatment of the disease. Further studies may be nedeed for evaluating articular fluid thiol-disulphide homeostasis.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The author disclosed that they did not receive any grant during conduction or writing of this study.

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The European Research Journal 2019;5(5):745-750 ORIGINAL ARTICLE

A comparison of C-MAC videolaryngoscope and Macintosh laryngoscope in intraocular pressure changes, throat pain, intubation time and hemodynamic variables

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ABSTRACT

Objective: The aim of the current study was to compare intraocular pressure (IOP), hemodynamic parameters and throat pain in the use of C-MAC videolaryngoscope and the Macintosh laryngoscope under general anesthesia requiring endotracheal intubation.

Methods: Seventy-eight patients aged 18-65 years, ASA (American Society of Anesthesiologists physical status). I-II, who underwent elective surgery under general anesthesia were scheduled in the study. The groups were allocated as Group M (Macintosh laryngoscope) and Group VL (videolaryngoscope). Standard anesthesia technique was used in both groups. To assess the depth of anesthesia which was kept between 40 and 60, a Bispectral Index Monitor Model 2000 (Aspect Medical Systems, Inc, Newton, MA) was used throughout the study. We recorded hemodynamic variables, oxygen saturation before induction, at the 3rd and at the 10th minutes after intubation. The duration of intubation was recorded as the time from the laryngoscope entering the mouth to removal with end-tidal carbon dioxide on the monitor. IOP was measured before induction, and at the 3rd and 10th minutes after intubation. Inhalation agent was given after intubation. 78 patients were included in the study. We recorded cough after extubation, and postoperative sore throat was evaluated by an anesthesiologist who was blinded to the group allocations at 10 minutes and at 24 hours postoperatively.

Results: There was no significant difference between the groups regarding age ($p > 0.05$), mean body mass index ($p = 0.157$), mean ASA ($p = 0.475$), mean bispectral index values ($p = 0.084$) and mean operating time ($p = 0.068$). The mean duration of intubation was determined to be statistically significantly longer in Group M than in Group VL ($p = 0.0001$). There was no statistically significant difference between the groups regarding Modified Mallampati Score ($p = 0.571$) and Cormack Lehane Score ($p = 0.819$). The mean IOP at 3rd minute after intubation was determined to be statistically significantly higher in Group M ($p = 0.0001$). There was no statistically significant difference between the groups in regarding cough after extubation ($p = 0.549$), throat pain at 10 minutes ($p = 0.662$) and at 24 hours postoperatively.

Conclusions: C-MAC videolaryngoscope can be recommended as the first choice in patients with high IOP requiring general anesthesia with endotracheal intubation.

Keywords: Airway management, videolaryngoscope, intraocular pressure

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Videolaryngoscopes are the new generation devices which were introduced into the difficult intubation algorithm by the American Society of Anesthesiologists (ASA) in 2013 [1].

Videolaryngoscopes are known to be superior to traditional direct laryngoscopy in cases of difficult airway, glottic visualisation is obtained more easily and less airway trauma is seen [2]. C-MAC (Karl Storz, Tutlingen, Germany) is a new portable videolaryngoscope which is used in difficult airways [3]. There are 2, 3, and 4 numbered D blades. In the light source of the blade of the C-MAC videolaryngoscope, there is a camera which is connected to a video screen monitor. In addition to passing soft tissues by visualisation, the camera is helpful in defining the glottic appearance [1].

There are studies which have compared the hemodynamic response and increase in IOP in intubation using direct Macintosh laryngoscope and various videolaryngoscopes and airway devices [4-6]. However, to the best of our knowledge there is no study comparing the effect on the increase in IOP of C-MAC videolaryngoscope and Macintosh laryngoscope. The aim of the current study was to compare IOP, hemodynamic parameters and throat pain in the use of C-MAC videolaryngoscope and the MacIntosh laryngoscope.

METHODS

Approval for the study was granted by the Ethics Committee of Dışkapı Yıldırım Beyazıt Training and Research Hospital, University of Health Sciences (decision no 32/27 dated 22/11/2016, Clinical trial Identifier: NCT03279172).The study included after written consent, 78 adulttotal of 78 patients, aged 18-65 years of American Society of Anesthesiologists physical status I-II, who were to undergo elective surgery under general anaesthesia. Patients were excluded if they had a known allergy, elevated IOP, glaucoma, a history of eye surgery or if it was considered that intubation would be difficult.

Protocol

Before induction the patients were randomly allocated by computer to one of two groups. The groups were named as Group M where the Macintosh laryngosope was used and Group VL where the videolaryngoscope was used. Standard anaesthesia was used in both groups and BIS monitorisation was applied. A record was made of IOP, hemodynamic changes and oxygen saturation at 3 and 10 minutes after intubation. IOP was measured before induction, and at the 3rd and 10th minutes after intubation. Inhalation agent was given after intubation. 78 patients were included in the study.

Throat pain was evaluated by questioning the patient at 10 minutes and 24 hours after waking from general anaesthesia. The duration of intubation was recorded as the time from the laryngoscope entering the mouth to removal with end-tidal carbon dioxide on the monitor.

Statistical Analysis

Statistical analyses of the study data were made using NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA). In the evaluation of the data, descriptive statistical methods were used (mean, standard deviation) and in the comparison of paired groups, the Independent t-test was applied. In the comparison of qualitative data, the Chi-square test was used. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

No statistically significant difference was determined between the groups in respect of age distribution ($p > 0.05$), mean body mass index ($p = 0.157$), mean ASA ($p = 0.475$), mean bispectral index values ($p = 0.084$) and mean operating time ($p = 0.068$). The mean duration of intubation was determined to be statistically significantly longer in Group M than in Group VL ($p = 0.0001$) (Table 1).

No statistically significant difference was determined between the groups in respect of cough after extubation ($p = 0.549$) and throat pain at 10 mins postoperatively ($p = 0.662$). No throat pain was observed in either group at 24 hours postoperatively (Table 2). No statistically significant difference was determined between the groups in respect of complications after extubation ($p = 0.601$).

No statistically significant difference was determined between the groups in respect of the

Table 1. Mean values of age, gender, BMI, ASA, intubation and operating time in both groups

		Group M	Group VL	*p* value
Age (years)		44.1 ± 12.23	48.44 ± 11.75	0.115[a]
Gender	**Male**	21 (53.85%)	20 (51.28%)	0.821[b]
	Female	18 (46.15%)	19 (48.72%)	
BMI		26.18 ± 2.69	26.9 ± 1.6	0.157[a]
ASA	**1**	24 (61.54%)	27 (69.23%)	0.475[b]
	2	15 (38.46%)	12 (30.77%)	
BIS		46.15 ± 4.39	48.15 ± 5.61	0.084[a]
Intubation time (mins)		41.49 ± 10.3	27.74 ± 7.2	**0.0001**

Group M = Macintosh laryngoscope, Group VL = videolaryngoscope, ASA = American Society of Anaesthesiologists, BMI = Body Mass Index, BIS = Bispectral Index
[a] Independent Samples *t* Test, [b] X^2 Test

Modified Mallampati Score (p = 0.571) or the Cormack Lehane Score (p = 0.819) (Table 3).

No statistically significant difference was determined between the groups in respect of the mean IOP value after induction and at 10 mins after intubation ($p > 0.05$). The mean IOP at 3 mins after intubation was found to be statistically significantly higher in Group M than in Group VL (p = 0.0001). After induction and at 3 and 10 mins after intubation, no statistically significant difference was determined between the groups in respect of the mean arterial pressure ($p > 0.05$), mean heartrate ($p > 0.05$) and mean peripheral oxygen saturation values ($p > 0.05$) (Table 4).

Table 2. The mean modified Mallampati score and Cormack Lehane scores of the groups

		Group M	Group VL	*p* value
Modified Mallampati Score	**Class 1**	24 (61.54%)	22 (56.41%)	0.571[a]
	Class 2	15 (38.46%)	16 (41.03%)	
	Class 3	0 (0.00%)	1 (2.56%)	
Cormack Lehane Score	**1st degree**	21 (53.85%)	22 (56.41%)	0.819[b]
	2nd degree	18 (46.15%)	17 (43.59%)	

Group M = Macintosh laryngoscope, Group VL = videolaryngoscope
[a] Independent Samples *t* Test, [b] X^2 Test

Table 3. IOP, mean arterial pressure, heart rate, and peripheral oxygen saturaton values of the groups

		Group M	Group VL	*p* value
Intraocular pressure	**After induction**	11.77 ± 3.84	12.41 ± 4.19	0.483
	3 mins after intubation	23.56 ± 8.23	16.26 ± 5.3	**0.0001**
	10 mins after intubation	16.72 ± 6.74	14.18 ± 5.01	0.063
Mean arterial presssure (mm Hg	**After induction**	81.15 ± 19.23	75.26 ± 15.2	0.137
	3 mins after intubation	88.90 ± 17.96	81.67 ± 19.07	0.089
	10 mins after intubation	83.67 ± 19.07	75.97 ± 17.55	0.061
Heart rate (bpm)	**After induction**	67.82 ± 14.67	67.15 ± 15.49	0.846
	3 mins after intubation	77.82 ± 10.94	73.31 ± 15.11	0.135
	10 mins after intubation	71.82±9.14	66.42±16.55	0.064
Peripheral oxygen saturation	**After induction**	98.77 ± 0.9	98.79 ± 0.92	0.902
	3 mins after intubation	99.05 ± 0.61	99.08 ± 0.62	0.854
	10 mins after intubation	99.31 ± 0.52	99.33 ± 0.53	0.830

Data are shown as mean ± standard deviation. Group M = Macintosh laryngoscope, Group VL = videolaryngoscope, IOP = intraocular pressure

Table 4. Mean values for cough after extubation, postoperative throat pain at 10 mins and 24 hours after extubation and complications aftter extubation

		Group M	Group VL	*p* value
Cough following extubation	**None**	27 (69.23%)	28 (71.79%)	0.549
	Mild	12 (30.77%)	10 (25.64%)	
	Moderate	0 (0.00%)	1 (2.56%)	
Throat pain at postoperative 10 mins	**None**	10 (25.64%)	13 (33.33%)	0.662
	Mild	18 (46.15%)	12 (30.77%)	
	Moderate	8 (20.51%)	6 (15.38%)	
	Severe	3 (7.69%)	2(5.13%)	
Throat pain at postoperative 24 hrs	**None**	0 (0.00%)	0 (0.00%)	-
Complications following extubation	**None**	28 (71.79%)	27 (69.23%)	0.601
	Moderate	11 (28.21%)	11 (28.21%)	
	Severe	0 (0.00%)	1 (2.56%)	

Group M = Macintosh laryngoscope, Group VL = videolaryngoscope

DISCUSSION

The traditional Macintosh laryngoscope is known to cause an increase in hypertension, tachycardia and IOP. These are unwanted changes in glaucoma and open globe damage. Apart from pharmacological agents directed at limiting the increase in IOP after laryngoscopy and intubation, various other approaches have been researched [7, 8]. In a study which compared the use of Macintosh laryngoscope with LMA, intubating LMA and McCoy laryngosope, the use of Macintosh laryngoscope was found to have a greater increase on sympathetic stimulation and IOP [5]. Ahmad *et al* [5] compared the use of GlideScope videolaryngoscope and Macintosh laryngoscope and reported that a lower increase in IOP and hemodynamic response was seen with the GlideScope videolaryngoscope. This result was attributed to there being less need for airway manipulation at the level of the mouth and pharyngeal and laryngeal axes to obtain clear visualisation of the glottis in intubation made with the GlideScope videolaryngoscope and there being less cervical neck movement and force applied to elevate tissues for glottis visualisation and there was therefore less stimulation of the sympathetic system [5]. The results of a study by Mahjoubifar *et al*. [7] supported this conclusion. In another study which compared the use of Airtraq laryngosope with the MacIntosh laryngoscope, a significantly lower increase in IOP and hemodynamic response to laryngoscopy and intubation was reported for the Airtraq laryngoscope [4]. Another study which compared the use of GlideScope videolaryngosope with the Macintosh laryngoscope reported that the hemodynamic parameters were better in the group where GlideScope videolaryngoscope was used [9].

Karaman *et al*. [10] compared the use of McGrath videolaryngoscope and MacIntosh laryngoscope in intubation and a lower increase in IOP was reported with the use of videolaryngoscope. In the current study, no statistically significant difference was determined between the two groups in respect of hemodynamic parameters. However, the increase in IOP was found to be significantly lower in the group where C-MAC videolaryngoscope was used.

The incidence of postoperative throat pain after endotracheeal intubation has been reported as 21%-65%. Although a minor complication, it increases morbidity and patient discomfort. It is a potential cause of airway trauma, mucosal oedema, congestion and aseptic inflammation [11]. In a study by Amini *et al*. [9] comparing the use of GlideScope videolaryngoscope and MacIntosh laryngoscope, the rates of throat pain were found to be similar. Cirilla *et al*. [12] reported that the risk of postoperative throat pain did not significantly affect the choice of intubation technique with MacIntosh or GlideScope videolaryngoscope. The results of the current study support the previous findings in literature. At 24 hours postoperatively, no throat pain was observed in any

patient. The difference between the groups at 10 mins postoperatively was not statistically significant.

Different results have been obtained in studies comparing the duration of intubation with videolaryngoscope and Macintosh laryngoscope. Serocki *et al*. [13] reported that the intubation time was significantly longer with the use of videolaryngoscope, whereas Smereka *et al*. [14] found intubation time to be significantly shorter with the use of videolaryngoscope. In the current study, the intubation time was determined to be significantly shorter in the group where videolaryngoscope was used. The experience of the practitioner can be considered to be a determinant on this issue.

CONCLUSION

In patients with high IOP who are to be applied endotracheal intubation under general anaesthesia, the use of C-MAC videolaryngoscope can be recommended as the first choice. After induction and at 3 and 10 mins after intubation, no statistically significant difference was determined between the groups in respect of the mean arterial pressure, mean heart rate and mean peripheral oxygen saturation values. No statistically significant difference was determined between the groups in respect of cough after extubation and throat pain at 10 mins postoperatively. No throat pain was observed in either group after 24 hours postoperatively. The mean duration of intubation was determined to be statistically significantly longer in Group M than in Group VL.

Authors' contributions

COC: Study design, data analysis, writing the first draft of the paper, data collection; GBA: Study design, patient recruitment; ES: Study design, patient recruitment, statiscal analysis; JE: Language editing, data collecting, literature search; ASD: Patient recruitment, data collection

Conflict of interest

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The European Research Journal 2019;5(5):751-756 ORIGINAL ARTICLE

The relationship of simplified acute physiology score 3 (SAPS 3) and C-reactive protein (CRP) levels with mortality rates and length of stay of patients in surgical intensive care unit

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ABSTRACT

Objectives: The individual risk of surgical patients is more often underestimated and < 15% of patients who underwent surgery were admitted to ICU. The prognostic scores were developed to assess the mortality rate and prognosis for critical patients including surgical ones. The Acute Physiology and Chronic Health Evaluation (APACHE) score and the Simplified Acute Physiology Score (SAPS) were most popular ones and they were revised with the improvements in health care opportunities. As a prognostic scoring system SAPS 3' results were defined as excellent in high risk surgical patient study group. CRP is useful as a prognostic indicator or an index of disease progression but its value has not been tested in acute settings adequately. The aim of this study is to test the calibration power of SAPS 3 score and identify correlations between hospital mortality and patient outcomes with SAPS 3 scores and CRP levels.

Methods: This retrospective and analytical study was conducted one year period in surgical ICUs of tertiary level of attention in a public institution. It was a case–control medical record review and the patients included in this study were those who admitted in the surgical ICU for any reason.

Results: A total of 806 patients admitted to the Gastroenterological surgical ICU was included in the study between March 2016 and March 2017. The relation between mortality rate, length of stay in ICU and SAPS 3 score was significant statistically and the relation of CRP levels with SAPS score and mortality rate was found significant statistically.

Conclusion: The discriminative power of SAPS 3 score was very good and the calibration was appropriate.

Keywords: Simplified Acute Physiology Score, C-reactive protein, mortality, surgical intensive care unit

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It has been widely accepted that surgical procedures are in a high risk procedure group and a significant proportion of intensive care unit patients is composed of surgical patients. But there is another fact that the individual risk of surgical patients is more often underestimated and less than 15% of patients who underwent those procedures were admitted to an intensive care unit [1, 2]. Adequate postoperative care affects surgical outcomes like preoperative surgical status so assessment of the risks of increased morbid-

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ity and mortality via predictors for this group of patients is mandatory [3]. There are many studies that have developed prognostic scores to assess the mortality rate and prognosis for critical patients including surgical ones. Probably the most used and the oldest general prognostic scoring models are the Acute Physiology and Chronic Health Evaluation (APACHE) and the Simplified Acute Physiology Score (SAPS) which were revised due to the improvements in treatment procedures and health care opportunities [4, 5]. Previous studies have suggested that the calibration of these scores may differ across countries, centers, and/or characteristics of patients and the most recent revision of the SAPS model- SAPS 3- was published in 2005 [6]. 20 simple parameters which are easy to measure are used in SAPS 3 system and the results were defined as excellent in high risk surgical patient study group [7]. There are two objective measures from the perspective of the performance of prognostic models: calibration and discrimination. It has been concluded that for clinical trials or comparison of care between ICUs, calibration –how closely the estimated probabilities of mortality correlate with the observed mortality- becomes superior to discrimination discrimination between survivors and individuals who will die [4]. While the calibration of the models studied by statistical goodness -of-fit showed that the observed hospital mortality was not distinct from the expected mortality in this particular group of patients for SAPS 3, pharmacological and medical improvements necessitates reassessment [8, 9]. C-reactive protein (CRP) which is a very well-known plasma protein and plays a role in inflammation and the acute-phase innate immune response has been used increasingly in clinical practice as an inflammatory marker [10]. Since the mid-1990s, there have been many studies reporting CRP is useful as a prognostic indicator or an index of disease progression. But this statement has not been studied adequately in an acute setting and serum CRP levels have not been used as a prognostic index [11]. The aim of this study is to test the calibration power of SAPS 3 score and identify –if any- correlations between hospital mortality and patient outcomes with SAPS 3 scores and CRP levels at the Türkiye Yüksek İhtisas Training and Research Hospital.

METHODS

This retrospective and analytical study was conducted during the period March 2016–March 2017.It was performed in Gastroenterological Surgical ICU of tertiary level of attention in a public institution. The study was approved by the Local Ethics Committee of the Türkiye Yüksek İhtisas Training and Research Hospital and exempted from the signed informed consent form requirement, because it was a case–control medical record review. The patients included in the study were those who admitted in the surgical ICU for any reason either after surgery or from another department like other ICU or emergency department. To calculate the SAPS 3 score, physiological data and laboratory analysis on the day of ICU admission were used. Records, which had been obtained from patients' files, were reviewed from hospitalization to medical discharge or hospital mortality. Data were imported into a spreadsheet (Microsoft Excel 2013, Microsoft Corporation) for the calculation of the scores and their derived probabilities of death using the published equations and coefficients. Patients with incomplete records and length of stay less than 24 hours and patients who referred from other ICUs other than their 1st day of admission were excluded from the study. Moreover, only the first data set of patients with a history of multiple admissions in ICU was included in the data analysis. Length of stay in the ICU, the outcome of treatment (excitation, referral to another clinic, or discharge) were recorded from patients' files. To forestall the variability in the data collection, all values were reviewed by the authors of the study.

Statistical Analysis

Data were analyzed, and the results were expressed as mean ± standard deviation, or percentage. Variables were first evaluated with Reliability Statistics and Cronbach's Alpha while Cronbach's Alpha if Item deleted levels were considered to choose variable parameters. To choose the type of statistical tests –parametric or non-parametric test–variables were evaluated by One-Sample Kolmogorov-Smirnov test as a normality test. And the results showed that Asymp. Sig. (2-tailed) levels ≤ 0.05 so we decided to

use non-parametric tests. For statistical analysis, variables were evaluated for significance by using the Spearman's rho test. Categorical variables were evaluated by the Kruskal Wallis Test and Mann-Whitney U test of contingency. p values presented are from two-tailed tests, and values below 0.05 were considered statistically significant. The Hosmer-Lemeshow test was used to calculate the calibration of SAPS 3 test which express the ability of the test to determine the probability of death in accordance with the observed mortality. The discrimination, which express the ability of the individual systems to distinguish survivors and non-survivors, according to the estimated mortality was assessed using receiver operating characteristic (ROC) curves. The ROC curves were established as discrimination measurements with distributions per 10%, according to the predicted mortality and the obtained curve was appraised using the calculated area under the curve (AUC). AUC values > 0.75 was appraised as satisfactory, AUC values > 0.8 was appraised as well, and AUC values > 0.9 was appraised as very good. The Statistical Package for Social Sciences (SPSS-IBM Corp., Armonk, NY, USA) 20.0 was the software used for the statistical analyses.

RESULTS

A total of 806 patients admitted to the Gastroenterological Surgical ICU were included in the study between March 2016 and March 2017. Patients older than 18 years of age, who stayed 24 h or more in the ICU, were included. Forty- nine patients' records were excluded due to incompleteness or the unavailability of significant values. 4 patients were younger than 18 years of age. Those patients were not included in the study, leaving 753 (93.4%) patients for analysis. The data used to derive SAPS 3 scores and probabilities of death were collected in all these patients. Patients' characteristics are presented in Table 1. Apart from basic and observational admission (n = 128/753, 17%), the main reasons for ICU admission were as follows: cardiovascular, respiratory, infectious and neurological. These reasons encountered for 81% of the ICU admissions. The mean age of the patients was 59.01 years, with a standard deviation of 14.68 years and the representatives of both sexes were relatively proportional (58.6% males versus 41.4% females). Their average SAPS 3 score was 36.73 with a standard deviation of 14.093. The total mortality at discharge was 11 % (83 patients). CRP levels were ranged 1 to 450 and mean level was calculated as high as 128.33 probably due to the fact that 56.83 % (n = 428) of the patients had either infectious or oncologic component at the time of admission. This expected condition was tested with reliability statistic and Cronbach's Alpha level was 0.23 and Cronbach's Alpha if CRP Item Deleted level was 0.68. So we decided not to take CRP levels as a part of prognostic index just to find out any relation to SAPS 3 and outcomes of patients. Besides that One-Sample Kolmogorov Smirnov test showed that our variables were not homogenous and the results showed that Asymp. Sig. (2-tailed) levels ≤ 0.05 so we decided to use non-parametric tests. Spearman's rho test showed that the relation between mortality rate, length of stay in ICU and SAPS 3 score was significant statistically (age factor was used as a control variable). The relation of CRP levels with SAPS 3 scores and mortality rate was found significant statistically, but it is not significant with length of stay in the ICU. Kruskal Wallis Test and Mann-Whitney U test showed that mortality factor was affected with the SAPS 3

Table 1. Patients' characteristics and data

	Mean/ total number	Standard deviation/ percent	*p** value
Age (years)	59.01	14.686	**0.007**
Length of stay in ICU (days)	10.36	16.975	**< 0.001**
In-hospital mortality	83	11%	NA
CRP levels	128.33	93.58	**0.001**
SAPS 3 scores	36.73	14.093	**< 0.001**

CRP = C-reactive protein, SAPS 3 = Simplified Acute Physiology Score 3, ICU = intensive care unit, NA = not applicable, p* = according to mortality variable.

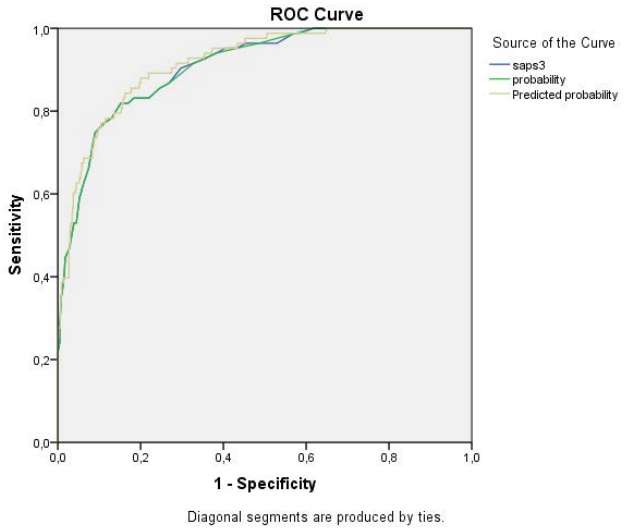

Figure 1. Receiver operating characteristic (ROC) curves of SAPS 3, probability of death and predicted probability with mortality dependent factor.

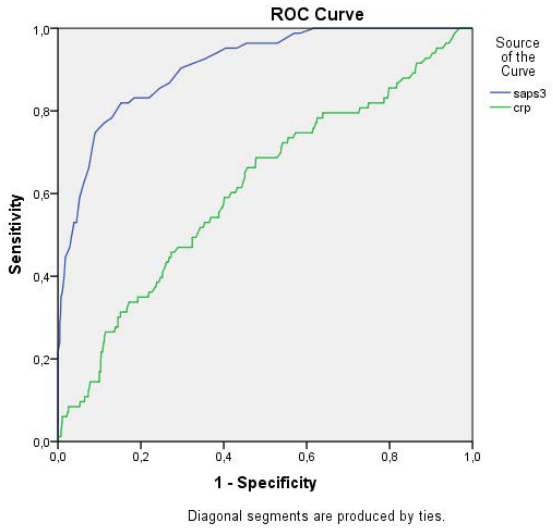

Figure 2. Receiver operating characteristic (ROC) curves of SAPS 3 and CRP.

Table 2. Area under the curve levels with SAPS 3, probability of death and predicted probability by SPSS

Test Result Variable(s)	Area	Std. Error	Asymptomatic 95% Confidence Interval	
			Lower Bound	Upper Bound
SAPS-3 scores	0.908	0.016	0.876	0.940
Probability of death by SAPS 3	0.908	0.016	0.876	0.940
Predicted probability by SPSS program	0.916	0.015	0.887	0.946

CRP = C-reactive protein, SAPS 3 = Simplified Acute Physiology Score 3, ICU = intensive care unit

score, length of stay in the ICU and CRP levels significantly as a statistical manner (Asymp. Sig. (2-tailed) < 0.01). The discriminative power, assessed using the AUC, was high enough with SAPS-3 scores and the probability of death estimation (AUC 0.908) while predicted probability obtained by SPSS program was higher (AUC 0.916). (Figure 1 and Table 2) Although we decided not to take CRP levels as a prognostic index due to the factors mentioned above, to test the accuracy of our decision we compare discriminative power of SAPS-3 and CRP by using AUC. As expected, AUC level found < 0, 75 for CRP. (Figure 2 and Table 3) The Hosmer–Lemeshow goodness-of-fit test revealed a good calibration for the SAPS 3 global model as shown in Table 4 and Table 5 with sig. level 0.817 and overall percentage 92.

Table 3. Area under the curve levels with SAPS 3 and CRP

Area Under the Curve	
Test Result Variable(s)	Area
SAPS 3	0.908
CRP	0.613

CRP = C-reactive protein, SAPS 3 = Simplified Acute Physiology Score 3

Table 4. Hosmer and Lemeshow Test for SAPS 3

Step	Chi-square	df	Sig.
1	4,426	8	,817

Table 5. Overall correct percentage value with SAPS 3

Classification Table[a]					
Observed			Predicted		
			Mortality		Percentage Corrected
			0	1	
Step 1	Mortality	0	660	10	98.5
		1	50	33	39.8
	Overall Percentage				92.0

[a]The cut value is 0.500

DISCUSSION

The aim of describing and quantifying the severity of the conditions of selected groups of critically ill patients necessitates prognostic scoring system development and these systems allow for the relatively objective assessments of the workloads required by intensive care units and comparison of the effectiveness of the care between these facilities. There are so many studies in the literature about scoring systems and the results are conflicting [12]. It is indispensable to contemplate that surgical patients have different physiological and functional characteristics than other patients, which may influence prognosis. The SAPS 3 system is one of the main scoring systems which has a convenient calibration and discriminative performance in general population admitted to an ICU [13]. It is demonstrated that SAPS 3 usage is valid for surgical patients as well with good discrimination and calibration power. Unlike the other scoring systems the SAPS 3 model prediction based on data within the first hours and it includes variables specific to the surgical procedures. SAPS 3' simplicity and requirement of non-sophisticated data makes it distinct from other prognostic scores [14]. Besides that, values above 24 hours often represent the standard of care more than the actual clinical state of the patient so it can be concluded that SAPS 3 is superior to other scoring systems like the SOFA or APACHE scores which fall to show actual clinical state. It has been known that CRP levels used to assist in management in conjunction with clinical findings and other investigations and many studies have shown that serum CRP levels correspond to the severity of the illness [15]. The present study aimed to assess SAPS 3 as a third generation scoring system and CRP levels with standard care of surgical patients and uses regression curve analysis. The discriminative power of SAPS 3 was very good, close to the one published in the original publication, and the calibration was appropriate. Moreover, this model showed the relation of SAPS 3 scores and CRP levels with mortality and length of stay in the ICU. So the SAPS 3 score system may be revised by using CRP levels with a good calibration and a perfect cut off value obtained from prospective studies.

Limitations

There are some limitations in this study that should be taken account like being a retrospective study. Relatively small sample size is limiting the power of the analysis of goodness-of-fit Hosmer and Lemeshow test which is poor to assess. Another potential limitation is being a single-center study with a different patients' case mix as compared to the original SAPS 3 hospital outcome cohort. So it can be questionable either these results may be generalized to other ICUs or not.

CONCLUSION

Finally, one could criticize the data collector reliability in the present study. Even though this is an important topic, we are quite reliant that, in this study, bias related to inadequate data collection was limited, since collection was done by the ICU doctors. In conclusion, in the present study, we found that the SAPS 3 admission score has a good discriminative

power and calibration while CRP levels are related to SAPS 3 score and mortality and not related to the length of stay.

Conflict of interest

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The European Research Journal 2019;5(5):757-762 ORIGINAL ARTICLE

Incidence of dentinal crack formation during root canal preparation with two NiTi instruments activated by adaptive motion and continuous rotation: an in vitro study

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ABSTRACT

Objectives: The aim of this study was to evaluate dentin crack incidence after root canal instrumentation using ProTaper Next (PT Next; Dentsply Maillefer, Ballaigues, Switzerland) and Twisted File Adaptive (TF Adaptive; Sybron Endo, Orange, California, USA) at different kinematics.

Methods: Sixty human extracted premolar teeth were selected and divided into 4 main groups. Group 1: PT Next with continuous rotation (n = 15); Group 2: PT Next with adaptive motion (n = 15); Group 3: TF Adaptive with continuous rotation (n = 15); Group 4: TF Adaptive with adaptive motion (n = 15). Fifteen unprepared teeth were used as control group. Crowns of the teeth were removed and roots were sectioned at 3, 6, and 9 mm from the apex using a diamond saw. Finally root dentin pieces were evaluated under stereomicroscope at x25 magnification. Digital images were evaluated by 2 researchers.

Results: No cracks were observed in the control group. In groups 2 and 4 no fracture was observed at the level of 9 mm and similarly in group 4 at 6 mm level. Group 3 showed a significantly higher dentin crack formation followed by Group 1, 2, 4 and control group respectively ($p < 0.039$). There was no significant difference between groups at 6 mm and 9 mm levels ($p = 0.497$) except for only 3 mm level ($p < 0.035$).

Conclusions: It was concluded, both adaptive motion and continuous rotationpromoted dentinal defect. Adaptive motion produced less dentinal defects all dentin levels but there was no significant difference.

Keywords: Dentinal crack, root canal preparation, protaper next, twisted file adaptive, nickel-titanium instruments, adaptive motion, continuous rotation

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The main goal of the root canal enlargement is to provide the biomechanical cleaning and shaping of the root canal dentin [1]. Stainless steel hand instruments may cause iatrogenic damages such as canal transportations, ledge formation and perforations especially in curved root canals [2]. To avoid these damages, Nickel-Titanium (NiTi) rotary instruments are the most preferred filesbydentists during the root canal shaping because of its shape memory and super elasticity properties [3, 4]. Usage of these tools has many advantages in endodontic treatment, such as shortening the working time and increasing the quality of irrigation too [1].

On the other hand the amount of remaining dentin volume is very important for strength of a root filled tooth [5]. Dentine removal during root canal shaping

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with NiTi rotary instruments may create crack formation or vertical root fracturesbecause of the aggressive cutting ability and tapered file design [6, 7]. NiTi instruments can be used at two different movements: Continuous rotation or Reciprocal motion. In addition alternative motion has been introduced in the recent years called as ‘’Adaptive Motion’’ which uses a combination of continuous rotation and reciprocal motion cinematics.

Root canal shaping movement with NiTi rotary systems may create dentinal damages to various degrees [1]. In addition torsional and flexural-related cracks due to shaping NiTi can occur at continuous rotation. On the other hand reciprocal motion reduces stress on the NiTi rotary instruments and help to reduce cyclic fatigue fracture [8]. But reciprocal motion decreased cutting efficiency of NiTi instruments because of the clockwise (CW/counterclockwise (CCW) movement at small or equal degrees. It means that more apical pressure of the files may create dentinal cracks [9]. But Liu *et al*. [10] reported that reciprocal motion creates less dentinal crack formationthan continuous rotation. However Bürklein *et al*. [8] study showed more dentinal crack formation in reciprocation movement in the apical root area and Karataş *et al*. [11] reported that dentinal micro-cracks formation ratio is dramatically increased with reciprocal motion compared to continuous rotation.There is no consensus on dentinal crack formation about NiTi rotary instruments in root canal shaping.

NiTi files with adaptive motion can change the movement from continuous rotation to reciprocal mode with CW and CCW angles varying from 0° to 600° up to 370–50° at high pressure values.The purpose of this technology is to allow the TF Adaptive file to adjust to the intra-canal torsional forces, depending on the amount of pressure placed in the file (TF Adaptive Brochure). So this movement seems to have the advantages of both technics.

Therefore, the aim of the present study was to investigate the effect of different kinematics (adaptive motion and continuous rotation) using two tested NiTi rotary systems (PT Next; Dentsply Maillefer, Ballaigues, Switzerland and TF Adaptive; TF Adaptive; Sybron Endo, Orange, California, USA) on dentinal crack formation. The tested null hypothesis was that there would be no significant differencesin the incidence of dentinal crack formation between the groups.

METHODS

The research protocol of this study was approved by the Istanbul Medipol University Ethical Board of Clinical Trials and Non-Interventional Research (Approval Number: 10840098-604.01.01-E.482). Freshly extracted, intact, non-carious, human mandibular premolar teeth with mature apices and straights roots (< 25˚) were selected for the study. The single-rooted teeth with single root canal formation are our first criteria for the present study. In addition, the cross-sectional anatomy anatomies of the lower premolar teeth were oval in the coronal third of the root and take round form towards to the tooth apex in all samples. Figure 1 showed only craze-lines and no-defects samples from different areas of the tooth which were chosen randomly. Therefore, due to this randomization some of the images included coronal third of the root canals from different samples whilst the others did not. Teeth were stored in distilled water and single canal formation was controlled by radiographs before starting the experiment.All of the samples were cleaned with water and the soft tissue and calculus were debrided mechanically. All roots were controlled with under ×45 magnification using a stereomicroscope (Carl Zeiss Axio Zoom V16, Jena, Germany)for the integrity of the root structure. The teeth with cracks on the root surface were not included in the study and replaced with solid teeth. The sample size was calculated as 15 in each group, a type I error of 0.05, and a statistical power of 80% using the G*Power software (version 3.1.9.2).

Finally 75 teeth were selected for the study according the all criteria.All crowns were removed using 0.19 mm thick diamond saw (Horico SH 394C190) under water cooling from the cemento-enamel junction all root sample length was equalized at 15 mm.Root canal lengths were measured by #15 file inserted into the canal until the tip of the file became visible at the apical foramen. Working length (WL) wasdetermined by subtracting 1 mm from the root canal length. Apical patency was also controlled by #10 K-file during the root canal preparation.

Teeth were randomly divided to fourexperimental group and one control group (n = 15). PT Next NiTi Rotary System (Dentsply Maillefer, Ballaigues, Switzerland) and TF Adaptive NiTi Rotary System (SybronEndo, Orange, California, USA) were used

with different kinematics in the present study:

Group 1: PT Next with Continuous Rotation

Group 2: PT Next with Adaptive Motion

Group 3: TF Adaptive with Continuous Rotation

Group 4: TF Adaptive with Adaptive Motion

Root canal instrumentation with adaptive motion was achieved by Elements Motor (SybronEndo, Orange, California, USA) and continuous rotation was achieved by X-smart Plus Endodontic Motor (Dentsply Maillefer, Ballaigues, Switzerland). The NiTi files at Group 1 and Group 4 were used at recommended values of torque and speed according to the manufacturers' instructions. After each instrument insertion, the teeth were irrigated with 10 ml of 2, 6% NaOCl solution (Canal Pro™ Coltene/Whaledent, Switzerland) with 30 gauge irrigation needle (Canal Clean, Biodent Co. South Korea) was used the irrigation solution at the all groups:

Group 1: PT Next with Continuous Rotation

The root canals were prepared using X-Smart Plus (Dentsply Maillefer) at 300 rpm with a torque 2 Ncm with in-out motion for all files. X1 (size 17, 0,04 taper) and X2 (size 25, 0,06 taper) was used at full WL.

Group 2: PT Next with Adaptive Motion

Instrumentation was achieved by Elements Motor (Sybron Endo, Orange, California, USA) with ''Adaptive Motion'' mode. X1 and X2 was used at full WL.

Group 3: TF Adaptive with Continuous Rotation

Instrumentation was achieved with Elements Motor (Sybron Endo, Orange, California, USA) by 500 rpm and the torque at 2 Ncm. SM1 (size 20; 0,04 taper) and SM2 (size 25; 0,06 taper) was used at working length.It was finished at SM2 (size 25; 0,06 taper).

Group 4: TF Adaptive with Adaptive Motion

Root canal preparation was achieved with Elements Motor (Sybron Endo, Orange, California, USA) by adaptive mode. SM1) and SM2 were used at working length. It was finished at SM2.

All preparations were achieved by one operator and two operators who were blinded examined the crack classification. The samples sectioned horizontally at 3, 6 and 9 mm from the apex with 0, 19 mm diamond saw (Horico SH 394C190)under water-cooling. All samples were observed under stereomicroscope (Carl Zeiss Axio Zoom V16, Jena, Germany) at a magnification of 25× to 80× to determine incidence of dentinal cracks. Crack classification was explained at 4 levels;

1) No Defect (Score 0): Root dentin devoid of craze lines, complete cracks, and incomplete cracks.

2) Craze Line (Score 1): Line extending from outer surface into dentin but does not reach the canal lumen.

3) Partial or Incomplete Crack (Score 2): Line extending from the canal wall into the dentin withoutreaching the outer surface of the root.

4) Fracture or Complete Crack (Score 3): Line extending from root canal space all the way to outer surface of root.

Statistical Analysis

The incidences of defects between groups were statistically analyzed by Chi-square test at a significance level of $p < 0.05$.

RESULTS

There was no statistical difference between all groups (p = 0.361) while Adaptive motion showed fewer defects than rotary motion groups at all part of the roots. Adaptive motion groups have also showed no defect at the coronal part of the teeth either. Moreover, all groups had defects as compared with control group (Figure 1).

Complete or partial fracture formation was not observed in all the specimens examined. The specimens with craze lines were classified in Table 1. There was no statistical difference between all groups while Adaptive motion showed fewer defects than rotary motion groups at all part of the roots. Adaptive motion groups have also showed no defect at the coronal part of the teeth too. In addition all groups had defect as compared with control group.

No cracks were observed in the control group. In groups 2 and 4 no fracture was observed at the level of 9 mm and similarly in group 4 at 6 mm level. Group 3 showed a significantly higher dentin crack formation followed by Group 1, 2, 4 and control group respectively ($p < 0.039$). There was no significant difference between groups at 6 mm and 9 mm levels ($p = 0.497$) except for only 3 mm level ($p < 0.035$) (see Table 1).

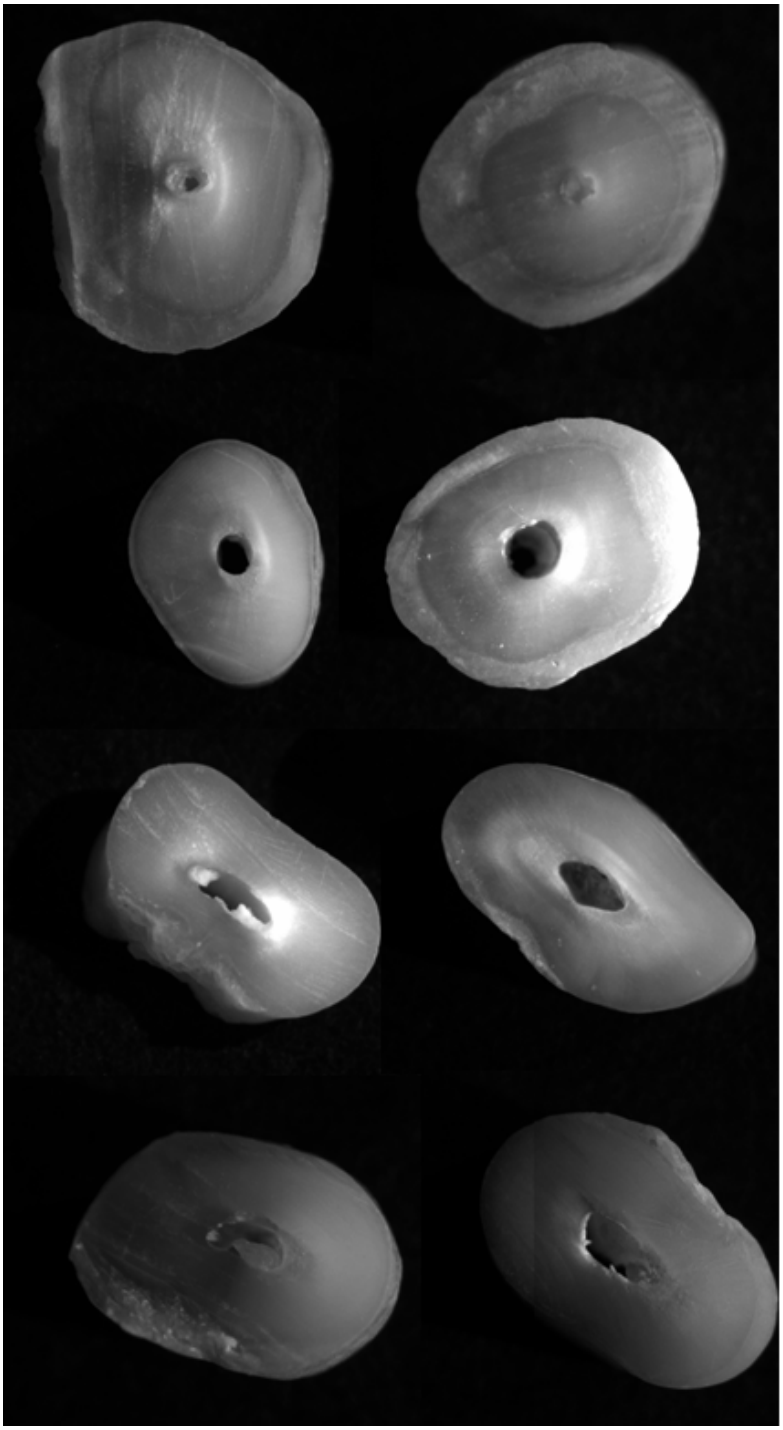

Figure 1. Craze lines at PT Next with adaptive motion (A), no defect at PT Next with adaptive motion (B), craze lines at PT Next with continuous rotation (C), no defect at PT Next with continuous rotation (D), craze Lines at TF with adaptive motion (E), no defect at TF with adaptive motion (F), craze Lines at TF with continuous rotation (G), no defect at TF with continuous rotation (H). PT = ProTaper, TF = Twisted File

Table 1. Incidence of dentinal crack formation in different root dentin levels

	Absolute Number of Defects			
	9 mm (%)	6 mm (%)	3 mm (%)	Total defected roots per group (%)
Group 1	3 (15)	3 (15)	3 (15)	9 (15)
Group 2	0 (0)	2 (10)	2 (10)	4 (7)
Group 3	5 (25)	5 (0)	3 (15)	13 (22)
Group 4	0 (0)	0 (0)	3 (15)	3 (5)
Control	0 (0)	0 (0)	0 (0)	0 (0)
***p* value**	0.497	0.497	**0.035**	**0.039**

Group 1 = PT Next with Continuous Rotation , Group 2 = PT Next with Adaptive Motion, Group 3 = TF Adaptive with Continuous Rotation, Group 4 = TF Adaptive with Adaptive Motion, PT = ProTaper, TF = Twisted File

DISCUSSION

As a result of current instrumentation systems, obturation techniques and operator related factors, there is no an effective method to avoid craze lines, dentinal defects or vertical root fracture [5, 9]. Endodontic treatments such as post space preparations, retreatment procedures or occlusal forces such as bruxism have a potential to create dentinal cracks too. In addition there is not certain evidence that craze lines produce complete dentinal cracks [12]. Previous studies have not been able to determine the exact role of reciprocal or rotary motion in the dentin crack formation. Burklein *et al*. [8] reported that at the apical level reciprocating motion produced more dentinal cracks than rotational systems. On the contrary, Liu *et al*. [10] showed that reciprocating files had better performance to produce dentin cracks. There is no definite consensus on this issue but in the present study, dentin defects were observed in all groups regardless of using file types and the NiTi files used at continuous rotation produced more dentinal defects on all root level.

Preliminary examination showed that any dentin defect was observed in extracted teeth. On the other hand it was very unacceptable that there was no crack after instrumentation at all groups. Unfortunately previous studies reported several complete dentin crack formation in similarly designed studies[5-8, 10, 11, 13, 14]. It can be explained that operator's skills and experiences are an effective factor for promoting crack formation and freshly extracted teeth are resistant to instrumentation. In addition it is clear that separation of crowns with diamond saw method is completely safe.

Dentin cracks studies have some limitation. The correlation between the present study method and clinical situation is questionable. For example patient age is an essential factor in the presence of dentinal cracks [13]. But we have no chance to determinate patient age of the extracted human molar teeth anyway. In addition using stereomicroscope should be questioned about dentinal cracks controlling at the same time.

Sectioning technique may be affected the defect formation. Because periodontal ligament absorb the occlusal forces and protect the dentinal wall against the crack formation. However no dentin defects observed in the control group,despite absence of periodontal ligament, indicated that the sectioning method was acceptable and safe. On the other hand extraction of the teeth is a major factor to promote dentin cracks. However stereomicroscope imaging using the present study may not be a suitable method to detect the micro-cracks. It is reported that optical coherence tomography and infrared thermography can be used in such studies to eliminated sectioning-related defects in the future studies [15].

Another parameter that needs to be emphasized is the cross-section design of the NiTi Rotary files. According to the manufacturer, rectangular cross-sectional design of PT Next instruments reduces the contact area between dentin and file which minimizes taper lock and screw effect while increasing cutting efficiency. This design also allows progressive tapers on the file production. Twisted File Adaptive NiTi

rotary files have triangular cross section design that results lower cutting efficiency and less chip space that accumulates more dentin chip in the root canal complex. More stress accumulates on the root canal wall so dentinal defects may occur. Present study found that triangular designed NiTi file on rotation mode products more crack formation. However our results also showed that there is no significant difference on crack formation between the groups. It means that preparation technique is an important factor than file designs.

CONCLUSION

Under the limitations of the present study, root canal preparation with two rotary systems, both continuous rotation and reciprocating motion resulted in dentinal defects. At all thesections of the related samples, adaptive motion produced less dentinal defects (craze lines) than rotary groups. However there was no difference between adaptive motion and rotary motion statistically.Therefore the null hypothesis was accepted.

Conflict of interest

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The European Research Journal 2019;5(5):763-767 ORIGINAL ARTICLE

Computed tomography features of traumatic pulmonary pseudocysts

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ABSTRACT

Objectives: To discuss the radiological characteristics of traumatic pulmonary pseudocyst (TPP) detected by thorax computed tomography.

Methods: Retrospective screening was made of 107 patients applied with thorax computed tomography due to blunt thoracic trauma between 2014 and 2017 at our hospital.

Results: TPP was detected in 6 (5.6%) patients. The patients comprised 5 males and 1 female with a mean age of 28 years (range, 15-49 years). Blunt thorax trauma was caused by traffic accidents in 4 patients and a fall from height in 2 patients. Eleven (64.7%) of the lesions were located in the lower lobes. The most common finding associated with TPP was ground glass opacities, which were present in all of the patients and represented the parenchymal contusion.

Conclusion: Thorax computed tomography is an effective and reliable method for early and definitive diagnosis of the rare development of TPP after blunt thoracic trauma.

Keywords: traumatic pulmonary pseudocyst, blunt chest trauma, computed tomography

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Pulmonary parenchymal injuries after blunt thoracic trauma vary from simple contusion to laceration. Traumatic pulmonary pseudocyst (TPP) is a rare complication of blunt chest trauma. It is a type of cavitary lesion that occurs in the lung parenchyma as a result of air leakage from the cleft caused by forces tearing the lung parenchyma. It constitutes 2.6-3% of parenchymal injuries after blunt thorax trauma [1]. TPP usually develops in children and young people and is characterized by the absence of a distinct epithelial wall within the cyst. These lesions are often asymptomatic and incidentally detected. Although computed tomography (CT) has an important role in diagnosis [2], there are very few studies in literature that have discussed the CT features of pseudocysts and they are mostly case reports.

The aim of this study was to discuss the radiological characteristics of TPP detected by thorax CT. in 6 patients.

METHODS

A total of 107 patients applied with thoracic CT due to blunt thoracic trauma between 2014 and 2017 were screened retrospectively. TPP was detected in 6 (5.6%) patients. The patients comprised 5 males and 1 female with a mean age of 28 years (range, 15-49

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Table 1. Demographic data and CT findings

Patients	Gender and age (years)	Cause of trauma	Number of pseudocysts	Lobar Distribution	Associated Findings
1. GD	Male 30 y	Fall from height	6	Right lower lobe (n = 6)	Hemothorax Pneumothorax Subcutaneous emphysema Rib fractures Ground glass opacities
2. DY	Female 43 y	Traffic accident	2	Left lower lobe (n = 2)	Rib fractures Ground glass opacities
3. FA	Male 17 y	Traffic accident	1	Left lower lobe (n = 1)	Ground glass opacities
4. Sİ	Male 26 y	Fall from height	5	Left upper lobe (n = 5)	Rib fractures Ground glass opacities
5. TT	Male 21 y	Traffic accident	2	Left lower lobe (n = 2)	Ground glass opacities
6. YKO	Male 15 y	Traffic accident	1	Left upper lobe (n = 1)	Pneumothorax Ground glass opacities Traumatic subarachnoid hemorrhage

years). CT scans were performed with a 16-slice CT scanner (Sensation 16, Siemens Medical Systems, Germany) using 100 ml of intravenous (IV) contrast material (300 mg/ml Omnipaque, GE Healthcare, Ireland) at a flow rate of 4 ml/sec. No oral contrast material was given. The thorax CT scans (tube voltage = 120 kV, effective mAs = 90, slice thickness 5 mm, collimation = 2×4 mm, pitch = 1.6) were acquired 40 seconds after the IV contrast injection. The images were retrospectively reviewed by 2 radiologists, one with 10 years of experience and the other with 5 years of experience. There was agreement between them for each case.

RESULTS

The patients with TPC detected on CT comprised 5 males and 1 female with a mean age of 25.5 ±10.1 years (range, 15-43 years). The CT findings of the patients are summarized in Table 1. Blunt thorax trauma was caused by traffic accidents in 4 patients

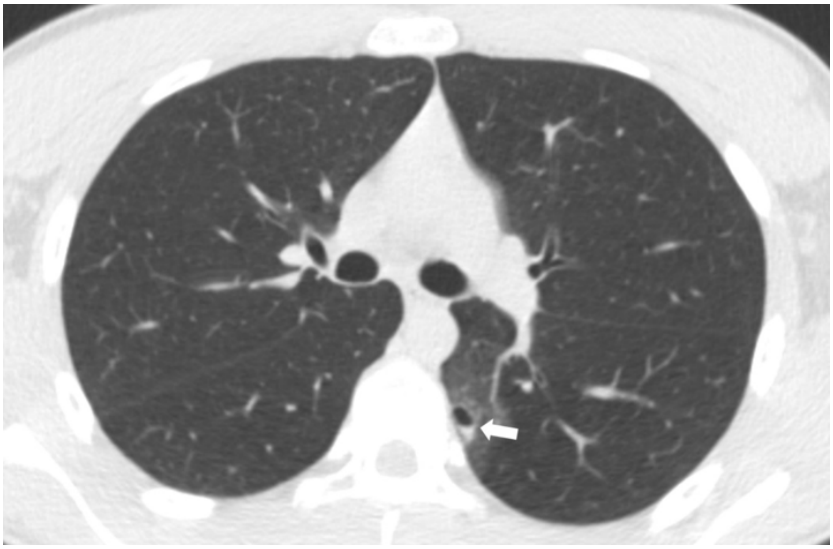

Figure 1. A 17-year-old male with blunt thoracic trauma after a traffic accident. Axial CT image showing traumatic pulmonary pseudocyst with air-fluid level (white arrow).

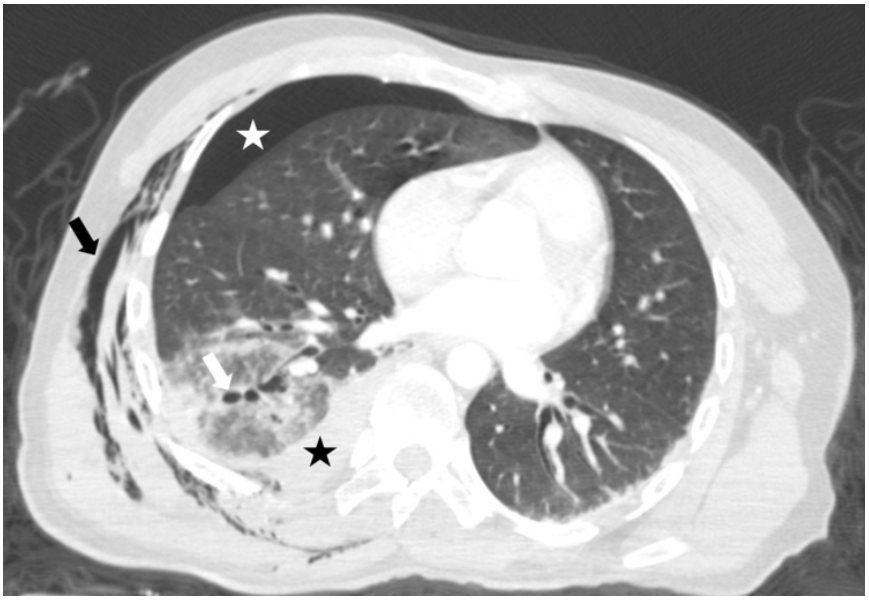

Figure 2. A 30-year-old male with blunt thoracic trauma after a fall from height. Axial CT image showing traumatic pulmonary pseudocyst (white arrow), subcutaneous emphysema (black arrow), pneumothorax (white asterisk) and hemothorax (black asterisk).

and a fallfrom height in 2 patients. All the patients had CT scans at the time of admission to hospital. A total of 17 lesions were detected in 6 patients. The mean number of lesions was 2.8 (range, 1-6), with 6 (35.3%) detected in the right lobe and 11 (64.7%) in the left lobe. There were 6 (35.3%) lesions in the right lower lobe, 5 (29.4%) lesions in the left lower lobe, and 6 (35.3%) lesions in the upper left lobe. In total, 11 (64.7%) of the lesions were located in the lower lobes, 8 (47.1%) lesions were subpleural and 9 (52.9%) lesions were intraparenchymal. There were air fluid levels in 4 (23.5%) of the lesions (Figure 1).

The most common finding associated with TPP was ground glass opacities, which were present in all of the patients and represented the parenchymal contusion. The second most common finding was rib fracture in 4 patients. One patient had pneumothorax and one patient had hemopneumothorax and subcutaneous emphysema (Figure 2). One patient had traumatic subarachnoid hemorrhage in addition to lung findings.

DISCUSSION

In this study, TPP was detected in 5.6% of the patients with blunt thoracic trauma. In literature, this ratio is reported as 2-3% in older studies [2-4] and 5-10% in more recent studies [5-8]. Cho *et al*. [7] attributed this to the increased use of CT on blunt thoracic trauma patients.

TPPs are cavitary lesions that can occur after blunt thoracic trauma. Two mechanisms have been proposed in TPP formation. The first is that an area of the lung is occluded by a sudden compression of a segment of the peripheral bronchial tree and the pressure created causes it to split in this closed area. The enclosed space then expands with the rupture of the alveolar walls. The second possible mechanism is explained by the production of concussion waves that create rippling forces that tear the lung parenchyma [9]. This complication is more common in children and young adults because the elastic structure of the chest wall causes a large part of the traumatic energy to be transferred to the lung parenchyma. It has been reported that 75-85% of the patients are males aged < 30 years [3]. Similarly, in the current study, 5 of the 6 patients were male and the mean age was 25.5 ± 10.1 years.

Traumatic pulmonary pseudocysts are usually oval or round in shape and are seen in the lower lobes [3]. In the current study, 64.8% of the lesions were located in the lower lobe. Plain chest radiographs are not suitable for TPP imagingbecause these lesions can be concealed by opacities formed by pulmonary contusion. In addition, incomplete formation of

pseudocysts in the early period after trauma is difficult to recognize with radiography [2]. In areview of 7 large series by Tsitouridis *et al*. [6], the sensitivity of chest radiography was found to be only 24% in the early period. In contrast, CT can easily detect pseudocysts as thin-walled cysts in the lung parenchyma. In some of these cysts, air-fluid level can be seen associated with blood arising from peripheral pulmonary vessels or alveolar capillary vessels [3]. In 4 of the pseudocysts of the current study, air-fluid levels were observed. The most common finding associated with pseudocysts is "ground glass" opacities representing parenchymal contusion. In a study of 5 patients by Tsitouridis *et al*. [6], all had parenchymal opacities. Similarly, in the current study, parenchymal opacities were present in all patients.

It is important to determine whether cystic lesions that are observed radiologically in TPP cases are pre-existing cystic structures. Other pathologies with cavitary lesions in the differential diagnosis should be kept in mind. In adults, these include blister, bleb, lung abscess, bronchial carcinoma, bronchogenic cyst, pulmonary infarction, tuberculosis, cyst hydatid and coccidoidomycosis, whereas in children, congenital pulmonary cysts and pulmonary sequestration are similar to traumatic pseudocysts. The history of trauma in the patient and the radiological change of the lesion over time suggest TPP, but if lesions do not show improvement in long-term follow-up,other pathologies should be considered in the differential diagnosis [1].

Although TPPs may be clinically asymptomatic, the most common symptoms are hemoptysis, chest pain and cough. However, these symptoms are not only related to the TPP itself, but also to other concomitant parenchymal injuries, especially pulmonary contusion. These lesions have a benign clinical course, and often do not require specific treatment [4]. Typically, any treatment applied is diagnostic and surgical treatment should not be considered unless complications develop such as infection, bronchial hemorrhage or rupture of the pleural space. Hemoptysis is not usuallylife-threatening and does not require surgical treatment [10]. However, to control bronchial hemorrhage, some cases requiring lobectomy have been reported. Pseudocysts are rarely complicated by infection. None of the patients in the current study had any complications and therefore no surgical intervention was required.

Limitations

This study had several limitations. First, the nature of the study was retrospective. Second, since the patients were not followed up in the long term, no data could be presented about the healing process. Finally, the study had a relatively small sample size, so no statistical analyses could be applied.

CONCLUSION

In conclusion, thorax CT is an effective and reliable method for early and definitive diagnosis of TPP, which is an uncommon development after blunt thoracic trauma.

Author contributions

Concept – O.T., B.G., E.K.; Design - O.T., E.K.; Supervision - B.G., E.K.; Resource - O.T., B.G., E.K.; Materials - O.T., E.K.; Data Collection and/or Processing - B.G., E.K.; Analysis and/or Interpretation - O.T., B.G., E.K.; Literature Search - O.T., E.K.; Writing - O.T., B.G., E.K.; Critical Reviews – O.T., B.G., E.K.

Conflict of interest

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The European Research Journal 2019;5(5):768-775 ORIGINAL ARTICLE

Idiopathic granulomatous mastitis: factors influencing recovery and recurrence

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ABSTRACT

Objectives: Idiopathic granulomatous mastitis (IGM) is an idiopathic, inflammatory, and benign disease of the breast. The aim of this study was to determine possible risk factors for the recurrence of IGM in patients treated with different treatment modalities.

Methods: It was planned to explore the risk factors of the disease through the evaluation of the medical records of 81 patients with the relevant diagnosis in the archives of Hacettepe University. The medical records of the patients were retrospectively screened for information regarding age, sex, total number of pregnancies, duration of breastfeeding, rheumatologic diseases, size and recurrence of the radiologically detected lesions. The results of two-year follow-up of the patients after the treatment were evaluated. The rates of recovery and recurrence after the treatment were determined for patients who received antibiotic therapy alone, who underwent wide excision alone, who received antibiotic therapy in combination with steroid therapy, and who received added azathioprine and/or methotrexate therapy.

Results: No significant difference was observed between 12 patients having recurrence and 69 patients having no recurrence. However, the recovery time was shorter for patients with a lesion size of ≤ 20 mm who underwent wide excision or received antibiotic therapy alone.

Conclusion: Among patients with a mass size ≤ 20 mm, those treated with wide excision and antibiotic therapy alone had shorter recovery times compared with those who received immunosuppressive therapy. In addition, it may take more than two years to terminate the treatment in patients who received medical treatment alone.

Keywords: idiopathic granulomatous mastitis, recovery, recurrence, treatment, breast

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Idiopathic granulomatous mastitis (IGM) is a rare, chronic inflammatory disease of the breast with unknown etiology. IGM was first defined by Kessler and Wolloch [1] in 1972 as a non-malignant chronic inflammatory breast disease. The actual prevalence of IGM is unknown; however, histopathologically-confirmed IGM has been reported in 1.8% of 1106 patients with benign breast disease [2]. Galactorrhea, inflammation, induration, palpable mass and ulcerative lesions are observed in the IGM. The disease recurs in most patients and may be complicated with abscess and fistulas [3]. These complaints may easily be confused with breast cancer; however, IGM and breast cancer can be differentiated on the basis of clinical and radiological findings, although a tissue diagnosis is required for differentiation definitive diagnosis.

An autoimmune hypothesis is widely accepted in the pathophysiology of IGM. Protein-rich secretion

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from ductal epithelial damage is thought to result in a granulomatous reaction stimulating the migration of lymphocytes and macrophages, first to the surrounding fat tissue, and then to the lobular connective tissue [4]. IGM is histopathologically-characterized by chronic granulomatous lobulitis without caseification [5].

The treatment of IGM remains controversial. Immunosuppressive therapy or surgical excision are preferable. Surgical treatment increases recurrence in complicated patients, and recovery may be achieved with close follow up in some patients [6]. In our hospital, patients diagnosed with IGM are treated with antibiotic therapy, immunosuppression, or surgical excision. In this study, we retrospectively investigated IGM patients to evaluate the efficacy of different treatment options. We compared the factors that possibly influenced the recurrence of IGM and patients' recovery times based on the chosen treatment method. Our aim was to determine possible risk factors for the recurrence of IGM in patients treated with different treatment modalities and increase the amount of available information for this unclear disease, by evaluating one of the largest known patient series.

METHODS

We retrospectively reviewed the records of patients who were diagnosed with granulomatous mastitis after being admitted to our clinic with redness, painful mass or purulent discharge.In this study, patients with other causes of granulomatous mastitis (sarcoidosis, tbc, etc.) were excluded. Eighty-nine patients histopathologically diagnosed with IGM between March 2003 and April 2012 were evaluated by retrospectively reviewing the archives of Hacettepe University School of Medicine and patient records. For diagnosis, excisional biyopsy was performed in 35 patients, incisional biyopsy in 22 patients and trucut biyopsy in 24 patients. Eight patients were excluded from the study because the details of their records could not be accessed from the system review. We evaluated the results of a two-year post-treatment patient's follow-up and recorded the rate of the response to treatment and the recurrence in patients who received antibiotic therapy alone, who underwent wide excision alone, who received antibiotic therapy in combination with steroid therapy, who received added azathioprine and methotrexate therapy in cases of resistance to initial treatment, or who underwent wide excision in cases of resistance to all initial treatments.

The recovered patients included those with symptom improvement and loss of mass size in two-year follow-up. The recurrence was defined as the emergence of a recurrent mass or fistula during a two-year follow-up of recovered patients. The persistent disease was defined as non-healing fistulas, abscess or mass during the treatment. Resection with surgical margin more than 1 cm was defined as wide excision. The choice of treatment method was made at the time of diagnosis, according to the current treatment recommendations in the literature. This study was approved by Hacettepe University Institutional Review Board (Project no: GO 13/230-29) and supported by Hacettepe University Research Fund.

Patients were treated with 40-60 mg/day prednisolone for 1 month. Then the prednisolone dosage was tapered to 30 mg on alternate days over a period of 1-2 months, and after 6 months the dosage was 10-15 mg on alternate days. The maintenance dosage of prednisolone was 5-7.5 mg on alternate days. Steroid was stopped after 1.5-2 years. In the case of relapse, the dosage was increased to 40 mg/day. Patients were treated with 2 mg/kg/day azathioprine as steroid-sparing agent as previously defined [7]. Methotrexate (MTX, 10-15 mg weekly, orally) was added in patients who had persistent disease and an unresolving breast mass despite steroid treatment. Also, MTX was introduced to help reduce prednisolone dosage, as previously reported [8]. All patients were re-examined within 3 months of therapy, and then at 6-month intervals.

The breast mass size was detected radiologically, using ultrasonography (USG), mammography (MMG) or magnetic resonance imaging (MRI) scans. Breast size was categorized into four groups: ≤ 10 mm, 11-20 mm, 21-30 mm, and ≥ 31 mm. The age at diagnosis, the duration of breast-feeding, abscess drainage, and the presence of fistula, erythema and ulceration in cases with recurrence, and the treatment outcomes were compared between these groups. We also evaluated recovery times on the effect of the treatment method.

Statistical Analysis

The data of patients were analyzed using SPSS 21.0 software package (SPSS, Chicago, IL). The normality of distribution of study variables was assessed by Levene test of variance homogeneity by Shapiro-Wilk test. The quantitative variables were shown as median range (minimum- maximum), and the categorical variables were shown as numbers. To compare categorical variables, Chi-squared or Fisher's exact test was used. Mann-Whitney test was used to compare continuous variables between the groups, because the data were not normally distributed. Variables were examined at a confidence level of 95% and a significance level of $p < 0.05$.

RESULTS

We evaluated 81 patients who were diagnosed histopathologically with IGM by examining the results of a mean of two-year post-treatment follow-up. All patients were female. The median age of the patients at diagnosis was 35 (range, 24-60) years. Patients had no history of diabetes mellitus and all had normal serum prolactin levels. Ten of the patients had no history of pregnancy. On other hand, the remaining patients had a history of pregnancy and labor. The median duration of breastfeeding was 10 (range, 6-24) months, and the maximum lesion size was 70 mm. Unilateral disease was present in all of the patients and there was no difference in the incidence of breast side involvement. There was no correlation between recovery and recurrence rates and patients' age at diagnosis, duration of breastfeeding, and lesion size (Table 1). Recurrence was observed in 4 of 10 patients without a history of pregnancy and breastfeeding. One of four patients with recurrence underwent wide excision and the remaining three patients received prednisolone, azathioprine and methotrexate treatment. The shortest duration of treatment was one week in patients with wide excision, and 104 weeks in patients who received prednisolone, azathioprine, and methotrexate treatment.

There were no adverse events related to azathioprine such as cytopenia, liver disfunction, or severe infection. Four patient had temporary steroid-induced diabetes mellitus. In these patients, by reducing the dose of steroid glucose intolerance improved spontaneously and no additional treatment was needed. No steroid-related complications occurred in other patients.

Thirty-one patients underwent abscess drainage because of erythema, purulent discharge and subcutaneous fluid collection at admission and were

Table 1. Demographic and clinical parameters of recovery and recurrence groups

Patients Characteristics	Recovery (n = 69)	Recurrence (n = 12)	*p* value
Age (year)	35 (24-60)	36 (24-49)	0.548
Breast-feeding (month)	12 (6-24)	12 (6-12)	0.122
Number of child	2 (0-3)	1 (0-3)	0.646
Lesion size (mm)	10 (10-70)	20 (10-50)	0.078
Smoking			
Yes	17	4	0.578
No	52	8	
Lesion side			
Right	29	5	0.236
Left	40	7	
Abscess drainage			
Yes	25	6	0.276
No	43	7	

Data are given as mean and ranges or number.

Table 2. Comprasion of recovery and recurrent groups according to lesion size

	Recovery (n = 69)	Recurrence (n = 12)	*p* value
Lesion size (mm) (n)			0.078
≤ 10	23	3	
11-20	22	2	
21-30	16	3	
≥ 31	6	4	
Treatment method (n)			
None	6	1	
Atb	19	2	
WE +/- Atb	14	2	
Pred +/- Mtx,Azat	28	7	
Duration of treatment (median) (week)			0.957
Atb	4	6	
WE +/- Atb	1	3	
Pred +/- Mtx,Azat	48	52	

Atb = antibiotics, WE = wide excision, Pred = prednisolone, Mtx = methotrexhate, Azat = azathioprine, n = number of patients

treated with oral antibiotics according to the culture results. Culture results revealed the growth of *Bacteroides capillosus* in one patient, *Acinetobacter baumannii* in one patient, *Klebsiella* in one patient and *Staphylococcus epidermidis* in four patients, with no resistant strains for ampicillin/sulbactam having been identified in the antibiogram results. Biopsy specimens from all patients were evaluated using acid-alcohol-fast staining, and all were negative. Abscess drainage was performed in 31 patients; 25 patients recovered, and 6 patients had recurrence. Among these patients, 3 patients were treated with antibiotics, 1 patient was treated with antibiotic and wide excision, 1 patient was treated with prednisolone and azathioprine, and 1 patient was treated with prednisolone and methotrexate. In patients who had recovery, the shortest duration of treatment was 4 weeks and the longest duration of treatment was 52 weeks (antibiotic treatment and prednisolone with methotrexate treatment, respectively). There was no significant difference between the groups with and without abscess drainage with respect to recurrence ($p = 0.559$).

We excluded two patients from the lesion size group because of the lack of evidence to confirm the mass using USG and MMG in one patient, and because of the mass involving the entire breast in another. Eight patients refused treatment, in one of which there was a lack of evidence about the exact nature of the mass; however, all of them returned for outpatient evaluation at random intervals through the two-year follow-up. The median lesion size of these patients was 27 mm (range, 0-40 mm) and, all of these patients had a history of breastfeeding. The median duration of breastfeeding was 12 (range, 6-12) months, and no significant difference was seen in this group. Seven patients in the "no treatment" group recovered, and one developed resistant fistulisation. After classifying the patients according to mass size, we compared the different treatment methods. Recurrence after follow-up without treatment or follow-up with antibiotics alone was lower in the ≤ 10 mm mass size group in comparison to the other groups. However, no significant difference was found between the groups. The effect of various treatment options on the time from the selected initial treatment to recovery was shown on Table 2. Two patients treated with prednisolone and methotrexate showed complete

Table 3. Duration of treatment and recovery

	Treatment method (n)	Treatment time (week)		
Lesion size		**Mean**	**Minimum**	**Maximum**
	ATB (7)	3.57	3.00	4.00
	Azat + Pred (6)	60.67	52.00	104.00
	W.E. (4)	26.75	1.00	104.00
≤ 10 mm	W.E. + ATB (3)	3.33	3.00	4.00
	Pred (1)	4.00	4.00	4.00
	Pred + MTX (3)	104.00	52.00	156.00
	Pred + MTX + Azat (2)	52.00	52.00	52.00
11-20 mm	None (2)	1.00	1.00	1.00
	ATB (8)	3.50	3.00	4.00
	Azat + Pred (4)	58.50	26.00	104.00
	W.E. (1)	1.00	1.00	1.00
	W.E. + ATB (2)	5.50	3.00	8.00
	Pred (2)	27.50	3.00	52.00
	Pred + MTX (1)	156.00	156.00	156.00
	Pred + MTX + Azat (4)	65.00	52.00	104.00
21-30 mm	None (3)	3.33	1.00	8.00
	ATB (4)	4.25	1.00	8.00
	Azat + Pred (6)	60.67	26.00	104.00
	W.E. (2)	1.00	1.00	1.00
	W.E. + ATB (1)	4.00	4.00	4.00
	Pred + MTX + Azat (3)	69.33	52.00	104.00
≥ 31	None (2)	1.00	1.00	1.00
	ATB (2)	4.00	4.00	4.00
	Azat + Pred (2)	52.00	52.00	52.00
	W.E. (3)	1.33	1.00	2.00
	Pred + MTX + Azat (1)	52.00	52.00	52.00

Atb = antibiotics, WE = wide excision, Pred = prednisolone, Mtx = methotrexhate, Azat = azathioprine, n = number of patients, $p = 0.370$.

recovery after approximately 3 years. One patient treated with wide excision showed complete recovery after 2 years. We found no significant difference between the treatment methods with respect to recurrence independent of mass size. The recovery time was shorter both after antibiotic therapy and after wide excision in cases with the mass size ≤ 20 mm. There was no statistical difference between differing lesion sizes with respect to the effects of the treatment methods on the duration of treatment, (p = 0.370) (Table 3). There were 9 patients who had mass size of ≤ 20 mm and treated with wide excision and antibiotic therapy, among whom only 1 patient had recurrent fistulas. At the end of the treatments all of patients had a complete recovery.

DISCUSSION

The two defined GM types are specific and

idiopathic types [9]. Specific GMs are seen in diseases causing granulomas, such as tuberculosis, sarcoidosis, mycotic and parasitic infections. IGM is characterized by non-caseified granulomatous inflammation, necrosis, giant cell formation, and neutrophil migration. Granulomatous changes are observed around the lobules and ducts in the breast in the absence of other diseases such as infection, trauma, foreign body reaction, or tuberculosis [10]. IGM is a benign disease; however, it may be confused with the local findings of breast cancer at admission.

IGM usually occurs in young women under the age of 50 years with a history of labor and lactation [10, 11]. There are only two cases of male patients from 537 patients published in the literature between 1972 and 2010 [12, 13]. All patients evaluated in the present study were female, and 87.5% of these patients had a history of pregnancy and lactation.

There was no significant relationship with duration of breast-feeding, total number of pregnancies and oral contraceptive use [14]. Former reports suggested that prolonged duration of breastfeeding could lead to distention of acini and ducts in the long-term, resulting in rupture, which might induce a granulomatous response [15]. This theory is partially true, but unexplained contralateral breast involvement alone has occurred in patients breastfeeding from only the opposite breast. Ten patients had no history of pregnancy in our evaluation. The remaining 71 patients had a history of pregnancy and labor. The median duration of breastfeeding was 10 months. The number of pregnancies and the duration of breastfeeding did not have a significant effect on recovery or recurrence.

Different rates of bilateral disease have been reported in the literature,with no significant difference being present between left and right breast involvement [16, 17]. In our study, three patients had bilateral involvement; 31 patients had right breast involvement; and 47 patients had left breast involvement, with no significant difference between both sides. Based on interviews with patients, they preferred bilateral breast-feeding.

Previous publications have reported a history of prolonged treatment duration in the presence of Group D *Corynebacterium* infection [18]. Thirty-one of our patients underwent abscess drainage because of purulent discharge, erythema and fluctuation at admission. The growth of *Staphylococcus* and its strains were observed only in ten patients. *Corynebacterium* was not isolated from these patients; however, as mentioned by Mathelin *et al*., [18] *Corynebacterium* may be found in repeat cultures in treatment-resistant cases; therefore, once it is isolated, treatment response may be evaluated on the basis of antibiotic therapy.

Lai *et al*. [19] investigated nine patients with IGM. Lumpectomy was performed only in one patient because of large lesion size, with no recurrence during the 30-month follow-up in this patient. The remaining eight patients received no surgical intervention or medical treatment, and complete recovery was observed in four patients during the 24-month follow-up. The disease remained stable during the 11-month follow-up after the first 12-month recovery period in four patients, and no abscess formation or fistulization was seen during the follow-up of any patient. These findings suggest that the disease has a self-limiting nature and complete recovery is achievable during conservative follow-ups. The authors also recommended using high-dose steroid therapy in recurrent cases with multiple fistulas. In our study, seven patients received no medical or surgical treatment, and only one patient had resistant fistulization, which was treated by wide excision and antibiotics.

A study by Konan *et al*. [20] from Hacettepe University Hospital investigated 15 patients diagnosed with IGM. Steroid therapy alone was administered to one of these patients because of concurrent pregnancy. The remaining 14 patients received simultaneous prednisolone and azathioprine. Prednisolone was maintained for 12-24 months with tapering the dose. No patients experienced pancytopenia or impaired liver function secondary to azathioprine during follow-up; however, four patients developed temporary steroid-related diabetes mellitus. Complete recovery was observed in 11 patients during the 6-month follow-up. Recurrence was observed in two patients at the 4th and 12th months, with a partial response in one patient. Kim *et al*. [8] reported the use of methotrexate with steroids in four patients with IGM]. During the medical therapy none of their patients had recurrence, after cessation of methotrexate treatment,

they reported two recurrences. Also, Raj *et al*. [7] reported three cases treated with medical therapy]. In their cases one patient had shortness of breath on methotrexate, which wasswitched to azathioprine treatment. All of three patients had complete recovery with medical therapy. Methotrexate is commonly used in autoimmune diseases such as rheumatoid arthritis. A low dose can help reduce concomitant steroid dose, while at the same time controlling the underlying autoimmune conditions. Also, azathioprine is widely used as a steroid-sparing agent after the initial control of autoimmune disease. It is a purine antagonist and inhibits both cellular and humoral immunity. Our data showed that 37 patients received medical treatment, with seven experiencing recurrent disease.

Surgical treatment of IGM is controversial because of delayed wound healing, high rates of local recurrence, and poor cosmetic outcomes. Yau *et al*. [21] carried out a retrospective analysis of 11 patients diagnosed with IGM treated at a tertiary care center. Eight patients had multiple surgical interventions because of recurrence. Five patients had excisional biopsy; five patients had partial mastectomy; and one patient had total mastectomy and transverse rectus abdominis musculocutaneous flap. Recurrence was identified in one patient who had undergone partial mastectomy. Most authors suggested that definitive surgical interventions exacerbate the clinical course because of local recurrence and poor cosmetic outcomes. Moreover, Yabanoglu *et al*. [22] reported successful surgical outcomes in patients with IGM. They compared 31 wide excision, one simple mastectomy and one subcutaneous mastectomy results to 44 steroid treatment results. In the surgical treatment group, they reported no recurrences, whereas in the medical treatment group nine patients had recurrence. In our study, the recovery time was shorter with wide excision and antibiotic therapy alone when necessary compared with immunosuppressive therapy in cases with the mass size ≤ 20 mm.

Limitations

The retrospective observational nature of our study was its limitation. It was difficult to assess a disease which pathophysiology was not fully understood. It is also difficult to compare the different treatment modalities at different time points. Nonetheless, it was important by being one of the largest series in the literature. Large patient populations and different treatment regimens were evaluated in a single study.

CONCLUSION

There is a limited number of reported cases of IGM in the literature because the disease is so rare. In this study, the size of the patient series used was quite extensive, that is 81 patients. No significant difference was found between the efficacy of different treatment methods administered according to patients' characteristics and the effect on recurrence. However, among cases with the mass size ≤ 20 mm, those treated with wide excision and antibiotic therapy alone had shorter recovery times compared with the patients who received immunosuppressive therapy. In addition, it may take more than two years to terminate treatment in patients treated with medical treatment alone.

We determined that no factor significantly affected the recovery and recurrence rates. Future multicenter prospective randomized controlled trials employing standardized treatment methods will help to establish factors affectingrecovery and recurrence rates in the disease.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2019;5(5):776-780 ORIGINAL ARTICLE

The incidence and clinical features of meconium aspiration syndrome: a two-year neonatal intensive care experience

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ABSTRACT

Objectives: The aim of this present study was to review the clinical characteristics, risk factors, frequency of meconium aspiration syndrome (MAS), development and maternal demographic characteristics of the newborns born with meconium stained amniotic fluid (MSAF) in our neonatal intensive care unit.

Methods: The files of the patients hospitalized in our neonatal intensive care unit between July 31, 2015 and July 31, 2017 and who were diagnosed with MAS or MBAS were examined retrospectively.

Results: A total of 1410 patients were included during this period. Of these patients, 98 were term infants and 3 (34 weeks) were preterm infants. One hundred and one infants (7.1%) had MSAF and/or MAS. Of the patients, 63 were boys, 38 were girls. MAS developed in 61 patients (60.3%) who were hospitalized due to MBAS. No difference was detected between two groups in terms of the systemic diseases, age, pregnancy number, gestation week, delivery type, length of hospital stay of mother and birth weight of infant. The fifth minute Apgar score and need for resuscitation were found to be statistically significant in patients with MAS. We did not have any mortality.

Conclusion: MAS frequency decreases in parallel with the developments in neonatal care but it is still a major cause of mortality and morbidity. We believe that chance of mortality and morbidity will decrease thanks to the close follow-up and early treatment in infants born with MSAF who are likely to develop MAS.

Keywords: Meconium aspiration syndrome, meconium stained amniotic fluid, newborn

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Diagnosis of meconium aspiration syndrome (MAS) is made by the presence of respiratory distress and other characteristic radiologic findings in babies born with meconium-stained amniotic fluid (MSAF) [1, 2,]. In the healthy newborn, the first meconium outflow is between 24th and 48th hours and it is rarely seen between 20 and 34 weeks of pregnancy [1, 2]. Due to increase in pregnancy age, especially after the 42nd week of pregnancy, the meconium passage is frequent. In this week, motilin hormone responsible for vagal stimulation and intestinal peristalsis is at the highest level [3]. Prenatal meconium outflow is controversial, but fetal stress and vagal stimulation are possible factors. In addition, risk factors such as placental insufficiency, preeclampsia, eclampsia, diabetes mellitus, cardiovascular disease, smoking, oligohydramnios, intrauterine growth retardation in the mother cause meconium outflow [4].

Meconium causes harm in lungs with various mechanisms and that was defined as MAS by the presence of respiratory distress and other characteristic radiologic findings in babies born with MSAF [2, 5].

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The clinical picture may vary from mild respiratory distress to severe respiratory failure. Hypoxic encephalopathy, air leaks, persistent pulmonary hypertension (PPH) and infections can also be added to the clinical picture [6, 7]. In this study, it was aimed to review the clinical characteristics, risk factors, frequency of MAS development and maternal demographic characteristics of babies born with MSAF in intensive care unit along with the information of the literature.

METHODS

We retrospectively reviewed the files of patients admitted to our neonatal intensive care unit between July 31, 2015 and July 31, 2017 and who were diagnosed with MAS or MSAF. Babies who are born dead have a major congenital anomaly and congenital heart disease were not included in the study although they were born with meconium. Concerning included patients, birth weight, gestational week, sex, first and fifth minute Apgar scores, need for resuscitation in birth-room, type of meconium, ventilatory support, duration of hospitalization, hemogram biochemistry, results of C-reactive protein (CRP), features regarding mother and birth and MAS related complications were evaluated. MAS diagnosis was made after seeing meconium presence in the amniotic fluid, respiratory failure together with increased oxygen demand in the first postnatal 4 hours and/or radiographic changes such as reticulogranular on chest x-ray [8-10]. The level of vitamin D was investigated, if the patients have hypocalcaemia. Asphyxia diagnosis in patients was made by pH ≤ 7.0 in umbilical cord arterial blood sample, and 0-3 Apgar score after thefifth minute and neurological findings belonging to neonatal period (seizure, hypothyroidism, coma and hypoxic-ischemic encephalopathy, multiorgan failure) [11].

Statistical Analysis

Statistical Analyses Independent samplest test or Mann-Whitney U test was used depending on the distribution of data in the group comparisons with respect to continuous variables, and Chi-Square or Fisher's Exact test was used to examine the relations between categorical variables. Statistical analyses were performed with the SPSS v.22 packet program and $p < 0.05$ was considered significant.

RESULTS

Between July 31, 2015 and July 31, 2017, a total of 1410 patients were interned in our neonatal intensive care unit. Of these, one hundred of one (7.1%) were infants with MSAF and/or MAS. 63 of the patients were male, 38 were female, 98 were term, and 3 (34 weeks) were preterm infants. The mean birth weight was 3391 ± 534 gr (1500 gr-4405 gr), the mean pregnancy week was 37.9 ± 7.9, and the average length of hospitalization was 7 ± 3.4 days. CRP was

Table 1. Demographic characteristics of patients

Birth weight (mean ± SD) (min-max), gr	3391 ± 534 (1500 - 4405)
Gestational week (mean ± SD)	37.9 ± 7.9
Gender (Male/Female)	63/38
Type of delivery (Cesarean /NSD)	64/37
Average length of hospitalization (mean ± SD), day	7 ± 3.4
MAS/ MSAF (n)	61/40
Ventilator support, n (%)	11 (10.8)
Need for resuscitation at birth, n (%)	15 (14.8)
Dark meconium, n (%)	6 (5.9)
The cord entanglement, n (%)	2 (1.9)
Elevation in liver enzyme, n (%)	16 (15.8)
Thrombocytopenia, n (%)	3 (2.9)
D vitamin deficiency, n (%)	8 (7.9)
CRP positivity, n (%)	54 (53.4)

NSD = Normal spontaneous delivery, MAS = Meconium aspiration syndrome, MSAF = Meconium-stained amniotic fluid, CRP = C-reactive protein, SD = standard deviation

Table 2. Demographic characteristics of mothers

The age of mothers, year (mean ± SD)	28.7 ± 5.1
The number of pregnancies (mean ± SD)	2 ±1.9
Systemic disease, n (%)	16 (15.8)
Urinary tract infection, n (%)	16 (15.8)
PROM, n (%)	11 (10.8)
Smoke, n (%)	9 (8.9)
Influenza infection, n (%)	2 (1.9)
Placental abruption, n (%)	1 (0.9)

PROM = Premature rupture of membrane, SD = standard deviation

positive in 54 (53.4%) of the patients. Demographic characteristics of the patients are shown in Table 1. Of the patients admitted due to MSAF, 61 (60.3%) developed MAS.

The mean age of mothers was 28.7 ± 5.1 years and the number of pregnancies was 2 ± 1.9. Systemic disease 16 (15.8%), urinary tract infection 16 (15.8%), premature rupture of membrane (PROM) 11 (10.8%) were the most common causes when the mothers were evaluated for risk factors (Table 2). In our study, ventilator support was given to 11 (10.8%) patients with MAS and general respiratory support was given to 50 (49.5%) patients by means of hood.

The rate of < 7 Apgar score in the fifth minute was significantly higher in patients with MAS than in patients with MBAS ($p < 0.047$). Similarly, when comparing ventilator requirement and need for resuscitation at birth, there was a statistically significant difference between the patients with MAS and the patients with MSAF ($p < 0.006$, $p < 0.007$; respectively) (Table 3). There were no differences between the two groups in terms of maternal systemic diseases, age, number and week of pregnancy, type of delivery, weight of birth and duration of hospitalization. We did not have any mortality.

DISCUSSION

In 8-15% of births, amnion fluid is contaminated with meconium, and MAS develops in 5-10% of these infants [12]. Meconium causes harm in lungs with various mechanisms such as mechanical obstruction in the early period, chemical pneumonia, surfactant inactivation, vasoconstriction in pulmonary veins and inflammation in the late period [13, 14].

The incidence of MAS is 16.5% in term infants and 27.1% in post-term infants, and is among the most

Table 3. Demographic characteristics of MAS and MSAF patients

	MAS (n = 61)	**MSAF (n = 40)**	***p* value**
Male, n (%)	40 (65.6)	23 (57.5)	0.413
Female, n (%)	21 (34.4)	17 (42.5)	
Cesarean, n (%)	37 (60.7)	27 (67.5)	0.485
Normal spontaneous delivery, n (%)	24 (39.3)	13 (32.5)	
APGAR 5 < 7, n (%)	6 (9.8)	0 (0.0)	**< 0.047**
APGAR1 < 7, n (%)	8 (13.1)	3 (7.5)	0.519
Urinary tract infection, n (%)	7 (11.5)	9(22.5)	0.138
Systemic disease, n (%)	7 (11.5)	7 (17.5)	0.391
PROM, n (%)	8 (13.1)	4 (10.0)	0.759
Asphyxia, n (%)	3 (4.9)	0 (0.0)	0.275
Ventilator support, n (%)	11 (18.0)	0 (0.0)	**< 0.006**
Need for resuscitation at birth, n (%)	14 (23.0)	1 (2.5)	**< 0.007**
Birth weight (mean ± SD) (min-max)	3391.80 ± 577.96 (1500-4300)	3392.13 ± 467.13 (1600-4405)	0.998
Gestational week (mean ± SD) (min-max)	38.77 ± 1.38 (34-40)	38,73 ± 1,62 (30-40)	0.880
Mother age (mean ± SD) (min-max)	28.17 ± 5.19 (19-42)	29.60 ± 4.96 (20-42)	0.172
Number of pregnancies, median (min-max)	1 (1-6)	1 (1-5)	0.896

MAS = Meconium aspiration syndrome, MSAF = Meconium stained amniotic fluid, PROM = Premature rupture of membrane, SD = standard deviation

frequent causes of hospitalization for neonatal intensive care unit for this group newborns [15]. Fetal distress, post-term pregnancy, low Apgar score, cesarean birth, advanced maternal age, maternal hypertension and cardiovascular disease are among risk factors for MAS [16, 17].

In the study made among the 394 term newborns who developed MAS with MSAF in the literature, the MAS development rate was determined to be 4.8%. In this study, low Apgar score in the fifth minute was found to be a significant risk factor [18]. In the study by Espinheira *et al*. [19], they found that staining of amnion mine with medium or thick meconium and low Apgar score in the first minute facilitated MAS formation. Şen *et al*. [20] found the MAS development frequency to be 18% in the series of 106 cases made. Low Apgar score in the first minute was reported as a risk factor for MAS. In the same study, mortality in 23 patients with low Apgar scores and complications (hypoxia, hypoxic-ischemic encephalopathy, pulmonary hypertension and mechanical ventilator support) in 52 patients were found to be more frequent. In our study, we found MAS development frequency to be 60.3%. The rate of MSAF was similar in the literature but the rate of MAS development in these babies was found to be high. The reason for this is that every baby born with meconium is not admitted to the neonatal intensive care unit and the newborn born with MBAS is followed by the mother if there is no problem. We found the 5th-minute lowness of the Apgar score, increased cesarean rate (63.3%), maternal systemic illness, UTİ, PROM, cigarette use to be risk factors. Among our patients, there were no advanced maternal age and no post-term pregnancy. Male clinical gender, oligohydramnios, and nulliparity have also been reported among the risk factors in some clinical trials [21, 22]. However, these risk factors were not identified in our study.

In patients with MAS, correct response, fast diagnosis, well-planned treatment has reduced mortality and morbidity. Adequate oxygenation-ventilation in mild and moderate MAS, restoring of metabolic abnormalities, evaluation of patients according to their clinic in terms of antibiotic treatment are main treatment approaches. In severe MAS, mechanical ventilation support, high-frequency ventilation, surfactant therapy and nitric oxide may be required [2, 12, 23, 24]. In 218 MSAF and/or MAS case studies of Özdemir *et al*. [25], 86 patients needed general respiratory support and 20 patients underwent mechanical ventilator treatment. In our study, ventilator support was given to 11 (10.8%) patients with MAS and general respiratory support with hood were given to 50 patients. We did not have any patient who needs high-frequency ventilation, surfactant therapy and nitric oxide therapy.

In cases with meconium and fetal distress in amniotic fluid, perinatal mortality was reported as 3-22.2% and neonatal mortality as 7-50% in studies reported in the literature [12, 24]. In 106 cases study of Şen *et al*. [20], mortality rate was found to be 21.7% and 34.7% of deceased patients were detected to have hypertension.

Deterioration in hypoxia-induced liver function tests, sepsis, necrotizing enterocolitis, sepsis, pulmonary hypertension, air leak syndromes are other problems affecting mortality and morbidity [26, 27].

We did not have patients with pulmonary hypertension. After obtaining the cultures of CRP positive patients, appropriate antibiotic therapy was applied. Our patients with elevated liver enzymes were also recovered with close follow-up supportive care. We did not have any mortality. The treatment of infants born to our hospital according to the guidelines of the Turkish Neonatology Association 2016 birth room management guide is among the reasons for the low mortality and morbidity.

CONCLUSION

In conclusion, although MAS frequency decreases in parallel with the developments in neonatal care, it is still a major cause of mortality and morbidity. We believe that chance of mortality and morbidity will decrease thanks to the close follow-up and early treatment in infants born with MSAF who are likely to develop MAS.

Conflict of interest

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The European Research Journal 2019;5(5):781-786 ORIGINAL ARTICLE

Frequency of physical therapy in knee osteoarthritis: a randomized controlled trial

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ABSTRACT

Objectives: This study is conducted to compare the three different frequency of the physical therapy application for knee osteoarthritis in female patients.

Methods: Consecutive 89 female patients with knee osteoarthritis were randomized into three groups of physical therapy as twice-daily, once-a-day and alternate day, by computerized random number generator. We used Visual Analog Scale (VAS); to determine pain level, Western Ontario McMaster Osteoarthritis Index (WOMAC); to determine osteoarthritis (OA) severity, 10-meter walking test (WD); to determine walking speed and Short Form (SF-36) questionnaire; to determine the quality of life. All groups received a total of 10 physical therapy sessions including hot pack, therapeutic ultrasound (US) and transcutaneous electrical nerve stimulation (TENS). We evaluated subjects at the beginning, at the end of treatment and at the third month control at post-treatment period.

Results: Improvement was observed in all groups after treatment ($p < 0.05$). While there was no significant difference in once-a-day treatment group at 3rd month control ($p > 0.05$), alternate day group showed a significant improvement ($p < 0.05$).

Conclusions: In the treatment of knee osteoarthritis, usually once-a-day physical therapy approach is preferred in daily practice. Alternatively twice a day or alternate day therapies can be applicable.

Keywords: Knee osteoarthritis, physical theraphy agents, frequency of treatment

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Osteoarthritis (OA) is a slowly progressive, non-inflammatory, chronic, degenerative arthropathy characterized with cartilage destruction, osteophyte formation and subchondral sclerosis especially in load bearing joints [1]. Knee OA is the joint disease with the highest incidence and the most important cause of pain and disability in middle-aged and elderly individuals [2, 3].

Aims of OA treatment are reducing pain, increasing physical function, preventing disability and increasing quality of life [4]. Clinical treatment guidelines suggest conservative treatment methods as first-line treatment in knee OA [5-8]. Even though there is no proven, effective treatment method that re-

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stores structural changes; there are evident-based and non-evident-based treatment guidelines derived from various studies [9]. Conservative treatment includes pain killers, anti- inflammatory drugs, weight loss, exercise and physical therapy [10]. In optimal OA treatment pharmacological therapy is combined with physical therapy [5-8].

Physical therapy agents, which are one of non-pharmacological treatment modalities, are important due to side effects of pharmacological and surgical treatments. In literature, different practices can be seen about number and duration of sessions in physical therapy [11]. In our country, generally 10-20 sessions are administered in total, combining deep tissue heating, superficial heat and analgesic current once a day. Considering the current literature regarding our topic, there is no standardization of number, duration and frequencies of sessions in physical therapy studies. In this study, we evaluated treatment effectiveness of modalities with different frequencies.

METHODS

This study included 100 knee osteoarthritis patients who applied to Physical Therapy and Rehabilitation outpatient clinic and were diagnosed as knee osteoarthritis according to American College of Rheumatology (ACR) criteria. 11 patients lost follow-up and excluded from the study. Study was completed with 89 patients. The inclusion criteria were defined as mechanical knee pain lasting more than 6 months, stage I, II or III osteoarthritis radiography according to Kellgren-Lawrence Radiological Staging System, being able to walk 20 meters without help and age above 40 years. The exclusion criteria was setted as patients with >10° flexion contracture, >15° varus/valgus deformity, knee operation history, enlarged varicose veins or skin lesions in the knee, lower extremity neuropathy, inflammatory, infectious, endocrinological, tumoral or severe decompensated systemicdisease, received intraarticular treatment in the last 3 months and received physical therapy in the last 1 year. Patients were randomized into three groups by a computerized random number generator. All patients received 10 total physical therapy sessions including hot pack, ultrasound (US), transcutaneous electrical nerve stimulation (TENS). First group received the therapy twice a day, second group once a day, and third group alternate day. Physical therapy program was administered as 20 minutes of hot pack for superficial heating, 10 minutes of 1 MHz, 1.5 watt US for deep tissue heating, 20 minutes of 100 Hz, 50 mAmp TENS for analgesic current. Treatments were administered by the same physiotherapist. Patients were told to use paracetamol up to 3000 mg/day in case of pain and record the tablet consumed. Sociodemographic data of patients were recorded. Evaluations were done before treatment, end of treatment and three months after the cessation of treatment by a physiatrist who was blind to the treatment group. Visual Analog Scale (VAS) was used to determine pain level, Western Ontario McMaster Index (WOMAC) [12] was used to determine OA severity, 10-meter walking test (WD) [13] was used to determine walking speed and Short Form 36 questionnaire (SF-36) [14] was used to determine quality of life.

This study was approved by local ethical committee of our hospital. All patients were informed about the aim of the study and written consent was obtained.

Statistical Analysis

Statistical analyses were performed with the SPSS software ver. 16.0 (SSPS, Chicago, IL, USA). The type of the distribution was evaluated using the Kolmogorov-Smirnov test. Comparisons of the treatment groups were assessed with the Student's t or Mann-Whitney U test for continuous variables which one is appropriate. and with chi-square test for categorical variables. Differences between pre- and after treatment values of groups were evaluated with paired t-test or Wilcoxon Signed Rank Test which one is appropriate. Results were considered statistically significant if the two tailed p value was < 0.05.

RESULTS

All 89 patients were female. The mean age was 56.6 ± 10.4 (40-77) years. Education level of 68.5% were below 5 years and 86.5% were unemployed. Patients were stratified into three groups for treatment as twice a day (n = 29), once a day (n = 30) and alternate day (n = 30) by random number generator.

Table 1. Demographic characteristics and clinical parameters

Treatment Groups	Total (n = 89)	Group 1 (n = 29)	Group 2 (n = 30)	Group 3 (n = 30)	*p* value
Age (years)	56.6 ± 10.5	54.9 ± 10.4	59.1 ± 10.8	55.7 ± 10.0	0.190
BMI (kg/m^2)	31.6 ± 5.2	32.0 ± 6.3	30.5 ± 4.7	32.3 ± 4.6	0.467
Pain duration (month)	41.4 ± 42.2	46.2 ± 46.0	38.5 ± 33.5	39.6 ± 47.1	0.769
VAS1	7.0 ± 2.0	7.0 ± 2.1	6.8 ± 2.0	7.2 ± 2.1	0.949
WOMAC1	37.9 ± 16.6	35.8 ± 14.6	35.6 ± 16.7	42.4 ± 17.9	1.000
WD1	14.0 ± 4.3	13.5 ± 3.9	13.1 ± 4.1	15.5 ± 4.6	0.898

BMI = Body mass index, VAS = Visual analog scale, WOMAC = Western Ontario and McMaster Universities Arthritis Index, WD = walking distance, 1 = Pre-treatment

The groups showed no differences by age, body mass index (BMI), education level, occupation, smoking, duration of disease, previous treatments, comorbidities and radiological stages ($p > 0.05$). Table 1 shows demographic characteristics and also initial VAS, WOMAC and WD values of patients.

There was a significant improvement in pre-treatment, post-treatment and control VAS scores ($p < 0.001$) and WOMAC total scores ($p = 0.001$) in twice-a-day treatment group, while there was a significant improvement in pre-treatment and post-treatment WD ($p = 0.002$) became insignificant at 3rd month control ($p = 0.050$). While there was an improvement in pre-treatment and post-treatment VAS scores ($p = 0.011$), and WOMAC total scores ($p = 0.008$) in once-a-day group, it became insignificant at the 3rd month control ($p = 0.765$, $p = 0.457$, respectively). Even though there was an improvement in pre-treatment, post-treatment and 3rd month control of WD in once-a-day group it was statistically insignificant ($p = 0.191$). In alternate day group, there was a significant improvement in pre-treatment, post-treatment and control VAS scores ($p < 0.001$). A significant improvement was found in pre-treatment, post-treatment and 3rd month control in both WOMAC total and WD scores (both $p < 0.001$).

There were no difference between pre-treatment and post-treatment VAS scores among groups ($p = 0.547$ and $p = 0.153$, respectively). But in the once-a-day and alternate day treatment groups there were significant differences in the pre-treatment and 3rd

Table 2. Changes in treatment parameters among groups

	Treatment Groups				*p value*		
Group	**Total (n = 89)**	**Group 1 (n = 29)**	**Group 2 (n=30)**	**Group 3 (n = 30)**	**Group 1-2**	**Group 1-3**	**Group 2-3**
VAS1	7.0 ± 2.0	7.0 ± 2.1	6.8 ± 2.0	7.2 ± 2.1	0.949	0.928	0.775
VAS2	5.3 ± 2.4	5.0 ± 2.2	5.7 ± 2.3	5.0 ± 2.6	0.488	0.998	0.521
VAS3	5.2 ± 3.0	4.7 ± 2.8	6.6 ± 2.5	4.5 ± 3.1	**0.044**	0.965	**0.025**
WOMAC1	37.9 ± 16.6	35.8 ± 14.6	35.6 ± 16.7	42.4 ± 17.9	1.000	0.271	0.252
WOMAC2	28.7 ± 15.6	27.6 ± 14.6	29.6 ± 16.7	28.9 ± 17.9	0.883	0.949	0.985
WOMAC3	27.9 ± 16.2	23.7 ± 13.4	32.2 ± 13.4	28.6 ± 18.9	0.150	0.490	0.72
WD1	14.0 ± 4.3	13.5 ± 3.9	13.1 ± 4.1	15.5 ± 4.6	0.898	0.184	0.071
WD2	12.9 ± 3.7	12.0 ± 2.7	12.1 ± 3.5	14.6 ± 4.4	0.994	**0.024**	**0.030**
WD3	12.7 ± 3.8	12.4 ± 3.1	12.0 ± 3.0	13.7 ± 4.9	0.929	0.452	0.285

VAS = Visual analog scale, WOMAC = Western Ontario and McMaster Universities Arthritis Index, WD = walkin distance, 1 = Pre-treatment, 2 = Post-treatment, 3 = 3rd month control

month VAS scores (p = 0.036 and p = 0.015, respectively). Pain reduction was found better in alternate treatment group. There was no statistically significant difference between WOMAC total subgrup scores (p = 0.131, p = 0.943 and p = 0.279). No statistically significant difference was observed for pre-treatment, post-treatment and 3rd month control results of 10-meter walking among 3 groups (p = 0.063, p = 0.113 and p = 0.730, respectively) (Table2). Paracetamol use was more often in once-a-day group (p = 0.019).

When examining for SF-36 scores, there was no difference among groups. After analyzing intra-group pre-treatment, post-treatment and 3rd month scores there was a significant improvement only in SF-36 body pain and physical component scores of twice a day group (p = 0.004 and p = 0.012, respectively). Other parameters of SF-36 showed no significant difference.

DISCUSSION

Pain is the most common and debilitating complaint in patients with OA. Aim of knee OA treatment is to reduce pain and eburnation of joint, preserve and improve joint mobility, minimize physical limitations, improve quality of life, prevent further joint destruction and inform about prognosis and results of the disease. Gastrointestinal and cardiac side effects of pharmacological agents used in the treatment are important subjects. Physical therapy agents should be administered to prevent these side effects of NSAIDs. Physiotherapy is a recommended non-pharmacological form of treatment in knee OA by European League Against Rheumatism (EULAR) and Osteoarthritis Research Society International (OARSI) [5, 7]. Most commonly used physical therapy agents are superficial heating (hot pack- infrared radiation), TENS and deep tissue heating (short wave diathermy, US) [11, 15, 16]. In our clinical practice, these agents are usually administered separately or in combination in one or 2 sessions per day. In literature 2 or 3 sessions per week are common. In this study, we evaluated the effectiveness of most common physical therapy agents such as TENS, hot pack and US combination treatments in different frequencies. We achieved our goal of pain reduction, improvement of functionality and quality of life in OA treatment among all 3 treatment groups.

In literature, especially therapeutic US and TENS studies are very common [17-21]. TENS is a cheap and non-invasive modality with extensive use in several kinds of pain. Previous studies showed that TENS increases pain threshold due to pressure and heat in healthy individuals [22-24] and also reduces pain due to mechanic causes and heat in animals [25]. In the systematic review of Osiri *et al*. [26], it was shown that TENS is effective in reducing pain of knee OA. Also in another meta-analysis [27], a substantial amount of pain reduction was shown with TENS in knee OA.

US is a deep tissue heating modality with analgesic and anti-spasmodic effects on muscles. It is a mechanical energy generated by high- frequency sound waves and can be applied as continue or pulse forms. While pulse US generates non-thermal effects, continue US generates thermal effects. Its analgesic effect originates from thermal and non-thermal effects [28]. Loyola-Sanchez *et al*. [29] made a meta-analysis about improvement of physical function and pain reduction in knee OA and showed that US reduced pain by %21 comparing to control group. Although it is commonly used in the treatment of knee OA, there is no consensus about dosage, frequency and duration of US treatment in the literature. In the study of Huang *et al*. [30], which compares intermittent US treatment with sham US in knee OA, 60 patients received 3 sessions per week for 4 weeks, 12 sessions in total. Tascioglu *et al*. [31] compared two different doses of US and sham US, 90 patients received 5 sessions per week for 2 weeks, 10 sessions in total. In the randomized study of Eyigor *et al*. [32], which analyzes efficacy of superficial hot, exercise treatment, TENS and US, 45 patients received 5 sessions per week for 3 weeks, 15 treatment session in total. Falconer *et al*. [33] searched the effect of US on knee OA and contracture, patients received 2-3 sessions/week for 4-6 weeks. As one can see, all these studies are conducted with different session numbers and frequencies. National studies [31, 32] used once a day approach as in second group in our study, while foreign studies [30, 33] used every other day approach as in third group in our study.

As seen in literature, there are studies with different treatment session numbers and frequencies.

The primary objective of our study was to observe if the success of physical therapy liable to the frequency of the treatment sessions, not the number of sessions; so all groups received 10 sessions of therapy. However, to our knowledge there is no study to research comparing different intervals of therapy to treatment success. In this study, we observed a significant improvement in 3rd month control results of both twice a day and alternate day treatment groups. Improvement of post-treatment parameters in once-a-day treatment group did not persist in 3rd month control. Improvement was observed in all groups in terms of walking speed, pain level, functionality and quality of life after treatment, but this improvement was not statistically important. We did not see this improvement at 3rd month control of once a day group. We can attribute the excess use of parasetamols in this group to this situation. Improvement in pain and functional status in twice a day group continued at 3rd month of therapy but there was no difference in walking speed. Improvement in all treatment parameters was seen in alternate day group, and the best improvements was seen in alternate day group. Physical therapy agents, especially heat and cold applications, creates stress on body and human organism activates an adaptation mechanism against this stress. These reactions against stress called 'general Adaptation Syndrome'. First response of body when it encounters stres called 'alarm period' and this period tooks 48 hours. For body adaptation to physical therapy agents and also for tissue repair this alarm period should be passed [34]. We can explain the effect of daily after treatment by this way.

Limitations

Most important limitation of our study is the small number of subjects. A further study with larger case series and control group is required. Our patient cohort constituted only by consecutive female patients with bilateral knee OA. Even though this limitation prevented us to compare the gender difference, it increased the homogeneity of the cohort.

CONCLUSION

Physical therapy is a cheap and reliable treatment method with proven-efficacy. In literature, there is no study to show at which frequencies physical therapy approaches are more effective. Our aim is not to question a method with proven-efficacy but to find out at which frequency treatment is more effective. To our knowledge, this is the first study in literature on this topic. In the treatment of knee osteoarthritis, mostly once-a-day physical therapy approach is administered in daily practice. As a result, even though larger studies with high number of patients are necessary, alternate day treatment provided an effective treatment modality with consuming less time and thus reduce cost and labor loss.

Conflict of interest

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The European Research Journal 2019;5(5):787-792 ORIGINAL ARTICLE

Postoperative analgesic effect of bupivacaine infiltration following lumbar disc surgery

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ABSTRACT

Objectives: Effectiveness of 0.5% bupivacaine administered onto dura, under lumbar superficial fascia and subcutaneous tissue on postoperative pain control was analyzed in patients undergoing lumbar microdiscectomy.
Methods: Sixty adult patients scheduled to undergo elective, single-level lumbar discectomy were randomly divided into four groups: the control group (Control), the subcutaneous tissue group (Group C), which received 20 ml of 0.5% bupivacaine in the subcutaenous tissue, the superficial fascia group (Group F), which received 12 ml bupivacaine in the subcutaneous tissue and 8 ml in the space below the lumbar superficial fascia, and the dura group (Group D), which received a total of 20 ml (100 mg) of bupivacaine, consisting of 10 ml in the subcutaneous tissue, 8 ml in the space below the lumbar superficial fascia, and 2 ml on the dura. Visual Analog Scale Values (VAS) on postoperative 0, 15, 30, 45 minutes, at 1, 2, 4, 6, 12 and 24th hour and time of the first analgesic need were evaluated for all patients and recorded.
Results: While mean VAS value measured at min 0 (as soon as the patient awakened) was 2.3 ± 1.2 in Group D; it was 2.7 ± 0.9 in Group C; 2.7 ± 1.0 in Group F and 3.1 ± 0.6 in control group (p = 0.232). At the end of 1th hour, mean VAS value was recorded as 2.8 ± 1.0 in Group D; 3.6 ± 1.5 in Group C; 3.6 ± 1.1 in Group F and 4.4 ± 1.1 in control group (p = 0.005). In Group D, 0.5% bupivacaine administered as 2, 8, 10 ml onto dura, fascia and subcutaneously was detected to provide significantly lower VAS values and significantly longer first analgesic need time.
Conclusions: 0.5% bupivacaine administered onto dura, under lumbar superficial fascia and in subcutaneous tissue was detected to be a simple, effective and safe method in lumbar microdiscectomy operations.

Keywords: lumbar microdisectomy, bupivacaine, pain, infiltration analgesia

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Microdiscectomy is performed on patients who have been diagnosed with lumbar disc hernia after experiencing low back pain and radicular pain, who have not recovered after conservative treatment, and who have neurologic deficits in addition to their physical complaints [1]. However, despite the modern surgical techniques developed within the past 20 years, 30-70% of patients have been shown to continue to complain of moderate to severe low back pain and radicular pain following lumbar disc surgery. Identifying effective pain control measures remains important for these patients [2, 3].

The severity of postoperative pain varies depending on the magnitude of the surgical trauma, the anesthesia approach, the patient's physiological, psychological, and emotional status, as well as the

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socio-cultural structures of the patient. Surgical trauma and related pain lead to a physiological stress response and, consequently, pulmonary, cardiovascular, gastrointestinal, metabolic, and neuroendocrinological complications [4, 5]. Thus, appropriate and sufficient postoperative pain treatment is an important factor for facilitating postoperative recovery, shortening hospital stay duration, and reducing treatment costs [6-8].

Local anesthetic applications for preoperative or postoperative incisional pain are known to be performed for lumbar disc surgery in various surgical disciplines [9-12]. We analyzed the effect of local bupivacaine, an amide class, potent, long-acting agent that significantly separates sensory and motor block, administrations on postoperative pain [13].

METHODS

A total of 60 adult patients aged between 20-58 years, who scheduled to undergo elective single-level lumbar discectomy operation for the first time, of whom 39 (65%) were in ASA I and 21 (35%) were in ASA II risk group were included in the study after informed consent and ethics committee approval had been obtained. The patients who had significant cardiovascular, pulmonary, hepatic, renal, neurologic, psychiatric or metabolic diseases and who had allergy to the local anesthetic were excluded from the study. The patients were instructed about Visual Analogue Scale (VAS) (0 = no pain, 10 = overwhelming pain) which is composed of a 10 cm of line indicating pain severity. The patients were monitored for electrocardiography (ECG), non-invasive blood pressure and oxygen saturation after they had been taken to operating table.

The patients were allocated to 4 groups according to postoperative analgesia. Each group was administered 20 ml (100 mg) of 0.5% bupivacaine. Following standard general anesthesia administration, all cases were performed single-level partial hemilaminectomy and lumbar microdiscectomy operation after median 2 cm midline incision. Patients in Group C were administered 20 ml of 0.5% bupivacaine into only subcutaneous tissue, Group F were administered 12 ml bupivacaine into subcutaneous tissue and 8 ml in space below lumbar superficial fascia at the end of the operation, Group D were administered a total of 20 ml (100 mg) bupivacaine of which 10 ml into subcutaneous tissue, 8 ml in space below lumbar superficial fascia and 2 ml onto dura after hemostasis had been provided. No drug was administered in control group. Afterwards fascia, subcutaneous tissue and skin were closed in accordance with anatomic structure and the operation was terminated. VAS scores on postoperative 0, 15, 30 and 45 minutes, at 1, 2, 4, 6, 12 and 24th hour were evaluated for all patients when the patient was unwitting and results were recorded. It was planned to administer diclofenac sodium 75 mg via intramuscular route when VAS value >5 or the patient demanded analgesic for his/her pain and metoclopramid via intravenous route when the patient had nausea and vomiting. Analgesia time was determined by recording the time of the first analgesic need. Complications developing due to intraoperative and postoperative local anesthetic use (hallucination, respiratory depression, sedation, nausea, vomiting, hypotension and bradycardia) were recorded.

Statistical Analysis

Statistical analyses were done using SPSS (Statistical Package for Social Sciences) for Windows 15.0 program. Pearson chi-square test was used for comparison of qualitative data beside descriptive statistical methods (frequency, percent, mean, standard deviation). Kolmogorov-Smirnov test was used for normality distribution. Mann-Whitney U test was used for inter-group comparisons in case of presence of two groups for comparison of quantitative data. When there were four groups in comparison of quantitative data, Kruskal-Wallis test was used for inter-group comparisons, Mann-Whitney U test was used for detection of the group causing difference. Friedman test was used for in-group comparisons for 10 measurements, Wilcoxon test was used for detection of the group causing difference. Results were evaluated as 95% confidence interval and a p level of < 0.05.

RESULTS

Of the patients included in the study, 31 (51.7%) were female and 29 (48.3%) were male with mean age of 43.25 ± 8.93 years. A statistically significant

Table 1. Duration of the first analgesic need according to groups

Duration of the first analgesic need **(min)**				
Group C	**Group F**	**Group D**	**Control**	
Mean ± SD	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	***p* value**
221.3 ± 188.3	376.7 ± 262.6	475.0 ± 245.8	94.0 ± 54.8	0.001

SD = standard deviation, Group C = subcutaneous tissue group, Grup F = superficial fascia group, Group D = dura group

difference was not found between groups with regard to demographic data of the patients ($p > 0.05$). Mean time of first analgesic need was significantly lower in control group compared to Group D and Group F ($p < 0.01$). The mean time of first analgesic need was found statistically significantly higher in Group D compared to Group C ($p < 0.05$) (Table 1).

Total amount of analgesic use in control group was found statistically significantly higher compared to Group C, Group F and Group D ($p < 0.01$). Mean amount of total analgesic was found lower in Group D compared to Group C ($p < 0.05$) (Figure 1).

A statistically significant difference was not detected between groups when systolic and diastolic arterial blood pressure, respiratory rate, heart beat and oxygen saturation were evaluated at different times ($p > 0.05$). Vomiting was observed during postoperative follow ups in two cases in each of Group C and Group D, in one case in each of Group F and control group.

Differences in the VAS were statistically significant at all postoperative intervals. While mean VAS scores at min 0 were 2.3 ± 1.2 in Group D; they were 2.7 ± 0.9 in Group C; 2.7 ± 1.0 in Group F and 3.1 ± 0.6 in control group ($p = 0.232$). There was a statistically significant difference between groups with regard to VAS values at 1th hour ($p < 0.01$). According to this, mean VAS scores at the end of 1st hour were found as 2.8 ± 1.0 in Group D; 3.6 ± 1.5 in Group C; 3.6 ± 1.1 in Group F and 4.4 ± 1.1 in control group ($p = 0.005$).

Mean VAS value in Group D at particularly 1th hour was found extremely lower compared to control group and significantly lower compared to Group F and Group C ($p < 0.01$).

VAS values were seen to go low until the end of 24th hour following the first analgesic administration

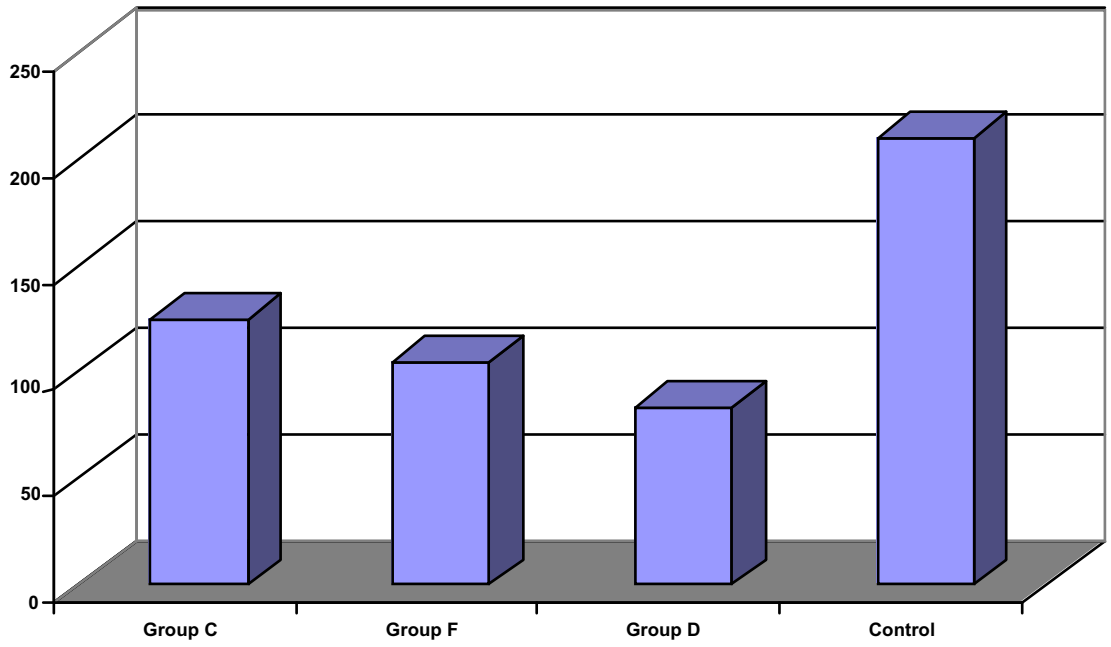

Figure 1. Distribution of total amount of analgesic according to groups.

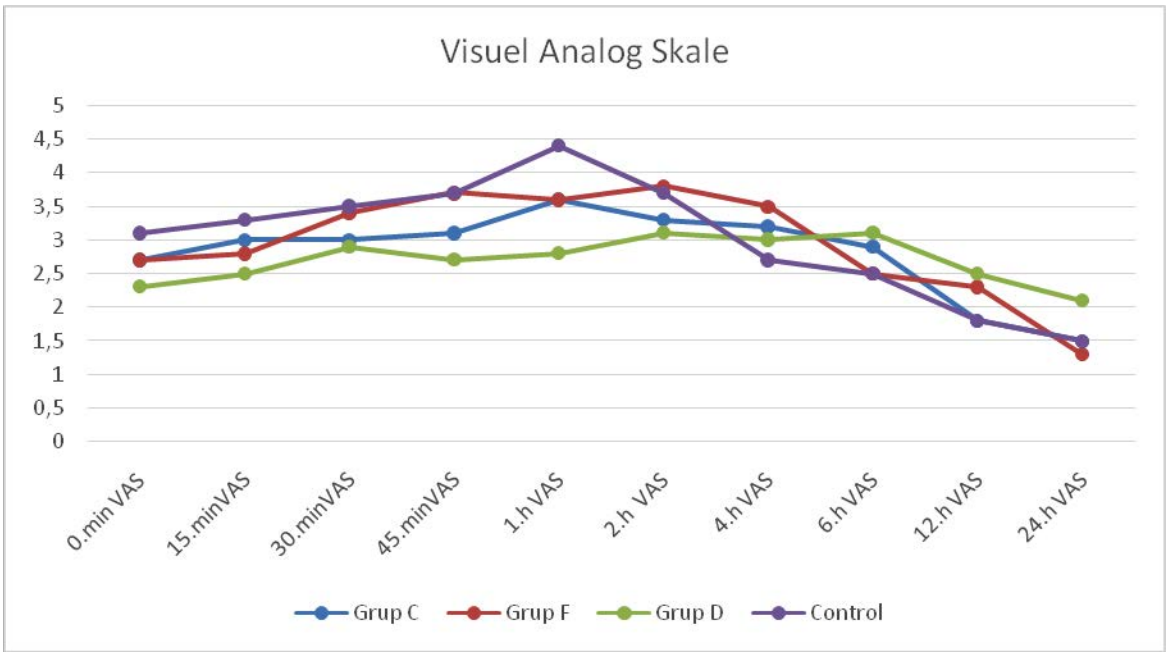

Figure 2. Change of VAS value according to time for each group.

in control group. At the end of 24th hour, although mean VAS value was found mildly higher in Group D compared to other groups, the difference was not statistically significant (P = 0,166). Alteration in VAS according to time is graphed in Figure 2.

DISCUSSION

Pain and burning sensation at the incision site are most prominent in the early postoperative period after lumbar disc operations [14]. The pain experienced during this early period is related to incision length and the duration of retraction. Kotil *et al*. [15] reported that continuous retraction increased serum creatine phosphokinase levels and postoperative pain when compared to intermittent retraction during discectomy operations, and Shin *et al*. [16] reported that the microendoscopic technique reduced postoperative pain by hindering iatrogenic tissue injury. These results suggest that the tissue injury that occurs during microdiscectomy may be related to postoperative pain. Moreover, moderate to severe pain following surgery may have negative effects on the pulmonary system (e.g., atelectasis, pulmonary edema, or hypoxemia) and cardiovascular system (e.g., arrhythmia, increased systemic vascular resistance, hypertension, or myocardial infarction). Such pain may also increase the risk of thromboembolism due to hindered early mobilization [4, 5, 7, 9, 17]. On the other hand, effective postoperative pain reduces morbidity and mortality rates [9, 10, 14].

Cherian *et al*. [18] reported that 0.375% bupivacaine applied to the wound in lumbar discectomy operations provided analgesia within the first nine postoperative hours in all cases. Ersayli *et al*. [9] reported a first analgesia need time similar to ours with a bupivacaine and steroid combination in lumbar discectomy operations. In their study investigating the influence of 0.25% bupivacaine, ropivacaine, and saline administered to the subcutaneous tissue and paraspinal muscles during wound closure following lumbar discectomy, Hernandez-Palazon *et al*. [19] reported a longer analgesia time in the bupivacaine group compared to the ropivacaine and saline groups.

The recent study by Puffer *et al*. [20] demonstrated that infiltrating 10cc of 0.5% bupivacaine with epinephrine under the skin and 40cc of a 50:50 mixture of liposomal bupivacaine and 0.5% bupivacaine without epinephrine in the subcutaneous tissue significantly decreased the time of intravenous narcotic pain medication. They also reported no significant differences in VAS scores or total morphine equivalents [20]. In a similar vein, Jackson Kim *et al*. [21] reported that liposomal bupivacaine was very

useful for pain control and reduced narcotic need and hospital stay in their studies that compared the local infiltrative effects of liposomal bupivacaine and nonliposomal local anesthetics in patients who underwent transforaminal lumbar interbody fusion.

In our study, we observed that bupivacaine provided significantly lower VAS values in the early postoperative period and significantly longer first analgesic need at a 0.5% concentration and in amounts of 2.8, and 10 ml applied to the dura, fascia, and subcutaneous tissues, respectively. Wound infiltration with bupivacaine resulted in a reduction of analgesic need and postoperative pain without the development of complications. We concluded that bupivacaine applied as doses of 2, 8, and 10 ml at a 0.5% concentration to the dura, fascia, and subcutaneous tissues, respectively, provided effective and safe pain control for the postoperative management of lumbar pain due to incision and retraction during lumbar disc hernia operations.

CONCLUSION

In this study, we aimed to achieve early discharge and early return to normal, daily activities through simple, safe, and inexpensive postoperative pain treatment independent of non-steroidal anti-inflammatory or opioid analgesic side effects by comparing the infiltrative anesthesia effects of bupivacaine in different compartments in lumbar discectomy operations. Wound site infiltration is one of the simplest and most effective ways of managing postoperative pain, and many reports have been published about this topic [9-12]. Bupivacaine, at a concentration of 0.5%,administered to the dura, fascia, and subcutaneous tissue may be used as an effective and safe pain management method following lumbar discectomy operations for patients who suffer gastrointestinal side effects from systemic analgesics.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2019;5(5):793-799 ORIGINAL ARTICLE

The efficacy of homeopathic *Arnica montana* 200 CH on dental surgical treatments: a double-blind, placebo-controlled study

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ABSTRACT

Objectives: The aim of this placebo-controlled study was to assess the efficacy of single dose homeopathic *Arnica montana* 200 CH in dental surgeries.

Methods: The study included 79 patients undergoing wisdom teeth extractions, implant placements, cystectomies, augmentation procedures, alveoloplasties, lefort-1 osteotomies at Istanbul Medipol University's Department of Oral and Maxillofacial Surgery. The patients were randomly divided into two groups using a computer program. Three globulesof *Arnica montana* 200 CH were administered in the sublingual area in the patients group 1, and glucose globules were administered in the sublingual area in the patients into group 2. After each patient's surgical operation, the surgeoncompleted a survey about operation time and scope. In addition,a self-assessment survey was completed by the patients the day after their operationsto evaluate their post-operational swelling and pain.

Results: *Arnica montana* did not appear to significantly prevent post-operative swelling and pain when compared to the placebo ($p < 0.05$).

Conclusions: This study showed that the use of *Arnica montana* before a physically traumatic procedure is not more effective than the use of a placebo. However, the results should be evaluated in other studies, including the administration of *Arnica montana* after a physically traumatic procedure to clearly demonstrate its homeopathic efficiency.

Keywords: Homeopathy, *Arnica montana*, placebo effect, dental surgery

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Homeopathy is an alternative source of medicine that was created by Samuel Hahnemann in 1796. "*Simila Similibus Curentur*" (like cures like) was the main part of Hahnemann's theory. He believed that a substance that causes the symptoms of a disease in healthy people could heal similar symptoms in sick people [1-3]. Homeopathic drugs or remedies are produced by systematic repetitive dilution in alcohol or distilled water [4]. These dilutions, called potencies,continue until none of the original substance's molecules are left the liquid. However, the solution remembers information from the original substance but it is controversial [5]. Homeopaths evaluate their patients' medical situations and life histories and choose appropriate remedies from a reference book. The remedies are often prepared from plants,

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minerals, or animals in the form of sugar pellets [6].

Homeopathy is an adjuvant therapy used in medicine. *Arnica montana*, commonly referred to as leopard's bane, is a homeopathic remedy used for preventing traumatic pain and edema. *Arnica montana*'s roots have many anti-inflammatory substances as well as thymol, which is fungicide. It has been used in alternative medicine for centuries and is very popular with patients undergoing surgery [6]. The globules *Arnica montana* globules are absorbed in once and allowed to slowly dissolve under the tongue. It is advised not to touch pellets or homeopathic globules with your fingers.

Homeopathy (HP) is used for a number issues in dentistry, including teething, dental abscesses, toothaches, surgical traumas, and nervousness or anxiety [7]. Homeopathic remedies are used by dentists as adjunct to other in daily practice, and many dentists are also homeopathstoo[4, 8]. Pinsent *et al*. [9] reported a reduction in pain when homeopathic *Arnica montana* was used in dental extractions. However, many clinicians have reported that no significant difference was found inplacebo-controlled studies that use homeopathic remedies [6].

This study investigated the efficacy of single-dose homeopathic *Arnica montana* 200 CH on dental surgical treatments. The placebo effects are also summarized.

METHODS

The patients, whosought wisdom teeth extractions, implant placements, cystectomies, augmentation procedures, alveoloplasties, and lefort-1 osteotomies at Istanbul Medipol University's Department of Oral and Maxillofacial Surgery and were ages 18 to 75 with no systemic diseases of both genders were chosen for the study. The exclusion criteria were: patients had used antibiotics and non-steroidal anti-inflammatory within the last 6 months. All the patients completed an informed consent. This study was approved by the Istanbul Medipol University Animal Care and Ethics Committee (Document number 350 from the Ministry of Health, Republic of Turkey).

First, the patients were divided into two groups using a computer program. The *Arnica montana* globules were prepared and classified into X and Y groups by a homeopath. The placebo and *Arnica montana* globules were given to the patients by a surgeon who did not know which participants were in groups X and Y. *Arnica montana* 200 CH globules were administered in the sublingual area in the patients in group 1. Glucose globules that seemed to be the same as *Arnica montana*, which was diluted with alcohol and distilled water, were given administered in the sublingual area in the patients in group 2. Three globules were placed in the patients' sublingual areasusing a plastic spoon15 minutes before their operations. Non-steroidal anti-inflammatory drugs (NSAID, flurbiprofen, 300 mg) and antibiotics (amoxicillin, 1g) were also prescribed to all the patients after their surgeries. Both groups took the same dose of NSAIDs and antibiotics. The patients completed a surveythe day after their surgical procedures (Table 1), and the results were evaluated using a four point scale. All surgical operations were achieved by two surgeons. The surgeon's observations about the scope and times of the operation werealso evaluated on a four point scale (Table 2). The operation type (conventional or piezo surgery) was also recorded.

A self-assessment questionnaire was given to the patients after their surgical procedures. The questionnaire asked the patients about the presence of pain, postoperative edema, sleep disorders, dysphagia, dysphonia, and daily activity disorders. These parameters were evaluated on afour-point scale ranging from 0 to 3, where'' 0'' was: not affected, ''1'' was mildly affected, ''2'' was moderately affected, and ''3'' was severely affected.

Table 1. Patients' self-assessment questionnaire for the day after the surgical operation

	Day after the surgical operation
Presence of pain	
Edema	
Sleeping disorders	
Dysphagia	
Dysphonia	
Daily activity disorders	
0: NOT AFFECTED	
1: MILDLY AFFECTED	
2: MODERATELY AFFECTED	
3: SEVERELY AFFECTED	

Table 2. Questionnaire for the surgeons' opinions about the operation.

Patient Group				
Name-Surname				
Age				
Gender				
Operation Option	**Conventional Yes**	**Piezo-Surgery No**		
Post-Op Emergency				
Observations from Operation	**Same**	**Better**	**Worse**	**No Idea**
Scope of the Operation				
Operation Time				
0 – Any Sight				
1 – Poor View				
2 – Good View				
3 – Excellent View				

Statistical Analysis

The study adopted a double-blinded design. A Mann Whitney U test was used for statistical analysis. The qualitative variants were evaluated using Pearson Ki-square and Fisher Ki- square tests. Statistical significance was $p < 0.05$.

RESULTS

A total of 100 patients were included the study but 6 patients were eliminated because theydid not meet the age criteria. In total, 94 patients were randomized. In the study, 5 patients in the *Arnica montana* group

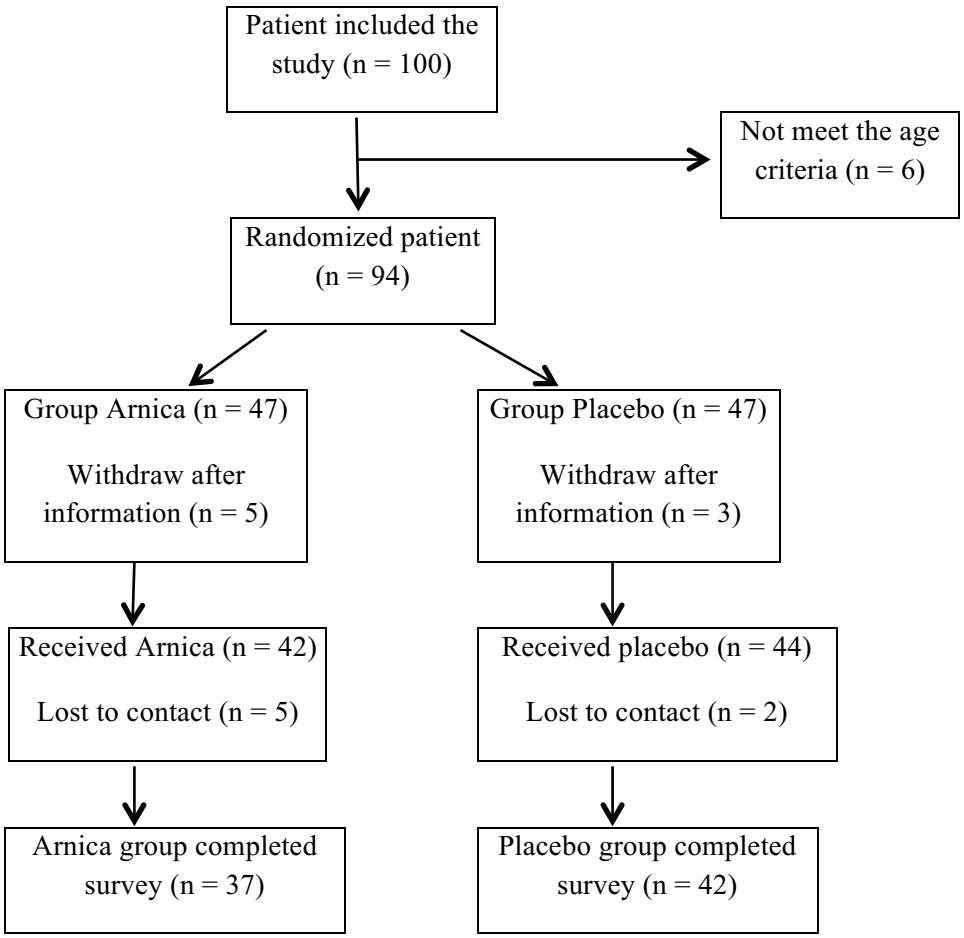

Figure 1. CONSORT flow chart of the study

Table 3. Gender distributions of the patients

			Gender		*p* value
			Female	Male	
Group	Arnica	n (%)	19 (51.4)	18 (48.6)	0.473
	Placebo	n (%)	26 (61.9)	16 (38.1)	
Total		n (%)	45 (57.0)	34 (43.0)	

Table 4. Age distributions of the patients

	Group	N	Median	Minimum	Maximum	*p* value
Age	Arnica	37	38.00	20	73	0.217
	Placebo	42	34.00	18	75	

and 3 patients in the placebo group were withdrawn after information about the present study. In addition 5 patients in *Arnica montana* group and 2 patients in the placebo group did not return for their self-assessment surveys. Therefore, the *Arnica montana* group (Group 1) included 37 patients and the placebo group (group 2) included 42 patients (Figure 1). In the study, 45 patients were female and 34 patients were male (Table 3).

The average age was 34 years in plasebo group and 38 years in Arnica group. There is no statistically significant difference in demographic distributions (Table 4).

Wisdom teeth extraction of 38 patients, implant placement of 28 patients, sinus lifting of 6 patients, oral cystectomy of 4 patients, alveoloplasty 1 patient and bone augmentation of 2 patients were performed in this study. No significant difference was found between patient groups (Table 5).

Surgeon experiences foroperation time and purview of the operation area during surgery were recorded after surgery. No significant difference was found between two groups (Table 6).

Patients who applied emergency service with unexpected reason were recorded. One patient in Arnica group (group 1) was applied emergency service with unexpected vomiting and nausea. The reason of this situation was not identified. No statistical significant difference was found between two groups.

There was no any significant difference in pain intensity between the groups on 24 hours. In addition there were not any significant differences between the groups swelling, regarding sleeping, eating, phonetics, and daily routine and missed work at above mentioned time intervals (Table 7).

Table 5. Performed different surgery operations*

Group	Surgery Options					
	Wisdom Teeth Extraction	Implant Placement	Sinus Lifting	Oral Cystectomy	Alveoloplasty	Bone Augmentation
Arnica, n (%)	17 (45.9)	13 (35.1)	3 (8.1)	3 (8.1)	0	1 (2.7)
Placebo, n (%)	21 (50.0)	15 (35.7)	3 (7.1)	1 (2.4)	1 (2.4)	1 (2.4)
Tota, n (%)	38 (48.1)	28 (35.4)	6 (7.6)	4 (5.1)	1 (1.3)	2 (2.5)

*$p = 0.897$

Table 6. Surgeon experience*

			Surgeon experience for operation time and purview of the operation area during surgery			
			Same	Better	Worse	No Idea
Group	Arnica	n (%)	31 (83.8)	4 (10.8)	2 (5.4)	0
	Placebo	n (%)	30 (71.4)	6 (14.3)	5 (11.9)	1 (2.4)

*$p = 0.586$

Table 7. Evaluation of patients' self-assessments survey of next day after surgery

	Groups		Never	Mild	Moderate	Severe	*p* value
Pain	Arnica	n (%)	14 (37.8)	18 (48.6)	3 (8.1)	2 (5.4)	1.000
	Placebo	n (%)	15 (35.7)	21 (50.0)	4 (9.5)	2 (4.8)	
Post-operative swelling	Arnica	n (%)	13 (35.1)	17 (45.9)	5 (13.5)	2 (5.4)	0.962
	Placebo	n (%)	16 (38.1)	19 (45.2)	6 (14.3)	1 (2.4)	
Sleeping	Arnica	n (%)	32 (86.5)	3 (8.1)	1 (2.7)	1 (2.7)	0.742
	Placebo	n (%)	35 (83.3)	4 (9.5)	3 (7.1)	0	
Eating	Arnica	n (%)	17 (45.9)	16 (43.2)	2 (5.4)	2 (5.4)	0.799
	Placebo	n (%)	17 (40.5)	20 (47.6)	4 (9.5)	1 (2.4)	
Phonetics	Arnica	n (%)	28 (75.7)	7 (18.9)	1 (2.7)	1 (2.7)	0.274
	Placebo	n (%)	29 (69.0)	13 (31.0)	0	0	
Daily routine and missed work	Arnica	n (%)	32 (86.5)	2 (5.4)	1 (2.7)	2 (5.4)	0.137
	Placebo	n (%)	33(78.6)	8 (19.0)	1 (2.4)	0	

DISCUSSION

Because HP is an individual treatment,it is very difficult to achieve an evidence-based study. HP treats the person, not the disease. In allopathic medicine given drugs related with the disease is contrary to the doctrine of Hahnemann. However in emergency cases HP drugs can also be used to relieve the symptomatic ailments [10]. *Arnica montana*, in allopathic medicine, is commonly used after acute trauma or operation to soothe pain, bleeding and swelling. *Arnica montana* is the most known remedy in homeopathy which is used at edema and trauma cases and it also can be easily found in the market.Usage of Arnica globules is only oral way for sublingual area. The dose was chosen on the recommendation of the homeopath. It's a common using of *Arnica montana* for dentistry. The hypothesis of our study is that use of *Arnica montana* could be helpful for reduction of post-operative pain and edema at dental surgical operation and could provide better operation conditions such as less bleeding for surgeon. However our findings indicated that single dose of *Arnica montana* 200 CH do not bring any change in post-operative conditions for surgeon and patients. In our study *Arnica montana* 200 CH was applied 15 minutes before the operation. No evidence was found relating with its decreasing or increasing the bleeding during the operation. It was found out that when compared with placebo, *Arnica montana* decreased pain and swelling to some extend but not a degree of statistical significance. Unfortunately *Arnica montana* could be more effective when gives post operation. In addition more than one dose is more potent from single dose. This is the biggest shortcoming of our study. We believe that lack of methodology of the study make the *Arnica montana* inactive. However using of NSAID and antibiotics may affect edema and pain naturally so the results can be easily affected at both of two groups.

In a randomly double blind study carried out by Caziro [6] in order to decrease the post-op complications of metronidazole, *Arnica montana* 200 CH and placebo were given to 118 patients who had their tooth extracted. In the decrease of pain and edema, there was no statistical difference between placebo and arnica but metronidazole was more effective. The reason for this is that metronidazole provides a better infection control. In our study no significant difference was found between the two groups. In their study, Pinsent *et al*. [9] showed a decrease in the bleeding and pain after the tooth extraction of 59 patients, using *Arnica montana* made no difference in terms of bleeding but was more effective in terms of pain.

Mazzocchi and Montanaro [11] observed a decrease in pain and swelling on 200 patients who were given another HP remedy of *Sympthytum* 5CH when they received dental implants. However study design was not a controlled prospective, it was retrospective. In a random study investigating the effect of using different dosage of *Arnica montana* on pain and swelling control after hand surgery, Stevinson *et al*. [12] found out that when compared with placebo no statistical difference was found in decreasing pain

and swelling. However the number of patients wasn't statistically enough for the study. In their random controlled study with 111 patients who had tonsillectomy surgery, Robertsson *et al*. [13] gave *Arnica montana* 30CH to patients and compared the results with the placebo group. As a result, *Arnica montana* showed a little difference in decreasing the pain but no statistical difference was found.

In a study carried out on 343 patients who had orthopedic arthroscopy, knee prosthesis and cruciate ligament reconstruction, *Arnica montana* was given for pain control and the results were compared with the group placebo applied. As a result in the group who were given *Arnica montana*, a significant difference was observed in decreasing swelling. In addition to this, a statistical difference was observed in decreasing pain in the group who had cruciate ligament reconstruction [3]. In another controlled study the effectiveness of *Arnica montana* was assessed on acute inflammation in the rats [2]. Less edema was observed on the group who took *Arnica montana* before the process then the group who took *Arnica montana* after the process. Also in a study investigating the effect of *Arnica montana* to the chronic inflammation in animals, a statistically significant decrease was observed in inflammation in the group which took arnica before the process [13].

Piezoelectric surgery techniques areminimally invasive techniques that reduce the risk of damage to soft tissues and important structures, such as nerves, blood vessels, and mucosa, so piezoelectric surgery help better healing. This surgery also reduces damage to osteocytes during the operations[14]. Even though it has been suggested that the use of a piezoelectric device provides distinct advantages in the surgical operations, it should not be forgotten that long operation time and heat generation during bone cutting decrease healing procedures [15]. In our study, we have no data on the postoperative effect of both surgical methods. We think that it does not directly affect the surgical outcomes because of advantages and disadvantages of both methods.

There is limited data on homeopathy in medicine and dentistry. Since the studies carried on were in inadequate in terms of the number of the subjects and because of the methodological errands homeopathy did not give enough scientific evidence [16]. The fact that we used different types of anti-inflammatory, antibiotics and anesthetic substances on patient in pre and post operation periods might affect the results. In addition, the patients weren't classified into age and other ailment and symptom groups. Applying for an operational procedure, every patient aged 18-75 and not having any serious systemic disease was included into the study. *Arnica montana* was given just before the operation and one day later the patients were assessed with 4 point assessment scale. However, homeopathic remedies recovering are observed as the person's subjective well-being. Testing subjective well-being could have made the study more meaningful.

Human being is positively or negatively affected with many audio stimulants. Although the studies performed on the patients are double blind designed, the patients always think that they are taking something which will make them well [17]. This is named as the placebo effect which is identified as a substance which increases the healing of the illness despite of having no healing effect [18]. Since Beecher stated that the effect of placebo on healing was 30%, academic circles have accepted this as such but it is known that the placebo affect can change between 0% and 100%. Even the posture and voice tone of the clinician can change the expectation of the patient and these types of differences affect the homeopathic treatment to a great extent [19].

Limitations

Our study is a placebo controlled one but how much the placebo affects our study is obscure. However, it is clearly observed that pain, swelling and discomfort are less than expected in both groups. The number of those who were affected from pain and swelling in high quantity ranged between 2.4% and 5.4%. Some researchers especially against the homeopathy believe that homeopathic remedies only make placebo effect.We believe that results cannot be evaluated a scientific failure because planning of methodology is not enough to understand homeopathic effect. In addition new study models can be created especially included pre and post-operative homeopathic medication for explain the all properties of *Arnica montana* clearly in later studies. Moreover, it is necessary to investigate the potency, time and the way of giving homeopathic remedies.

CONCLUSION

When compared with placebo group, no statistical difference was found in the group who took a single dose of Arnica montana before 15 minutes from the operation especially using NSAID and antibiotics. What's more, our study has proved that when compared with placebo, the usage of *Arnica montana* is neither superior nor shows a negative effect. However, the results must be evaluated by taking into consideration that they are just one in the few studies done in this field.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

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The European Research Journal 2019;5(5):800-808 ORIGINAL ARTICLE

Evaluation of high molecular weight cytokeratin (HMWCK), p27, C-X-C chemokine receptor type 4 (CXCR-4) and stromal cell-derived factor 1 (SDF-1) expressions related to tumor progression in breast cancer

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ABSTRACT

Objectives: Breast cancer is the most common cancer and the most common reason for cancer death in women population. The immunohistochemical markers which could have prognostic information are always needed.
Methods: This study included 365 cases of invasive ductal carcinoma (IDC), ductal carcinoma in situ (DCIS) and ductal epithelial hyperplasia. The cases divided into the following two groups according to the presence of cancer: 1) cancer group (298 cases; cases with IDC and DCIS), 2) non-cancer group (67 cases without cancer; cases with usual ductal epithelial hyperplasia [UDH] and atypical ductal epithelial hyperplasia [ADH]). All histological slides stained with high molecular weight cytokeratin (HMWCK), p27, C-X-C chemokine receptor type 4 (CXCR-4), stromal cell-derived factor 1 (SDF-1) immunohistochemically.
Results: IDC was present in 277 cases, of which 213 had pure IDC, and 64 had DCIS component adjacent to the invasive tumor. Twenty-one cases had only DCIS. Of 67 cases with epithelial hyperplasia, 31 had ADH, and 36 had UDH. Among cases with IDC, 143 had lymph node excision, of which 73 had metastasis in one or more lymph nodes, and 70 did not have metastatic disease. The expression of p27 was found to be significantly lower in the cancer group as compared to that in the non-cancer group ($p < 0.0001$). CXCR-4 expression in IDC was found to be higher than that of DCIS group. SDF-1 expression was observed to be significantly higher in cancer cases than that of non-cancer cases ($p = 0.03$).
Conclusions: The higher CXCR-4 and SDF-1 expressions are associated with tumor progression, tumor size, and lymph node status. In benign proliferative lesions, both HMWK and p27 expressions were helpful in differential diagnosis of borderline atypical ductal hyperplasia and DCIS.

Keywords: CXCR-4, SDF-1, p27, HMWCK, benign proliferative breast lesions, ductal carcinoma in situ, invasive ductal carcinoma, tissue microarray

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Breast cancer is the most common cancer type and the leading cause of cancer-related deaths in women. Invasive ductal carcinoma (IDC) constitutes the largest group of malignant breast tumors. Precursor lesions of IDC can be found around the primary tumor mass in mastectomy specimens as well as in biopsy

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specimens obtained from patients presenting with the complaint of breast mass [1, 2]. Precancerous lesions of the breast include usual ductal epithelial hyperplasia (UDH), atypical ductal epithelial hyperplasia (ADH), and ductal carcinoma in situ (DCIS). Women with UDH have 2.5 times lower risk of subsequent cancer development as compared to those with ADH, the later stage of UDH [3]. It is known that these lesions are in fact part of a progressive process, which shows continuity and the steps of which are not explicit. In breast cancer, which is a biologically heterogeneous disease with a clinical course that may vary from slow to rapid progression, immunohistochemical markers are needed to predict prognosis and metastatic disease and to overcome problems associated with differential diagnosis [4].

Cytokeratins are intracellular fibrous proteins found in almost all epithelial tissues. There exist at least 20 subtypes defined according to the molecular weight. High molecular weight cytokeratin (HMWCK), also known as 34βE12, is specific to keratin in basilar cells [5]. Its expression is of benefit in the differential diagnosis of benign lesions such as UDH or ADH, which maintain basal differentiation character. Some researchers observed a decrease in the expression of HMWCK in the order of UDH, ADH and DCIS lesions and advocated that this marker could be useful in the differential diagnosis of intraductal proliferative lesions of the breast [5].

In cell cycle, p27 possesses a key role. It is known that apoptosis regulator Bcl-2 affects cell cycle progression by increasing p27 levels [6]. The decrease in the expression of p27 protein has been reported correlated with poor prognosis, disease recurrence, and disease-related deaths in patients with early-stage breast cancer, and decreased expression of p27 has been supported to be an independent indicator of poor prognosis [7]. In various studies, decreased p27 expression suggested being an important option for targeted therapy in cancer treatment [8].

The chemokines are small molecules from the chemo-attractive cytokine family. They are divided into four subgroups, according to their characteristic residual cysteine component, as α (C-X-C), β (C-C), γ (C) and δ (C-X-X-X-C) [9]. SDF-1, or CXCL-12, is a member of chemokine α subgroup and is the sole ligand ever known of G-protein coupled chemokine receptor called CXCR-4 [10, 11]. SDF-1 is produced in many organs including lungs, liver, bones, brain, thymus and lymph nodes, basically by the stromal cells [12]. Disruption in the SDF-1/CXCR-4 interaction negatively affects the development of hematopoietic, cardiovascular and neural systems, leading, in turn, to defective embryonic development [13].

In the present study, we aimed to evaluate the prognostic value of HMWCK, p27, CXCR-4 and SDF-1 markers in benign proliferative diseases, DCIS, and IDC immunohistochemically. As well as the utility of these markers in eliminating the problems associated with a differential diagnosis of these diseases and in tumor progression steps.

METHODS

Case Selection

A review of all modified radical mastectomy specimens, excisional breast biopsies, and needle core biopsies of the breast that evaluated between 2006 and 2008. The cases divided into the following two groups according to the presence of cancer: 1) cancer group (298 cases; cases with IDC and DCIS), 2) non-cancer group (67 cases without cancer; cases with UDH and ADH). Among five hundred and thirty-five breast biopsies, three hundred and ninety-six cases with the diagnosis of UDH, ADH, DCIS, and IDC selected, and 365 cases which were suitable for tissue microarray, included in the study.

The ethical review committee of Gazi University Medical Faculty approved the study. The authors declare that they had all necessary consent from any patients involved in the study.

Tissue Microarray and Preparation of Paraffin Blocks

Tissue microarray (TMA) is a method that allows for analysis of multiple tissues from different patients or different blocks on the same slide by obtaining tissue cores fromconventional paraffin blocks [14]. During the examination of breast biopsies, we choose four representative microscopic fields of the lesion. We removed tissue cores from the marked fields in paraffin-embedded donor blocks using a 0.1-cm needle (Veridiam advanced tissue arrayer, VTA-100, USA). We arrayed these tissue cores into a recipient TMA block. Accordingly, we constructed 22 TMA

paraffin blocks each containing 20 different tissue cores (on average). Paraffin blocks were sectioned at 5 µm, and sections were then mounted on polylysine-coated slides.

Immunohistochemical Staining and Evaluation

Staining was performed using three-step indirect streptavidin-biotin immunoperoxidase method to determine HMWCK, p27, CXCR-4 and SDF-1 expression. HMWCK (Thermo Scientific, Mouse monoclonal IgG1, Runcorn. Cheshire, UK), p27 (Thermo Scientific p27 Kip1, Runcorn. Cheshire, UK), CXCR-4 (Santa Cruz, Fusin H-118, CA, USA) and SDF-1 (Santa Cruz, P-159X, CA, USA) antibodies were diluted 1:50 in phosphate buffered saline (pH 7.4, PBS). Biotinylated secondary linking antibody, streptavidin-biotin complex, and the chromogens 3,3'-diaminobenzidine (DAB) and 3-amino-9-ethylcarbazole (AEC) were available as ready-to-use commercial kits. Cytoplasmic staining for HMWCK, CXCR-4, SDF-1 and nuclear staining for p27 were considered positive in the evaluation of immunohistochemical staining. Normal skin, normal spleen and normal liver tissues used as a positive control for HMWCK, CXCR-4 and SDF-1 antibody, respectively, whereas prostaticadenocarcinoma and normal prostate tissue selected as positive controls for the p27 antibody. The staining intensity and extensity noted as percentages.

Statistical Analysis

Multi-group comparisons were performed using analysis of variance (ANOVA) for normally distributed numerical variables and the Kruskal-Wallis test for non-normally distributed variables. Paired comparisons were carried out using the Student's t-test for normally distributed numerical variables and the Mann-Whitney U test for non-normally distributed numerical variables. A p-value < 0.05 was considered statistically significant. In subgroup analyses, the level of significance was evaluated with Bonferroni-corrected p values. The Statistical Package for Social Sciences (SPSS, Inc., Chicago, IL, USA) version 12 was used in statistical analyses.

RESULTS

Three hundred and sixty-five cases included in the study. IDC was present in 277 cases, of which 213 had pure IDC,and 64 had DCIS component adjacent to the invasive tumor. Twenty-one cases had DCIS. Of 67 cases with epithelial hyperplasia, 31 had ADH, and 36 had UDH. Of 298 cases with IDC and DCIS, 157 were mastectomies, and excisional biopsy specimens and 141 were needle biopsy specimens. Data on tumor diameter was available only for mastectomy or excisional biopsy specimens. Of 157 cases, tumor diameter was ≤ 2 cm in 80 cases and > 2 cm in 77 cases. Among cases with IDC, 143 cases had lymph node excision, of which 73 had metastasis in one or more lymph nodes,and 70 did not have metastatic disease.

The intensity of staining with HMWCK, p27, CXCR-4 and SDF-1 antibodies was 14%, 10%, 15% and 23% in average in the UDH group, 20%, 18%, 15% and 33% in the ADH group, 5%, 3%, 37% and 50% in the DCIS group, 5%, 4%, 34% and 33% in the IDC group without DCIS component, and 8%, 6%, 43% and 34% in the IDC group with DCIS component

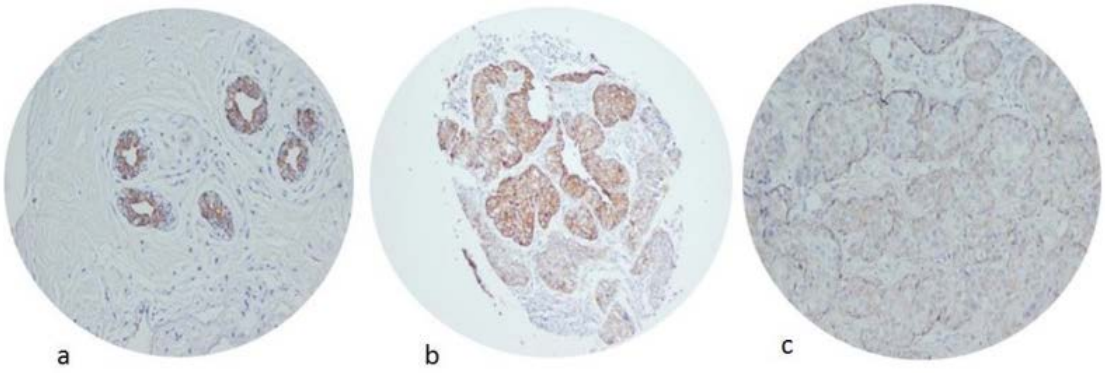

Figure 1. HMWCK expression was found to be higher in the UDH (a) and ADH (b) group than in the IDC (c) group. (a) HMWCK ×100, (b) HMWCK ×40, and (c) HMWCK ×100.

Table 1. Distribution of HMWCK, p27, CXCR-4 and SDF-1 expressions according to the cases

	No of cases	Staining intensity (mean of %)				*p value*			
		HMW CK	p27	CXCR-4	SDF-1		HMWCK	p27	CXCR-4	SDF-1
UDH	36	14 ± 19	10 ± 17	15 ± 23	23 ± 28	**ADH**	0.55	**0.001**	0.66	0.21
						DCIS	**0.03**	0.29	**0.04**	**0.004**
						IDC (w/o DCIS)	**0.0007**	**0.005**	**0.001**	**0.01**
						IDC (w/ DCIS)	**0.02**	0.48	**0.00001**	0.07
ADH	31	20 ± 28	18 ± 14	15 ± 27	33 ± 32	**DCIS**	**0.01**	**0.0001**	**0.04**	0.06
						IDC (w/o DCIS)	**0.0001**	**0.0001**	**0.001**	0.65
						IDC (w/ DCIS)	**0.006**	**0.0001**	**0.00001**	0.75
DCIS	21	5 ± 11	3 ± 4	37 ± 39	50 ± 38	**IDC (w/o DCIS)**	0.91	0.13	0.91	0.06
						IDC (w/ DCIS)	0.66	0.66	0.40	0.12
IDC w/o DCIS	213	5 ± 15	4 ± 10	34 ± 34	33 ± 28	**IDC (w/ DCIS)**	0.56	**0.004**	0.03	0.98
IDC w/ DCIS	64	8 ± 21	6 ± 11	43 ± 33	34 ± 32	**IDC (w/o DCIS)**				

HMWCK = high molecular weight cytokeratin, CXCR-4 = C-X-C chemokine receptor type 4, SDF-1 = stromal cell-derived factor 1, UDH = Usual ductal hyperplasia, ADH = Atypical ductal hyperplasia, DCIS = Ductal carcinoma in situ, IDC w/o DCIS = Invasive ductal carcinoma without DCIS, IDC w/ DCIS = Invasive ductal carcinoma with DCIS

Table 2. Distribution of HMWCK, p27, CXCR-4 and SDF-1 expressions according to other variables.

	No of cases	Staining intensity (%)				*p value*			
		HMWCK	p27	CXCR-4	SDF-1	HMWCK	p27	CXCR-4	SDF-1
Presence of cancer									
Cancer	298	6 ± 16	4 ± 10	36 ± 34	34 ± 30	**< 0.0001**	**< 0.0001**	**< 0.0001**	**0.03**
Benign	67	17 ± 24	14 ± 16	15 ± 25	27 ± 30				
Tumor diameter									
2 cm ↓	80	7 ± 18	5 ± 11	34 ± 34	34 ± 28	0.14	0.16	0.10	0.45
2 cm ↑	77	6 ± 18	2 ± 7	42 ± 31	29 ± 25				
Lymph node metastasis									
Present	73	6 ± 16	4 ± 11	39 ± 33	34 ± 27	0.93	0.07	0.61	0.23
None	70	8 ± 20	4 ± 8	37 ± 33	30 ± 28				

HMWCK = high molecular weight cytokeratin, CXCR-4 = C-X-C chemokine receptor type 4, SDF-1 = stromal cell-derived factor 1

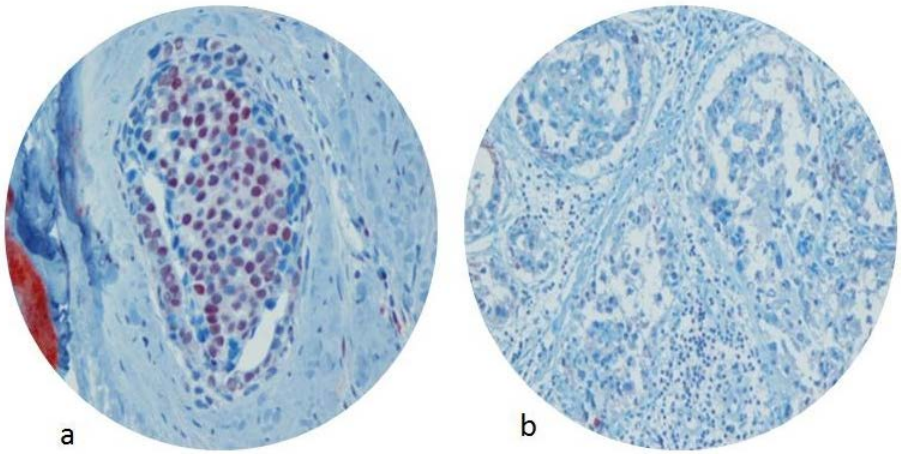

Figure 2. The expression of p27 was found to be significantly higher in the non-cancer group (a) as compared to that in the cancer group (b). (a) p27 ×200 and (b) p27 ×200.

(Table 1). Also, HMWCK, p27, CXCR-4 and SDF-1 expressions compared with the presence of cancer, lymph node metastasis status and tumor diameter (Table 2).

In the present study, there was no significant difference between the UDH and ADH groups regarding HMWCK expression; however, both epithelial hyperplasia groups exhibited significantly higher staining intensity as compared to the IDC group ($p < 0.005$ for each) (Figure 1). The expression of p27 was found to be significantly lower in the cancer group as compared to that in the non-cancer group ($p < 0.0001$) (Figure 2). Furthermore, p27 expression was significantly higher in the ADH group when compared individually to the IDC and DCIS groups ($p < 0.0001$) for each. When the epithelial hyperplasia groups compared, p27 expression found higher in the ADH group than that in the UDH group.We could not find a significant association between tumor size and HMWCK or p27 expression or between the presence of metastatic disease and HMWCK or p27 expression.

After DCIS step, CXCR-4 receptor expression increased markedly ($p < 0.001$) through carcinogenesis. CXCR-4 expression in IDC was found to be higher than that of DCIS group (Figure 3). Although it wasn't statistically significant, a directly proportional increment between CXCR-4 expression and the presence of lymph node metastasis and the increase in tumor diameter was detected. SDF-1 expression was observed to be significantly higher in cancer cases than that of non-cancer cases ($p = 0.03$) (Figure 4). It is remarkable that each group in the cancer cases showed more SDF-1 expression than ADH and UDH groups. In epithelial hyperplasia group, SDF-1 expression was found to be higher in ADH group than UDH group. Also, SDF-1 expression was also higher in tumors with lymph node metastasis.

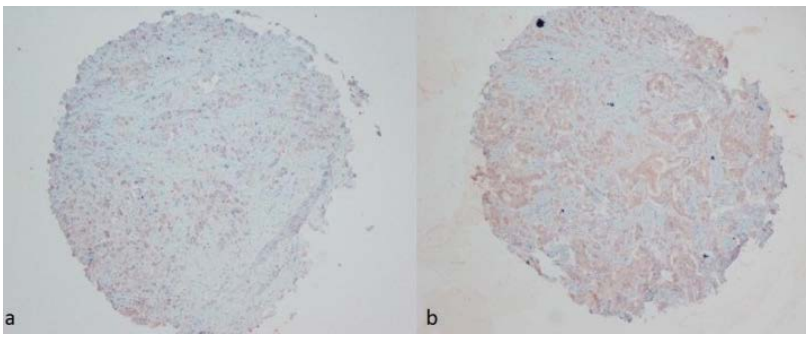

Figure 3. Comparison between the ADH (a) and IDC (b), CXCR-4 receptor expression increased markedly after DCIS step, through carcinogenesis [CXCR-4 stain (a) ×40, (b) ×40].

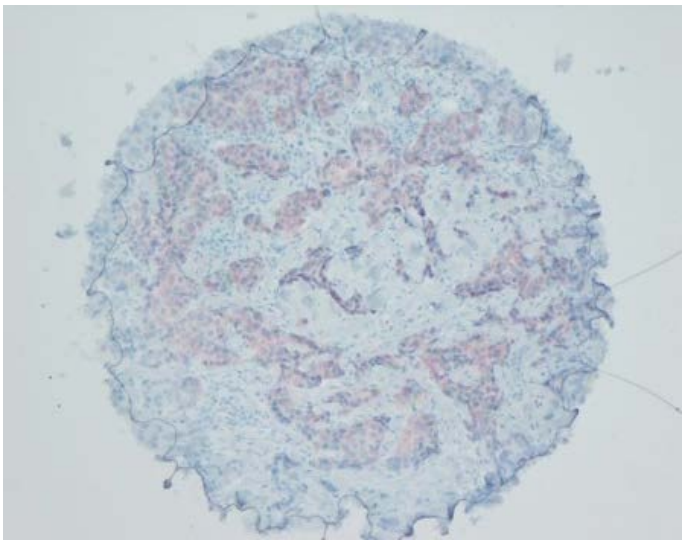

Figure 4. SDF-1 expression was observed to be significantly higher in cancer cases (SDF-1 stain ×40)

DISCUSSION

Breast cancer is a biologically heterogeneous disease. Clinical parameters associated with prognoses such as tumor size and lymph node status are utilized [15]; however, there is still research on markers that could predict clinical course in patients with negative lymph nodes.

In the carcinogenesis of breast cancer, it is known that ADH progress to DCIS with an increase in atypia and eventually to invasive carcinoma [16]. It has been demonstrated that cases with DCIS have chromosomal instability similar to those with IDC and low/moderate- and high-grade DCIS have different small chromosomal changes [17]. Transition across these steps may not be explicit. Differentiation between ADH and DCIS or between DCIS and IDC can be challenging [18]. Immunohistochemical markers could be helpful in such diagnostic challenges. The HMWCK expression is of benefit in the differential diagnosis of benign lesions such as UDH or ADH. It has been stated that HMWCK is helpful in determining intraductal proliferative lesions and could be a supportive finding in the presence of atypia [19]. Some researchers observed a decrease in the expression of HMWCK in the order of UDH, ADH and DCIS lesions and advocated that this marker could be useful in the differential diagnosis of intraductal proliferative lesions of the breast [5].

In another study, diffuse and intense staining for HMWCK was demonstrated in UDH and ADH areas, loss of staining or focal and weak expression was determined in DCIS cases; in the light of these findings, the authors regarded HMWCK as a helpful marker in problematic cases [20].

In this study, both epithelial hyperplasia groups exhibited significantly higher HMWCK staining intensity as compared to the IDC group. This finding suggested that HMWCK expression might have been upregulated in benign proliferative lesions of the breast and down-regulated in the course ofthe progressive disease. As HMWCK expression was found to be higher in the ADH group than in the DCIS group, we thought that HMWCK expression could be beneficial in diagnosing cases who fall into a transitional zone in tumorigenesis and who, therefore, could represent diagnostic challenges.

In various studies, the decreased p27 expression has been accepted as the fundamental finding in breast cancer,and suggested to be an important option for targeted therapy in cancer treatment [8]. Moreover, it has been considered that increased p27 expression could be evaluated as an independent indicator of the prognosis [15, 21]. The decrease in the expression of p27 protein has been reported to be correlated with poor prognosis, disease recurrence, and disease-related deaths in patients with early-stage breast cancer, and decreased expression of p27 has been supported to be an independent indicator of poor prognosis [7].

When the epithelial hyperplasia groups were compared, p27 expression was higher in the ADH group than that in the UDH group; this could be due to the lower number of cases with epithelial hyperplasia. The expression of p27 was found to be significantly lower in the cancer group as compared to that in the non-cancer group. p27 expression was significantly higher in the ADH group when compared individually to the IDC and DISC groups. These findings suggested that p27 expression disappeared with the development of cancer.

CXCR-4 was documented to play a role in the process of metastasis of numerous types of tumors [22], in organ-specific tumor extension stages [23]; in the induction of proliferation of tumor cells [24]; in the processes of invasion [25], and in neo-angiogenesis [26]. Although CXCR-4 cannot be shown in the epithelium lining normal breast ducts, it

commences being expressed after ADH step, representing a quite earlier step of malignant transformation [27].

In our study, after DCIS step, CXCR-4 receptor expression increased markedly through carcinogenesis. CXCR-4 expression in IDC was found to be higher than that of DCIS group. It was documented to reveal an increase in CXCR-4 expression with the progression through the steps of tumor generation. SDF-1 expression was observed to be significantly higher in cancer cases than that of non-cancer cases. Also, in epithelial hyperplasia group, SDF-1 expression was found to be higher in ADH group than UDH group. These results suggest that SDF-1 expression can be used as one of the poor prognostic markers.

The presence of metastasis has proven to be one of the most important prognostic factors determining life expectancy for breast cancer patients. The axillary lymph nodes are the most commonly encountered metastasis site in patients with invasive breast cancer, occurring in 38% of these cases [28]. The CXCR-4 receptor was also reported to be expressed in the anatomic regions to which distinct types of cancerous tumors spread, and this observation was considered to be in favor of the theory regarding organ-specific attracting molecules in the process of migration of tumor cells to specific regions [29]. Genetic investigations suggested that the interaction between SDF-1 and CXCR-4 was associated with the aggressive course, increased invasion potential and rapid tumor growth [30]. Moreover, it has been advocated that the breast cancer cases possessing SDF-1/CXCR-4 complexes were more invasive and more rapidly migrating and that SDF-1 level was useful in predicting lymph node involvement, recurrences and disease-free survival time [31].

SDF-1 has been expressed very intensely aroundcancer and in the lymph nodes draining the cancerous area [32]. In addition to metastatic axillary lymph nodes, high levels of CXCR-4 expression was also reported in the metastatic breast carcinomas to the liver and the lungs [33]. A significant correlation has been detected between diffuse nuclear CXCR-4 positivity and lymph node metastasis [34].

In our study, a directly proportional increment between CXCR-4 expression and the presence of lymph node metastasis and the increase in tumor diameter was detected. SDF-1 expression was also higher in tumors with lymph node metastasis. Thus prompting us to consider that CXCR-4 and SDF-1 might be used as an ominous prognostic indicator in general tumor pathogenesis steps.

CONCLUSION

Breast carcinoma is one of the tumors of which early diagnosis and treatment are of vital importance. Researches have resulted in an array of immunohistochemical markers that would have prognostic value in tissues accessible by needle biopsy, which is relatively an easy method. In the present study, we found that HMWCK and p27 were expressed in the non-cancer group and when used together, they could be beneficial in biopsies particularly in cases with ADH and DCIS where the lesions lie in the transitional zone and represent a challenge in the differential diagnosis.We concluded that the indicators, CXCR-4 and SDF-1, could be used as poor prognostic factors compatible with an increase in tumor diameter and the presence of lymph node metastasis during the steps of tumorigenesis.

Authors'Contributions

GO = designed and performed the research analyzed the data and wrote the manuscript. GA = analyzed the data and designed the research. All authors read and approved the final manuscript.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2019;5(5):809-815 ORIGINAL ARTICLE

Ultrasound-guided percutaneous drainage as an alternative to surgery in treating breast abscesses

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ABSTRACT

Objectives: The aim of this study was to assess whether ultrasound-guided (US-guided) percutaneous drainage of breast abscesses could be used as an alternative to surgery.

Methods: We performed a retrospective study. Twenty patients were included in the study who were diagnosed as having a non-specific breast abscess. Eleven patients underwent surgery whereas nine patients were treated with US-guided drainage. Ultrasonographic findings, results of treatment and follow-up were evaluated between the two groups.

Results: In the US-guided drainage group, 5 patients were treated with needle aspiration and 4 were treated with catheter drainage. All cases within the needle aspiration group totally recovered. However, one case within the catheter drainage group failed. The total success rate of US-guided drainage was 88.8%. The median follow-up period was 21.0 days in the US-guided drainage group and 45.0 days in the surgical drainage group. There were no statistically significant differences in terms of recovery ($p = 0.450$) and follow-up periods ($p = 0.112$) between the surgical drainage and US-guided drainage groups.

Conclusions: US-guided percutaneous drainage may be preferred as a first method of choice in treatment of a breast abscess. The most appropriate approach to breast abscess treatment will be possible with a multidisciplinary approach of surgery and radiology.

Keywords: Breast abscess, percutaneous drainage, US-guided drainage

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Breast abscesses often develop as a complication of infectious mastitis in young women [1]. Traditional treatment includes surgical drainage and systemic administration of antibiotics. Surgery, which usually requires general anesthesia, leads to scar tissue, also requires the cessation of breast-feeding during treatment and is more expensive. However, ultrasound-guided (US-guided) percutaneous drainage is a feasible, safe, well-tolerated and successful method [2-4].

In our study, we aimed to show that US-guided drainage of breast abscesses may be an alternative to surgical incision and drainage.

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METHODS

Written consent of the ethical committee of Uludağ University School of Medicine, dated February 10th, 2015 and numbered 2015-3/21, was received for this study planned retrospectively. We evaluated 9 patients who were diagnosed with breast abscess and underwent US-guided abscess drainage between December 2013-December 2014 and 11 patients who were diagnosed with breast abscess and underwent surgery between January 2009-December 2014. The patients who had a suspected breast abscess on ultrasound examination and were reported to have a non-specific infection in cutting needle biopsy (CNB) were included in the study. We evaluated clinical information, ultrasound images, antibiotic therapies, biopsy results, US-guided drainage method, microbiology and antibiotic susceptibility test results that were obtained from the files of the patients. The patients were divided into two groups, including those undergoing surgical drainage and those undergoing US-guided drainage. Ultrasound examinations were performed using a 7.5 MHz linear probe (Toshiba Medical Systems Corporation, Otawara, Tochigi, Japan) with a Xario device (Toshiba Medical Systems Corporation, Otawara, Tochigi, Japan).

The patients underwent CNB during percutaneous drainage to exclude conditions that imitate breast abscess. The procedure was performed under local anesthesia. CNB was performed using a fully automatic gun (Bard MAGNUM, Covington, GA) and a 14G needle with the freehand method under ultrasound. At least 2 samples were taken from each lesion, and the materials were sent for pathological examination in 10% formaldehyde solution.

US-guided drainage

US-guided drainage was performed under sterile conditions with local anesthesia. Abscesses smaller than 5 cm firstly underwent fine needle aspiration. 18-20G one-wall needles (Seldinger) were used for aspiration. If abscess material was highly viscous, 18G needles were preferred. Catheter drainage was performed for abscesses larger than 5 cm and also for abscesses larger than 3 cm repeating within 7-14 days after fine needle aspiration. Catheter drainage was performed under ultrasound and fluoroscopy device (AXIOM Artis, Siemens, Erlangen, Germany). Fluoroscopy was performed to determine the depth of the abscess cavity and its relation to the chest wall. The abscess cavity was entered using an 18G needle (Seldinger) under local anesthesia. The abscess cavity was then evaluated by giving contrast agent after about 1-2 cc of aspiration. After guidewire placement, a drainage catheter was placed over the guidewire. 6-8F drainage catheters (Neo-Hydro, Bioteq, Taiwan) were used for drainage.

Saline lavage was also applied during drainage of the abscesses. Saline was injected with a 10 ml syringe into the abscess and aspiration was performed until the aspirated content was cleaned.

Oral antibiotic treatment was given by the department of breast surgery for patients who underwent percutaneous drainage. The material obtained during the aspiration process was sent to microbiology for culture. Antibiotherapy was revised during the follow-up according to the antibiotic susceptibility profile.

A decrease in inflammatory symptoms such as fever, erythema and pain was evaluated as treatment response and good clinical response. Only clinical follow-up was done after drainage for abscesses showing a good clinical response. An ultrasound control was done once 14 days later to show that the abscess fully regressed. Ultrasound was repeated until complete regression occurred for patients with a partial clinical response. Controls were done at 7 or 14-day intervals. Control intervals were adjusted according to the clinical findings of the patients.

Statistical Analysis

Categorical data are summarized as number and percentage. Fisher's exact and chi-square test were used to compare the data. Numerical data were defined as median, minimum and maximum values. Mann-Whitney U-test was used to compare numerical data. The significance level was accepted as $p < 0.05$ for all tests.

RESULTS

Demographic information, lesion characteristics and follow-up period of the patients included in the study are shown in Table 1. The age of the patients included in the study ranged from 20 to 63 and the

Table 1. Distribution of lesions according to the form of drainage

	US-guided drainage (n = 9)	Surgical drainage (n = 11)	Total (n = 20)	*p* value
Age (years) (median (min-max))	29.0 (20-63)	33.0 (26-54)	33.0 (20-63)	0.603
Lactational status (P/ NP)	1/8	0/11	1/19	0.450
Localization (right/ left)	5/4	4/7	9/11	0.653
Size (mm) (median (min-max))	40.0 (16-80)	20.0 (10-80)	30.5 (10-80)	0.261
Follow up (day) (median (min-max))	21.0 (7-80)	45.0 (18-65)	37.5 (7-80)	0.112

min = minimum, max = maximum, P = Puerperal, NP = Non-puerperal

median age was 33.0 years.

Of 20 abscesses included in the study, 1 (5%) was within the puerperal period and 19 (95%) were within the non-puerperal period. One patient with puerperal abscess was within the tenth month postpartum and underwent US-guided drainage (Figure 1). This patient was treated with US-guided needle aspiration. Of the patients with non-puerperal abscess, 8 (42.1%) underwent US-guided drainage and 11 (57.9%) underwent surgical drainage. One of the patients with non-puerperal abscess was 7 weeks pregnant. Of the non-puerperal abscesses that underwent US-guided drainage, 4 (50%) were treated with needle aspiration and 4 (50%) were treated with catheter drainage (Figure 2).

The patients were followed for periods ranging between 7-80 days. The median follow-up period was 21.0 days (7-80 days) in the group that underwent US-guided drainage and 45.0 days (18-65 days) in the group that underwent surgical drainage.

When looking at the culture results of the abscesses that underwent US-guided drainage, Staphylococcus aureus (S. aureus) was isolated from one patient, Enterococcus faecalis was isolated from

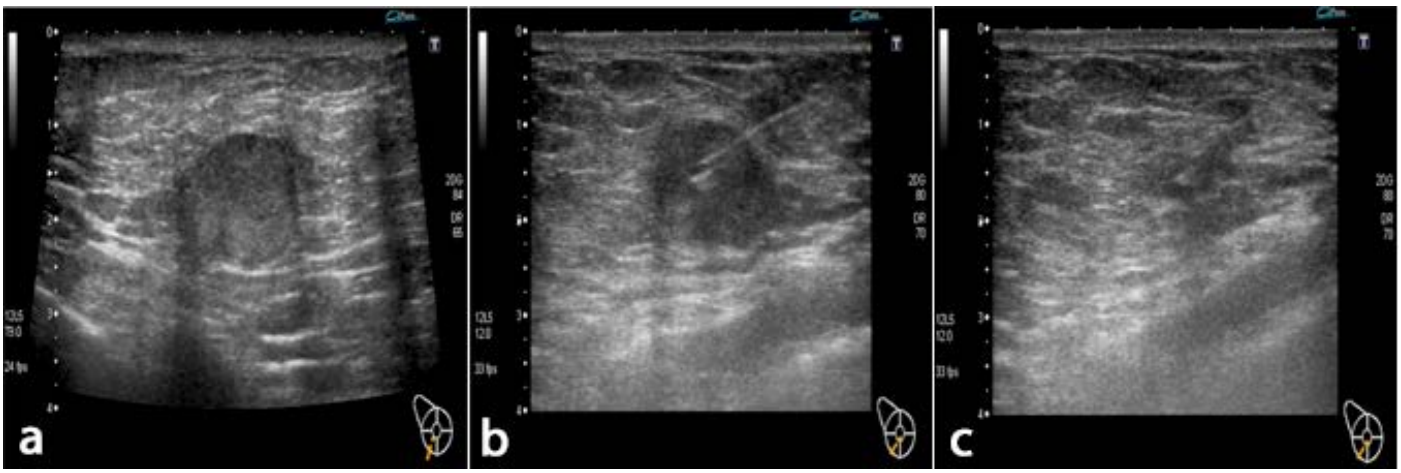

Figure 1. A 28-year-old puerperal female patient noticed tenderness and redness in the lower outer quadrant of the right breast during breastfeeding. (a) On ultrasound examination, a heterogeneous abscess was seen in the right breast at 7 o'clock position with a size of 18x13 mm. (b and c) Aspiration was performed with an 18G needle and CNB was performed with a 14G needle under ultrasound. The aspirated purulent material was sent for culture. The abscess disappeared on ultrasound examination made immediately after the aspiration. There was no growth in culture and the pathological result was reported as non-specific mastitis.

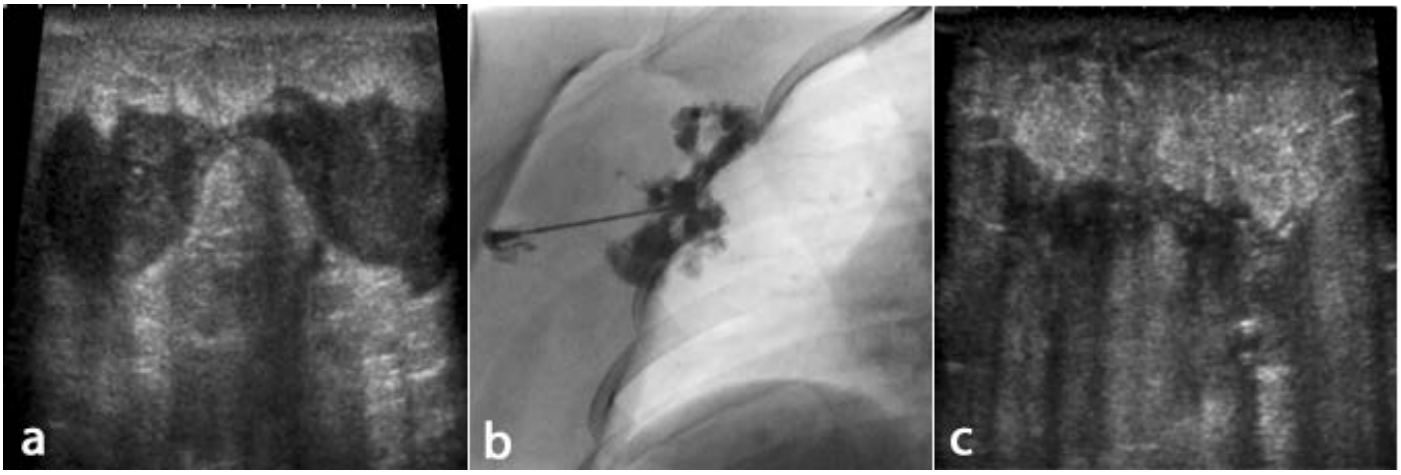

Figure 2. A 34-year-old non-puerperal female patient. She was admitted with ongoing pain and swelling in the right breast for three months. She had received antibiotherapy before she was admitted to our department. (a) Interconnected and content-heavy collections were found in a 61×45 mm area in the right breast at 2 o'clock position on ultrasound examination. (b) She underwent catheter drainage and also the abscess was seen to be multilocular with contrast agent injected into the abscess cavity during the process. (c) 8F drainage catheter was inserted into the abscess and 15 ml of purulent material was aspirated. There was no growth in culture. The patient recovered after antibiotic therapy and drainage.

one patient and Escherichia coli was isolated from one patient. In the surgical drainage group, S. aureus was isolated from one patient, Actinomyces israelii was isolated from one patient and Mycobacterium tuberculosis was isolated from one patient. There was no growth in the cultures of the other patients.

In the non-puerperal group who underwent US-guided drainage, 3 (37.5%) of 8 patients presented with a recurrent abscess. There was no recurrent abscess in the puerperal group. The patients with a recurrent abscess underwent repeat aspiration. Of these patients, 2 (66.6%) improved after the second aspiration and 1 underwent a third aspiration. In this patient, the subareolar abscess was seen on ultrasound examination done on the 7th day after the third aspiration, and then this patient was referred to surgery. In this patient, who was reported to have a non-specific infection in CNB at the initial diagnosis, the postoperative pathology result changed to granulomatous lobular mastitis.

In our study, of 9 abscesses that underwent US-guided drainage, 5 (55.5%) underwent needle

Table 2. Characteristics and follow-up results of patients who underwent US-guided drainage

Age	Lactation status	Localization of abscess	Structure of abscess	Size (mm)	Type of treatment	Number of aspirations	Pathogenic organism	Follow up
29	NP	Peripheral	Multilocular	45×22	Catheter	3	-	Surgery
26	NP	Peripheral	Multilocular	43×20	Catheter	2	-	Resorption
28	P	Peripheral	Unilocular	18×13	NA	1	-	Resorption
34	NP	Peripheral	Multilocular	61×45	Catheter	1	-	Resorption
27	NP	Peripheral	Multilocular	37×16	NA	2	-	Resorption
48	NP	Peripheral	Multilocular	26×14	NA	1	*S. aureus*	Resorption
57	NP	Central	Multilocular	80×50	Catheter	1	-	Resorption
63	NP	Peripheral	Unilocular	16×9	NA	1	*E. faecalis*	Resorption
20	NP	Central	Unilocular	40×20	NA	1	*E. coli*	Resorption

P = Puerperal, NP = Non-puerperal, NA = Needle aspiration, *S. aureus* = *Staphylococcus aureus, E. faecalis* = *Enterococcus faecalis, E. coli* = *Escherichia coli*

Table 3. Characteristics and follow-up results of patients who underwent surgical drainage

Age	Lactation status	Localization of abscess	Structure of abscess	Size (mm)	Pathogenic organism	Follow up
33	NP	Peripheral	Unilocular	10×8	-	Resorption
54	NP	Central	Unilocular	20×20	*A. israelii*	Resorption
35	NP	Central	Unilocular	15×13	*S. aureus*	Resorption
42	NP	Central	Multilocular	50×50	-	Resorption
29	NP	Peripheral	Multilocular	60×40	-	Resorption
39	NP	Central	Unilocular	20×15	-	Resorption
26	NP	Peripheral	Unilocular	35×20	*M.tuberculosis*	Resorption
30	NP	Peripheral	Unilocular	17×8	-	Resorption
33	NP	Central	Multilocular	80×10	-	Resorption
32	NP	Peripheral	Multilocular	20×12	-	Resorption
34	NP	Central	Multilocular	20×20	-	Resorption

NP = Non-puerperal, *A. israelii* = *Actinomyces israelii, S. aureus* = *Staphylococcus aureus, M. tuberculosis* = *Mycobacterium tuberculosis*

aspiration and 4 (44.5%) underwent catheter drainage. All patients who underwent needle aspiration improved (100% success rate). Of the patients who underwent catheter drainage, 1 did not improve and was sent to surgery (75% success rate). The total success rate of US-guided drainage was calculated as 88.8%. Compared with the surgical group, there was no statistically significant difference between the two groups in terms of recovery rate ($p = 0.450$).

The data and follow-up results of the US-guided drainage group and surgical drainage group are shown in detail in Tables 2 and 3.

DISCUSSION

The traditional treatment of breast abscesses has been considered to be surgical drainage and systemic antibiotics until the 1990s. In 1990, Karstrup *et al*. [3] showed that US-guided drainage can be applied as an alternative to surgery. In light of many studies, today US-guided drainage combined with oral antibiotic therapy is used as an effective treatment for breast abscesses. US-guided percutaneous drainage is an advantageous method in many ways in terms of the patient. It does not require general anesthesia and there is no need for hospitalization and postoperative care. It is a minimally invasive method and can be performed in a short time under outpatient conditions. The other advantages of this method may be that it results in minimal or no scar tissue, does not require stopping breastfeeding, is cheaper than a surgical approach and has similar or lower complication rates compared to surgery. However, it has disadvantages such as the formation of cutaneous fistula after percutaneous drainage and a repeating collection, especially in puerperal patients.

The success of percutaneous drainage varies in a wide range of 54-100% [5-9]. The large difference between the percentage of successes may be due to many factors such as the type of abscess, the size of abscess, the technique used, using antibiotic therapy along with drainage and the success criteria selected.

Different techniques can be used in percutaneous abscess drainage. Ultrasound is usually preferred as a guide method. However, drainage was performed with direct palpation without using ultrasound in some studies [10, 11]. US-guided drainage facilitates entering especially small and multilocular abscesses and performing adequate drainage. All percutaneous interventions in our study were conducted under ultrasound. In addition to ultrasound, the abscess cavity was evaluated by giving contrast agent under fluoroscopy to determine the depth of the abscess cavity and its relation to the chest wall in patients who underwent catheter drainage.

The thickness of the needle used for aspiration can influence success. In reported studies, 14-25G needles were usually used [5, 6, 8, 12]. The choice of needle thickness varies according to the content of the abscess. For example, a dark and viscous abscess is more easily aspirated with a thick needle. However, the use of a thick needle may be a risk factor for development of a cutaneous fistula. Moreover, a thick needle can lead to pain in the sensitive breast due to inflammation, despite local anesthesia. In our study, 18 and 20G needles were preferred. If the abscess material was highly viscous, 18G needles provided sufficient aspiration. Because of the small number of patients in our study, there was no comment on changes in the success rate with needle thickness.

Aspiration may not always be sufficient in percutaneous drainage of large collections and abscesses. In some studies in the literature, catheter drainage was preferred instead of needle aspiration in the treatment of large collections and abscesses larger than 3 cm [6, 8, 13]. In our study, at the time of diagnosis, abscesses larger than 5 cm underwent catheter drainage and abscesses smaller than 5 cm underwent fine needle aspiration. Abscesses that repeated within 7-14 days after fine needle aspiration during the follow-up and were larger than 3 cm underwent catheter drainage. It is an advantage that the catheter remains within the cavity until the abscess is completely drained. Thus, it is not necessary to enter with the needle again and again. However, the catheter remaining for a long time can also cause cutaneous fistula and it can be a source of infection. The presence of the catheter within the breast may affect patient comfort. The catheter should be taken out as early as possible. In the studies in the literature, the residence time of the catheter varies. For example, in the study of Ulitzsch *et al*. [8], the residence time of the catheter within the breast ranged from 1 to 25 days and the mean duration was 6.4 days. In the study of Christensen *et al*. [6], in which a drainage catheter was performed in puerperal and non-puerperal abscesses, the residence time of the catheter within the breast ranged from 2 to 6 days and the median residence time was stated as 4 days. In our study, the median residence time was 8 days (between 6-10 days) in abscesses. The median residence time was longer in our study compared to other studies in the literature due to the small number of patients. The catheter stayed for 10 days in one patient and also it was changed on the 7th day in this patient. This patient decreased the homogeneity of the residence time due to the small number of patients.

Recent studies have shown that breast abscesses can be treated by repeated needle aspiration without the use of a catheter [7, 8, 12]. In a case series of 26 patients, Imperial *et al*. [7] stated that the success rate was 96%. In a case series of 39 patients, Elagili *et al*. [12] stated that the success rate was 83.3%. In our study, 5 (55.5%) of 9 abscesses that underwent US-guided drainage underwent needle aspiration. All patients who underwent needle aspiration improved and the success rate was 100% in these patients. An 80% decrease was achieved after the first aspiration and complete regression (100%) was achieved after the second aspiration. They were treated with percutaneous drainage without the need for surgery.

Systemic antibiotics should always be given at any time in addition to percutaneous drainage in the treatment of breast abscess. Antibiotherapy is regulated according to the most common agent. Although the material that was taken for determining the appropriate antibiotic was sent for culture, there was no growth in the culture because antibiotherapy had been initiated. In the literature, Ozseker *et al*. [2] and Imperiale *et al*. [7] reported that sterile culture results were 36% and 23%, respectively. Many studies have shown that the most common organism obtained in culture was S. aureus [14, 15]. In our study, there was no growth in a significant part (66.6%) of the culture results. This rate was higher compared to the other studies in the literature and this is due to the high use of antibiotics before drainage.

A breast abscess is a disease whose treatment is difficult. Surgical treatment, as well as percutaneous treatment, may fail. After US-guided percutaneous drainage, patients are recommended to surgery if several attempts (at least 3-5) fail but this decision may also vary depending on the clinical condition of the patient [1]. In a case series of 13 patients, Hook and Ikeda [5] reported that the recovery rate was 54%. In this study, treatment failure was seen in abscesses larger than 3 cm or subareolar abscesses. In a case series of 26 patients, Imperiale *et al*. [7] stated that one patient with a large and subareolar abscess did not improve and this patient was directed to surgery. In our study, only one patient (1 of 9 patients) failed and

also this patient was directed to surgery because recurrence occurred after the third attempt.

Limitations

Our study had some limitations. The first limitation of our study was the retrospective design. Our study had a limited number of patients, and our results should be verified with a larger series.

CONCLUSION

In conclusion, as shown in previous studies, our study confirms with a success rate of 88.8% that US-guided percutaneous drainage can be used as an alternative treatment to surgery. US-guided percutaneous drainage combined with oral antibiotics should be preferred as the primary treatment in the treatment of breast abscesses, and also a surgical approach should be performed for recurrent abscesses in which percutaneous drainage has failed. Radiologists should play a role in the treatment as well as in the diagnosis of breast abscesses, and also the management of breast abscesses should be performed by a multidisciplinary team with a surgeon.

Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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Adrenal hemorrhage in the neonatal intensive care unit: a four-year experience

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ABSTRACT

Objectives: Adrenal hemorrhage is relatively uncommon and usually underestimated. This study aimed to review the clinical, predisposing factors and ultrasonographic findings of adrenal hemorrhage newborns treated in hospital neonatal intensive care unit.

Methods: The medical records of 14 newborns with adrenal hemorrhage who had been admitted to our neonatal intensive care unit were retrospectively reviewed.

Results: During the study period, 1979 patients were admitted to our neonatal intensive care unit. Throughout the four-year follow-up of patients in the neonatal intensive care unit, adrenal hemorrhage was diagnosed with ultrasonography in 14 (0.70%) infants; thirteen of them were term babies, one of them was a premature baby. Among these 14 patients, 10 (71.4%) were males, 4 (28.6%) were females. The average birth weight was 3809.1 ± 358.5 g. Neonates had risk factors such as: birth trauma in 5 (35.7%) newborns, perinatal asphyxia in 4 (28.6%) newborns, sepsis in 2 (14.3%) newborns, large gestation age in 3 (21.4%) newborns. Resuscitation was performed in 7 (50%) infants in the delivery room. The most common clinical presentations of the newborn with adrenal hemorrhage was hypotonia and lethargy (n = 5; 35.7%). Nine (64.3%) newborns had adrenal hemorrhage on the right side, three (21.4%) of them had bilateral adrenal hemorrhage, and the last two (14.3%) had adrenal hemorrhage on left side. Resolution time of adrenal hemorrhage was a minimum of one month and maximum of three months in ultrasonographic follow-up.

Conclusions: If there are anamneses of strenuous and traumatic deliveries, and any clinical suspicion, ultrasonography should be performed to exclude adrenal hemorrhage, since it is non-invasive, and also straightforward to apply. In babies with hematomas that are increasing in size, adrenocorticotropic hormone and cortisol levels should be analyzed to prevent any possible adrenal insufficiency, even if there is no clinical sign.

Keywords: Adrenal hemorrhage, neonatal intensive care unit, traumatic delivery

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The frequency of adrenal hemorrhage in neonates has been reported to be 1.7-2.1 per 1,000 live births. The adrenal gland is extremely sensitive to trauma and asphyxia, because of its relatively large size, and vascularity [1, 2]. Any factor that causes hypoxia leads to a disordered blood flow to the heart, adrenal gland, and the central nervous system [3]. Increased pressure leads to congestion and hypoxia, which cause damage in the endothelial cells and damage in the endothelial cells may result in adrenal hem-

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orrhage [3, 4]. Its most common occurrence is due to the delivery of large babies, perinatal asphyxia, sepsis, traumatic delivery, coagulation defects, and treatment with anticoagulants. With the wide use of ultrasonography in recent years, the diagnostic frequency of adrenal hemorrhage in neonates is gradually increasing.

AH's clinical signs vary, depending on the degree and diffuseness of bleeding. It can be asymptomatic, or may be diagnosed by chance. The most frequent clinical signs include vomiting, persistent jaundice, unexplained anemia, poor nutrition, and abdominal mass [3-5]. Ultrasonography (USG) is a preferred method in the diagnosis and follow-up of the newborns, since it is non-invasive, rapidly applied, portable, sensitive, and it does not cause radiation [3]. The objective of the present study was to review the related knowledge in literature and investigate the risk factors, clinical, laboratory and ultrasonographic signs, in cases that were delivered in our hospital and followed-up in the neonatal intensive care unit and that were shown to have adrenal hemorrhage in the ultrasonographic examination.

METHODS

This retrospective study was carried out into newborns with adrenal hemorrhage at our hospital neonatal intensive care unit between 2008-2014. This study was approved by the local Ethics Committee. We reviewed the medical records of patients with adrenal hemorrhage admitted to the neonatal intensive care unit. Infant with congenital anomalies or referred to other centers babies are excluded. We recorded from patients files to reasons for hospitalization, birth weight, gender, delivery type, need for resuscitation in delivery room, existing symptoms, predisposing causes, site of adrenal hemorrhage and resolution time, levels of hemoglobin, biluribin, glucose, sodium, potassium, coagulation test and C-reactive protein (CRP). Coagulation tests included both prothrombin time (PT), and partial thromboplastin time (PTT). Adrenocorticotropic hormone (ACTH) and cortisol levels were measured into many patients with adrenal insufficiency.

In our neonatal intensive care unit protocol, USG is performed in neonatal with perinatal asphyxia; defined as resulting in hypoxemia and hypercapnia, accompanied by metabolic acidosis, neonatal sepsis, unexplained jaundice, infants of diabetic mothers, premature, convulsions, traumatic birth, and large gestation age.

All the patients were examined and diagnosed using USG, and two of the patients were diagnosed using abdominal computed tomography. The patients were followed with serial USG. In cases with adrenal hemorrhage, the first ultrasonographic follow-up examination was performed in 7 days later. USG was in the first month with one week break. Afterwards, ultrasonographic examinations were performed every month for the first three months. Perinatal asphyxia was defined as based on an Apgar score of for < 5min and /or neurologic manifestation in postnatal period (for example; seizures, hypotonia, coma and multiorgan system dysfunction).

RESULTS

During the study period, 1979 patients were admitted to our neonatal intensive care unit.

Table 1. Clinical and laboratory results of infants with adrenal hemorrhage

Number of patients	14	%
Male	10	71.4
Female	4	28.6
Birth weight (g, mean±SD)	3809.1 ± 358.5	
Birth trauma	5	35.7
Perinatal ashyxia	4	28.6
Sepsis	2	14.3
Large for gestational age	3	21.4
Resuscitation in delivery room	7	50
Hypotonia and lethargy	5	35.7
Hypotonia and seizure	1	7.15
Respiratory distress	3	21.4
Anemia	1	7.15
Jaundice	1	7.15
Vomit	1	7.15
Adrenal insufficiency	1	7.15
Right sided adrenal hemorrhage	9	64.3
Bilateral adrenal hemorrhage	3	21.4
Left sided adrenal hemorrhage	2	14.3

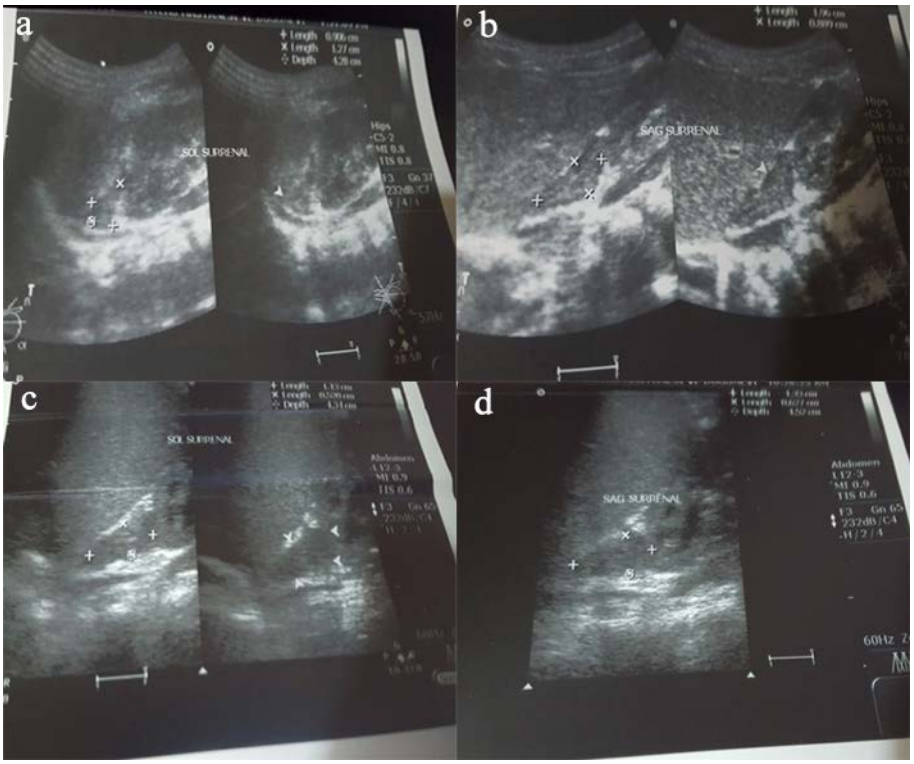

Figure 1. Bilateral adrenal hematoma patient one month apart USG image.

Throughout the four-year follow-up of patients in the neonatal intensive care unit, adrenal hemorrhage was diagnosed with ultrasonography in 14 (0.70%) infants; thirteen of them were term babies, one of them was a premature baby. Among these 14 patients, 10 (71.4%) were males and 4 (28.6%) were females. The average birth weight was 3809.1 ± 358.5 gr (3400-4230 g). Clinical and laboratory results of infants with adrenal hemorrhage are presented in Table 1.

Neonates had risk factors such as: birth trauma in 5 (35.7%) newborns, perinatal asphyxia in 4 (28.6%) newborns, sepsis in 2 (14.3%) newborns, large gestation age in 3 (21.4%) newborns.

The clinical presentations of the newborns were hypotonia and lethargy (n = 5; 35.7%), sepsis (n = 2; 14.3%), respiratory distress (n = 3; 21.4%), anemia (n = 1; 7.15%), hypotonia and seizure (n = 1; 7.15%), vomit (n = 1; 7.15%) , and jaundice 1 (n = 1; 7.15%). Resuscitation was performed in 7 (50%) infants in the delivery room. Nine (64.3%) newborns had adrenal hemorrhage on the right side, three (21.4%) of them had bilateral adrenal hemorrhage, two (14.3%) newborn had adrenal hemorrhage on left side. Minimum and maximum adrenal hemorrhage sizes 40×36 mm and 12×14 mm respectively. Bilateral adrenal hematoma patient one month apart USG image is shown is Figure 1.

One patient with jaundice was treated phototherapy applied. One patient with anemia and prolonged PT and PTT was given transfusion and fresh frozen plasma. Three of adrenal hemorrhage patients have with bilateral hematoma. One of them has liver hematoma and plus in the left sternocleidomastoid hemorrhage+ left Klumpke paralys. Liver hematom and the left sternocleidomastoid hemorrhage had been regressed after 3 months. Klumpke paralys was taken because of the physical therapy program. One of them with bilateral adrenal hemorrhage developed in adrenal insufficiency and was treated with both glucorticoid and mineralocorticoid .The other one has plus cranial hemorrhage. Cranial hemorrhage was regressed. Computed tomography image of bilateral adrenal hemorrhage is shown in Figure 2.

The other coagulation tests were all normal for the rest of the patients in our study group. Two patients with bilateral adrenal hemorrhage underwent abdominal computed tomography. There was no

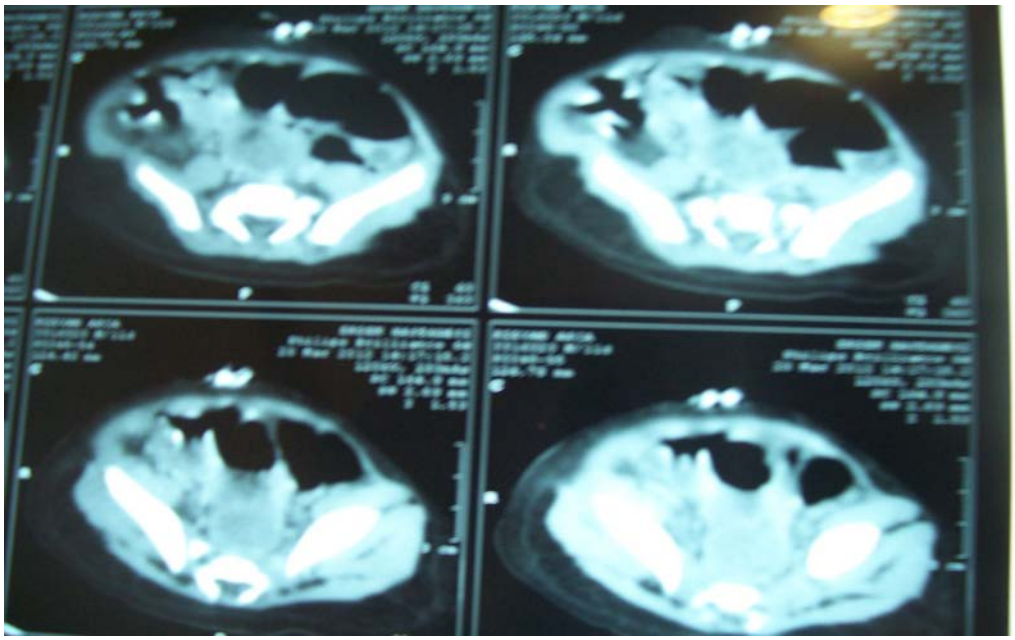

Figure 2. Computed tomography image of bilateral adrenal hemorrhage.

complication due to adrenal hemorrhage. Resolution time of adrenal hemorrhage was a minimum of one month and a maximum of three months in ultrasonographic follow-up.

DISCUSSION

Adrenal hemorrhage is a relatively common condition. Some cases may be completely asymptomatic and are diagnosed by chance [5]. It was in 1924 that Corcoran and Strauss [6] first reported a neonate was with massive adrenal hemorrhage; this neonate underwent surgery for sustained bleeding. Adrenal gland development begins in the fifth gestational week of the intrauterine life. The adrenal gland is the site for the synthesis of dihydroepiandrostenedione sulphate, which is the main androgenic precursor for the synthesis of placental estrogen in the intrauterine period. This is why the adrenal gland is 20 fold larger in the intrauterine period, compared with that of an adult human, and it is about 2-4 g at birth [7].

The etiology of adrenal hemorrhage is not yet known, and it is considered to be multifactorial. The larger than normal size of the adrenal gland, and its excessive vascularity, make this organ more susceptible to hemorrhage in neonates. Besides this, any situation that causes hypoxia may result in the interruption of the blood supply to the vital organs. Moreover, the release of endogenous ACTH increases during physiological stress, and thus hypoxia results in damage to the endothelial cells, making them more susceptible to hemorrhage. Some predisposing factors for this situation include strenuous delivery, particularly babies born to diabetic mothers, perinatal asphyxia, trauma, hypoxia, the delivery of a large baby, coagulation defects, shock, and sepsis [8, 9]. Its frequency has been reported in the literature to be between 1.7 and 2.1 per 1,000 live births; however, in neonates undergoing USG screening, the frequency is reported as 3% [2, 10]. In the study of Demirel *et al*. [11], comprising 37 cases that they followed-up for 3.5 years, the frequency of adrenal hemorrhage was reported to be 1.6%; of these babies, 10.8% experienced traumatic delivery, 10.8% had perinatal asphyxia, 18.9% underwent resuscitation in the labor room, and 21.6% were large for their gestational age [11].

In the study of Mutlu *et al*. [12], that included 13 cases, the most frequent predisposing factor was reported to be the birth of large babies in term deliveries, and perinatal hypoxia and DIC, secondary to sepsis, in premature babies. In our study, that

included 14 cases, the frequency of adrenal hemorrhage was 0.70%, which was lower than that reported in literature; the most common predisposing cause was traumatic delivery (35.7%).

The right adrenal gland was affected three to four fold more than the left one, due to its possible compression between the liver and spine. The right adrenal vein generally drains directly into the inferior vena cava, and is therefore more usually affected by changes in venous pressure [13]. In the literature, the frequency of bilateral hemorrhage has been reported to be between 8% and 38% [5]. Adrenal hemorrhage occurs more frequently in males, than in females [11, 13]. In our study, 71.4% of the cases were male, and the hematoma was observed in the right adrenal gland in 64.2% of the cases, which is in accordance with the literature. In the study of Demirel *et al*. [11], comprising 37 cases, 67.6% of the patients were male, and adrenal hemorrhage was reported in 24 cases as having occurred mostly in the right gland [11]. The clinical signs are variable, and depend on the quantity of bleeding. Clinical presentation with adrenal hemorrhage can vary from asymptomatic minimal bleeding, to adrenal failure, or fulminate bleeding that result in death. A small amount of bleeding occurs in the capsule, whereas larger amounts of blood escape into the peritoneal space. It results in symptoms like anemia, hemoperitoneum, abdominal mass, persistent jaundice, and scrotal hematoma [5, 14]. Adrenal failure related to adrenal hemorrhage is rarely observed, since the hemorrhage is commonly subcapsular, and at least 90% of the adrenal tissue has to be affected for adrenal insufficiency to occur. The clinical signs of adrenal failure include vomiting, food intolerance, hypoglycemia, electrolyte imbalance, coma, convulsions, and shock [15]. In our patient with bilateral adrenal hemorrhage, we did not detect any clinical signs associated with adrenal failure. Because the size of hematoma was determined to have increased in the second ultrasonographic control, conducted on the postnatal 15th day, precautionary ACTH and cortisol analyses were conducted, and diagnosis was made. Mean ACTH value was 103.0 (reference value: ≤ 46), and cortisol was 3.0 (reference value: 5-25). In our patient with bilateral adrenal hemorrhage, who was diagnosed with adrenal failure using laboratory analyses and USG indicators, treatment was started with glucocorticoid and mineralocorticoid. Treatment was ended three months later by gradually decreasing the dosages, and the levels of ACTH and cortisol were maintained within the normal ranges.

One case in our study had anemia. In this patient, PT was also prolonged. PT was improved by transfusions of erythrocyte and fresh frozen plasma. Our patient with jaundice improved with phototherapy. In our patient with Klumpke paralysis, liver complications, sternocleidomastoid injury and bilateral adrenal hemorrhage, the hematomas regressed within three months; however physiotherapy for the Klumpke paralysis is continuing.

Two cases had no symptoms (they are being followed-up for sepsis and respiratory distress, respectively); in these patients, adrenal hemorrhage was determined in the ultrasonographic evaluation, which was conducted due to their being large babies. In the study of Chang *et al*., which continued for four years, 1,373 asymptomatic babies underwent USG, and of these babies, ten were determined to exist with adrenal hemorrhage [9]. When USG is routinely applied for large babies without anamneses of strenuous delivery, it might be possible to diagnose many asymptomatic cases.

In most cases, conservative treatment is sufficient. The vital signs have to be followed-up, and hydration must be maintained. In cases with uncontrolled massive bleeding, surgery is indicated [16]. In our series, none of the cases required surgical treatment, and conservative therapy was sufficient for improvement. In the differential diagnosis of adrenal hemorrhage, one must primarily consider neuroblastoma or adrenal abscess, which cause intraabdominal mass, and other diseases, like cystic renal illnesses. Abdominal USG is especially useful in differential diagnosis, and also in diagnosis and follow-ups. In serial USG, resolution occurs with hematomas, but the masses do not get smaller[14]. We have followed up our cases with serial USG. The patients underwent ultrasonography once a week in the first month, which was followed by ultrasonographic investigations monthly. In two cases, abdominal tomography was applied. In the study of Chang *et al*. [9], which included ten cases, hematomas were found to regress within one to four months. Hematomas were determined to regress within three to nine months in the study by Demirel *et al*. [11],

comprising 37 cases, and within one to four months in the study of Mutlu *et al*. [12], that included 13 cases. In our study, comprising 14 cases, hematomas regressed within one to three months, and this was in accordance with the literature. There were no complications in our patients.

CONCLUSION

Adrenal hemorrhage frequently develops secondary to traumatic delivery and asphyxia. If there are anamneses of strenuous and traumatic deliveries, and any clinical suspicion, USG should be performed to exclude adrenal hemorrhage, since it is non-invasive, and also straightforward to apply. In large babies, USG should be recommended in order not to overlook these cases, even in the absence of an anamnesis of strenuous delivery, and in cases of a normal delivery. In babies with hematomas that are increasing in size, ACTH and cortisol levels should be analyzed to prevent any possible adrenal insufficiency, even if there is no clinical sign. In order not to overlook these cases, patients attending with non-specific signs like jaundice, unexplained anemia, vomiting, and decreased sucking, specifically in the neonatal period, and if there is an anamnesis of strenuous delivery, a possible adrenal hemorrhage should always be considered.

Conflict of interest

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The European Research Journal 2019;5(5):822-826 ORIGINAL ARTICLE

The frequency of nodular gastritis in adult patients and the relation of this type of gastritis with *Helicobacter pylori* and histopathologic findings

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ABSTRACT

Objectives: Endoscopic nodular gastritis is usually used to describe the miliary nodular appearance of the gastric mucosa during endoscopy. Recent studies have shown that nodular gastritis is closely related to *Helicobacter pylori* (*H. pylori*) infection and may cause stomach cancer, especially in young women. We aimed to determine the frequency of nodüler gastritis in this study, other lesions seen during endoscopy, *H. pylori* frequency and histopathological findings.

Methods: Adult patients who underwent endoscopy between March 2015 and April 2017 were identified. Medical records of patients; demographic characteristics, endoscopic features and pathologic were investigated retrospectively. Patients with nodular gastritis were compared with age and gender matched control group.

Results: Of the 1877 patients evaluated, 39 patients with endoscopic nodular gastritis and 72 as control group were enrolled. The prevalence of *H. pylori* infection was significantly higher in patients with endoscopic nodular gastritis than in the control group (74.35% versus 63.88, $p < 0.0001$). The most common concurrent endoscopic findings were erosions (25.64%). Histopathologically, the prevalence of atrophic gastritis and intestinal metaplasia in the patients with endoscopic nodular gastritis was also higher than in the control group ($p < 0.05$).

Conclusions: Nodular gastritis is often caused by chronic *H. pylori* infection. It is observed more frequently in women and children. Most patients with *H. pylori* infection have no specific symptom or complication, but some patients may develop premalign conditions such as active gastritis, atrophic gastritis and intestinal metaplasia. For this reason, *H. pylori* eradication in patients with nodular gastritis may reduce the development of peptic ulcer and possibly gastric malignancy.

Keywords: *Helicobacter pylori*, nodular gastritis, atrophic gastritis, metaplasia

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Helicobacter pylori (*H. pylori*) is a gram-negative bacteria which has the ability to be colonized in and to infect the stomach. After feco-oral transmission, the bacteria pierces the mucous membrane of the stomach and settles on the luminal surface of the stomach, then causes an intense inflammatory response.

H. pylori infection is strongly associated with the risk of stomach cancer. Stomach cancer rates vary between countries. These differences can be explained by the variability in the *H. pylori* genotypes and their variability in the expression of the cagA and vacA genes (virulence genes associated with the develop-

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ment and progression of gastric atrophy). It is known that CagA-positive *H. pylori* infection is responsible for various gastric diseases such as chronic gastritis, gastroduodenal ulcers, mucosa associated lymphoid tissue lymphoma, immunological thrombocytopenia and stomach cancer [1]. It is known that there are precursor lesions as superficial gastritis-atrophic gastritis-intestinal metaplasia-gastric displasia before stomach cancer occurs [2].

Endoscopic nodular gastritis is usually used to describe the miliary nodular appearance (similar to chicken skin) of the gastric mucosa during endoscopy. There is no consensus about the precise endoscopic definition of nodular gastritis and whether it can be classified as an acute or chronic lesion. Nodular gastritis is a well-known, common form of *H. pylori* infection in children. It characterized by the pathologically distinct lymphoid follicles in the stomach antrum and the infiltration of mononuclear cells. Macroscopic nodularity is thought to be a reflection of the presence of these lymphoid follicles [3-4]. Recent studies have shown that nodular gastritis is closely associated with *H. pylori* infection and may cause stomach cancer, especially in young women [5].

In this study, it was aimed to determine the frequency of nodular gastritis and the relationship of this gastritis with *H. pylori* among adult patients who were evaluated endoscopically in our clinic; and at the same time, it is aimed to reveal the demographic data and associated histopathological findings of patients with nodular gastritis.

METHODS

A total of 1877 adult patients underwent endoscopy between March 2015 and April 2017 were identified. The medical records were retrospectively reviewed regarding the demographic characteristics, clinical features, endoscopic features and pathologic features of the patients. Thirty-nine patients with nodular gastritis were included in the study. Endoscopic nodular gastritis was defined as a miliary nodular appearance in the antrum and/or corpus of the gastric mucosa on the endoscopy. The control group consisted of 72 randomly selected patients whose biopsies were taken and had an endoscopic appearance of 3 normal. All endoscopic procedures were performed by a specialist gastroenterologist with a high resolution white light source endoscopy instrument (Olympus). Two biopsies from the antrum and two biopsies from the corpus were taken from all patients in the control group with endoscopic nodular gastritis. Biopsy specimens were fixed in 10% formalin and transferred to the laboratory under appropriate conditions. Giemsa, and hematoxylin and eosin staining were performed to detect *H. pylori* histologically.

Statistical Analysis

Comparisons between the two groups were analyzed using chi-square test for categorical variables and t-test for continuous variables. Two-way $p < 0.05$ values were considered statistically significant. Statistical analyzes were performed with SPSS 15.0. The proportions of pathological lesions were adjusted according to gender and age, and analyzed with logistic regression.

RESULTS

The mean age of the patients with endoscopic nodular gastritis and control group was 47.19 ± 15.32 years and 46.72 ± 14.26 years, respectively. Patient ages ranged from 17 to 91 years. In the study group 14 (35.89%) males and 25 (64.10%) females were detected.

In adults who underwent endoscopy, the incidence of nodular gastritis was 1.97% (39/1877). Histological *H. pylori* infection was detected in 74.35% of patients with endoscopic nodular gastritis, whereas this rate was 63.88% in the control group. The prevalence of *H. pylori* infection was significantly higher in patients with endoscopic nodular gastritis than in the control

Table 1. Endoscopic findings accompanying gastric nodules.

Endoscopic findings	n	%
Erosion	10	25.64
Bulbit	9	23.07
Duodenal ulcer	4	10.25
Gastric ulcer	1	2.56
Gastric polyp	1	2.56

Table 2. Histopathological findings

	Study group n = 39	Control group n = 72
Atrophic gastritis	2 (5.12%))	2 (2.77%)
Intestinal metaplasia	3 (7.69%)	2 (2.77%)
Dysplasia	-	-
Lymphoid follicle	12 (30.76%)	11 (15.27%)

group ($p < 0.0001$).

Regarding the endoscopic findings in 39 patients with nodular gastritis, noduls were found in 27 (69.23%) patients in the antrum and in 12 (30.76%) patients in the other regions in addition to antrum. Duodenal ulcer was found in 4 (10.25%) patients, gastric ulcer in 1 (2.56%) patient and erosive gastritis in 10 (25.64%) patients. In 9 (23.07%) of the patients bulbitis besides gastritis was detected. One (2.56%) patient had gastric polyps. There was no appearance suggesting atrophy, metaplasia or stomach cancer (Table 1).

In the histopathological examination, the rate of atrophic gastritis in endoscopic nodular gastritis patients and control group were 5.12% (2/39) and 2.77% (2/72), respectively. Intestinal metaplasia was detected in 7.69% (3/39) of patients with endoscopic nodular gastritis, but only 2.77% of the control group had intestinal metaplasia findings. These findings were statistically significant ($p < 0.05$). Lymphoid follicle formation was higher in patients with nodular gastritis (30.76%) than in the control group (15.27%) ($p < 0.05$) (Table 2). Displasia was not found histopathologically in neither the study group nor the control group.

DISCUSSION

While the prevalence of nodular gastritis in this study was 1.97%, Chen *et al*. [6] reported a rate of 2.9%; Miyamoto *et al*. [7] 0.19%; Önal İK *et al*. [8], 1.86%; Maghidman *et al*. [9] 7.2%. These differences in proportions may be due to sample selection. Symptomatic patients were taken in our study; studies reporting a lower prevalence rate also included symptomatic and asymptomatic individuals during endoscopy. Other reasons for variability in prevalence may be related to study design, host, bacterial or environmental variables. On the other hand, there is no common definition for the endoscopical appearance of nodules and the term "nodular gastritis" needs to be clarified further. The great difference in nodular gastritis prevalence in various studies may be mainly due to this subjective definition of endoscopists instead of different *H. pylori* prevalence among study groups.

As in previous studies [6-10], we have seen that female patients are affected more than men. The incidence of *H. pylori* infection does not differ according to sex, but the high proportion of women corresponds to this idea. However, it supports the hypothesis that the result of *H. pylori* infection may be related to a sex-specific host immune factor [11].

Previous studies have reported *H. pylori* positivity in 67-98.5% of patients with nodular gastritis [6-10].In our study, the prevalence of *H. pylori* in patients with nodular gastritis was 74.35% which is higher than the control group (63.88%). Several studies suggest that the presence of antral nodularity is highly indicative of *H. pylori* infection. Similarly, it has been suggested that the specificity and the positive predictive value of nodular gastritis for *H. pylori* infection are high [12,13]. For this reason, endoscopically detected nodular gastritis may be indicative of the possibility of *H. pylori* infection.

In this study, atrophic gastritis and intestinal metaplasia were more frequent in patients with endoscopic nodular gastritis. Dysplasia is not detected in neither of the groups. These results were consistent with the literature [8-10, 14-16].

Our study revealed that the formation of lymphoid follicle and/or aggregate was more frequent in patients with *H. pylori* positive nodular gastritis. In a series of 261 patients, Maghidman *et al*. [9] found that nodular gastritis was not associated with the presence and

number of lymphoid follicles. In contrast, Sokmensuer *et al*. [14] have shown that intraepithelial lymphocytosis is more prominent in nodular gastritis patients and may contribute to nodule formation. Rafeey *et al*. [15] have shown that nodular gastritis frequency is associated with the presence, density and histological grade of gastritis of *H. pylori* infection. Nodularity is probably associated with the intensity of *H. pylori* at the onset of infection, so large inoculations trigger an exaggerated immune response [16]. *H. pylori* is predominantly acquired in childhood and nodular gastritis is often found in children who undergo endoscopy [12, 15]. However, nodular gastritis is present in the minority of adult patients with *H. pylori* infection. It is not clear how and why this particular model develops in only a small part of adult patients. Variations in bacterial strains, host factors, or complex interactions between host and bacterial factors have all been considered as explanations [17].

In this study, none of the patients had stomach cancer. Recent studies have shown that nodular gastritis is closely associated with *H. pylori* infection and may cause gastric cancer in young women in particular [5]. The prevalence of premalign lesions such as atrophic gastritis and metaplasia was higher than that of non-nodular gastritis group, although dysplasia was not detected in this study. These results were consistent with other studies in the literature [5, 8-10, 16, 17]. On the other hand, the high prevalence of *H. pylori* infection in histologic premalign lesions and in cancer patients has been described [17, 18]. For this reason, *H. pylori* infection may be one of the possible causes of histologic premalign lesions in endoscopic nodular gastritis patients.

CONCLUSION

Nodular gastritis is caused by chronic *H. pylori* infection. They are more common in women and children. Patients infected with *H. pylori* at an early age do not have a specific symptom or complication in the majority, but some patients may develop premalign conditions such as active gastritis, atrophic gastritis and intestinal metaplasia. For this reason, *H. pylori* eradication in patients with nodular gastritis possibly reduces the risk of peptic ulcer and gastric malignancy. The definition and clinical significance of nodular gastritis and associated histopathology will become clearer with prospective long-term follow-up studies, including a large number of patients.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2019;5(5):827-835 ORIGINAL ARTICLE

Preoperative and postoperative features of non-functioning pituitary adenomas: a single center experience

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ABSTRACT

Objectives: The main purposes of surgical treatment for non-functioning pituitary adenomas are removal of the pressure on the surrounding structures, especially the hypophyseal gland and visual tissue, and the normalization of hypophyseal functions. In our study, we retrospectively reviewed postsurgical follow-up of patients with non-functioning pituitary adenoma treated at our institution in a period of 15 years of monitoring and evaluated surgical success, complication rate and recurrence rates in accordance with the literature.

Methods: This study included 55 patients who had undergone surgery between 2000 and 2014 and who were followed-up postoperatively at our center. Preoperative and postoperative anterior pituitary hormones, complete resection and recurrence and also postoperative recovery of endocrinological and ophthalmological functions were statistically evaluated using file data of the patients.

Results: There were 33 (60%) males and 22 (40%) females. It was observed that the adenoma caused pressure on the optic chiasm in 11 patients and infiltrated cavernous sinus in 9 patients. Postoperative mean follow-up was 75.14 ± 43.01 months. Seventeen (30.9%) patients had recurrence after complete resection. Postoperative persistence and deterioration rates were 12.2% and 26.6% in adrenal insufficiency, 12.2% and 26.6% in central hypothyroidism, respectively, while 12.2% worsening in central hypogonadism. Ophthalmologic findings were resolved in 62.5% of patients and persisted in 37.5% of the patients.

Conclusions: The adenoma size and experience of the surgeon in non-functioning pituitary adenomas are the most important factors affecting surgical success. We recommend that operations should be performed in experienced centers, preoperative and postoperative endocrinological evaluations and long-term follow-up should be done.

Keywords: Pituitary adenoma, non-functioning, surgery

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The prevalence of pituitary adenomas ranges from 1 in 865 adults to 1 in 2688 adults and 15-54% of all pituitary adenomas constitute non-functioning pituitary adenomas (NFPA) [1]. In a study of Swedish Pituitary Registry, it is observed that NFPA was the most common cause of pituitary adenomas (54%), followed by prolactinomas (32%), acromegaly (9%), Cushing's disease (4%), thyroid stimulating hormone (TSH) secretory pituitary adenomas (0.7%); respectively [2]. Of the pituitary adenomas detected in au-

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topsy series, 40% constitute NFPA [3].

Because of NFPA do not cause excessive hormone secretion, patients are often diagnosed when the symptoms due to the pressure effect of the mass are under investigation [4]. The most important symptoms and findings are the bitemporal hemianopsy that develops due to the mass effect on the surrounding tissues such as optic chiasm and hypophyseal insufficiency in varying degrees due to pressure-dependent destruction of the hypophyseal cells [5]. Hemorrhagic infarction (hypophyseal apoplexy) in the tumor can be observed as an initial finding in NFPA and causes severe headache, visual impairment and hypopituitarism due to sudden intra-sella pressure increase [6, 7]. However, with the increasing use of imaging modalities in recent years, NFPA can be detected in the asymptomatic period. Hypophyseal lesions detected on cranial images without symptoms are called hypophyseal incidentalomas. Lesions smaller than 1 cm are classified as microinsidentalomas and lesions larger than 1 cm are classified as macroinsidentalomas [8].

Surgery is recommended in symptomatic patients with impaired vision in the ophthalmologic examination or hypophyseal insufficiency in the evaluation of the hypophyseal functions [7]. Nevertheless, in a retrospective evaluation of surgical outcomes in asymptomatic and symptomatic NFPA, Messerer *et al*. [9] found that total resection success of adenoma in asymptomatic patients was statistically significantly higher (82% vs. 58%) than symptomatic patients [9]. In the same study, the risk of developing postoperative hormonal insufficiency was found to be 10 times lower in asymptomatic patients. In asymptomatic NFPA, surgical decision is recommended to be based on tumor size, age of the patient, localization of the tumor, and accompanying comorbidities [9].

The main purpose of surgical treatment is removal of the pressure on the peripheral structures, especially the hypophyseal gland and visual tissues, normalization of hypophyseal function and prevention of tumor recurrence [10]. However, surgical success is primarily associated with preoperative adenoma size [11].

In our study, we retrospectively reviewed postsurgical follow-up of patients with NFPA at our institution in a period of 15 years of monitoring and evaluated surgical success, complication rate and recurrence rates in the view of the literature.

METHODS

This study included 55 patients (33 males and 22 females) who had undergone surgery due to NFPA between 2000 and 2014 and who were followed-up postoperatively at our center. The complaints of the patients at the time of first admission were evaluated using the patients' file data. In preoperative endocrinological examination prolactin, growth hormone (GH), insulin like growth factor-1 (IGF-1), adrenocorticotropic hormone (ACTH), cortisol, TSH, free T4 (fT4), follicle-stimulated hormone (FSH), luteinizing hormone (LH), estradiol in women and testosterone levels in men were evaluated. Acromegaly was excluded in patients with presence of clinical findings of acromegaly and high serum IGF-1 levels based on age and sex. Cushing disease and prolactinoma were also excluded in patients with clinical findings and high serum ACTH, cortisol and prolactin, respectively. The age, sex, and postoperative follow-up period of the patients included in the study were analyzed using file data. The presence of hypopituitarism was also investigated by evaluating the preoperative pituitary hormones of the patients. In preoperative hormonal evaluation morning serum cortisol < 3 μg/dl, accompanied by low or inappropriate normal ACTH levels were defined as central adrenal insufficiency. Adrenal insufficiency was excluded if serum cortisol was ≥ 18 μg/dl and low dose ACTH stimulation test was performed between 3-18 μg/dl of cortisol. Adrenal insufficiency was excluded if the serum cortisol level was ≥ 18 μg/dl at one of the 0, 30, 60 and 90. minutes values after 1 μg ACTH stimulation. TSH and fT4 levels were evaluated in the diagnosis of central hypothyroidism. If sT4 level was low, TSH was low or inappropriate, central hypothyroidism was diagnosed. Concomitant low testosteron in men and low eostrogen in women with low or inappropriate normal FSH and LH levels were defined as central hypogonadism. Panhypopituitarism was assessed as the insufficiency of all pituiatry hormones.

Preoperative sella magnetic resonance imaging (MRI) was used to assess the diameter of adenoma based on the longest diameter. The presence of extracellular expansion, cavernous sinus invasion and compression of optic chiasm were examined on MRI.

Table 1. Characteristics and follow-up results of patients (n = 55)

Characteristics	Data
Gender, n (%)	
Female	22 (40%)
Male	33 (60%)
Age (years) mean ± SD (range)	54.27 ± 10.75 (30-75)
Preoperative adenoma size (mm) mean ± SD (range)	28.91 ± 9.67 (11-52)
Postoperative complete resection, n	
Yes	39 (70.9%)
No	16 (29.1%)
Postoperative follow-up (month) mean ± SD (range)	75.14 ± 43.01 (34-233)
Postoperative recurrence, n (%)	
Yes	17/39 (43.6%)
No	22/39 (46.4%)

SD = Standard deviation

The presence of visual field loss was evaluated in preoperative visual field examination using file data of all patients. Patients who had lost preoperative visual field were reevaluated postoperatively and the improvement and persistence rates of visual impairment were recorded. Pathological immunohistochemical examination of postoperative material was examined. In the early postoperative period, all patients were examined for diabetes insipidus (DI). Detection of polyuria (> 3 lt/24 h) and low urine osmolality (< 300 mOsm) in the presence of normal or high serum sodium levels was interpreted as DI. Patients who developed DI were reevaluated in the follow-up and temporary or permanent DI were investigated. Postoperative hypopituitarism development, postoperative complete resection rates and recurrence rates were analyzed.

Statistical Analysis

Statistical evaluations were performed on IBM SPSS version 21 (IBM Acquires SPSS Inc., Somers, NY, USA). Frequency values and/or descriptive statistics were calculated for variables that showed clinical characteristics of patients. The descriptive statistics of the continuous variables of the patients are given as the mean and standard deviation in the appropriate data or as the minimum-maximum.

RESULTS

There were 33 (60%) males and 22 (40%) females. The mean age was 54.27 ± 10.75 years (Table 1). All patients underwent pituitary surgery due to macroadenoma. Preoperative complaints of patients are given in Table 2. MRI and ophthalmologic examination was performed in 47 patients. The mean

Table 2. Preoperative clinical findings of patients (n = 55)

Clinical Findings	Data
Visual field disturbance	30 (54.5%)
Headache	20 (36.4%)
Loss of vision	7 (12.7%)
Diplopia	2 (3.6%)
Fatique	13 (23.6%)
Dizziness	3 (5.4%)
Nause-vomiting	2 (3.6%)
Diminished libido	7 (12.7%)
Menstrual irregularities	3 (5.4%)
Ptosis	1 (1.8%)
Tinnitus	2 (3.6%)
Weight gain	1 (1.8%)

Table 3. Preoperative MRI and ophthalmological data of patients (n = 47)

MRI	No extrasellar extansion	12 (25.5%)
	Suprasellar extansion	35 (74.5%)
	Infrasellar extansion	5 (10.6%)
	Compression of optic chiasm	11(23.4%)
	Invasion of cavernous sinus	9 (19.1%)
Ophthalmologic examination	Normal	10 (21.3%)
	Temporal hemianopsia	2 (4.3%)
	Bitemporal hemianopsia	24 (51.0%)
	Quadranopsia	2 (4.3%)
	Concentric narrowing	5 (10.6%)
	Total loss of vision	4 (8.5%)

MRI = Magnetic rezonance imaging. MRI and ophthalmologic examination was performed in 47 patients.

adenoma size in preoperative sella MRI was 28.91 ± 9.67 (11-52) mm. Sellar localization without expansion in MRI was observed in 12 (25.5%) patients. Suprasellar expansion was observed in 35 (74.5%) patients and both supra- and infrasellar expansion in 5 (10.6%) patients. In 11 (23.4%) patients, adenoma caused pressure on the optic chiasm and in 9 (19.1%) patients adenoma infiltrated cavernous sinuses. In the evaluation of the preoperative visual field, the visual field was normal in 10 (21.3%) patients, while the remaining patients had visual field defects (Table 3). Central adrenal insufficiency was present in 6 patients (10.9%), central hypothyroidism in 7 patients (12.7%), central hypogonadism in 1 patient (1.8%) and DI in 2 patients (3.6%) in preoperative endocrinological evaluation. None of patients had preoperative panhipopituitarism. Postoperative mean follow-up was 75.14 ± 43.01 (34-233) months.

Among 55 patients included in our study 54 were treated surgically at our center and one patient had a surgery at a different center. In 51 (94.4%) patient the surgical method was chosen to be transsphenoidal surgery and 3 (5.6%) patient underwent transcranial surgery in our center. In pathological immunohistochemical evaluation positive staining was not detected in 13/48 (25.5%) patients, whereas FSH positivity in 19 (34.5%) patients, LH positivity in 12 (21.8%) patients, ACTH positivity in 6 (10.9%) patients, prolactin positivity in 5 (9.0%) patients, TSH positivity in 5 (9.0%) patients and GH positivity in 1 (1.8%) patient were detected (Table 4). Complete resection was achieved in 39 patients (70.9%) postoperatively, while residual adenoma was detected in 16 patients (29.1%) in pituitary MRI performed at 3 months postoperatively (Table 1). Two patients did not undergo postoperative MRI evaluation at the third month. In the patients who had complete resection, recurrence was seen in 17/39 patients (43.6%) (see Table 1). In the follow-up, 12 patients had 2nd operation and 2 patients had 3rd operation (Table 5). All the patients included in the study were examined for the development of electrolyte disturbances, especially DI during the postoperative hospitalization. 12 (21.8%) patients had postoperative DI. Six (10.9%) patients were observed to develop permanent DI. Sixteen (29.0%) patients had central adrenal

Table 4. Immunohistochemical staining patterns of adenomas

FSH	19 (34.5%)
LH	12 (21.8%)
GH	1 (1.8%)
ACTH	6 (10.9%)
TSH	5 (9.0%)
Prolactin	5 (9.0%)
Negative	13 (27.1%)

Immunohistochemical staining was performed in 48 patints. More than one immunohistochemical staining positivity can be found in adenomas. FSH = follicle-stimulated hormone, LH = luteinizing hormone, GH = growth hormone, ACTH = adrenocorticotropic hormone, TSH = thyroid stimulating hormone

Table 5. Operation techniques of the patients

	Male	Female	Total
First surgery (n = 54)			
TSS	31 (93.9%)	20 (95.2%)	51 (94.4%)
TCS	2 (6.1%)	1 (4.8%)	3 (5.6%)
Second surgery (n = 12)			
TSS	5 (62.5%)	3 (75%)	8 (66.7%)
TCS	3 (37.5%)	1 (25%)	4 (33.3%)
Third surgery (n = 2)			
TSS	1 (100%)	1 (100%)	2 (100%)
TCS	-	-	-

TSS = Transsphenoidal surgery, TCS = Transcranial surgery

Table 6. Data of preoperative and postoperative endocrinological and ophthalmological findings

Adrenal insufficiency (n = 49)	None[a]	30 (61.2%)
	Persistence[b]	6 (12.2%)
	Recovery[c]	0
	Impairment[d]	13 (26.6%)
Central hypothyroidism (n = 49)	None	29 (59.1%)
	Persistence	6 (12.2%)
	Recovery	1 (2.1%)
	Impairment	13 (26.6%)
Central hypogonadism (n = 49)	None	42 (85.7%)
	Persistence	0
	Recovery	1 (2.1%)
	Impairment	6 (12.2%)
Oftalmologic (preop.) (n = 47) (postop) (n = 16)	None[e]	10/47 (21.3%)
	Persistence	6/16 (37.5%)
	Recovery	10/16 (62.5%)

Preop. = Preoperative, Postop. = Postoperative. [a]There are no pathologic findings in preoperative and postoperative examination. [b]There are pathologic findings in preoperative and postoperative examination. [c]There are pathologic findings in preoperative examination and there are no pathologic findings in postoperative examination. [d]There are no pathologic findings in preoperative examination and there are pathologic findings in postoperative examination.[e]There are no pathologic findings in preoperative examination.

insufficiency, 16 (29.0%) patients had central hypothyroidism, 3 (5.4%) patients had central hypogonadism and 6 (10.9%) patients had panhypopituitarism. The rates of improvement, persistence and deterioration of endocrinological and ophthalmological findings at postoperative evaluation are given in Table 6.

Gammaknife was given to 9 16.3%) patients (and conventional radiotherapy was given to 3 (5.4%) patients in postoperative period. After gammaknife and conventional radiotherapy treatments, central hypothyroidism was observed in 1 (8.3%)patient, central hypothyroidism and adrenal insufficiency in 1 (8.3%) patient, central hypothyroidism and hypogonadism in 1 (8.3%) patient and panhypopituitarism was observed in 1 (8.3%) patient.

DISCUSSION

NFPA constitutes approximately one third of all pituitary adenomas. In a recent autopsy study, adenoma frequency was found to be 10.5% and 35% of adenomas were observed to be composed of NFPA. In this study, the median tumor diameter was found to be 1.6 mm, and macroadenomas were detected in only two patients [3]. Our study included patients with non-functional pituitary macroadenomas with a mean tumor diameter of 28.91 ± 9.67 mm. The mean age at diagnosis at NFPA is around 50-55 years and the frequency is slightly higher in males (56.7%) [18]. In our study, the frequency of male gender was found to be more frequent (60%) and the mean age of diagnosis was 54.27 ± 10.75 (30-75) years.

NFPA is rarely seen as a component of multiple endocrine neoplasia-1 (MEN-1) and familial idiopathic pituitary adenoma (FIPA) [12]. Atypical pituitary adenomas and pituitary carcinomas are characterized by Ki-67 index ≥ 3 and p53 protein positivity and are resistant to conventional treatments. Pituitary carcinomas also causecerebrospinal and/or systemic metastases. While atypical pituitary adenomas are observed at 2.7%, the incidence of carcinomas (0.1-0.2%) is very low [13]. In our study atypical pituitary adenomas were present in 3 (5.4%) patients and no pituitary carcinoma was found.

According to the structural and immunohistochemical characteristics, NFPA are divided into 3 groups (gonadotropic adenomas, null cell adenomas and oncocytomas). Gonadotropic adenomas show positive staining with FSH, LH or subunits, while null cell adenomas and oncocytomas are not stained. These three groups constitute 85% of all NFPA, while the remaining 15% constitute silent adenomas, which are immunohistochemically positive and do not cause any symptom [14, 15]. In our study, immunohistochemical evaluation was performed in 48 patients. Immunohistochemical staining was negative in 13 (27%) patients. Gonadotropic adenomas were detected in 25 (52%) patients while silent adenomas were detected in 10 (21%) patients.

NFPA are usually diagnosed by symptoms such as headache, visual disturbances, cranial nerve palsy, and hypopituitarism, which are caused by mass pressure on the surrounding tissues [16]. Depending on the mass effect of adenoma, headache may occur in 25% of the macroadenoma patients, most likely due to the expansion of the sella. Suprasellar enlargement in the tumor leads to pressure on the optic chiasm, leading to visual field defects, primarily bitemporal hemianopsy. Prolonged compression of the optic nerve can lead to atrophy of the nerve resulting in decreased visual acuity. Extension of the adenoma to the lateral lobe and invasion of the cavernous sinuses does not always result in clinical signs, but may result in pitosis, ophthalmoplegia, and diplopia, leading to involvement in the 4th and 6th nerves, primarily cranial nerve 3. Rarely, parasellar enlargement can cause compression in the temporal lobe and seizure development, inferior enlargement to the sphenoid sinus may cause rhinorrhea very rarely [12, 17, 18]. Among the patients included in the study, the most common complaint was visual impairment (54.5%) and headache (36.3%). In MRI, compression of optic chiasm was detected in 11 (23.4%) patients. Pitozis was present in 1 (1.8%) patient and diplopia in 2 (3.6%) patients. The most common findings in ophthalmologic examination were bitemporal hemianopsia (51.0%) and concentric narrowing (10.6%) in the visual field. No ophthalmologic problem was found in 21.3% of the patients.

Pituitary apoplexy is a rare condition characterized by sudden hemorrhage into the pituitary macroadenoma. It causes severe headache and impaired vision. It can be developed spontaneously however may be associated with pregnancy, surgery and anticoagulant use [19, 20]. Pituitary apoplexy was not observed in the patients included in our study.

The purpose of treatment in patients with symptoms is to provide rapid decompression and relieve symptoms [18]. Successful total surgical resection of NFPA can be achieved in the literature with a wide spectrum, varying between 18-81% [21, 22]. In our study, total surgical resection was observed in 39 (73.5%) of the 53 patients whose evaluation was performed.

Radiotherapy may be effective in residual tumor patients with postoperative growth potential. Radiotherapy is recommended to patients which has a tendency to grow in post-operative follow-up, residual tissue remaining and life expectancy is more than 10 years [23]. However, there is a risk of hypopituitarism in the long term. It may also lead to visual deterioration, secondary brain tumor development,

seizure and possibly neurocognitive and neuropsychological impairment [16, 24]. In our study, 9 (16.3%) patients were treated with gammanife and 3 (5.4%) patients were treated with radiotherapy.

Total or partial improvement is seen in 80-90% of cases after surgery. This improvement continues up to 1 year after surgery. The urgency of the surgery is related to the severity of visual impairment [25, 26]. In our study, preoperative ophthalmological evaluation was performed in 48 patients and pathological findings were found in 38 (79.2%) of the patients. At postoperative 3rd month, only 16 of 38 patients had reevaluation and 10 (62.5%) patients had total or partial healing and 6 (37.5%) patients had persistent findings. It is thought that the low number of patients with post-operative evaluation may be due to insufficient file records.

30-40% of macroadenomas are accompanied by partial or total hypophyseal insufficiency and there is a risk of developing 12% hypophyseal insufficiency every year in macroadenomas [27, 28]. Loss of hypophyseal functions can be explained by the expanding adenoma leading to pressure on pituitary stalk and portal veins [29]. The development of hypopituitarism occurs in GH, FSH/LH, TSH and ACTH hormones respectively. Clinical findings are associated with the type and severity of hormonal deficiencies and may be nonspecific [30]. In the patients included in our study, TSH deficiency was the most prominent findings, followed by ACTH and FSH/LH deficiency. None of patients had preoperative panhypopituitarism.

In cases with preoperative hypophyseal insufficiency, surgery achieves to lead an improvement in the anterior pituitary hormones in 30% of the patients during one year follow-up after surgery [9]. The risk of postoperative hypophyseal insufficiency is approximately 10% [31]. Pituitary insufficiency develops due to the resection or injury of anterior pituitary or stalk. Risk is variable due to the adenoma size, extent of resection and the experience of the surgeon. Stalk injury or resection results in DI. Temporary DI is approximately 10-20% while permanent DI is 2-7%. Surgical mortality is below 2% in experienced centers [32]. Twelve (21.8%) of the patients included in our study had temporary DI and 6 (10.9%) had persistent DI in postoperative period. According to the literature in the patients included in our study, high DI ratios can be explained by the large adenoma size and the high extracellular expansion rates.

In postoperative follow-up at 3-6. month and at 1 year pituitary MRI control is recommended [33]. Imaging is not rutinly recommended in the early postoperative period, but it may be helpful to remove the suspicion of postoperative complications and early surgical revision [34]. Unless a postoperative residual is detected, long-term follow-up of the first 5 years is recommended every year, followed by imaging at 7, 10 and 15 years. In the presence of postoperative residue or residual doubt, it is recommended to determine the MRI control intervals in the first 5 years every year, if there is no progression in the next period, once every 2-3 years, considering the tumor diameter, distant to the optic nerve and progression suspicion [35].

Control of the anterior pituitary hormones is recommended at 3rd month postoperatively to assess possible hypopituitarism. At the same time, ophthalmologic evaluation should be performed at postoperative 3rd month in patients with preoperative ophthalmologic abnormalities and should be followed every 6 months until maximum improvement is achieved. Follow-up can be discontinued in patients who have no abnormalities at the first postoperative follow-up and those who do not have a residual tumor close to the optic nevre [35].

Surgical revision may be required in 30-48% of NFPA patients due to the presence of large residual tumor in the early period or progression in follow-up after transsphenoidal surgery [36]. In the series published in the literature, it was observed that in a series with 160 microadenomas, MRI showed more than 10.6% tumor growth, 6.3% tumor shrinkage and 83.1% tumor size change in a longer follow-up than 8 years. In the same period follow-up of 353 patients with macroadenoma, 24.1% of the patients had tumor size growth, 12.7% had tumor size reduction and 63.2% of the patients showed similar persistence in the tumor size [37]. In a study conducted by Losa *et al*. [37], postoperative recurrence was found to be lower in patients undergoing early surgery. In the present study the mean postoperative follow-up time was 75.14 ± 43.01 months and 43.5% of the patients had recurrence. It has been showed that the risk of mortality was higher in NPHAs than in healthy

control. The causes of mortality were cardiovascular diseases, respiratory diseases and infections [38]. It has been alsofound that overall survival in patients with pituitary carcinomas was significantly worse than in patients with invasive pituitary adenomas [39]. In our study, no pituitary carcinoma was found.

Limitations

The retrospective nature of our study, the low number of patients and the possible deficits in patient file datas are among the limitations of our study. We believe that prospective studies with more patient numbers will provide clearer results on postoperative monitoring and follow-up of NFPAs.

CONCLUSION

As a result, NFPAs are often asymptomatic and are frequently diagnosed as incidental because of the increased imaging modalities currently available. The decision of the treatment is based on adenoma size, growth potential and presence of symptoms. Preoperative detailed endocrinological evaluation is very important in preventing complications due to operation and anesthesia. The urgency of the surgery is related to the severity of visual impairment. Adenoma size and experience of the surgeon are the most important factors affecting surgical success. Hypopituitarism may be developed in patients with normal hypophiseal functions, and also, hypopituitarism may be resolved with surgery. Operation performed in experienced centers, preoperative and postoperative endocrinological evaluation and long-term follow-up are recommended.

Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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ERRATUM

In the original article "*Preoperative and postoperative features of non-functioning pituitary adenomas: a single center experience*" published in The European Research Journal, September 2019, vol. 5, Iss. 5, pp. 827-835, the second author is Buket Biçer instead of Buket Özbiçer.

The evaluation of the relationship between fetuin-A and traditional and non-traditional cardiovascular risk factors in kidney transplantation recipients

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ABSTRACT

Objectives: Kidney transplantation recipients (KTRs) have higher cardiovascular complications risk compared to the general population. Cardiovascular risk factors (CVRF, Traditional and non-traditional) are widely studied to understand the causes of increased cardiovascular disease (CVD) risk in KTRs. Fetuin-A prevents from vascular calcification (VC) by inhibiting production and collapsing of apatite crystals to the vascular wall. The relationship between fetuin-A levels and CVRF in KTRs was investigated in this study.

Methods: Sixty-two KTRs with no prior CVD history participated. Anthropometrical, laboratory (fetuin-A, inflammation markers, antioxidants, lipid peroxidation products) and cardiological (echocardiographic, pulse wave velocity) measurements were performed. Participants were divided into two groups according to normal (≥ 0.5 g/L, n = 32, NFA) and low (< 0.5 g/L, n = 30, LFA) fetuin-A levels according to manufacturer's reference range, and the results were compared.

Results: No significant difference was observed in demographic features, body mass index, systolic and diastolic blood pressures, left ventricle mass index, waist and hip circumferences, left ventricle hypertrophy and waist-hip ratios between the two groups ($p > 0.05$). The ratios of drug usage such as immunosuppressives, anti-hypertensives and statin were comparable between two groups. Parathormone levels were significantly higher in the NFA group ($p = 0.015$) and glomerular filtration rate was calculated significantly higher in LFA group ($p = 007$). The comparison of other CVRF reveals no significant difference ($p > 0.05$).

Conclusions: Although many CVRF improved in KTRs, subclinical inflammation markers were still higher than the healthy population. Identification and early recognition of CVRF in high-risk individuals may contribute to the reduction of cardiovascular mortality. In our study, we observed no significant relationship between fetuin-A levels and CVRFs. We evaluated the relationship between serum fetuin-A levels on cardiovascular risk factors by its role in pathophysiology.

Keywords: Kidney transplantation, cardiovascular risk factor, fetuin A

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The most common cause of death in dialysis patients is cardiovascular disease (CVD) [1]. Although CVD risk after a successful kidney transplantation decrease compared with waitlisted patients on dialysis, transplant patients still have high risk of vascular complications compared with the general population [1, 2]. The causes of increased CVD risk in recipients are an exacerbation of traditional risk factors [advanced age, male gender, low HDL cholesterol, diabetes mellitus, smoking, race, family history, left ventricular hypertrophy (LVH), dialysis vintage, hypertension, increased low density lipoprotein (LDL) cholesterol, menopause, low levels of physical activity] due to the effect of immunosuppressive drugs, and non-traditional risk factors [proteinuria, hyperhomocysteinemia, elevated levels of lipoprotein (a) and apolipoprotein A isoforms, anemia, abnormal calcium (Ca) and phosphorous (P) metabolism, extracellular volume overload, oxidative stress, inflammation (elevated C-reactive protein and interleukin-6 levels), malnutrition, thrombogenic factors, sleep disorders, nitric oxide and endothelin balance changes] related to immunosuppressive drugs or to chronic kidney disease (CKD) [3, 4].

Vascular calcification (VC) and inflammationare common complicationscontributed to the development of CVD in patients with CKD.Disturbances of Ca and P homeostasis may induce calcification processes in these patients. Other factors related with the pathogenesis of VC in CKD include increased duration of uremia, increased dialysis vintage, low serum fetuin-A level and high serum level of fibroblast growth factor 23 (FGF23) [5]. Inflammation in CKD patients may contribute to endothelial dysfunction that observed in patients even in the early stages of the disease, and accelerated atherosclerosis [6]. In addition, inflammationis associated with VC or valvular calcification in CKD patients [7]. The presence of VC in hemodialysis patients is associated with increased stiffness of large capacitative elastic-type arteries like common carotid artery and aorta [8]. Arterial stiffness (AS) is known to occur before the onset of clinical disease in CKD patients and it is an independent risk factor for CVD. Transplantation improves large and to some extent small artery elasticities.Damaged large arterial compliance has an important role in the genesis of high systolic blood pressure (BP), high pulse pressure and increased LVH, while small arterial elasticity is related to endothelial dysfunction [9].

Fetuin-A is a glycoprotein that prevent from VC by inhibiting production and collapsing of apatite crystals to the vascular wall. Fetuin-A levels found to be very low in patients with kidney failure who have high risk for VC, and increased CVD frequency can be related with low fetuin-A levels in hemodialysis patients [10]. It is remarkable that inflammation markers related VC is seen in transplant recipients rather than traditional risk factor related AS [11]. The present study aimed to evaluate the relationship between serum fetuin-A levels with traditional and non-traditional CVD risk factors in transplant recipients.

METHODS

The cohort includedstable consecutive kidney transplant recipients who were older than 18 years and on regular outpatient clinic visits. We used the following exclusion criterias; presence of known CVD (coronary artery disease, heart failure, peripheral vascular disease, prior myocardial infarction), acute or chronic liver disease, any inflammatory disease, malignancy and history of hospitalization or surgery within the preceding 6 months. The study was carried out in accordance with Good Clinical Practice and the Declaration of Helsinki. The local ethics committee approved the study protocol and informed written consent was obtained from all individuals before they entered the study. Anamnestic information retrieved from all participants. A complete physical examination was performed to all recipients.

Normal fetuin-A serum concentrations (ninety-five percentile) range between 0.5 and 1.0 g/L with a mean value of 0.733 g/L and a standard deviation of 0.178 g/L. Kidney recipients were divided into two groups with normal (≥ 0.5 g/L, n = 32, NFA) and low (< 0.5 g/L, n = 30, LFA) fetuin-A levels.

Anthropometrical Measurements and Definitions

In all patients, body weight, waist (WC) and hip circumferences (HCs) were measured. WC was measured at the umbilicus level after normal breath to the nearest 0.1 cm. HC was measured at the most salient point between the waist and the thigh. Height was measured to nearest 0.1 cm and weight measured using a digital scale to nearest 0.1 kg. Body mass

index (BMI) was calculated as weight in kilograms divided by the square of height in meters [weight/height^2 (kg/m^2)]. The BMI was classified using the adult scheme proposed by the World Health Organization (WHO), which defines obesity as a BMI ≥ 30 kg/m^2 [12]. Abdominal obesity was defined using WC points of > 102 cm for men and > 88 cm for women.

Blood Pressure Measurements

Systolic and diastolic BPs were measured by one of the study investigators using standard mercury sphygmomanometer. BP cuffs of an appropriate size for each subject were attached to the upper arms. BP was measured in the arms over the brachial arteries. BPs were measuredfrom firstly right arm or arm without fistula in recipients with arterio-venous fistula.

Laboratory Measurements

Venous blood samples were taken after an overnight fasting. Routine biochemical and hematological parameters were studied on the day that the blood was collected. Plasma samples were centrifuged and frozen in aliquots at -80 °C until other assays were performed. Complete blood count (with CELL-DYN 3700), the levels of serum glucose, urea, creatinine, uric acid, Ca, P (by enzymatic method), total cholesterol (T-chol), triglyceride (by enzymatic hydrolyse method) and high-density lipoprotein (HDL) cholesterol (by enzymatic elimination method) were measured with Abbott kit in Aeroset device. LDL cholesterol was calculated with Friedewald formula [13].

Serum intact parathyroid hormone (iPTH) measured by immunoassay with Immulite 2000 AnalyserDpc. High-sensitive C-reactive protein (hsCRP) measured with solid phase chemiluminesans immune measurement method by Immulite 2500 kits in Immulite 2500 device. 24-hour urinary protein excretion (UPE) was measured by immunoassay (DCA 2000 system, Siemens AG, Munich, Germany). We calculated estimated glomerular filtration rate (eGFR) using 2009 the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation [14]. Bone mineral density (BMD) was measured with DEXA method (Hologic QDR-2000, Waltham, MA, USA) from femoral and lumbar regions.Anemia after transplantation defined as hemoglobin falls to less than 11 g/dL in premenopausal females or to less than 12 g/dL in males and postmenopausal females [15]. Inflammation markers [interleukin 6 and 8 (IL-6, IL-8), tumor necrosis factor alpha (TNF-α), fibronectin, transforming growth factor beta (TGF-β)], anti-oxidant enzymes [whole blood glutathione peroxidase (Gpx), serum superoxide dismutase (SOD) and total antioxidant status (TAOC)], antioxidants (vitamin C) and lipid peroxidation products [red blood cell malondialdehyde (RBC MDA)] were measured.

Serum fetuin-A levels were measured byan enzyme-linked immunosorbent assay (ELISA) kit for human fetuin-A (BioVendor Laboratory Medicine, Brno, Czech Republic) according to manufacturer's instructions. Intra- and inter-assay coefficients of variation were both less than 5.0%. Normal serum concentrations of fetuin-A in healthy adults range between 0.5 and 1.0 g/L [16].

Cardiac Measurements

The cardiac parameter's measurement in recipients was performed by the same physician at the lab of cardiology department. Echocardiographic measurements were done with Vivid 3 device (General Electrics, Vivid 3 echocardiography, Milwaukee, WI, USA). Left ventricle mass index (LVMI) was calculated by division of left ventricle mass calculated with Dewereux [13] formula (Left ventricle mass (g) = 0.8×1.04×[(LviDD+IVS+PWT)^3-LviDD^3] + 0.6) to body surface area with Mostellar formula [17] (√height × weight/3600). LVMI ≥ 110 g/m^2 and ≥ 134 g/m^2 is accepted as LVH in women and men, respectively. All AS measurements were performed on radial artery. Stroke volume, cardiac output, systemic vascular resistance impedance and large/small vascular elasticity indexes were measured with PulseWave Sensor HDI (Hypertension Diagnostics, Eagan, MN).

Statistical Analysis

The data was analyzed using the IBM SPSS Software package of version 23.0 (IBM Corp, Armonk, NY, USA) licensed to Uludag University. Normality of variables was assessed by the Shapiro - Wilk's normality test. Categorical variables were given as number and percentage, and numerical variables as mean ± standard deviation or median

(minimum-maximum). Continuous variables were compared using the parametric two independent samples t-test or the non-parametric Mann-Whitney test in intergroup comparisons. Chi square test and Fisher-Freeman-Halton test were used to test the differences in proportion of the categorical variables. Associations between variables were estimated using Pearson or Spearman correlation coefficients. A *p* value less than 0.05 was considered to be significant.

RESULTS

Characteristics of recipients

The cause of chronic kidney disease in 23 recipients was unknown. The primary disease of the rest was glomerulonephritis (n = 8), diabetic nephropathy (n = 2), hypertensive nephropathy (n = 11), obstructive nephropathy with vesicoureteral reflux (n = 6), polycystic kidney disease (n = 5), nephrolithiasis (n = 3) and rare diseases (n = 4). Before kidney transplantation, 42 patients were on hemodialysis (HD), 8 patients were on peritoneal dialysis (PD), 7 patients were converted from PD to HD and 5 patients underwent preemptive transplantation. Mean dialysis durations were 44.1 ± 5.2 months. All patients underwent first kidney transplantation and mean follow-up time after transplantation was 36.9 ± 4.8 months. Numbers of diabetic and hypertensive recipients were 12 and 44, respectively.

There was no significant difference between demographic features of the two groups (Table 1). The ratios of drug usage such as immunosuppressives, anti-hypertensives and statin were comparable between two groups. Also, BMI, systolic and diastolic BPs, LVMI, waist and hip diameters, LVH and WHRs of the groups were similar (Table 1). LVMI was 145.9 ± 22.1 g/m^2 (min-max: 110-187) in patients with LVH (n = 27) and 107.3 ± 19.4 g/m^2 (min-max: 62.9-133.7) in patients without LVH (n = 35), $p < 0.001$. Family history for HT, DM, CAD and obesity was similar (Table 1).

Table 1. Comparison of Demographic data and traditional cardiovascular risk factors between the groups with normal and low fetuin-A levels

	Normal (n = 32)	Low (n = 30)	*p* value
Male/female ratio	13/19	16/14	0.316
Age (years)	37.9 ± 10.3	37.7 ± 11.9	0.934
Dialysis duration, [months, median (min-max)]	34.5 (0-145)	31 (0-190)	0.925
Dialysis modality, n (%)			0.480
HD	20 (62.5)	22 (73.3)	
PD	5 (15.6)	3 (10)	
HD+PD	3 (9.4)	4 (13.3)	
Pre-emptive	4 (12.5)	1 (3.3)	
Donor type (living/deceased)	19/13	18/12	0.960
Donor age, [years, median (min-max)]	50.5 (15-73)	46.5 (11-62)	0.179
Transplant duration [months, median (min-max)]	16.5 (7-147)	23 (6-157)	0.388
HT, n (%)	24 (75)	20 (66.7)	0.470
DM, n (%)	7 (21.9)	5 (16.7)	0.604
CAD, n (%)	-	1 (3)	0.298
Obesity, n (%)	3 (9.4)	8 (26.7)	0.075
Abdominal obesity, n (%)	13 (40.6)	16 (53.3)	0.316
Smoker (n, %)	2 (6.3)	4 (13.3)	0.346
Physical activity, n (%)	15 (46.9)	20 (66.7)	0.116

Table 1 Continued.

Medication History			
Immunosuppressive regimens, n (%)			0.167
Tac+MMF+P	18 (56.3)	17 (56.7)	
CsA+MMF+P	5 (15.5)	8 (26.7)	
Tac+AZA+P	-	2 (6.7)	
CsA+AZA+P	2 (6.3)	-	
Tac+P	-	2 (6.7)	
EVR+CsA+P	1 (3.1)	-	
EVR+Tac+P	3 (9.4)	1 (3.3)	
EVR+MMF+P	1 (3.1)	-	
SRL+MMF+P	2 (6.3)	-	
Statin use, n (%)	6 (18.7)	4 (13.3)	0.409
Anti-hypertensive, n (%)			
None	8 (25)	10 (33)	0.470
Combination	16 (50)	14 (46)	0.793
ACEI or ARB	9 (28)	7 (23)	0.667
β-Blocker	15 (46)	7 (23)	0.053
α-Blocker	1 (3)	5 (16)	0.071
CaCB	19 (59)	16 (53)	0.632
Family history, n (%)			
HT	10 (31.3)	7 (23.3)	0.485
DM	7 (21.9)	5 (16.7)	0.604
CAD	8 (25)	5 (16.7)	0.421
Obesity	6 (18.8)	9 (30)	0.301
Measurements			
BMI (kg/m^2)	25.3 ± 3.6	26.5 ± 5.4	0.295
Systolic BP (mmHg)	136.2 ± 18.1	133.1 ± 15.8	0.485
Diastolic BP (mmHg)	81.3 ± 11.2	78.2 ± 12.2	0.300
Waist circumference (cm)	93.2 ± 10.2	95.0 ± 14.1	0.570
Hip circumference (cm)	101.5 ± 9.5	105.7 ± 11.6	0.127
Waist to hip ratio	0.91 ± 0.07	0.89 ± 0.06	0.204

HD = hemodialysis, PD = peritoneal dialysis, Tac = tacrolimus, MMF = mycophenolate mofetil or sodium, P = prednisolone, CsA = cyclosporine, AZA = azathioprine, EVR = everolimus, SRL = sirolimus, ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CaCB = calcium channel blocker HT = hypertension, DM = diabetes mellitus, CAD = coronary artery disease, BMI = body mass index, BP = blood pressure

Treatments

All patients were treated with tacrolimus (Tac, 0.05-0.1 mg/kg/d, n = 43) or cyclosporine A (CsA, 6 mg/kg/d, n = 16) or mammalian target of rapamycin (mTOR) (everolimus, n = 6 or sirolimus, n = 2) combined mycophenolic acid (1440 mg/d) or mycophenolate mofetil (2 g/d) (n = 51) or azathioprine (100 mg/d, n = 4) and corticosteroids (methylprednisolone, 500 mg intravenous; then, prednisolone, 1 mg/kg/d oral). All patients received induction treatment with basiliximab (20 mg, before and 4 days after transplantation). The dosages of Tac and CsA were adjusted to achieve target trough levels (CsA: first 3 mo, 200-300 ng/mL; subsequently, 100-200 ng/mL and Tac: first 3 mo, 8-12 ng/mL; subsequently, 5-8 ng/mL). Oral prednisolone dosage

was tapered to 20 mg/d after 1 month, 10 mg/d after 2 months and 5 mg/d after 6 months.

Some recipients received antihypertensive monotherapy (n = 14) or combination therapy (n = 30) (calcium channel blockers, n = 35; beta-blockers, n = 22; renin-angiotensin-aldosterone-system blockers, n = 16 and alpha-blockers, n = 8). Other medications were insulin therapy (n = 8), oral anti-glycemic agents (n = 4), statin (n = 10), vitamin D (n = 13), bisphosphonate (n = 5) and oral calcium replacement (n = 4).

While the mean serum creatinine (1.52 ± 0.6 vs. 1.29 ± 0.4 mg/dL, p = 0.112) and UPE (0.44 ± 0.83 vs. 0.52 ± 1.23 gr/day, p = 0.754) values of groups with normal and low fetuin-A level did not differ, eGFR (54.8 ± 15.3 vs. 67.9 ± 21.1 ml/min/m^2, p = 0.007) levels are higher in low fetuin A group (Table 2).

No significant differences were observed among two groups in Ca and P levels, Ca×P product and normal/pathological DEXA measurement rates. Serum PTH levels are significantly higher in normal fetuin A group (167.1 ± 128.1 pg/mL vs. 95.2 ± 47.86 pg/mL, p = 0.015). AS (large and small vessel elasticity indexes and total vascular impedance measurements), inflammatory (hsCRP, fibrinogen, fibronektin, TNF-α, IL-6, IL-8) and oxidative stress (SOD, MDA) parameters shows no significant differences between the two groups (Table 3).

In the study group, fetuin-A levels were positively correlated with creatinine (r = 0.312, p = 0.013) and negatively with eGFR (r = -0.299, p = 0.018). There was no correlation between fetuin-A level and other parameters.

DISCUSSION

Serum fetuin-A levels are significantly increased after successful kidney transplantation compared to CKD patients, but it is still lower than healthy population [18]. Kidney transplantation improves vascular function [19], but early cardiovascular death risk remains increased [20]. In order to reduce CV mortality, it is crutial to understand the clues for progressing CV diseases. For this purpose, traditional and non-traditional cardioavascular risk factors are defined as mentioned in introduction section.

Increased fetuin-A levels after transplantation thought that there is a relationship between low fetuin-

Table 2. Comparison of laboratory results in two groups with normal and low fetuin-A levels

	Normal (n = 32)	Low (n = 30)	*p* value
Hemoglobin (g/dL)	12.7 ± 2.0	12.9 ± 2.1	0.722
Urea [mg/dL, median (min-max)]	41 (15-119)	38.5 (23-87)	0.307
Creatinine [mg/dL, median (min-max)]	1.32 (0.94-3.46)	1.27 (0.6-2.81)	0.112
eGFR (mL/min/m^2)	54.8 ± 15.3	67.9 ± 21.1	**0.007**
Uric acid [mg/dL, median (min-max)]	6.1 (2.9-9.2)	5.7 (3.2-10)	0.578
Glucose (mg/dL)	97.1 ± 28.2	87.9 ± 13.9	0.110
T-chol (mg/dL)	199.0 ± 48.1	203.0 ± 44.7	0.740
HDL (mg/dL)	52.6 ± 14.9	49.7 ± 19	0.507
LDL (mg/dL)	115.4 ± 36.9	122.1 ± 33.5	0.456
Triglyceride (mg/dL)	147 (64-390)	134 (84-346)	0.916
LVMI (g/m^2)	127.8 ± 27.9	120.2 ± 28.2	0.295
LVH, n (%)	16 (50)	10 (33.3)	0.184
UPE [g/day, median (min-max)]	0.170 (0.01-3.35)	0.027 (0.01-4.87)	0.754

eGFR = estimated glomerular filtration rate, UPE = urinary protein excretion, T-chol = total cholesterol, HDL = high density lipoprotein, LDL = low density lipoprotein, LVMI = left ventricle mass index, LVH = left ventricle hypertrophy

Table 3. Comparison of non-traditional cardiovascular risk factors between the groups with normal and low fetuin-A levels

	Normal (n = 32)	Low (n = 30)	*p* value
Fetuin-A (g/L)	0.616 (0.511-1.079)	0.406 (0.153-0.497)	**< 0.001**
Proteinuria, n (%)	7 (21.9)	5 (16.7)	0.751
Anemia, n (%)	9 (28.1)	5 (16.7)	0.367
Calcium (mg/dL)	9.42 ± 0.71	9.41 ± 0.57	0.927
Phosphorus (mg/dL)	3.20 ± 0.68	3.18 ± 0.67	0.880
Ca×P	30.03 ± 5.71	29.79 ± 5.82	0.872
PTH [pg/mL, median (min-max)]	113.2 (33.8-522)	83.9 (28-207)	**0.015**
Osteoporosis, n (%)	7 (21.9)	4 (13.3)	0.511
Osteopenia, n (%)	17 (53.1)	21 (70)	0.173
C1 (ml/mmHgx10)	12.75 ± 5.70	13.57 ± 4.99	0.565
C2 [ml/mmHgx10, median (min-max)]	3.9 (2.5-7.9)	5.2 (1.9-10.2)	0.185
TVI, [median (min-max)]	141.5 (58-295)	125 (79-277)	0.477
hsCRP [mg/L, median (min-max)]	2.55 (0.2-45)	2.1 (0.2-30.9)	0.689
Fibrinogen (mg/dL)	4.26 ± 1.24	4.19 ± 1.23	0.888
Fibronectine (µg/mL)	112.2 ± 25.6	115.3 ± 27.3	0.644
TNF-α [ng/mL, median (min-max)]	0.081 (0-0.53)	0.050 (0.02-0.5)	0.557
IL-6 [ng/mL, median (min-max)]	1.04 (0.76-44.8)	0.89 (0.77-23.5)	0.523
IL-8 [ng/mL, median (min-max)]	6.34 (0.4-71.9)	6.71 (0.4-33.1)	0.791
TGF-β [pg/mL, median (min-max)])	4913 (917-47651)	5363 (974-29643)	0.817
SOD [U/mL, median (min-max)])	977 (408-3059)	1140 (565-2178)	0.613
GSHpx [U/mL, median (min-max)]	18.4 (9.75-40.5)	15.8 (6.46-56.8)	0.987
MDA [nmol/mL, median (min-max)]	1.04 (0.15-3.52)	1.05 (0.38-2.67)	0.986
Vitamin C [mg/dL, median (min-max)]	2.07 (0.17-12.7)	2.18 (0.51-15.2)	0.234
TAOC [mmol/L, median (min-max)]	1.15 (0.48-5.56)	1.07 (0.43-6.37)	0.768

Ca×P = calcium × phosphorus, PTH = parathormone, DEXA = Bone mineral density, C1 = large vessel elasticity index, C2 = small vessel elasticity index, TVI = total vascular impedance, hsCRP = high sensitive C-reactive protein, TNF-α = tumor necrosis factor alpha, IL-6 = interleukin 6, IL-8 = interleukin 8, TGF-β1 = transforming growth factor β1, SOD = superoxide dismutase, GSHpx = glutathione peroxidase, TAOC = total antioxidant status, MDA = malonyl dialdehyde

A levels and glomerular dysfunction [18]. Another study in patients with coronary artery disease reported no relationship between GFR and fetuin-A concentrations [21]. Impaired endothelial functions in transplanted patients were reported in several studies [22-24]. Our data shows that patients with lower fetuin A concentration has greater eGFR (p = 0.007), but urea and creatinine levels were similar (Table 2). Several factors may be responsible for the discrepancies including the effect of calcineurin inhibitors [23].

In our cohort, there was no relationship between fetuin-A levels and cholesterol levels, diabetes mellitus and obesity and waist to hip ratios as other studies revealing fetuin-A levels did not correlated renal and metabolic parameters [25].

Cardiovascular events and all-cause mortality rates were significantly increased in transplant

recipients with low serum fetuin-A levels [26]. The main lesions underlying and ultimately responsible for the clinical manifestations of CVD are atheroma and VC, which often exist together [27]. Marechal *et al*. [26] have pointed out the difference in the determination of coronary artery and aortic calcification by fetuin-A levels in a multiple linear regression analysis. Although lower serum fetuin-A level was reported as an independent predictor of aortic calcification (p = 0.008) no relationship was found in coronary artery calcification [26]. In our study, the number of patients with the history of defined coronary artery disease in the groups with low and normal fetuin-A levels were similar (Table 1).

It is reported that although, coronary artery calcification (CAC) progress is lower in transplanted patient compared with HD patients, but progression still exist. This data explained with the calcification burden during the pre-transplant dialysis period [28, 29]. No relationship between pre-transplant dialysis duration, dialysis modality, transplant duration and fetuin-A levels was observed in our study.

Diabetes mellitus is a risk factor for the presence of CAC in kidney transplant paitents but has not been independently associated with CAC progression [27]. The relationship with diabetes mellitusexistance and fetuin-A levels were not statistically significant in our study.

Serum fetuin-A levels are determined by variants in the plasma cholesterol levels, and a history of smoking, independently of inflammation [26]. Our data showed no difference in cholesterol levels and smoking rates depending on fetuin-A levels.

Kidney transplantation restores endothelial functions. Some studies reported impaired endothelial functions in kidney transplant recipients compared to healthy controls [22-24] which attributed to the effect of calcineurin inhibitors [23]. Inducible nitric oxide inhibition with steroids and calcineurin inhibitors that cause endothelial dysfunction, associated with onset and progression of atherosclerosis and VC. While mycophenolate mofetil has a more favorable effect on endothelial activity than do calcineurin inhibitors and steroids [30], vascular effects of mTOR inhibitors are much more complex. Rapamycin inhibits smooth muscle cell proliferation, while everolimus impairs the vasoactive and antithrombotic function of endothelial cells. In particular, sirolimus inhibits osteoclast formation, unlike steroids and cyclosporine [31]. Our results showed no relationship between fetuin levels and immunosuppressive protocol regimens given. Hypothetical effect of immunosuppressive therapy on VC could be mediated indirectly, by interfering with post-transplant bone loss, and directly through effects that the same drugs exert on vascular cells (endothelial cells, vascular smooth muscle cells) through intermediation of the RANKL, RANK, and OPG systems [27]. Since osteoporosis rate was higher in normal fetuin A group (7 [21.9%] vs 4 [13.3%], p = 0.511) and osteopenia rate was higher in low fetuin A group (21 [70%] vs 17 [53.1%], p = 0.173), both results could not reach statistically significant difference.

Fetuin-A inhibits Ca-P precipitation in the serum [32]. An analysis of data obtained from 40,000 patients [33] shows that relative death risk increased 1.5 times in patients whom CaxP is 70 to 75 mg^2/dL^2, and 1.8 times with a Ca×P > 80 mg^2/dL^2. A significant increase in mortality risk was associated with even relatively small rises in Ca×P to 50 to 55 mg^2/dL^2 [33]. In our study Ca×P values were similar in both groups.

Progression of CAC slows down but does not halt after kidney transplantation. There is a strong association between baseline CAC score and CAC progression. A significant improvement in secondary hyperparathyroidism after transplantation favorably affects the progression of CAC. Low 25(OH)D3 levels are an independent determinant of CAC progression [27]. Ciancialo et. al. [27] reported a significant improvement in secondary hyperparathyroidism after transplantation that slow-down the progression of CAC. No relationship was found between PTH and VC in a VC progression speed study [34]. Sumida *et al*. [35] observed strong correlation between carotid plaque and male sex, presence of DM, PTH and VC. DM is a risk factor but has not been identified as an independent risk factor for coronary artery calcification progression [27]. The VC was found associated with the Ca and P multiplication (Ca×P). In our study, no significant difference was observed in Ca, P levels and CaxP between the groups. Number of patients with low bone mineral density between the groups was also similar. However, PTH levels were significantly higher in patients with normal Fetuin-A levels, no correlation was observed between Fetuin-A levels and bone mineralization parameters (Ca, P,

Ca×P, PTH, DEXA total lumbar score, DEXA total hip score).

Inflammation is an independent predictor of renal allograft loss [36, 37]. Patients with lower fetuin-A levels (< 0.47 g/L) and higher hsCRP levels (> 4.36 mg/L) had worse survival, with a risk of death and cardiovascular events 3.48 times higher compared with patients with higher fetuin-A and lower hsCRP combination [26]. Fetuin-A has significant anti-inflammatory functions such as inhibition of TGF-β, tyrosine kinase activity, inflammatory cytokines IL-1β, IL-6 and TNF-α [38, 39]. Although fetuin-A acts as a negative acute phase reactant, no correlation was found between fetuin-A levels and markers of inflammation [26]. Our study did not show association between fetuin-A levels and inflammatory markers such as hsCRP, fibronectine, TNF-α, IL-6, IL-8 and TGF-β.

Vascular cellular calcification is indepentantly promoted by oxidative stress which show procalcific effects over oxysterols, oxidized lipids and inflammatory cytokines [40]. It has been shown that, vascular smooth muscle cells' osteochondrocytic differentiation is promoted by the classical oxidant stressor, H_2O_2 [41]. Serum SOD, GSHpx and MDA levels were similar, TAOC and Vitamin C levels were not differ between the groups in this study.

Chronic inflammation in CKD patients leads to lower serum fetuin-A levels [42] and that serum fetuin-A showed important association with coronary, valvular calcification and inflammation in CKD patients [43]. In pediatric population serum fetuin-A levels did not identify as an independent predictor of vascular stiffness [44]. Aortic wall stiffness, as reflected by aortic pulse-wave velocity, is a strong predictor of cardiovascular events [45]. Our observation reveals no relationship between fetuin-A levels and total vascular impedance, large and small vessel elasticity indices.

CONCLUSION

We evaluated the effect of kidney transplantation on cardiovascular risk factors and relationship of serum fetuin-A levels with cardiovascular risk factors by its place in pathophysiology in this study and we observed that although many cardiovascular risk factors improved after kidney transplantation, subclinical inflammation markers were still higher than healthy volunteers. We found no relationship between serum fetuin-A levels and inflammatory, oxidative stress markers and AS parameters. Comparison of non-traditional risk factors that have an important place on cardiovascular illness pathophysiology in large transplanted and healthy volunteer population may contribute to increased survival after kidney transplantation by understanding underlying inflammatory process.Atherosclerosis and most of the cardiovascular risk factors progress silently. Early recognition of these risk factors and identification of high-risk individuals may contribute to the reduction of cardiovascular mortality.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2019;5(5):847-852 ORIGINAL ARTICLE

Retrospective analysis of patiens with brain death

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ABSTRACT

Objectives: We aimed to retrospectively analyze brain death cases in the our intensive care units.

Methods: We examined archive records of brain death cases diagnosed between January 01, 2014 and October 01, 2018. We recorded patients' demographics (age, gender, place of birth, blood type and diagnosis on admission), time to the preparation of the report, additional tests performed, rate of organ donation, donor rate, and number of organs removed.

Results: A total of 151 brain death cases were detected. Of these, 69 were female. The average age was 53.96 ± 19.52years. A Rh + was the most common type (39.7%) in blood type analysis. Intracranial hemorrhage was the primary reason (54.3%) for admission. Apnea test was performed for 88 patients. Radiological imaging was used in 129 (85.4%) cases; computed tomography angiography being the most commonly performed method with 79 (52.3%) cases. Forty four patients' families consented to organ donation. Considering the place of birth for donors, Marmara Region was the leader with 18 (40.9%) donors. Of the 82 brain death cases diagnosed with intracranial hemorrhage, 35 (42.68%) donated organs and this rate was significantly high (p = 0.002). The mean follow-up period for brain death was 1.49 days.

Conclusions: Health team is responsible for identifying brain death and shoud be conscious about it, attempting to increase organ donation. They should act rapidly and avoid wasting time after the diagnosis. Family interviews to be conducted by an experienced and trained organ donation coordinator may increase donations by emphasizing the importance of organ donations. Giving wide media coverage to organ donation may increase awareness of the community of organ donation.

Keywords: Brain death, intensive care, donor

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The advancement of modern medicine provides the patients to recover with organ transplantation, thus the importance of it increases gradually [1]. Organ transplantation occurs in two ways, either from live donors or cadavers. Cadavers are the safest source for transplantation and the heart, pancreas, lungs, small intestine, and cornea are organs that can be obtained from them [2]. In order to perform an organ transplant from a cadaver, the diagnosis of brain death must be established first. Brain death is irreversible loss of all brain functions, including the brain stem, and physiopathological termination of the intracranial circulation. The diagnosis of brain death is a clinical diagnosis in which the presence of irreversible coma, areflexia and apneaare observed [3]. Today, in most of the countries around the world, the criterion of brain

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death is accepted and the moment when the brain death occurs is regarded as the moment of death. The most common causes of brain death in adults are anoxic brain injury following the cardiopulmonary arrest, traumatic brain injury, intracerebral hemorrhage, subarachnoid hemorrhage, and ischemic stroke; as for children, they are motor vehicle accidents, asphyxia and child abuse [4]. The diagnostic criteria of brain death in our country were identified by the Ministry of Health [5]. Clinical explanation of the cause of deep coma and absence of the brain stem reflexes, lack of spontaneous breathing efforts, and positive apneatesting are required for the diagnosis, and unanimous consent of two experts, one of which is a neurology or neurosurgery specialist and the other one is an intensive care or anesthesiologyand reanimation specialist, is mandatory. It should be observed that the clinical situation in the first neurological examination, in which brain death is diagnosed, remains samein the second neurological examination performed after 48 hours in infant under two months, 24 hours in children between 2 months and 1 year, 12 hours in children and adults over 1 year of age and 24 hours in anoxic brain deaths. In cases in which individuals under two months are diagnosed with clinical brain death, two supportive tests and in other cases in which individuals are two months old and older, a suitable laboratory method is used to confirm the diagnosis a supportive testshould be performed, there is no need to wait for a second neurological examination [5]. Supportive methods are intended to show that cerebral blood flow is stopped or that brain functions are irreversibly shut down. The gold standard examination is four-vessel angiography [6]. Computed tomography (CT), computed tomography angiography (CTA), magnetic resonance angiography (MRA), transcranial doppler ultrasonography (TCDU), brain scintigraphy and electroencephalography (EEG) can also be performed [7]. Despite all advances in the field of intensive care, the insufficient number of brain death diagnoses and organ donations stands as the most serious problem for patients waiting for organ transplantation. Therefore, it is suggested that the diagnosis of brain death should be made without delay and appropriate donor care should be in place, organ transplant coordinators should visit intensive care units more frequently, and should closely monitor the cases whose Glasgow Coma Scale (GCS) is under seven [8].

In this study, demographic characteristics of the brain death cases detected in the intensive care unit (ICU) of Bursa Yüksek İhtisas Training and Research Hospital, the supportive tests used, the rate of acceptance or rejection of organ donation by families and the rate of use of donated organs will be examined.

METHODS

The study was performed retrospectively between January 1, 2014, and October 7, 2018, after the approval of the ethics committee (2011-KAEK-25 2018/10-28) by examining the records of all patients who were hospitalized in the intensive care units of our hospital and diagnosed with brain death. Demographic characteristics of the cases, such as age, gender, place of birth, blood type, diagnosis on admission, elapsed time from the moment clinical suspicion of brain death began until the report was prepared, additional tests applied to detect brain death, the rate of organ donation by families, the rate of donors among the cases and the number of organs removed were recorded. The data was obtained by examining archive files and computer records.

Statistical Analysis

Statistical analyses were performed using the SPSS 21.0 Windows (SPSS, Armonk, New York, IL, USA) software. Variables were expressed as mean, minimum-maximum and percentage.

RESULTS

In the ICU of the hospital, 151 cases with brain death were identified between January 1, 2014, and October 1, 2018. Of the examined cases, 69 were female and 82 were male. The mean age was 53.96 ± 19.52 (3-87 years), and most of the brain death cases were observed in the age range of 46-64, 62 people (41.1%). In the blood type of examination, the most common one was A Rh-positive with 39.7%. Demographic data are shown in Table 1. Of the hospitalized patients, 144 were from the emergency clinic and other services of our hospital and 7 patients were referred from other centers. The admission diagnoses of the patients were evaluated in 5 groups,

Table 1. Demographic characteristics

Characteristics	n (%)
Age groups (years)	
1-17	7 (4.6)
18-45	36 (23.8)
46-64	62 (41.1)
65-74	24 (15.9)
75-84	17 (11.3)
85-100	5 (3.3)
Gender, female	82 (54.3)
Blood type	
A Rh +	60 (40)
A Rh -	7 (4.7)
B Rh +	21 (13.9)
B Rh -	4 (2.6)
AB Rh +	7 (4.6)
AB Rh -	-
O Rh +	48 (31.8)
O Rh -	3 (2)
Region of birth	Brain death/Donor
Marmara	59 (39.1)/18 (40.9)
Aegean	13 (8.6)/5 (11.6)
Mediterranean	1 (0.7)/-
Inner Anatolia	6 (4)/1 (2.27)
Southeast Anatolia	11 (7.3)/2 (4.54)
East Anatolia	11 (7.3)/4 (4.09)
Black Sea	25 (16.6)/9 (20.45
Abroad	25 (16.6)/5 (11.6)

namely intracranial hemorrhage, occlusive cerebrovascular accident (CVA), brain tumor, post cardiopulmonary resuscitation (CPR), head trauma and others. Intracranial hemorrhage came first with 54.3% (Figure 1). Apnea test was performed on 88 patients, but it could not be performed on 63 patients due to hemodynamic instability. Radiological imaging methods were utilized to support the diagnosis in 85.4% (n = 129) of the cases clinically diagnosed with brain death. CTA, MRA, TCDU, diffusion magnetic resonance and cranial CT were applied on 79 (52.3%), 42 (27.8%), 3 (2%), 1 (0.7%) and 1 (0.7%) cases respectively. There was no discrepancy between the clinical diagnosis and imaging methods.

Of the 151 cases diagnosed with brain death, 44 (29.1%) approved family donations and 107 (70.9%) refused. The birth places of donors were evaluated in 8 regions. Marmara region ranked first with 18 (40.9%) donors (Table 1).

No statistically significant difference was detected regarding donor and age group, gender place of birth. Of the 82 brain death cases diagnosed with intracranial hemorrhage, 35 (42.68%) were donors and the patients with intracranial hemorrhage were statistically and significantly higher ($p = 0.002$).

The mean elapsed time to follow brain death was 1.49 days (1-15). Removed from the donors, 6 kidneys, 9 hearts, 8 livers, 4 lungs, 2 corneas, 3 pancreases and 1 small intestine could not be used due to such medical reasons as horseshoe kidney, prolonged period of cold ischemia, eld, unsuitability as a result of biopsy, high troponin value, grade 3 fatty liver, severe sepsis and lack of appropriate recipient. The organs removed from the donors and used were shown in Table 2.

Table 2. Organs removed and used

Organs	Removed (n)	Used (n)
Kidney	41	35
Liver	45	37
Heart	14	5
Lungs	10	6
Cornea	26	24
Pancreas	3	0
Smal bowel	1	0

DISCUSSION

In the world and in our country, organ transplantation is a significant health problem for patients whose treatment and life depend on it. While kidneys and livers can be taken from live donors, single organs such as heart, lung, and pancreas can only be obtained from cadavers. There is a multi-step organ donation process which includes detection of the potential donor, reporting, controlling medical contraindications, donor care, obtaining family approval, removal of organs and directing them to recipients, keeping the removed organs alive in an

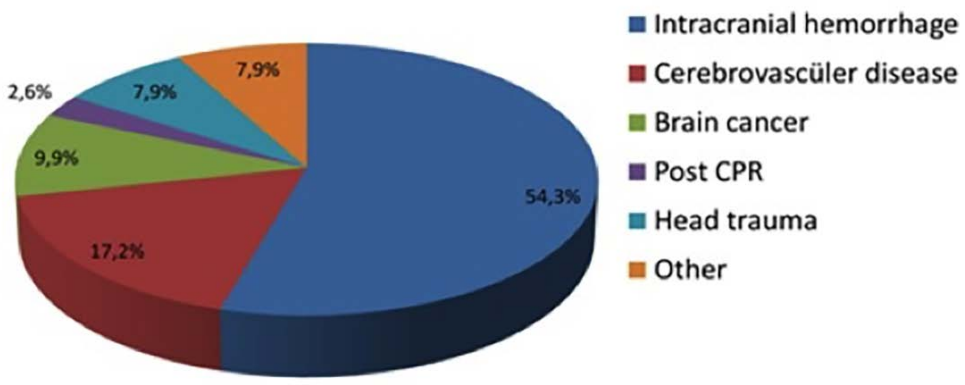

Figure 1. The admission diagnoses of the patients.

artificial environment and finally transferring them to the recipient [9]. Donor loss might occur in any of these steps, while it most frequently occurs during the detection of the potential donor, reporting and family approval steps. In order to prevent this, training and motivation of physicians, nurses and health professionals working in ICU in the recognition of brain death and donor care are among fundamental factors.

National and international standardization on brain death diagnostic criteria is provided. In our country, there are two experts in the committee on legal determination of brain death. They are neurosurgery or neurology specialists, and anesthesiology and reanimation specialist. It is of great importance that the people assigned in this commission are well-trained and experienced in the diagnosis of brain death and that the organ transplant coordinators responsible for the family approval step are trained, and that they work in close cooperation with the primary care physician.

The first case of brain death was observed in 2007 in Bursa Yüksek İhtisas Training and Research Hospital. In a study conducted by Karasu *et al*. [10] between 2007 and 2014, 79 brain deaths were identified and 27 of them were reported to be donors. In our study, the cases with the diagnosis of brain death between 2014 and 2018 were examined. A total of 151 cases were identified and the total number of donations was found to be 44. An increase in the intensive care team and organ transplant coordinator pieces of training throughout the process of the study may have increased the number of brain death determinations.

When the gender of those diagnosed with brain death is referred, the majority of them were male, just like in other studies [10, 12]. In other studies, the mean age of the cases with brain death was between 40 and 48 years while the mean age of our study was found to be 53.96 ± 19.52 [10, 12.13].

Battal *et al*. [12] examined the records of 62 patients diagnosed with brain death. They reported the diagnosis of brain death in an average of 3 days and found the organ donation rate as 29.03%. Karasu *et al*. [10] reported that 86% of 79 patients were diagnosed with brain death within the first week of their hospitalization and the organ donation rate was 34.2%. In our study, the diagnosis of brain death was made in an average of 1.49 ± 1.53 days and the organ donation rate was found to be 29.1%.

The admission diagnoses of the brain death cases were classified differently in many studies. The most common one was trauma with 58% in a study by Battal *et al*. [12] and with 48.3% in another study [14]. In our study, the most common admission diagnosis was intracranial hemorrhage with 54.3% as in the study by Karasu *et al*. [10].

Family approval rate was 34.2% in a study with 79 notifications in 7 years [10], 69% in a study with 48 notifications in two years [12], and 29% in another study with 62 notifications in 4.5 years [15]. In our study, family approval could be obtained from 29.1% of the cases. This explicit difference in family approval may be due to the experience of the hospital staff and cultural differences in the regions. In our study, the birthplaces of the donor cases were

examined in 8 different regions and 18 donors were from the Marmara region, which made it take the first place with 40.9%. In other studies, no evaluation was made in terms of the place of birth.

In our study, the blood types of 151 cases with brain death were investigated. A Rh-positive blood type was found the highest with 39.7%.

Once brain death is detected, auxiliary methods may be required to confirm the diagnosis [16, 17]. In our study, radiological imaging methods were utilized to confirm the diagnosis in 85.4% (n = 129) of the cases diagnosed with brain death. The most commonly used method was CTA with seventy-nine (52.3%) cases.

2046 brain death cases were reported according to the 2017 data in Turkey. Family approval was obtained in 357 (28.45%) of these cases. In our hospital, family approval was obtained from 11 (30.5%) of 36 brain death cases that were reported in 2017. Family approval in our study was 29.1% which is similar to the general population [18].

Spain was reported as the country with the highest donor rate in the world. In 2017, in Spain (population = 46.4 million), there were 2183 donations from cadavers, PMP (per million population) value was 47, and in Turkey (population = 80.7 million), there were 554 donations from cadavers, PMP value was 6.9 [18]. This low rate in our country cannot be overcome only by raising awareness of health personnel. It is vital that the Ministry of Health, health directorates and hospital administrations establish the necessary authority.

Limitations

The limitations of this study were its retrospective nature, the lack of detailed analysis of the causes of family refusal in non-donor cases, and the fact that the time between the diagnosis of BD and cardiac arrest in non-donors was not recorded as data.

CONCLUSION

Our study shows that the diagnosis of brain death has increased, but we think that there is still need to raise awareness of people about perceiving and approving organ donation and that training, programmes by media related to this subject should be extensively increased. An experienced and trained organ transplant coordinator should try to explain that brain death brain death is a real death during family interviews, and the significance of organ donation should be emphasized and donation rates should be increased. The results of the study may be a guide in determining the missing and inadequate points.

Author's contribution

Idea/concept = ŞE, ŞEÖ; Check = ŞEÖ; Welding and function: ŞE, ŞEÖ; Materials = ŞE; Data collection and/or processing = ŞE; Analysis – Comment = ŞE, ŞEÖ; Literature screening = ŞE, ŞEÖ; Article writing: ŞE; Critical review = ŞEÖ and Responsible author = ŞE.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2019;5(5):853-860 ORIGINAL ARTICLE

The drug adherence and lifestyle factors that contribute to blood pressure control among hypertensive patients

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ABSTRACT

Objectives: To investigate drug adherence and lifestyle behaviors affecting the blood pressure (BP) control among hypertensive patients that have uncontrolled and controlled BP.

Methods: Seventy-eight uncontrolled BP and 98 controlled BP hypertensive patients matched on age, gender, time since hypertension diagnosis and the number of antihypertensive drugs used were investigated using a standardized questionnaire to evaluate lifestyle behaviors, drug adherence, the use of complementary and alternative medicine, and health related quality of life. Drug-drug interactions were evaluated with an electronic drug reference software.

Results: Not taking therapy when feeling better was observed significantly more frequently in the uncontrolled hypertensive group (OR: 0.297, %95 CI: 0.115-0.770). Uncontrolled BP hypertensive patients live more frequently in extended family settings (p = 0.043), they sleep less controlled BP hypertensive patients (OR: 0.749, %95 CI: 0.605-0.929). The groups did not differ statistically in terms of Complementary and Alternative Medicine (CAM) use (p = 0.795) and informing doctors about the use of CAMs (p = 0.910). The EuroQol five-dimensional 3 level (EQ5D3L) questionnaire Visual Analogue Scale (VAS) score was significantly higher in the control group (p = 0.011). In both groups over 70% of patients should be monitored for therapy due to drug interactions evaluation.

Conclusions: Our study shows that increasing the drug adherence and sleeping hours and living in the nuclear family is associated with improvement in blood pressure control and health related quality of life. A comprehensive approach and good patient-physician communication and trust are essential for well-managed hypertension.

Keywords: Hypertension, drug adherence, drug interaction

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Hypertension is responsible for about 4.5% of the recent overall disease load in the world, and leads to cerebrovascular diseases, ischemic heart diseases, and cardiac failure. Treatment can significantly reduce these devastating problems [1]. Success rates in treatment and risk management vary among countries. Using a blood pressure (BP) hypertension cut-off point of 140/90 mmHg, 29% of patients in the

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United States of America had their BP controlled. The same ratio for European countries ranged from 5-10%, 17% for Canada, and the highest rate was 38% in Barbados [2, 3]. Also, in Turkey, the BP control rates among hypertensive patients are low and vary between 16%-30% according to geographical regions [4, 5].

In addition to drug treatment, lifestyle changes including diet and exercise are recommended for patients with hypertension [6].

Adherence to antihypertensive treatment has been shown to be low in literature, with similar findings reported in Turkey [5, 7]. Most patients do not adhere to recommended lifestyle changes regarding diet and exercise [8].

A major proportion of patients who receive drug treatment for hypertension also uses complementary and alternative medicine (CAM) [9]. In Turkey, the research done in Eastern Anatolia region shows that majority of patients reported using CAM [10].

Drug-drug or drug-herb interactions is a necessary risk that should be kept in mind when prescribing antihypertensive agents. A study done by Carter *et al*. [11] reported a very high frequency of potential drug interactions with agents used for hypertension treatment.

It has been shown in literature that patients with hypertension have poorer health related quality of life (HRQoL) than normotensives [12, 13]. Hypertensive patients are a vulnerable group in the health system and merit special attention due to low HRQoL among this group increases the risk of cardiovascular events [14].

To our knowledge, there is limited information regarding Turkish hypertensive patients' lifestyle behavior and antihypertensive treatment adherence affecting BP control. In the present study, we aimed to investigate drug adherence, drug-drug interacitons, complementary alternative medicine use, lifestyle behaviors affecting the blood pressure and qualitity of life among patients has uncontrolled and controlled blood pressure.

METHODS

This study was undertaken in the Pharmacology Department of Istanbul Faculty of Medicine, Clinical Pharmacology Division, from June to November 2014.

Seventy-eight randomly selected patients with uncontrolled hypertension and 98 controls with controlled hypertension matched on age, sex, the number of hypertensive agents used and time since hypertension diagnosis were enrolled in the study.

Patient inclusion criteria were as follows: aged between 38 and 74 years, hypertension diagnosis history of at least 6 months and use of at least one antihypertensive medication.

After participants were informed about the study and their informed consent obtained, data were collected through researcher-administered patient interviews using a standardized questionnaire consisting of sociodemographic variables such as age, sex, marital status, and educational level. It also comprised clinical variables such as other chronic diseases seen during the diagnosis of hypertension, other drugs used, and drug adherence-related questions, the use of CAM, lifestyle behaviors, and quality of life. To determine the participants' quality of life, we used EuroQol five-dimensional 3 level (EQ5D3L) questionnaire [15]. Indexing was undertaken as with the method used in the Turkish validation and reliability study of Eser *et al*. [16].

Patients' height was measured using a height rod and weight was measured with a digital scale. Blood pressure and heart rate were measured using a calibrated digital blood pressure monitor. Drug interactions were evaluated with an electronic drug reference software, Lexi-Comp's Comprehensive Drug-to-Drug, Drug-to-Herb, and Herb-to-Herb Interaction Analysis Program (Lexi-Interact Online).

Controlled hypertension was defined as systolic blood pressure (SBP) $\leq$ 139 mmHg and/or diastolic blood pressure (DBP) $\leq$ 89 mmHg for non-diabetic patients, and as SBP $\leq$ 139 mmHg and/or DBP $\leq$ 84 mmHg for diabetic patients, based on the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) guidelines [6]. Individuals who had blood pressure levels above these values were defined as uncontrolled hypertensive patients. The study was approved by the Ethics Committee of Istanbul School of Medicine on 10/06/2014.

Statistical Analysis

The descriptive statistics used in the study were

mean ± standard deviation (SD) for normally distributed variables, median and IQR for non-normally distributed variables, as well as frequency counts and percentages of participant characteristics. Independent samples t-test or Mann-Whitney U were used to compare groups' variables. The Chi-square and the Likelihood ratio were used to evaluate categorical variables. OR and 95% CI is calculated using Logistic regression. The Statistical Package for Social Sciences (SPSS) version 21 was used to analyze data, and $p < 0.05$ was considered to be significant.

RESULTS

The age, sex distribution, body mass index (BMI), education status, the number of antihypertensive medications used, the time since hypertension diagnosis, SBP and DBP and heart rate are summarized in Table 1.

Not taking therapy when feeling better was observed significantly more frequently in the uncontrolled hypertensive group (OR: 0.297, %95 CI: 0.115-0.770) (Table 4). Cases; uncontrolled hypertension patients tend to live in extended family settings ($p = 0.043$) (Table 1) and sleep less than controls OR: 0.749 (%95 CI: 0.605-0.929) (Table 4). The groups did not differ statistically in terms of Complementary and Alternative Medicine (CAM) use ($p = 0.795$) and informing doctors about the use of CAMs ($p = 0.910$) (Table 2). In both groups over 70% of patients should be monitored for therapy due to drug interactions evaluation (Table 2). Less than half of both groups partook in regular physical activity but there was no statistically significant difference between the two groups (Table 3). There were no significant differences in smoking and alcohol drinking habits between the groups (Table 3). No significant differences were found in eating frequency habits between the groups (Table 3). The EQ5D3L

Table 1. Characteristics and health parameters of study population

	Uncontrolled hypertension n = 78)	Controlled hypertension n = 98)	*p* value
Age (years)	58.39 ± 8.84	57.85 ± 7.63	0.664§
Sex			
Male	21 (26.9%)	23 (23.5%)	0.599*
Female	57 (73.1%)	75(76.5%)	
BMI (kg/m2)	30.75 ± 4.7	31.06 ± 5.51	0.698§
Antihypertensive drugs used daily	2 (1-2)	2 (1-2)	0.783¶
Time from hypertension diagnosis	8 (3-14)	8 (4-11)	0.911¶
Education			
Can't read	2 (2.6%)	0(0%)	
Collage	60 (76.9%)	67 (68.4%)	0.056¥
University and post graduate	16 (20.5%)	31 (31.6%)	
Family			
Nuclear	57 (73.1%)	80 (81.6%)	
Extended	18 (23.1%)	10 (10.2%)	**0.043¥**
Divorced/Widowed	3 (3.8%)	8 (8.2%)	
SBP	150 (140-160)	120.5 (116-130)	**< 0.0001¶**
DBP	80 (73.7-90)	75 (70-80)	**< 0.0001¶**
Heart Rate/min	79 (71-86)	76 (72-82)	0.228¶

Data are shown as mean±standard deviation or median (IQR) or number (percent). SBP = systolic blood presure, DBP = dastolc blood presure, §-Independent Samles t-test, *-Pearson Chi Square test, -Independent samples Mann Whitney U test, ¥-Likelihood Ratio test.

Table 2. Number of drugs used, drug intake habits and drug interaction

	Uncontrolled hypertension n = 78)	Controlled hypertension n = 98)	*p* value
Forgets to take drugs	27 (34.6%)	38 (38.8%)	0.570*
Doesn't take drugs when feel better	16 (20.5%)	8 (8.2%)	0.018*
Forgets to prescribe drugs when ends	16 (20.5%)	22 (22.7%)	0.730*
Drug interaction (n = 70 vs 82)			
Drug interaction A	14 (20%)	9 (11%)	0.193¥
Drug interaction B	1 (1.4%)	0 (0%)	
Drug interaction C	51 (72.9%)	62 (75.6%)	
Drug interaction D	3 (4.3%)	9 (11%)	
Drug interaction X	1 (1.4%)	2 (2.4%)	

Data are shown as number (%). Drug interaction Risk Rating = A - No Known Interaction, B - No Action Needed, C - Monitor Therapy, D - Consider Therapy Modification, X - Avoid Combination, *-Pearson Chi Square test, ¥-Likelihood Ratio test.

Table 3. CAM use, eating habits, regular exercise and EQ5D3L index and VAS score

	Uncontrolled hypertension n = 78)	Controlled hypertension n = 98)	*p* value
CAM use	20 (25.6%)	28 (28.6%)	0.665*
Tells to doctor that use CAM	10 (43.5%)	13 (53.5%)	0.910*
Smokers	14 (17.9%)	27 (27.6%)	0.134*
Drinks alcohol	14 (17.9%)	17 (17.3%)	0.917*
Mean meals per day	3 (2-3)	3(2-3)	0.219¶
Number of meals except main meals	2 (1-4)	3 (1-4)	0.742¶
Do regular physical activity per week	29 (37.2%)	31 (31.6%)	0.441*
EQ5D3L index	0.725 (0.62-0.845)	0.743 (0.656-1)	0.300¶
EQ5D3L VAS score	75 (50-80)	80 (70-90)	0.011¶

Data are shown as median (IQR) or number (percent). CAM = complementary and alternative medicine, EQ5D3L = EuroQol five-dimensional 3 level, VAS = Visual Analogue Scale, þ-walking or exercising at least 5 days per week not less than 30 minutes, *-Pearson Chi Square test, ¶-Independent samples Mann Whitney U test

Table 4. Independent predictors of blood pressure with logical regression analysis

	Uncontrolled hypertension n = 78)	Controlled hypertension n = 98)	Odds Ratio (%95 CI)	*p* value
Doesn't take drugs when feel better	16 (20.5%)	8 (8.2%)	0.344 (0.139-0.854)	**0.021**
Living in extended family	18 (23.1%)	10 (10.2%)	2.526 (1.086-5.878)	**0.031**
Sleeping (hours per day)	6.53 ± 1.78	7.13 ± 1.45	0.789 (0.647-0.962)	**0.019**

Data are shown as mean ± standard deviation or number (percent).

Visual Analogue Scale (VAS) score was significantly higher in the control group (p = 0.011) (Table 3). Further data are not shown here.

DISCUSSION

Lower drug adherence when feeling better, living with an extended family, sleeping less and a poorer health related quality of life of cases than controls plus the need for therapy monitoring amajority of patients due to drug interactions can be listed as main findings in our research.

Drug adherence is important in blood pressure management. Some qualitative research on factors of medication adherence in patients with hypertension found that feeling well and absence of hypertension symptoms were disease-specific barriers [17]. A study by Sengul *et al*. [18] reported that Turkish hypertensive patients have improved awareness about being hypertensive between 2003 and 2012. With regards to adherence to therapy, Altun *et al*. [5] reportedthat most of the Turkish hypertensive patients declare that they follow the recommendations.

Better antihypertensive drug adherence and BMI lower than 30 (kg/m2) are found to be predictors of controlled BP in Turkish hypertensive patients [19]. In our study, forgetting to take medication and requirement for prescription renewal did not differ significantly between the groups as reasons for non-adherence, but not taking therapy when feeling better was observed significantly more frequently in the uncontrolled hypertensive group (20.5%) when compared to the controlled hypertensive group (8.2%). In a qualitative study by Wai *et al*. [20] on lowering blood pressure medications, one in twenty patients declared that they did not take their drugs when they felt well [32]. As regards to treatment, compliance was better among those taking one antihypertensive tablet per day, those who had never changed their antihypertensive regimen, and those who had never changed their physician [7]. Altun *et al*. [5] reported that Turkish hypertensive patients that used one medication do not adhere to therapy by 15 %.

Family and friends'social support is important in the management of chronic diseases and differs in various cultures. A study of Karakaş *et al*. [21] showed that social support of family and friends are higher in hypertensive patients than in asthmatic patients. In our study, we found that hypertension control rates in nuclear family settings were higher compared with extended families. In contrast, a study conducted in Japanese hypertensive patients living in the nuclear family has been found to have higher systolic BP than patients living in extended families [22]. In a study from Turkey evaluating cardiovascular risk factors in postmenapousal woman found hypercholesterolemia is a risk factor in nuclear family setting but there was no correlation between hypertension and family structure [23]. When we evaluate our study result as female gender, our results also do not support female gender and nuclear family. Gender may be a factor on nuclear family setting and better blood pressure control. Unlike to our study population, Sekuri *et al*. [23] investigated rural population. Family structure and blood pressure control relation is interesting and warrants further attention.

Carter *et al*. [11] showed that there is a potential high drug interaction associated with increasing age and number of drugs among hypertensive patients.

Sleeping disorders are well known for increasing a wide variety of health conditions. Hypertensive patients' sleep duration is associated with ischemic or nonspecified stroke mortality in the Singapore Chinese study and both short and long sleeping duration increased the risk [24]. To our best knowledge, there are missing data regarding hypertensive patients habitual sleeping time in Turkey. But a recent article in pediatric population aged 11-17 reported that increased blood pressure is correlated with sleeping less than 8 hours a day [25]. A small sample sized interventional study to increase average nightly sleep duration about 30 minutes resulted in the reduction of beat-to beat systolic and diastolic BP in hypertensive and pre-hypertensive subjects [26]. Our study also found that habitual higher sleeping duration is related to better blood pressure control but we need further evidence to recommend sleep time adjustment as lifestyle modification in the hypertensive population. Evaluating patient for insomnia and if necessary consulting a sleep center may be beneficial. According to drug-drug interaction evaluation, groups did notdiffer significantly but need to monitor therapy (72.9% vs 75.6%) is high and considering change intherapy is needed in about 4% in cases and 11% in controls. In the study done in Croatia drug interaction

in elder hypertensive patients was reported to behigher, being over 90% for considering to monitor therapy and about 20% for considering to change the therapy [27].

In the present study, CAM use was high (25.6% vs 28.6%) and about 50% had not informed their physicians about their CAM use. Similar results were found by Tan *et al*. [10] who found morethan 2/3 of the patients use CAM and most of them do not talk to their physician about thisuse.

Hypertensive patients can adopt different lifestyle changes for improving BP control and reducingCVD risk [28].Increasing physical activity, smoking cessation, salt reduction are important targets that should be considered in blood pressure control.
In our research, less than half of both groups (37.2% vs 31.6%) adhered to the recommendation for physical activity for adults of 5 days a week not less than 30 minutes per day [29].

In literature, it is shown that alcohol consumption raises the prevalence of hypertension compared to lifetime non-users [30]. Increase in alcohol consumption has been found to be associated with increases in BP among hypertensive patients in Turkish men [31]. In our study, we found that alcohol consumption is frequent (one in five hypertensives)in both groups and doesn't differ statistically.

We found that smoking rates among hypertensive patients between cases and controls (17.9% vs 27.6%) is far from cessation recommendations and doesn't differ significantly among uncontrolled and controlled hypertensives. Neuhouser *et al*. [32] also reported similar rates of smoking (15%) among hypertensive patients.

Patients with a chronic condition such as hypertension, diabetes, dyslipidemia or cardiovascular disease tend not to adhere to diet recommendations guidelines [32]. In obese people, it is found that they have 1.4 main meal per day and have about 4.2 eating occasions per day [33]. In our study, both groups' patients have similar eating frequency patterns as they have 3 mean meals per day and in total 5 (4-6) eating occasions per day.

In a study done by Ucan *et al*. [34] HRQoL was found to belower in Turkish hypertensive patients when compared to diabetic patients and diabetes and hypertensive conditions combined. It has been shown in literature that with the intensification of antihypertensive treatment, HRQoL is improved [35, 36]. We found that HRQoL is lower in the uncontrolled BP group. In this context the medication therapy should be evaluated for possible drug interactions.

Limitations

Our study has some limitations. Sample size is one of the limitations and study design leads to a potential bias due to subjective evaluation.

CONCLUSION

Our study shows that increasing the drug adherence and sleeping hours and living in the nuclear family are associated with improvement in blood pressure control and health-related quality of life. Also, less physical activity, lack of awareness about drug adherence and frequent use of CAM was seen in our study groups. A comprehensive approach and good patient-physician communication and trust are essential for well-managed hypertension. Higher VAS scores health-related quality of life subjective rating represent an improvement in the quality of life and can be a therapeutic motivation and goal for patients with hypertension and could be included in physicians' patient information booklets.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2019;5(5):861-867 ORIGINAL ARTICLE

Public knowledge about traditional and complementary medicine

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ABSTRACT

Objectives: The aim of this study was to investigate public knowledge about traditional and complementary medicine.

Methods: In a physical medicine and rehabilitation hospital, questionnaires were administered to 534 volunteers. The questionnaires comprised of questions regarding demographic data such as age, gender and educational level and 16 additional questions about traditional and complementary medicine defitions. These definitions were directly adopted from Ministry of Health Department of Traditional and Complementery Medical Practices. The results were recorded and statistical analysis were carried out.

Results: The volunteers were 44.6% male and 55.4% female). Acupuncture definition was known to 57.7% volunteers; this rate was 26.6% in phytotherapy, 32.2% in apitherapy, 43.4% in hypnosis, 15.2% in hirudotherapy, 28.7% in homeopathy, 11.9% in chiropractic, 32.2% in cupping therapy, 40.4% in wet cupping therapy, 29% in maggot therapy, 27.3% in mesotherapy, 18% in prolotherapy, 22.1% in osteopathy, 38.8% in ozone therapy, 40.6% in reflexology, 55.2% in music therapy. Women's correct answers regarding hypnosis, reflexology and music therapy were found to be statistically significantly higher than men. Acupuncture and osteopathy definitions are better known to 18-30 years old volunteers than volunteers that are older than 65 years of age. Apitherapy, homeopathy, cupping, wet cupping, maggot therapy, mesotherapy, prolotherapy, ozon therapy, reflexology were less known by the older population; as the age increased the correct answers for these therapies decreased. In addition, correct answer ratio increased with the educational level, in acupuncture, apitherapy, phytotherapy, hypnosis, charіopractic, cupping, wet cupping, mesotherapy, ozone therapy and reflexology.

Conclusions: The traditional and complementary therapies need to be explained to the public. Women are more intersted in some therapies than men. Public knowledge about the definition of most traditional and complementary therapies increases with educational level. People with different demographic properties have different levels of awareness regarding traditional and complementary therapies. For example while elder people require more basic training about these methods in general, young and highly educated women who already have some awareness about these methods can go through more elaborate training programs which are designed to guide them to benefit more from these therapies.

Keywords: health literacy, acupuncture, cupping therapy, complementary health approaches, osteopathy

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People, especially those with chronic diseases, sometimes seek treatment options other than modern medicine, such as complementary and traditional therapies. In 2011, General Directorate of Health Services at Ministry of Health established a spesific unit named as Department of Traditional and Complementery Medical Practices in Turkey. In 2014 regulation on traditional and complementary medical practices was published [1]. In this guide there were 16 traditional and complementary treatments. These treatments are: acupuncture [2], apitherapy [3], phytotherapy [4], hypnosis [5], hirudotherapy [6], homeopathy [7], chiropractic [8], cupping [9], wet cupping [9], maggot therapy [10], mesotherapy [11], prolotherapy [12], osteopathy [13], ozone therapy [14], reflexology [15], and musical therapy [16]. The definition of these therapies were given in the respected references cited above. The explanation of these theraphies, exactly as provided by the Ministry of Health of Turkey are given in the following: (1) Acupuncture: It is a treatment method in which, special points (selected from the ear or the whole body) are stimulated with special needles or laser-like stimulants; (2) Apitherapy: It is a complementary and preventive method, where bee and bee products are used; (3) Phytotherapy: A traditional and complementary method that benefits from herbs which are scientifically proven to have protective effects against diseases and to promote treatment; (4) Hypnosis: An artificially induced altered state of consciousness which is achieved by inculcation; (5) Hirudotherapy: A treatment method which uses leeches; (6) Homeopathy: A method which uses homeopathic medicine for holistic treatment; (7) Chiropractic: It is a supportive practice area dealing with biomechanical disorders of the muscles, spine and skeletal system and preventing the problems it creates on the nervous system. In appropiate patients it focuses onmanually fixing mobility of joints that have lost their mechanical movement; (8) Cupping: Traditional treatment method based on creating regional vacuum to increase blood circulation and improve healing; (9) Wet cupping: Dirty blood is taken from capillaries and thin veins at certain points where waste materials are collected intensively to get rid of disease or to protect health; (10) Maggot therapy: Application of, Lucilia (Phaenicia) Sericata, a sterile larvae for the purpose of biological cleansing in chronic wounds; (11) Mesotherapy: It is an injection method of herbal and pharmacological drugs for the healing of mesoderm originated organs; (12) Prolotherapy: It is a treatment method based on the principle that the proliferation-inducing and irritating solutions given to the muscles or joints increases flexibility of the skeletal system; (13) Osteopathy: It is a non-invasive (needle-free, non-surgical) complementary medicine technique that helps strengthen the musculoskeletal system, including joints, muscles, connective tissue and the vertebrae, focuses on whole body health and emphasizes the effectiveness of the musculoskeletal system in diseases; (14) Ozone therapy: Ozone is a traditional and complementary medical method that is applied by mixing the ozone gas obtained from pure oxygen with the patient's own blood or serum physiologic, or by giving it to various parts of the body in gas; (15) Reflexology: It is a treatment method which is based onthe principle that there are reflex areas on hand, feet and ears which are connected to the whole body; and (16) Musical therapy: It is a therapy and rehabilitation approach aimed at improving and acquiring the functions and skills that are corrupted, lost or underdeveloped for various reasons through music.
The aim of this study is to evaluate the public knowledge about these traditional andcomplimentary medical approaches.

METHODS

Five hundred and thirty-four people at a government owned physical medicine and rehabilitation hospital were included in the study. The study is a cross-sectional and descriptive study, performed between April 1st, 2018 and April 20th, 2018. Volunteers were patients at the outpatient clinic, inpatient clinic, patient companions and relatives which accepted to fill the form.

Inclusion criteria are the following: (1) to be older then 18 years old and younger then 90 years old; (2) able to read or understand Turkish; (3) to volunteer to fill the test. Also exclusion criteria include not volunteer to fill the test or not understanding Turkish. Questionnairesabout the traditional and complimentary medicine definitions are distributed to the volunteers at the hospital. The definitions of traditional and complimentary medicine techniques were taken from Ministry of Health Department of

Traditional and Complementery Medical Practices web site. Volunteers' age, gender, educational levels were collected via the same questionnaire. There were no personal information on the questionnaires, hence they were all anonymous. After the demographic characteristics of the volunteers were recorded, all traditional and complimentary medicine definitions are evaluated as correct, incorrector blank. We investigated if there is any statistically different relationship between volunteers' age, gender or educational level and the knowledge about the traditional and complimentary medicine.

Statistical Analysis

For the statistical analyses, the IBM SPSS statistic 22 program was used. When the study data were evaluated, descriptive statistical methods (mean, standard deviation, median, crosstabs) as well as paired sample t test were used for intra-group comparison of normal distribution parameters and Anova test was used for intra-group comparison of non-normal distribution parameters. The results were assessed at a 95% confidence interval and at a significance level of p <0.05.

RESULTS

There were 534 participants including 296 (55.4%) females and 238 (44.6%) males. One hundred and eleven (20.8%) volunteers were between 18-30 years old, 116 (21.7%) were 31-40 years old, 109 (20.4%) were 41-50 years old, 114 were 51-65 years old (21.3%), 84 (15.7%) were 66-90 years old.

According to their education, participants were divided into six levels: (1) Unable to read and write: 39 (7.3%); (2) Primary school: 110 (20.6%); (3) Secondary school: 108 (20.2%); (4) High school: 140 (26.2%); (5) University: 122 (22.8%) and (6) Postgraduate: 15 (2.8%).

The highest number of correct answers about the definitions of traditional and complemantary medicine was in acupuncture (57.7%) and lowest was in chiropractic (11.0%). The other percentages of correct answers were as follows: music therapy 55.2%, hypnosis 43.4%, reflexology 40.6%, wet cupping 40.4%, ozontherapy 38.8%, apitherapy 32.2%, cupping 32.2%, maggot therapy 29.0%, homeopathy 28.7%, mesotherapy 27.3% phytotherapy 26.6%, osteopathy 22.1%, prolotherapy 18.0%, and hirudotherapy 15.2%.

Whether there is a significant correlation between the gender of participants and their knowledge of traditional and complementary medical practices was evaluated with T-test and it was seen that the correct answers of women regarding hypnosis, reflexology and music therapy are higher than men (Table 1). Table 1 only includes data which resulted in statistically significant differences between men and women.

There is a significant difference between the age of the participants and their knowledge of traditional and complementary medical practices. Acupuncture (p = 0.13) and osteopathy (p = 0.30) definitions are better known to 18-30 years old participants than those 65 years and older. Apitherapy, homeopathy, cup therapy, wet cupping, maggot therapy, mesotherapy, prolotherapy, ozone therapy and reflexology correct

Table 1. Relationship between gender and knowledge about traditional and complimentary medicine

n = 534	True	False	No Answer	*p* value
Hypnosis				**0.018**
Female (n = 296)	142 (61)	110 (52%)	44 (48%)	
Male (n = 238)	90 (39%)	101 (48%)	47 (52%)	
Reflexology				**0.014**
Female (n = 296)	137 (63%)	97 (49.5%)	62 (51%)	
Male (n = 238)	80 (37%)	99 (50.5%)	59 (49%)	
Music therapy				**0.035**
Female (n = 296)	179 (60.6%)	78 (47%)	39 (52.7%)	
Male (n = 238)	116 (39.4%)	87 (53%)	35 (47.3)	

answers seem to decrease as the age increases (Table 2).

Relationship between level of education and knowledge about traditional and complimentary medicine is shown in Table 3.

Table 2. Relationship between age and knowledge about traditional and complimentary medicine

n = 534	18-30 years n = 111	31-40 years n = 116	41-50 years n = 109	51-65 years n = 114	> 65 years n = 84
Apitherapy					
True	52 (46.8%)	42 (36.2%)	29 (26.6%)	33 (28.9%)	16 (19%)
False	47 (42.4%)	53 (45.7%)	58 (53.2%)	60 (52.6%)	33 (39.3%)
Blank	12 (10.8%)	21 (18.1%)	22 (20.2%)	21 (18.4%)	35 (41.7%)
Homeopathy					
True	45 (40.5%)	32 (27.6%)	28 (25.7%)	28 (24.6%)	20 (23.8%)
False	52 (46.8%)	56 (48.3%)	55 (50.5%)	51 (44.7%)	30 (35.7%)
Blank	14 (12.6%)	28 (24.1%)	26 (23.8%)	35 (30.7%)	34 (40.5%)
Cupping					
True	47 (42.4%)	43 (37.1%)	28 (25.7%)	32 (28.1%)	22 (26.2%)
False	52 (46.8%)	56 (48.3%)	55 (50.5%)	63 (55.3%)	39 (46.4%)
Blank	12 (10.8%)	17 (14.6%)	26 (23.8%)	19 (16.6%)	23 (27.4%)
Wet Cupping					
True	55 (49.5%)	50 (43.1%)	38 (34.9%)	42 (36.9%)	31 (36.9%)
False	48 (43.3%)	46 (31.7%)	51 (46.8%)	47 (41.2%)	25 (29.8%)
Blank	8 (7.2%)	20 (17.2%)	20 (18.3%)	25 (21.9%)	28 (33.3%)
Maggot therapy					
True	43 (38.7%)	36 (31%)	24 (22%)	33 (28.9%)	19 (22.6%)
False	49 (44.1%)	48 (41.4%)	55 (50.5%)	50 (43.9%)	29 (34.5%)
Blank	19 (17.2%)	32 (27.6%)	30 (27.5%)	31 (27.2%)	36 (42.9%)
Mesotherapy					
True	39 (35.1%)	33 (28.4%)	29 (26.6%)	27 (23.7%)	18 (21.4%)
False	55 (49.5%)	54 (46.6%)	44 (40.4%)	59 (51.7%)	33 (39.3%)
Blank	17 (15.3%)	29 (25%)	36 (33%)	28 (24.6%)	33 (39.3%)
Prolotherapy					
True	27 (24.3%)	24 (20.7%)	17 (15.6%)	18 (15.8%)	10 (11.9%)
False	64 (57.7%)	56 (48.3%)	62 (56.9%)	62 (54.4%)	38 (45.2%)
Blank	12 (10.8%)	36 (31%)	30 (27.5%)	34 (29.8%)	36 (42.9%)
Ozone Therapy					
True	52 (46.9%)	50 (43.1%)	42 (38.5%)	41 (36%)	22 (26.2%)
False	44 (39.6%)	37 (31.9%)	37 (34%)	40 (35.1%)	31 (36.9%)
Blank	15 (13.5)	29 (25%)	30 (27.5%)	33 (28.9%)	31 (36.9)
Reflexology					
True	57 (51.4%)	43 (37.1%)	49 (45%)	44 (38.6%)	24 (28.6%)
False	42 (37.8%)	47 (40.5%)	36 (33%)	42 (36.8%)	29 (34.5%)
Blank	12 (10.8%)	26 (22.4%)	24 (22%)	28 (24.6%)	31 (36.9%)

Table 3. Relationship between level of education and knowledge about traditional and complimentary medicine

n = 534	Postgraduate n =15	University n =122	High School n =140	Secondary School n =108	Primary School n =110	Non-reader or writer n =39
Reflexology						
True	11 (73.3%)	73 (59.8%)	66 (41.1%)	39 (36.1%)	23 (20.9%)	5 (12.8%)
False	3 (20%)	35 (28.7%)	46 (32.9%)	47 (43.5%)	49 (44.5%)	16 (41%)
Blank	1 (6.7%)	14 (11.5%)	28 (20%)	22 (22.4%)	38 (34.5%)	18 (46.2%)
Acupuncture						
True	13 (86.7%)	100 (82%)	90 (64.3%)	43 (39.8%)	50 (45.5%)	12 (30.8%)
False	2 (13.3%)	17 (13.9%)	41 (29.3%)	58 (53.7%)	50 (45.5%)	16 (41%)
Blank	0	5 (4.1%)	9 (6.4%)	7 (6.5%)	10 (9.1%)	11 (28.2%)
Apitherapy						
True	9 (60%)	68 (55.7%)	43 (30.7%)	22 (20.4%)	27 (24.5%)	3 (7.7%)
False	5 (33.3%)	39 (32%)	65 (46.4%)	70 (64.8%)	54 (49.1%)	18 (46.2%)
Blank	1 (6.7%)	15 (12.3%)	32 (22.9%)	16 (14.8%)	29 (26.4%)	18 (46.2%)
Cupping						
True	9 (60%)	65 (53.3%)	45 (32.1%)	23 (21.3%)	26 (23.6%)	4 (10.3%)
False	6 (40%)	47 (38.5%)	69 (49.3%)	67 (62%)	57 (51.8%)	19 (48.7%)
Blank	0	10 (8.2%)	26 (18.6%)	18 (16.7%)	27 (24.5%)	16 (41%)
Wet Cupping						
True	10 (66.7%)	81 (66.4%)	57 (40.7%)	23 (21.3%)	35 (31.8%)	10 (25.6%)
False	4 (26.7%)	32 (26.2%)	62 (44.3%)	62 (57.4%)	47 (42.7%)	10 (25.6%)
Blank	1 (6.7%)	9 (7.4%)	21 (15%)	23 (21.3%)	28 (25.5%)	19 (48.7%)
Mesotherapy						
True	11 (73.3%)	49 (40.2%)	40 (28.6%)	19 (17.6%)	21 (19.1%)	6 (15.4%)
False	3 (20%)	53 (43.4%)	64 (45.7%)	62 (57.4%)	49 (44.5%)	14 (35.9%)
Blank	1 (6.7%)	20 (16.4%)	36 (25.7%)	27 (25%)	40 (36.4%)	19 (48.7%)
Ozone Therapy						
True	11 (73.3%)	75 (61.5%)	51 (36.4%)	31 (28.7%)	33 (30%)	6 (15.4%)
False	4 (26.7%)	32 (26.2%)	51 (36.4%)	46 (42.6%)	43 (39.1%)	13 (33.3%)
Blank	0	15 (12.3%)	38 (27.1%)	31 (28.7%)	34 (30.9%)	20 (51.3%)

DISCUSSION

In recent years, the estimated life span and incidence of chronic diseases have increased. As a result people began to seek for alternative therapies which will be used in conjunction with modern medicine [17, 18]. To establish a legal basis on application of complamentary and alternative medicine in our country; in 2011, General Directorate of Health Services at Ministry of Health appointed a spesific unit called Department of Traditional and Complementery Medical Practices. In 2014 the regulation for traditional and complementary medical practices was published [1].

This step taken by the state is very important because this issue is very vulnerable to abuse. With this regulation, education curriculum of traditional and complementary treatments was determined and standardized. Institutions that can provide education were specified and those without proper certification

have been prevented from applying traditional and complementary medicine [19].

In a study conducted in 8 countries across Europe on health literacy, it was observed that the level of education was high in groups with high health literacy scores [20]. This data is compatible with our study. As a matter of fact, it seems that the number of correct answers of high school, university and post-graduate education levels in acupuncture, apitherapy, cupping, wet cupping, mesotherapy, ozone therapy and osteopathy questions increases as education level increases. The number of correct answers given by people who are unable to read and write, primary school graduates and junior high school graduates are less than those of high school and post-education groups. Another consequence of the study done in Europe is that as age increases, health literacy decreases [20]. In our study, it is observed that the number of correct answers decreases as the age of the volunteers increases for apitherapy, homeopathy, cupping, wet cupping, maggot therapy, mesotherapy, prolotherapy, ozone and reflexology questions. Although these treatments have been used traditionally, they are less known by the older population and this may have been caused by the expected reduction in health literacy scores with age.

Another statistically significant finding in our study is that women have given higher number of correct answers in reflexology, hypnosis, and music therapy. This data is also compatible with traditional and complementary studies. Gözüm *et al*. [21] have reported that in a study conducted in 107 cancer patients, women were significantly more likely to use complementary health approaches. Akyol *et al*. [22] also found that women use more complementary and alternative therapies than man. In 207 chronic kidney disease patients only 5.8% of the patients used these alternative and complementary therapies with doctor advice. Also, it is reported that 67.3% of the patients who resort to alternative and complementary methods do not report their involvement in such therapies to their doctors [22].

Traditional and complementary medical practices should be planned and implemented in accordance with the regulation, by competent health professionals. In order to increase health literacy in a wider range of patients proper training programs should be established.

CONCLUSION

As suggested by the literature survey and our own findings, people with different demographic properties have different level of awareness regarding traditional and complementary therapies. While elder people require more basic training about these methods in general, young and highly educated women who already have some awareness about these methods can go through more elaborate training programs which are designed to guide them to benefit more from these therapies.

Authors Contribution

BBK = study planning, consultant, last reading, corrections and article writing; MŞ = data collection, statistics.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2019;5(5):868-872 ORIGINAL ARTICLE

Intracytoplasmic sperm injection outcomes after anti-oxidant treatment in repeated implantation failure

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ABSTRACT

Objectives: Aim of this study was to explore the effects of three months oral anti-oxidant treatment in normozoospermic men with high DNA fragmentation index (DFI) and recurrent intracytoplasmic sperm injection (ICSI) failures.

Methods: This is a retrospective analyses of normozoospermic patients with high DFI levels (> 30%) with at least two unsuccessful ICSI attempts. Among the participants, the study group included men who had oral anti-oxidant treatment. The men who did not receive any treatment during the study period were taken as controls. The outcomes of new ICSI cycles were compared.

Results: During the study period 24 men have used three months of oral anti-oxidant treatment before a new ICSI cycle whereas the remaining 46 had ICSI-only without any other intervention. Duration of stimulation, the number of metaphase II oocytes, fertilization rate and implantation rates were similar between two groups. Although not statistically significant, cases in anti-oxidant group have slightly better pregnancy rates compared to ICSI-only group (37.5% vs 19.6%, $p > 0.05$). Only one case in each group had abortion.

Conclusions: This study reveals that there is no statistically significant difference in the ICSI outcomes of the patients with high DFI levels, following unsuccessful ICSI attempts after oral anti-oxidant treatment. The possible benefit derived from the anti-oxidant therapy needs to be clarified with clinical studies with greater study populations.

Keywords: Oxidative stress, DNA fragmentation, intracytoplasmic sperm injection, spermatozoa

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Among reproductive age couples, approximately 15% suffer from infertility [1]. A relatively high number of women fail to have a pregnancy despite the apperent absence of a male or female factor of infertility. Normal semen analysis in these couples mandates some other analyses which address the integrity of sperm DNA. Recent studies have documanted an association between high levels of sperm DNA fragmentation and impaired fertilization/embryo development, lower implantation rates and higher miscarriages [2]. In animal studies, sperm DNA damage vas found to be related with birth defects in the offsprings due to impaired DNA integrity [3]. DNA damage in spermatozoa may be induced by different

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mechanisms that include; apoptosis, abnormal chromatin packaging and post-testicular causes of sperm DNA fragmentation ensued from reactive oxygen species (ROS) during transit through the mail reproductive tract, DNA fragmentation caused by endogenous endonucleases, radiotherapy and chemotherapy or enviromental causes (smoking, pollution) [4].

Oxidative stress to spermatozoa is very common, affecting between 30% and 80% of infertile men [5]. Seminal plasma the primary source of ROS is spermatozoa and polymorphonuclear leukocytes. In fact production of ROS is an outgrowth of physiological process during capacitation and acrosome reaction. Yet, high levels of ROS in seminal plasma is associated with poor semen quality. In one study it has been demonstrated that ROS causes almost 4-fold higher levels of DNA fragmentation and can be treated with anti-oxidants [6].

Antioxidant treatment has been widely used and accepted treatment for men with high sperm DNA fragmentation [7]. Several studies have suggested the use of anti-oxidant therapy in the treatment of male infertility to improve semen quality, especially in DNA damage and sperm motility [8]. Aim of this study was to explore the effects of three months oral anti-oxidant treatment in men with high levels of sperm DNA fragmentation and normozoospermia and history of recurrent intracytoplasmic sperm injection (ICSI) failures.

METHODS

This is a retrospective analyses of patients who admitted to private in vitro fertilization (IVF) center between January and December 2016. This study included normozoospermic patients (according to WHO 2010 criteria) with high DFI levels (> 30%) detected by TUNEL assay. All patients had experienced at least two unsuccessful ICSI attempts with ejaculated spermatozoa. Among the participants, the study group included men who had oral anti-oxidant treatment. The men who did not receive any treatment during the study period were taken as controls. Heavy smokers (> 20 cigarettes/day) and patients with; abnormal medical history, abnormalities physical examination, impaired endocrine profile, genital infections, leukocytospermia, cancer or cancer therapies, varicocele, cryptorcidism and genetic disorders were excluded. Couples with female partners fulfilling the Bologna criteria, preimplantation genetic screening and cryo cycles were also excluded.

All participants underwent ICSI using antagonist protocol. On day 2 of menstruel cycle, gonadotropins were started at doses ranging from 150 to 225 IU (Menopur, Ferring). On day 6 Gonadotropin-releasing hormone (GnRH) antagonist was added (0.25 mg/day, Cetrotide, Serono). The gonadotropin doses are adjusted according to patients response. When at least three follicules are > 17 mm in diameter ovulation is triggered with human chorionic gonadotropin (hCG) (Ovitrelle, Serono). Oocyte pick up is performed under sedation. The number of metaphase II (MII) oocytes, fertilization, embryo quality, and the cycle outcomes (implantation, clinical pregnancy, early pregnancy loss) of all couples were recorded. Patients in the study group underwent ICSI after receiving 3 months of anti-oxidant treatment (Proxeed Plus, İstanbul, Eczacıbaşı), while ICSI was the sole treatment for controls. Pregnancy was recorded after betahCG test at day 12 after embryo transfer.

This retrospective study was conducted in accordance with the ethical principles defined in the Helsinki Declaration.

Statistical Analysis

Statistical analyses performed by IBM SPSS for Windows Version 22.0 statistical package. Continuous variables presented as mean±standard deviation or median (minimum-maximum). Categorical variables summarized as frequencies and percentages. Normality of the continuous variables was evaluated by Kolmogorov Smirnow test. Differences between the two groups according to continuous variables were determined by independent samples t-test or Mann Whitney U test as appropriate. Categorical variables were compared by Chi-square or Fisher's exact test. Univariate associations between variables were estimated by Pearson's coefficient correlation. A p value less than 0.05 was considered significant.

RESULTS

Analysis of the recorded revealed that there are 70 couples fulfilling the inclusion criteria. Among these cases 24 men have used three months of anti-oxidant

Table 1. Demographic characteristics of groups

	OA (n = 24)	ICSI-only (n = 46)	*p* value
Age of females (years)	33.25 ± 5.18	34.1 ± 3.68	0.423
BMI (kg/m^2)	24.33 ± 3.17	25.76 ± 2.36	0.170
Previous failed attempts (n)	3.17±1.55	3.86 ± 1.42	**< 0.05**
Infertility duration(years)	7.21 ± 2.78	8.2 ± 2.60	0.144
AMH (ng/ml)	2.20 ± 1.39	2.12 ± 1.16	0.810
DFI (%)	43.33 ± 5.87	41.8 ± 6.48	0.337

Data are presented as mean±standard deviation. OA = oral antioxidant, ICSI = intracytoplasmic sperm injection, BMI = Body mass index, AMH = Anti-Mullerian Hormone, DFI = DNA fragmentation index

treatment before a new ICSI cycle whereas the remaining 46 had ICSI-only. The study and control groups had comparable demographic characteristics by means of female partner's age, body mass index (BMI), duration of infertility, anti-Mullerian hormone (AMH) levels and DNA fragmentation index (DFI); suggesting that the confounding factors supposed to influence ICSI outcomes were almost matched (Table 1). The only statistically significant differences between the treatment and control groups were the number of previous failed attempts.

The cycle characteristics and outcomes are given in Table 2. Duration of stimulation, the number of MII oocytes, fertilization rate and implantation rates were similar between two groups. Although not statistically significant, cases in anti-oxidant group have slightly better pregnancy rates compared to ICSI-only group (37.5% vs 19.6%, $p > 0.05$, Table 2). Only one case in each group had abortion.

DISCUSSION

Although there have been previous studies searching for the effect of anti-oxidant treatment on sperm DNA fragmentation incidence or DFI, up to our knowledge, this is the first study that evaluates the effects of anti-oxidant treatment on ICSI outcomes in normozoospermic patients with recurrent ICSI failure who have high DFI levels.

Data in this study suggest that anti-oxidant treatment for patients with high DFI levels, following unsuccessful ICSI attempts does not offer any advantage in terms of improving the ICSI outcomes. Yet it's difficult to conclude that anti-oxidant treatment has no beneficial effect in terms of decreasing ROS formation and improving fertility. The literature on the effect of anti-oxidant treatment on DNA fragmentation is conflicting. While some studies suggested beneficial effects, others reported a lack of improvement in the

Table 2. Cycle characteristics and cycle outcomes of study and control groups

	OA (n = 24)	ICSI-only (n = 46)	*p* value
Stimulation duration (days)	11.26 ± 1.25	11.46 ± 1.68	0.610
No of MII oocytes	6.39 ± 4.18	7.24 ± 2.45	0.287
Fertilization rate (%)	74.30 ± 18.94	70.30 ± 20.26	0.406
Implantation rate (%)	26.50 ± 6.61	24.50 ± 8.25	0.176
Clinical pregnancy, n (%)	9 (37.5)	9 (19.6)	0.103
Abortion rate, n (%)	1 (4.2)	1 (2.2)	0.634

Data are presented as mean ± standard deviation. OA = oral antioxidant, ICSI = intracytoplasmic sperm injection, MII = metaphase II

outcomes. Menezo *et al*. [9] reported that anti-oxidant treatment led to a decrease in sperm fragmentation. An unexpected negative effect was also reported for anti-oxidant treatment which is an increase in sperm decondensation. The author concluded that this observation may be the cause of the discrepancy regarding the improvement in male fertility with anti-oxidant treatment [9]. In a similar way Amar *et al*. [10] stated that although anti-oxidant treatment limit ROS generation and related DNA damage, current anti-oxidant therapies might not be efficient and lead to decondensation and offered sequential treatment for handling the stiuation. On the contrary Greco *et al*. [11] suggested that antioxidant treatment reduces the proportion of spermatozoa with DNA damage and improves ICSI outcomes in men with high levels of sperm DNA fragmentation. However, similar to our study, no statistically significant difference was found in fertilization rates after anti-oxidant treatment. Of particular concern, in the study patients with no apperent improvement of ejaculated spermatazoa after the treatment were switched to an invasive alternative. Authors stated that; they did not address whether keeping up with the same treatment instead of switching to a more invasive one would make any difference and they also concluded this treatment may not be equally effective in a subgroup of patients who have no improvement after anti-oxidant treatment [11]. There are other studies consistent with the main finding of this study. Tunc *et al*. [12] reported that anti-oxidant treatment improves sperm DNA integrity. Greco *et al*. [13] reported that short term anti-oxidant supplementation is efficient for treating men with high sperm DNA damage. Abad *et al*. [14] suggested that in addition to improving semen quality in terms of key seminal parameters and basal DNA damage, anti-oxidant treatment also promotes better outcomes following assisted reproductive techniques. Gaul-Frau *et al*. [7] also showed beneficial effect of oral anti-oxidant treatment in grade 1 varicocele cases. However they also stated that despite better outcomes in terms of pregnancy by natural conception, higher rates of miscarriages were reported after oral anti-oxidant treatment [7].

Limitations

One of the limitations of our study apart from its retrospective nature is that the sample sizes were small. Literature in general keeps up with the hypothesis that anti-oxidant oral treatment appears to decrease the amount of sperm with DNA damage. However, mostly the effects are reported after short term treatment and there is no long-term follow-up results and the endpoint that is measured is sperm DNA integrity. Besides, most of the clinical studies have limited number of pariticipants and there is a great variation in the subpopulations. Therefore, this type of statement underlying the benefit derived from the anti-oxidant therapy needs to be balanced until more clinical studies with greater study populations are performed.

CONCLUSION

This study reveals that there is no statistically significant difference in the ICSI outcomes of the patients with high DFI levels, following unsuccessful ICSI attempts after oral anti-oxidant treatment.

Author Contribution

Research conception & design: ST, GSÇ, AHH; Data acquisition/analysis and interpretation: EGP; MK; Statistical analysis: ST; Drafting of the manuscript: ST, GSÇ, MK, AHH; Critical revision of the manuscript and approval of final manuscript: ST, GSÇ, EGP, MK, AHH.

Ethics statement

Recently published The National Code on Clinical Trials has declared that ethics approval is not necessary for real retrospective studies. This is a retrospective study based on recorded data. Therefore approval from owners of the data (ST, GSÇ, EGP and AHH) is obtained.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2019;5(5):873-878 ORIGINAL ARTICLE

Fibromyalgia in the mothers of the children with cerebral palsy, and determination of the related depression and anxiety situations

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ABSTRACT

Objectives: In this study, it was aimed to evaluate maternal functional status, quality of life, depression and anxiety measurements according to the child's functional level in the mothers, who were diagnosed with fibromyalgia syndrome (FMS), of children with cerebral palsy (CP).

Methods: Ninety-seven mothers diagnosed with FMS, whose children had CP, were included in the study. Children with CP were divided into two functional levels with the Gross Motor Function Classification System (GMFCS) as mild-moderate (level 1, 2 and 3) and severe (level 4 and 5). On mothers, The Fibromyalgia Impact Questionnaire (FIQ) was used to assess the functional levels and quality of life, Beck Depression Inventory (BDI) was used to evaluate the depression level, and Beck Anxiety Inventory (BAI) was used to determine the anxiety level.

Results: The mean age of the 97 female patients participating in the study was 35.93 ± 8.72 years. According to GMFCS, 67% of children with CP were mild to moderate while 33% were severe. There was a significant positive correlation between GMFCS levels of children with CP and their mother's FIQ, BDI, and BAI scores ($p < 0.05$).

Conclusions: Maintaining the daily life of a child with CP is a parenting-focused situation. Especially it affects the mother physically and mentally. Our study suggests that the severe physical condition of the child with CP increases the mother's FIQ, depression, and anxiety. It has been determined that studies on CP should not ignore the parental factor as well as research on the disease itself.

Keywords: .cerebral palsy, depression, anxiety, fibromyalgia

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Cerebral palsy (CP) is a persistent motion and posture disorder associated with damage to the brain that maintains its development [1]. Although rates vary according to different countries around the world, incidence in a prevalence study in Turkey was found as 4.4/1000 [2]. Many factors, such as clinical types, motor loss in the affected extremities, sensorial, communicative, and mental disorders of the children with CP determine their ambulatory abilities and performance of their self-care skills. Treatment of the child with CP is multidisciplinary teamwork. This includes physiatrists, pediatricians, physiotherapists, orthopedists and neurosurgeons, educators, occupational therapists and speech therapists, and parents. However, at

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the center of the team is the family, especially the mother [3, 4]. For this reason, maternal health is an essential parameter in the treatment of children with CP.

Fibromyalgia Syndrome (FMS) is a multisystemic disease characterized by chronic widespread musculoskeletal pain. There are regional studies on FMS prevalence in our country; for Diyarbakır region, this rate was determined as 8.8% [5]. It is seen more frequently in female gender and age range of 40-55 years. Many symptoms such as body pain, the absence of energy, stiffness, sleep disturbances, anxiety, depression, memory problems, balance problems, sensitivity to touching, heat, and sound are evaluated in FMS. In previous studies, the prevalence of anxiety and depression in FMS patients was found to be higher than in the healthy population [6]. Besides, widespread chronic pain, fatigue, sleep disturbance, and psychiatric symptoms disrupt the daily living activities and quality of life of patients [7].

In this study, we aimed to determine the relationship between the anxiety, depression level and quality of life of the FMS mothers with CP children and their children's functional status.

METHODS

Ninety-seven mothers, who were diagnosed with FMS, of the ninety-seven childrren with CP who received rehabilitation treatment at the Inönü University Turgut Özal Medical Center Physical Medicine and Rehabilitation Unit were included in the study. Ethic committee approval (2016/106) of the study was obtained from the Malatya Clinical Research Ethics Committee. All patients included in the study were informed about the study and received their approval.

Mothers, who were between 18-60 years of age and who had FMS diagnosis according to the 2013 ACR diagnostic criteria, of the children with CP were included in the study. Having physical therapy and medical treatment for FMS in the last six months, the presence of cervical disc hernia, radiculopathy and myelopathy story, antidepressant treatment within the last six months, and the presence of more than one child with CP were defined as exclusion criteria.

In the assessment of the patients diagnosed with FMS; the demographic data of the mother and the child, CP type of the child and the Gross Motor Function Classification System (GMFCS) were evaluated by the same physical medicine and rehabilitation specialist. The way the child was carried by the mother, the duration, and frequency of the home exercise and the use of orthosis were recorded.

Gross Motor Function Classification System (GMFCS)

GMFCS is a standard measurement method for children with CP who divides to the levels according to the motor function. Children in the first level are independent of the motor functions, while children in the fifth level are defined as the dependent [8]. In our study, GMFCS levels 1, 2 and 3 were defined as mild-moderate, while levels 4 and 5 were defined as the severe group.

Functional Assessment and Quality of Life

In order to evaluate the quality of life and functional status in FMS in our study, The Fibromyalgia Impact Questionnaire (FIQ) which Turkish validity and reliability was shown by Sarmer *et al*. [9] was used. At this scale, ten different features are measured: physical function, feeling good or not, not being able to go to work, difficulty at work, pain, fatigue, morning fatigue, stiffness, anxiety, and depression. The maximum score is 100. While an average patient with FMS receives 50 points, a severely affected patient usually scores over 70 [10].

Depression Assessment

The presence and severity of depression were determined using the Beck Depression Inventory (BDI) [11]. This scale which Hisli [12] made its validity and reliability in our country in 1988, consists of 21 items. Each item consists of 4 sentences, ordered by neutral (0 points) and severest (3 points). In our study, 0-9 points were assessed as not depressed, 10-16 points as mild depression, 17-29 points as moderate depression and ≥ 25 points as severe depression [13].

Anxiety Assessment

Beck Anxiety Inventory (BAI) was used to determine the anxiety level. This scale which was developed by Beck *et al*. [11] in 1988 consists of a total of 21 items. Each item is scored between 0-3 with a Likert type scale. The total score range is 0-63. 0-7

points are considered normal, 8-15 points mild, 16-25 points moderate, and ≥ 26 points for severe anxiety. Validity and reliability study for the Turkish population was done by Ulusoy *et al*. [14]..

Statistical Aanalysis

Statistical Package for the Social Sciences (SPSS) 17 Windows software program was used for statistical analysis. The mean of the quantitative data was expressed as median (minimum-maximum) and mean ± standard deviation. Qualitative data were expressed as number (n) and percentage (%). The Kolmogorov-Simirnov test assessed the suitability of the normal distribution of measurable values. Pearson correlation analysis was performed for the analysis of the linkages of the variables. A p value < 0.05 were considered statistically significant.

RESULTS

The mean age of the 97 female patients participating in the study was 35.93 ± 8.72 years. Fourty-two (43.3%) mother had gone to primary school, and 92.8% were not working. Although 73.2% did not receive physical help in the care of the child, 86.6% of them have their child regularly exercised. Sociodemographic data are summarized in Table 1. Fifty-one (52.6%) children with CP were girls, 47.4% were boys. The mean age of the children was 6.42 ± 4.72 years. According to GMFCS, 67% were mild to moderate while 33% were severe. Table 2 summarizes the sociodemographic characteristics of children with CP.

Table 1. Sociodemographic sharacteristics of the mother

Characteristics	Data
The average age (mean ± SD)	35.93 ± 8.72
Age distribution, n (%)	
≤ 44 Years	85 (87.6)
> 44 Years	12 (12.4)
Education status, n (%)	
Not literate	14 (14.4)
Primary school	42 (43.3)
Mid school	10 (10.3)
High school	21 (21.6)
University	10 (10.3)
Working Status, n (%)	
Yes	7 (7.2)
No	90 (92.8)
Does She Get Physical Help For Caring?, n (%)	
Yes	26 (26.8)
No	71 (73.2)
Does She Get Exercises Done at Home?, n (%)	
Yes	84 (86.6)
No	13 (13.4)
The frequency of Exercise at Home, n (%)	
Not doing	13 (13.4)
5-30 min.	55 (56.7)
31-60 min.	25 (25.8)
61-90 min.	4 (4.1)

SD = Standart deviation

Table 2. Socio-demographic characteristics of children with CP

Characteristics	Data
Gender, n (%)	
Girl	51 (52.6)
Boy	46 (47.4)
The average age (mean ± SD)	6.42 ± 4.72
Age distribution, n (%)	
0-2 Years	23 (23.7)
3-6 Years	38 (39.2)
7-12 Years	21 (21.6)
13-18 Years	15 (15.5)
Weight (mean ± SD)	23.28 ± 13.9
Height (mean ± SD)	111.62 ± 26.95
GMFCS level, n (%)	
I	14 (14.4)
II	31 (32)
III	20 (20.6)
IV	21 (21.6)
V	11 (11.3)
Orthotic use, n (%)	
Yes	41 (42.3)
No	56 (57.7)
Carriage way, n (%)	
On lap	63 (64.9)
Device assisted	34 (35.1)
Special education, n (%)	
Yes	65 (67)
No	32 (33)

SD = Standart deviation, GMFCS = Gross motor function classification scale

Table 3. Scale scores

Parameter	Mean ± SD	p value
FIQ	41 ± 21.23	**< 0.001**
BDI	15.32 ± 12.07	**< 0.001**
BAI	15.92 ± 13.95	**< 0.001**

FIQ = The Fibromyalgia Impact Questionnaire, BDI = Beck Depression Inventory, BAI = Beck Anxiety Inventory, SD = Standart deviation

Table 4. Evaluation of some parameters of patients with FIQ <50 and FIQ ≥50 scores

Mother age (n)	FIQ < 50 (n)	FIQ > 50 (n)	TOTAL
≤ 44 Years	58	27	85
> 44 Years	5	7	12
Child age (n)			
0-3 Years	16	7	23
4-6 Years	24	14	38
7-12 Years	11	10	21
13-18 Years	12	3	15
Depression (n)			
No (0-9 Points)	22	0	22
Yes (10-63 Points)	41	34	75
Anxiety (n)			
No (0-7 Points)	25	3	28
Yes (8-63 Points)	38	31	69
Exercise frequency(n)			
5 - 30 Min.	39	16	55
31 - 60 Min.	12	13	25
61 - 90 Min.	2	10	4
Never	10	2	13
Carriage way (n)			
With Device	18	16	34
On Lap	18	45	63
Level (n)			
Mild-Moderate (I-III)	53	12	65
Severe (IV-V)	10	22	32
Job (n)			
Not working	59	31	90
Working	4	3	7
Special education (n)			
Not Receiving	18	14	32
Receiving	45	20	65
Orthotic use (n)			
Yes	22	19	41
No	41	15	56

The results of the FIQ, BDI, and BAI of the mothers are shown in Table 3. Table 4 shows that mothers with FIQ ≥50 experience more severe depression and anxiety than those with FIQ <50, have more extended hours of exercise for their children, often carry them on their lap, and children have a higher GMFCS score.

There was a statistically significant difference between the two groups when the results of FIQ, BDI, and BAI were compared between the mild-to-moderate group levels and the severe group levels of children according to GMFCS (Table 5).

Tablo 5. Relationship between GMFCS levels of children with CP and FIQ, BDI, and BAI levels assessed in the mothers

GMFCS	**Mild-Moderate Level (Level 1, 2, 3)**	**SevereLevel (Level 4, 5)**	***p* value**
FIQ	34.54 ± 16.67	55.79 ± 22.59	< 0.05
BDI	12.92 ± 10.49	20.21 ± 13.67	< 0.05
BAI	12.93 ± 11.94	22.03 ± 15.85	< 0.05

Data are given as mean ± standard deviation. FIQ = The Fibromyalgia Impact Questionnaire, BDI = Beck Depression Inventory, BAI = Beck Anxiety Inventory, GMFCS = Gross motor function classification scale

DISCUSSION

This study aimed to show the effect of the dependent functional status of children with CP on the quality of life and functional status, depression, and anxiety in FMS-diagnosed mothers and concluded that this had a negative effect.

The treatment process for a child with CP is a long and challenging process. In this process, the family-based multidisciplinary approach is the basis of treatment. The fact that parents are always involved with active participation at every stage of treatment and in the center of the rehabilitation process presents a number of challenges and limitations, especially in the lives of mothers who undertake the primary care. However, studies on children with CP have mostly focused on the disease itself and have been relatively neglected the family side. In the literature review, limited studies were made on the quality of life of mothers of CP children. In the study performed by Ones *et al*. [15], the mothers of children with CP and healthy children's mothers were compared, and the quality of life in the mothers of children with CP were found to be significantly lower. In a study in Bangladesh, Mobarak *et al*. [16] found that 41.8% of 91 mothers of the children with CP had a risk of psychiatric morbidity. Eker and Tüzün [17] examined the quality of life difference between the mothers who have children with CP and the mothers with minor health problems (fever, cough, diarrhea) with Short Form-36 (SF-36). Comparisons were made both in comparison to two groups and when children with CP were self-rated according to GMFCS; significant differences were found in all parameters except for the physical function subsystem of SF-36 [17]. In FMS patients, depression and sleep disturbances are seen at high rates and quality of life is already very low [7]. At the same time, due to both physical and psychological deprivation in many areas such as heavy lifting, turning, bathing, supporting toilet needs, dressing, feeding, supporting sleeping needs and helping movements, which are essential for the child's caring tasks, the quality of life for the FMS-diagnosed mothers of the children with CP, is expected to be lower. In this context, we have found that the quality of life and the functional status of the mothers of children with CP, who already have FMS diagnosis, are closely related to the increased dependence of the child in our study.

On the other hand, FMS is a multisystemic disease with chronic widespread musculoskeletal pain. Musculoskeletal pain in mothers of children with CP is among the problems they often face because they cover all the needs of the child and are exposed to physical difficulties. However, there is a limited number of studies evaluating the musculoskeletal system in the literature. In the study by Terzi and Tan [18], musculoskeletal system pain and related factors were investigated in the mothers of children with CP and the total number of children, the age of the child with CP, functional level and the depression level of the child were found to be independent risk factors. In a study made by Prudente *et al*. [19], following a 10-month rehabilitation program, the motor function of the children with CP and maternal quality of life were investigated, and improvement in gross motor functions was found after recovery and rehabilitation in children and there was a corresponding decrease in the lower body pain of the mothers.

We evaluated our patients with BDI and BAI, which are commonly used in depression and anxiety frequently accompanies the disease, which is also included in the 2013 ACR fibromyalgia diagnostic criteria. Statistically significant high scores were found when the depressed values were compared between mothers with healthy children and those with CP children in the study made by Terzi *et al*. [18]. Rosenbaum has shown that parents of the children with chronic illness experience twice as much anxiety and depression than parents with healthy children [20]. Parents of children with chronic illness are at risk of losing their psychosocial health. Interventions to protect and improve their health are urgently needed [21]. Mothers of children with CP can not only try to overcome the difficulties and complications of their children's condition but also face the difficulties of not meeting their social needs [15]. The association of these problems is similar to the other studies in the literature, and in our study, we found that the results of the high GMFCS and FIQ, BDI, BAI scores showed a significant positive correlation.

CONCLUSION

In conclusion, we found that mothers of the

children with CP had increased fibromyalgia, depression and anxiety as GMFCS scores of the children increased. We believe that interventions to protect and improve the physical and psychosocial well-being of parents and parent-focused literature studies will increase the quality of life for children with CP.

Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

Authors' Contributions

Research Design: ŞT, AB, ZTA; Data Collecting: ŞT, ZTA; Literature Review: ŞT; Statistical Analysis: AB, RB

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2019;5(5):879-885 ORIGINAL ARTICLE

Endobronchial management of malignant central airway obstruction: the first 6-year single center experience

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ABSTRACT

Objectives: Central airway obstruction (CAO) develops in 20-30% of lung malignancies during the disease. The symptoms related to obstruction often result in poor quality of life and poor prognosis. Interventional bronchoscopic treatments are now recommended in guidelines to improve quality of life and symptom palliation in this patient group. In our study, we aimed to determine the efficacy and safety of our methods in the malignant CAO caused by endobronchial exophytic tumors.

Methods: Between May 2012 and August 2018, 432 endobronchial debulking procedures were performed in 388 patients with symptomatic malignant CAO due to endobronchial exophytic or mixed lesions.

Results: Primary lung tumors were the most common cause of airway stenosis (84.0%). The most common debulking technique was argon plasma coagulation assisted mechanical debridement (APC+MD) (79.9%). Airway patency was achieved with additional stents (10.2%) in the operations. The success rate of airway patency was 85.5% in APC+MD method, 75.6% in cryorecanalisation method, 91.7% in electrocautery assisted MD method, 100% in MD method and overall success rate was 85.4%. Stent use rate was significantly higher in the stenosis around main carina (42.9%) than in other localizations ($p < 0.001$). The overall serious complication rate was 2.1%. Procedure-related dead rate was 0.2%.

Conclusions: Endobronchial treatment of malignant CAO with interventional bronchoscopic procedures is effective and safe. The first 6 years of experience in our interventional pulmonary clinic show that it has similar characteristics with the world experience in the endobronchial treatment of malignant CAO.

Keywords: Interventional bronchoscopy, debulking, malignant central airway obstruction

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Central airway obstruction (CAO) develops in 20-30% of lung malignancies during the disease and constitutes 40% of disease-related deaths [1, 2]. The symptoms related to obstruction, such as dyspnoea, haemoptysis, and atelectasis with post-obstructive pneumonia, often result in poor quality of life and poor prognosis. The average life expectancy in these patients does not exceed 1-2 months [3-5]. For such complications, surgery is contraindicated in proximal lesions, chemotherapy has uncertain and delayed benefits, radiotherapy solves atelectasis in half of cases (54%), but results are delayed also [6]. Interventional

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bronchoscopic treatments are now recommended in guidelines to improve quality of life and symptom palliation in this patient group [7]. Many useful interventional bronchoscopic techniques have been developed to rapidly treat the endoluminal exophytic part of a malignant tumor that causes CAO such as mechanical debridement (MD), laser (L), electrocautery (EC), argon plasma coagulation (APC), cryorecanalization (CR) [8-17]. Combined methods are currently preferred in combination with each other (eg, APC+MD) and in combination with stents [8, 12, 18]. In our study, we aimed to determine the efficacy and safety of our methods in the malignant CAO caused by endobronchial exophytic tumors.

METHODS

Patients

This retrospective cross-sectional study was approved by the local ethics committee and was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients. Between May 2012 and August 2018, 432 endobronchial debulking procedures were performed in 388 patients with symptomatic malignant CAO due to endobronchial exophytic or mixed lesions. Interventional procedures other than debulking during this period (such as interventions to external compression stenosis, hemoptysis, fistulae and, benign airway strictures) were not eveluated.Patients with large vessel tumor invasion, clotting disorders, or low platelet count, as well as pregnant subjects, those under the age of 18, and those who did not sign the informed consent were excluded.

Operative Technique

General anesthesia was administered by an total intravenous anesthesia technique. Patients were intubated with a rigid bronchoscope (Efer-Dumon, 11 mm diameter, 43 cm length, Efer Endoscopy, Marseille, France) and respiration were achieved by conventional balloon method. Debulking procedures were performed by MD using the tip of the rigid bronchoscope, rigid pliers or APCor EC assisted MD (APC+MD, EC+MD) (ERBE ICC 200/APC 300 electrosurgical unit, rigid APC probe, 50 cm length, 2.3 mm diameter or rigid EC probe 50 cm length, 2.3 mm diameter; ERBE, Medizintechnik, GmbH, Tübingen, Germany) or CR (ERBOKRYO® CA unit, rigid cryoprobe 3 mm diameter, 53 cm length; ERBE, Medizintechnik, GmbH, Tübingen, Germany) (Figure 1, 2). When using APC or EC for coagulation, FiO2 was kept below 40%. After extubation, the patients

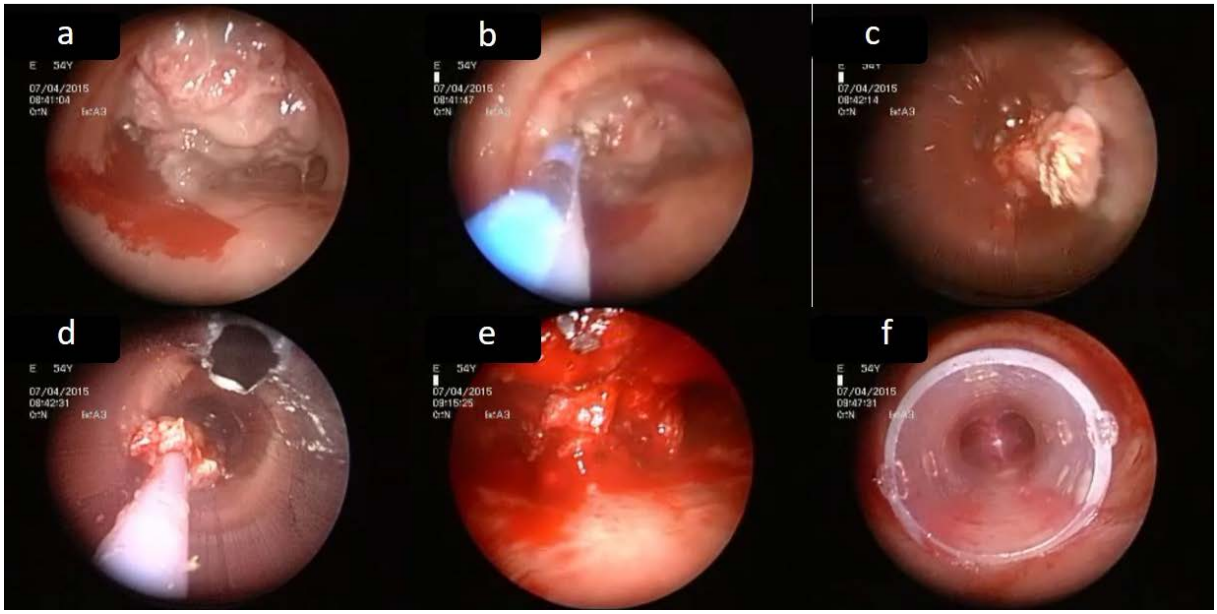

Figure 1. Argon plasma coagulation assisted mechanical debridement plus silicone Y stent. (a) malignant tumor on the main carina, (b) argon plasma coagulation, (c) mechanical debridement with tip of rigid bronchoscope, (d) tumor extracting by aspiratory probe, (e)residual tumor occluding both main bronchus, and (f) silicone Y stent appearance.

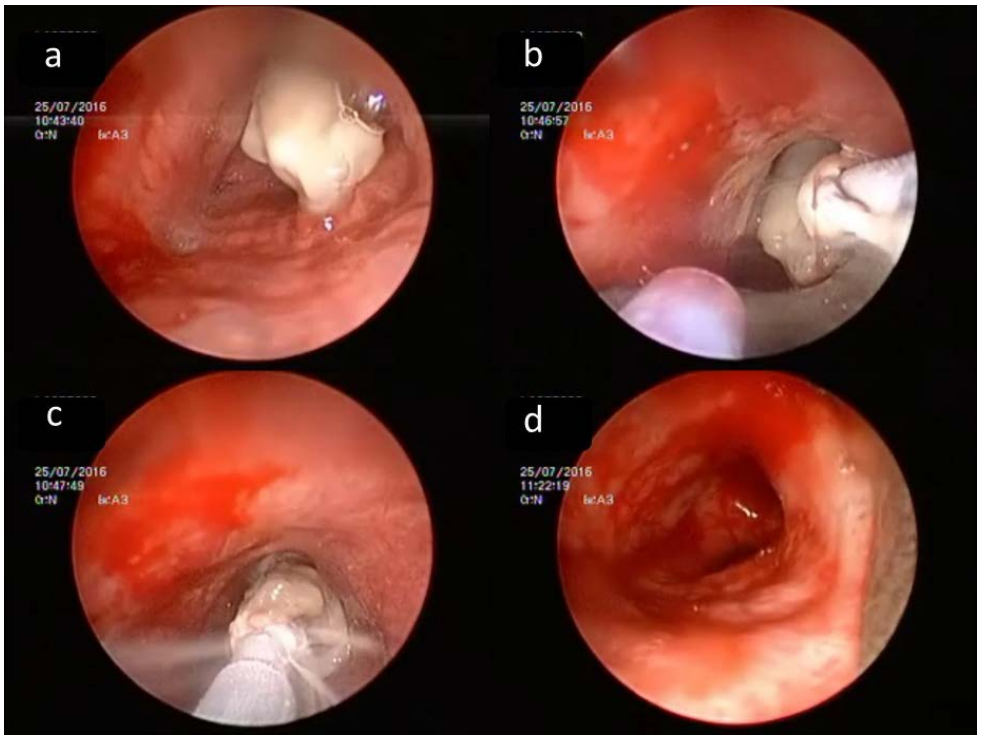

Figure 2. Cryorecanalization. (a) malignant tumor that narrows the right main bronchus, (b) cryorecanalization with rigid cryo probe, (c) repeated cryorecanalization with rigid cryo probe, and (d) airway patency provided in the right main bronchus.

were followed up in intensive care unit. Anteroposterior chest radiography and an arterial blood gas test were performed routinely. All patients were consulted to the oncology unit for chemotheraphy and/or radiotherapy treatment according to the stage of their tumor.

More than 50% ordinary diameter expansion of the bronchus diameter with malignant airway obstruction and the presence of distal healthy bronchus were accepted as a successful procedure. Silicone stents (Novatech® GSS ™ / Dumon®, Novatech SA, La Ciotat, Cedex, France) were placed in patients with expansion below 50% due to external compression despite after debulking of endobronchial exophytic part of tumor and reaching the healty bronchi.

Statistical Analysis

The statistical analyses were conducted with PASW Statistics for Windows (SPSS Inc. Version 18.0, Released 2009, Chicago, USA). Descriptive statistics were presented with frequency, percentage, mean, standard deviation (SD) and median values. Pearson chi-square test was used to analyze the relationships between categorical variables. The significance level was taken as $p < 0.05$

RESULTS

Three hundred eighty eight patients with malignant exophytic or mixed endobronchial lesions underwent a debulking procedure 432 times. The mean age of the study population (87.4% males) was 59.6 ± 11.2 (range 20-83) years. Primary lung tumors were the most common cause of airway stenosis (84.0%). 43.0% of the patients underwent interventional bronchoscopic procedures under emergent or urgent conditions. The first anatomic region, which caused more than 50% stenosis under the cord vocal, was accepted as the main stenosis. The majority of the procedures (47.7%) were applied for right-sided stenosis (right main bronchus, intermediate bronchus, right upper, middle, lower lobe bronchi). The most common debulking technique was APC+MD (79.9%). Airway patency was achieved with additional stents (10.2%) in the operations, that had robust bronchi in the distal area after debulking but residue airway stenosis was more than 50% due to external compression (Table 1).

The success rate of airway patency was 85.5% in APC+MD method, 75.6% in CR method, 91.7% in EC+MD method, 100% in MD method and overall

Table 1. Patient demographics and clinical data

Variables	n	%
Age (years) (mean±standard deviation)	59.6 ± 11.2	
Sex		
Male	339	87.4
Female	49	12.6
Origin of malignancy		
Primary lung tumors	326	84.0
Low grade tumors	31	8.0
Metastatic tumors	31	8.0
Operative indication		
Urgent	167	43.0
Elective	221	57.0
Site of main stenosis		
Trachea	107	24.8
Main carina	21	4.9
Right side	206	47.7
Left side	98	22.7
Techniques used		
APC+MD	345	79.9
CR	41	9.5
EC+MD	36	8.3
MD only	10	2.3
Additional silicone stent used		
Trachea	27	25.2
Main carina	9	42.9
Right side	7	3.4
Left side	1	1.0
Total	44	10.2
Complications		
Carbon dioxide retention	5	1.2
Pneumothorax	3	0.7
Severe bleeding	1	0.2
Total	9	2.1

APC+MD = Argon Plasma Coagulation assisted Mechanical Debridement, CR = Cryorecanalization, EC+MD = Electrocautery assisted Mechanical Debridement, MD = Mechanical Debridement

success rate was 85.4% (Table 2). The success rate of airway patency in left-sided lesions (65.3%) was significantly lower than other localizations ($p < 0.001$) (Table 3).

Stent use rate was significantly higher in the stenosis around main carina (42.9%) than in other localizations ($p < 0.001$). The need for stenting in tracheal lesions (25.2%) was higher than right (3.4%) and left (1.0%) sided stenosis ($p < 0.001$, $p < 0.001$ respectively) (Table 4).

Table 2. The success rates of debulking techniques in our study and literature

Technique	n	Succesfull	%	In literature %	References
APC+MD	345	295	85.5	67-96%	[8, 9]
CR	41	31	75.6	73-91%	[10-12]
EC+MD	36	33	91.7	88-89%	[13-15]
MD only	10	10	100.0	76-90%	[8, 16, 17]
Total	432	369	85.4	85-93%	[18, 20, 21]

APC+MD = Argon Plasma Coagulation assisted Mechanical Debridement, CR = Cryorecanalization, EC+MD = Electrocautery assisted Mechanical Debridement, MD = Mechanical Debridement

Table 3. Success rates according to localization

Localization of obstruction	Number of interventions	Succesfull	%	Unsuccesfull	%	*p* value
Trachea	107	106	99.1	1	0.9	
Main carina	21	21	100.0	0	0.0	
Right side	206	178	86.4	28	13.6	< 0.001
Left side	98	64	65.3	34	34.7	
Total	432	369	85.4	63	14.6	

The overall serious complication rate was 2.1%. In 5 (1.2%) patients had carbon dioxide retention treated with invasive mechanical ventilation support for an average of 2 hours and after extubation did not recur. Three (0.7%) patients had pneumothorax treated with tube thoracostomy. One patient (0.2%) with severe bleeding intubated with the double-lumen endotracheal tube and 2 units of erythrocyte suspensions were given. The patient died in the fifth day of the procedure in intensive care unit due to respiratory failure and this was considered as only 1 (0.2%) perioperative mortality related to the procedure (Table 1).

Table 4. Use of stents according to localization

Localization of obstruction	Number of interventions	Stent usage	%	*p* value
Trachea	107	27	25.2	
Main carina	21	9	42.9	
Right side	206	7	3.4	< 0.001
Left side	98	1	1.0	
Total	432	44	10.2	

Recurrent CAO was observed in 36 of 388 patients (9.3%). Due to recurrence, debulking was performed 44 times (range 1-4 times) in 36 patients. The median time to relapse was 74 days (range 7-1646 days). Of the 44 procedures, 7 (15.9%) resulted in unsuccessful. Treatment success was achieved with additional silicone stents in 12/36 (33.3%) in these patient group.

DISCUSSION

Malignant CAO is synonymous with poor prognosis [3-5]. Conventional treatments do not alter the poor outcome in this patient group. However, patients with airway patency provided by interventional bronchoscopic techniques have the same survival with patients without CAO [19].This evidence suggests that interventional bronchoscopy should be part of conventional therapies in this group of patients.

There are many useful studies on rapidly debulking of endobronchial exophytic part of tumor in malignant

CAO [8-21]. The success rates of patency of the techniques (used in our study) in the literature are APC+MD 67-96%, CR 73-91%, EC+MD 88-89%, MD 76-90% [8-17]. Although the number of interventions except APC+MD were small, our success rates were consistent with the literature (Table 2). The overall success rates found in three major studies were between 85-93% [18, 20, 21]. The overall success rate we found in our study (85.4%) is consistent with the literature in this respect. These data show that the techniques we use for endobronchial management of malignant CAO are effective.

We detected low success rate of patency among patients with left side tumors in accordance with the literature [21]. We think that the cause of the failure is related to the anatomical structure and lymphatic flow of the left bronchial system. Anatomically, the left upper lobe and left lower lobe are separated by the same angle in the same plane. There are left interlobar lymph nodes (11L) between them. In our experience, when the tumor in any part of the left lung invades to occlude the left main bronchus, it usually enlarges the 11 L ganglia with lymphatic spread. Growing 11L ganglia are narrowed by external compression in both lobe bronchus. Even if you remove the endobronchial exophytic tumors obstructing the left main bronchus, the left upper and lower lobe bronchi remain narrow due to external compression caused by the enlarged of 11L lymph nodes. This situation causes a failure of the operation.

The best palliative treatment of malignant tumors stenosis around the main carina is silicone Y stent placement [7, 22]. Therefore, it is expected that we will use silicone stents at a significantly higher rate (42.9%) in the main carina lesions after debulking.

It is reported that the overall complication rate is 1.6-11.0% and mortality rate is 0.8-3.0% due to techniques for endobronchial management of CAO [9, 18, 23-26]. Complication rate (2.1%), types of complications and mortality rate (0.2%) in the current study are consistent with the research in this field [9, 18, 23-26]. Our findings provide an evidence that our techniques are safe for the treatment of malignant CAO.

Recurrence rate after successful interventional bronchoscopic procedures in malignant CAO is 12.5% [27]. The rate of failure in repetitive processes increases. One of the indications for stent is recurrent endobronchial malignant tumors [28]. In our study, we found the recurrence rate is 9.3%, failure rate is 15.9% and, additional stent use rate is 33.3% in these group. Our data consistent that these results.

Limitations

Our study has a few limitations, this was a retrospective study and single-institution design. The retrospective nature of our study is a source of recall bias and does not allow us to evaluate improvements in quality of life. Prospective, multicenter trials are ideal and recommended in the future.

CONCLUSION

Endobronchial treatment of malignant CAO with interventional bronchoscopic procedures is effective and safe. The first 6 years of experience in our interventional pulmonary clinic established in 2012 show that it has similar characteristics with the world experience in the endobronchial treatment of malignant CAO. We think that there should be a team and equipment for treat malignant CAO by endobronchial methods in oncology centers.

Clinical Trial Registration

This study was approved by Ethical Committee of University of Health Sciences, Atatürk Chest Disease and Thoracic Surgery Training and Research Hospital with the number of 107.12.2018/583.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript .

Financing

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The European Research Journal 2019;5(5):886-893 ORIGINAL ARTICLE

The experience of İstanbul Protocol: efficiency, quality, difficulties in practice

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ABSTRACT

Objectives: Physicians who witness torture and ill treatment can be placed in a difficult position if their evidence was not accurately documented. The guidelines and ethical codes of the Istanbul Protocol require doctors to attend first and foremost to the well-being of their patients and to remain bound by the principles of medical ethics. The objective of this study was to compare the efficiency and the quality of the examination of detainees or alleged torture cases by medical doctors and the difficulties encountered in this activity.

Methods: A questionnaire was developed and sent to physicians in Black Sea Shore region of Turkey before and 1 year after their receiving training according to the Istanbul Protocol.

Results: There were 42 physicians who had undergone training according to the Istanbul Protocol and had answered the questionnaire; 28.6% of these were women and 71.4% men. These physicians applied the Istanbul Protocol more frequently after having received training on the Protocol Manual as compared to before the training. The 52.4% of these physicians reported having been the object of violence or intimidation.

Conclusions: It was determined that the physicians' knowledge of physical and psychological examination increased following their training according to the Istanbul Protocol.

Keywords: İstanbul Protocol, human right, torture

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According to the United Nations Convention Against Torture and Other Cruel, Inhuman or Degrading Treatment and Punishment, "torture means any act by which severe pain or suffering, whether physical or mental, is intentionally inflicted on a person for such purposes as obtaining from him or a third person information or a confession, punishing him for an act he or a third person has committed or is suspected of having committed, or intimidating or coercing him or a third person, or for any reason based on discrimination of any kind, when such pain or suffering is inflicted by or at the instigation of or with the consent or acquiescence of a public official or other person acting in an official capacity" [1].

Physicians who witness or diagnose torture or ill treatment are responsible for fully reporting physical and psychological findings and photographically documenting bodily lesions [2].

According to the 1975 World Medical Association (WMA) Declaration and the Professional Ethical Rules of the Turkish Medical Association, "The physician shall not participate in or help torture and similar practices using his medical knowledge or skill, and shall not originate false reports concerning the same. The physician witnessing cases in which torture is alleged shall use all professional knowledge and skills

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for discovering the facts" [3].

Many years of accumulating momentum resulted in 1996 in the Manual on the Effective Investigation and Documentation of Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment ("the Istanbul Protocol"). The Istanbul Protocol was prepared as a reference set of international guidelines for the assessment of persons who allege torture and ill treatment, for investigating cases of alleged torture, and for reporting such findings to the judiciary and any other investigative body [4-8].

Health care workers participating to the investigation of torture or ill treatment have to perform their examination following established and ethical medical practice standards; the resulting report must indicate the interview conditions, history, physical and psychological examination findings, and the opinion and identity of the preparer. The prepared report should be kept confidential and submitted in writing to the authority responsible for the investigation of torture or ill treatment [3-7].

The majority of cases requiring an investigation of torture or ill treatment in Turkey are seen under the titles of examinations at start or end of detention or examination of battery, by physicians working either in university and state hospital emergency services or in first-level health care facilities. Given the inadequacy of the conditions under which the examination is conducted and/or the absence of training for the satisfactory performance of an examination, these physicians are unable, in many cases, to perform complete and detailed examination and reporting.

One Hundred and twenty-eight physicians in Black Sea Shore Region of Turkey underwent training according to the Istanbul Protocol, designed to familiarize them with said Protocol within the framework of a common project of the Turkish Medical Association and the International Rehabilitation Council for Torture Victims (IRCT) in 2009. This study was designed to determine the problems experienced by physicians during the examinations at the start or end of detention or arrest, their compliance with the Protocol principles, their ethical tenets and general knowledge of examination methods, both before and after their Istanbul Protocol training, and to characterize any changes due to this training. The analysis of the questionnaire results intended to identify problems experienced by physicians in examining detained, released or arrested persons, and to develop proposals to solve such problems.

METHODS

Before the training and 1 years after the training session for non-forensic physicians on the Istanbul Protocol, which took place in Turkey, supported by European Union Forensic Medicine institutions and Ministries of Justice and Health and implemented by the IRCT, a questionnaire was replied by 42 physicians obtained from the eastern Black Sea Shore region state hospitals and first-level health care facilities who had undergone training.

The questions asked included the following, concerning the conditions and the physician performance before and after receiving the training. At the first part of questionary, questions related to the presence of an adequate room for examination; sufficient time for the examination; unshackling of the detainees during examination; keeping the security personnel outside the examination room; availability of the detainees' photographic identity documents; the obtaining of written or oral informed consent by the physician after having introduced oneself; presence of another health care professional at the examination; performance of a full examination after disrobing the patient; use of standard forensic medicine forms during the examination; eliciting exhaustive and correct history from the subject; performance of both bodily and psychological examination; the reaching conclusions by using the obtained information; availability of additional and radiologic examination or consultations; possibility of photographic documentation of observed lesions; transmission of reports to the prosecutor in sealed envelopes; and transmission of findings to judiciary authorities if findings of torture were present.

At the second part of the questionary, additional questions were the physician's age, sex, specialty, length of professional practice; total and monthly number of detained and arrested subjects examined; the physician's having been victim of violence or intimidation as a consequence of examining detainees and, if yes, the author and the type of such violence or intimidation, and how the physicians had responded to it.

The Questionary was constituted by the close-ended questions with a list of possible answers(Yes/No) from which respondant must choose.

Statistical Analysis

The study findings were evaluated using the Statistical Package for Social Sciences (SPSS) 13.0 software. Descriptive statistics were calculated. But comparisons couldn't be performed with data at the second part of the questionary because respondant space was small. So the percentage or number of relevant answers had been shown.

RESULTS

A total of 42 study subjects undergone training according to the Istanbul protocol had answered the questionnaire before and after training. Of these, 12 (28.6%) were women and 30 (71.4%) male.

The facilities in which detainee examinations were performed were mostly public hospitals (n = 18), followed by public health centers (n = 9), chest and tuberculosis centers (n = 5), emergency services (n = 4) and family medical practices, village or neighborhood outpatient clinics, and teaching or research hospitals (n = 2 each).

The physicians or cases were specialized in general practitioner (n = 34), emergency medicine (n = 4), family practice (n = 3) and pulmonary disease (n = 1). Their length of professional practice was 8.1 ± 6 years (mean ± 1 SD), with a range of 1-20 years.

The number of cases in monthly examination performed were 25 in the 0-10 case range, while 10 in 11-25 range, 5 with 26-50 range and 2 physicians saw more than 50 cases. As for the number of cases examined in the entire professional life of any single physician, they totaled less than 20 for 6 of the respondents, 21-50 for 3, 51-100 for 10, 101-250 for 9, 251-500 for 6 and more than 500 for 8 of them.

The physicians who answered the questionnaire (n = 42) had applied the Istanbul Protocol guideline more frequently after having received training on the Protocol (Figure 1 and 2).

The 52.4% (n = 22) of these physicians reported having been the object of violence or intimidation, distributed as follows by type: 8 in psychological, 2 in both verbal and psychological, 8 in verbal, 1 in verbal and physical, 1 in verbal, psychological and physical, and 2 in sexual in total respondents (Table 1). Of the 19 physicians who had been the victims of violence or intimidation, reported that the authors of it were security forces, a colleague, the examined person, and a relative of the detainee (Table 1).

The study subjects or respondents reported experiencing, as a consequence of the past violence or

Table 1. Distribution (n) by author and type of the cases of violence and intimidation (n = 22)

Authors of violence/ intimidation (n) / Type of violence/ intimidation	Security forces	Both security forces and administrator or colleague	Both security forces and patient	Patient	Relative of patient	Unknown
Psychological			3	5		
Verbal	3			5		
Both verbal and psychological		1		1		
Both verbal and physical					1	
Sexual						2
Verbal, psychological and physical						1

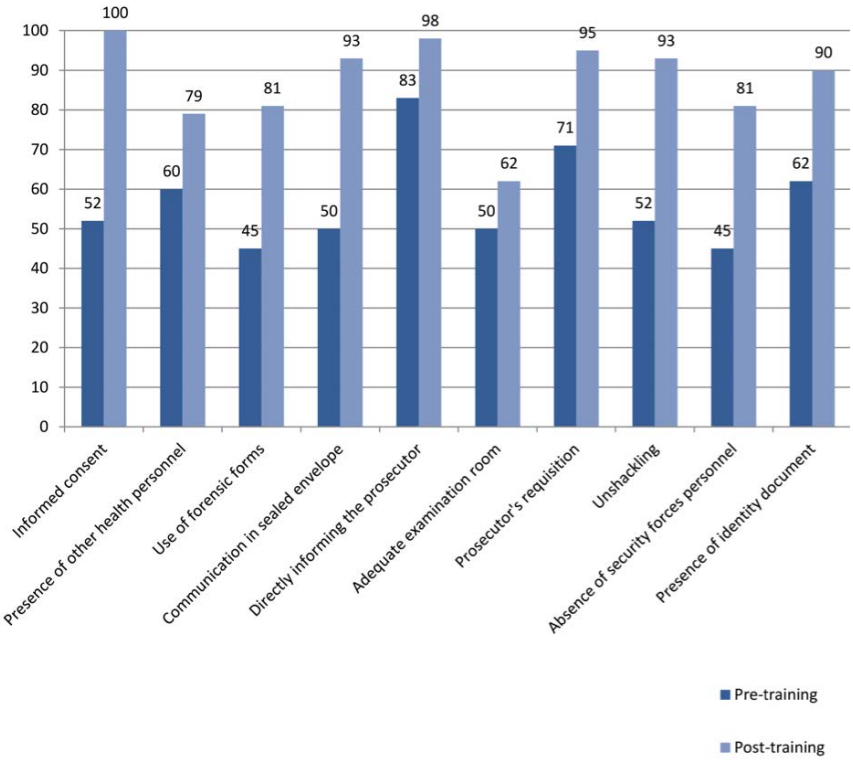

Figure 1. Compliance rates (%) of physicians (n = 42) with medical and ethical rules for the examination of detainees, before and after receiving training according to the Istanbul Protocol.

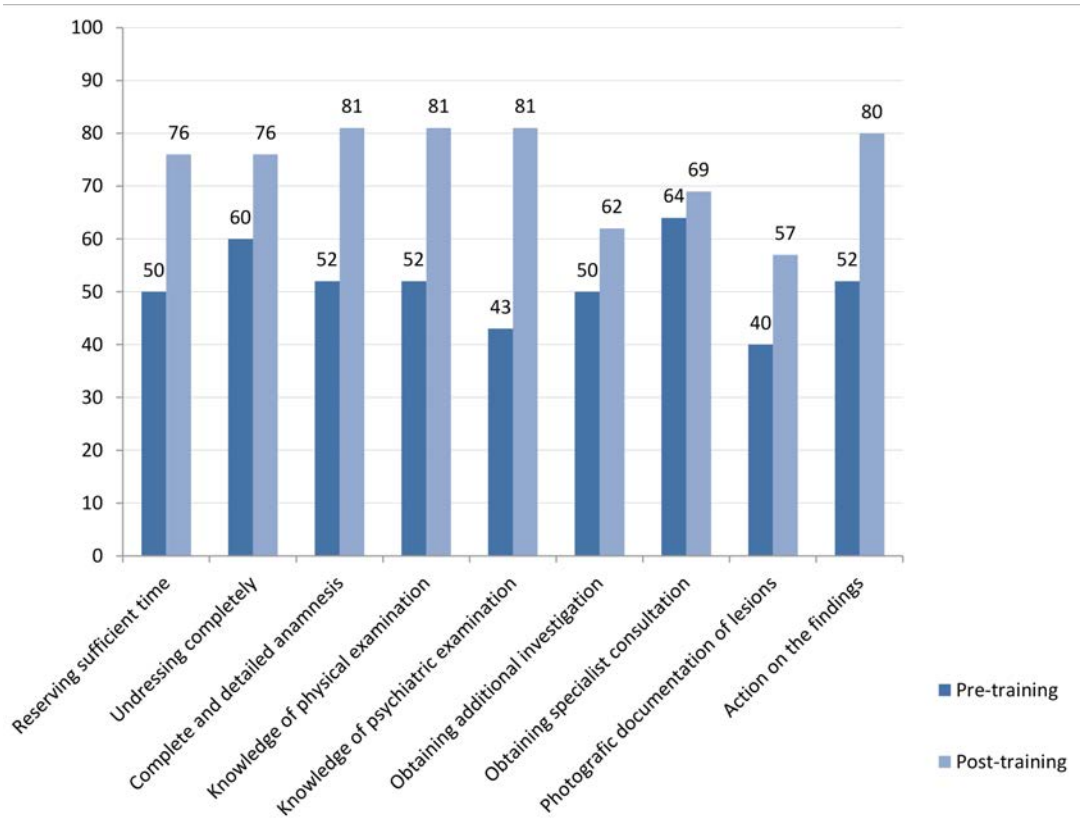

Figure 2. Knowledge, skill and thoroughness (%) in the examination of detainees by physicians (n = 42) before and after receiving training according to the Istanbul Protocol.

intimidation, thoughts, feelings or nightmares of the fears caused by remembering the events, trying not to think about the experience of violence or intimidation and keep away from situations that may remind them of it, or feeling continually on the alert (in 1 case); feeling emotionally numb, petrified, having severed close ties or indifferent (in 3 cases); or nurturing rage, indifference, or the contrary feeling of exaggerated protectiveness with regard to judiciary cases (in 11 subjects). None of the subjects had sought or received medical assistance with relation to their emotional reactions.

Of the physicians experiencing violence or intimidation by the authorities, five (27.8%) were female and thirteen (72.2%) were male. Of these cases, ten physicians had been practicing during 1-4 years, five for 5-9 years, and four for 10 years or longer. Because of the small number of the physician sample experiencing violence or intimidation, comparison couldn't be made with gender, practice time.

DISCUSSION

Only 42 physicians could be reached among the 128 who received training according to the Istanbul Protocol, directed at non-forensic physicians who were in a position to examine detainees, arrested persons and subjects undergoing ill treatment. Even though the data obtained in this study remain insufficient due to the limited in number of participating physicians, they still manage to show both the need for training in the examination of forensic cases and the contribution of such training to the result. It was established that nearly half of the detainee examinations in our area are conducted in the emergency services of public hospitals. A large majority of the physicians who perform these examinations are general practitioners. It was determined that specialists only rarely conduct detainee examinations. Consultations are also rare among these examinations.

An evaluation of graphed and numeric data shows that training on the Istanbul Protocol is generally successful. Information relative to the examination of persons who had been detained, arrested or subjected to ill treatment and the resulting action was part of the study questionnaire. According to the results, the examination should be performed in a stress-free environment that allows easy communication between the doctor and the subject. A health care worker can also be present in the examination room together with the doctor and the patient. The subject's shackles, if any, must be taken off and no security personnel allowed into the room. The report must record the identity of the persons present in the examination room. The doctor must identify himself and the procedure to be performed, and obtain oral or written informed consent, which is to be appended to the report. Prior to the examination, a recent, official identity document bearing the subject's photograph must necessarily be available in order to compare the appearance and identifying data to the examined subject. The physician must also obtain the prosecution's written request for the examination. The use of forensic forms to record the examination is required in order to standardize examinations performed by different persons at different times and ensure the completeness of the examination. The reports are to be prepared in triplicate, which is also how standard forensic examination forms are usually printed. For examinations at the start of detention, one copy is given to the security forces for transmittal to the prosecutor and one to the examined subject or an empowered representative if available; the third copy is kept on file at the health care facility. As for examinations at the end of detention, two copies should be transmitted to the prosecution directly through the health care institution to which the examining physician belongs [4, 7, 9]. The following actions were performed clearly more frequently following the training as compared to before it: performance of the examination in an adequate environment; securing the written requisition from the prosecution and the subjects' picture ID and verification of identity; obtaining the subject's informed consent; unshackling the subject for the examination; keeping security personnel outside the room during the examination; use of forensic forms for the examinations; and transmittal of judiciary reports directly to the prosecution in a sealed envelope.

To achieve an exhaustive examination, the physician should record the following on the examination form in a wording compatible with the patient's own: the detention procedure and its follow-

up, the subject's allegations, complaints, past and recent medical history and family history. The physician must reserve enough time to the patient in order to obtain a thorough history, physical examination and psychological examination. A complete physical examination after taking off all clothing and a complete record of the examination in the report will be of primary importance in case of future allegations of additional or incomplete findings. The person examining cases in which torture is alleged must be familiar with the torture methods and the lesions caused by these; it must be kept in mind that physical lesions may be missing after the application of torture by several methods, or that some lesions may have healed if the patient has been brought late to the examination. Collecting the correct samples, ordering the correct examinations and obtaining photographs of any lesions must be achieved at the earliest moment possible. The importance of a psychiatric examination is beyond discussion in all cases in which torture is alleged [1, 4, 5, 7, 9-11]. Many cases can still be diagnosed by psychiatric signs and symptoms even years after the alleged events, when no physical signs are present [2, 12]. A mechanism to obtain the needed consultations is necessary in case the examining physician has doubts [11, 13, 14].

It was determined that the physicians' knowledge concerning the physical and psychological examination of the cases increases following the Istanbul Protocol training, as does also their self-reliance. The physicians evaluated the examination findings and acted on these with increased efficacy following their training [10, 11, 15].

It was found, however, that there was no similar increase of the following: photographic documentation of the observed lesions; examination after completely undressing the patient; and availability of the required additional examinations including radiology and other specialized consultation. Meaningful change is observed after training in the attitude and activity of the physicians as far as their personal sphere of responsibility, especially for their adherence to ethical principles. The absence, however, of any improvement in the conditions and the environment of the examinations, which are the responsibility of the administration, remains a problem. It was observed that nearly half the physicians examining detainees experienced violence or intimidation.

The proportion of male physicians who encountered violence or intimidation was higher than among the women but, due to the fact that the overwhelming majority of physicians participating in the study were men, the number of women was insufficient to test for a correlation. Different publications on medical communications and violence against physicians reported, however, that while female physicians experience sexual violence more often than their male counterparts, they also command better communication skills and more confidence in the patients, and have a smaller probability of being victims of violence [16-18].

Approximately half our cases experienced violence or intimidation while examining detainees; the abuse consisted in verbal intimidation in a majority of cases [19-21]. On the other hand, a study by Franz *et al*. [22] in Germany found that health care workers were most frequently subjected to both verbal and physical attacks. In a majority of cases in our study, the parties exerting violence and intimidation were security forces and/or the examined subjects. Ayranci *et al*. [21] report a similar finding in a study of health care workers, in which most violence against physicians was perpetrated by patients and their relatives. Several reports indicate that violence against physicians happens mostly in emergency services and psychiatry clinics [19, 20, 22, 23]. Forensic examinations in our country are performed in emergency services and other outpatient clinics. The need for the physicians to attend to forensic cases, for which the operating procedures mandate immediate attention, simultaneously with cases of emergency, put them in the middle of a conflict between security forces and patients [22, 23].

It was shown that of the physicians who were subjected to verbal intimidation those who did not become insensitive to forensic cases developed an overprotective attitude to the patients. One physician who had stated having been victim of physical and sexual violence reported having thoughts, emotions and nightmares recalling the event, its place and its actors with resulting fears and anxieties, being continually on the alert and having to make an effort in order to avoid reminding oneself of the violence [19]. Even though this participant experienced the

symptoms of post-traumatic stress disorder, no medical aid was sought or obtained by this person [20]. The decrease in violence and intimidation against physicians in an inverse relationship with the duration of their professional life has been thought to be due to a growing experience of detainee examination, increased coping skills in the face of pressure by authorities and better stress management [21].

The Istanbul Protocol is an international guideline for the ethical and comprehensive examination of detainees and arrested persons. This study determined that the examination of detainees and arrested persons following the Istanbul Protocol training did comply better with the international standards [10, 24]. As long as administrative measures are not taken to regulate the environment and the conditions, the physicians themselves seem to be held responsible of this dysfunction by the patients, patient families, and all concerned authorities; this increases the likelihood of the physicians becoming victims of violence or intimidation. For the application of the Istanbul Protocol, not only physicians but also the police, gendarmerie and prison personnel as well as prosecutors, judges and administrators must also be included in the training and acquire awareness of human rights [25].

CONCLUSION

Physicians must be protected from all administrative and official pressures in their examination of detainees and arrested persons in order to improve the conditions for examination and obtaining additional investigations and consultation. This study, realized with a limited number of physicians, has the character of a pilot study. A comprehensive study of all physicians who took part in the training and an exhaustive evaluation are indicated.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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The author disclosed that they did not receive any grant during conduction or writing of this study.

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The European Research Journal 2019;5(5):894-904 ORIGINAL ARTICLE

Social disconnectedness among widows in Nigeria: probing the effects of self-monitoring intervention

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ABSTRACT

Objectives: There could be no group more affected by social disconnectedness than widows and many who suffer from social disconnectedness live a lonely life, suffer depression, anxiety, low self-esteem and self-worth, and are hunted by the constant thought of suicide. Developing an intervention to provide reprieve may help widows take back their lives. This article therefore, presents the results of a study probing the effectiveness of self-monitoring intervention in reducing social disconnectedness among the widows in Kaduna state, Nigeria.

Methods: The study used the quasi-experimental method involving pretest and posttest. The data were collected using Social Disconnectedness Questionnaire from 47 widows in the treatment group and 45 widows in the waitlist control group. The mean age of the participants (42.33 ± 6.38 years [95%CI = 41.02-43.63], range; 28.0-56.0 years).

Results: Analysis of the data suggests that self-monitoring intervention is significantly effective in reducing social disconnectedness behaviour problem among the widows in the study area. After eight weeks of self-monitoring intrevention, social disconnectedness behaviour among the widows reduced by 39% compared to 5.63% observed in the waitlist control group.

Conclusions: The outcome adds to the literature as one of few studies investigating self-monitoring intervention among widows and calls for increased probing to establish the efficacy of self-monitoring in reducing social disconnectedness in widows in Nigeria and elsewhere in the world.

Keywords: Social disconnectedness, widows, self-monitoring intervention

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The state of having lost one's spouse to death is becoming prevalent in the present worldbecause of natural or man-made disaster and thus, rendering lots of women into Widowhood. There are an estimated 258 million widows across the world, and more than 115 million live in poverty, 86 million have suffered physical abuse and 1.5 million children whose mothers who have been widowed will die before reaching the age of five [1]. Usually, with the death of a husband, the world of a woman falls apart and she has to dwell in a cruel world, full of misery and shame and abuses for the rest of her life. There is no group more affected by the sin of omission than widows. They are painfully absent from the statistics of many developing countries, and they are rarely mentioned in the multitude of reports on women's poverty, development, health or human rights published in the last twenty-five years [2]. Their plight is one of the most important, yet under-reported issues facing the world today. For many women, however, becoming a widow

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does not just mean the heartache of losing a husband, but often losing everything else as well. In too many countries, a woman who is widowed becomes in effect a non-person. Through no fault of her own, she can suffer social discrimination, stigma and even violence, sometimes, as in parts of sub-Saharan Africa, being forced to "cleanse" herself by having sexual intercourse with a relative or a stranger. A widow may also be denied inheritance and land rights or forced to drink the water that was used to clean her dead husband's body. Although, much has been made, and rightly so, of gender inequality, but widows have truly been at the bottom of the pile - invisible and unheard - for too long. These sufferings could lead to serious mental and physical health problems. While some emotional reactions can hardly be avoided following the loss of a loved one, a key question is how can the society protect the bereaved from unduly long-lasting and/or extreme consequences?

Most bereaved people suffer from loneliness, isolation or social disconnectedness. This is a situation characterized by behavioral, social, or emotional problem. Although, some individuals appear content to spend most of their hours and days removed from others, there are individuals who have little choice in the matter of solitude because they are isolated or rejected by others in their social communities and or having feeling of worthless and therefore decide to live alone. Vasa and Pine [3] believe that social disconnectedness is linked to psychological maladaptation as it represents a behavioral expression of internalized thoughts and feelings of social anxiety or depression.In the cases of the avoidance of social company and the disconnection from social company, solitude could hardly be construed as psychologically or socially adaptive. It is not the display of solitude per se that may pose a problem; rather, the central issue is that social disconnectedness may reflect underlying difficulties of a social or emotional nature.

The term "social disconnectedness" is not a diagnosis for a specific psychiatric disorder. Disconnectedness means both the phenomenon of social isolation and the pathology of introverted behaviour. The former refers to the condition of staying in one's own house to avoid relationships with others, including family members, the latter means pathology due to some psychiatric disorders or personality of introversion. Patients in isolation are classified into a "secondary isolation group" due to psychiatric disorders, and a "primary isolation group" characterized by isolation itself [4]. It is also viewed as an individual's subjective experience of a lack of satisfying human relationships, usually accompanied with a negative feeling, causing distress to an individual. It is related to several characteristics that impair the quality of life of widows, like depressive symptoms and decreased subjective health. It may lead to cognitive decline, increased need of help and use of health services, as well as early institutionalization of the widows after the loss of the spouse [5-8].

Generally, socially disconnected people often experience a subjective sense of inner emptiness or hollowness, with feelings of separation or isolation from the world, and a woman grieving for the loss of her husband is not an exemption [6, 7]. Sure, the loss of a spouse is a challenging and life changing experience, this is even worse among elderly and young married women. Whether the spouse dies expectedly or unexpectedly, socially withdrawn behaviour among the widows whose social network has already been reduced, affects the widows' quality of life and they become more vulnerable to loneliness. Although social support may buffer the effects of loneliness such as mental problems, depression, insomnia and hallucinations of the dead, widows arguably have lower levels of social support in Nigeria than married individuals do. Social disconnectedness has been identified as a risk factor for psychosocial maladjustment [9], and associated with such negative, interpersonaland intrapersonal difficulties as low self-esteem, negative self-perceptions of social competence, and anxiety [9, 10].

Research shows that widows who suffer from social isolation are hunted by the constant thought of suicide. They are emotionally down cast and as well view the future hopelessly and helplessly. This condition is even worse among widows with children to care for. Growing evidence of their vulnerability to isolation and loneliness, socioeconomic and psychological challenges in the society present a danger waiting to happen. In many developing countries, the exact numbers of widows, their ages and other social and economic aspects of their lives are unknown. However, almost worldwide, widows comprise a significant proportion of all women, ranging from 7 per cent to 16 per cent of all adult women [11]. It is a common knowledge

that in African context, widows receive some of the worse of treatment, and endure the worst of ordeals, which makes them susceptible to lots of psychological distress.

In Nigeria as in many parts of the developing world, the exact number of widows is unknown if it is available, it will be a matter of gross estimates. Beside the ages of these women and much of their socio-economic conditions are poorly accounted for. Broadly stated, while widowhood is largely experienced by elderly women in the developed world, the reverse is the case in developing countries such as Nigeria where younger women, many of whom may still be bearing children are widows. With early marriages still largely in practice in Nigeria, many girls given out in marriage are turned widows before adulthood.

The phenomenon of widowhood is attributed to death of a husband which causes are varied. In contemporary societies like Nigeria, the first notable variety of death worth considering due to its profound and immediate impact on widowhood in terms of creating many widows at a given time is war or armed conflict. World War I and II, the Ibo pogroms of 1966, the violent political crisis in Western Nigeria in the mid-1960s, the Nigerian civil war of 1967-1970 all produced more widows than any period in modern Nigeria [12]. Ethnic and religious conflicts such as the Tiv riots of the 1960s; the Tiv-Jukun crises of the early 1990s and 2001; the Ife-Modakeke crisis of 2000, the Amuleri-Aguleri in South-Eastern Nigeria in 2001; the Maitatsine religious crisis of the 1980s that erupted in Kaduna and spread across northern Nigeria with flash points in states like Kano, Bauchi and Plateau; countless acts of suicide bombing, the recurring ethno-religious crises in Jos, Plateau State and Kaduna metropolis since 2000 have all combined to produce additional widows in huge numbers [13-16). In between these are unreported cases of violent conflicts between minority ethnic groups that result in male causalities. Since 1999, the Niger Delta crisis, electoral related violence and the Boko Haram menace in Maiduguri and Yobe and the Fulani herdsmen and Farmers crises have caused substantial deaths in Nigeria. The group has carried out heavy attacks since 2007 in Maiduguri, Kano, the Police Headquarters in Abuja, churches in Abuja and Suleija in Niger state and at the United Nations house in Abuja [17-20] and most recently, the killings of Reverend Fathers and worshippers in Benue state.

Without debate, majority of those who lost their lives in all these wars and crises and bombings are men many of whom were married. Those left behind include widows and children in a sizeable proportion. Once upon the death of a husband, irrespective of the age of the wife, she descends into widowhood and depending on the cultural background of the marriage; the widow's conduct and activities are henceforth regulated by customary practices and norms. In general, according to Eweluka [21], widowhood rites include isolation and confinement, restrictions in movement and association and hair shaving.

Nigerian widows like their counterpart elsewhere in especially Africa and Asia are a special social category that is scantly acknowledged in social policy but is potently vulnerable to psychological, socioeconomic and health risks because of the widowhood practices prevalent in Nigeria. One of the major effects of widowhood is poverty and emotional trauma. Many Nigerian widows are pauperized by those. These practices drastically reduce the economic status of widows upon the death of a husband. It is difficult to achieve a good life by a widow when she has no right to inheritance. Upon the death of a husband, widows may be completely dispossessed and chased off [22]. Widowhood is simply a life of deprivation.

In Nigeria, women outlive their husbands, because they marry men older than themselves, that is why widows outnumber widowers and the average woman can expect to survive her husband. In fact, widows make up a substantial proportion of the elderly population. The pattern of grieving will repeat itself over and over again, month after month, and that all the unbearable feelings and fears, of being unable to function as a human being any more, are normal. During this period, fatigue, anxiety, lack of interest and reduced functioning are common. Social disconnectedness is the most radical life events one can experience and it can have far-reaching consequences for the mental wellbeing. In order to promote mental and general wellbeing and to alleviate loneliness and social disconnectedness among widows, intervention programs must be developed to improve existing or develop new relationships such as friendships [23-25].

Decades of research, using self-monitoring technique, a personality trait that refers to an ability to regulate behavior to accommodate social situations has

proven to be an effective behavioral intervention used in modifying various behavior problems. Based on the effects of this behavior, this study was carried out to assess the extent to which self-monitoring technique can alleviate the effect of social disconnectedbehavior among the widows in Kaduna metropolis. Hawton *et al*. [26] suggested that practices should target people at risk of social disconnectedness, as individuals need to be identified early with interventions before deterioration of their health or quality of life occurs.

METHODS

Research Design

The research is a quasi-experimental study involving two-group pre-test/posttest design [27, 28]. The design is helpful as it enable the researcher to select sample on purpose for the study, and help to assess the effectiveness of a given intervention by comparing before and after outcome of participants [29]. Usually, if the intervention is effective, participants' outcome scores will improve compared to baseline,but scores will remain constant if the intervention has no effect [30].

Participants

The population of the study includes all widows in Kaduna metropolis who show symptoms of Social disconnectedness. Although, there are many widows in Kaduna state, there is however, no documented or published report about their exact number by local authorities. They however, comprised a good proportion of all women. A 2015 world report estimate puts the population in Nigeria at over two million, 2,145,605 [1]. VanVoohis and Morgan [31], and De Winter [32] suggested that using small sample size can help the researcher to give adequate attention to the subjects and it can eliminate rowdiness and possibility of attrition. The following shows the sample size of the study and the sample recruitment procedure: Out of the two hundred and three widows accessed, one hundred and twenty-eight widows agreed to participate in the study (Figure 1). They agreed to participate in the study in order to resolve their social disconnectedness behaviour. All the volunteers were gotten via notices placed at the gate to the church building, sharing of handbills, and through one-on-one

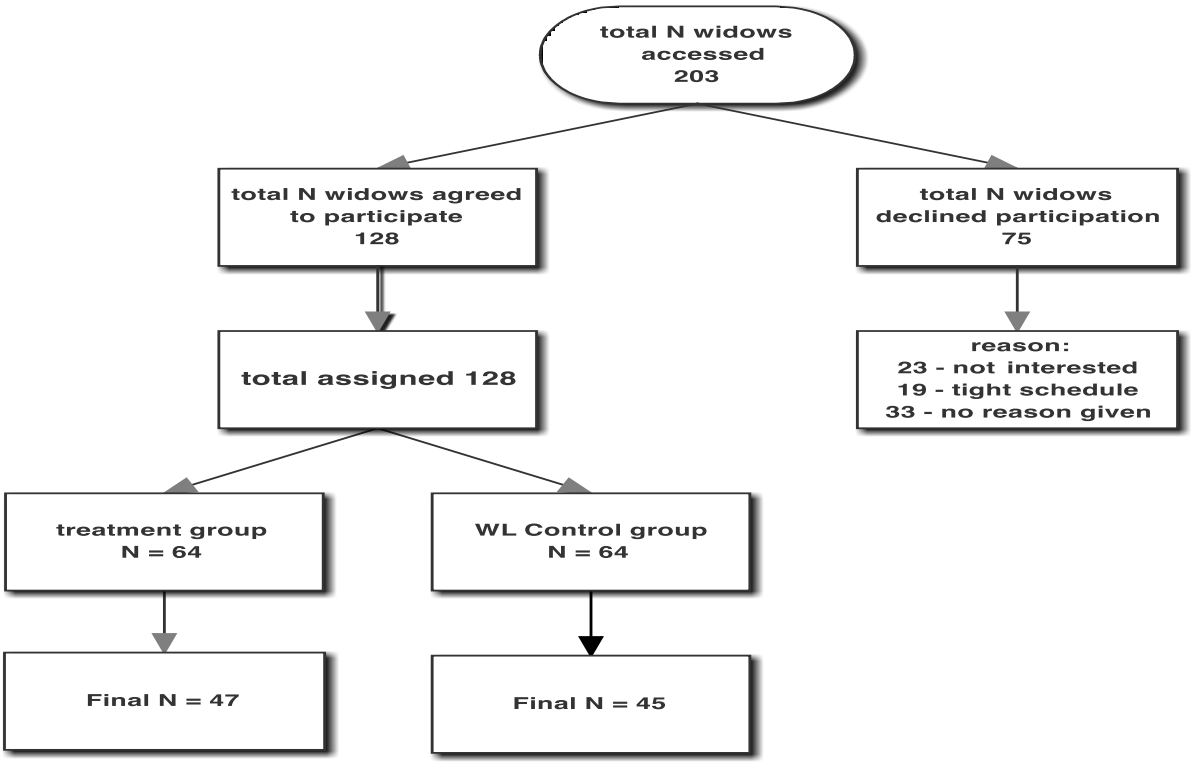

Figure 1. Sample size of the study. N = the number of the the widows

contact at the widows meeting. Several researchers [27, 28, 33, 34] used similar strategy for recruiting volunteers for insomnia research. It is a recommended recruitment technique [35]. The 128 volunteers were randomly assigned into two groups of 64 each. After eight weeks, 17 [26.56%] and 19 [29.69%] participants from the treatment group and the control group respectively withdrew from the study.

Ethical Consideration

Participation in this research was voluntary. Only widows identified with the social disconnectedness and have agreed to participate after signing a consent form, took part in the study. The consent form as attached to the scale reads;

The essence of the study has been explained to me, and I have been given the opportunity to ask questions about this research. I understand the aims, duration of the intervention and have agreed to participate. I was also assured of confidentiality of any information I gave. I understand that my participation is voluntary, so I can withdraw from the study at any time.At the end of the study, the waitlist control group was introduced to the treatment and was given handout on how to use it at home.

Treatment Credibility

Two items from the Treatment Evaluation Questionnaire [36] were used to assess treatment credibility, and these items were completed at post treatment. These items were chosen because they appeared less likely to beaffected by treatment success or failure, though it remained possible that treatment response biased these findings. Participants reported whether they felt the treatment was logical and reasonable and whether they would recommend the intervention to a friend with a similar problem. The items were measured on a Likert scale ranging from 0 (strongly disagree) to 5 (not sure) to 10 (strongly agree).

Measure

The social disconnectedness questionnaire (SDQ) developed by Russell [37] was used to assess social disconnectedness behaviour among participants during pretreatment and post treatment phases. The Social isolation questionnaire includes 20 questions used to assess how lonely the respondent feels. Each question begins with the statement "How often do you feel" followed by a positive or negative description of social interactions with others. The respondent is asked to indicate the frequency he/she feels that way (never = 1, rarely = 2, sometimes = 3, always = 4) for each question. The instrument is suitable for respondents between the ages of 18 and above. Items 1, 5, 6, 9, 10, 15, 16, 19, and 20 were scored in reversed. All scores were summed together with higher scores indicating greater degrees of isolation or disconnectedness [37].

Generally, the instrument was divided into sections. The first section was made up of demographic characteristics of the respondents (age, personal income, years of widowhood, number of children, and source of financial assistance), while the second section consists of statements used to assess the dependent variable (social disconnectedness). The social disconnectedness questionnaire produced a satisfactory reliability index and consistency and it is the most commonly used instrument to assess social isolation behaviour. The scale has internal consistency of 0.89 to 0.94 and test retest of 0.73 [37]. It has been used successfully in several countries with different cultures [38-40].

Intervention

The data collection procedure was discussed in three phases; the first is pretreatment phase, then second; treatment phase, and third; post-treatment phase (Table 1).

Pretreatment Phase (week 1)

During week 1, the researcher introduced himself to the volunteered research participants. The participants received briefing on the essence of the study and filled consent form approving their voluntary participation in the study. We (researcher and 2 assistants) administered self-monitoring questionnaire, whichwe used to measure widows level of social disconnectedness. We used the datacollected at this stage to serve as the pretest data and bases for inclusion to the study. Participants were directed on how to fill the instruments and after that, advance arrangements were made concerning further meetings.

Treatment Phase (week 2-7)

The treatment was done in-group, so all the

Table 1. Brief explanation of self-monitoring intervention

Session	Self-Monitoring Technique (Group B)	Description
Session one	Introduction and Pretest/intake	This stage involves familiarization, intake and pretest administration of outcome instrument and SDQ.
Session two	Identifying target behavior	Participants worked with the investigator to identify target behaviour that needs to be addressed
Session three	Defining the target behavior	The behaviour identified were defined, and analysed so as to come up with a better behaviour replacement
Session four	Developing replacement behavior	The investigator helped the participants to develop alternative behaviour that could counter withdrawal symptomatology
Session five	Teaching subjects to self-monitor behaviour	After helping participants develop alternative behaviour, they learned how to implement such behaviour to regain lost behaviour standard
Session six	Monitoring progress and reviewing strategies	Strategies were reviewed while monitoring progress of the intervention. SDQ was administered to monitor progress
Session seven	Monitoring progress and reviewing strategies	Continue monitoring progress
Session eight	posttest/termination	Participants filled the SDQ for the last time to access the effects of intervention. Contact terminates and participants were told to keep up good behaviour to avoid relapse

SDQ = social disconnectedness questionnaire

participants in the experimental group received self-monitoring intervention from week 2-7. Ten o'clock every Saturday morning was scheduled as the meeting time and the intervention took 58 minutes per session. The self-monitoring techniques used by Harrri *et al*. [41]; Jolivette and Ramsey [42]; and Carr and Punzo [43] was used for the study with some modification to suit the need of the problem under investigation. Other researchers have used the techniques and procedures and they have shown to be effective in reducing behaviour problems, but there appears to be a dearth of researches using the techniques in treating social disconnectedness among widows.

Post-treatment Phase (week 8)

At this phase, posttest using SDQ was administered. The essence was to compare with pretest outcome of both group and to examine group differences that have occurred over the course of the treatment. The rate of attrition among the study participants was 26.5% and 29.7% for experimental and waitlist control group respectively. One reason for this rate of attrition was the fact that some of the participants actually do come from far distances to the treatment venue. Before termination, the participants were informed on what to do when there is a relapse. Lastly, the participants were made to understand that longitudinal datahad shown that treatment gains achieved are extremely durable with time,they aremost often maintained or improvedover time, so relapse rates will be small so far they continue a good habit (that is, abstaining from behaviour that leads to and perpetuate the condition). Usually in experiment like this, the untreated waitlist control group needs help alsoafter the study. Thus, for ethical reason, widows in the waitlist control group were given the treatment handout explaining the systematic implementation of the treatment. The self-help method in experimental research has been shown toproduce some durable benefits.

Statistical Analysis

The data collected were statistically analysed with the aid of a computer software: JMP ver. 13.2. The study used ANCOVA to test for treatment effects. ANCOVA is suitable when two or more groups are subjected to pre-test and post-test while the pre-test is treated as a covariate to 'control' for pre-existing differences between the groups. However, prior to testing the treatment effects, a test of assumption of homogeneity of regression slope was carried out (see Figure 1). A

0.05 criterion of statistical significance was used in testing the treatment effect.

RESULTS

There is a significant difference between treatment and control group in term of educational attainment ($\chi^2 = 12.805$, $p < 0.01$) (Table 2). The outcome showed that 19% of the participants in the treatment group had no formal education, unlike control group with only 4.4%. Almost 49% of the participants in the control group had only primary education compared to 38% in the treatment group. In addition, almost 32% in the treatment had secondary education when compared to a higher 42% in the control group. Only 5 participants representing 10.6% of the total sample in the treatment group attained tertiary level of education compared to 2 participants representing 4.4% in the control group.

Regarding family size, as per number of children, analysis showed that 25.5% of the participants in treatment groupreported having 1-3 children compared to 11% in the control group. Over 36% in the treatment group have 4-6 kids compared to 73% in the control group. There were also 38% having 7 and above number of children in the treatment group compared to 15.6% in the control group. Generally, there is no significant difference in number of children between treatment and control group, $\chi^2 = 6.570$, $p = 0.087$. No significant difference rate of employment between participants in the treated and control group, $\chi^2 = 0.005$, $p = 0.943$.

The mean response and standard errors of participants' social disconnectedness before and after the self-monitoring intervention are given in Table 3. Mean pre self-monitoring intervention of social disconnectedness among treatment group was 52.914 ± 1.064; 95CI = 50.799-55.030, but after intervention, mean social disconnectedness reduced to 32.256 ± 0.905; 95CI = 30.457-34.055. The outcome showed a 39% remission in social disconnectedness behaviour among the treated patient. Waitlist (WL) control group on the other hand had a mean social disconnectedness

Table 2. A comparative descriptive statistics of the respondents by group

Group	Description	Levels				Statistic	
	Education	No formal Education	Primary Education	Secondary Education	Tertiary Education	Chi^2	*p* value
1		9 (19.1%)	18 (38.3%)	15 (31.9%)	5 (10.6%)	12.805	**0.002**
2		2 (4.4%)	22 (48.9%)	19 (42.2%)	2[4.4%]		
	Number of Children	1-3	4-6	7+			
1		12 (25.5%)	17 (36.2%)	18 (38.3%)		6.570	0.087
2		5 (11.1%)	33 (73.3%)	7 (15.6%)			
	Employment status	Employed	Unemployed				
1		16 (34.0%)	31 (66.0%)			0.005	0.943
2		15 (33.3%)	30 (66.7%)				

1 = Treatment Group (n = 47), 2 = Waitlist (WL) control group (n = 45)

Table 3. Pre and post mean response of treatment group and WL control group

Level	Group	Least Sq Mean	Std Error	Lower 95%	Upper 95%
Pre-SD	Treatment Group	52.914	1.064	50.799	55.030
	WL Control Group	54.266	1.088	52.104	56.428
Post-SD	Treatment Group	32.256	0.905	30.457	34.055
	WL Control Group	51.210	0.930	49.362	53.059

Treatment Group (n = 47), Waitlist (WL) control group (n = 45)

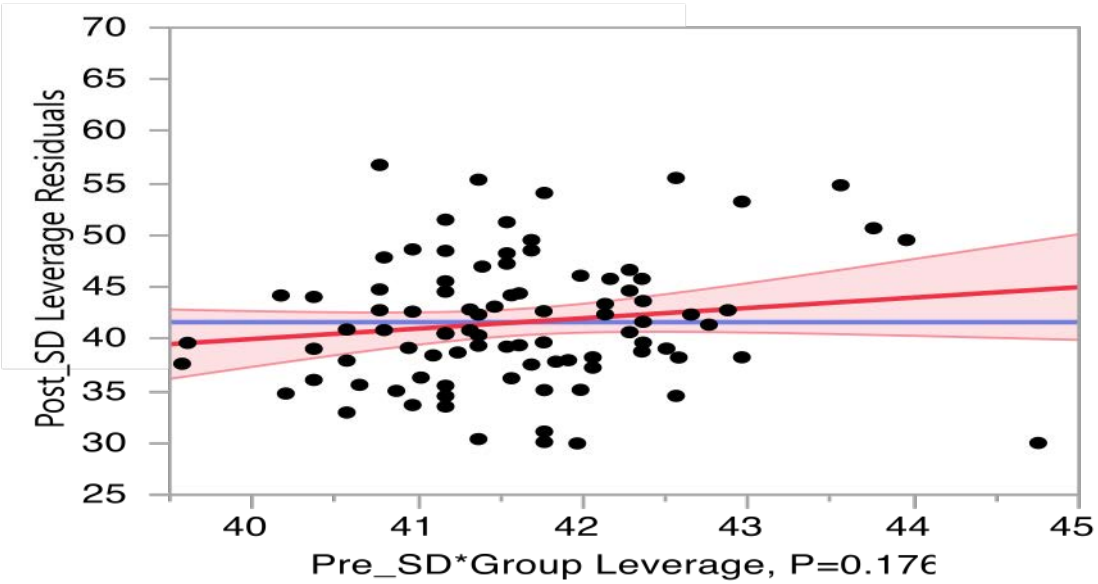

Figure 2. Leverage plot for pre_SD* group testing the homogeneity of regression slope assumption. SD = social disconnectedness.

of 54.266 ± 1.088; 95CI = 52.104-56.428 at pre intervention stage, but at the end of the study, WL control group mean response reduced to 51.210 ± 0.930; 95CI = 49.362-53.059, implying a remission of only 5.63% after eight weeks.

Figure 2 showes the analysis of covariance (ANCOVA) assumption test that requires that the relationship between the covariate and dependent variable for each of the groups is the same. Usually, similar slopes on the regression line for each group indicate this. Unequal slopes would indicate that there is an interaction between the covariate and the treatment. If there is an interaction then the results of ANCOVA could be misleading [44, 45]. In this study, the interaction is not significant, F (1, 88) = 1.854, p = 0.1768, thus supporting the appropriateness of ANCOVA.

Analysis of covariance, which was employed to determine the effects of group on social disconnectedness is shown in Table 4. Outcome showed that generally, there is a significant effect of group F (2, 89) = 111.1635, $p < 0.0001$; RMSE = 6.189, implying that the two groups (treatment and WL control group) responded significantly different due to self-monitoring intervention. The overall model was found to explain 71.4% variance.

The expanded estimates nominal factors expanded to all levels are shown in Table 5. It showed that pretreatment outcome did not significantly influence the later outcome of the study, β = 0.1399 [95%CI = -0.039 - 0.318], t = 1.56, p = 0.123. The intervention was significantly effective for the participants in the treatment group, β = -9.521 [95%CI = -10.815 - -8.227], t = -14.62, p < 0.0001 compared to those in the WL control group, β = 9.521 [95%CI = 8.227 - 10.815], t = 14.62, $p < 0.0001$. Participants in the treatment group had higher reduction in their social disconnectedness behaviour than did those in the WL control group.

Table 4. Analysis of variance showing model effects for groups

Source	DF	Sum of Squares	Mean Square	F Ratio	Prob > F
Model	2	8596.436	4298.22	111.1635	**< 0.0001**
Error	89	3441.249	38.67		
C. Total	91	12037.685			

Summary of Fit: RSquare = 0.714; RSquare Adj = 0.707; Root Mean Square Error = 6.218; Mean of Response = 41.619; N = 92

Table 5. Expanded estimates nominal factors expanded to all levels [treatment vs WL control]

Term	Estimate	Std Error	t Ratio	Prob>|t|	Lower 95%	Upper 95%
Intercept	34.337	4.855	7.07	**< 0.0001**	24.689	43.984
Pre_SD	0.1399	0.090	1.56	0.1230	-0.039	0.318
Treatment Group	-9.521	0.651	-14.62	**< 0.0001**	-10.815	-8.227
WL Control Group	9.521	0.651	14.62	**< 0.0001**	8.227	10.815

WL = Waitlist

DISCUSSION

The basic essence of the study was to examine the effectiveness of self-monitoring intervention in reducing problem behaviour of social disconnectedness among widows. The result suggests that self-monitoring intervention is an effective strategy to help reduce social disconnectedness behaviour among widows in Nigeria. In this study, SM reduced SD by 39% in eight weeks. This corroborate findings on multiple baseline study across participants by Craanen [46], which investigates the effect of a self-monitoring treatment intervention on academic productivity component behaviors among students with Autism Spectrum Disorder. Results show all participants achieved marked improvements in their academic productivity composite scores from baseline to intervention to the maintenance phase. Furthermore, previous finding by Cassidy [47] using self-monitoring to improve the academic performance of a male student with attention deficit hyperactivity disorder (ADHD) shows that the student improved grade average in all five classes. The improvement was classified as from 0% of the time to 50% of the time, showing the helpfulness of self-monitoring intervention. In another multiple-baseline-across-subjects design study, Hughes *et al*. [48] used a multiple-baseline-across-participants design to examine the effects of self-monitoring on selected social behaviors of students with mental retardation. Result shows occurrences of self-monitoring were associated with improvement in target behaviors across participants. In another similar finding, Car *et al*. [49] reported that volunteerism successfully attenuate loneliness among widows to the extent that loneliness among widows was found to be similar to those of continuously married individuals. A previous study by Constantino *et al*. [50] on bereavement using group intervention showed that resulted to statistically significant changes in psychological wellbeing. There was a significant increase in social adjustment among widows survivors' of suicide. In line with outcome of this intervention, Onrust *et al*. [51] in their study on effects of visiting service for older widowed individuals found that visiting service improved the socially lonely, physically ill, and low educated widows than in experimental group than in the control group.

Limitations

This present study has several limitations, though. Firstly, the study relied on self-reported measures of social disconnectedness instead of objective measure. Secondly, other physical and mental health problems not included or taken care of in this study may create asymmetries in widows' social relationship and limit their abilities and desires to develop and maintain healthy social relationships. Secondly, the study only questioned the participant's level of education, number of children and employment status. Other sociodemographic features like the number of siblings, the degree of closeness with siblings, the existence of close friends, the time of loss of spouse, the number of years of widowhood, may all related to losing reaction. The fact that these variables were not looked at is a limitation of this study. Thirdly, using individual rather than group intervention may produce better outcome as each participants would be given adequate attention. Based on these limitations, we therefore state categorically that causal connections implied by the findings of this study should be interpreted and taken with caution. It is hope that further research will refine these concepts, address the study limitations to reveal causal mechanisms, and help researchers and

policymakers to better understand the health risks of social disconnectedness among widows and developing behavioural methods to help widows to take back their lives.

CONCLUSION

The present research is an early step forward towardsprobing the relative effects of self-monitoring intervention on social disconnectedness among widows. In this study, we found out that the treatment successfully reduced social disconnectedness among widows in Kaduna state, Nigeria by 39% after eight weeks of contact compared to the 5.6% for the control. The study outcome may advance the area of grieve support and aid a healthy adaptation to widowhood.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

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The European Research Journal 2019;5(5):905-908 CASE REPORT

Arachnoid cyst of the cavum velum interpositum associated with cavum septum pellucidum and cavum vergae

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ABSTRACT

A cavum velum interpositum is a normal variaton which is often detected incidentally in asymptomatic individuals. However, arachnoid cyst of the cavum velum interpositum is extremely rare and may cause symptoms similar to those of a third ventricular mass. On imaging, the main differentials of this cyst are; cystic dilatation of the cavum velum interpositum, cavum vergae cyst, arachnoid cyst of the quadrigeminal cistern, and epidermoid cyst. We present a case of an arachnoid cyst of the cavum velum interpositum coincidentally associated with the cavum septum pellusidum and cavum vergae. The cavum velum interpositum is a rare location for the arachnoid cysts. Accurate diagnosis of the arachnoid cysts of the cavum velum interpositum is important as they cause serious symptoms which can be reversed by surgical treatment.

Keywords: Arachnoid cyst, cavum velum interpositum, cavum septum pellucidum, cavum vergae

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The cavum septum pellucidum (CSP), along with the cavum vergae (CV) is a persistence of the embryological fluid-filled space between the leaflets of the septum pellucidum and is a common anatomical variant. The CSP and CV normally close in sixth intrauterine week, but may persist in 30% of term infants and 15% of adults [1]. The cavum velum interpositum [CVI], a normal variation, is a dilated cerebrospinal fluid-filled space involving the velum interpositum. It extends below the splenium of the corpus callosum and the column of fornix and above the internal cerebral veins. This variation is often detected incidentally in asymptomatic individuals [2]. However, arachnoid cyst of the CVI is extremely rare and may cause symptoms similar to those seen with a third ventricular mass [3]. We report a case of an arachnoid cyst of the CVI coincidentally associated with CSP and CV, who presented with headache and memory disturbance.

CASE PRESENTATION

A 64-year-old man with complaints of headache and memory disturbance for three months, was referred to the Department of Radiology for a brain magnetic resonance imaging (MRI). His neurological examination findings were unremarkable. MRI study revealed CSP and CV. There was a 48×42×24 mm sized, thin-walled cystic lesion lying just posterior to the CV (Figure 1). The cyst was located between the posterior halves of the lateral ventricles and the roof of the third ventricle (Figure 2). It was isointense with the cerebrospinal fluid in all pulse sequences (Figure 3). By the compressive effect of the cyst; posterior half of the corpus callosum was elevated, the fornices were splayed and the internal cerebral veins were inferiorly displaced. The lateral ventricles were mildly dilated but the quadrigeminal cistern was normal (Figures 2

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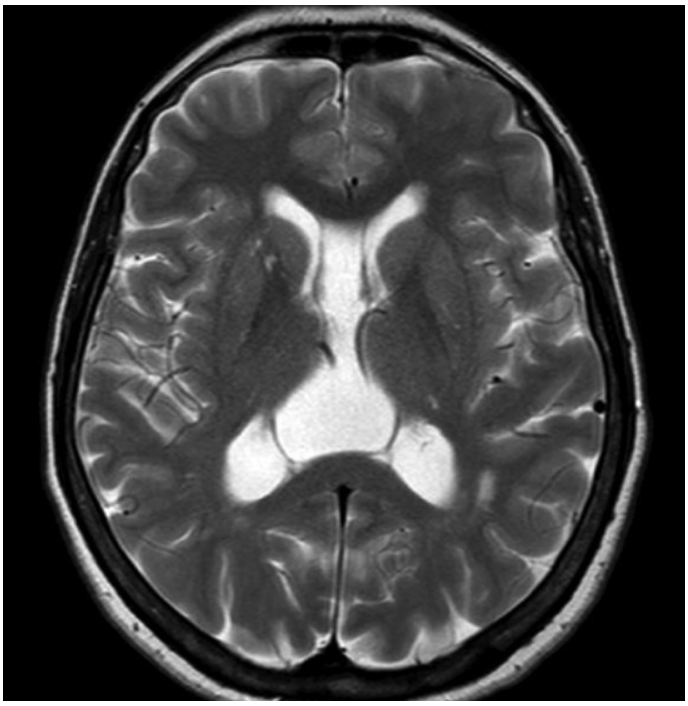

Figure 1. Axial T2-weighted section through lateral ventricles shows cavum septum pellucidum and cavum vergae. An arachnoid cyst of the cavum velum interpositum, of which the anterior border is invisible in this section, is also present.

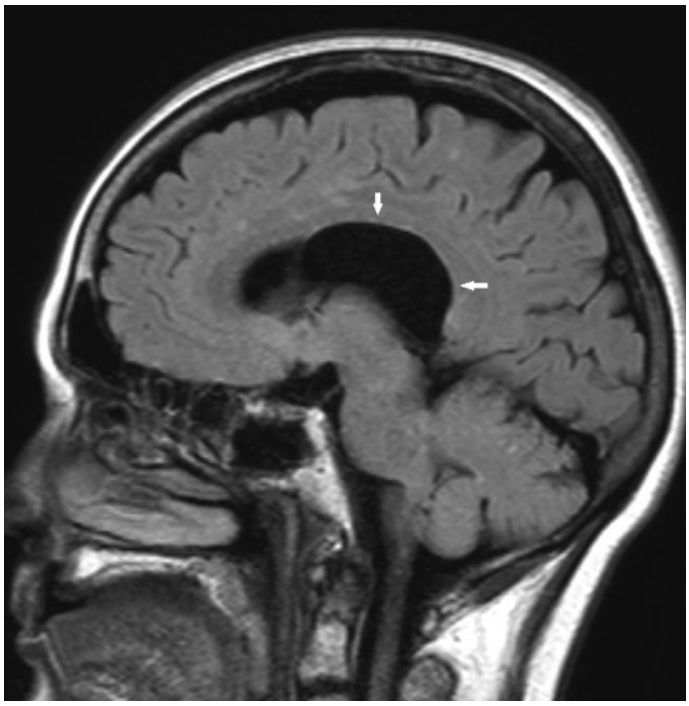

Figure 2. Sagittal FLAIR image reveals a large cystic lesion located in the cavum velum interpositum. The posterior half of the corpus callosum is elevated, the splenium is slightly depressed (arrows). Note the quadrigeminal cistern is normal.

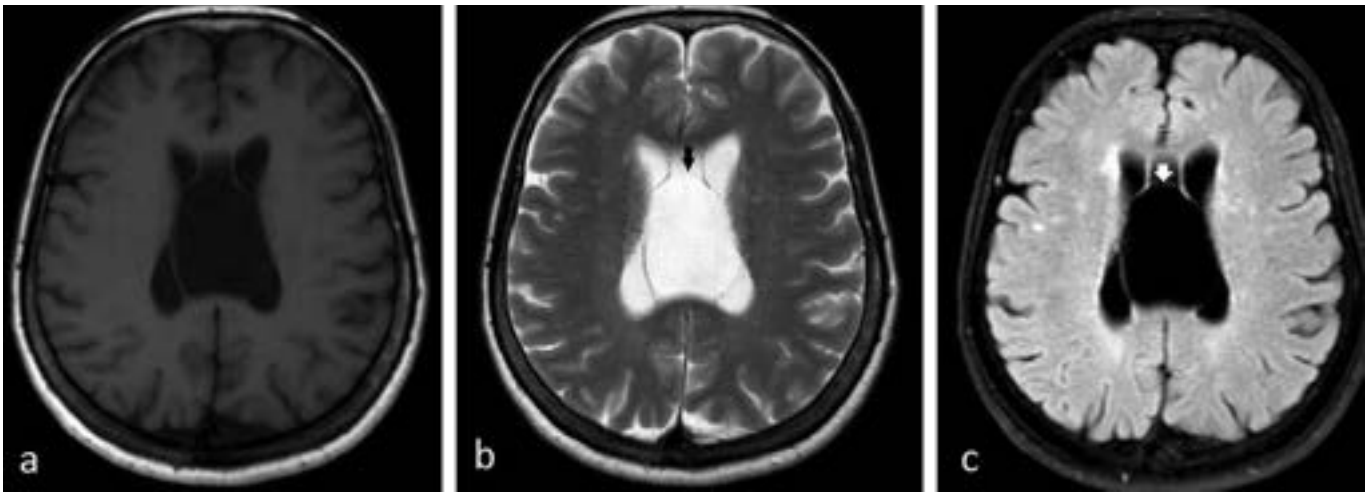

Figure 3. The cyst is isointense with the cerebrospinal fluid in T1-weighted [a], T2-weighted [b], and FLAIR [c] sequences. The anterior wall of the cyst is seen in b and c [arrows]. Note the slight dilatation of the lateral ventricles.

and 4). On diffusion weighted images, no restriction of diffusion was revealed (Figure 5). By these imaging findings, the patient was diagnosed as having an arachnoid cyst of the CVI.

DISCUSSION

The CSP is regarded as a part of the longitudinal cerebral fissure, which becomes walled off by the union of the hemispheres forming the corpus callosum above and the fornix below. The cerebrospinal fluid-filled space between the septa pellucida, two paired clear membranes, is a cavity of which the anterior part is called CSP, whereas the posterior part is called CV [4]. During development, these spaces obliterate antero-posteriorly: the CV followed by the CSP, and it is common that both occur together. This variation is often detected incidentally and individuals are usually asymptomatic, however, there are some

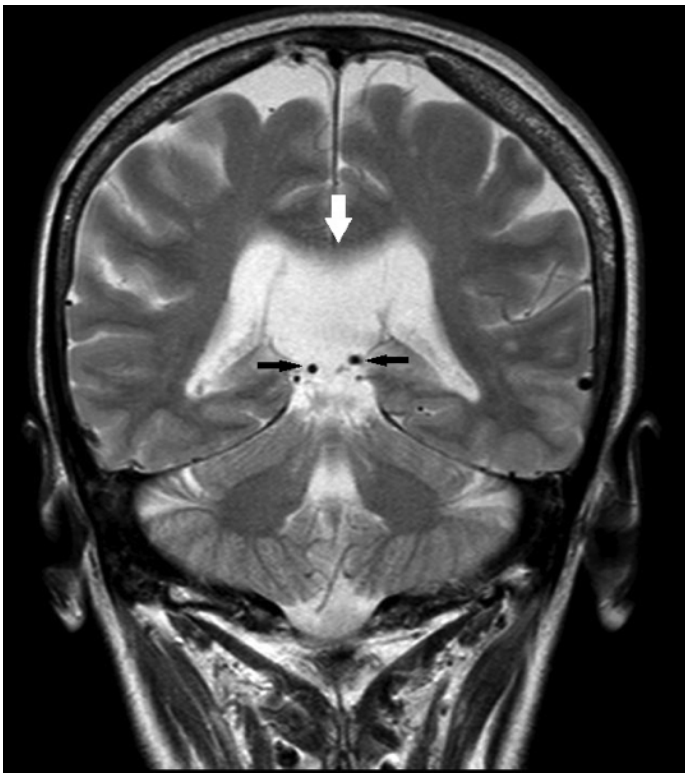

Figure 4. Coronal T2-weighted image demonstrates a large cyst between the lateral ventricles and above the third ventricle (white arrow). Internal cerebral veins are displaced inferiorly (black arrows). The lateral ventricles are slightly dilated.

studies reporting an association between the CSP and neuropsychiatric disorders [5].

CVI is a potential space which is actually a forward extension of the quadrigeminal cistern. It is located below the splenium of the corpus callosum and the column of fornix, and above the internal cerebral veins. It has a triangular shape of which the apex anterorly reaches the foramina of Monro [2]. A CVI is a frequent finding among infants and young children, and it is supposed to close by aging. If not closed, it may be detected in adulthood, mostly as an incidental asymptomatic finding [6].

Arachnoid cyst of CVI is extremely rare. To the best of our knowledge, to date, there have only seven cases of arachnoid cyst of this location been reported [3, 7-12]. The probable origin of the arachnoid cyst of CVI is thought to be tela choroidea, a vascular connective tissue which lies in the space between the lateral and third ventricles [12]. It can cause similar symptoms of a third ventricular mass [3, 8]. Furthermore, an intracranial arachnoid cyst can cause reduced perfusion and metabolism in the surrounding cortical regions [9]. These changes can result in mental impairments including memory disturbances as they do in the present case. In the previous cases, the presenting symptoms of the arachnoid cyst of the CVI were reported to be; headache, loss of consciousness, dizziness, disorientation, confusion, and memory disturbances. Our patient presented with headache and memory impairment.

The imaging characteristic of an arachnoid cyst of the CVI is a midline cyst located between the third ventricle and the posterior halves of the lateral ventricles which causes elevation and splaying of the fornices and inferiorly displacing the internal cerebral veins [3]. On imaging, the main differentials of this cyst are; cystic dilatation of the CVI, CV cyst, arachnoid cyst of the quadrigeminal cistern, and epidermoid cyst. The major characteristic of the cystic dilatation of the CVI is that it has free communication with the quadrigeminal cistern, thus it typically does

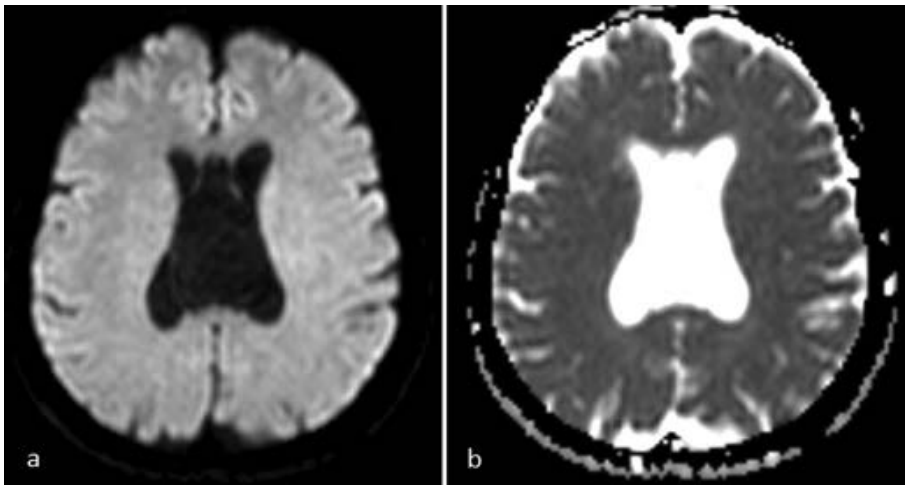

Figure 5. No restriction of diffusion is noted in diffusion weighted images (a) and ADC mapping (b).

not cause mass effect or hydrocephalus [9]. However, as in the present case, an arachnoid cyst is prone to obstruct the ventricles causing symptoms closely similar to those of a third ventricular mass. To differentiate a CV cyst from an arachnoid cyst of CVI, the internal cerebral veins are used as a landmark. As CV lies above the veins, the cyst of the CV is seen separately from the veins. However, as CVI encloses the veins, an arachnoid cyst of the CVI encloses the veins at its lower and lateral borders [3]. The close relation of the veins and the cyst was clearly seen in our case (Figure 4). An arachnoid cyst originating from the quadrigeminal cistern can mimic the arachnoid cyst of the CVI if it extends in the superoanterior direction. However, different from the arachnoid cyst of the CVI, it displaces the internal cerebral veins upward as arachnoid membrane in the quadrigeminal cistern is topologically below the veins. An epidermoid cyst of any location can easily be differentiated from an arachnoid cyst by diffusion weighted imaging. Epidermoid cysts show diffusion restriction, whereas arachnoid cysts do not [3, 9].

Arachnoid cysts of the CVI should be treated if they become symptomatic. A communication between the cyst and the ventricular system is provided by endoscopic ventricular fenestration in order to reduce the mass effect of the large cyst. In the previous cases, most of the symptoms were reported to be reversed by surgical treatment [7, 9, 10].

CONCLUSION

The CVI is a rare location for the arachnoid cysts. Accurate diagnosis of the arachnoid cysts of the CVI is important as they cause symptoms similar to those of a third ventricular mass, and these symptoms can be reversed by surgical treatment.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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The European Research Journal 2019;5(5):909-912 CASE REPORT

Vestibular neuritis presenting in pregnancy: case report of rare entity and treatment options

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ABSTRACT

Vestibular neuritis in pregnancy is not often and it may be difficult for obstetricians and ENT doctors to evaluate a pregnant woman and to choose best treatment because of drug contrandications. A 33-year-old woman presented with vertigo at 28 weeks of the gestation. After physical examination and audiological and vestibular tests, vestibular neuritis was diagnosed, and the treatment was initiated. The patient completely recovered without any complaints; neither vestibular nor gynecological. There are few studies in the literature pointing out the evaluation of pregnant women with vestibular neuritis. However, there are safe ways to manage such patients.

Keywords: pregnancy, vertigo, vestibular neuritis, treatment

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Vertigo in pregnancy directly affects the quality of life both physically and emotionally [1]. Vestibular neuritis in pregnancy is not often and it may be difficult for obstetricians and ear, nose and throat (ENT) doctors to evaluate a pregnant woman and to choose best treatment because of drug contrandications. Since no guidelines exist for the management of vestibular neuritis in pregnancy, literature review is conducted to following case report to suggest the most effective method.

CASE PRESENTATION

A 33-year-old female patient, in 28th week of her pregnancy, consulted from obstetrics clinic to our ENT department with complaints of sudden onset of vertigo, nausea, vomiting, having difficulty in standing up. There were no auditory complaints and no history of significant passed disease, except common cold history two weeks ago. In the general ENT examination of the patient; oropharyngeal, anterior rhinoscopic and otoscopic examination were observed healthy. In otoneurological examination, spontaneous horizontal nystagmus to the left and positive head impulse test on the right side were observed. She tended to fall right side while her eyes were closed.

The pure tone audiogram showed normal hearing of all frequencies tested (Figure 1). Biochemical parameters were also normal. We performed vestibular evoked myogenic potential (VEMP) test which revealed a prolonged P1-N1 latency (means reduced vestibular function) on the right side (Figure 2). Considering 28 week-gestation, we did not perform

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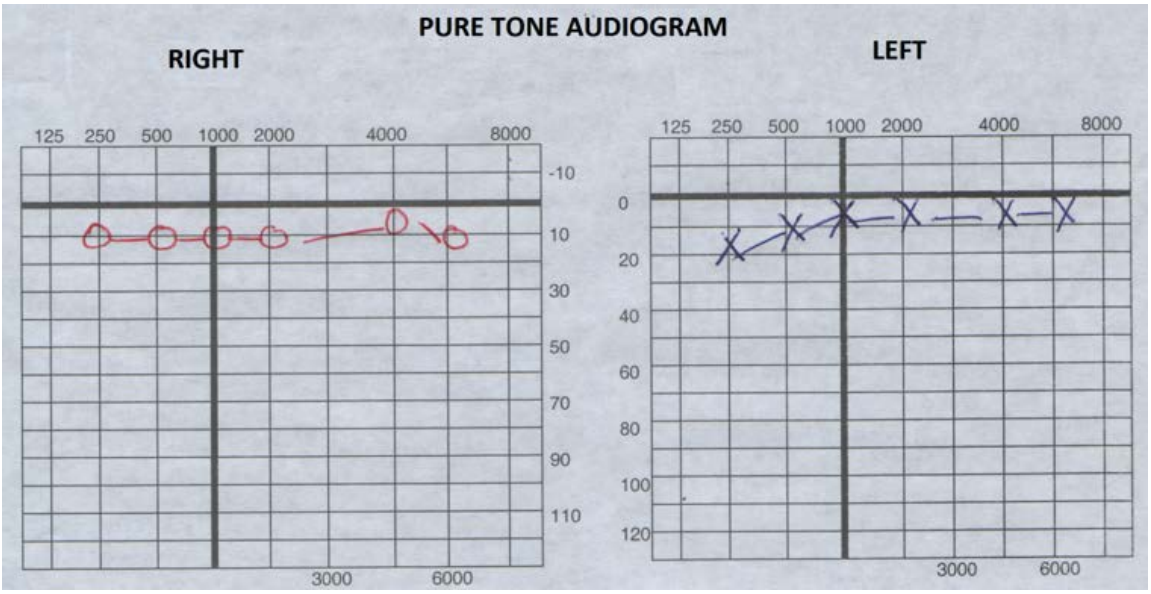


Figure 1. The pure tone audiogram of the patient.

caloric test, since it would exacerbate the vertigo, moreover, could have worsen the pregnancy.

We began medical treatment for acute vestibular neuritis. For 3 days, 2 times a day, we administrated intravenous treatment of dexamethasone, vitamin B6-B12 complex and metoclopramide. Because of pregnancy, we did not give vestibular suppressants like diazepam.

After medical treatment, vestibular rehabilitation exercises were explained to the patient to ensure complete recovery. One month later, vestibular system examination was repeated and all evaluation was normal. The term delivery of a healthy baby without any complication was pleased the mother. Written informed consent was obtained from the patient since no ethics committee approval is needed for case reports in our institution.

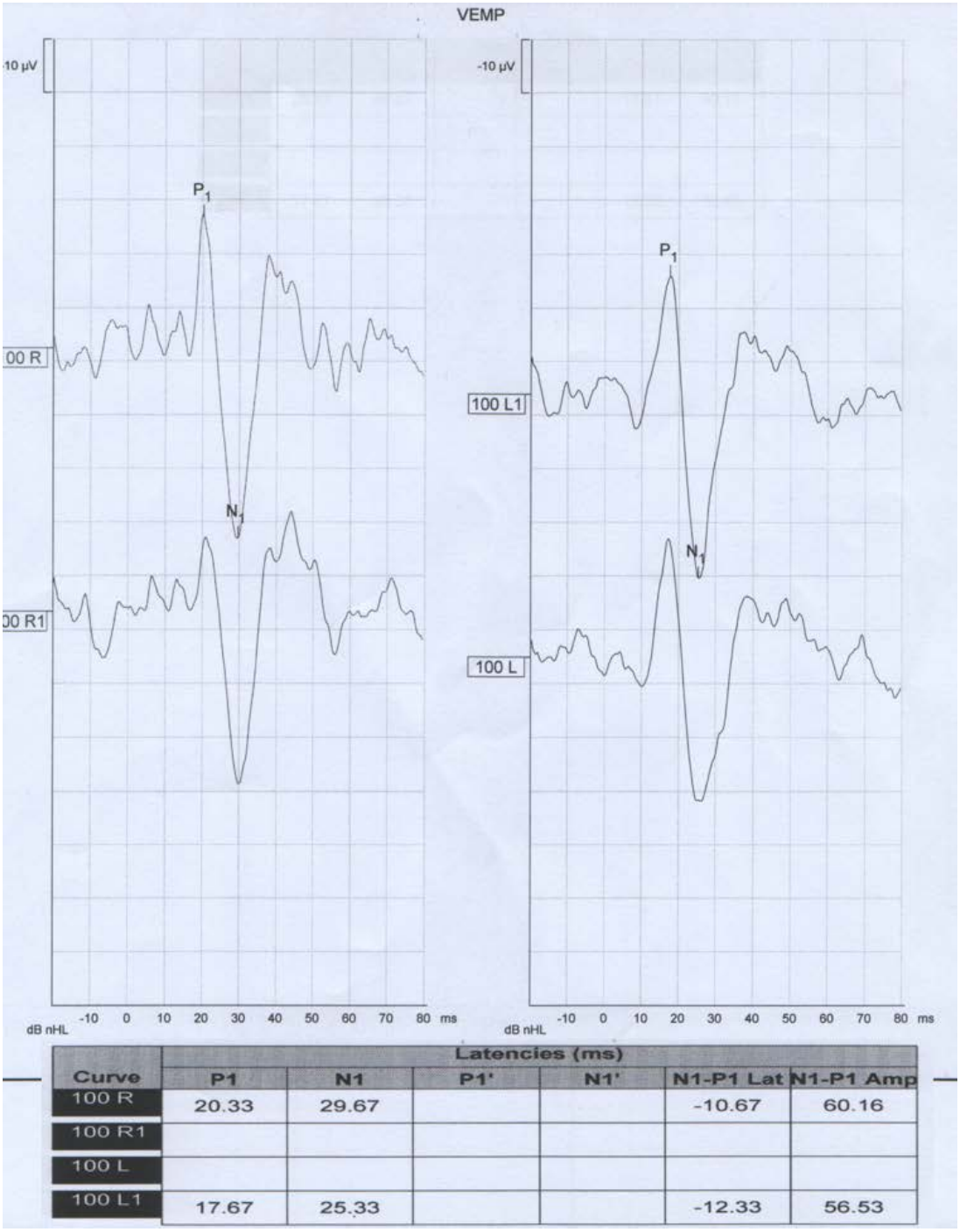
DISCUSSION

More than 80% of pregnant women receive medication for any reason and ENT causes are leading [2]. The study evaluating hearing and vestibular complaints in pregnant women demonstrated that the most frequent auditory complaint in pregnants is tinnitus [1]. Dizziness is another frequent complaint in pregnants. As mostly seen and treated in many ENT clinics, vestibular neuritis is a peripheral vestibular disease which is thought tobe caused by neurotropic viruses. It is characterized by sudden onset of severe dizziness, nausea and vomiting. Generally there are no symptoms related to hearing and pure tone audiogram is normal. Vestibular neuritis treatment in pregnant women has not been reported sufficiently in the English literature.

VEMP is used to determine whether the saccular, inferior vestibular nevre and central connections are working normally. Peripheral vestibular pathologies such as vestibular neurinitis may show increased amplitudes of P1-N1, prolongation of latency, or absence of response. In our patient, latency was prolonged and pathological appearance could persist after the acute process [2].

Vlastarakos *et al*. [3] found that first and some second generation antihistamines (according to trimester) can be used in pregnant women if required. As antiemetics for vertigo attacks, they suggest meclizine, dimenhydrinate or metoclopramide. They also mentioned that betahistine, one of the most widely used antivertiginous drug, and vasodilatory agents are contraindicated in pregnancy.

Diazepam is used as a vestibular suppressant by many otolaryngologists. It is contraindicated in pregnancy (category: D), if used in a long time or high doses in pregnant women, may cause side effects such as floppy infant syndrome and benzodiazepine withdrawal syndrome [4]. So we did not apply



Curve	Latencies (ms) P1	N1	P1'	N1'	N1-P1 Lat	N1-P1 Amp
100 R	20.33	29.67			-10.67	60.16
100 R1						
100 L						
100 L1	17.67	25.33			-12.33	56.53

Figure 2. Vestibular evoked myogenic potential (VEMP) of the patient.
Right = P1: 20.33, N1: 29.67; left = P1: 17.67, N1: 25.33.

diazepam treatment to our patient.

Corticosteroids in vestibular neuritis for anti-inflamatory effect, rapidly and significantly reduces nerve inflamation and improves the recovery of vestibular deficit [5]. Dexamethasone/betamethasone may be given to women at risk of premature birth to promote maturation of the fetus' lungs. In the United States, pregnancy category of steroids is "C", on the other hand, pregnancy category is "A" in Australia.

Metoclopromide is commonly used to treat nausea and vomiting in vestibular neuritis. Its pregnancy category is "B" in the United States and "A" in Australia. A large cohort study of babies born to Israeli women exposed to metoclopramide during pregnancy

found no evidence that the drug increases the risk of perinatal mortality [6].

Based on the literature, we applied dexamethasone and metoclopromide treatment for 3 days to our patient by keeping in touch with the obstetrics clinic. We did not observe any clinical or laboratory side effects during follow-up. At the end of medical treatment, we suggested vestibular rehabilitation exercises to the patient, founded by Davis and O'Leary [7], that can be performed easily without any assistance:"Patient must perform a series of head movements horizontally, gradually faster, as if expressing a "no", keeping a fixed gaze on a point ahead. When the maximum frequency of the movement is reached, the patient stops and, 10 seconds later, restarts the procedure, that must be repe¬ated ten times. Next, the series of movements must be done vertically, as if the patient expresses a "Yes" with the head." Then we recommended the modified Cawthorne-Cooksey exercises (first described in 1946 and then modified in 1995) as a home protocol to the patient. These exercises or instrumental rehabilitation training consisting of standing with eyes open or closed on a platform moving, relative to the subjects, in the anteroposterior or mediolateral direction, training sessions for both interventions were twice daily, 30 minutes per session, for 5 days.

CONCLUSION

To conclude, as one of the common causes of vertigo, vestibular neuritis during pregnancy affects the quality of life. First of all, obstetricians and ENT surgeons should make the differantial diagnosis and then provide appropriate treatment of vestibular neuritis in pregnant by taking safety precautions related to any drug.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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The European Research Journal 2019;5(5):913-915 CASE REPORT

Minimally invasive beating heart full coronary artery bypass in a patient with pancreatic ductal adenocarcinoma

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DOI: 10.18621/eurj.431204

ABSTRACT

There are various problems associated with cardiopulmonary bypass in cardiac operations of patients with cancer. Our patient was a 73-year-old male patient diagnosed with pancreatic ductal adenocarcinoma. Coronary angiography of the patient who was planned to undergo tumor surgery revealed severe anomalies extending to the proximal of the diagonal 1 at the left anterior descending artery osteal and diagonal 1 distinction. Minimally invasive off-pump direct coronary artery bypass was performed in the patient. The patient was discharged on the 4th postoperative day and he was operated with the cause of pancreatic cancer at the third week. We think that minimally invasive coronary bypass without cardiopulmonary bypass can be performed with delayed prevention of cancer treatment and faster healing in patients with cancer of various systems.

Keywords: Coronary artery disease, cancer, minimally invasive direct coronary artery bypass, beating heart coronary bypass

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The mean age of patients with coronary artery bypass grafting (CABG) is increasing day by day due to the progress of endovascular treatment methods. The advancing age causes additional diseases such as cancer in patients. Coronary artery revascularization is recommended in patients with coronary artery disease prior to the treatment of neoplasia and it is also known that coronary artery bypass grafting is a safe and effective method [1]. Pancreatic ductal adenocarcinoma has poor prognosis and surgical tumor resection is the only curative treatment [2]. In this study, we presented a patient with pancreatic cancer and coronary artery disease. Minimally invasive full coronary bypass was performed.

CASE PRESENTATION

A 73-year-old male patient was diagnosed with pancreatic adenocarcinoma and planned for distal pancreatectomy. Preoperative evaluation, coronary angiography showed a stenosis of 80% in the left anterior descending artery (LAD) osteal and 90% in the LAD-diagonal 1 (D1) bifurcation. The patient was operated for coronary bypass. The patient was positioned 30° to the right lateral decubitus position. Right great saphenous vein graft was prepared. A left internal mammary artery (LIMA) was prepared from the fourth intercostal space with an 8 cm incision. The pericardium was opened from the thoracotomy

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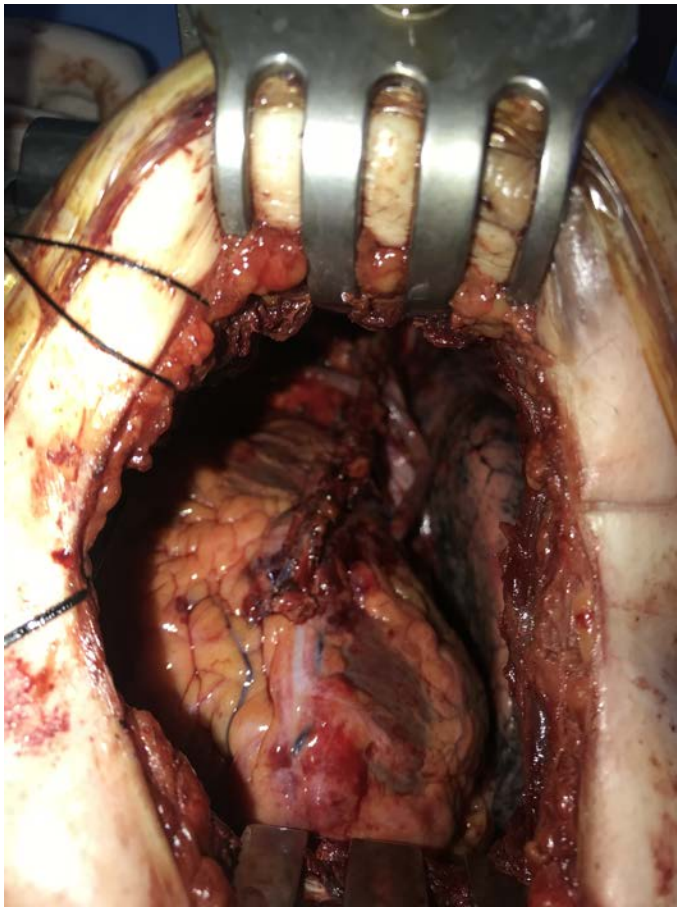

Figure 1. Intraoperative image shows completed anastomoses.

incision. Aorta prepared for proximal anastomosis. Proximal anastomosis was completed after lateral clamp placed on the aorta. LIMA-LAD and Aort-D1 distal anastomoses with saphenous vein graft were performed with the aid of a cardiac stabilizer (Figure 1). After the operation, the patient was transferred to intensive care unit. The patient was discharged on the fourth postoperative day. The patient underwent distal pancreatectomy 3 weeks after discharge.

DISCUSSION

CABG with extracorporeal circulation may cause metastatic spread of cancer in cancer patients, so it is emphasized that CABG is more suitable for these patients without cardiopulmonary bypass (CPB) pump [3, 4].

Surgery for coronary artery disease and malignancy can be performed simultaneously or in two phases. Both approaches have advantages and disadvantages. In a study conducted on a total of 350 patients by Darwazah *et al*. [5], they recommended a two-stage procedure [5]. We prefer to perform coronary bypass first.

If cancer patients have LAD or left main coronary lesion, coronary revascularization should be performed before cancer surgery [6]. Percutaneous coronary intervention (PCI) or CABG may be performed in coronary revascularization. Antiplatelelet therapy is recommended for at least 1 month in bare metal stents (BMS) and 6 to 12 months in drug-eluting stents (DES). In addition, 16%-44% restenosis was detected in BMS. Non-cardiac surgery under antiplatelelet treatment may cause high bleeding risk, surgical excision of antiplatelelet therapy may result in stent thrombosis. Waiting for 6 or 12 months may cause delayed treatment of cancer [7]. Our patient also had a LAD lesion and planned operation with the cause of pancreatic cancer.

Minimally invasive direct coronary artery bypass (MIDCAB) causes less pain, bleeding and infection. Besides this, patients can return to daily life faster [8]. In cancer patients in particular, the healing process is important for accelerating cancer treatment. That's why we decided to do MIDCAB. The patient was discharged on the 4th postoperative day and he was operated with the cause of pancreatic cancer at the third week.

CONCLUSION

In conclusion, if coronary artery disease is detected in cancer patients and coronary revascularization is planned, we think that minimally invasive coronary bypass can be performed in appropriate patients, patients can heal faster and cancer treatment can be started early.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of interest

The author declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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The European Research Journal 2019;5(5):916-919 CASE REPORT

Acute bilateral paramedian thalamic and mesencephalic infarcts due to occlusion of the Percheron artery: a case report

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ABSTRACT

The thalamus and midbrain mesencephalon have a complex blood supply with a great number of feeding arteries. The blood build up of thalamus is being provided by four arteries originating from the vertebrobasilar system and posterior communicating artery. The paramedian thalamic artery is derived from the posterior cerebral artery proximal P1 segment. The infarcts of arterial constitute approximately 35% of all thalamic infarcts. However, bilateral infarctions of this region are very infrequent. Percheron artery originates from the first branch of the posterior cerebral artery and gives bilateral medial thalamic perforating branches. We described a patient of a 88-year-old woman with acute bilateral thalamic and midbrain infarcts due to occlusion of Percheron artery demonstrated on magnetic resonance imaging.

Keywords: Percheron artery occlusion, thalamic infarct, mesencephalic infarct, magnetic resonance imaging

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The thalamus and midbrain mesencephalon have a complex blood supply with a great number of feeding arteries [1]. The blood build up of thalamus is being provided by four arteries originating from the vertebrobasilar system and posterior communicating artery. From these, the paramedian thalamic artery (thalamoperforan) also feeds the medial region of the upper brain stem. The paramedian thalamic artery is derived from the posterior cerebral artery proximal P1 segment. The infarcts of arterial constitute approximately 35% of all thalamic infarcts [2]. However, bilateral infarctions of this region are very infrequent. The proposed mechanism in bilateral thalamic infarction; is a single paramedian thalamic artery occlusion without central dissociation.

The artery of Percheron (AOP) is named after the frenchman, Gerard Percheron, who described it in 1973. This artery originates from the first branch of the posterior cerebral artery and gives bilateral medial thalamic perforating branches. The occlusion was frequently aetiology of cardiac embolism occuring as a result of atrial fibrillation [3]. According such studies, AOP infarct acoount for %0.1 and %0.3 of all ischemic strokes and 22 to 35% of all thalamic infarcts [4]. An ischemic stroke in the territory of an artery of Percheron usually present with several symtoms, which are found in patients with bilateral paramedian thalamic and mesencephalic infarct. These are; memory impairment, vertical gaze palsy, and coma [1].

We described a patient of an 88-year-old woman with acute bilateral thalamic and midbrain infarcts due to occlusion of AOP demonstrated on magnetic resonance imaging.

CASE PRESENTATION

An 88-year-old woman with a past history of

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hypertension, ischemic cardiopathy and atrial fibrillation was found unconscious in the early morning by her relatives. She was treated with long-term oral anticoagulants (warfarine), but with poor therapeutic range. On admission, his heart rate was 110/minute and regularly, blood pressure was 140/90 mmHg, respiratory rate was 15/minute and axillary temperature was 36.2 °C.

On neurogical examination, her Glasgow Coma Scale (GCS) score was 6/15 (E1M4V1); small but reactive pupils of the same size, absent oculocephalic reflexes, and Babinski's sign bilaterally. There was no vertical gaze palsy. At presentation, patient had minimal motor response to painful stimuli on the right arm and leg. These findings suggested a brainstem infarction. Complete blood picture, routine biochemistry, throid function tests, vitamin B12 and folate were all within normal limits.

The initial computed tomography (CT) showed no acute hemorrhage or brain lesion. ECG showed atrial fibrillation. Transthoracic echocardiography showed grade 2 diastolic dysfunction. The electroencephalogram (EEG) showed diffuse slowing teta-delta waves.

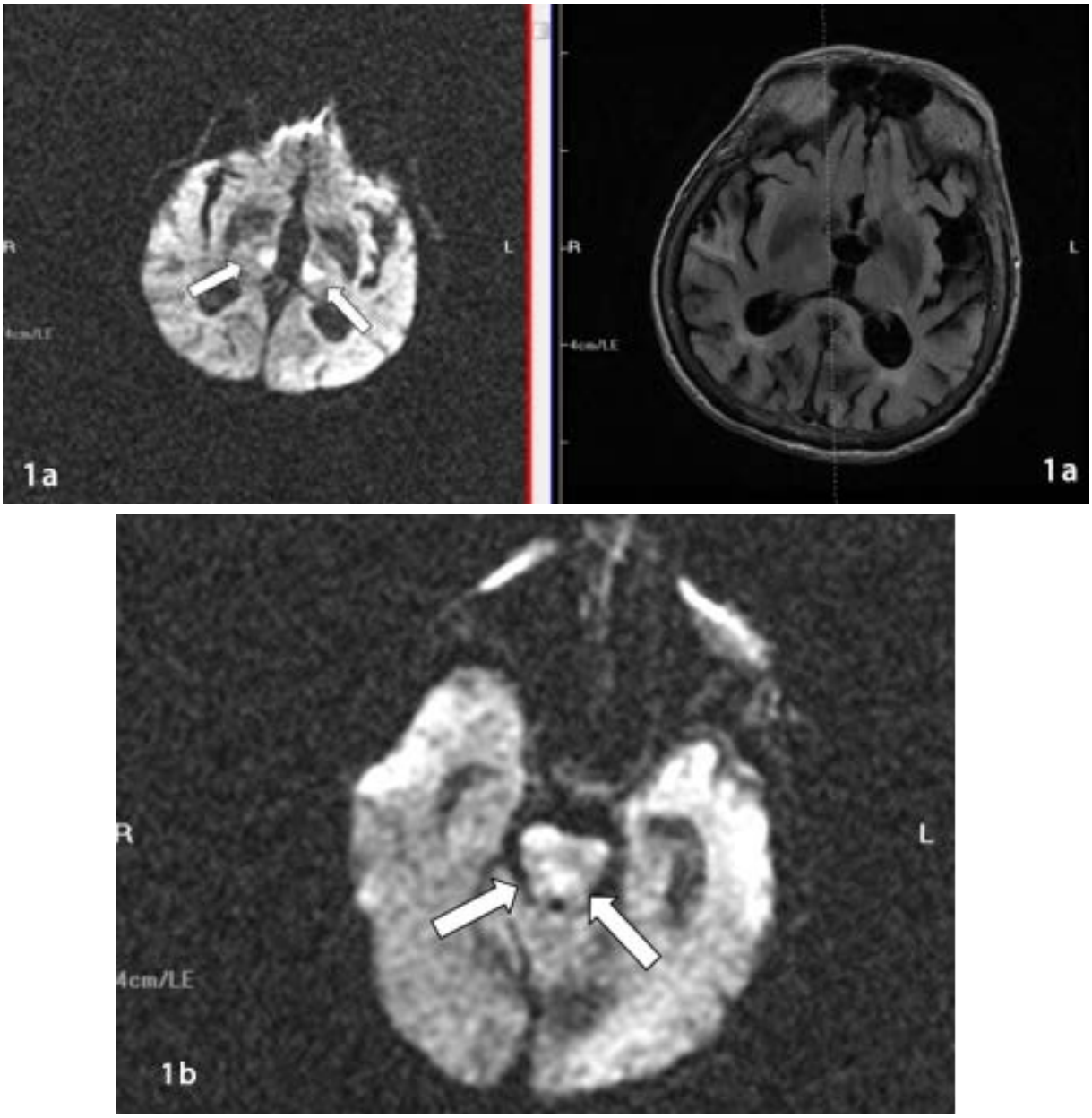

Figure 1. Magnetic resonance imaging shows high signal intensity areas on T2 weighted, FLAIR and diffusion sequences bilaterally and symmetrically infarcts in the medial thalamic region and rostral mid-brain region, right anterior, posterosuperior cerebellar hemisphere and left occipital lobe. (1a and 1b).

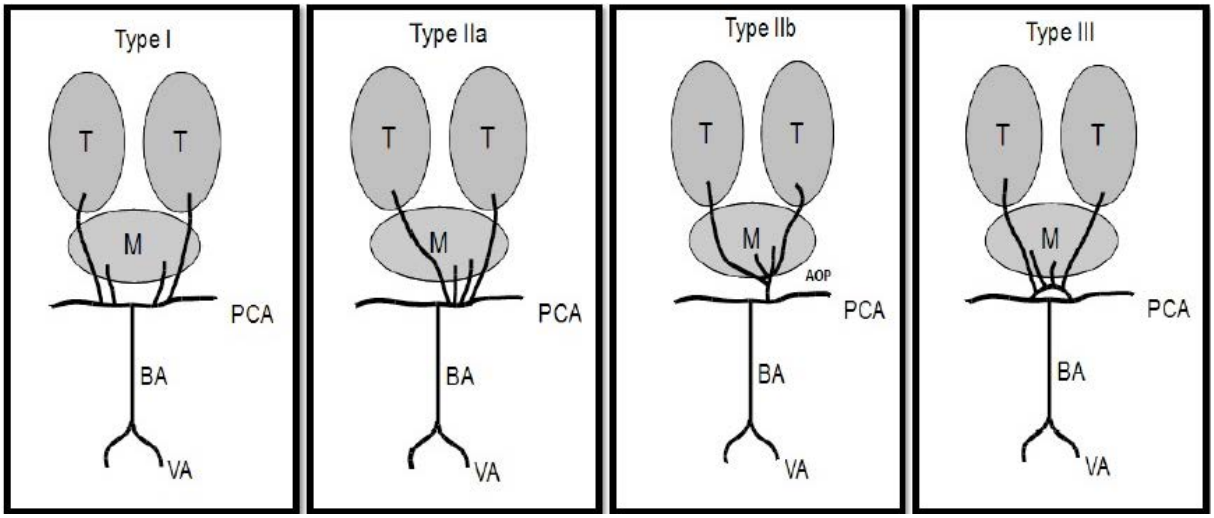

Figure 2. According to Percheron; there are four types of vascular anatomy of the thalamus and mesencephalon. (Type I) Each perforating artery occurs from each right and left posterior cerebral artery, (Type IIa) Perforating arteries occurs directly proximal segment of one of posterior cerebral arteries, (Type IIb) The bilateral perforating arteries arise from one central artery called the artery of Percheron , which arises from the P1 segment of one posterior cerebral artery., and (Type III) An arcade of perforating branches arising from an artery bridging the P1 segments of both posterior cerebral arteries.

Magnetic resonance imaging (MRI) showed high signal intensity areas on T2 weighted, FLAIR and diffusion sequences bilaterally and symmetrically infarcts in the medial thalamic region and rostral midbrain region, right anterior, posterosuperior cerebellar hemisphere and left occipital lobe (Figure 1a and 1b). MR angiography did not reveal any significant finding.

Low-molecular-weight heparin, mannitol, aspirin, atorvastatin, metoprolol in standard recommended dosages was started to patient. At sixth day she became pulmonary infection. She was treated with antibiotics. During her hospitalization, at the 30th day of coma, the patient has passed away due to sysmetic complications.

DISCUSSION

The main thalamic blood supply comes from the posterior communicating arteries and the perimesencephalic segment of the PCA. Although there is a significant variation and overlap, thalamic vascular territories: inferolateral, anterior, paramedian and posterior. The paramedian thalamic arteries have great variability with respect to number, size and territorial contribution.

According to Percheron; there are four types of vascular anatomy of the thalamus and mesencephalon (Figure 2). Type I is most common. Each perforating artery occurs from each right and left posterior cerebral artery. Type IIa is asymmetrical variant. Perforating arteries occurs directly proximal segment of one of posterior cerebral arteries. Type IIb: The bilateral perforating arteries arise from one central artery called the artery of Percheron, which arises from the P1 segment of one posterior cerebral artery. Type III is an arcade of perforating branches arising from an artery bridging the P1 segments of both posterior cerebral arteries.

In the AOP infarcts, as a result of anatomical variations of paramedian arteries, ischemic patterns are being developed. Bilateral paramedian and / or polar thalamic infarcts as well as bilateral thalamic infarcts and mesencephalon infarcts can be observed [4]. In a study conducted, four types of ischemic patterns were identified that matched the AOP feeding area. The most common is bilateral paramedian thalamic infarct and mesencephalon infarction association, and is observed in 43%. Types of paramedian thalamic infarcts without a mesencephalon infarction of 38%, 14% were accompanied by anterior thalamus and mesencephalon involvement, and presence of bilateral paramedian infarct and 5% of the cases in which the mesencephalon was preserved and the anterior

thalamus was retained, were being described [4]. When we look at the ischemic pattern of our case, it is observed that it is the most frequent type.

The most frequent cause of arterial occlusion in the pathogenesis is small vascular disease. In these cases where thromboembolic processes are occured in the second most frequent, it has been reported that the embolic source is mostly the heart, vertebrobasilar system and aorta. It is known that the greatest cause of bilateral thalamic infarcts is cardioembolism [5]. Another possible causes of bilateral thalamic lesions may also due to infections, infiltrative neoplasm, venous occlusison and inflammatory lesions [6].

Infarcts in midbrain and/or bilateral paramedian thalamic region may result in various clinical symptoms; altered mental status, memory impairment (58%), vertical gaze palsy (65%), motor deficits, confusion (53%) and coma (42%) [6]. Altered mental status may present ranging from drowsiness or confusion to hypersomnolance or coma. In our patient presented with coma and persisted until death.

Early diagnosis in percheron arterial infarcts is important in terms of thrombolytic therapy. Kostanian *et al*. [7], reported that they had a positive result in a patient with percheronian artery occlusion with intra-arterial thrombolysis.

CONCLUSION

Percheron arterial occlusion should be considered if no pathology is detected in the basilar artery in patients admitted to clinic with basilar peak syndrome.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Acknowledgement

This case report was presented as a poster in lEFNS-ENS Congress, Istanbul, Turkey, 2014.

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The European Research Journal 2019;5(5):920-925 CASE REPORT

A rare cause of gallbladder perforation: Burkitt's lymphoma

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ABSTRACT

Although the perforation of gallbladder rarely occurs, it is a high-risk and life-threatening condition. High rates of mortality and morbidity are associated with late diagnosis. Burkitt's lymphoma is a disease, which starts in B-cells and develops with leukemia and extranodal involvement. Involvement of gallbladder wall is a very rare location of extranodal lymphomas. In this case, a 68-year-old woman with severe pain in the left arm referred to our outpatients' clinic where anti-HCV (+), leukocytosis, elevated sedimentation rate, and thrombocytopenia were found in her initial tests. On the basis of these findings, further tests were performed and she was diagnosed with Burkitt's lymphoma. She had acute abdomen and gallbladder perforation was detected by radiologic study. Urgent laparotomy was performed and she subsequently underwent cholecystectomy and drain insertion. Postoperative septic shock developed and she died due to multiple organ dysfunction syndrome. The determined diagnosis was described as gallbladder wall perforation associated with Burkitt's lymphoma infiltration in the pathology report. It is very important for the clinicians to take into the consideration that a rare cause of gallbladder perforation is Burkitt's lymphoma and it has an aggressive postoperative clinical course.

Keywords: Gallbladder perforation, Burkitt's lymphoma

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Gallbladder perforation is a rare but life-threatening condition. Acute cholecystitis may be seen in 2-15% of the patients and it is usually observed with gallbladder stones [1, 2]. Although gallbladder perforation has been uncommonly seen, mortality is high with a rate of 12-42% [1, 3, 4]. Thus, it is very important to establish an early diagnosis and immediate medical treatment.

The associating illnesses in the patients with gallbladder stone disease predispose the development of gallbladder perforation. In immunocompromised patients, when the cholecystitis cannot be contained the disease may progress causing perforation. Besides, the diseases involve the gallbladder wall may also cause perforation. In this case report, we aim to scrutinize the gallbladder perforation developed secondary to Burkitt's lymphoma which both impairing the immune system and infiltrating the gallbladder wall and also to share this case illustrating a sample that is not described in the literature so far.

CASE PRESENTATION

A 68-year-old woman was admitted to our orthopedic clinic with the complaints of pain in her left arm. Since no fractures has been identified in her initial examination, she was referred to infectious

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diseases department with the pre-diagnosis of liver cirrhosis process based on anti-HCV (+), leukocytosis, elevated sedimentation, and thrombocytopenia findings. Patient was hospitalized for further examinations and treatment. In her anamnesis, she reported appetite loss, night sweats, weight loss, and fever. She had no specific past medical history but hypertension. During her hospitalization, no significant clinical manifestation has been found with the exception of slight hyperemia in the upper inner (superomedial) quadrant of the left breast and edema in the left upper extremity.

Upper extremity venous color doppler Ultrasonography showed thick, heterogeneous, and edematous tissue layer under the skin surface and multiple lymphadenopathies (maximum 25×26 mm in diameter). Furthermore, presence of lymphadenopathies in the left supraclavicular region and edema caused pressure on the left subclavian and axillary arteries have also been detected.

Abdominal ultrasonography showed gallbladder wall thickness of 10 mm and edematous appearance (cholecystitis). Deformation on gallbladder lateral walls was observed and found to be equivocal with respect to gallbladder perforation. Hypoechoic images were observed in the gallbladder, with the largest of which was matching with a 1 mm stone. Abdominal Computed Tomography (CT) showed increased gallbladder distention and wall thickening, and also fluid collection in the pericholecystic area (acute cholecystitis). A collection area of 2.5×2 cm has been detected on the gallbladder lateral walls between the gallbladder and the liver. Poorly defined gallbladder walls have been noted (perforation). There were large numbers of lymph nodes in the paraaortic region none of which regarded as pathological (Figure 1). Thoracic CT showed diffuse thickness on the left thoracic wall and beneath the skin surface of the left breast, and increased density (abscess? or hematoma?).

The patient was administrated with 4×1 gr of ampicillin sulbactam for the cellulitis in her left breast. Hematology consultation was made when the thrombocyte level decreased from 40,000 to 19,000. Since Burkitt's-like cells had been observed in the peripheral smear, the patient was pre-diagnosed with acute lymphocytic leulemia (ALL) or lymphoma. Lymph node excisional biopsy and bone marrow biopsy were planned for the patient. Meanwhile, general surgery consultation was requested since she manifested acute abdomen clinical table.

After the general surgery consultation; the results were evaluated as follows; her general condition was poor, body temperature was 37.5 ^{0}C, (99.5^{0}F), had a positive Murphy's sign, and there was sensitivity in the other quadrants of the abdomen but no muscular defance. As a result of patient's clinical and radiologic evaluation, she was transferred into general surgery clinic for emergency laparotomy with the diagnosis of lymphoma? + ALL? Preoperative fluid resuscitation, antibiotherapy, and thrombocyte replacement were performed. Patient, whose anesthetic risk reported as ASA IV E, underwent an emergency laparotomy. Exploration revealed that gallbladder wall at the liver side was perforated and abscesses formed in the intraparenchymal area. Open cholecystectomy + debridement + drainage processes were applied.

Thrombocyte apheresis and erythrocyte replacement were performed during and after the surgery. In the first preoperative day, general condition of the patient worsened and hemorrhagic exudate leaving the drains and incision lines were observed. The patient had 38.5^{0}C (101.3 ^{0}F) fever, oliguria, hypotension, tachycardia, and tachypnea, then she also had septic shock and subsequently multiple organ dysfunction syndrome. The patient not responding to resuscitative interventions died. Morphological and immunohistochemical findings of the case are "Burkitt's lymphoma".

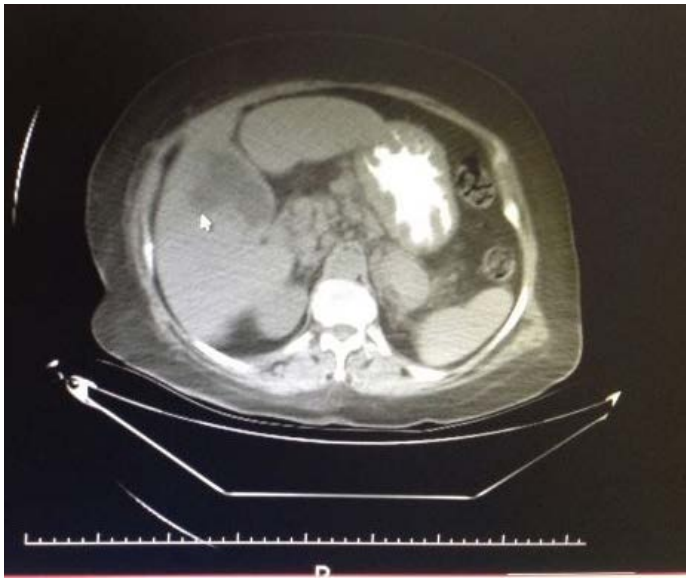

Figure 1. Gallbladder perforation area.

DISCUSSION

Gallbladder perforation is an uncommon but life-threatening condition. Sometimes it may not be differentiated from uncomplicated acute cholecystitis and may result in morbidity and mortality due to delayed diagnosis [1, 2]. While gallbladder perforation rate could be seen as 2-15 % in the patients with acute cholecystitis, this rate was observed between 3.3-5.9% when evaluated along with acute and chronic gallbladder perforations [3-5].

According to Neimer classification, gallbladder perforation divides into three subtypes. Type-1 is called acute free perforation and associated with generalized biliary peritonitis. Type-2 is called subacute pericholecystic abscess and associated with peritonitis. Type-3 is called chronic cholecystoenteric fistulation and associated with fistula [6]. The appearances of these types are different from each other. Type-1 patients are usually immune impaired thus, the disease cannot be localized and consequently lead to free perforation and generalized peritonitis. While Type-2 patients are monitored in subacute care clinics, Type-3 patients develop chronic cholecystitis and it is very difficult to diagnose unless they present with obstructive hepatitis symptoms [2, 3]. In the pathological analysis of this case, it has been considered that; Type-2 perforation was developed due to Burkitt's lymphoma infiltration into gallbladder wall, and also as secondary to immune insufficiency caused by Burkitt's lymphoma and probable bone marrow suppression, disease could not be controlled and the prognosis rapidly progressed into multiple organ dysfunction syndrome.

Gallbladder perforation may occur within the 24 hours after acute cholecystitis, as well it may develop in between a couple of days and weeks [7]. It is not possible to predict in which patient gallbladder perforation will develop [2, 3, 8]. Prognostic risk factors such as older age, male gender, associating illnesses, fever 380C (100.4 0F), elevated white blood cell (WBC) count may indicate the patients in whom the complications such as gangrene, empyema, emphysematous cholecystitis, and perforation could occur [9, 10].

Some associate systemic diseases such as atherosclerotic heart disease, diabetes among these prognostic risk factors may induce ischemia of the gallbladder wall, causing to necrosis and perforation [1, 3]. Furthermore, in the medical conditions where immune system is suppressed, the disease may also progress leading to perforation. In this case report, 68 years-old patient's higher age group, Burkitt's lymphoma and hypertension as associating illnesses, fever >37.5^{0}C (99.5^{0}F), WBC of 17.3 109/L are all matching with the literature in terms of the risk factors. It has been thought that these risk factors led to gallbladder perforation.

It is very difficult to preoperatively diagnose gallbladder perforation. Perforation of the gallbladder wall appears as defect on abdominal ultrasonography, furthermore abdominal CT contributed to increasing the accuracy in diagnosis [8]. Once the gallbladder perforation was diagnosed, it is of most importance that an immediate surgical intervention should be performed for diminishing morbidity and mortality [2]. In this case, gallbladder perforation was accurately diagnosed with both abdominal ultrasonography and abdominal CT and immediate laparotomy was performed.

One of the diseases, which cause to immune system impairing, is Burkitt's lymphoma. Burkitt's lymphoma is a disease, which starts in B-cells, aggressively progressing and developing a course with leukemia and extranodal involvement [11]. It has a low incidence of occurring in the adults [12]. Its incidence is 0.3/100.000 in US [13]. Appetite loss, night sweats, weight loss and fever symptoms present in the clinical table of Burkitt's lymphoma. Our patient had also presented appetite loss, night sweats, weight loss and fever at the time of admittance. So BL's stage accepted stage4B because of organ infiltration (gallbladder) and probable bone marrow infiltration (thrombocytopenia).

In the classification, there are three types of Burkitt's lymphoma: endemic, sporadic, and immunodeficiency-associated. While the endemic variant usually observed as tumors of the Jaw, sporadic type seen in the abdomen [14]. In our country Burkitt's lymphoma occurs mainly with abdominal diseases (70%) then with the involvement of orbit and jaw (45%) [15-18]. Although sporadic Burkitt's lymphoma is rarely seen in adults, it has an aggressive prognosis. Involvement of the gastrointestinal system is typical and it occurs most commonly in the ileocecal region, rarely seen in stomach or duodenum primarily.

[19, 20].

Common clinical presentations of Burkitt's lymphoma include intestinal obstruction and intussusception [21]. Liver, spleen, bone marrow, central nervous system; and less commonly skin, eyes, thyroid, bones, breasts and gonads are the regions where extranodal involvement occurs [22]. In literature, Burkitt's lymphoma coexisting in gallbladder and rectum has been reported only for an 11-year-old boy and it was presented as an unusual case [23]. Extranodal site of involvement of Burkitt's lymphoma was also gallbladder in that case.

Acute phase reactants such as sedimentation rates, C-reactive protein and procalcitonin levels found to be elevated in the biochemical blood analysis and hemogram testings. Expected high levels of lactate dehydrogenase and elevated uric acid levels in most patients with Burkitt's lymphoma were also measured greater than the reference ranges in this case. High levels of tumor markers were measured. Furthermore, it has been thought that the presence of thrombocytopenia in hemogram analysis and post-

Table 1. Laboratory results of the patient in admission, pre- and postoperative periods

	Admission	Preoperative	Postoperative
White blood cells (4-10 10^9/L)	11.5	17.3	25.1
Hemoglobin (3.5-5 gr/dl)	11.5	13.7	10.3
Hematocrit (34-47 %)	33.6	29.5	41
Platelets (110-300 10^9/L)	40.000	53.000	83.000
CRP (0-5 mg/L)	216	-	-
Sedimentation (1-20 mm/h)	70	-	-
Procalcitonin (0-0.046 ng/dl)	0,92	-	-
Anti HCV (0-1 COI)	+	+	+
HCV RNA	Negative	Negative	Negative
Anti-HBs (2-10 IU/L)	< 2	< 2	< 2
Anti HIV (0-1 COI)	Negative	Negative	Negative
HbsAg (0-1 COI)	Negative	Negative	Negative
AST (15-37 IU/L)	98	185	56.5
Urea (15-38.5 mg/dl)	21	40.6	53.9
Creatinine (0.6-1 mg/dl)	1.19	1.99	1.57
Total bilirubin (0.2-1 mg/dl)	1.7	1.8	1.9
Direct bilirubin (0-1.2mg/dl)	0.4	0.4	0.19
LDH (5-248 U/l)	1630	1850	2444
Uric acid (2.6-6 mg/dl)	8	11.2	14.5
Albumin (3.4-5 mg/dl)	2.6	2.41	2.01
INR (0.8-1.3)	1,09	1,4	2.6
CA 19.9 (0-39 U/ml)	578	-	-
CA 125 (0-35 U/ml)	55.73	-	-
Blood culture	No growth	No growth	No growth
Urea culture	No growth	No growth	No growth
Peripheral cmear	-	Burkitt's-like cells	-

INR = international normalized rate, AST = aspartate aminotransferase, CRP = C-reactive protein, LDH = lactate dehydrogenase, CA = cancer antigen, HCV = hepatitis C virus, RNA = ribonucleic acid, HbsAg = hepatitis B surface antigen, HIV = human immunodefiency virus

operative increase in international normalized ratio starting the bleeding diathesis caused by a probable bone marrow infiltration (Table 1).

Chemotherapy and radiation therapy are very effective in Burkitt's lymphoma treatment, while surgery is required only for the treatment of developed complications [24]. The surgical indication in this case is the development of gallbladder perforation. The development of this condition increasing the risk of mortality and morbidity has warranted an emergency laparotomy.

CONCLUSION

Gallbladder perforation is a rare disease but has a high rate of mortality and morbidity when left untreated. One of the causes of gallbladder perforation is the disorder directly infiltrating the gallbladder wall. Also in this case, Burkitt's lymphoma caused perforation by infiltrating gallbladder wall as the extranodal site of involvement. In conclusion, the clinicians should keep in mind that Burkitt's lymphoma might be a rare cause of gallbladder perforation, and also mortality and morbidity rates in the treatment period might be high depending on the magnitude of the systemic involvement.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of interest

The author declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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The European Research Journal 2019;5(5):926-927 LETTER TO THE EDITOR

Neuroglobins: a look into the future

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Dear Editor,

Out of the various novel insights in the ever expanding knowledge about neurology, neuroglobin has come up as an important concept. It is a recently discovered endogenous molecule of the human body with its distribution in various tissues. Staying in apparent in healthy state, it is expressed in conditions like acute hypoxia or ischemia. In the initial studies, it has shown promise as a neuroprotective agent as well as a treatment option for conditions like carbon monoxide poisoning. A brief introduction has been presented here.

There have been many recent developments in the field of neurology in the last two decades. One of them has been the discovery of neuroglobin in humans in 2000 by Burmester [1]. Neuroglobin is a third type of newly discovered vertebrate globin alongside hemoglobin and myoglobin.. It is an intracellular hemoprotein expressed in both central and peripheral nervous system, cerebrospinal fluid, retina and endocrine tissues and is involved in cellular oxygen homeostasis. Neuroglobin is a monomer that reversibly binds oxygen with an affinity higher than that of hemoglobin. It also increases oxygen availability to brain tissue and provides protection under hypoxic or ischemic conditions, potentially limiting brain damage. It is of ancient evolutionary origin, and is homologous to nerve globins of invertebrates [2].

Neuroglobin expression is low and may be at a 'rest state' under normoxia. Upon hypoxia, neuroglobin is up-regulated by transcriptional factors. However, the elevation of neuroglobin level does not persist when being exposed to prolonged hypoxia/ischemia, which indicates that neuroglobin induction is mainly an acute response of hypoxia or ischemia. Moreover, prolonged hypoxia or ischemia may promote neuroglobin degradation through oxidation and ubiquitination. Upon hypoxia or oxidative stress, neuroglobin tends to transfer to penta-coordinated ferrous status, which facilitates nitric oxide production. Nitric oxide, in turn binds to cytochrome c oxidase to inhibit cellular mitochondrial respiration, oxygen consumption and reactive oxygen species production [3].

Various studies are coming up with role of neuroglobin in different conditions. Apart from acute hypoxic states, human neuroglobin overexpression has been hypothesized to protect neurons from mitochondrial dysfunctions and neurodegenerative disorders such as Alzheimer's disease, and to play a shielding role in cancer cells where neuroglobin binds to Raf-1, suppresses Raf/ extracellular signal-regulated kinase (Erk) signaling and functions as a tumour suppressor in hepatoclellular cancer [4]. Neuroglobin is abundant in the ganglion cell layer. It's knockdown leads to reduced activities of respiratory chain complexes I and

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III, degeneration of retinal ganglion cells, and impairment of visual function. Hence, neuroglobin is considered as a novel mitochondrial protein involved in respiratory chain function which is essential for retinal ganglion cell integrity [5]. Ischemic stroke leads to an increase in the expression of neuroglobin in the peri-infarct cerebral cortex compared with the adjacent normal brain and ischemic core. Significance of increased neuroglobin expression in clinical stroke stands unclear, but in rodent model, overexpression of neuroglobin is associated with reduction of infarct size and thus improved functional outcome. Accordingly, neuroglobin might also serve a similar neuroprotective role in humans. Neuroglobin is detected in human cerebrospinal fluid, which might warrant future clinical studies on the relationship between level of neuroglobin and stroke severity or outcome. Seeing the neuroprotective effect of neuroglobin in animal stroke models, and other neurological diseases, certain drugs that stimulate neuroglobin expression could well be therapeutically useful in these disorders [6]. More recent studies also indicate that neuroglobin can be a potential treatment option for cases of carbon monoxide poisoning . This is based on near irreversible binding of carbon monoxide by neuroglobin with a mutated distal histidine (H64Q) [7, 8]. Apart from the protective effects of neuroglobin in response to hypoxia/ischemia/oxidative stress, neuroglobin plays a physiological role in neuron or brain development through promoting neurite outgrowth [3].

Thus, neuroglobin is a very important molecule which has shown promising results in the initial studies for various conditions and further research will lead to better knowledge and its use in various neurological disorders.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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