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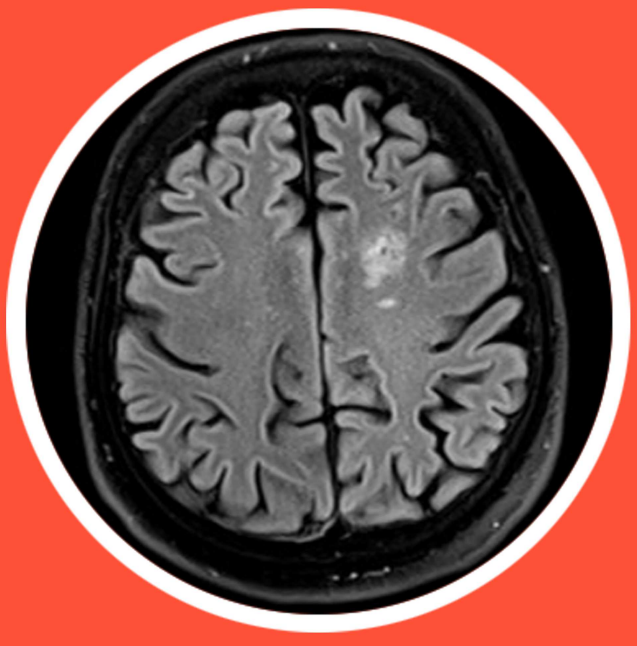

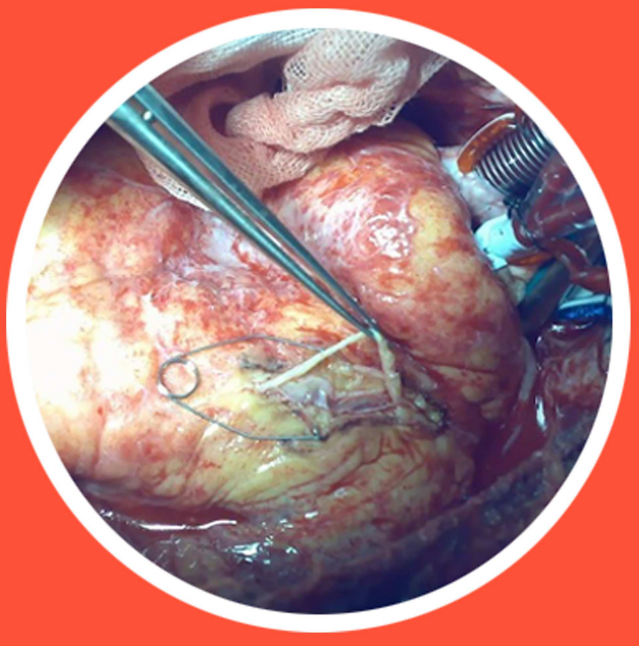

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Original Articles

The European Research Journal 2021;7(3):218-224 Original Article

DOI: 10.18621/eurj.900847 *Medical Pharmacology*

Effect of the Wnt/β-catenin pathway inhibitors on cell proliferation and migration of HEC-1A endometrial adenocarcinoma: experimental cell culture model

Yaşam Çirçirci, R. Nalan Tiftik, İsmail Ün

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ABSTRACT

Objectives: The most diagnosed tumor among infiltrating tumors of the female genital tract is endometrial carcinoma. The Wnt/β-catenin signaling pathway has an important role in organogenesis, self-renewal of tissues, and adult stem cell maintenance. However aberrant activation of it causes many types of tumors and also related to the prognosis of patients. Therefore, we aimed to investigate whether Wnt/β-catenin pathway inhibitors have any effect on the proliferation and migration of tumor cells.

Methods: As cancer cell line, HEC-1A endometrial adenocarcinoma was used. The Wnt/β-catenin pathway inhibitors effects on proliferation and migration were demonstrated by real-time cell analysis device and wound healing model respectively.

Results: Wnt/β-catenin pathway inhibitors FH535 (25 μM at 36th hour, $p < 0.05$; 50μM at 48th hour $p < 0.001$) and niclosamide inhibited cell proliferation (10, 25 and 50μM at 60th hours; $p < 0.01$, $p < 0.05$ and $p < 0.001$, respectively) whereas ICRT14 and IWP-2 did not. However only niclosamide which is also an antihelmintic drug inhibited migration of the cells in all concentrations tested (10, 25 and 50μM, $p < 0.05$).

Conclusions: The present study shows that the Wnt/β-catenin pathway has an substantial role in both proliferation and migration of endometrial adenocarcinoma. We suggest that the antihelmintic drug niclosamide could be further investigated for its potential therapeutic effect in endometrial adenocarcinoma.

Keywords: Wnt/β-catenin, endometrial adenocarcinoma, niclosamide, migration

In the female genital tract most frequent infiltrating tumor is endometrial carcinoma which mostly occurs in the postmenopausal age [1, 2]. Endometrial cancers are mainly diagnosed at early stages, and 5-year of survival is between 20% to 91% depending on the stage. Hormone therapy, older age, exercise, diet and, diabetes are risk factors for developing endometrial cancer [3].

The Wnt/β-catenin signaling pathway has important roles in organogenesis, development, adult stem cell functions, and renewal of tissues. However abnormal activation of it causes many types of tumors [4, 5]. It has been reported that mutations of the β-catenin gene result in endometrial tumorigenesis [6-8]. Besides malignant transformation and tumor progression also proposed to require activation of the pathway [9]. Estrogens could induce Wnt/β-catenin signaling and may cause endometrial hyperplasia even cancer. In contrast, progesterone was suggested as an inhibitor of this signaling [9]. This pathway also have coopera-

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tive with other pathways such as cyclooxygenase, EGFR signaling and Notch signaling [10].
In endometriosis patients inhibition of Wnt/β-catenin signaling reported to prevent migration, invasion and proliferation, of epithelial and stromal cells of [10].

Although Wnt/β-catenin signaling inhibitors have not yet been in clinical practice for endometrial cancer treatment, experimental data have promising consequences [9]. Wnt/β-catenin signaling pathway has a substantial role in cell proliferation, migration and cell fate specification, [10]. HEC-1A cells are experimental models for postmenopausal endometrial cancer and it enables investigations for regulatory and signaling mechanisms [11, 12]. Therefore, we aimed to investigate whether Wnt/β-catenin signaling inhibitors have any effect on the proliferation and migration of HEC-1A endometrial adenocarcinoma cells.

METHODS

Cell Line

HEC-1A which is a human originated endometrial carcinoma and often used as an experimental model for type 2 postmenopausal endometrial cancers was used as a cell culture (provide from ATCC® HTB-112™). 10% fetal bovine serum (Biological Industries USA) 1% Penicillin/streptomycin (Biological Industries USA), L-glutamine (PAN-Biotech, Germany) were added to McCoy's 5A (Lonza, US) and served as medium for cells. The incubator was adjusted to 5% CO_2 at 37°C. Cells were getting confluent approximately in 10-14 days and had a 95-99 % viability rate. Cells that were contaminated or had phenotypic changes were excluded from the study.

Preparation of Drugs

Wnt/β-catenin pathway inhibitors FH535, ICRT14, IWP-2, and niclosamide were purchased from Sigma-Aldrich, USAFH535, ICRT14, IWP-2, and niclosamide (10, 25, and 50μM each) were dissolved in the 0.5% dimethyl sulfoxide (DMSO). The data recorded from the migrations and proliferation with Wnt/β-catenin pathway inhibitors were compared against control group (DMSO 0.5%).

Proliferation Studies

The effect of the Wnt/β-catenin pathway inhibitors on proliferation was recorded by real-time cell analysis (xCELLigence) device. The xCELLigence is used for real-time monitoring of cell proliferation. It enables recording of electronic impedance of E-Plates. Each well of the E-plate were seeded with 10000 cells and incubated for 24 hours. Thereafter Wnt/β-catenin pathway inhibitors FH535, ICRT14, IWP-2, and niclosamide (10, 25, and 50μM each) were added to the wells. E-plates were put into the incubator which also contains the device.

Migration Model

The wound healing model used for migration studies. Each well of 24 well plate were seeded with 30000 cells. When cells were reach to confluency after approximately 10 days they were incubated with serum-free medium for 24 hours. Thereafter, by using a 20 μl pipette the wound lines were opened on cells that grown on plates. After the administration of 1% FBS medium to wells, FH535, ICRT14, IWP-2, and niclosamide (10, 25, and 50μM each) were applied. After the inhibitor agent administration (t = 0) and subsequently at 24th and 48th hours, the wound images were measured. Relative cell motility was calculated by the formula (wound width at t = 0 hours) - (wound width at t = 24 or 48 hours).

Statistical Analysis

Cell proliferation obtained from xCELLingence system was expressed as cell index "CI" and CI > 0.2 was considered as positive. Data were presented as mean ± SEM. One-way analysis of variance and post hoc Bonferroni test was used for statistical evaluation or t-test were used when appropriate. A *P* value smaller than 0.05 was considered significant.

RESULTS

The Effect of DMSO on Cell Proliferation and Migration

Following the incubation cells were gradually proliferated in both saline and DMSO groups (Fig. 1a). The concentrations of DMSO in both E-plate wells and migration wells were 0.5% and did change neither cell proliferation (Fig. 1a, $p > 0.05$) nor cell migration (Fig. 1b, $p > 0.05$).

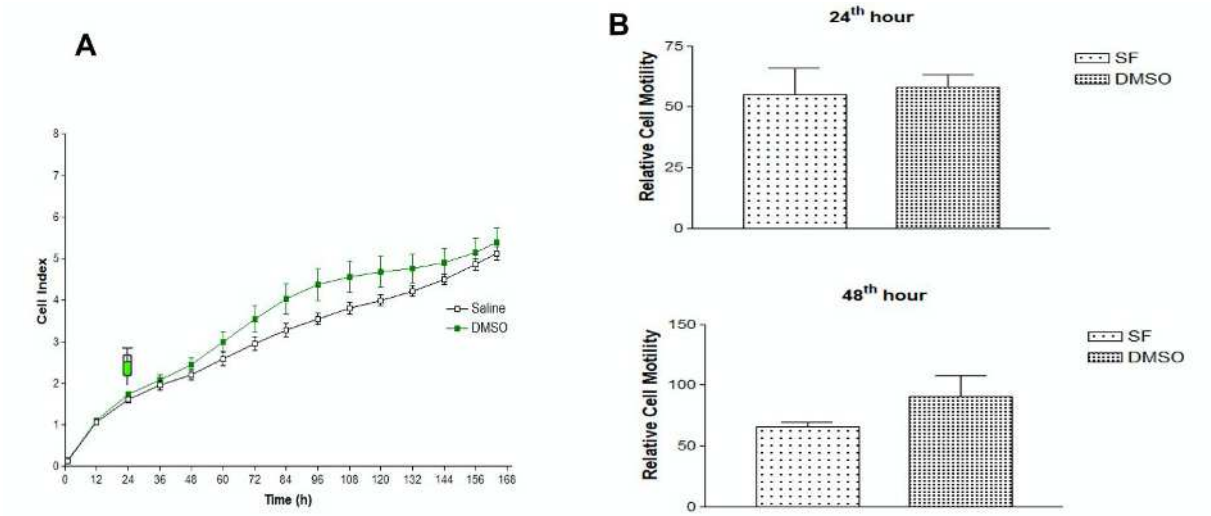

Fig. 1. Effect of DMSO (vehicle) on the proliferation (a) and migration (b) of HEC1A cells by real-time cell analysis and wound healing model respectively. (a) DMSO was added at the 24th hour (↑). DMSO (0.5%) did not altered cell proliferation (n = 4) ($p > 0.05$). (b) Treatments were made at the 0th hour for migration. The concentration of DMSO was 0.5 % in wells and did not change cell migration ($p > 0.05$).

The Effect of FH535 on Cell Proliferation and Migration

10 µM of FH535 did not change cell proliferation (Fig. 2a, $p > 0.05$). 25 µM of FH535 starts to inhibit cell proliferation 12 (36th hour on the graph) hours after the application (Fig. 2a, $p < 0.05$). 25 µM of FH535 decreased proliferation between the 36th and 84th hours and after the 84th hours started to cause cell death (Fig. 2a, $p < 0.001$). The higher 50 µM concentrations of FH535 start to cause cell death at earlier times between the 48th and 168th hours (Fig. 2a, $p < 0.001$). However FH535 did not change the cell migration of HEC-1A cells (Fig. 2b, $p > 0.05$).

The Effect of ICRT14 on Cell Proliferation and Migration

10, 25, and 50µM of ICRT14 did not change cell proliferation of endometrial adenocarcinoma HEC-1A cells (Fig. 3a). ICRT14 did not change the cell migration of HEC-1A cells (Fig. 3b, $p > 0.05$).

The Effect of IWP-2 on Cell Proliferation and Migration

10, 25, and 50µM of IWP-2 did not change cell proliferation of endometrial adenocarcinoma HEC-1A cells (Fig. 4a). IWP-2 did not change the cell migration of HEC-1A cells (Fig. 4b, $p > 0.05$).

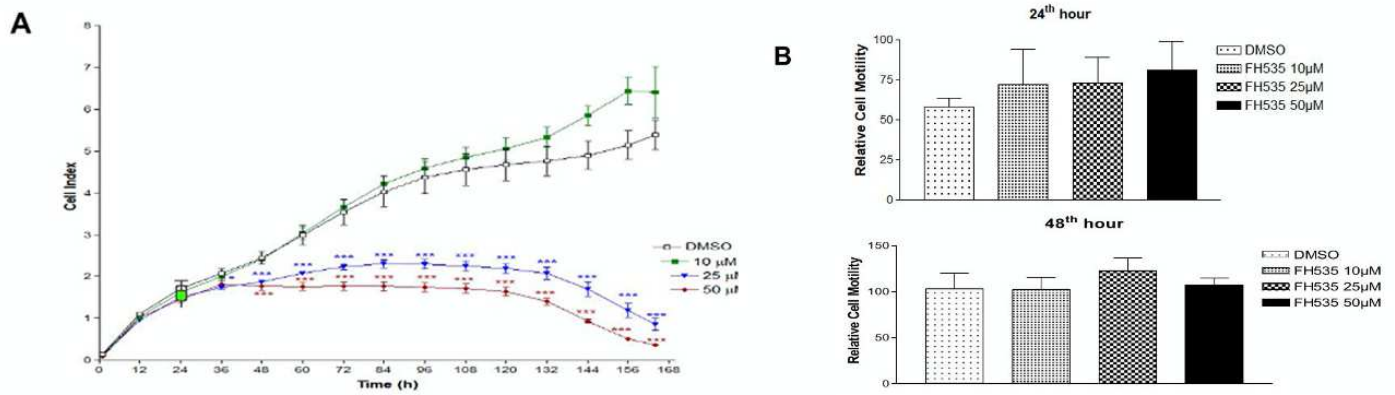

Fig. 2. The effect of FH535 on cell proliferation (a) and migration (b). (a) Treatments were made at the 24th hour (↑) for proliferation.10 µM of FH535 did not change cell proliferation. 25 µM of FH535 started to inhibit cell proliferation at 36th hour. 25 µM of FH535 decreased proliferation between the 36th and 84th hours and after the 84th hours started to cause cell death. 50 µM concentrations of FH535 start to cause cell death at earlier times between the 48th and 168th hours (*$p < 0.05$, *** $p < 0.001$). (b) Treatments were made at the 0th hour for migration. FH535 did not change the cell migration of HEC-1A cells ($p > 0.05$).

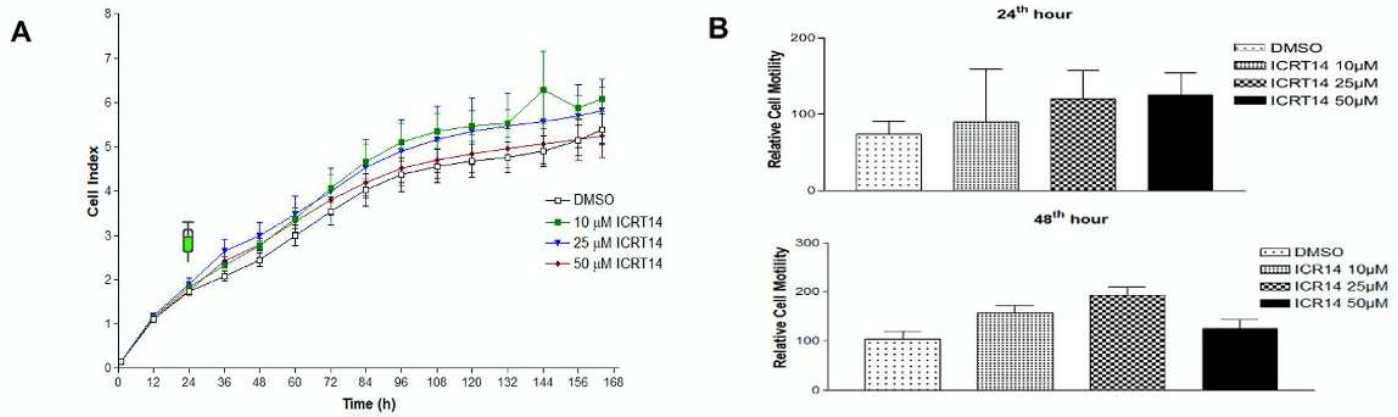

Fig. 3. The effect of ICRT14 on cell proliferation (a) and migration (b). (a) Treatments were made at the 24th hour (▼) for proliferation. 10, 25, and 50μM of ICRT14 did not change cell proliferation of endometrial adenocarcinoma HEC-1A cells. (b) Treatments were made at the 0th hour for migration. ICRT14 did not change the cell migration of HEC-1A cells (p >0.05).

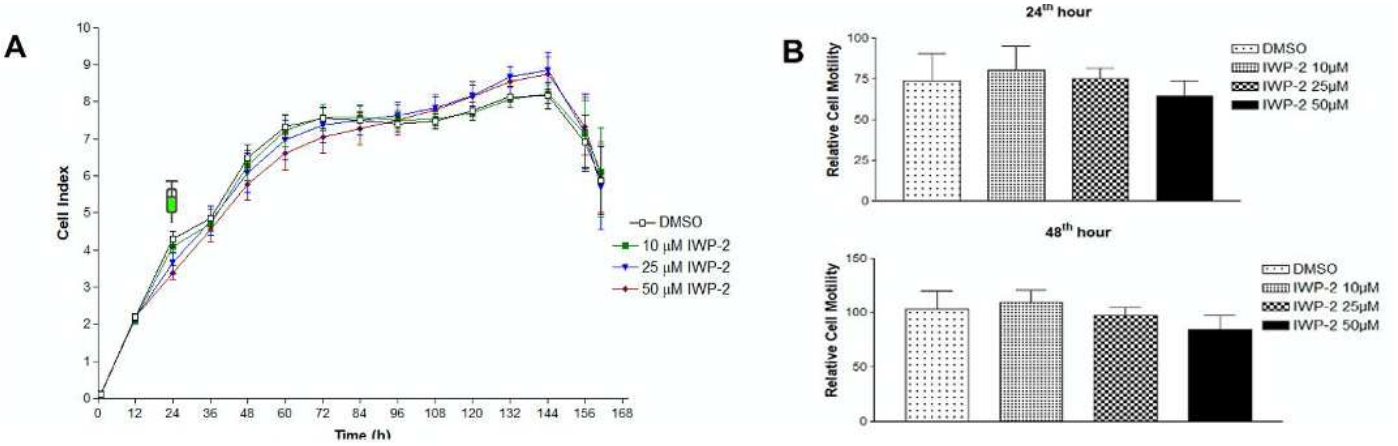

Fig. 4. The effect of IWP-2 on cell proliferation (a) and migration (b). (a) Treatments were made at the 24th hour (▼) for proliferation. 10, 25, and 50μM of IWP-2 did not change cell proliferation of endometrial adenocarcinoma HEC-1A cells. (b) Treatments were made at the 0th hour for migration. IWP-2 did not change the cell migration of HEC-1A cells (p > 0.05).

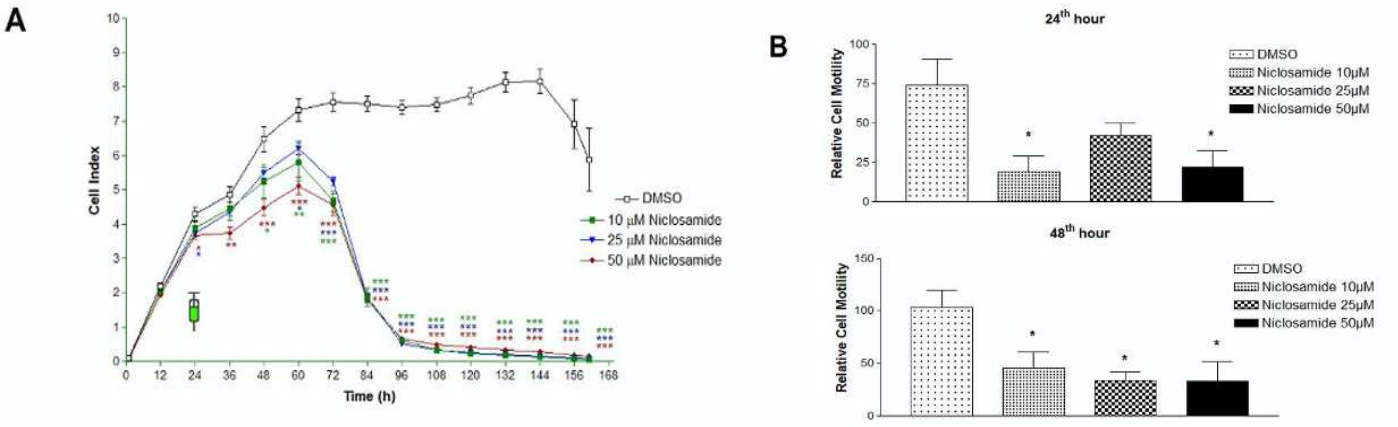

Fig. 5. The effect of niclosamide on cell proliferation (a) and migration (b). (a) Treatments were made at the 24th hour (▼) for proliferation. 10, 25, and 50μM of niclosamide inhibited cell proliferation. While the effect of 25 and 50μM of niclosamide started immediately after the application, the effect of 10μM observed at 48th hour. After the 60th hour there was a fast decrease in cell index with al concentrations used (*p < 0.05, ***p < 0.001). (b) Treatments were made at the 0th hour for migration. Niclosamide significantly inhibited cell migration of HEC-1A cells at all concentrations tested (p < 0.05).

The Effect of Niclosamide on Cell Proliferation and Migration

10, 25, and 50μM of niclosamide inhibited cell proliferation. While the effect of 25 and 50μM of niclosamide started immediately after the application, the effect of 10μM observed at 48th hour. After the 60th hour, there was a fast decrease in cell index with all concentrations used (Fig. 5a). Niclosamide significantly inhibited cell migration of HEC-1A cells at all concentrations tested (Fig. 5b, $p < 0.05$).

DISCUSSION

The effects of four Wnt/β-catenin pathway inhibitors on cell proliferation and migration that are important for cancer prognosis were tested in HEC-1A cells which are being used an experimental model for type 2 postmenopausal endometrial cancers [12]. Wnt/β-catenin pathway inhibitors, FH535, and niclosamide inhibited cell proliferation whereas ICRT14 and IWP-2 did not. However, only niclosamide which is also an antihelmintic drug inhibited migration of the cells.

FH535 is a cell-permeable sulfonamide compound that inhibits β-catenin-Tcf/LEF interaction in the Wnt/β-catenin pathway but also suppresses the Peroxisome Proliferator-Activated Receptor (PPARγ/δ) signal. PPARs belong to the nuclear receptor protein group and act as transcription factors that regulate the gene expression [13].

In hepatocellular carcinoma cells, FH535 suppressed the proliferation, and 50μM significantly reduced the distance between the two lines in the wound healing test [14]. It has been reported that FH535 inhibited cell proliferation (10μM, 20μM, and 40μm) and migration at 24 hours in wound healing experiment (20μM and 40μM) in colon cancer cell lines [15]. In another study, the effect of FH535 on pancreatic cell lines were examined (PANC-1 and BXPC-3), and 20μM FH535 concentration did not change the expression of β-catenin in BXPC-3 cells but decreased the expression of β-catenin in PANC-1 cells. In the wound healing experiment, the 20 μM concentration of FH535 significantly reduced migration at 8 and 12 hours [16]. Also, it has been reported that FH535 inhibits proliferation at concentrations of 0.1μM, 1μM, and 10μM in osteosarcoma cells [17]. The antiproliferative effect observed in hepatocellular carcinoma cells with the addition of FH535 at 50μM concentration is similar to our study, but the antiproliferative effect observed in colorectal cancer cells with the addition of FH535 at 10μM concentration was not noticed in HEC1A cells. Besides, inhibition of migration in the wound healing experiment in hepatocellular carcinoma, colorectal cancer, pancreas, and osteosarcoma cells was not observed in HEC1A cells. Different effects observed in the same concentration in the cell lines suggested that the inhibitory action of FH535 may change depending on the cell type.

In our study, the 25 μM concentration of FH535 reduced proliferation starting from the 24th hour, as well as reducing the number of cells after the 84th hour. 50μM concentrations of FH535 tend to decrease proliferation after 12 hours and started to decrease the number of cells after 24 hours. Niclosamide administration reduced proliferation from the first moment of administration and additionally decreased the number of cells after 36th hour at all concentrations. In this study, cell death mechanisms have not been studied, but we suggest that the decrease in the number of cells at the specified hours may be related to the activation of cell death mechanisms. Because the cells in the control group at the same time were still growing at their normal rate.

Niclosamide inhibits the co-receptor LRP6 via increasing the Wnt receptor Fzd1 internalization, inhibits Dvl2 expression via inhibiting the β-catenin/TCF complex formation, and thereby inhibits the Wnt/β-catenin signaling at multiple levels. In addition, niclosamide also inhibits Notch, STAT, 3NF-κB, and mTORC1signaling pathways. At the same time it may induce growth inhibition, apoptosis and cell cycle arrest via targeting the mitochondria of cancer cells. [18].

Gyamfi *et al*. [19] have shown that niclosamide inhibits both proliferation and migration in breast cancer cell lines. Arend *et al*. [20] showed antiproliferative effects of it in ovarian cancer cells (0.1-4μM). Zhao *et al*. [21] have demonstrated that it inhibits proliferation in renal cell carcinoma lines. Wang *et al*. [22] showed that it inhibits proliferation in hepatocellular cell lines, induces apoptosis, and increases the cisplatin sensitivity of cancer cells. Liu *et al*. [23] reported that 0.1μM, 0.25μM, and 0.5μM niclosamide suppress cell migration in prostate cancer cells. Li *et*

al. [24] have demonstrated that different concentrations of niclosamide between 0.1μM-10μM in human osteosarcoma cell lines inhibit cell proliferation by stopping the cell cycle. Likewise in our study niclosamide prevented both proliferation and migration in endometrium adenocarcinoma HEC1A cells. Among other inhibitors tested in this study, only niclosamide inhibited migration. Based on this finding, it could be suggested that this effect by niclosamide is due to a nonspecific effect of it rather than the Wnt/β-catenin pathway inhibition. However, further and detailed molecular studies are needed to confirm this suggestion. One of the limitations of this study is that expression and activation studies have not been performed for the Wnt /β-catenin pathway.

ICRT14 belongs to the thiazolidinedione class of β-catenin responsive transcription inhibitors, and also prevents TCF binding to DNA [13]. In one study, ICRT14 has been shown to induce significant G0/G1 cell cycle arrest in colon cancer cell lines, and in another study, increased sensitivity to chemotherapy in pediatric acute lymphocytic leukemia patients by inhibiting Wnt [25, 26]. IWP-2 blocks Wnt production by directly inhibiting the porcupine active site, it can also affect CK1δ/ε related pathways [27]. Kleszcz *et al*. [28] have demonstrated that IWP-2 inhibits porcupine, reducing the Wnt signal, thereby inducing apoptosis in neck and head carcinoma cells. Tong *et al*. [29] showed that artemisinin derivatives can significantly inhibit tumor metastasis and lung tumorigenesis via Wnt/β-catenin signaling. In our study, ICRT14 and IWP2 did not change proliferation and migration at the concentration and time intervals tested.

CONCLUSION

In this study, we examined the possible effects of Wnt/β-catenin pathway inhibitors on proliferation and migration in endometrial adenocarcinoma HEC1A cells, which are important parameters for cancer. We have shown that FH535 inhibits proliferation, and niclosamide both proliferation and migration. We suggest that antihelmintic drug niclosamide which is a cheap antiparasitic drug could be regarded as a potential therapeutic agent in endometrium adenocarcinoma. Further studies on the effects of niclosamide and its derivatives on proliferation and migration and other parameters of cancer are needed to elucidate the pathogenesis of endometrial cancers, prevent progression of the disease and develop new treatment strategies.

Authors' Contribution

Study Conception: YÇ, İÜ; Study Design: YÇ, RNT, İÜ; Supervision: İÜ; Funding: İÜ; Materials: İÜ, RNT; Data Collection and/or Processing: YÇ, RNT, İÜ; Statistical Analysis and/or Data Interpretation: YÇ, RNT, İÜ; Literature Review: YÇ, İÜ; Manuscript Preparation: İÜ, RNT and Critical Review: İÜ, RNT.

Conflict of interest

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

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Serum undercarboxylated osteocalcin levels are related to bone disease in hemodialysis and peritoneal dialysis patients

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ABSTRACT

Objectives: In our study, we investigated whether the undercarboxylated osteocalcin (ucOC) is an indicator of bone turnover for patients treated with hemodialysis (HD) or peritoneal dialysis (PD). Furthermore, we have examined the relationships between ucOC levels and other bone inidicators such as osteocalcin (OC), bone specific alkaline phosphatase (B-ALP), calcitonin, vitamin D, intact parathyroid hormone (iPTH), calcium (Ca), phosphate (P), magnesium (Mg) and bone mineral density (BMD).

Methods: Study group was consisted of 24 HD, 30 PD patients and 30 control subjects. ucOC measurements were based on precipitation of carboxylated OC with barium sulfate. After precipitation, ucOC was measured in supernatant by ELISA.

Results: In chronic kidney disease (CKD), increased ucOC levels were present both in HD and PD groups. The ucOC levels in HD group were higher than those of PD group. ucOC levels in samples after HD were lower than in samples before HD. But there is no difference between groups for ucOC% levels. We observed that ucOC levels for CRF were higher compared to that of control group and statistically significant. ucOC levels were positively correlated with OC, B-ALP, ALP, iPTH, P and Mg levels. There were negative and significant correlations between ucOC levels and BMD values. ucOC has a good discrimination power for both high and low turnover ROD groups.

Conclusions: ucOC is a useful marker to evaluation of bone metabolism in patients undergone hemodialysis or peritoneal dialysis in end-stage renal disease.

Keywords: Renal bone disease, hemodialysis, peritoneal dialysis, undercarboxylated osteocalcin, osteocalcin, bone mineral density

Patients with chronic kidney disease (CKD) have a wide spectrum of bone diseases, such as secondary hyperparathyroidism, osteomalacia, and adynamic bone disease [1]. Mineral and bone metabolism disorders in dialysis patients have been associated with cardiovascular calcifications, bone fractures, increased morbidity and mortality risks [2, 3]. Therefore, it is important to identify bone and mineral disorders in patients with renal failure. Bone biopsies, scintigraphic screening studies, invasive and/or expensive proce-

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dures such as a computed tomography are used after double tetracycline labeling in the diagnosis of bone diseases [4]. For this reason, specific biochemical markers are needed which can be used to measure bone metabolism in both uremic and other diseases.

Serum osteocalcin (OC) is a bone formation marker, including three gamma carboxyglutamic (Gla) residues. Vitamin K is a cofactor for OC. OC is provided to be activated by vitamin K-dependent carboxylation of these Gla residues. The non-gammacarboxylated form is called undercarboxylated osteocalcin (ucOC). Hydroxyapatite (HA) crystals cannot bind to ucOC and these results in changes in the bone matrix [5-7].

In the patients with CKD, the relationship between ucOC and and chronic kidney disease-mineral and bone disorder (CKD-MBD) is not fully understood. ucOC may play a role in the pathogenesis of bone metabolism disorders that occur as a result of both vitamin K concentration changes and hyperparathyroidism in dialysis patients. In one study it was founded that suboptimal vitamin K deficiency in hemodialysis patients was associated with increased prevalence of hyperparathyroidism and increased risk of bone fracture. In this study, a significant inverse correlation was found between the parathyroid hormone (PTH) and vitamin K [8]. Although many bone markers have been studied in patients with CKD, there are not enough studies in the literature showing the relation between ucOC and CKD-MBD.

ucOC concentration is measured indirectly by using the binding properties of barium sulfate (BS) or HA with osteoclastic glutamic acid residues. ucOCis stayed in the supernatant after carboxylated OC is precipitated by BS or HA. ucOC is measured with immunochemistry OC analysis methods [9]. ucOC concentration is also measured directly with ucOC specific ELISA methods [10].

The purpose of this study was to determine the relationship between serum UCOC concentrations and renal bone turnover in patients on hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD), and to determine the correlation of ucOC concentrations with bone mineral density (BMD), OC, alkaline phosphatase (ALP), bone-specific alkaline phosphatase (B-ALP), intact parathyroid hormone (iPTH), calcium (Ca), ionized calcium (iCa), magnesium (Mg), phosphate (P) and vitamin D [25(OH)D3)] concentrations in patients and control samples. We also planned to compare indirectly measured ucOC concentrations using the binding properties of OC, with BS.

METHODS

Patient and Control Groups

The study was conducted at the Biochemistry Department of Ankara Training and Research Hospital, Ministry of Health, with the support of the Nephrology Clinic. The study was approved by the local Ankara Training and Research Hospital Ethics Committee (Decision no: 2736/2009) and conducted in accordance with the principles of the Declaration of Helsinki. All patients were informed of the study and signed written approvals.

The patient group included a total of 30 patients for CAPD and 24 for HD. The control group included 30 healthy subjects free from hypertension, diabetes mellitus, thyroid disease, liver and renal diseases, and any other known disease. Dialysis patients that had any bone diseases or broken bones and diabetes mellitus were excluded from the study. Demographic properties of the patients are shown in Table 1.

In patients with CKD, iPTH measurement is important in the diagnosis and follow-up of ROD. Simply, ROD was classificated by iPTH results. < 100 pg/mL and > 300 pg/mL iPTH concentrations were separated low-turnover bone disease and high-turnover bone disease, respectively.

Blood Samples

Blood was collected from the HD patients before and after dialysis, and from the CAPD patients and control group in the morning before meals. Blood samples were drawn into evacuated serum separator tubes containing clot activator (SST Vacutainer®, Becton Dickinson). All blood samples were centrifuged within 30 minutes, at 1500 g (rpm) for 10 minutes. Serum samples obtained were collected into Eppendorf tubes (Eppendorf® Safe-Lock microcentrifuge tubes, Turkey). The routine biochemistry analysis and iPTH were measured within the same day. 25(OH)D3, OC anducOC serum samples was stored in a deep freezer at -80 ºC until working day.

Table 1. Descriptive characteristics of patient and control groups

Variables	CAPD patients (n = 30)	HD Patients (n = 24)	Control (n = 30)
Gender (n, %)			
Female	13 (43.3%)	8 (33%)	12 (40%)
Male	17 (56.7%)	16 (67%)	
Age (years)(x±SD)	46.8 ± 13.3	49.2 ± 15.3	47.9 ± 14.5
BMI (kg/m²)(x±SD)	22.52 ± 3.6	22.58 ± 3.2	24.7 ± 3.7
KT/V		1.64 ± 0.31	
URR (Urea reduction rate), %		71.47 ± 7.29	
Duration of initiating dialysis (year)			
< 1year	5	7	-
1-5years	19	12	-
5-10years	6	5	-
Drugs used			
Anti-lipidemic (%)	11%	16%	-
Antihypertensive (%)	65%	38%	-
T3 agonist	9%	-	-
Folic acid derivative (%)	29%	79%	-
Iron drugs	30%	76%	-
Phosphate binding	45%	91%	-
Recombinant erythropoietin analogs	11%	78%	-
Anti-aggregate drugs	32%	1%	-
D vitamin analogs	95%	100%	

HD = hemodialysis, CAPD = continuous ambulatory peritoneal dialysis, BMI = body mass index

Laboratory tests

Analysis of serum glucose, urea, creatine, uric acid, ALP, B-ALP, Ca, Mg, and P were made with the original reagents in the Olympus AU 2700 (Mishima Olympus Co. Ltd. JAPAN). For B-ALP analysis the method described by Mass *et al*. [11] was used. ALP derived liver was measured in the supernatant after serum B-ALP was inhibited with urea. The obtained ALP values were subtracted from total ALP and B-ALP was determined. Serum iPTH was measured with the original reagents using the chemiluminescence enzyme immunoassay method in Advia Centaur (Siemens Diagnostic Products Corporation, LosAngeles, CA, USA). 25(OH)D3 was measured by DIA source 25OH-VIT. D3-RIA-CT reagent (DIA source IMMUNOassays S.A., Nivelles, Belgium) with methodin Gamma counter C12 NE 1600 (Bio DPC , USA). OCwas measured by ELISA method using the osteocalcin BioSource Host-EASIA Kit (BioSource Europe SA, Nivelles, Belgium) in the Triturus® EIA (GRIFOLS, Los Angeles, USA) analyzer.

Measurements of Serum Undercarboxylated Osteocalcin with Barium Sulphate

50 mg BS (Sigma Chemical Co., St. Louis, Mo.) were weighed on a precision scale. Each one was placed in separate Eppendorf microcentrifuge (Eppendorf® Safe-Lock microcentrifuge tubes, Turkey) tubes.

Serum samples stored at -80°C were dissolved by leaving the mat room temperature and mixing them using a vortex mixer. 50 mg of BS were mixed with 500 µl of serum sample. The mixtures were vortexed and then stirred at 4°C for 30 minutes in the mixer. The carboxyl OC was then precipitated with BS by

centrifugation at 2000g for 15 min at 4°C. The supernatants containing ucOC were transferred to another tube and these samples were run on the same day. ucOC concentrations were measured by the ELISA method using the OC BioSource Host-EASIA Kit (BioSource Europe SA, Nivelles, Belgium) in the Triturus® EIA (GRIFOLS, Los Angeles, USA) analyzer.

Two separate serum pools were constructed containing low and high ucOC concentrations for the inter-day and intra-study precision of the ucOC measurement methods. The total coefficient of variation (CV) was calculated for intra-assay (n = 21) and between-days (n = 25).

For the recovery work, the two pools were prepared at low and high ucOC concentrations for BS. The two pools were found to have1.87 ng/mL and 16.28 ng/mLucOC concentrations for the BS precipitation method.

% Recovery (R) was calculated by taking the average of recovery values obtained by mixing in ratio 1High (H)/1H, 1Low (L)/1H, 1H/2L, 2H/3L, 3L/2H, 1L/3H, and 1L/2H.

Bone Mineral Density Measurement

BMD measurements for the patient and control groups were done within a week after blood samples were received. BMD was measured by Dual Energy X-Ray Absorbtiometry (DEXA-hologic® QDR-4500W, Waltham, MA, USA). BMD is expressed as grams per square centimeter. All BMD measurements were performed in the supine position and obtained for the lumbar spine at the L1 through L4 level and for left hip measurement at the femur neck, trochanteric region, Wards triangle in the patients. Results for lumbar spinal BMD were expressed as the average of L1 through L4 values. The World Health Organization (WHO) definition was applied for osteoporosis (T-score ≤ −2.5 SD), osteopenia (T-score between −1.0 and −2.5 SD) and normal BMD (T-score ≥ −1.0 SD) according to the T score of the lumbar spines (1-4.) and/or left femur neck [12].

Dialysis Procedure

All patients underwent hemodialysis three times per week for a duration of four hours a day, using a synthetic low-flux hollow-fiber filter (polysulfone membrane) (surface area 1.25 m2), a mean blood flow speed of 200-300 mL/min, and a dialysate flow speed of approximately 500 mL/min during the HD procedure. For peritoneal dialysis patients, CAPD involves four or five dwells per day of 2-2.5 liters per dwell.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows v15.00 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean (X), standard deviation (SD), median (M), interquartile range (IQR), while the Distribution of the groups was evaluated using the Kolmogorov-Smirnov test. Biochemical variables were not normally distributed. The differences between the control, CAPD and HD groups compared by Kruskal Wallis test. Bonferroni posthoc test performed after Kruskal Wallis test. BMD variables were normally distributed. The comparison of BMD variables was conducted one-way ANOVA test. Comparison of analyties concentrations of serum collected before and after HD was made using the Wilcoxon sing test. Correlations between ucOC and all variables (biochemical and BMD) were assessed by non-parametric Spearman's rank correlation test. A p - value of < 0.05 was considered statistically significant. ROC analysis was performed to determine the renal osteodystrophy (ROD) discrimination of ucOC and other parameters. Cut off was made 300 pg/mL iPTH to identify as high turnover bone ROD for ROC analysis (n = 26).

RESULTS

Both ucOC concentrations in the CAPD group were significantly higher than in the control group (p < 0.001). There was no significant difference between the ucOC% values in the CAPD and control groups (p = 0.568, base on posthoc comparison) (Table 2).

The ucOC concentrations in the HD group were higher than in the control group and the difference between the two groups was statistically significant (p < 0.001). There was no significant difference between the HD and control groups in ucOC% values (p = 0.639, base on posthoc comparison). The values of ucOC and other parameters measured in the patient and control group are shown in Table 2. Box plot graphs of ucOC levels in HD, CAPD and control groups are shown in Fig. 1.

Pre-HD ucOC levels were higher than post-HD.

Table 2. Comparison of measured analytes of serum in the study groups

Variables	CAPD patients (n = 30)	Pre-HD patients (n = 24)	Post-HD patients (n = 24)	Control (n = 30)	*p* value*
ucOC, ng/mL	6.73 (5.19)	9.82 (11.99)	4.46 (3.57)	0.29 (0.21)	**< 0.001**[a,b,c,d]
ucOC %	15.36 (6.98)	16.79 (8.75)	20.7 (18.31)	18.6 (10.21)	0.265[c]
OC, ng/mL	46.64 (25.68)	53.94 (40.96)	35.56 (33.88)	2.3 (1.87)	**< 0.001**[a,b,c,]
B-ALP, U/L	70 (47.0)	82 (70.25)	89.5 (116.5)	46 (16)	**0.001**[a,b,c]
ALP, U/L	102 (34)	98 (82.5)	105.0 (128.5)	65 (16)	**< 0.001**[a,b,c]
25(OH)D, ng/mL	18.0 (11.8)	28.25 (18.50)		28.19 (23.40)	0.598[a]
iPTH, pg/mL	328.1 (225.1)	266.5 (230.0)		50.50 (8.10)	**< 0.001**[a,b]
Ca, mg/dL	9.08 (1.00)	8.94 (1.03)	10.37 (1.38)	9.40 (0.50)	**< 0.001**[a,b]
iCa, mmol/L	0.9 6 (0.28)	0.93 (0.29)	1.11 (0.10)	1.03 (0.11)	0.160[c]
P, mg/dL	4.53 (1.31)	4.48 (2.40)	2.75 (1.25)	3.01 (0.60)	**< 0.001**[a,b,c]
Ca × P (mg2/dl2)					
Mg, mmol/L	1.0 (0.1)	1.05 (0.10)	0.80 (0.08)	0.81 (0.10)	**< 0.001**[a,b,c]

Values are presented as median (inter quartile range). *The differences between the control, CAPD and HD groups compared by Kruskal Wallis test. [a]Comparison between control and CAPD, [b]Comparison between control and HD, [c]Comparison between Pre-HD and Post- HD, [d]Comparison between Pre-HD and CAPD. The same letters (a, b) indicate significant differences between groups base on Bonferroni posthoc comparison. *p* - value < 0.05 is statistically significant. ucOC = undercarboxylated osteocalcin, HD = hemodialysis, CAPD = continuous ambulatory peritoneal dialysis, OC = osteocalcin, ALP = alkaline phosphatase, B-ALP = bone specific alkaline phosphatase, iPTH = intact parathyroid hormone, Ca = calcium, *P* = phosphate, Mg = magnesium

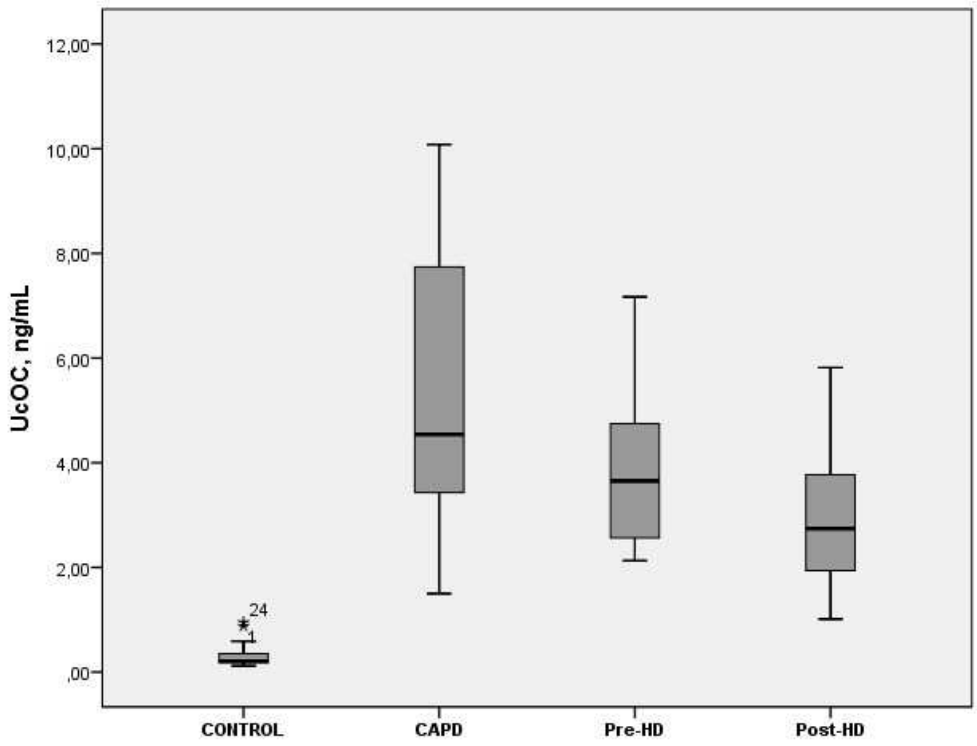

Fig. 1. ucOC levels in control, CAPD, pre-HD and post-HD groups. Box, inter quartile range (IQR): between 25th and 75th percentiles, horizontal line: median (M)

Table 3. The correlation coefficients between ucOC and biochemical variables and BMD values in the study groups

	CAPD patients (n = 30)	HD Patients (n = 24)	Control (n = 30)	All groups
Variables	**ucOC**	**ucOC**	**ucOC**	**ucOC**
ucOC, ng/mL	1.000*,#	1.000*,#	1.00	1.000*,#
OC, ng/mL	0.781*	0.831*,#	0.642	0.828*,#
B-ALP, U/L	0.152	0.278	0.280	.456*
ALP, U/L	0.181	0.310	0.206	0.469
25(OH)D, ng/mL	-0.181	-0.027	-0.206	-0579*
iPTH, pg/mL	0.059	0.600*	0.045	0.691*
Ca, mg/dL	-0.145	-0.200	-0.083	-0.148
iCa, mmol/L	-0.186	-0.29	-0.174	-0.043
P, mg/dL	0.232	0.005	0.069	0.348
Mg, mmol/L	0.215	0.115	0.203	0.492
L1-L4, g/cm2	-0.168	-0.241	-0.176	-0.115
FemurTotal, g/cm2	-0.149	-0.104	-0.367	-0.455*

*Indicates statistically significant correlation ($p < 0.05$), #Indicates statistically a strong significant correlation. BMD = bone mineral density, ucOC = undercarboxylated osteocalcin, HD = hemodialysis, CAPD = continuous ambulatory peritoneal dialysis, OC = osteocalcin, ALP = alkaline phosphatase, B-ALP = bone specific alkaline phosphatase, iPTH = intact parathyroid hormone, Ca = calcium, P = phosphate, Mg = magnesium, L = Lumbar

This difference was statistically significant ($p< 0.005$). Although the %UcOC levels were slightly higher in the pre-DH, there was no significant difference between the two groups.

There is significant strong correlation between ucOC and ALP, B-ALP and iPTH concentrations when all groups were combined. Table 3 are shown the correlations among ucOC and other biochemical and

Table 4. Comparison of BMD values in the study groups.

BMD (g/cm2)	CAPD Patients (n = 30)	HD Patients (n = 24)	Control (n = 30)	*P* value*
L1	0.870 ± 0.16	0.781 ± 0.224	1.02 ± 0.205	**< 0.001**[a,b]
L2	0.896 ± 0.237	0.844 ± 0.216	1.087 ± 0.204	**< 0.001**[a,b]
L3	0.948 ± 0.218	0.867 ± 0.245	1.121 ± 0.202	**< 0.001**[a,b]
L4	0.965 ± 0.192	0.877 ± 0.214	1.125 ± 0.196	**< 0.001**[a,b]
L1-L4	0.933 ± 0.174	0.846 ± 0.212	1.106 ± 0.215	**< 0.001**[a,b]
Femur neck (g/cm^2)	0.734 ± 0.118	0.646 ± 0.116	0.919 ± 0.152	**< 0.001**[a,b,c]
Trochanteric region	0.597 ± 0.119	0.518 ± 0.137	0.774 ± 0.156	**< 0.001**[a,b]
Wards Triangle (g/cm^2)	0.651 ± 0.133	0.535 ± 0.203	0.738 ± 0.146	**< 0.001**[a,b]
Femur Total	0.835 ± 0.136	0.709 ± 0.177	0.989 ± 0.159	**< 0.001**[a,b]

Values are presented as mean±standart deviation. *one- way ANOVA test [a]Comparison between control and CAPD, [b]Comparison between control and HD, [c]Comparison between Pre-HD and CAPD The same letters (a,b) indicate significant differences between groups base on Scheffe multiple comparison. *p*-value < 0.05 is statistically significant. BMD = bone mineral density, L = Lumbar

Table 5. AUC values of the variables in determining high-turnover ROD according to iPTH (> 300 pg/mL) results

Variables	AUC	*p value*	Asymptotic 95% Confidence Interval	
			Lower bound	Upper bound
ucOC	0.869	**< 0.001**	0.785	0.953
ucOC%	< 0.5	0.060	0.299	0.575
OC	0.875	**0.001**	0.795	0.956
B-ALP	0.783	**0.001**	0.669	0.897
ALP	0.815	**0.001**	0.702	0.927
25(OH)D	< 0.5	0.771	0.099	0.332
L1-L4	< 0.5	0.251	0.344	0.616
FemurTotal	< 0.5	0.286	0.212	0.474

AUC = Area under curve, ucOC = undercarboxylated osteocalcin, OC = osteocalcin, ALP = alkaline phosphatase, B-ALP = bone specific alkaline phosphatase, ROD = renal osteodystrophy, iPTH = intact parathyroid hormone

BMD variables.

When compared to the control groups, BMD values were found to be statistically and significantly-higher than in both the HD andCAPD groups. The BMD values are shown in Table 4.

Patients were classified according to iPTH concentrations (n = 84) to identify high turnover ROD. Patients with iPTH > 300 pg/mL were identified as high turnover bone ROD (n = 26). Cut off was made 300 pg/mL iPTH for ROC analysis. The area under curve (AUC) values of the ROC analysis of the variables is shown in Table 5.

Precision results in our study were as follows: variation coefficients (CV) of intra- assays for ucOC were 9.1% for 1.86 ng/mL and 5.11% for 16.13 ng/mL; between-days for CVwere 10.32% for 1.86 ng/mL and 5.16% for 16.13 ng/mL. The average %R was 94% for BS. The % recovery values are shown in Table 6.

DISCUSSION

In our study, we aimed to determine the relationship between serum ucOC concentrations and renal bone turnovers in hemodialysis and peritoneal dialysis patients. It is also comparable to indirectly measured ucOC concentrations by taking advantage of the BS and HA binding properties of OC. In our study, it was determined that uCOC concentrations were high in pa-

Table 6. Recovery (%) values of ucOC

	Expected value (ng/mL)	Measured value (ng/mL)	R (%)
	ucOC	ucOC	ucOC
1H/1H	16.28	15.07	92
2H/1L	11.75	12.01	114
3H2L	10.49	9.08	86
1H/1L	9.07	8.19	90
2H/3L	7.03	6.19	84
1H/2L	6.60	7.19	108
1L/1L	1.87	1.67	89
Total R%			94

L = Low, H = High, ucOC = undercarboxylated osteocalcin

tients with CKD than those in the healthy control groups. Also, the ucOC concentrations in the HD group were higher than in the CAPD group. ucOC showed a good correlation with other bone formation markers ALP, B-ALP and iPTH. When iPTH with a value > 300 pg/mL was taken as a cut-off, ucOC concentrations for determining high-turnover ROD had a better value than other measured bone markers.

The relationship between ucOC and patients with CKD is not fully understood. In a study carried out by Kohmeier *et al*. [13], the role of ucOC in bone metabolism, the relationship between ucOCand vitamin K, the old fracture bone story, and the risk of bone fracture was investigated in patients with renal failure. In the study, the relation between bone fracture risk and high hyperparathyroidism prevalence with increased ucOC concentrations due to vitamin K deficiency was shown in HD patients. In a study carried out by Nagata *et al*. [14], serum ucOC was found to be significantly lower in pre-dialysis patients with chronic kidney disease (CKD) than in HD. In their study, there are significant correlations between ucOC and eGFR levels in pre-dialysis CKD patients [14]. In a the study carried out by Kuzniewski *et al*. [15], the serum ucOC concentrations in HD patients were significantly higher than in healthy subjects. These studies showed significant correlation between ucOC and iPTH. Our study was consistent with the results of these studies. In our study, the serum ucOC concentration was higher in the HD group than in the healthy control group. There was also a significant correlation between ucOC and OC, B-ALP and ALP concentrations in the HD group. When all study groups were combined, there was significant correlation between ucOC and iPTH concentrations. Increasing iPTH concentrations in patients with CKD may have a positive effect on ucOC concentrations. Or conversely, ucOC elevation may be contributing to PTH elevation.

When we investigated ucOC concentrations in a CAPD patients group, the subclinical vitamin K deficiency and resulting changes in ucOC concentrations due to K vitamin status was studied [16]. In their study, the cut off for ucOC% ratio was described to be > 20% in ROC analysis for determine high turnover ROD according for iPTH (> 300 pg/mL) concentrations. This study showed positive correlation between phosphate, iPTH and ucOC%. In another in a study, theucOC/OC ratio was significantly higher in HD than in pre-dialysis patients with CKD [14]. In our study there wasn't a significantly different ucOC% when all the groups were compared.

There are many factors thatcan affect bone metabolism in patients with CKD. High PTH concentrations, hypocalcemia, hyperphosphatemia, low vitamin D and many uremic toxins affect bone formation and destruction. There is therefore a marked increase in the markers of bone formation and destruction. In our study, ucOC concentration was high in patient groups. However, the lack of statistical difference between ucOC% values suggests that not only UCOC but also OC concentrations are increased in HD and CAPD patients.

In our study, we measured ucOC before and after HD to investigate the effect of dialysis process on ucOC. Pre-HD ucOC levels were higher than post-HD. This difference was statistically significant ($p < 0.005$). Although the %ucOC levels were slightly higher in the pre-DH, there was no significant difference between the two groups. According to this result, there is a decrease in ucOC concentrations due to the dialysis procedure. There is no information on the effect of dialysis in the literature search. Our prediction may be loss of ucOC or an increase in OC fragment due to dialysis.

OC is normally a molecule that undergoes rapid glomerular filtration. Increase in OC concentration is expected in renal failure. In uremic patients, osteoblastic activity is increased due to hyperparathyroidism, and consequently, OC is increased. It is indicated that different fragments of osteocalcin are released from bone tissue in renal failure [17]. Furthermore, different OC fragments occur due to proteolytic degradation of the OC molecule in the plasma. In CRF patients, 26% of total OC has been shown to be intact OC. The remaining 74% are reported to be composed of N-terminal, mid-region, mid-region C-terminal and C-terminal regions, which are mainly OC fragments. In the measurement of osteocalcin, these fragments may also contribute to high outcome [18]. In addition, the epitopes used in antibody production for OC measurements are important. In our study, the OC reagent used for detecting intact OC. This reagent used develops monoclonal antibodies against different epitopes of the molecule. The regions of these epitopes were not specified in the prospectus of the OC reagent.Thus, the ELISA reagent used for OC may have been measuring fragments that were outside the "intact" mole-

cule in patients with CKD. This explains why ucOC% does not differ between groups. If the different fragments of OC are measured, the increase in ucOC in the patient groups will not reflect the increase in ucOC%.

In patients with CKD, secondary hyperparathyroidism is associated with the development of ROD and iPTH measurement is important in the diagnosis and follow-up of ROD < 100 pg/mL and > 300 pg/mL iPTH concentrations suggest low-turnover bone diseaseand high-turnover bone disease, respectively [18]. In our study, iPTH concentrations were found to be > 300 pg/mL in 22 patients, 100-300 pg/mL in 22 patients and <100 pg/mL in 5 patients. When iPTH with a value > 300 pg/mL was taken as a cut-off, ucOC concentrations when determining high-turnover ROD according to PTH results had a better value than other measured bone markers. However, ROD is the gold standard of bone biopsy in diagnosis and typing. Therefore, evaluation based on bone biopsy is necessary. There is insufficient information in literature to determine the relationship between ROD and ucOC, which is the basis of bone biopsy. Therefore, further work is needed to determine the relationship between ROD and ucOC.

Relationship between BMD values and bone markers in CKD

DEXA is a cheap, rapid and non-invasive technique for determining osteopenia. Although the value of BMD is low in determining the ROD type, it is used to show the bone mineral status of patients with CKD. It is known that kidney disease is a well-established risk factor for many changes in bone mineral metabolism and development of osteoporosis [19]. In our study, the prevalence of osteopenia and osteoporosis in the CKD subjects was 73 % and 20%, respectively. In a study by Rix *et al*. [20], BMD and biochemical bone markers were measured in patients with CKD. In this study, the BMD values of the patient group were found to be significantly lower than in the control group. In our study, the BMD values of CKD patients were statistically significantly lower compared to the control group. There is no study showing the relationship between BMD and ucOC concentration in patients with CKD. In other studies [22-24], there was a negative correlation between ucOC concentration and BMD. Similar to these studies in our study, a strong negative correlation was found between ucOC concentrations and BMD values in all patients and control groups.

CONCLUSION

ucOC concentrations in the CKD group were higher than those in the healthy control groups. Also, the ucOC concentrations in the HD group were higher than in the CAPD group. HD affects ucOC concentrations. ucOC% levels, unexpectedly, did not differ between groups. This may be due to the increased number of OC fragments in the serum of the CKD patients. ucOC showed a good correlation with other bone formation markers ALP, B-ALP and iPTH. This suggests that ucOC may be a good bone marker in CRF. ucOC also showed a good discrimination in high and low alternating ROD groups compared to iPTH cut-off concentrations.

Authors' Contribution

Study Conception: MA, DY; Study Design: MA, DY; Supervision: MA, VF, DY; Funding: MA, GS, DY; Materials: MA, VF, AA, MD, DY; Data Collection and/or Processing: MA, VF, AA, MD; Statistical Analysis and/or Data Interpretation: MA, MFA, DY; Literature Review: MA, GS, MD, DY; Manuscript Preparation: MA, MFA and Critical Review: MA, DY.

Conflict of interest

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Does the use of the dominant hand affect the direction of sinus extension to orient towards the right and left in pilonidal disease?

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ABSTRACT

Objectives: The etiology of pilonidal sinus disease is still controversial. Acquired theory in its etiology has become more popular nowadays. The aim of this study was to investigate the effects of dominant hand use on sinus features and sinus direction.

Methods: Eight hundred and sixty-five patients with diagnosis of primer pilonidal sinus disease were included. Data on patients' ages, BMI, over-sitting histories, duration of disease, dominant hand use histories, the condition of their sinuses at the time of presentation, the number of sinus openings, sinus directions, and sinus extension directions were collected. Relationship was evaluated between dominant hand use and sinus direction or sinus extension direction.

Results: There was no statistically significant difference between the patients' ages, sexes, BMI figures, the durations of disease and over- sitting history and dominant hand use. While the sinus directions of patients who had shorter duration of disease were towards the midline, it was seen that as the duration of disease increased the sinus extensions were oriented any side ($p = 0.01$). There was, however, a significant relationship between the sinus extension direction and dominant hand use. It was observed that the sinus extension direction of the patients who dominantly used their right hands was towards the left, while the sinus extension direction of the patients with dominant left hands was towards the right ($p = 0.04$, RR:2.05).

Conclusions: The fact that sinus extension directions can change against factors affecting body positions proves to be another factor which shows that pilonidal sinus disease is an acquired disease.

Keywords: Dominant hand, acquired theory, pilonidal disease, sinus direction

Pilonidal sinus disease (PSD), a chronic inflammation affecting the skin on the intergluteal cleft and the posterior of the anus, is one of the most common diseases in surgical practice. It had been previously suggested that the disease was congenital as it led to the entrapment of hair follicles in the sacrococcygeal area due to fusion failure on the dorsal midline. However, recent studies have been strongly supporting an acquired etiology [1]. According to Bascom, hair follicles in the gluteal cleft get infected by keratin leading to local infection and abscess formation, and their local suction force causes the hair to enter the infected pit and settle in the abscess cavity [2]. On the other hand, Karydakis [3] argues that it brings the disease

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about by loose hair penetrating the normal tissue which leads to foreign body reaction followed by additional hair inserting into the subcutaneous tissue from the secondary openings.

It has published an ample number of studies on the factors that played a role in its etiology as it is regarded to be an acquired disease today. The results of these studies have revealed many cofactors including body weight, sweating, repeated exposure to trauma (e.g., truck drivers, over-sitting history), body hygiene, hair type, and right sacrococcygeal angle might have contributed to this disease [4, 5]. However, over-sitting history is the most important cofactor among its because of loose hair penetrating the normal tissue and repeated exposure to trauma [6-8]. Although many studies have been conducted to find out the factors that caused PSD, there has been no study in literature to determine the factors affecting sinus features.

Individuals use their right or left hands according to the dominant side in their brains. We have thought that the gluteal area is prone to positioning according to the surface on which one sits based on the dominant hand, especially in individuals who carry out desk jobs by sitting as clinical observation. Moreover, we observed that sinus abscess openings are more frequently on the left side of gluteal area in the crystallized phenol treatments we have been applying for about 20 years. Therefore, we hypothesized that it can be suggested that individuals tilt their gluteal areas towards the dominant hand side causing the abscess to incline towards that direction because the pressure on the other side is lower. The aim of this study was to investigate the effects of dominant hand use on sinus direction and sinus extension direction, thereby, to contribute to the acquired theory.

METHODS

The study was conducted in accordance with the Declaration of Helsinki of the World Medical Association. Ethics committee approval numbered 2018/015 was obtained by the Ethic Committee of Karatay University. It made an informed consent form to all patients before procedure. The data of 1,089 patients, who had presented to Konya Training and Research Hospital's General Surgery Clinic because of PSD between January 2005 and February 2015, were prospectively collected, and retrospectively analyzed. A total of 224 patients were excluded from the study including 160 postoperative recurrence patients and 64 patients whose data on dominant hand use were available but data on sinus direction were unavailable. Eight hundred and sixty-five (79.4%) patients were included in the study. Data on patients' ages, body mass index (BMI, kg/m^2), working or travel with prolonged sitting histories (over-sitting histories), duration of disease, dominant hand use histories, the condition of their sinuses at the time of presentation, the number of sinus openings, sinus directions, and sinus extension directions were collected.

Demographic Features of the Patients

Body mass index of the patients were calculated as kg/m^2. The patients were classified according to whether they had an over-sitting history in daily life because of their professions. Sitting anamneses of those who spent at least 6 hours of their working or travelling sitting because of their professions were regarded to be positive. Duration of the disease (month) was calculated as the time from the first onset of the disease to the presentation time. The patients' hands that they used to write were regarded to be their dominant hands.

Sinus Features

The sinus features of the patients at the time of presentation were evaluated according to be chronic PSD or acute PSD with abscess. If patients had sinus openings supporting abscess like drained abscess opening and exerting purulent fluid in the sacrococcygeal area at the time of presentation, their cases were regarded to be pilonidal sinus with acute abscess. The patients' number of primary openings and secondary openings were recorded individually. Moreover, primary and secondary opening directions were classified into 4 groups as cephalad, caudal, sacral, and multiple. Sinus extension directions were classified according to the extension direction of the sinus as right, left, and the midline when the patients were laid down in the prone position (Table 1). However, since we aimed to examine the sinus extension direction in our study, midline direction was neglected in the analyzes.

Statistical Analysis

Mean, standard deviation, the lowest and the high-

Table 1. The classification of sinus directions and sinus extension directions

Sinus directions	
Cephalad	Upward sinus extension
Caudal	Downward sinus extension
Sacral	Sinus deepening towards the sacrum not towards the cephalad or the caudal
Multiple	Cases in which the sinus incorporates more than one of the above-mentioned localizations
Sinus extension directions	
Right	Sinus extension extending towards the right lateral to midline or secondary openings located on the right lateral to midline
Left	Sinus extension extending towards the left lateral to midline or secondary openings located on the left side
Midline	Sinus extension or secondary openings on the midline like pores in the natal cleft

est values, median, frequency, and ratio figures were used in the descriptive statistical analyses of the collected data. The distribution of the variables was measured with the Kolmogorov-Smirnov test. The Mann-Whitney U test was used for the analyses of quantitative independent data. Chi-square Test was used for the analyses of qualitative independent data, while Fischer's Exact Test was conducted when the conditions of the Chi-square Test were not met. Relative risk (RR) and Confidence Interval (CI) was calculated for risk ratio of dominant hand use. SPSS 22.0 software was used in the analyses.

RESULTS

The mean age of the patients was 26 ± 8.2 (12-67) years. Seven hundred and forty-one of the patients were males (85.7%). The mean BMI was 26.3± 3.9 (13.9-44.3). The median duration of disease was 12 (0-240) months. Five hundred and six (58.5%) patients had over-sitting anamneses. Eight hundred and twelve (93.8%) of the patients covered by the study were right-hand dominant, while 53 (6.2%) were left-hand dominant.

There was no statistically significant difference

Table 2. Distribution of demographic data according to dominant hand use of patients

	Right Hand		**Left Hand**		***p value***
	Mean ± SD/ N-%	**Median**	**Mean ± SD/ N-%**	**Median**	
Age	26.1 ± 8.3	25.0	24.2 ± 7.3	22.0	0.057[m]
Sex					
Male	696 (85.7%)		45 (84.9%)		0.871[X²]
Female	116 (14.3%)		8 (15.1%)		
Height (cm)	174.1 ± 8.0	175.0	175.2 ± 8.3	174.0	0.611[m]
Weight (kg)	80.0 ± 14.1	80.0	80.2 ± 15.9	78.0	0.646[m]
BMI	26.3 ± 3.9	26.0	26.0 ± 4.0	25.2	0.282[m]
Duration of disease complaint (Month)	21.3 ± 32.5	12.0	21.9 ± 33.3	12.0	0.658[m]
Over-sitting History					
None	342 (42.1%)		17 (32.1%)		0.151[x²]
Yes	470 (57.,9%)		36 (67.9%)		
Total	812 (100.0%)		53 (100.0%)		

[m] Mann-whitney u test / [X²] Chi-square Test

between the patients' ages, sexes, BMI figures, the durations of disease complaint, over-sitting history, and dominant hand use (Table 2). Physical examination at the time of first presentation revealed that 757 (87.5%) of the patients had chronic, while 108 (12.5%) had acute PSD.

It showed the sinus extensions and sinus directions extensions in Table 3. The sinus directions extended towards the right side in 139 (16.1%) patients, towards the left side in 198 (22.9%) patients, and towards the midline in 528 (61.0%) patients (Table 3).When the sinus extension direction was grouped as midline and other extension directions (left and right direction), the average duration of disease was 15.63 ± 32.85 in the midline group, 23.96 ± 32.01 months in the other directions group, and duration of disease was significantly shorter in the midline group than the other directions ($p = 0.001$).

It is shown that evaluation of sinus characteristics according to dominant hand use in Table 3. We found no statistically significant difference in the number of primary openings and the number of secondary openings according to dominant hand use ($p = 0.304$ and p = 0.507, respectively). We found no relationship between acute presentation and dominant hand use either ($p = 0.488$). There was no relationship between sinus directions and dominant hand use as well ($p = 0.628$).

There was, however, a significant relationship between the sinus extension direction and dominant hand use. It was observed that the sinus extension direction of the patients who dominantly used their right hands was towards the left, while the sinus extension direction of the patients with dominant left hands was towards the right ($p = 0.04$, relative risk is 2.05 [%95 CI 0.97-4.30] (Table 3).

DISCUSSION

Congenital and acquired theories have been still argued in the pathogenesis of PSD [9-11]. During the period beginning with the description of PSD until the last quarter of the 20th century, the idea that the congenital theory played a role in its etiology was dominant. However, it has been recently suggested that PSD is an acquired disease rather than a congenital one. This idea has been supported by various observations like it was formed in different areas of the body with skin folding such as the axilla, umbilicus, the penis and fingers of barbers; it was also seen in adults, and the recurrence seen in the related tissue despite total excision [12-14]. In this study, we aimed to evaluate a hypothesis that we observed based on our clinical experience which we believe will contribute to the

Table 3. Evaluation of sinus characteristics according to dominant hand use

	Right Hand		Left Hand		*p value*
	Mean±SD/ N-%	Median	Mean±SD/ N-%	Median	
Number of primer opening	2.1 ± 1.6	2.0	2.3 ± 1.6	2.0	0.304[m]
Number of seconder opening	0.5 ± 0.7	0.0	0.5 ± 0.8	0.0	0.507[m]
Sinus presentation					
Chronic	709 (87.3%)		48 (90.6%)		0.488[x²]
Acute	103 (12.7%)		5 (9.4%)		
Sinus Direction					
Cephalad	687 (93.9%)		45 (6.1%)		
Caudal	47 (96.0%)		2 (4.0%)		0.628[x²]
Sacral	35 (89.7%)		4 (10.3%)		
Multipl	42 (95.5%)		2 (4.5%)		
Direction of sinus extention					
Right	127 (91.4%)		12 (8.6%)		**0.040**[x²]
Left	193 (97.5%)		5 (2.5%)		

[m] Mann-whitney u test / [X²] Chi-Square test

acquired theory with a unique perspective.

According to acquired theory, it is known that however a lot of factors affecting etiology (local trauma, obesity, family history, and over-sitting history etc.) the major cause of the disease was the penetration of loose hair in both theories [15-17]. Loose hairs get chronic inflammation to enter the vulnerable skin because of recurrent trauma [18]. The sinus formed is in the midline in the first stage. However, sinus moves forward because of reasons we do not know. Although PSD is frequently seen in cephalad direction after formation, it may be caudal, sacral, and rarely in multiple directions in some patients. Also, sinus extension direction is towards the right or left gluteal region after recurrent abscess attacks. To date, it has connected no studies on the factors affecting sinus extension direction in the literature. This is the first study that performed on risk factors affecting sinus extension direction.

Undoubtedly, one of the most important factors accused in the etiology of PSD is over-sitting [6, 7, 19]. Bolandparvaz *et al*. [6] reported that the risk of PSD development increased in individuals who sat daily for 4 or more hours on average. Moreover, many studies have demonstrated the relationship between profession and the PSD disease [7, 20]. Kaymakcioglu *et al*. [7] in their study investigating the relationship between PSD and profession found that it was most seen in office staff (24.4%). The reason for this is the fact that over-sitting leads to trauma in the sacrococcygeal area.

We saw in our clinical observations that especially right-handed patients' sinus openings extended towards the left gluteal area. So, we developed a hypothesis like this: During sitting for a long time, especially writing, we are positioned on the gluteal region toward the dominant hand used. This situation leads to an increase in pressure in the gluteal area on that side while bringing about a decrease in pressure on the opposite side. According to the acquired theory, the increase in pressure causes the loose hair in the sacrococcygeal area to penetrate the skin [3, 21]. We believe that this is caused because the sinus abscess orients towards the opposite side where there is less pressure, and the sinus tract moves along that side since the pressure increases in the gluteal area on the dominant hand side during writing in office staff and students. Nevertheless, this situation is not only related to over-sitting because of one's profession because individuals lean towards the side of their dominant hands in their daily activities when sitting.

The results of our study revealed that the SPD initially developed on the midline in lots of patients (61%) but as the duration of disease complaint got longer sinus extension oriented towards the right or the left according to the dominant hand. The duration of disease of patients who sinus extension direction is midline was significantly shorter than patients with any sinus extension direction ($p = 0.01$). Therefore, we excluded patients who have midline sinus extension direction to analyze whether dominant hand use is a risk marker that affects the sinus extension direction in our study. The direction of sinus extension has already been more towards the left side because of the dominance of the right hand is widespread (Table 3). Also, we have revealed that the fact that patients with dominant hands had sinus extensions towards the opposite side was statistically significant ($p = 0.04$, RR= 2.05). In our study we have contributed to the acquired theory by explaining that the SP disease was an acquired disease and acquired factors changed the development of the disease.

CONCLUSION

Consequently, the fact that sinus extension dimensions can change against factors affecting body positions proves to be another factor which demonstrates that PSD is an acquired disease.

Authors' Contribution

Study Conception: SK, OD; Study Design: SK; Supervision: OD, RSK; Funding: SK, ET; Materials: SK, ET, RSK; Data Collection and/or Processing: SK, OD, ET; Statistical Analysis and/or Data Interpretation: OD, RSK; Literature Review: SK, OD; Manuscript Preparation: SK and Critical Review: OD, ET.

Conflict of interest

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Efficiency of the endovenous cyanoacrylate for the treatment of varicose veins using the Venablock™ system: a 24-month follow-up study of 116 patients

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ABSTRACT

Objectives: Dilation of superficial veins and valvular insufficiency cause the common condition, varicose veins (VVs) on the lower extremities. The treatment modalities for VVS include endovascular thermal ablation techniques using laser, steam and radiofrequency, surgery, foam sclerotherapy, which has various adverse effects. N-butyl cyanoacrylate (NBCA) is a relatively novel polymerizating agent that is used for the treatment of VVs. The aim of this study is to evaluate and present the 24 months outcomes results of endovenous NBCA treatment in 116 patients with VV.

Methods: This is a prospective study on 116 patients (71 females, 45 males), treated in a single-center between August 2017 and March 2019. NBCA administration (Venablock®, Invamed, Turkey) was carried out with local anesthesia under ultrasound guidance. All patients were scheduled for follow-up evaluation at 2 weeks, 3, 6, 9, 12, and 24 months. Clinical assessment, VCSS, and ultrasound were performed on patients in the follow-up visits.

Results: The mean follow-up period was 16.27 ± 5.62 months. The preoperative and postoperative VCSS values were 6.93 ± 2.60 and 2.40 ± 1.12, respectively ($p < 0.0001$). The patients with a greater GSV diameter experienced an unfavorable outcome following the NBCA procedure ($p < 0.001$). The overall complication rate was 12.9%. The complete occlusion was achieved in 101 (87.0%) patients.

Conclusions: The NBCA administration is a safe treatment method for the VVs, and provides a satisfactory occlusion ratio with improved outcomes.

Keywords: cyanoacrylate, varicose veins, chronic venous insufficiency, Venablock™

Varicose veins (VVs) of the lower extremities are common chronic conditions that occur due to the dilation of superficial veins and valvular insufficiency. It has been reported that every one out of three people suffers from this condition in varying degrees, and their life quality is impaired gradually [1]. The most affected vessels are great and small saphenous veins, and the symptoms vary in a great diversity from fatigue, pain, and swelling to skin ulcers on the frontal side of the tibial surface [2]. Older age, female gender, pregnancy, family history of deep venous thrombosis and venous diseases, longer durations of standing and walking, Caucasian origin are among the risk factors for VV development [3, 4].

Clinical-Etiologic-Anatomic-Pathophysiologic (CEAP) classification is employed for the worldwide

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classification of venous diseases since 1994 subcategorizing the severity of the VVs depending on numerous variables [5].

The treatment options for VVS include thermal ablation techniques with laser, steam and radiofrequency, surgery, foam sclerotherapy, which has their own disadvantages and complications including anesthesia requirement, embolism, rec]urrence, and hematoma formation [6, 7]. Recently, an endovenous mechanochemical treatment agent, n-butyl cyanoacrylate (NBCA) has been popularized with favorable outcomes and easy-to-use methodology for the treatment of VVs. When contacted with the anions in blood, the NBCA administered into the vessel rapidly polymerizes and provides the occlusion of the VVs by an inflammatory response resulting in fibrosis [8, 9].

In this study, we aimed to evaluate and present the short-term results of endovenous NBCA treatment in 116 patients with different levels of venous insufficiency and VV severity. The patients were compared in terms of the occlusion status (partial occlusion, complete occlusion, recanalization) following the NBCA treatment procedure.

METHODS

This prospective study involved a total of 116 patients (71 female, 45 male) who were treated for VVs with NBCA administration (Venablock®, Invamed, Turkey) in a single-center between August 2017 and March 2019.

Inclusion/exclusion Criteria

All patients were evaluated according to the CEAP classification. A Doppler ultrasonography in standing position was also performed. Patients >18 years of age with a CEAP class C2-C6 VVs, GSV diameter of >5.5mm, reflux current 2 sec or longer were included. Patients with a GSV diameter of <5.5mm or >13 mm, with chronic or acute thrombophlebitis, deep venous insufficiency or thrombosis, systemic infection, hypercoagulability state, previous history of phlebectomy or sclerotherapy were excluded. Pregnant and lactating patients and patients who preferred another treatment method were also excluded.

The Venous Clinical Severity Score (VCSS) was calculated for each patient before and after the procedure. For the evaluation of The VCSS, 0 corresponds to no significant venous disease and 30 is the worst available score [10].

Informed consent of all patients was obtained. The study was conducted in accordance with the Declaration of Helsinki.

Procedure

All procedures were carried out with local anesthesia under ultrasound guidance as previously described with the patient in the supine position. The administration of the Venablock® system technique has been previously described. Briefly, a 7F vascular sheath was inserted into the GSV, and a J-guide wire was inserted into the saphenofemoral junction through the sheath. The 4F micro delivery catheter was inserted and a total of 1.5-2 ml of NBCA was applied to the GSV segments with as increments of 0.2-0.3 ml. An immediate external compression was applied for 30 sec. After the procedure, a full-length elastic bandage was applied on the index leg and asked to unwrap after 24 hours. Patients were asked to walk for 15 minutes and discharged on the same day. All patients are scheduled for follow-up evaluation at 2 weeks, 3, 6, 9, 12, and 24 months. Clinical assessment, VCSS, and ultrasound were performed on patients in the follow-up visits.

Evaluation of the Patients

All patients who underwent VV treatment using NBCA were subgrouped into two main outcome groups depending on their occlusion status: Group 1: Partial occlusion and recanalization; Group 2: Complete occlusion. The occlusion status was evaluated in accordance with the Merchant *et al*. [12]. Complete occlusion (CO) was defined as the lack of flow in the treated segment of varicose GSV, whereas partial occlusion (PO) was defined as the ≤5 cm segment of flow in the treated vein. Recanalization was defined as >5 cm segment of flow in the treated vein.

Two comparative groups with different outcomes after NBCA treatment were compared in terms of weight, age, gender, diameter of the GSV, follow-up duration, the length and side of the affected vessel, a history of pake excision, CEAP class, degree of insufficiency, complications after the procedure, and VCSS before and after the procedure.

Statistical Analysis

The statistical evaluation of this study was performed using the statistical program SPSS v.11.5 (SPSS Inc, Chicago, IL). Descriptive statistics were given as mean±standard deviation for continuous variables and, as frequency and percentage for categorical variables. The student's t-test was performed if the normal distribution was provided, and Mann-Whitney U test if otherwise. When the relationship between the two qualitative variables was examined, Chi-square and Fisher's exact t-tests were used. The comparison of the variables before and after the procedure was performed using the paired samples t-test and Chi-square test. The time for occlusion was determined using a Kaplan-Meier survival curve. The statistical significance level was considered as < 0.05.

RESULTS

In our study setting, we compared the outcome characteristics of the patients who underwent NBCA treatment for the management of VVs during the follow-up. The mean follow-up was 16.27± 5.62 months. The CO was achieved in 101 (87.0%) patients. Twelve (10.3%) of the patients experienced an PO, whereas recanalization was present in three (2.7%) patients.

While patients were categorized into two subgroups depending on their occlusion status after the procedure, Group 1 consisted of 15 patients (8 females, 7 males) with an outcome of partial occlusion and recanalization after the procedure. Group 2 included 101 individuals (63 female, 38 male) with total occlusion of the affected vein. The comparison of variables between the groups was presented in Table 1.

The mean age of the patients was 52.67 ± 8.74 years with a mean weight of 74.00 ± 12.72 kg in the artial occlusion and recanalization group. The patients in the total occlusion group aged 47.85 ± 10.48 years with a mean weight of 71.59 ± 13.24 kg. The age and weight of the patients in two different outcome groups were not statistically significant ($p = 0.093$ and $p = 0.437$, respectively). The mean GSV diameter before the NBCA treatment was 8.71 ± 1.52 mm in the partial

Table 1. Comparison of the quantitative variables between the outcome groups depending on the occlusion status

Variables	Outcome Following NBCA Treatment				*p* value
	Partial occlusion & recanalization (n = 15)		Complete occlusion (n = 101)		
	Mean ± SD	Median (Min - Max)	Mean ± SD	Median (Min-Max)	
Weight (kg)	74.00 ± 12.72	73.00 (54.00-91.00)	71.59 ± 13.24	70.00 (51.00-105.00)	0.437
Age (years)	52.67 ± 8.74	53.00 (39.00-68.00)	47.85 ± 10.48	49.00 (26.00-71.00)	0.093
Diameter of the GSV (mm)	8.71 ± 1.52	8.00 (6.80-12.00)	7.26 ± 0.95	7.10 (5.50-11.00)	**< 0.001**
Follow-up duration (months)	14.73 ± 5.51	13.00 (8.00-23.00)	16.50 ± 5.63	17.00 (8.00-26.00)	0.221
Length of the affected segment on the vessel (cm)	39.13 ± 4.75	40.00 (29.00-49.00)	40.64 ± 4.90	40.00 (28.00-53.00)	0.341
Preop VCSS	6.93 ± 2.60	7.00 (3.00-14.00)	6.85 ± 2.82	6.00 (3.00-18.00)	0.623
Postop VCSS	2.40 ± 1.12	2.00 (0.00-5.00)	2.18 ± 1.04	2.00 (0.00-5.00)	0.453

NBCA = N-butyl cyanoacrylate, GSV = great saphenous vein, VCSS = The Venous Clinical Severity Score

Table 2. Comparison of the categorical variables between the outcome groups depending on the occlusion status.

Variables		Outcome Following NBCA Treatment				*p* value
		Partial occlusion & recanalization (n = 15)		Complete occlusion (n = 101)		
		N	%	N	%	
Gender	**Male**	7	46.7	38	37.6	0.502
	Female	8	53.3	63	62.4	
Side	**L**	10	66.7	59	58.4	0.544
	R	5	33.3	42	41.6	
Pake Excision	**No**	2	13.3	20	19.8	0.733
	Yes	13	86.7	81	80.2	
CEAP	**C2**	4	26.7	28	27.7	0.857
	C3	8	53.3	56	55.4	
	C4	3	20.0	11	10.9	
	C5	0	0.0	3	3.0	
	C6	0	0.0	3	3.0	
Complications	**None**	13	86.6	87	86.2	1.000
	Ecchymosis	1	6.7	7	6.9	
	Phlebitis	1	6.7	6	5.9	
	Hematoma	0	0.0	1	1.0	
Degree of the Insufficiency	**2 sec**	0	0.0	6	5.9	0.098
	3 sec	10	66.7	83	82.2	
	4 sec	5	33.3	12	11.9	

CEAP = Clinical-Etiologic-Anatomic-Pathophysiologic classification, NBCA = N-butyl cyanoacrylate

occlusion and recanalization group and 7.26 ± 0.95 mm in the complete occlusion group ($p < 0.001$). The mean length of the affected segment on the vessel was 39.13±4.75 for the partial occlusion and recanalization group and 40.64 ± 4.90 for the complete occlusion group ($p = 0.341$).

The preoperative and postoperative VCSS values were 6.93 ± 2.60 and 2.40 ± 1.12 for the partial occlusion and recanalization group, whereas, 6.85 ± 2.82 and 2.18 ± 1.04, respectively for the complete occlusion group ($p = 0.623$ and $p = 0.453$, respectively). The number of patients with different CEAP classes was not significantly different between the outcome groups ($p = 0.857$).

The gender, the side of the affected extremity, history of a pake excision and the degree of insufficiency did not differ between the groups ($p = 0.502$, $p = 0.544$, $p = 0.733$ and $p = 0.098$, respectively) (Table 2).

The complication rates were also compared between the groups. The overall complication rate was 12.9%. The most common complication was ecchymosis in eight (6.9%) patients, followed by phlebitis in seven (6.0%) and hematoma in one (0.9%) patient. While we evaluated patients overall, the mean VCSS was 6.86 ± 2.78 before the procedure, whereas it was 2.20 ± 1.05 following the NBCA application ($p < 0.0001$). The number of patients distributed in different CEAP score groups was significantly different before the procedure and at the end of the follow-up period ($p < 0.01$) (Table 3).

Kaplan-Meier curve presents the analysis results of the treatmenr with a statistical uncertainty of 95% confidence interval (CI) in dot plots (Fig. 1). The ratio

Table 3. Comparison of the variables before and after the NBCA treatment.

	Before the NBCA treatment (n = 116) Mean ± SD	After the NBCA treatment (n = 116) Mean ± SD	*p* value
VCSS	6.86 ± 2.78	2.20 ± 1.05	**< 0.0001**
CEAP (n)			
C1	0	101	
C2	32	5	**< 0.01**
C3	64	8	
C4	14	2	
C5	3	0	
C6	3	0	

VCSS = The Venous Clinical Severity Score, CEAP = Clinical-Etiologic-Anatomic-Pathophysiologic classification, NBCA = N-butyl cyanoacrylate

of cases with CO was 100% on the first nine months of the study period. At the end of the first year, 93.4% of the cases still had CO. At the end of the second year follow-up duration, 75.5% of the cases were with CO.

DISCUSSION

Vascular surgeons are in search of a method with high efficiency, which requires the absence or minimal amount of anesthesia and allows the patient to return to routine daily activities within a shorter amount of time. Recently, minimally invasive techniques have replaced the surgical procedures for the treatment of lower extremity VVS. Although techniques using radiofrequency or laser beam are used frequently, they still manifest complications and adverse reactions in a range from pain and swelling to the development of hematoma and ecchymosis [13, 14].

NBCA is a relatively novel agent in the management of VVs with high efficacy, minimum pain control and complication ratio, and a higher amount of patient satisfaction. As the use of NBCA increases in vascular practice worldwide, the number of newly developed NBCA-based products increase in the markets. Since the method does not use a thermally-induced closure, the risk of thermal injury and unfavorable cosmetic outcomes such as increased skin pigmentation are also out of concern. On the other hand, thermal ablation techniques were shown to be

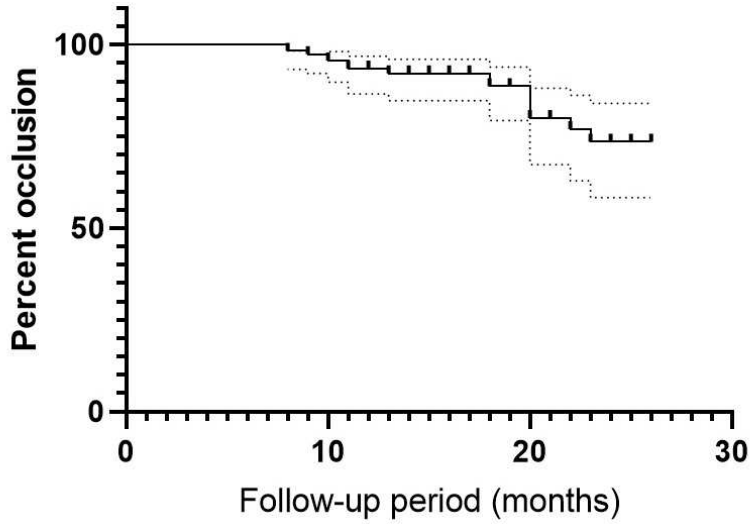

Fig. 1. The Kaplan-Meier curve analysis of occlusion rate of incompetent saphenous veins after NBCA treatment. The results were given within 95% CI. NBCA = N-butyl cyanoacrylate, CI = Confidence interval.

more traumatic and require tumescence analgesia, and require correct setting of the power and energy in terms of Watt and Joule.

This study followed up a total of 116 patients who underwent embolization with NBCA for the treatment of lower extremity VVs. In the study setting, we attempted to compare the demographics and post-procedural data between the patients with total, partial, and no evidence of occlusion.

We defined the CO as the absence of patency or recanalization in any treated segment of >5 cm in length as described earlier by Merchant *et al*. [12]. The CO was achieved in 87% of our patients within the 24 months of the follow-up period, whereas 10.3% patients had PO and 2.7% did not show evidence of occlusion. There are similar studies with varying follow-up times reporting a total occlusion between 92-96% with NBCA treatment. However, their sample size is relatively small compared to our sample size (23 and 77 vs. 116 patients). The follow-up period of these studies was 6-12 months, and we suggest that a longer follow-up period would result in a higher ratio of recurrence cases [15, 16]. Supporting this, several reports present a decline in the rate of patients with CO during the time, as the ratio of 100% reversed to 78.5% after one year [17]. We suggest that the type of the NBCA product, the characteristics of the patient, and the experience of the treating physician might have an important effect on the outcomes. Besides, Tang suggested that the distance of the catheter tip from the saphenofemoral junction (SFJ) is of concern for the prevention of adverse effects including incomplete occlusion and recurrence [16].

In our study group, the patients with a greater GSV diameter experienced an unfavorable outcome following the NBCA procedure. This might be a consequence of a decline in the efficiency of the procedure in patients with a greater GSV diameter. We suggest that, the incidence of a CO is decreased in this patient group.

In our study, we have also evaluated the clinical improvement in patients' conditions using the VCSS System. Although the VCSS did not differ between the favorable and unfavorable outcome groups, taken together, the scores significantly improved in the patient population following the procedure as an indicator of the procedur's efficiency. These data suggest that there might be additional factors contributing to the outcomes, and these factors should be evaluated before choosing the most appropriate option for an individual patient in the treatment of VVs.

Despite various adverse effects reported following the treatment with NBCA, the complications we experienced in our patients were ecchymosis in eight patients, phlebitis in seven patients, and hematoma in one patient. Our data is comparable to those of endovascular thermal ablation techniques and surgery, with a low ratio of complications which completely resolved in a short amount of time without decreasing the life quality of the patients. We also did not experience serious reactions including DVT and embolism, which are previously described with the use of thermal ablation methods. Possibly, some predictive markers such as homocysteine, lupus anticoagulant, high sensitive-CRP, D-dimer, fibrin-derived products should be used before the procedure, in order to define and exclude the patients with an increased risk of thrombotic events [18]. Furthermore, Tang *et al*. [19] reported an acellular foreign body reaction in the adventitia tissue suggesting that possible extravasation of the NBCA should be taken into consideration. In their series of VV patients, Acıpayam *et al*. [20] demostrated that a lower than 1 mL dose of NBCA was related to a fewer complication ratio and greater patient satisfaction at the end of the first month following the procedure. Thus, studies established with various dosing regimen of NBCA are required to consider the appropriate dosing for each individual in order to lower the complication rate and obtain a greater procedure efficiency.

Limitations

Our study has several limitations to discuss. First of all, we did not compare the CEAP classes during the follow-up period. Also, we used VCSS in the evaluation of postprocedural outcomes, other scoring techniques such as the Aberdeen Varicose Vein Questionnaire might yield an additional perspective.

CONCLUSION

In conclusion, the NBCA system provided a satisfactory occlusion ratio with improved outcomes and comparable results with the previous data in the literature. Of the patient group, only GSV diameter dif-

fered, whereas other study variables gender, weight, the side of the affected extremity, length of the GSV, VCSS before and after the procedure, implementation of a pake excision, CEAP classification, and the degree of insufficiency were shown to not affect the outcome following the NBCA administration. Thus, the NBCA administration is a safe approach in the treatment of VVs, and key safety measures should be considered as suggested by the guidelines.

Authors' Contribution

Study Conception: ACD; Study Design: ACD; Supervision: FK; Funding: ACD; Materials: ACD; Data Collection and/or Processing: ACD; Statistical Analysis and/or Data Interpretation: Eİ; Literature Review: Eİ, FK; Manuscript Preparation: Eİ and Critical Review: Eİ.

Conflict of interest

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

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Early postoperative results of on-pump coronary endarterectomy: is it still a controversy?

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ABSTRACT

Objectives: The coronary endarterectomy combined with coronary artery bypass grafting (CABG) is an useful but still controversial surgical technique in diffuse coronary artery disease. The aim of this study was to analyze the operative and early postoperative outcomes of the patients who underwent CABG with and without coronary endarterectomy.

Methods: This retrospective study included a total of 312 consequtive patients undergoing on-pump CABG from December 2018 to December 2020 in the Department of Cardiovascular Surgery, Bursa Yüksek İhtisas Training and Research Hospital. Patients were divided into 2 groups as those who underwent coronary endarterectomy combined with on-pump CABG (Group 1, n = 48) and those who underwent isolated on-pump CABG (Group 2, n = 264). Peroperative variables were obtained from our hospital's computerized database and retrospectively analyzed.

Results: Previous percutaneus coronary intervention rate and the number of patients with diabetes mellitus was significantly higher in the endarterectomy group. The demographics and characteristics of the patients were similar between the two groups. The median number of distal anastomoses was 4 (2-5) in Group 1 and 2 (1-5) in Group 2. Median cross-clamp duration and perfusion times in Group 1 were longer than Group 2 (82 min vs. 63 min; $p < 0.001$ and 120 min vs. 95 min; $p = 0.003$, respectively). A total of 54 coronary endarterectomy practices were performed on 48 patients, and the LAD artery (73%) was the most endarterectomized vessel. In Group 1, postoperative 24 hours high-sensitive troponin I levels were significantly higher than in Group 2 ($p < 0.001$). There was no significant difference between the groups in terms of operative mortality, low cardiac output rates and perioperative myocardial infarction rates. Postoperative atrial fibrillation was significantly higher in Group 1 ($p = 0.023$).

Conclusions: Although coronary endarterectomy is a complex procedure, in patients with diffuse coronary artery disease, it is an essential and sometimes mandotary method in order to achieve complete revacularization and can be performed safely with acceptable operative and early postoperative outcomes.

Keywords: Coronary artery disease, complete myocardial revascularization, coronary endarterectomy, postoperative period

Recently, with its less invasive nature and good results, percutaneous coronary interventions have become the treatment of option for coronary artery disease (CAD) even in patients affected by diffuse dis-

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ease in the presence of a low Syntax Score [1]. As a result, more complex patients with high comorbidity are now referred to coronary artery bypass grafting (CABG) surgery.

Principal aim of CABG is to provide complete revascularization of diseased coronary arteries because complete revascularization [2]. In addition, previous studies have shown that complete revascularization reduces the risk of perioperative myocardial infarction, in-hospital mortality, and relapse of late symptoms [3, 4].

Patients with diffuse calcific disease, long segment or sequential coronary lesions constitute a controversial and challenging group for surgical revascularization. It is essential for surgeons to have an effective for patients with diffuse severe calcific obstructive CAD [5, 6]. Despite initial negative results in the past decades [7], several recent publications have demonstreated that coronary endarterectomy combined with CABG is a useful and sometimes a mandatory surgical option [8].

The aim of this study was to compare the operative and early postoperative clinical results of patients who underwent CABG together with coronary endarterectomy or without coronary endarterectomy.

METHODS

This retrospective study was conducted between December 2018 and December 2020 at Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey. A total of 48 patients who underwent coronary endarterectomy combined with on-pump CABG (Group 1) and also 264 patients who underwent isolated on-pump CABG (Group 2) were analyzed. All cases included the study were operated by two surgeons and the same surgical team. The study was conducted in accordance with the Decleration of Helsinki Ethical Principles and Good Clinical Practices and ethics committee approval was obtained (Decision no. 2011-KAEK-25 2020/60-03, date: 24.06.2020).

Patients' variables were obtained from our hospital's computerized database. Data collection was based on hospital clinic records and intensive care data and observational records. Age, sex, body mass index (BMI), diabetes, hypertension, smoking history, hypercholesterolaemia, peripheral artery disease (PAD), preoperative left ventricular ejection fraction (LVEF) between two groups were compared. Cross-clamp times, perfusion times, number of bypass grafts used, left internal thoracic artery (LITA) use, defibrilation needs, intraaortic baloon pump (IABP) requirement, inotrope agent requirement, perioperative electrocardiogram changes, development of new atrial fibrillation, extubation times, intensive care unit (ICU) stay times, hospital discharge times were compared. Blood samples were drawn from each patient 1 day before the operation, 24 hours postoperatively to measure the myocardial biomarker, high sensitive troponin I (hsTnI). The patients with valvular heart diseases, emergency cardiac operations, those who had undergone additional cardiovascular operation were excluded from the study. All patients had continuous electrocardiographic monitoring at the ICU. Twelve-lead electrocardiographic recordings were performed preoperatively, postoperative first hour at ICU, daily for at least the first 3 postoperative days and at discharge day. LVEFs were measured and compared preoperatively and postoperatively by 2D echocardiography before discharge.

Surgical Technique

All the operations were performed under cardiopulmonary bypass (CPB) with mild hypothermia (30-32°C) after aortic cross-clamping and cardioplegic arrest. Cardiac arrest was provided with a single dose cold blood cardioplegia given from the aortic root antegradely. During CPB period, myocardial protection was provided with a half dose antegrade and a half dose retrograde cold blood cardioplegia given at every 20 minutes in all cases. Last dose of isothermal blood cardioplegia was given before removing the cross clamp.

Although the decision to apply coronary endarterectomy was considered as an option during preoperative coronary angiographic examination, the actual decision and choice of technique were based on intraoperative findings of the target coronary artery. If graft placement was not possible due to insufficient lumen diameter or diffuse thread-like appearance could be an indication for endarterectomy. Coronary endarterectomy can be performed by either through an open or closed technique [9]. In the closed technique, the endarterectomized plaque is pulled out from a smaller arteriotomy by gently applied steady traction

proximally and distally (Fig. 1). In all cases, closed technique is our primary option because the closed technique is shorter, simple and it requires a smaller anastomosis. Open coronary endarterectomy is performed when plaque extraction cannot be completed through a limited arteriotomy or when the plaque is broken, which provides sufficient exposure to remove the atherosclerotic core completely.

When we performed open endarterectomy technique in the right coronary and circumflex artery, we used the saphenous vein graft as an on-lay patch, and when we applied the closed technique saphenous vein graft was directly anastomosed to the arteriotomy. In the LAD artery, we have always preferred the open endarterectomy technique and we used the LITA as an on-lay patch graft. We applied LITA graft anastomosis on the saphenous vein patch in arteriotomies longer than 6 cm.

Postoperative Anticoagulation Protocol

Postoperatively, depending on the amount of drainage low-molecular-weight heparin (5,000 U/d) was initiated at the ICU, at 6th hour. After the patients were extubated, aspirin (100 mg/day) and clopidogrel (75 mg/day) were oraly administered together. Low-molecular-weight heparin (5,000 U/day) treatment was continued for one month, clopidogrel (75 mg/day) for one year and aspirin (150 mg/day) was recommended to continue for lifelong.

Statistical Analysis

Statistical analysis was performed with SPSS 21.0 (IBM Statistical Package or the Social Sciences Statistic Inc. version 21.0, Chicago, IL, USA). Normality distribution of data was assessed with Kolmogorov-Smirnov and Shapiro-Wilk tests. Student's t-test was used for normally distributed data (expressed as mean±standard deviation) and Mann Whitney U test was used for non-normally distributed data (expressed as median interquartile range). Nominal variables were expressed in frequency and percentage and Chi-Square test was used for analysis. A p value less than 0.05 was considered as statistically significant.

RESULTS

Data from the 48 (22%) patients who underwent coronary endarterectomy combined with on-pump CABG were evaluated as Group 1 (n = 48; 35 (72.9%) of them were males; median age 62 years (range: 42-81 years). The data from the 264 (78%) patients who underwent isolated consecutive on-pump CABG were evaluated as Group 2 (n = 264; 182 (69%) of them were males; median age 59 (range: 40-84 years). The data for these two groups were compared. Previous PCI and the number of patients with diabetes mellitus was significantly higher in the endarterectomy group. Except those there was no statistically significant difference between two groups in terms of demographic characteristics (Table 1).

Operative and postoperative clinical data are summarized in Table 2. The aortic cross-clamping times and perfusion times were significantly longer in Group

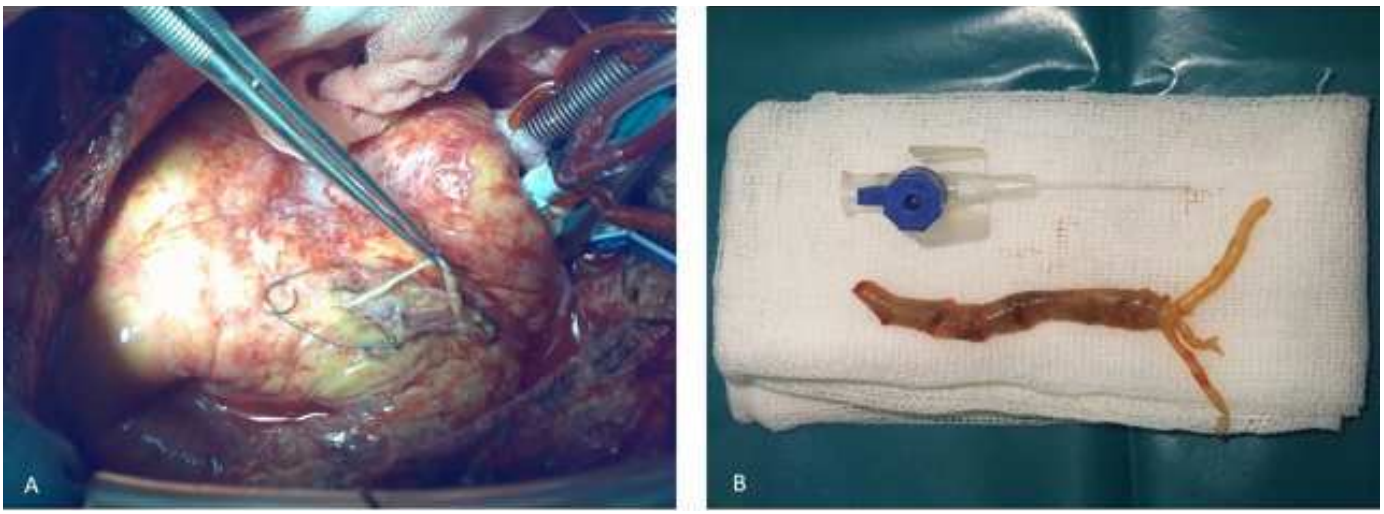

Fig. 1. (A) Intraoperative view of endarterectomy procedure. (B) The removed endarterectomy material.

Table 1. Demographic data and preoperative features of the patients

Variables	Group 1 (n = 48)	Group 2 (n = 264)	*p* value
Age(years), mean (range)	62 (42-81)	59 (40-84)	0.119
Male gender, n (%)	35 (72.9)	182 (69)	0.712
BMI (kg/m^2), mean (range)	27.9 (24-35)	28.3 (24-36)	0.196
Hypertension, n (%)	33 (68.7%)	175 (66.2%)	0.833
Previous PCI, n (%)	23 (47.9%)	74 (28%)	0.011
PAD, n (%)	13 (27%)	51 (19%)	0.421
Hiperlipidemia, n (%)	36 (75%)	175 (66.2%)	0.378
Diabetes mellitus, n (%)	18 (37.5%)	53 (20%)	0.014
COPD, n (%)	12 (25%)	44 (16.6%)	0.238
Smoking, n (%)	20 (41.6%)	77 (29.1%)	0.108
History of CVA, n (%)	3 (6%)	13 (4.9%)	0.978
Preoperative EF (%), mean (range)	50 (35-65)	50 (35-65)	0.778

Group 1 = CE combined with on-pump CABG, Group 2 = isolated on-pump CABG, BMI = body mass index, CABG = coronary artery bypass grafting, CE = coronary endarterectomy, CVA = cerebrovascular accident, COPD = chronic obstructive pulmonary disease, EF = ejection fraction, PAD = peripheral arterial disease, PCI = percutaneus coronary intervention

1 than in Group 2 (isolated CABG group) (82 min vs. 63 min; $p < 0.001$); (120 min vs. 95 min; $p = 0.003$) respectively. At the time of cross-clamp release more cases in Group 1 (39%) needed defibrillation compared with Group 2 (30%) but there was no significant difference ($p = 0.180$).

LITA use was similar between the groups. Coronary endarterectomy was applied to a total of 54 target coronary artery in 48 patients. Thirty-five patients had LAD endarterectomy, 15 patients had RCA/RPD endarterectomy, and 6 patients had multiple endarterectomies. The target vessel distribution and procedure types for which we applied CE were shown in Table 3.

Inotropic agent support was needed 25% in Group 1 and 19% in Group 2 at the time of weaning from CPB. Postoperative ejection fractions were not significantly different between the two study groups. We also found that postoperative cerebrovascular accident (CVA) rates (2% versus 1.5%), postoperative IABP need (8.3% versus 3%) was not significantly different. In Group 1, postoperative hsTnI levels were statisti-

Table 2. Operative variables of the patients

Variables	Group 1 (n = 48)	Group 2 (n = 264)	*p* value
Total perfusion time (min), median (range)	120 (85-175)	95 (80-164)	**0.003**
Cross-clamp time (min), median (range)	82 (60-140)	63 (50-110)	**< 0.001**
LITA use, n (%)	46 (95.8%)	255 (96.5%)	0.974
Inotropic support need, n (%)	12 (25%)	50 (19 %)	0.108
Intraaortic balon pump need, n (%)	4 (8.3%)	8 (3%)	0.177
Defibrilation, n (%)	19 (39%)	79 (30%)	0.180
Number of distal anastomoses, median (range)	4 (2-5)	2 (1-5)	0.154

Group 1 = CE combined with on-pump CABG, Group 2 = isolated on-pump CABG, CABG = coronary artery bypass grafting, CE = coronary endarterectomy, LITA = left internal thoracic artery

Table 3. Target vessels undergoing coronary endarterectomy

	n = 48
CE on LAD, n (%)	35 (73%)
CE on diogonal branches, n (%)	2 (4%)
CE on RCA/RPD, n (%)	15 (31%)
CE on OM, n (%)	2 (4%)
Multivessel CE, n (%)	6 (12%)
Open CE, n (%)	40 (74%)
Closed CE, n (%)	14 (26%)

CE = coronary endarterectomy, LAD = left anterior descending, OM = Obtuse marginal, RCA = right coronary artery, RPD: right posterior descending

cally significantly higher at 24 hours (p = < 0.001) postoperatively than in Group 2 (Table 4). Postoperative atrial fibrillation was signigicantly higher in Group 1 (27.1% vs 14) (p = 0.023).

DISCUSSION

Principal goal of CABG is to achieve complete revascularization because incomplete revascularization of the coronary arteries may lead to poor outcomes and high mortality rates after CABG [10]. Up to 25% of patients with extensive CAD cannot be safely and successfully treated with standard CABG. Therefore, the technique of coronary endarterectomy, which involves removal of the atherosclerotic core from the coronary artery lumen, can sometimes become risky but mandotary [11].

Coronary endarterectomy has been a controversial since its first application in 1957 by Bailey *et al*. [12]. In the 1990s, this method was not recommended in routine practice due to its high mortality and morbidity rates [13]. However, in recent years, the coronary endarterectomy procedure can be performed more successfully. This is the result of improved surgical techniques and surgical experience, improvements in cardiopulmonary bypass management, and better myocardial protection methods.

Shapira *et al*. [13] stated that, mortality and morbidity rates after CABG operations were similar in patients with coronary endarterectomy or without coronary endarterectomy. And also coronary endarterectomy was not an independent predictor of postoperative MI. Tiruvoipathy *et al*. [10] considered that the higher mortality rate of the CABG procedure with coronary endarterectomy compared to isolated

Table 4. Postoperative features and complications of the patients

Variables	Group 1 (n = 48)	Group 2 (n = 264)	*p* value
Chest tube drenaige (ml), median (range)	800 (400-1600)	750 (350-1400)	0.114
hsTnI (ng/L, 24th hours), median (range)	480 (400-1100)	250 (150-900)	**< 0.001**
Total ICU stay (days), median (range)	2 (2-18)	2 (2-10)	0.321
Total hospital stay (days), median (range)	9 (7-25)	7 (6-30)	0.228
Mortality, n (%)	2 (4.1%)	5 (1.8%)	0.328
LCOS, n (%)	3 (6,2%)	11 (4.1%)	0.214
Perioperative myocardial infarction, n (%)	2 (4.1%)	4 (1.5%)	0.124
Cerebrovascular accident, n (%)	1 (2%)	4 (1.5%)	1.000
Infection, n (%)	1 (2%)	4 (1.5%)	1.000
Reoperation due to bleeding, n (%)	2 (4.1%)	10 (3.7%)	0.432
Atrial fibrillation, n (%)	13 (27.1%)	37 (14%)	**0.023**
Respiratory failure, n (%)	2 (4.1%)	5 (1.8%)	0.124
Postoperative EF (%),median (range)	45(25-60)	45 (30-60)	0.694

Group 1 = CE combined with on-pump CABG, Group 2 = isolated on-pump CABG, CABG = coronary artery bypass grafting, CE = coronary endarterectomy, EF = ejection fraction, hsTnI = high-sensitive troponin I, ICU = Intensive care unit, LCOS = low cardiac output syndrome,

CABG was more associated with the patient's comorbidities such as age, renal failure and diabetes mellitus. Perioperative MI is another important point in patients who underwent CABG with coronary endarterectomy. The perioperative myocardial infarction rate ranges from 3% to 25% in the literature [14]. In a meta-analyses conducted by Wang *et al*. [15], they stated that CABG with coronary endarterectomy was significantly associated with 30-day mortality and higher rates of early term postoperative complications. However log-term survival was similar in CABG + coronary endarterectomy and isolated CABG patients. The authors stated that early poor results were due to the high risk profile of patients undergoing coronary endarterectomy [15].

In an another meta-analyses conducted by Soylu *et al*. [16], they reported that adjunctive CE was associated with increasing 30-day mortality, perioperative and postoperative myocardial infarction when compared with isolated CABG. The relatively high rate of postoperative MI (9.0%) in their study could have resulted from the inclusion of patients with an enzymatic definition of postoperative MI. In our study the operative mortality of patients undergoing coronary endarterectomy was 4.1%, which is superior to other clinical reports and 1.8% for the patients with isolated CABG. There was no significant difference in terms of mortality between two groups. The percentage of perioperative MI in our study was slightly higher in group 1, but it was not statistically significant (4.1% vs 1.5%; p = 0.124).

The combination of coronary endarterectomy with CABG prolongs aortic cross-clamping and CPB times compared to isolated CABG. As a result, this situation increases the risk of ischemia reperfusion injury and end-organ damage with worse outcomes in the early postoperative period [16]. In order to minimize myocardial ischemic damage, we used the retrograde cardioplegia method in addition to antegrade cardioplegia in all patients that we applied coronary endarterectomy. We think that retrograde cardioplegia method both provides more widespread cardioplegia distribution through the significantly developed collaterals and increases the success rate of the procedure by clearing debris in the distal coronary bed.

In the literature, LAD is the most common endarterectomized vessel (40%-83%) that feeds a significant part of the left heart and also is the most important target artery for complete revascularization [17]. Endarterectomy of the right coronary artery is performed more courageously due to the technical simplicity and a lower risk. In our study, 73% of the patients underwent LAD endarterectomy. We observed that RCA was the second common endarterectomied vessel with 31% in our study. In the literature, this ratio varies between 21.1% and 83% [14]. In our study, we determined that multiple coronary endarterectomies were performed simultaneously in 12.5% of the patients.

It is also controversial whether the open or closed coronary endarterectomy method is the optimal technique. The basic principle of coronary endarterectomy is the complete removal of the atherosclerotic core without leaving an obstructing plaque. In the closed technique, a shorter arteriotomy and thus a shorter anastomosis is performed, but it requires more experience. Distal and proximal embolism risk is higher since most of the procedure is performed under a closed area [18]. On the other hand, the open method is safer in terms of distal embolism since the complete cleaning of the atherosclerotic core is performed under direct vision [9]. The disadvantage of the open method is that the arteriotomy is longer, requiring a longer anastomosis and therefore a longer ischemic time.

In the study of Nishi *et al*. [19] comparing the open method with the closed method, the perioperative mortality rate (2.9% vs 6.8%) was found to be lower in patients who underwent open endarterectomy, although it was not significant. In addition, long-term results in terms of morbidity (85% vs 77%) were significantly better in the open endarterectomy group. At a mid-term follow up (16-22 months) graft patency rates were 89.1% vs 81% in favor of open endarterectomy [19]. In our study, the open endarterectomy method was mostly used (74% vs 26%), and the onlay patch LITA was used for vascular reconstruction, especially in the LAD region.

Poor outcomes of coronary endarterectomy especially the high incidence of myocardial infarction may be attributed to endothelium damage which can lead platelet aggregation and finally acute thrombosis of the endartherectomised vessel [20]. Therefore we started acetylsalicyclic acid (100 mg) and clopidogrel (75 mg) treatment for all patients immediately after surgery.

Limitations

Our study had several limitations: first of all, it was a single center, retrospective and non randomized study. The number of patients was relatively small. Also, our study focused on clinical follow-up, and graft patency rates were not examined with imaging techniques (i.e., conventional or CT angiography). Follow-up angiography was performed for only a minorty of patients. Therefore, further studies with a larger number of patients are needed.

CONCLUSION

Coronary endarterectomy appears as a satisfactory and sometimes mandatory surgical option in the presence of diffuse CAD. It can be performed safely with acceptable mortality and morbidity rates, as a result of the increased surgical experience and advances in myocardial protection techniques, especially the use of retrograde cardioplegia. In addition, we think that postoperative aggressive anticoagulation especially dual antiplatelet therapy increases the success of the technique.

Authors' Contribution

Study Conception: CE, USS; Study Design: CE, ME; Supervision: ŞY; Funding ŞY; Materials: CE, USS; Data Collection and/or Processing: USS, ME; Statistical Analysis and/or Data Interpretation: CE; Literature Review: USS; Manuscript Preparation: CE, ME and Critical Review: ŞY.

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 2020;7(3):256-264 Original Article

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Is there a relationship between the morphological characteristics of developmental venous anomalies and the presence of parenchymal abnormalities?

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ABSTRACT

Objectives: Developmental venous anomaly (DVA) is a benign vascular malformation. Hyperintensity in the fluid-attenuated inversion recovery (FLAIR) sequence in the adjacent white matter has been previously identified. Although there are different theories, it is not yet clear why these hyperintensities occur. In this study, we aimed to investigate the factors affecting hyperintensity formation by examining the relationship between the morphological findings of DVA and the presence of FLAIR hyperintensity.

Methods: The study included 84 cases diagnosed with DVA. Patients with susceptibility weighted imaging (SWI) and/or postcontrast T1-weighted sequences in addition to conventional MRI sequences were included. The patients were divided into two groups as hyperintensity FLAIR (+) and FLAIR (-) in the examination performed around DVA. There were 24 patients in the FLAIR (+) group and 60 patients in the FLAIR (-) group. The localization of DVAs, drainage localization of the intramedullary vein, collector vein diameter, collector vein length, DVA location depth, and patient ages were compared between the two groups.

Results: When examining the relationship between the groups and variables in the statistical evaluation, there was no difference between the groups in terms of DVA localization, the venous system of drainage, DVA depth, and the length of the collector vein. However, a significant difference was observed between the groups in terms of the collector vein diameter and age.

Conclusions: The results of this study indicating a relationship between collector vein diameter and patient age. The relationship between this diameter and age suggests that there is a correlation between the degree and duration of venous congestion and the change in white matter.

Keywords: Developmental venous anomaly, susceptibility weighted imaging, FLAIR hyperintensity

Developmental venous anomaly (DVA), also called venous angioma, is the most common vascular malformation in the brain [1]. Recently, it has become controversial concerning whether DVA is a vascular malformation or venous variation [1]. DVAs consist of a large number of small intramedullary veins that form the appearance of an umbrella or caput medusa, draining into a single collector vein. They are often considered benign and asymptomatic and are detected incidentally in imaging tests. There is no consensus on the formation mechanisms of DVAs; however, there are theories indicating that they

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develop to compensate for an undeveloped cerebral venous system in a certain area of the brain parenchyma [2-4].

Although they are often asymptomatic, DVAs can also be symptomatic, causing venous infarction with the thrombosis of the collector vein. In addition, DVAs may be accompanied by cavernoma, white matter change in drainage localization, dystrophic calcification, and local atrophy [5-7].

DVAs are easily detected by susceptibility weighted imaging (SWI) or contrast-enhanced MRI and CT examinations. DVAs can be identified in conventional MRI sequences and CT if only they are large enough. During imaging, the large intramedullary vein and venous vascular structures draining into this vein are contrast-enhanced. Deoxygenated hemoglobin in the lumen of venous structures described in SWI sequences is used as an intrinsic contrast agent, allowing a kind of venography examination to be performed without using contrast media [8].

DVAs drain a certain parenchymal area, such as other cerebral venous structures. The intensity difference in white matter drained by DVA has been previously described [5-9]. Although white matter change is considered to occur due to venous hypertension, its pathophysiology remains unclear [10].

In this study, we aimed to investigate the factors affecting the formation of hyperintensity by examining the relationship between the morphological findings of DVAs and the presence or absence of FLAIR hyperintensity.

METHODS

This retrospective study was approved by the Bilkent City Hospital Ethics committee (E-19-108). The study was designed according to declaration of Helsinki and written consent was obtained from all participants.

The reports of brain MRI scans performed at the radiology department of our hospital between January 2017 and February 2019 were retrospectively screened. A total of 189 patients diagnosed with DVAs based on these reports were included in the study. In addition to the conventional sequences, the presence of contrast-enhanced examination and/or SWI sequence was accepted as a criterion for the diagnosis of DVA. Diffuse white matter disease, brain MRI scans not including SWI/post-contrast-enhanced T1-weighted sequences were the exclusion criteria of the study.

Patients with white matter disease, which causes diffuse hyperintensity in white matter, was excluded from the study because it was not possible to determine whether hyperintensity formation was secondary to venous angioma or not. Two DVAs located in the brainstem were excluded due to the brain MRI scans not including SWI/post-contrast-enhanced T1-weighted sequences.

A 3 Tesla system (SKYRA Siemens) with a 16-channel head coil was used for the MRI examination. Conventional sequences consisted of axial T1-weighted, axial T2-weighted, axial FLAIR, sagittal T2-weighted and axial diffusion examinations. Conventional sequences were accompanied by T1-weighted or SWI examination in two post-contrast-enhanced planes (axial and sagittal). For contrast enhancement, 0.1 mmol/kg gadolinium was used. The SWI examination consisted of magnitude, phase, and minimum intensity projection (MIP). The visualization of a DVA in one of the contrast-enhanced or SWI sequences was considered to be sufficient for the diagnosis.

The images of cases diagnosed based on brain MRI reports were reevaluated by a neuroradiologist with 13 years of experience. The diagnosis of DVA was made by demonstrating the drainage of thin venous segments into the wide collector vein, resulting in the typical caput medusa appearance in the contrast-enhanced T1-weighted or SWI sequence. For all DVA lesions, localization, drainage localization of the intramedullary vein, collector vein length, intramedullary vein diameter, FLAIR hyperintensity in the drainage area, and diffuse white matter hyperintensity extending to the drainage area were noted.

According to whether there was white matter hyperintensity around DVAs, the patients were divided into two groups as FLAIR (+) and FLAIR (-). White matter hyperintensity was evaluated using the axial FLAIR sequence due to its superiority to the T2-weighted sequence in showing white matter lesions. Since the flow in the DVA lumen may also create hyperintensity in the FLAIR sequence, care was taken to ensure that hyperintensity was not at the lumen level when performing the evaluation. DVA-associ-

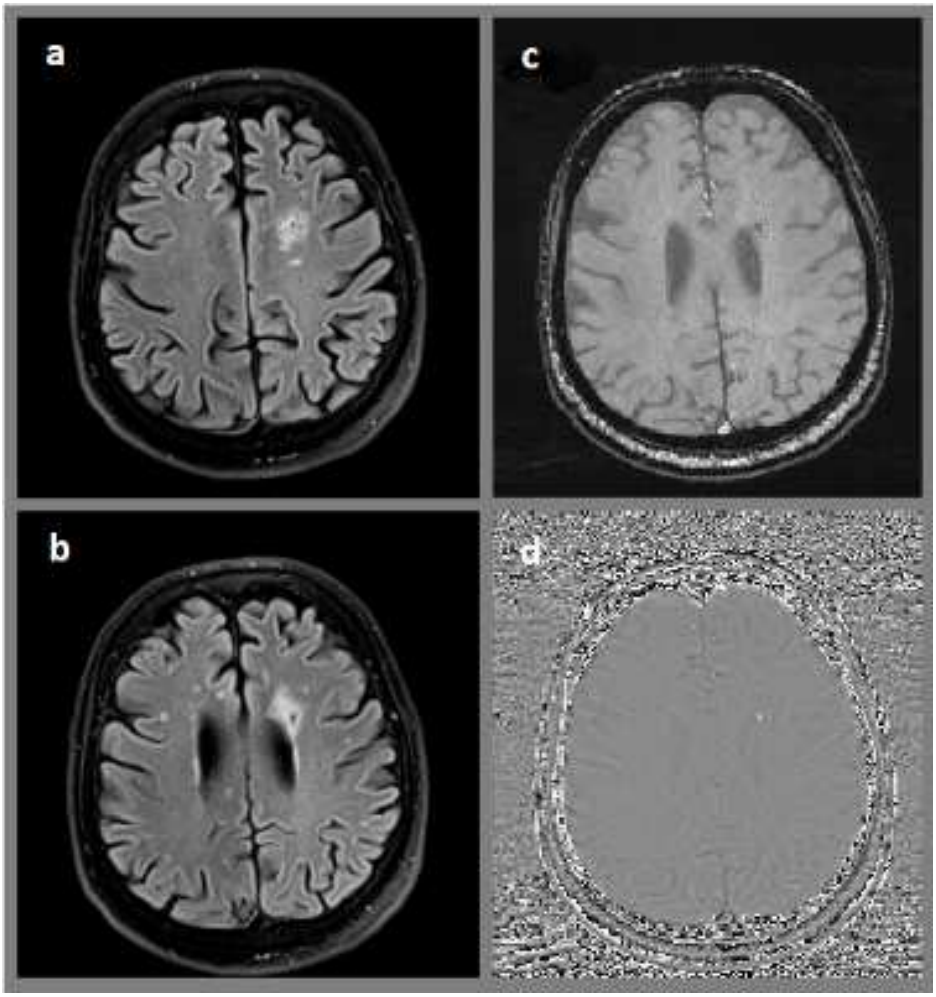

Fig. 1. (a, b) DVA associated hyperintensity at FLAIR sequence, (c, d) DVA collector vein at SWI and phase images.

ated signal abnormalities and DVA collector vein at SWI-Phase Images are shown in Fig. 1.

The lesions diagnosed with DVA based on the contrast-enhanced T1-weighted or SWI sequence were classified for both groups according to their following characteristics:

- Localization: DVAs located in cerebral lobes were defined as lobar, and basal ganglion, brainstem and cerebellum locations were classified separately.
- Depth: For this classification, the widely adopted method from Lee *et al*. [11] was used based on the localization of multiple small intramedullary veins draining into the collector vein. Accordingly, the DVAs were classified as periventricular, juxtacortical, and subcortical.
- Drainage system: Deep or superficial descriptions were used to indicate the venous system into the vein drained. DVAs that equally participated in both systems were noted as D+Y.
- Length of the collector vein: DVAs were visually classified as small, medium, and large as previously described by Santucci *et al*. [9]
- Width: This classification was made visually, taking into account the size of the intramedullary vein in the contrast-enhanced T1-weighted or SWI sequence. DVAs were classified as 'thin', 'medium', and 'wide'. Of the DVAs that were not seen in conventional sequences, those that were visualized in SWI or contrast-enhanced T1-weighted sequence were classified as 'thin' if they appeared as a thin line, 'wide' if they were larger than 2.5 mm, and 'medium' if between the two sizes. The collector vein diameter was determined at the parenchymal level. DVA collector vein at contrast-enhanced T1-weighted sequence are shown in Fig. 2.

Statistical Analysis

IBM SPSS Statistics v. 23.0 was used for statisti-

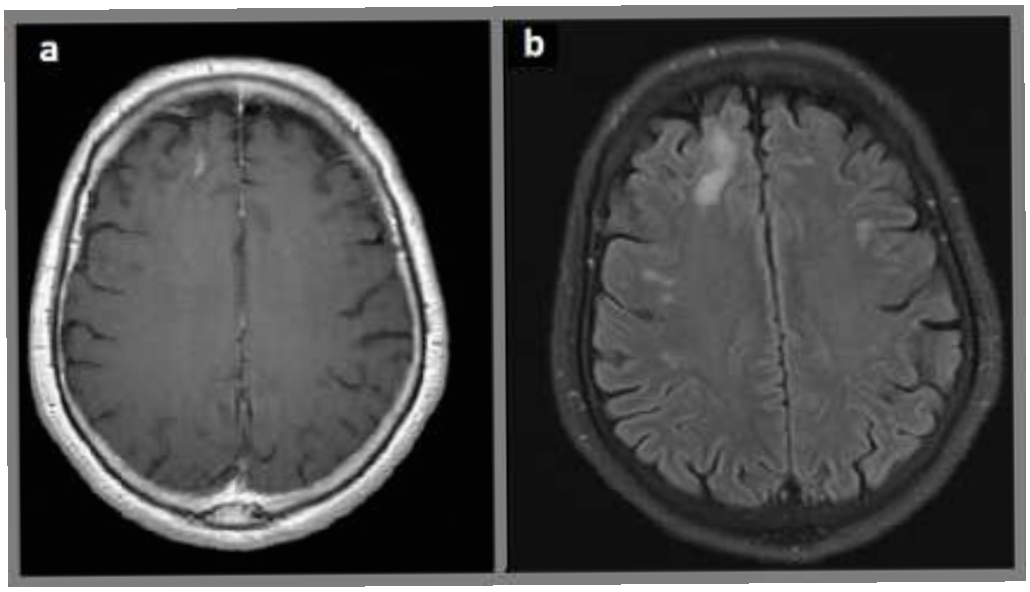

Fig. 2. (a) DVA collector vein at contrast-enhanced T1-weighted sequence, (b) DVA associated hyperintensity at FLAIR sequence.

cal analysis. For both groups, the statistical analysis was performed using chi-square and logistic regression methods for the defined characteristics of DVAs and age.

RESULTS

There were 84 patients in two groups. The age of the patients ranged from 12 to 80, with the mean age being 38 years. The demographic findings and clinical presentations of the patients are given in Table 1, and their morphological findings in Table 2. There were 24 patients in the FLAIR (+) group 60 patients in the FLAIR (-) group.

Table 1. Demographic characteristics and clinical presentations of the patients

Number of patients	84
Female	44
Male	40
Mean age	38
Headache	38
Vertigo	15
CVE	12
Follow-up of mass	9
Metastasis screening	7
Epilepsy	3

CVE =cerebro vascular event

When comparing the morphological variables in the chi-square test (Table 3), there was no statistically significant difference between the two groups in terms of DVA location and length ($p > 0.05$); however, a statistically significant difference was found in terms of DVA width, and the logistic regression analysis revealed that medium and wide lesions had a higher probability of forming FLAIR hyperintensity compared to those that were thin. In terms of the DVA depth variable, no statistically significant difference was found between the FLAIR groups ($p = 0.499$); however, periventricular localization was observed in 33% of the patients in the FLAIR (+) group and 15% of those in the FLAIR (-) group.

In the evaluation of drainage localization, there was a statistically significant difference in the chi-square analysis of drainage to deep+superficial (D+Y) veins, but here it is necessary to note a statistical limitation resulting from the D+Y observation value being zero. Consistent with this idea, the logistic regression analysis revealed that the drainage variable was not significant.

There was also a significant statistical difference in the age variable between the two groups, and the logistic regression analysis showed that the probability of DVA accompanied by FLAIR hyperintensity increased with age (Table 4).

Table 2. Morphological findings of the groups

	FLAIR (-) n = 60	FLAIR (+) n = 24
DVA location		
Lobar	40	21
Basal ganglion	8	1
Cerebellum	12	2
Length		
Short	17	5
Medium	22	6
Long	21	13
Width		
Thin	31	4
Medium	21	16
Wide	8	4
Drainage location		
Superficial	32	8
Deep	28	13
Deep + Superficial	-	3
Depth		
Periventricular	15	8
Juxtacortical	16	7
Subcortical	29	9

DVA = developmental venous anomaly

When the FLAIR classification of the variables was examined using logistic regression analysis, width and age were determined to be significant variables. Accordingly, as the age increased, the probability of being FLAIR (+) increased. In addition, the patients with medium and wide DVAs were more likely to be in the FLAIR (+) group compared to patients with thin DVAs (Table 5).

DISCUSSION

DVAs, similar to other venous structures of the brain, drain a parenchymal area. It is known that cavernoma, dystrophic calcification, and focal atrophy accompany DVAs at varying rates. Another finding observed in white matter areas that DVAs drain is FLAIR and T2-weighted hyperintensity in this area that is prominent in the FLAIR sequence. In histopathological studies, demyelination in hyperintense areas, degenerative changes in nerve cells, and leukomalacia have also been described [12]. In the current study, we compared the hyperintensities in white matter with the morphological findings of DVAs and found that 26 of 189 patients (14%) had hyperintensity in white matter. The rate of hyperintensity accompanying DVAs was reported as 12.5% by Santucci *et al*. [9] and 28.3% by Ruíz *et al*. [5]. These different rates may be due to the varying routine imaging protocols of the centers. In addition, the reason for the increased changes in white matter in the study of Ruíz *et al*. may be related to their higher rate of CT procedures [5].

No significant relationship was found between the

Table 3. Chi-square analysis between FLAIR and investigated variables

			DVA location			X^2	*p* value
			lobar	basal ganglion	cerebellum		
FLAIR	negative	N	40	8	12	3.316	0.228
		%	66.7%	13.3%	20.0%		
	positive	N	21	1	2		
		%	87.5%	4.2%	8.3%		
			length				
			short	medium	long		
FLAIR	negative	N	16	22	22	2.078	0.392
		%	26.7%	36.7%	36.7%		
	positive	N	5	6	13		
		%	20.8%	25.0%	54.2%		
			width				
			thin	medium	wide		
FLAIR	negative	N	31*	21**	8	9.406	**0.007**
		%	51.7%	35.0%	13.3%		
	positive	N	4*	16**	4		
		%	16.7%	66.7%	16.7%		
			Drainage location				
			superficial	deep	S + D		
FLAIR	negative	N	32	28	0*	7.754	**0.011**
		%	53.3%	46.7%	0.0%		
	positive	N	8	13	3*		
		%	33.3%	54.2%	12.5%		
			Depth				
			periventricular	juxtacortical	Subcortical		
FLAIR	negative	N	15	14	31	1.391	0.499
		%	25	23.3	51.7		
	positive	N	8	7	9		
		%	33.3	29.2	37.5		

DVA = developmental venous anomaly

Table 4. The relationship between FLAIR groups and age

	FLAIR	N	Mean	Std. Deviation	t	*p* value
Age	Negative	60	37.1667	16.10892	-2.109	0.038
	Positive	24	45.3750	16.11862		

Table 5. Results of logistic regression analysis

	B	SE	Wald	Df	Significance	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Age	.051	.020	6.642	1	.010	1.052	1.012	1.094
Width (thin)			8.484	2	.014			
Width (medium)	2.118	.755	7.872	1	.005	8.318	1.894	36.533
Width (wide)	2.154	.985	4.786	1	.029	8.617	1.251	59.352
Constant	3.121	7257.867	.000	1	1.000	22.673		

SE = standard error, CI = confidence interval

presence of hyperintensity and DVA location, drainage system and length among the variables examined between the two groups, and this is consistent with the findings reported by Santucci *et al*. [9]. However, in contrast to Santucci *et al*. [9], we did not find a statistically significant relationship between the presence of hyperintensity and deep localization of DVAs. Santucci *et al*. [9] found periventricular localization at a higher rate in the DVA group accompanied by hyperintensity. Similarly, in our study, we observed periventricular localization to be more common in the FLAIR (-) group (33%) than in the FLAIR (+) group (15%), albeit non-significant. The depth classification of DVAs is made according to the localization of multiple small intramedullary veins draining into the collector vein, which may be difficult to distinguish, especially if the intramedullary veins are long and dense. This difficulty in evaluation may be the cause of the inconsistency between our findings and those of Santucci *et al*. [9].

Considering the system into which the collector vein is drained, no relationship was found between superficial or deep system drainage and hyperintensity, but it is interesting that in the sample of 84 patients, all three that showed D+Y drainage were in the FLAIR (+) group. Since we were not able to perform a statistical analysis due to the limited number of these patients, there is a need for further evaluations of DVAs exhibiting deep and superficial drainage to clarify this issue.

With increasing age, FLAIR hyperintensity occurs due to chronic small vessel disease in white matter. These changes in white matter are graded by the Fazekas classification according to their extent. While FLAIR hyperintensities are in the form of discrete punctate foci in Fazekas grade 1, grades 2 and 3 show diffuse and confluent tendencies. Grade 2 and 3 changes are common and were from the current study since they cannot be distinguished from DVA-induced hyperintensity. Thus, age-related white matter changes were excluded, allowing for a more accurate evaluation of the relationship between age and DVA hyperintensity.

Our patients had heterogeneous clinical presentation and primary pathology. It may be the limitation of the study if primary pathology effect the white matter. Because of this we exclude patient that have extensive white matter hyperintensity anywhere of the brain and cerebellum.

The collector vein diameter of DVAs differed between the FLAIR (+) and (-) groups. In the evaluation of the collector vein diameter, Santucci *et al*. [9] did not find any significant difference. [9] However, while Santucci *et al*. performed the collector vein diameter evaluation using numerical values for all veins, we divided the veins into three according to their diameters, as we previously described. We also performed the measurements from the SWI or contrast-enhanced T1-weighted sequence, in which the diameter of the collector vein can be seen more clearly. The results of our statistical analysis, show that the probability of accompanying hyperintense increased in DVAs with medium and wide collector veins compared to those with thin veins. This supports the hypothesis that chronic venous congestion plays a role in the formation of hyperintensity in white matter. In our opinion, the greater occurrence of chronic venous congestion in the presence of large-scale drainage veins may be the cause of detectable FLAIR hyperintensity in white matter. Venous congestion is also considered in the etiology of other pathologies of white matter drained by DVAs. For example, DVAs

are thought to induce vascular proliferation by leading to hemodynamic instability in drainage localizations, thus leading to cavernoma [4], a theory that has been supported by DVA de-nova cavernoma cases reported in drainage localization [13, 14]. If venous congestion occurs more in large collector veins, the collector veins of DVAs accompanying cavernoma may be wider. Further studies are needed to confirm this idea.

DVAs can also cause symptoms without concomitant cavernoma, albeit rarely. Symptomatic DVAs were classified by Pereira *et al*. [15] as mechanical due to the compression effect of the of the collector vein, increased inflow, decreased outflow or idiopathic. However, it remains unclear whether DVAs are more symptomatic in the presence of concomitant hyperintensity. In our study group, the rate of comorbidities was high; thus, we could not evaluate the relationship between the presence of hyperintensity and symptom formation.

In their study on FLAIR hyperintensities around DVAs, Rogars *et al*. [16] showed that concomitant demyelinating disease increased the rate of accompanying hyperintensity around DVAs. Histopathological studies also reveal demyelination in FLAIR hyperintense areas around DVAs. Concomitant demyelinating disease may increase the rate of demyelination in drainage localization. This hypothesis was supported by congestion shown in perfusion studies, but the number of perfusion cases in the literature is limited [17, 18].

Limitations

Our study has certain limitations. First, this study aimed to obtain information concerning the pathophysiology of white matter intensities that accompanied DVAs, but SWI scans were not available for all patients. The SWI sequence, now also known as SWI venography, has superior success in showing venous structures. In addition, considering that there may be cavernoma and micro bleeding accompanying DVAs, SWI and similar sequences are ideal for the diagnosis of these entities. The second limitation concerns the inability to eliminate cavernomas considering that the focus of the study was to investigate the etiology of white matter. In the literature, the most comprehensive studies on this subject belong to Ruíz *et al*. [5] and Santucci *et al*. [9]. In the study of Ruiz *et al*. [5], MRI was performed in 60 of 122 patients, but the scans did not include the SWI or gradient sequence. In the study of Santucci *et al*. [9], only three of the MRI examinations among 125 patients included the gradient sequence. In the current study, 17 of 84 patients did not have SWI examinations, and DVAs were diagnosed based on contrast-enhanced T1-weighted images. Two of these 17 patients were in the FLAIR (+) group. Further studies with available SWI sequences in all patients and a higher number of cases in all groups can provide more useful results in the etiology of hyperintensity accompanying DVAs.

CONCLUSION

In this study, we evaluated the changes in white matter in the drainage areas of DVAs and found a relationship between the collector vein diameter and patient age, supporting the association between hyperintensity formation and venous congestion. The findings suggest that there is a correlation between the degree and duration of venous congestion and the changes in white matter. Considering the results of our study and the literature, DVAs that are considered as benign and asymptomatic may actually form the basis of some pathologies. The issues of changes in white matter in relation to clinical presentation and cavernoma formation are still controversial and require more comprehensive longitudinal studies.

Authors' Contribution

Study Conception: ANŞÖ, BH; Study Design: ANŞÖ, BH, ÖÜ; Supervision: ANŞÖ, BH, ÖÜ; Funding: ANŞÖ; Materials: ANŞÖ; Data Collection and/or Processing: ANŞÖ, BH, ÖÜ; Statistical Analysis and/or Data Interpretation: ANŞÖ, BH, ÖÜ; Literature Review: ANŞÖ, BH, ÖÜ; Manuscript Preparation: ANŞÖ, BH, ÖÜ and Critical Review: ANŞÖ, BH, ÖÜ.

Conflict of interest

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

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Analysis of the relationship between fetal magnetic resonance imaging indications and findings with ultrasonographic examination

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ABSTRACT

Objectives: We aimed to examine the indications for the use of fetal MRI in obstetrics practice and the relationship between fetal MRI and ultrasonographic findings.

Methods: Seventy-three patients were examined with Fetal MRI for various reasons between July 2017 and July 2020, and whose results were available were evaluated retrospectively. Ultrasonographic and MRI findings were recorded. The detected pathologies were divided into groups according to systems. The relationship between the findings was examined.

Results: In our study, ultrasonographic findings of fifty-five (75.3%) cases were confirmed by MR findings. MRI detected additional findings in eight (10.9%) cases, most of which were intracranial pathologies. The most detected ultrasonographic findings as an indication for the request were in the intracranial region (54.8%).

Conclusions: Fetal MRI indications in perinatal care and follow-up are not clear. Determining these indications is also essential in preventing unnecessary use in obstetric practice and determining the cost-effectiveness.

Keywords: Fetal MRI, fetal ultrasonography, prenatal diagnosis, congenital anomalies

Ultrasonography is the first step diagnostic method in the diagnosis and screening of fetal anomalies [1]. Reliability, easy accessibility, cheapness, real-time imaging are the beneficial aspects of ultrasonography. However, ultrasonography may not always be sufficient to detect fetal anomalies mainly due to maternal obesity, oligohydramnios, fetal position. In such cases, fetal magnetic resonance imaging (MRI) comes into prominence to clarify the ultrasonographic diagnosis or to detect the presence of additional anomalies [2, 3]. MRI is also useful in detecting placental invasion anomalies.

In parallel with the development of MRI techniques, the artifact of fetal mobility is minimized by obtaining the image concisely. In parallel with this, fetal MRI as a complement to ultrasonographic findings has increased in recent years. It is challenging to determine fetal MRI indications due to experience and regional differences in perinatal management. It varies according to the individual pathology studied [2].

In this study, we aimed to evaluate the relationship between ultrasonography and MRI findings and fetal MRI indications in the diagnosis and screening of fetal anomalies.

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METHODS

This retrospective study was conducted by including 75 patients admitted to our tertiary hospital between July 2017 and July 2020 and underwent fetal MRI imaging for various indications. The study was approved by the Bursa Yüksek İhtisas Training and Research Hospital Ethics Committee (2011-KAEK-25 2020/06-22).

Demographic, clinical, ultrasonographic, MRI and delivery data were obtained from electronic patient records. MRI request indications were recorded. Pathological conditions detected as a result of the examination were divided into groups according to organ systems. Ultrasonography and MRI findings were examined in terms of compatibility and inconsistency between each other.

The gestational week, fetal birth weight, and neonatal intensive care requirement of the patients whose pregnancy and delivery results were available were recorded.

Statistical Analysis

For proper statistical analyses, Windows-based SPSS 24.0 statistical analysis program was used (SPSS Inc., USA). To determine whether they were normally distributed or not, variables were examined via visual (histograms, probability plots) and analytical methods (Shapiro-Wilk's test). Variables were descriptively specified as mean ± standard deviation (X ± SD), mean difference between groups, 95% confidence interval (95%CI), median (minimum-maximum (min-max)), U value, frequency (n) and percentage (%).

RESULTS

In the study, we evaluated the fetal MRI indications and findings of seventy-three pregnant women. We analyzed the remaining forty-seven cases' delivery results by removing twenty-six pregnant women who did not have labor outcomes. The mean age of the patients was 28.1 ± 6.2 (Table 1).

Of the fetuses evaluated ultrasonographically before MRI, forty (54.8%) of them had intracranial findings, fourteen (19.2%) had gastrointestinal system findings, and six (8.2%) had placental invasion anomalies. Five (6.8%) of the cases were examined by MRI for the genitourinary system, four (5.5%) for the spinal cord and vertebra, two (2.7%) for cardiorespiratory system findings, and two (2.7%) for head and neck masses. (Fig. 1).

Table 1. Descriptive analyses of values regarding the mothers and the babies

Characteristics of Mothers and Babies	Pregnant women
Age (year) (n = 73)	28.1 ± 6.2
Week of birth (n = 47)	38.3 (28-41)
Birth weight (g)	2913.3 ± 761.4
Postpartum with mother, breastfeeding, n (%)	24 (51.1%)
Neonatal intensive care, n (%)	22 (46.8%)
Intrauterine ex fetus, n (%)	1 (2.1%)

Data are shown as mean ± standard deviation or median (minimum-maximum), n (percent).

In our study, the ultrasonographic findings of fifty-five cases were confirmed with MRI findings. In eight cases, most of which were intracranial pathologies, additional findings were detected by MRI.

Of the seventy-three fetuses undergoing fetal MRI examination; Intracranial anomalies in thirty-six (49.3%), placental invasion anomaly in four (5.5%), gastrointestinal system anomalies in five (6.8%) cases, genitourinary anomalies in six (8.2%) cases, spinal cord anomaly in three (4.1%) cases, a head or neck mass anomaly was detected in two patients (2.7%). No apparent pathology was found in the MRI findings of

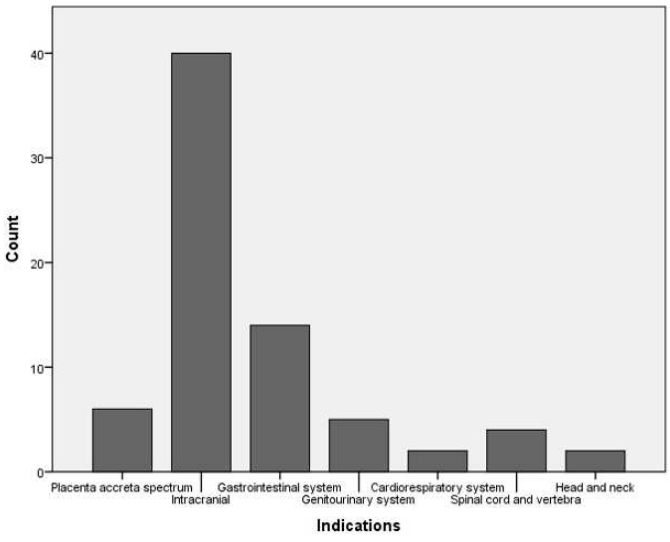

Fig. 1. The distribution of fetal MRI indications.

seventeen (23.3%) fetuses scanned (Fig. 2).

Four of the gastrointestinal system findings that we detected ultrasonographically and evaluated with MRI were tracheoesophageal fistula, and one of them was dilated bowel loops. In all of the five cases, MRI results were correlated with ultrasound findings. However, we found no consistent findings in any MRI evaluation of six fetuses with suspected esophageal atresia or tracheoesophageal fistula. We did not find any MRI finding of two cases with small stomach suspicion.

We planned further evaluation of sonographically detected intracranial neurological findings in forty patients. Ten fetuses had more than one intracranial finding. There were twenty-two fetuses with ventriculomegaly. We performed MRI to evaluate posterior fossa anomalies in six cases (mega cisterna magna, cerebellar hypoplasia, and vermian agenesis), twenty cases of cavum septum pellucidum, and corpus callosum anomalies, and one case of intracranial mass formation.

Fetal MRI findings were correlated with ultrasonography in thirty of forty cases, and MRI findings in four cases were natural. In two cases, we found ventriculomegaly ultrasonographically; Dandy-Walker Malformation was diagnosed with additional findings on MRI. In two patients with cavum septum pellucidum anomaly, we detected the congenital variation of cavum vergae with MRI. Additionally, lobar holoprosencephaly was observed in one patient with ventriculomegaly, and colposephaly was observed in another case. Additional findings to antenatal sonography were detected in six cases.

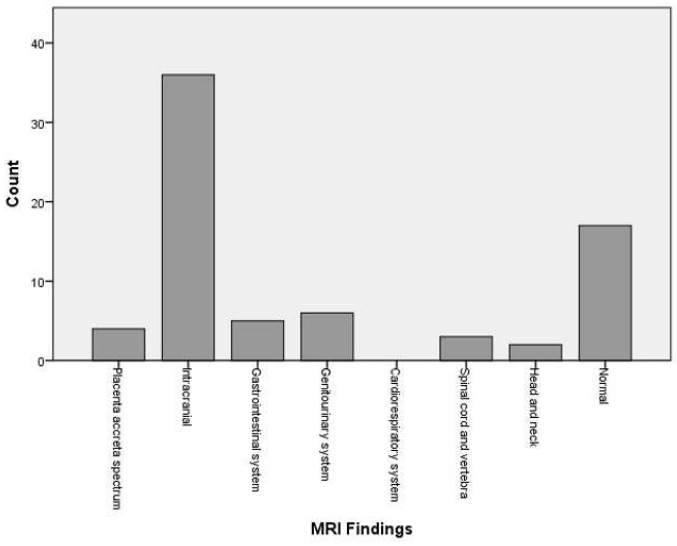

Fig. 2. Scatter plot of MRI findings.

In the evaluation of six cases with suspected placental invasion anomaly in ultrasonography, four cases were found as placenta accreta in MRI.

Three fetuses were evaluated with MRI for renal agenesis, one fetus for multicystic kidney, and one fetus for hydronephrosis, and both images were correlated in all cases.

We found a suprarenal mass in a fetus we examined MR with a pre-diagnosis of pulmonary sequestration. MR imaging of a case with suspected diaphragmatic hernia was normal.

There was suspicion of sacrococcygeal teratoma in two fetuses and suspicion of spina bifida in one fetus, and MRI findings of all three fetuses were correlated. MR image of a fetus with suspicion of scoliosis and hemivertebra was natural.

We visualized the findings more clearly in MR images of both fetuses with oral and neck masses. The solid mass in the neck was compatible with teratoma.

DISCUSSION

Although ultrasonography is the basis of antenatal imaging today, fetal MRI is an increasingly crucial prenatal diagnosis method.

MRI has become an important screening method in recent years for multisystem evaluation of the fetus and diagnosis of congenital malformations [4, 5]. Magnetic resonance imaging (MRI) is most significant after the 20th week of gestation and provides more advantages than ultrasonography in evaluating the fetal brain. It is superior to ultrasonography in excluding CNS anomalies in a fetus with fetal malformation suitable for treatment. Standard gyral models, ventricular size, posterior fossa are best evaluated with MRI. Detailed observation of the cerebellar vermis is necessary for the diagnosis of Dandy-Walker malformation [5, 6]. The most common indication for fetal MRI is suspicion of central nervous system anomalies. Ventriculomegaly, posterior fossa, and corpus callosum anomalies are the three most critical cerebral causes for fetal MRI [2]. In our study, intracranial pathology suspicions constituted the majority of fetal MRI indications. Almost half of this group included fetuses with ventriculomegaly.

One of the essential points in the presence of ventriculomegaly is the presence of additional anomalies.

Because isolated ventriculomegaly has a better prognosis, however, ultrasonography may be insufficient to detect additional anomalies. Therefore, MR imaging can be used for detailed examination [2, 7].

Studies in the literature show that; in detecting fetal anomalies, ultrasonography may be correlated with fetal MRI, and imaging with MRI may also reveal additional findings. A review stated that 65.4% of the ultrasonographic findings were confirmed with Fetal MR, and additional findings were found in 22.1% [8]. In our study, while the confirmation rate was 75.3%, additional findings were detected in 10.9% of the cases.

Placental invasion anomalies are life-threatening serious obstetric problems that can lead to massive peripartum hemorrhage. Early diagnosis is essential because it enables preparing for a cesarean section in a planned way. The superiority of MR and ultrasonography over each other in these cases still being discussed, and there are publications in the literature stating that both imaging methods should be used in combination in suspected cases [9, 10]. In our study, six cases with suspicion of placental invasion anomaly in ultrasonography were evaluated with fetal MRI, and invasion anomaly was observed in four of them. Maternal or fetal complications did not occur in any of these pre-diagnosed and planned cases.

MRI helps to identify lesions in the abdominal and cervical or spinal regions more efficiently by providing a wider field of view. Since only a small part of the lesion may be present in the acoustic window with ultrasonography, the entire anomaly and its anatomical relationships can be viewed more clearly with MRI. Also, MRI has become more valuable in anomaly diagnosis in recent years due to conditions that limit ultrasonographic evaluation, such as maternal obesity, excessive fetal activity, or technical problems [11].

CONCLUSION

Ultrasonography has a very effective and essential place in fetal anomaly screening. With the increasing technology, fetal MRI is also used in cases where ultrasonography is insufficient. Fetal MRI use and indications are not determined depending on many factors. Determining these indications is also essential in preventing unnecessary use in obstetric practice and determining the cost-effectiveness.

Authors' Contribution

Study Conception: BA, SSK; Study Design: BA, SSK; Supervision: BA; Funding: BA; Materials: BA, SSK, BŞK; Data Collection and/or Processing: BA, BŞK; Statistical Analysis and/or Data Interpretation: BA, SSK; Literature Review: BA, BŞK; Manuscript Preparation: BA, SSK and Critical Review: BA, SSK, BŞK.

Conflict of interest

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

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Relationship between automated perimetry and Heidelberg retina tomograph, optic coherence tomography and laser polarimetry in moderate to severe glaucomatous eyes

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ABSTRACT

Objectives: To determine the correlations between the measurements obtained with Heidelberg retina tomograph III (HRT III), optic coherence tomography (OCT), and laser polarimetry (GDx) with the indices of automated perimetry (AP) in moderate and severe glaucoma patients.

Methods: Forty-nine eyes of 30 patients were included in the current study and were divided into two groups: 23 eyes with moderate and 26 eyes with severe glaucoma defined by Hodapp-Parrish-Anderson grading system. Pearson's correlation coefficients were used to evaluate the correlation between the indices of AP including mean deviation (MD) and pattern standard deviation (PSD), and structural parameters of the retinal nerve fiber layer (RNFL) and optic disc acquired by using three devices in both groups.

Results: In moderate glaucoma OCT and GDx measurements were not correlated to MD only the exception of inferior RNFL (r = 0.57, p = 0.007 and r = 0.52, p = 0.008, respectively). Mild to moderate correlations were calculated between the structural parameters of HRT III and AP indices. In severe glaucoma, the most correlated measurements were obtained by OCT compared to the other devices. The correlations for MD were more powerful compared to PSD. Parameters based on the study of the RNFL showed stronger correlations than those of the optic nerve head. No devices showed significant correlations in patients with MD less than -12 dB.

Conclusions: OCT measurements showed the best correlations with the AP indices in both moderate and severe glaucoma patients. However, AP still seems to be more effective in the follow-up of glaucoma progression in more advanced glaucomatous damage.

Keywords: automated perimetry, Heidelberg retina tomograph, laser polarimetry, optic coherence tomography, glaucoma

Glaucoma is an optic neuropathy associated with the loss of retinal ganglion cells and their axons which create the retinal nerve fiber layer (RNFL) [1]. Several studies have shown that morphological

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changes of optic disc and defects in visual field (VF) are valuable indicators for diagnosis of glaucoma.

Although automated perimetry (AP) is the gold standard method for glaucoma diagnosis and progression documentation, morphological changes of optic disk and RNFL may precede VF defects in some cases [2]. Several studies have shown the efficacy of Heidelberg Retina Tomograph laser scan (HRT), laser polarimetry (GDx) and optic coherence tomography (OCT) for detecting glaucomatous changes of optic nerve and RNFL [3, 4].

Automated perimetry is useful to determine cases with moderate and advance glaucoma however it may be insufficient to detect patients in early stages [5, 6]. In the other hand the recently imaging techniques have been reported to detect early stages of glaucoma [7]. In this study, we aimed to evaluate the structural parameters of the optic nerve head and RNFL obtained by using a HRT III, OCT and GDx with global indices of conventional AP and reveal the diagnostic precision of these devices for detecting and following subjects with moderate and severe primary open angle glaucoma (POAG).

METHODS

Patients

In this prospective study 49 eyes of 30 patients with POAG were included and were classified into two groups: 23 with moderate and 26 with severe glaucoma. Exclusion criteria were the presence of corneal opacity or cataract, refractive errors higher than -7.0 to +4.0 Diopters (D) sphere and/or 3.0 D cylinder, visual acuity less than 20/100. The study was conducted in accordance with the ethical standards stated in the 1964 Declaration of Helsinki and approved by the Local Ethics Committee of the participating center. All patients were informed about the purpose of the study and provided their consent.

The definition of glaucoma was made by the findings of VF defects. The severity of the VF defect was graded as moderate, or severe visual field loss as defined by Hodapp-Parrish-Anderson (HPA) grading system criteria [8]. In this staging system, glaucomatous eyes were classified into three groups according to the mean deviation (MD) values (mild, MD < -6 dB; moderate, MD > -6 dB and < -12 dB; severe, MD > -12 dB).

A complete ophthalmic examination and also measurements of AP, HRT III, OCT and GDx were obtained in all patients.

Conventional Automatic Perimetry

In all patients 30-2 central field test which uses the Swedish Interactive Threshold Algorithm (SITA) standard software program version 24-2 (Carl Zeiss Meditec, Oberkochen, Germany) on a Humphrey 750i automatic visual field analyzer (Carl Zeiss Meditec) was performed [9]. The test object was size III; the duration time was 200 ms; and the background brightness was 31.5 asb (10 cd/m^2). Refractive errors and presbyopia were corrected before the examination. The test was accepted to be confidential when fixation loss, false-negative and false-positive rates were less than 30%. Abnormality was evaluated using the instrument's software through calculating the global Indices of MD or pattern standard deviation (PSD).

Confocal Scanning Laser Ophthalmoscope Imaging

Confocal scanning laser ophthalmoscopy measurements were obtained with the HRT III (Heidelberg Engineering) as described previously [10]. The same examiner performed 3 sequential measurements and these were aligned to combine unique image. The margins of the optic disc were marked by the same examiner manually. Once the margins were marked, disc parameters were estimated automatically by the device. The evaluated parameters in our study were rim area, rim volume, linear cup to-disk ratio, cup-to-disk area ratio, rim-to-disk area ratio, RNFL cross-sectional area, mean RNFL thickness, cup area, cup volume, and mean cup depth.

Optical Coherence Tomography

One examiner performed the peripapillary RNFL thickness measurements by the Stratus TD OCT (Carl Zeiss Meditec) which were described previously [11]. The accepted images had at least 7 signal quality. Study protocols were carried out for RNFL thicknesses (mean, superior and inferior), central foveal thickness and total foveal volume.

Laser Polarimetry

Scanning Laser polarimetry measurements were

obtained by using GDx VCC (Carl Zeiss Meditec Inc.). Details of the GDx-VCC operation have been described [12]. The device calculated the RNFL thicknesses for temporal, superior, nasal and inferior quadrants and nerve fiber indicator (NFI). Measurements with quality score grading less than 7 and scan score less than 70 were excluded.

Statistical Analysis

Statistical analyses were calculated using SPSS software (version 21.0, SPSS, Inc. Chicago, IL, USA). Kolmogorov–Smirnov test revealed that the data was normally distributed ($p > 0.05$). The results are presented as the mean ± the standard deviation (SD). The measurements between each group were compared by Paired t test. Correlation of measured parameters obtained by OCT, HRT III and GDx VCC with MD and PSD was analyzed with Pearson correlation coefficient. *P* value < 0.05 was considered statistically significant.

RESULTS

A total of 49 eyes of 30 patients (20 males, 10 females) with POAG were evaluated. The mean age of the patients was 56.2 ± 10.0 years. As defined by HPA grading system 14 patients (23 eyes) had moderate

Table 1. Comparison of the measured parameters obtained by OCT, HRT III and GDx between the groups

	Moderate POAG (n = 23)	Severe POAG (n = 26)	*p* value
OCT parameters			
RNFL superior (µm)	86.76 ± 17.74	57.80 ± 15.45	**0.001**
RNFL inferior (µm)	75.42 ± 16.32	54.76 ± 14.12	**0.001**
RNFL average (µm)	65.81 ± 7.88	51.72 ± 9.08	**0.001**
CFT (µm)	209 ± 24	175 ± 16	**0.001**
Total macular volume (µm)	5.83 ± 0.43	6.38 ± 0.37	**0.001**
GDx parameters			
TSNIT average (µm)	45.08 ± 2.50	38.40 ± 5.44	**0.001**
RNFL superior (µm)	52.38 ± 4.80	39.35 ± 8.26	**0.001**
RNFL inferior (µm)	51.21 ± 7.16	41.76 ± 9.17	**0.001**
NFI	47.04 ± 10.45	74.48 ± 15.94	**0.001**
HRT III parameters			
Cup area (mm^2)	1.03 ± 0.40	1.34 ± 0.42	**0.017**
Rim area (mm^2)	0.96 ± 0.30	0.76 ± 0.21	**0.026**
Rim volume (mm^3)	0.17 ± 0.07	0.14 ± 0.07	0.057
Cup/Discarea	0.53 ± 0.17	0.63 ± 0.13	**0.027**
Cup/Discarea (linear)	0.70 ± 0.12	0.79 ± 0.09	**0.010**
Average cup depth (mm)	0.27 ± 0.08	0.37 ± 0.15	**0.009**
Maximum cupdepth (mm)	0.57 ± 0.14	0.76 ± 0.26	**0.003**
Cup shape measure	-0.060 ± 0.002	-0.020 ± 0.001	**0.041**
RNFL average (µm)	0.14 ± 0.05	0.10 ± 0.07	**0.027**

Values are given as mean ± standard deviation. POAG = Primary open angle glaucoma, OCT = Optical coherence tomography, HRT = Heidelberg retina tomograph, GDx = Laser polarimetry, RNFL = Retinal nerve fiber layer, CFT = Central foveal thickness, TSNIT = Temporal-superior-nasal-inferior-temporal, NFI = Nerve fiber indicator. $p < 0.05$ indicates statistically significance difference.

POAG, 16 patients (26 eyes) had severe POAG. There were no significant differences in age and sex among the two groups ($p = 0.31$ and $p = 0.28$, respectively). Comparison of the measured parameters obtained by OCT, HRT III and GDx between the groups are shown in Table 1. All the measured parameters among the two groups were significantly higher for OCT and GDx ($p < 0.001$) and statistically significant for HRT III ($p < 0.05$).

Any correlations between the measured parameters and the AP indices of the moderate glaucoma patients are shown in Table 2. OCT and GDx measurements were not correlated to MD only the exception of inferior RNFL for both devices (r = 0.57, $p = 0.007$ and r = 0.52, $p = 0.008$, respectively). In addition there was no significant correlation between these devices and PSD. Regarding the measurements of HRT III, significant correlations were found between cup area, cup/disc area, cup/disc area (linear) and maximum cup depth and MD (r = -0.50, $p = 0.02$, r = -0.41, $p = 0.04$; r = -0.44, $p = 0.03$; r = -0.43, $p = 0.05$, respectively). Additionally, cup area, cup/disc area, cup/disc area (linear) and average RNFL were significantly correlated to PSD (r = -0.59, $p = 0.005$, r = -0.54, $p = 0.01$, r = -0.50, $p = 0.02$; r = 0.45, $p = 0.04$, respectively).

Correlations between the measured parameters and the AP indices of the severe glaucoma patients are

Table 2. Correlations between the measured parameters and the MD-PSD of the moderate POAG

	MD (n = 23)		PSD (n = 23)	
	r	*p* value	r	*p* value
OCT parameters				
RNFL average (µm)	0.20	0.38	-0.07	0.75
RNFL superior (µm)	0.10	0.67	-0.05	0.81
RNFL inferior (µm)	0.57	0.007	-0.05	0.83
CFT (µm)	0.43	0.051	-0.19	0.41
Total macular volume (µm)	0.20	0.41	0.05	0.84
GDx parameters				
TSNIT average (µm)	0.22	0.36	0.21	0.35
RNFL superior (µm)	0.18	0.45	-0.16	0.49
RNFL inferior (µm)	0.52	0.008	0.20	0.39
NFI	-0.14	0.54	0.06	0.78
HRT III parameters				
Cup area (mm^2)	-0.50	0.02	-0.59	0.005
Rim area (mm^2)	0.27	0.23	0.04	0.86
Rim volume (mm^3)	0.27	0.23	0.15	0.50
Cup/Disc area	-0.41	0.04	-0.54	0.01
Cup/Disc area (linear)	-0.44	0.03	-0.50	0.02
Average cup depth (mm)	-0.34	0.12	-0.30	0.18
Maximum cup depth (mm)	-0.43	0.05	-0.16	0.49
Cup shape measure	-0.03	0.88	-0.35	0.12
RNFL average (µm)	-0.06	0.79	0.45	0.04

POAG = Primary open angle glaucoma, OCT = Optical coherence tomography, HRT = Heidelberg retina tomograph, GDx = Laser polarimetry, RNFL = Retinal nerve fiber layer, CFT = Central foveal thickness, TSNIT = Temporal-superior-nasal-inferior-temporal, NFI = Nerve fiber indicator, MD =median deviation, PSD = pattern standard deviation. $p < 0.05$ indicates statistically significance difference.

shown in Table 3. The RNFL (average, superior and inferior) as measured by OCT was significantly correlated with MD (r = 0.74, p = 0.001; r = 0.68, p = 0.001; r = 0.70, p = 0.001, respectively). However, no significant correlation was found between OCT measurements and PSD (p > 0.05). The inferior RNFL and NFI obtained by GDx were significantly correlated with MD (r = 0.66, p = 0.001; r = -0.66, p = 0.001, respectively). Similarly no significant correlation was found between GDx measurements and PSD (p > 0.05). Regarding the measurements of HRT III, significant correlations were found between cup area, cup/disc area, cup/disc area (linear), average and maximum cup depth and cup shape measure and MD (r = -0.51, p = 0.01; r = -0.45, p = 0.03; r = -0.44, p = 0.03; r = -0.57, p = 0.003; r = -0.61, p = 0.001, respectively). Additionally, cup area and rim volume were significantly correlated to PSD (r = -0.54, p = 0.005; r = -0.47, p = 0.02, respectively).

In patients with MD less than -20 dB (12 patients), the measurements of OCT, GDx and HRT III did not show any significant correlation with MD and PSD (p > 0.05) (Table 4).

DISCUSSION

In this study we compared the structural parame-

Table 3. Correlations between the measured parameters and the MD-PSD of the severe POAG

	MD (n = 26)		PSD (n = 26)	
	r	*p* value	r	*p* value
OCT parameters				
RNFL average (µm)	0.74	**0.001**	0.16	0.45
RNFL superior (µm)	0.68	**0.001**	0.18	0.40
RNFL inferior (µm)	0.70	**0.001**	0.19	0.36
CFT (µm)	0.35	0.08	0.08	0.71
Total macular volume (µm)	0.33	0.11	0.14	0.50
GDx parameters				
TSNIT average (µm)	0.43	**0.045**	0.04	0.85
RNFL superior (µm)	0.47	**0.032**	-0.13	0.53
RNFL inferior (µm)	0.66	**0.001**	0.40	0.05
NFI	-0.66	**0.001**	-0.07	0.74
HRT III parameters				
Cup area (mm^2)	-0.51	**0.01**	-0.54	0.005
Rim area (mm^2)	0.34	0.09	0.04	0.79
Rim volume (mm^3)	0.20	0.34	0.47	0.02
Cup/Disc area	-0.45	0.03	-0.28	0.35
Cup/Disc area (linear)	-0.44	0.03	-0.35	0.06
Average cup depth (mm)	-0.57	0.003	-0.26	0.06
Maximum cup depth (mm)	-0.41	0.035	-0.34	0.06
Cup shape measure	-0.61	0.001	-0.38	0.06
RNFL average (µm)	-0.01	0.96	0.156	0.46

POAG = Primary open angle glaucoma, OCT = Optical coherence tomography, HRT = Heidelberg retina tomograph, GDx = Laser polarimetry, RNFL = Retinal nerve fiber layer, CFT = Central foveal thickness, TSNIT = Temporal-superior-nasal-inferior-temporal, NFI = Nerve fiber indicator, MD =median deviation, PSD = pattern standard deviation. p < 0.05 indicates statistically significance difference.

Table 4. Correlations between the measured parameters and the MD-PSD of the patients with MD less than -20 dB

	MD (n = 12)		PSD (n = 12)	
	r	*p* value	r	*p* value
OCT parameters				
RNFL average (µm)	0.50	0.12	-0.23	0.95
RNFL superior (µm)	0.42	0.20	0.32	0.34
RNFL inferior (µm)	0.50	0.12	-0.42	0.90
CFT (µm)	0.36	0.28	0.33	0.32
Total macular volume (µm)	0.35	0.62	0.01	0.96
GDx parameters				
TSNIT average (µm)	-0.53	0.09	-0.60	0.05
RNFL superior (µm)	-0.40	0.22	-0.43	0.06
RNFL inferior (µm)	-0.17	0.61	-0.23	0.37
NFI	0.20	0.55	0.47	0.05
HRT III parameters				
Cup area (mm^2)	-0.30	0.38	-0.38	0.22
Rim area (mm^2)	0.09	0.77	0.20	0.51
Rim volume (mm^3)	0.19	0.57	0.14	0.63
Cup/Disc area	-0.21	0.53	-0.22	0.42
Cup/Disc area (linear)	-0.24	0.47	-0.29	0.46
Average cup depth (mm)	-0.23	0.50	-0.35	0.51
Maximum cup depth (mm)	-0.11	0.75	-0.49	0.13
Cup shape measure	-0.50	0.11	-0.47	0.12
RNFL average (µm)	-0.34	0.30	-0.22	0.51

OCT = Optical coherence tomography, HRT = Heidelberg retina tomograph, GDx = Laser polarimetry, RNFL = Retinal nerve fiber layer, CFT = Central foveal thickness, TSNIT = Temporal-superior-nasal-inferior-temporal, NFI = Nerve fiber indicator, MD =median deviation, PSD = pattern standard deviation. $p < 0.05$ indicates statistically significance difference.

ters of the optic disc head and RNFL obtained by using a HRT III, OCT and GDx with global indices of conventional AP to reveal the diagnostic precision of these devices for detecting and following subjects with moderate and severe POAG.

Wollstein *et al*. [13] suggested that OCT has a closer relationship in glaucomatous progression than VF. In another study Kanamori *et al*. [14] showed that OCT has the capability to reveal early glaucomatous damage by calculating the RNFL thickness especially in the inferior quadrant. In addition, the RNFL thickness measurements were favorably correlated with the MD. In this study the measurement of inferior RNFL was significantly correlated with MD and PSD in moderate POAG patients. Regarding the severe POAG patients the measurements of superior, inferior, and average RNFL showed statistically significant correlations with MD and PSD. We observed that RNFL thickness obtained by OCT was decreased in the progression of POAG which was well correlated with MD indices. However, there was no significant correlation between OCT measurements and PSD in both moderate and severe POAG patients.

Previous studies demonstrated that macular retinal thickness and volume has been capable of revealing glaucomatous damage, nevertheless peripapillary RNFL thickness measurements showed higher sensitivity and specificity to determine VF abnormalities

[15, 16]. In this study macular retinal thickness and volume were significantly different between moderate and severe POAG patients and these measurements were not correlated with MD indices of AP.

In a previous study, Brigatti *et al*. [17] found a statistically significant correlation between optic disc parameters measured with HRT and functional measurements that were obtained with AP. Wollstein G *et al*. [18] also compared the confocal laser scanning ophthalmoscope parameters with the MD indices of AP in early glaucomatous patients. They found that MD indices were significantly correlated with the measurements of neuroretinal rim area, optic/disc area, cup/disc area ratio and optic disc area. In our study cup area, cup/disc area, cup/disc area (linear) and maximum cup depth were significantly correlated with MD in moderate POAG. In addition significant correlations were found between cup area, cup/disc area, cup/disc area (linear), average and maximum cup depth and cup shape measure in patients with severe POAG.

Previous studies demonstrated that GDx VCC system can be as sensitive as Stratus-OCT in demonstrating the RNFL thickness decrease in glaucoma. In these studies the NFI was found to be the best discriminating parameter which increases as the glaucoma progresses [19, 20]. In our study the NFI value was significantly higher in severe POAG than moderate POAG. In addition it was significantly correlated to MD in severe POAG.

Medeiros FA *et al*. [3] also evaluated the diagnostic capability of GDx VCC, HRT II, and Stratus OCT and showed similar results for all devices. Zangwill *et al*. [21] compared the ability of 3 instruments to differentiate healthy eyes from eyes which had early to moderate glaucomatous visual field defects. They found that measurements obtained with OCT and HRT achieved higher sensitivities compared to GDx. In our study OCT achieved the most correlated measurements with AP indices among the three devices in both moderate and severe POAG patients.

DeLeón Ortega *et al*. [22] found that the measurements of GDx, HRT II and Stratus OCT had high reproducibility in early glaucoma however the repeatability was worse in advanced glaucoma which is probably to conclude the use of NFI by GDx-VCC, rim area, cup area, and cup-to-disc area ratio from both HRT II and Stratus OCT in advanced glaucoma. In our study no significant correlation was found between these imaging devices and AP in patients with MD values less than -20 dB. This may probably be associated with the loss of glial tissue in the advanced glaucoma which may result the false high measurements.

CONCLUSION

OCT measurements had the highest correlations with the indices of AP in both moderate and severe POAG patients whereas HRT III had the lowest values. The correlations of all devices decreased in patients with more advanced glaucomatous damage hence AP still seems to be useful in the follow up disease progression in these glaucoma patients.

Authors' Contribution

Study Conception: MEA, MB, EG, ÖBT, SY; Study Design: MEA, MB, EG, ÖBT, SY; Supervision: MEA, MB, EG, ÖBT, SY; Funding: MEA, MB, EG, ÖBT, SY; Materials: MEA, MB, EG; Data Collection and/or Processing: MEA, MB, EG; Statistical Analysis and/or Data Interpretation: MEA, MB, EG; Literature Review: MEA, MB, EG; Manuscript Preparation: MEA, MB, EG and Critical Review MEA, MB, EG.

Conflict of interest

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The European Research Journal 2021;7(3):278-283 Original Article

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The role and efficacy of multidisciplinary council in the bone and soft tissue tumor patients

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ABSTRACT

Objectives: Bone and soft tissue tumors have become more common and recognized diseases with developing medical technologies. The life span of the patients has been prolonged with more effective treatment methods and developing technology. Regardless of their area of expertise, the concept of multidisciplinary tumor approach has emerged in recent years, since it is difficult for a single physician to manage a malignant mass treatment process. For this purpose, we aimed to share our multidisciplinary bone and soft tissue tumor council data results.

Methods: Patients who were evaluated at the Department of Orthopedics andTraumatology of Ondokuz Mayis University between January 2004 and June 2017 were evaluated retrospectively. For this study, the weekly archived tumor council forms were evaluated and the data were transferred to the computer via Microsoft Excel and SPSS programs. The database for the specified years was created and the results were evaluated and the database was evaluated.

Results: A total of 2788 patients were included in the study. After the patients with data deficiency were removed, 2397 patients were the subject of the study. In the evaluation of the first 1960 patients, 658 primary bone tumors, 577 primary soft tissue tumors, 356 cases of metastases and 374 non-tumoral cases were detected. The most common benign bone tumor was enchondroma, while the most common malignant bone tumor was osteosarcoma. The most common benign soft tissue tumor was lipoma, whereas the most common malignant soft tissue tumor was malignant mesenchymal tumor. The most common non-tumor cause was chronic infection. The diagnosis of 203 patients was different from the definitive diagnosis.

Conclusions: In this study, we determined the epidemiological distribution of the cases evaluated in the multidisciplinary tumor council in the Middle Black Sea and the role of multidisciplinaryapproach in treatment and survival has a positive effect especially in selected patient groups.

Keywords: Multidisciplinaryapproach, benign bone tumor, soft tissue tumor, sarcomas

Before the modern treatment approaches in current use, amputation was the primary treatment method for the cases with a malignant bone or soft tissue tumor. With developments over time, adjuvant chemotherapy or radiotherapy was introduced to the treatment protocols of sarcoma patients. Even with these innovations on bone and soft tissue tumors field, the 5-year survival rates of these protocols were meager. In recent years, there has been an increase in the determination of musculoskeletal system tumors with

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the development and widespread use of the diagnostic methods of computed tomography (CT) and magnetic resonance imaging (MRI) and these tumors are well recognized nowadays.

Experienced centers are at the forefront of diagnosis and treatment of musculoskeletal system tumors. When examined from the perspective of a single specialty, the diagnosis and treatment of malignant bone and soft tissue tumors is usually insufficient. In this context, the treatment of musculoskeletal system tumors started to be planned by a multidisciplinary council worldwide. With the multidisciplinary tumor council, delayed diagnosis of malignant sarcomas have been avoided, the time to initiation of treatment has been shortened, and there has been a positive effect on survival rates. The Council is formed of specialists from orthopedics and traumatology, pathology, radiology, nuclear medicine, radiation oncology, internal medicine, and pediatric oncology. In Turkey, a similar council method of working was first implemented by Güven Yücetürk *et al*. [1].

This study aimed to emphasize the importance of a multidisciplinary approach in the diagnosis and treatment of bone and soft tissue tumors by retrospectively evaluating the data of the database of Bone and Soft Tissue Tumour Council (BSTTC) of Ondokuz Mayis University School of Medicine between June 2004 and June 2017. It was also aimed to share the data of a bone and soft tissue tumor center.

METHODS

The study included patients evaluated by the BSTTC, which operates within the Orthopaedics and Traumatology Department of Ondokuz Mayis University School of Medicine. The study parameters were formed based on the BSTTC form, including patient name, age, gender, complaints, in brief, initial diagnosis, definitive diagnosis, and BSTTC decision. The study database was created from a retrospective scan of these data.

Ethical Committee Approval

Approval for this study was granted by the Clinical Ethics Committee of Ondokuz Mayis University (decision no: OMUKAEK 2017/259, dated: 20.07.2017). No financial support was obtained from any source for this study.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS for Windows 21.0 software (SPSS Inc, Chicago, IL, USA). Descriptive statistics were presented as mean ± standard deviation, median (minimum-maximum) values, frequency (n) and percentage (%)

RESULTS

Between 2004 and 2017, a total of 2788 patients were evaluated by BSTTC of Ondokuz Mayis University School of Medicine. When the BSTTC evaluation forms were screened, the data of 391 patients were incomplete, so these patients were excluded from the study. The data of the remaining 2397 patients were, and it was determined that 437 patients were discussed more than once by BSTTC. These 437 patients were excluded, and the study sample was formed of 1960 patients who received an initial diagnosis of bone or soft tissue tumor. These patients comprised 996 males and 964 females with a mean age of 40.54 years (min 17 days-max 96 years). The primary bone tumor was determined in 658 patients, primary soft tissue tumor in 577, metastatic disease in 356, and non-tumoral conditions in 369. The study parameters are shown in Table 1.

In some cases, a single patient was evaluated several times by BSTTC. For example, one patient with a diagnosis of osteosarcoma was discussed by BSTTC eight times. This situation was generally observed in patients diagnosed with malignant bone or soft tissue tumor. Sometimes evaluation of complications that developed in the treatment process and if necessary, a review of the treatment, meant that the patient was re-evaluated by BSTTC.

Taking this information into consideration, BSTTC re-evaluated 72 (20%) of all the metastatic cases, 64 (53.33%) patients with Ewing sarcoma, 48 (66.66%) with osteosarcoma, 19 (27.76%) with malignant mesenchymal tumour, 12 (21.81%) with giant cell bone tumour, all the cases with atypical lipomatous mass (19 times, 190%), 11 (44%) patients with chondrosarcoma, 10 (62.5%) with desmoid tumour, and 10 (18.51%) with osteoid osteoma.

Table 1. Details of the patients included the study

	The number of patients (n)
Patients evaluated by BSTTC 2004 and 2017	2788
Total number of patients after exclusion of those with incomplete data	2397
Patients discussed more than once by BSTTC	437
Total number of patients included the study	1960
Gender	
Male	996
Female	964
Mean age (years)	40.54
Primary bone tumour	658
Benign (n = 447)	
Malignant (n = 211)	
Primary soft tissue tumour	572
Benign (n = 353)	
Malignant (n = 219)	
Metastatic disease	356
Non-tumoral conditions	374

BSTTC = Bone and Soft Tissue Tumour Council

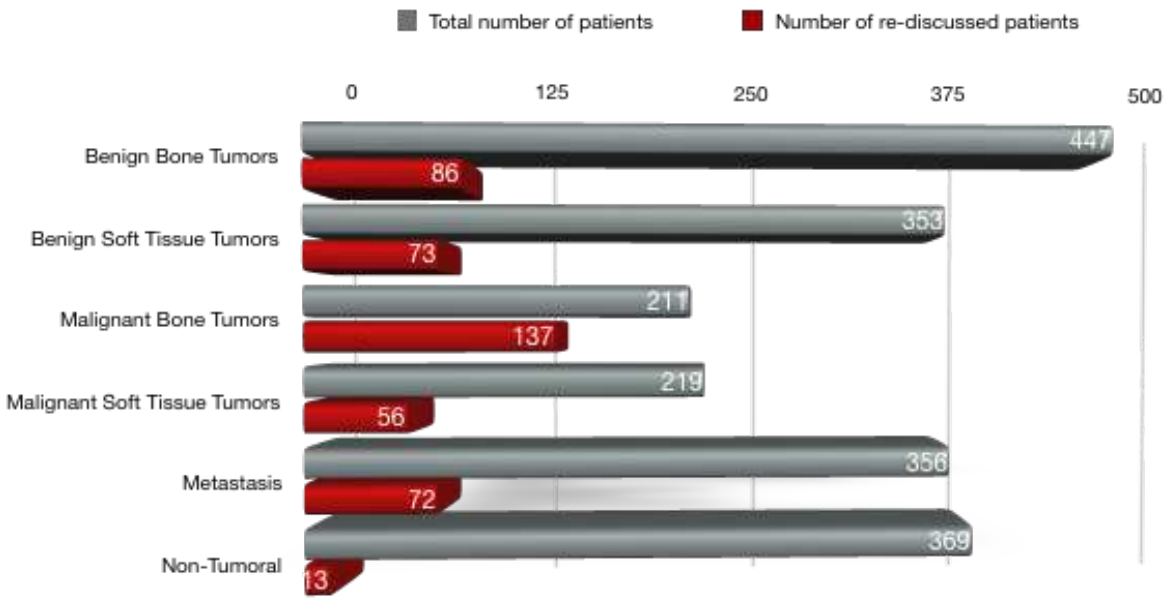

Fig. 1. The ratios of re-evaluated patients to the totals of all diagnosed patients.

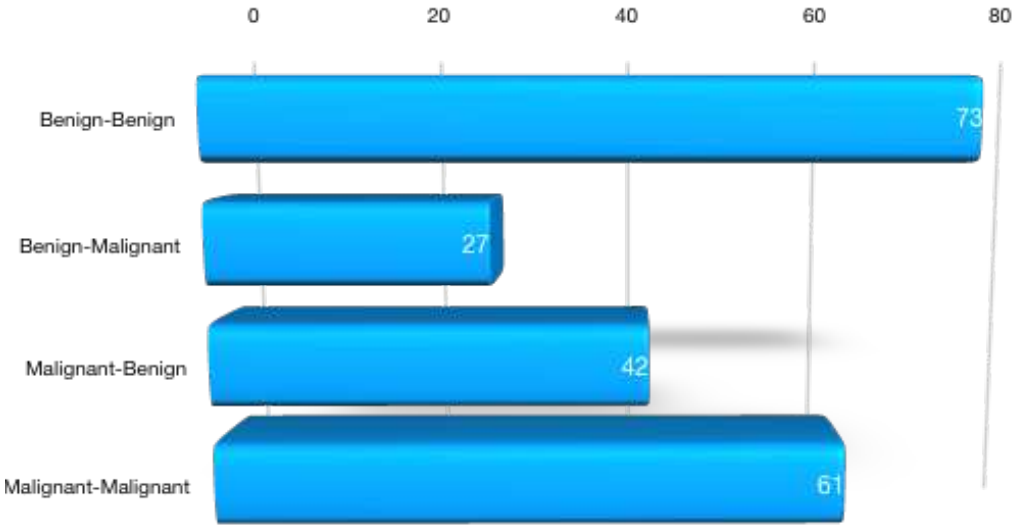

Fig. 2. Patients with a re-evaluation of diagnosis. The first word refers to the initial diagnosis of the patients and the second word to the definitive diagnosis.

In other words, re-evaluation was made of 86/447 (19%) benign bone tumor cases, of 137/211 (65%) malignant bone tumors, of 73/353 (20%) benign soft tissue tumors, of 56/219 (26%) malignant soft tissue tumors, and of 72/356 (20%) metastatic cases. The detailed analyses of the cases re-evaluated by BSTTC are shown in Fig. 1.

The diagnosis of some patients was changed after re-evaluation or histopathological examination. The findings of these patients are shown grouped as the initial diagnosis and definitive diagnosis in Fig. 2.

DISCUSSION

In comparison with data in the literature, some of the most frequently seen bone and soft tissue tumors seem to be quantitatively low in our series. The reason for this is that the multidisciplinary BSTTC deals more with the evaluation of diagnoses with a treatment process open to discussion. One of the frequently seen bone tumors in literature is enchondroma [2-4], which was seen in the current series as 8.6% of all bone tumors, and osteosarcoma was determined at the rate of 10.94%.

The higher number of Ewing sarcoma than the relatively more often seen osteochondroma can be attributed to the tendency for the Council to evaluate malignant cases and there is a lesser need for the Council in the diagnosis and treatment of benign masses. This was not very different for the soft tissue tumors in this study. For example, while cystic hygroma is among the most frequently seen soft tissue tumors [5], only 17 patients diagnosed with cystic hygroma were found in the 14-year archive of the BSTTC. The number of cases diagnosed with the malignant soft tissue tumor such as liposarcoma was 33, usually expected less common than cystic hygroma.

One of the aims of the multidisciplinary tumor council is to increase patient comfort and extend survival of these patients with collaboration between disciplines by organizing the optimum conditions for the treatment of patients with malignant bone or soft tissue tumors. In light of this information, the study data were examined of 1960 patients of 2397 who were first discussed by the Council and diagnosis was made for these 1960 patients. A total of 437 patients (18.23%) were re-evaluated by the Council. The treatment protocols and survival rates of patients evaluated more than once by the Council, and the prognostic effect of the Council are targets for future studies.

When literature is examined, it can be seen that the treatment algorithm has generally been formed with a multidisciplinary approach for metastatic bone disease [6, 7]. There are also studies related to a multidisciplinary approach for malignant bone tumors such as osteosarcoma and Ewing's sarcoma [8, 9]. In a study that evaluated the multidisciplinary approach

to 8 cases of malignant mass within the pelvis, satisfactory short-term results were obtained in all eight patients who received multidisciplinary treatment. According to that study, the survival rate of patients undergoing appropriate surgery for bone tumors in the pelvic region can be increased with a multidisciplinary approach comprising interventional radiologists, pediatric and medical oncologists, orthopedic surgeons, urologists, colorectal surgeons and plastic surgeons [10].

Re-opening the discussion of a case evaluated by the BSSTC is the result of a multidisciplinary approach. Since bone and soft tissue sarcomas are not common, there can be difficulties in the interpretation of imaging and histology, and because of the options of treatment methods and the complexity of treatment, systematic multidisciplinary team management is needed for these patients. A team with an integrated multidisciplinary clinic and a structured sarcoma tumor management panel facilitate team coordination and communication [11].

The management of soft tissue sarcomas requires multidisciplinary care [12]. When a multidisciplinary team is not used for patients with soft tissue sarcoma, surgery may not be optimal in the first intervention, and this can lead to a need for more extensive surgery than for the original tumor and radiation at later stages [13, 14]. Also, there may be a more significant treatment costs for patients with bone and soft tissue tumors in the future because of the nonoptimal treatment process. Alamanda *et al*. [15] stated that there was an additional cost of 3679 USD in patients applied with re-excision following primary excision. Furthermore, primary operations performed without care by inexperienced hands can cause unnecessary amputations [16]. In the data of the current study, the three diagnoses most often repeatedly discussed were the metastatic bone disease, Ewing sarcoma, and osteosarcoma. When literature is examined, the importance of a multidisciplinary approach in the diagnosis and treatment of these types of malignant tumors can be observed [6-12].

It was observed that the diagnosis of some patients was changed after discussion in the Council or after histopathological examination. The findings of these patients were then shown as different patient groups with the initial and definitive diagnoses. In this section, when the tumors were separated into four groups according to the histopathological behavior, the most dramatic difference was in 27 patients with a benign diagnosis that became malignant. This can be considered to demonstrate that malignant tumors were captured at a lower grade and that the survival rate was increased with appropriate treatment. The diagnosis of malignant tumor of these 27 patients was confirmed with biopsy and surgery, and the importance of a multidisciplinary approach was observed on this point.

For the other groups, a less radical change was seen (initial benign diagnosis was definitively diagnosed as the benign and initial malignant diagnosis was definitively diagnosed as malignant). While 42 patients were considered to have an initial malignant diagnosis, a definitive benign diagnosis prevented unnecessary surgical interventions which would cause unnecessary costs, and this is another benefit of the multidisciplinary Council. In other words, in 69 (33.99%) of 203 patients with a different definitive diagnosis from the initial diagnosis (a benign diagnosis becoming malignant and vice versa), the treatment was radically changed. As the ratio of all the patients evaluated by BSTTC, this number (69/1960) constituted 3.52%. This group can be considered to represent the patient group for whom the multidisciplinary tumor approach provided the most benefit.

When the diagnoses of the patients with the different initial diagnosis were examined, the three leading diagnoses that changed as a result of the detailed evaluation were formed of changes associated with infection, metastasis, and trauma. Several bone tumors are seen in forms similar to those of inflammation processes. The difference between osteomyelitis and primary bone tumor, especially Ewing sarcoma, always creates a problem. Consequently, it is generally difficult to interpret the difference between clinical and radiological findings. Osteomyelitis and bone tumors usually occur in young people. In several conditions, direct radiographs cannot be fully interpreted, and therefore, this method must not be significantly trusted when establishing the diagnosis. If a diagnosis is made by only direct radiographs, errors can be made [17].

CONCLUSION

In the treatment of a malignant tumor, working

collaboration must be provided between the disciplines, and there must be specialists from radiology, pathology, medical oncology, radiation oncology and nuclear medicine in the team in addition to the orthopedic oncologist. In some patients thought to have a benign mass in the initial diagnosis, a diagnosis of a malignant mass was revealed as a result of the evaluation by the Tumour Council. Thus significant treatment changes were made in the early stages to prolong the survival rate of these patients, and the biopsychosocial healing process of the patients was accelerated. In some patients initially thought to have a malignant mass, a definitive diagnosis of a benign mass was revealed as a result of the Tumour Council evaluation, and for these patients unnecessary surgery, treatments and its costs were avoided.

Authors' Contribution

Study Conception: HSC, NB; Study Design: NB; Supervision: NB; Funding: HSC, NB; Materials: HG, FS; Data Collection and/or Processing: HSC, NB, HG, FS; Statistical Analysis and/or Data Interpretation: HG, FS; Literature Review: HSC; Manuscript Preparation: HSC and Critical Review: NB.

Conflict of interest

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

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The effect of different tonsillectomy techniques on taste sensation in the early and late postoperative periods

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ABSTRACT

Objectives: Impairment in taste sensation is a rare complication of tonsillectomy. We aimed to reveal the effects of different tonsillectomy techniques on taste sensation by assessing the impairment in taste sensation in the early and late postoperative periods.

Methods: In this prospective clinical study, fifty-seven (22 females, 35 males, mean age, 25 ± 9.8 years) patients who underwent tonsillectomy were included. All patients were operated on under general anesthesia, and a chemical stimulation taste test was performed one week prior to the surgery, at first week and first month postoperatively. Four basic taste sensations were assessed in the test (sweet, sour, salty, and bitter), and impairments in taste sensation in the early and late postoperative periods for each tonsillectomy technique were evaluated.

Results: In the early postoperative period, there was a statistically significant increase bitter taste sensations in patients who underwent tonsillectomy (p = 0.020). In the late postoperative period, sour and bitter taste sensations were significantly increased in the patients (p = 0.001, p = 0.002 respectively). In contrast to the early postoperative period, total taste sensation was significantly increased in the late postoperative period (p = 0.034).

Conclusions: The bitter sensation in the early postoperative period and the bitter and sour sensations in late postoperative period were found to be significantly increased in this present study. With regard to these results, a thorough preoperative explanation should be done.

Keywords: Tonsillectomy, taste sensation, chemogustometry

Tonsillectomy is one of the oldest and most commonly performed surgery worldwide. Impairment in taste sensation after tonsillectomy is a rare complication, and it can affect quality of life in the postoperative period. Few studies reported on this complication, which is thought to be due to lingual nerve branch of the glossopharyngeal nerve traction during tonsillectomy or from indirect thermal injury [1, 2]. Impairment in taste sensation can lead to malnutrition, significant gains or losses in weight, and changes in dietary. To reduce the risk of complications of tonsillectomy which can cause significant morbidities, many techniques have been described, such as cold dissection, mono-polar and bipolar dissections, laser tonsillectomy cryosurgery, harmonic scalpel electro surgery, coblation, thermal welding, and

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plasma knife. The most frequently performed technique among these is cold dissection, but none of these techniques has been universally accepted.

Many studies compare the effects of various tonsillectomy techniques, but, to our knowledge, the effect of different techniques on taste sensation has not been investigated. In this study, we aimed to evaluate the effect of different techniques on taste sensation in the early and late postoperative periods following tonsillectomy.

METHODS

Study Design and Population

Fifty-seven (35 [61.4%] males, 22 [38.6%] females) patients with an age range of 12 to 50 (mean: 25 ± 9.8) years who underwent different tonsillectomy techniques were enrolled to this randomized and prospective study. Patients with chronic systemic diseases which could affect taste sensation (e.g., chronic kidney disease and middle ear diseases) and patients who were previously diagnosed with taste disorders, who were on medication, or who were operated on for bleeding as a complication of tonsillectomy were excluded from the study.

All patients were informed preoperatively about the study and surgical procedure, and written consent was obtained from each patient. The study protocol was approved by the local Ethics Committee (KAEK 2016/1145).

Surgery Procedures

Randomization of the groups to determine surgical technique was decided by lot. All patients were operated on under general anesthesia. The harmonic scalpel was used in 13 (22.8%) patients, bipolar cautery was used in 18 (31.6%) patients, cold dissection was used in 14 (24.6%) patients, and thermal welding was used in 12 (21.1%) patients. Preoperatively, 0.5mg/kg of dexamethasone was administered intravenously to all patients (max. 8 g). Oral feeding with cold liquids was started in patients without active bleeding or nausea/vomiting in the fourth postoperative hour. All patients were discharged on the first postoperative day.

Evaluation of Taste Sensation

Nowadays the two most commonly used tests are electrogustometry and chemogustometric test. Bitter, sour, sweet, salty and umami solutions are used in the chemical tests and electrical current is used in electrogustometry to create the sense of taste. Electrogustometry makes quantitative measurements whereas chemogustometry makes both quantitative and qualitative measurements [3]. For this reason, we used chemogustometric tests in our study.

Preoperative taste sensation was evaluated, and results were recorded one week prior to the surgery. Postoperative taste sensation was evaluated first week (early period) and first month (late period). The patients were informed about not eating, smoking or brushing their teeth for an hour before the test.

Four basic taste sensations were evaluated (sweet, sour, salty, and bitter) by using a chemical stimulation test. Filtered paper strips (Taste Strips; Burghart, Wedel, Germany) were used for the test. The strips were 8 cm long, with 2×2 cm area of impregnated taste materials on the tip [3]. On the strips, four different concentrations for all four basic taste sensations were present. Distilled water was used as diluent and taste materials used, and the concentrations were as follows: (1) Sweet: 0.4, 0.2, 0.1, and 0.05 gr. sucrose/ml, (2) Sour: 0.3, 0.165, 0.09, and 0.05 gr. citric acid/ml, (3) Salty: 0.25, 0.1, 0.04, and 0.016 gr. sodium chloride/ml, (4) Bitter: 0.006, 0.0024, 0.0009, and 0.0004 gr. kinin hydrochloride/ml.Taste solutions were freshly prepared at regular intervals. Strips were put on the left or right side of the tongue. Taste sensation is carried by chorda tympani nerve, which is a branch of facial nerve, on the anterior part of the tongue. Posterior part of the tongue is innervated by the lingual nerve which is a branch of glossopharyngeal nerve. Taste strips were applied to both parts of the tongue. Tonsillectomy can affect the taste sensation on the posterior part of tongue by damaging the lingual branch of glossopharyngeal nerve. However tonsillectomy does not cause any damage to chorda tympani which innervates the anterior part of the tongue. Therefore, our results reflects the effects of tonsillectomy on taste sensation of posterior part of tongue.

In total, 32 results were recorded. Prior to putting the strips on the tongue, patients were asked to rinse out their mouths. The test was done in increasing concentrations, and taste sensation was evaluated by randomly changing the sides for all four concentrations.

Patients were asked to choose one of the four basic tastes for each strip. Taste scores were recorded for each side of the tongue for each concentration [4]. For each taste, both sides were analyzed statistically.

Statistical Analysis

SPSS 15.0 for Windows software (IBM, Armonk, NY, USA) was used for statistical analysis. Mean, standard deviation (SD), and median values were used in descriptive statistics. The one-way analysis of variation (ANOVA) and Kruskal Wallis test were used to compare independent variables. The Friedman test and the repeated measures ANOVA were used to compare more than two groups. *P-values* of 0.05 or less were considered significant.

RESULTS

Bitter taste sensation was found to be increased in the early postoperative period and was statistically significant ($p = 0.020$) when evaluating the results, regardless of the technique used. In the late postoperative period, sour, bitter, and total taste sensations were increased and were also statistically significant ($p = 0.001$, $p = 0.002$, $p = 0.034$; respectively) (Table 1).

As it is defined, cold dissection is a cold knife technique, while hot dissection includes thermal welding, bipolar cautery, and harmonic scalpel techniques. In the early postoperative period, there was no statistically significant difference between the cold and hot technique groups in total taste sensation. However,

Table 1. Rate of taste changes in early and late postoperative period regardless of technique used

		Mean ± SD	*p* value
Early period			
Sweet	Preoperative	5.79 ± 2.27	0.425
	Postoperative	5.98 ± 2.09	
Sour	Preoperative	4.04 ± 2.28	0.107
	Postoperative	4.54 ± 2.04	
Bitter	Preoperative	4.42 ± 2.91	**0.020**
	Postoperative	5.30 ± 2.47	
Salty	Preoperative	4.84 ± 2.81	0.743
	Postoperative	4.98 ± 2.59	
Total taste	Preoperative	19.02 ± 8.20	0.133
	Postoperative	16.33 ± 9.52	
Late period			
Sweet	Preoperative	5.79 ± 2.27	0.061
	Postoperative	6.32 ± 1.89	
Sour	Preoperative	4.04 ± 2.28	**0.001**
	Postoperative	5.07 ± 1.88	
Bitter	Preoperative	4.42 ± 2.91	**0.002**
	Postoperative	5.47 ± 2.44	
Salty	Preoperative	4.84 ± 2.81	0.264
	Postoperative	5.25 ± 2.34	
Total taste	Preoperative	19.02 ± 8.20	**0.034**
	Postoperative	20.86 ± 8.35	

SD = standard deviation

Table 2. Postoperative early period taste sensation rates of hot and cold technical tonsillectomy

		Technique			
		Cold		Hot	
		Mean ± SD	Median	Mean ± SD	Median
Early period					
Sweet	Preoperative	6.1 ± 2.0	6.5	5.7 ± 2.4	6
	Postoperative	5.9 ± 1.9	6	6.0 ± 2.2	6
	***p* value**	0.633		0.280	
Sour	Preoperative	3.7 ± 2.2	4	4.1 ± 2.3	4
	Postoperative	4.4 ± 2.1	4	4.6 ± 2.0	4
	***p* value**	0.394		0.193	
Bitter	Preoperative	4.6 ± 3.1	4	4.4 ± 2.9	4
	Postoperative	4.2 ± 2.5	5.5	5.7 ± 2.4	6
	***p* value**	0.421		**0.003**	
Salty	Preoperative	5.0 ± 3.2	5.5	4.8 ± 2.7	4
	Postoperative	4.9 ± 3.2	6	5.0 ± 2.4	5
	***p* value**	0.680		0.655	
Total taste	Preoperative	19.4 ± 8.6	20.5	18.9 ± 8.2	20
	Postoperative	15.7 ± 9.8	18.5	16.5 ± 9.5	19
	***p* value**	0.135		0.299	

SD = standard deviation

when each taste sensation was evaluated, the postoperative bitter taste sensation was significantly increased compared to that of the preoperative period ($p = 0.003$) (Table 2). In the late postoperative period, total taste, bitter taste, and sour taste were significantly increased in the hot technique groups compared to those in the preoperative period ($p = 0.002$, $p = 0.001$, $p = 0.031$; respectively) (Table 3).

Posttonsillectomy bleeding and oral intake limitation were seen as complications, and complication rates for each technique were recorded; posttonsillectomy bleeding was observed in 7 patient, posttonsillectomy infection was observed in 3 patients but no statistically significant differences were found among the different tonsillectomy techniques.

DISCUSSION

Tonsillectomycarries a significant risk of morbidities and can even be fatal. The most common morbidities of tonsillectomy are dehydration, oral feeding deficiency, bacteremia, otalgia, and bleeding. Taste disorders following tonsillectomy are a rare complication, but can significantly affect the patient's quality of life. Some reported studies exist in the literature about this complication [1, 2]. Chronic and recurrent inflammation in the oral cavity and oropharynx can also significantly affect taste sensation [5].

Tonsils are innervated by two discrete cranial nerves: the lesser palatine branch of the maxillary nerve and the tonsillar branch of the glossopharyngeal nerve. The main innervation of the tonsillapalatina is by the tonsillar branch of the glossopharyngeal nerve. The lingual branch of the glossopharyngeal nerve, runs adjacent to the capsule of the tonsillapalatina in 21% of the adult population, and it can be injured during tonsillectomy, causing taste disorders on the posterior part of the tongue [4]. Inflammations in the tonsillar region can also cause otalgia via the tympanic branch of the glossopharyngeal nerve.

In the literature, it is reported that direct injury or

Table 3. Postoperative late period taste sensation rates of hot and cold technical tonsillectomy

		Technique			
		Cold		Cold	
		Mean ± SD	Median	Mean ± SD	Median
Late period					
Sweet	Preoperative	6.1 ± 2.0	6.5	5.7 ± 2.4	6
	Postoperative	6.4 ± 1.8	7	6.3 ± 1.9	7
	***p* value**	0.435		0.098	
Sour	Preoperative	3.7 ± 2.2	4	4.1 ± 2.3	4
	Postoperative	4.7 ± 2.0	5	5. 2 ± 1.9	5
	***p* value**	0.242		**0.002**	
Bitter	Preoperative	4.6 ± 3.1	4	4.4 ± 2.9	4
	Postoperative	4.2 ± 2.6	5.5	5.7 ± 2.4	6
	***p* value**	0.748		**0.001**	
Salty	Preoperative	5.0 ± 3.2	5.5	4.8 ± 2.7	4
	Postoperative	4.9 ± 2.9	6	5. 3 ± 2.1	5
	***p* value**	0.776		0.184	
Total taste	Preoperative	19.4 ± 8.6	20.5	18.9 ± 8.2	20
	Postoperative	20.0 ± 8.5	21.5	21.1 ± 8.4	23
	***p* value**	0.674		**0.031**	

SD = standard deviation

indirect thermal injury of the lingual branch of the glossopharyngeal nerve during tonsillectomy can also cause a significant decrease in taste sensation [3]. Anatomical variations of the lingual branch of the glossopharyngeal nerve play an important role in this. In 21% of the adult population, the lingual branch of the glossopharyngeal nerve runs adjacent to the capsule of the tonsillapalatina, which puts it at risk of injury [6].

In the present study, irrespective of which technique was used, bitter and sour taste sensations were significantly increased in the late postoperative period. Bitter taste sensation was also increased in the early postoperative period. Unlike the expectation of deterioration in the taste sensation, these results were notable. However, our findings did not match the literature regarding this point.

Taste sensation on the posterior part of the tongue is innervated by the lingual branch of the glossopharyngeal nerve; therefore, following tonsillectomy, it is expected to see taste changes in sour and bitter tastes [7]. Previous reports on this mostly considered the taste sensation in the anterior part of the tongue, but the lingual nerve, a branch of the glossopharyngeal nerve, innervates the posterior part of the tongue [8]. However, in our study, contrary to the previous findings, bitter and sour taste sensations were significantly increased. This is thought to be the effect of inflammation of the oropharynx on taste sensation.

In a study by Stathas et al. [7], 60 patients who underwent cold knife and electrocautery tonsillectomy were evaluated for taste sensations with chemogustometry on the 1st, 15th, and 30th postoperative days. On the first postoperative day, the posterior part of the tongue was found to be more affected than the anterior part of the tongue. Bitter and sour tastes were more affected than salty and sweet tastes. On the 30th postoperative day, except for two patients, normal taste functions were regained [7]. This data shows that taste disorders following tonsillectomy are temporary. The authors suggest that this could be due to direct or indirect lingual branch of the glossopharyngeal nerve in-

jury during the operation. Indirect injury can be due to compression of the mouth gag or local anesthetic infiltration.

In the literature, it is reported that lingual branch of the glossopharyngeal nerve injury is the main cause of taste disorders following tonsillectomy. During tonsillectomy, if the superior constrictor muscle cannot be conserved properly, lingual nerve injury may occur, and this can cause significant taste disorders [6]. In our study, regardless of the technique used, the patients did not experience any taste disorders postoperatively. This can be due to successful dissection during surgery, considering the first postoperative week as the early postoperative period, and a decrease in the chronic inflammation.

In one study, inflammation was found to affect taste sensation by toll-like receptors and type I-II interferons, which caused a decrease in taste sensations [5]. Our patients were 12 to 50 years of age and had experienced recurrent infections or chronic inflammation over a long time. In addition, the medications used for treatment, including anti-inflammatory and antibiotic medications, can also affect taste sensation [9]. Oral sprays that contain chlorhexidinegluconate are used for antiseptic purposes; they also can affect taste sensation [10]. All these findings are associated with the increase in taste sensation. The increase can also be related to decreased inflammation.

The increase in taste sensation in the harmonic scalpel, bipolar cautery, and thermal welding tonsillectomy groups, compared to cold techniques, is thought to be due to local injury which is more prevalent in cold techniques. The inflammation phase of wound healing occurs on days one to six. In this study, we tested the patients at the 1st week in the postoperative period, when the inflammation phase of wound healing was nearly over. At the 1st postoperative week, we believe, the effect of inflammation of taste sensation is at a minimum.

In this study, the results for the postoperative 1st week and 30th day are similar, and this data is thought to be the result of the inflammation phase of wound healing which is usually over by the 6th postoperative day. Irrespective of the techniques used, in the early postoperative period, bitter taste was significantly increased, and, in the late postoperative period, bitter, sour, and total taste sensations were significantly increased. These tastes are associated with the posterior part of the tongue, and this data can be explained by the decline in chronic inflammation, which has negative effects on taste sensation and shows that the lingual nerve was not injured during tonsillectomy.

A research was published on this subject in 2018. The highest prevalence of self-reported taste disturbances occurred two weeks after surgery (32%). Two studies reported post-operative chemical gustometry scores consistent with hypogeusia. However, in the two studies that compared pre- and post-tonsillectomy test scores, one found no difference and the other found a significant difference only for the left rear of the tongue 14 days post-op. In the two studies that employed electrogustometry, elevated post-operative thresholds were noted, although only one compared pre- and post-operative thresholds. This study found no significant differences. No study employed a normal control group to assess the influences of repeated testing on the sensory measures. Overall, this review indicates that studies on post-tonsillectomy taste disorders are limited and ambiguous. [11].

Limitations

This study has a number of limitations. Small sample sizes and lengths of follow-up are the major limitations. However, the best of our knowledge, our analysis is the first study which evaluate taste disorders after different tonsillectomy techniques prospectively. When viewed from this aspect this study could flash on novel investigations. Further studies with larger cohorts should be conducted in evaluating the effects of tonsillectomy and its various surgical techniques on taste sensation.

CONCLUSION

In conclusion, although tonsillectomy may cause taste disorders as a rare complication, the bitter sensation in the early postoperative period and the bitter and sour sensations in late postoperative period were found to be significantly increased in the present study. With regard to these results, a thorough preoperative explanation should be done.

Authors' Contribution

Study Conception: ZNE, BT, MC; Study Design: ZNE, BT, AA; Supervision: ZNE, BT, BUC; Funding:

ZNE, BT, AA; Materials: ZNE, NS, MC; Data Collection and/or Processing: ZNE, NS, MC; Statistical Analysis and/or Data Interpretation: ZNE, BT, MC; Literature Review: ZNE, BT, MC; Manuscript Preparation: ZNE, NS, MC and Critical Review: ZNE, NS, BUC.

Conflict of interest

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The effect of cesarean section on the incidence of congenital nasolacrimal duct obstruction

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ABSTRACT

Objectives: The aim of this study is to evaluate the effect of cesarean section (CS) on the incidence and recovery of congenital nasolacrimal duct obstruction (CNLDO).

Methods: The files of patients diagnosed with CNLDO, epiphora, and dacryocystitis under the age of 24 months were identified retrospectively. Patients were divided into 2 groups according to whether they were born via normal vaginal delivery (VD) or CS. Demographic data, gestational age, birth weight, application of lacrimal massage, and surgical treatment modalities were recorded from medical records.

Results: The study included 173 consecutive patients, 68 were females and 105 were males. Eighty-two (47.4%) patients were born via VD and 91 (52.6%) patients were born via CS. The frequency of CS delivery in children with CNLDO (47.4%) was significantly higher than the same hospital's total frequency of CS delivery (40.2%) ($\chi^2 = 11$, df = 1, $p = 0.001$). At presentation, the mean age of the patients born via CS was lower than patients born via VD (9.4 ± 6.8 months vs 12.07 ± 8.8 months) ($p = 0.027$). In 40 patients who had a family history of CNLDO, 23 patients recovered through non-surgical treatment, while 17 patients had a surgical intervention, which was found to be statistically significant ($p = 0.009$). The gestational age and birth weight of patients born via CS were significantly lower than patients born via VD ($p < 0.001$ and $p = 0.01$, respectively).

Conclusions: Cesarean section delivery could increase the incidence of CNLDO.

Keywords: cesarean section; vaginal delivery; congenital nasolacrimal duct obstruction

Congenital nasolacrimal duct obstruction (CNLDO) is one of the most common eye disorder in infants with an incidence of 5.7% and 20% [1-3]. Symptoms begin in the first month after delivery in 95% of patients [2]. In addition to epiphora, bacterial infections can develop secondary to tear stasis, resulting in burrs and crusting of the eyelids [4]. The development of nasolacrimal canal ranges from 6th months of intrauterin life to weeks following birth. Hasner valve (HV) is located at the distal end of nasolacrimal canal which opens into the inferior meatus. The most common cause of obstruction is the presence of the Hasner membrane (HM), a thin mucous membrane that persists after birth. Rarely, bony canal obstructions may also occur [5, 6]. It has been reported that in 70% of cases, the lacrimal canal opened spontaneously in the first 3 months and a total of 96% in the first year [7, 8].

The first line of treatment for CNLDO is lacrimal sac therapy massage (Crigler massage) for patients

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younger than 12 moths old. The massage is performed with the purpose of increasing the hydrostatic pressure, in order to open the obstruction by rupturing the membrane at the distal end of the canal. Lacrimal canal probing and irrigation is required in patients older than 12 months old. In case of the obstruction still persists after the lacrimal canal probing, silicone intubation and dacryocystorhinostomy are required [10].

The number of studies investigating the effect of cesarean section (CS) delivery on children's general health status has raised due to the increase of cesarean delivery rates in recent years. These studies suggested that babies born via CS delivery had a higher risk in the development of diseases such as obesity, diabetes mellitus, asthma, dermatitis, allergic diseases and immune system deficiencies [11]. Uterine contractions during normal vaginal delivery (VD) may naturally increase the hydrostatic pressure on the lacrimal sac which Crigler massage aims to mimic. Therefore, symptomatic nasolacrimal duct obstruction may be fewer in babies born via vaginal delivery. Some studies suggested that frequency of CNLDO was higher in children born via CS [12-15], whereas some data indicated no association between the mode of delivery and CNLDO [16-18]. The aim of this study is to evaluate the probable effect of mode of delivery, gestational age, and birth weight on CNLDO.

METHODS

The records of children diagnosed with epiphora, CNLDO, and dacryocystitis between January 2016 and January 2020 at department of ophthalmology, were analyzed retrospectively. The study was approved by the Institutional Ethics Committee (2011-KAEK-26/269, dated 20.05.2020). All protocols adhered to the tenets of the Declaration of Helsinki. Patients that were under the age of 24 months were included to the study. Patients who had incomplete information about birth records and a history of ocular or nasolacrimal trauma, craniofacial malformation, and lacrimal system anomaly were excluded from the study.

Following the routine ophthalmologic examinations, fluorescein dye disappearance test was performed patients with epiphora. A 2% fluorescein solution was dropped into the conjunctival sac. Delayed clearance of fluorescein dye within 5 minutes indicates lacrimal drainage system obstruction. The parents of the patients younger than 12 months were educated about the appropriate massage methods. Antibiotic eyedrops were added to the treatment in patients accompanying conjunctivitis. Lacrimal probing under short anesthesia was carried out in symptomatic patients older than 12 months and lacrimal irrigation was performed in order to ensure the obstruction was cleared up. Two months after the probing, if the epiphora was still persisting, the lacrimal probing was repeated. Monocanalicular silicone intubation was performed in patients whose epiphora persisted after the second probing.

Demographic data, mode of delivery, gestational age, birth weight, application of lacrimal massage, surgical treatment type, recovery age, and family history were recorded from the patient's file records.

Statistical Analysis

The data was examined by the Shapiro Wilk test to verify whether or not it presented normal distribution. The results were presented as mean ± standard deviation or frequency and percentage. Normally distributed data were compared with independent samples t-test. Categorical variables were compared using Pearson's chi-square test and Fisher's exact test between groups. Significance level was considered as $p < 0.05$. Statistical analyses were performed with IBM SPSS ver.23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

RESULTS

Of the 173 consecutive patients, 68 were females and 105 were males. Of these, 82 (47.4%) were born via VD and 91 (52.6%) were born via CS. Frequency of CS delivery in the same hospital between the years of 2016 and 2020 was calculated as 40.2% from the reports of obstetrics clinic. Current hospital CS rates (40.2%) were found to be significantly lower ($\chi^2 = 11$, df = 1, $p = 0.001$) than the rate of CS delivery (47.4%) in patients with CNLDO.

The mean age at presentation was significantly lower in patients born via CS than patients born via

Table 1. Patient characteristics and clinical progression

	Total	VD	CS	*p* value
Total, n (%)	173 (100)	82 (47.4)	91 (52.6)	0.400
Age (months)		12.07 ± 8.8	9.4 ± 6.8	0.027
Gender, n (%)				0.943
Female	68 (39.3)	32 (39.0)	36 (39.6)	
Male	105 (60.7)	50 (61.0)	55 (60.4)	
Birth weight (grams)		3411.87 ± 486.9	3171.94 ± 673.51	0.01
Gestational age (weeks)		39.4 ± 1.3	38.1 ± 2	0.001
Family history, n (%)				0.729
Yes	133 (76.9)	64 (78.0)	69 (75.8)	
No	40 (23.1)	18 (22.0)	22 (24.2)	
Recovery status, n (%)	69 (39.9)	30 (43.5)	39 (56.5)	0.400
Non-surgical				
Surgical	104 (60.1)	52 (50)	52 (50)	
Recovery age (months)		15.3 ± 9	14.5 ± 7.4	0.506

Data are shown as mean±standard deviation or n (%). VD = vaginal delivery, CS = cesarean delivery

VD ($p = 0.027$). The gestational age and birth weight of patients born via CS were significantly lower than patients born via VD ($p < 0.001$, $p = 0.01$, respectively) (Table 1).

Patients were divided into 2 groups in regard of their recovery status, 69 (39.9%) who recovered with non-surgical treatment (group 1) and 104 (69.1%) who underwent surgical intervention (group 2). In group 1, 30 patients (43.5%) were born via VD and 39 patients (56.5%) were born via CS. In group 2, 52 patients (50%) were born via VD and 52 patients (50%) were born via CS. There was no statistical difference between the mode of delivery and the recovery status ($p = 0.40$) (Table 2).

The parents of the patients were questioned about the adherence of the lacrimal sac massage. The answers were indicated that 54 patients (31.2%) did not receive any massage, 34 patients (19.7%) received infrequent massage and 83 patients (48%) received regular massage. Forty patients had a family history of CNLDO. In these patients, while 7 of them (17.5%) did not receive any massage, 7 patients (17.5%) received infrequent massage and 26 patients (65%) received regular massage, which was found to be statistically significant ($p = 0.042$). Twenty three of 40 patients recovered though non-surgical treatment while 17 had a surgical intervention, which was found to be statistically significant ($p = 0.009$).

Table 2. Association between mode of delivery and outcomes of surgical treatment

Treatment	VD n (%)	CS n (%)	*p* value
Non-surgical	30 (43.5)	39 (56.5)	0.400
Surgical	52 (50)	52 (50)	0.553
First lacrimal probing	41 (50)	41 (50)	
Second lacrimal probing	5 (38.5)	8 (61.5)	
Silicone intubation	4 (57.1)	3 (42.9)	
Failed	2 (100)	0 (0)	

VD = vaginal delivery, CS = cesarean delivery, n = number

When patients were divided into two groups based on gestational age (over and under 37 months), in both groups, there was no relationship found between the mode of delivery and recovery status ($p > 0.05$).

DISCUSSION

In recent years, there has been a notable increase in CS delivery in all over the world. From 1960s to nowadays, CS delivery rates have raised from 5% to 50% [19]. In Turkey, it has been reported that CS delivery rates have increased up to 40-50% [20]. Respiratory complications are more frequent in babies born via personal preference cesarean. During the labor, intrauterine pressure raised up to 200 cmH20 compared to CS delivery in which the intrauterine pressure remains at 75 cmH20. Due to the pressure not increasing during CS, fetal lung fluid retention and respiratory system diseases are more common in children born via CS [21, 22]. Lacrimal massage is the most effective method in treatment of CNLDO, and the rationale of this technique is depend on increasing the hydrostatic pressure in lacrimal sac. Through a similar mechanism, lacrimal irrigation can also open the HM. Since exposure to the intrauterine pressure is lower in babies born via CS compared to VD, the incidence of CNLDO may be higher in these children.

In this study, there was no difference between CS and VD rates in patients with CNLDO however, rates of CS delivery of CNLDO patients in our hospital was significantly higher than the rates of CS delivery in the study region overall. The mean presentation age of patients born via CS was significantly lower than patients born via VD. The delivery mode did not have an impact on the recovery status and response to surgical intervention.

Spaniol *et al*. [12] found no significant difference between the overall CS rate and incidence of CNLDO. Patients born via CS delivery were further divided to primary CS (elective and before the onset of labor) and secondary CS (after the active phase of the labor). The authors reported that the relative risk of CNLDO was 1.7-fold higher in patients born via primary CS compared to the patients born via vaginal delivery and via secondary CS [12]. Due to the lack of normal birth mechanisms in primary CS, they suggested that the risk of CNLDO was higher. In our study, primary and secondary CS was not distinguished in patients born with CS. Despite this, CS delivery rate in patients with CNLDO (47.4%) was found higher than CS delivery rate in general population of the study region (40.2%). Some studies reported that the pressure created during normal delivery on the nose leads to nasal septal deviation. It is also believed that this compression due to the pressure also affects the nasolacrimal canal and HV [23, 24].

Fetus passing through the pelvic canal and increase in the intrauterine pressure cause certain mechanical changes in the soft tissue and facial structures as well as affecting the hydrostatic pressure in the lacrimal drainage system and could facilitate the opening the HM. Due to the fetus being exposed to the intrauterine pressures of normal vaginal delivery and, swallowing and aspirating the collagenolytic enzymes in the amniotic fluid into the nasal cavity, the opening of HM is facilitated. In the study conducted by Tavakoli *et al*. [13], CS delivery rate (60.6%) of 104 CNLDO patients was significantly higher than the CS delivery rate (47.9%) of the general population in their study region ($p = 0.0097$). Patients born via CS presented to their institution at an earlier age than patients born via VD, which was also the case in our study. Patients born via VD had a tendency to improve with conservative treatment ($p = 0.001$). In this study, the higher age at presentation of those born with VD might indicate that they recovered earlier with conservative treatment however, there was no statistical difference between CS and VD group in terms of tendency to improve with conservative treatment.

Karti *et al*. [25] found that almost half (45.5%) of the CNLDO patients who improved with conservative treatment were 6 months of age or younger, and 78.8% were 9 months or younger. Due to the mean age of the patients presenting at our hospital was 10.7 ± 8 months, they passed the stage of high likelihood of improvement with conservative treatment. We believe that this is the reason of the lower than expected number of patients recovered with conservative treatments in our study.

In a recent study, first lacrimal probing procedure was failed in 29 of 50 patients. Twenty five of 29 patients who received additional treatment, were born via CS through an unclear mechanism, they believed that patients born with CS were more complex CNLDO cases and required more additional therapies

[13]. The absence of swallowing and aspirating the collagenolytic enzymes may result in a more resistant HM requiring additional intervention.

In our study there was no statistically significant difference between surgical success and mode of delivery. Our surgical success rate after the first probing was 78.8% which is consistent with the literature (72-97%) [26-28]. Similar to our study, Kuhli Hattelbach *et al*. [15] showed that cesarean delivery increased the prevalence of CNLDO however they did not find a relationship between the mode of delivery and surgical success. Palo *et al*. [16] found no relationship between mode of delivery and CNLDO in their study conducted with to 200 patients (97 VD, 103 CS) who underwent surgical intervention. However, they found a significant relationship between the complex type CNLDO (n = 28) and cesarean delivery ($p = 0.016$). Alakus *et al*. [17] suggested no relationship between CNLDO and CS delivery. However, in patients born via first delivery, the CS delivery rate in patients with CNLDO (58.7%) was significantly higher than those without CNLDO (20.7%) ($p < 0.001$) [17]. They stated that permanent pelvic floor damage develops in the first vaginal delivery, which causes less labor pressure and fetus compression in the following vaginal deliveries.

In our study, the frequency of regular lacrimal massage was higher in patients who had a family history of CNLDO. Therefore, in this group of patients, the number of patients requiring surgery was less than the patients recovering spontaneously. We deduced that this outcome was due to the prior experience of the parents about the disease and lacrimal sac massage.

Limitations

The limitations of the study include retrospective data collection, small number of patients and surgical interventions were performed by different surgeons. Also, patients who recovered with conservative treatment in earlier months of life could not be included to the study.

CONCLUSION

CS delivery may increase the incidence of CNLDO. Prospective studies with larger patient series are required for assessing the association between CNLDO and mode of delivery.

Authors' Contribution

Study Conception: HGU, GUG; Study Design: HGU; Supervision: HGU, GUG; Funding: HGU; Materials: HGU; Data Collection and/or Processing: HGU, GUG; Statistical Analysis and/or Data Interpretation: HGU; Literature Review: HGU; Manuscript Preparation: HGU and Critical Review: GUG.

Conflict of interest

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The European Research Journal 2021;7(3):297-303 Original Article

DOI: 10.18621/eurj.710303 *General Surgery*

Comparison of the outcomes of 'component separation with mesh', 'component separation without mesh' and 'primary prosthetic repair' methods in complex abdominal wall reconstruction

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ABSTRACT

Objectives: The aim of this study is to compare the results of different surgical methods used in giant midline incision hernias.

Methods: The records of 90 patients operated on for a midline abdominal incisional hernia were reviewed retrospectively. The patients were divided into three groups based on the surgical method used primary prosthetic repair (PPR), component separation with mesh (CSM) and component separation without mesh (CS). Two-year follow-up results were compared.

Results: A statistically significant difference was noted between the groups in the transverse diameter measurement of the defect ($p = 0.003$). Subgroup analyses revealed that the median transverse diameter was higher in the CSM group than in the CS group ($p = 0.003$). There was also a statistically significant difference in the duration of surgery ($p < 0.001$), with a subgroup analysis revealing that the duration of surgery was longer in the CSM group than in the PPR and CS groups (PPR-CSM; $p = 0.008$, CSM-CS; $p < 0.001$). Recurrent incisional hernia, smoking and postoperative morbidity development were found to be statistically and significantly associated with recurrence ($p = 0.005$, $p = 0.002$, $p < 0.001$; respectively).

Conclusions: The use of the CSM method for the repair of giant incisional hernias may reduce recurrence.

Keywords: Component separation, incisional hernia, mesh, recurrence

Patients undergoing abdominal surgery are likely to develop incisional hernias at a rate of 9-20% [1]. The primary treatment approach to incisional hernias is surgery, with an increased likelihood of morbidity and mortality due to hernia complications in untreated patients [2, 3]. The reconstruction approach in the presence of giant midline abdominal wall incisional hernias is challenging in terms of the selection and implementation of the optimum method, and the high morbidity and relatively high recurrence rates in the postoperative period [4].

One of the most common surgical approaches to incisional hernias is reconstruction with prosthetic materials [5]. The component separation technique was first described as "tension relieving" in epigastric hernias, and is today used to repair incisional hernias [6, 7]. The component separation technique has been reported to result in a lower tension at the repair site,

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and lower postoperative morbidity and recurrence rates [8-10].

The present study aimed to compare the outcomes of the primary prosthetic repair (PPR), component separation with mesh (CSM) and component separation without mesh (CS) techniques in giant midline incisional hernias.

METHODS

In the present study, the data of 90 patients who were operated on for a midline abdominal incisional hernia, and who completed two years of follow up between January 2016 and 2018, were reviewed retrospectively. The patients were divided into three groups based on the surgical method used (PPR, CSM and CS), with each group including 30 patients. Prior to surgery, detailed information of the surgical method was provided to the patients, and their written informed consent was obtained. The study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki.

The study included patients over the age of 18 that completed two years of follow up. Patients operated on using different methods, those with a hernia with a transverse diameter < 6 cm, those undergoing emergency surgery and those with a stoma were excluded from the study.

Demographic information, Body Mass Index (BMI), American Society of Anesthesiologists (ASA) scores, transverse diameter of hernia defect, status of being primary or recurrent hernia, duration of surgery, morbidity, length of stay in hospital and recurrence rates after two-year follow up of all patients were recorded and compared. Patients that had undergone previous incisional hernia surgery were assessed as "recurrent incisional hernia".

Operative Technique

Primary Prosthetic Repair (PPR) Technique

After intraabdominal adhesions were removed and the intact fascia rims were exposed, the abdomen was closed using absorbable continuous sutures. The skin and subcutaneous tissue were mobilized laterally through the anterior rectus sheath to create space for the mesh placement. A non-absorbable polypropylene synthetic mesh (Prolene mesh, Ethicon) was then placed into this space.

Component Separation with Mesh [CSM] or without Mesh [CS] Technique

After intraabdominal adhesions were removed and intact fascia rims were exposed, the skin and subcutaneous adipose tissue were dissected bilaterally around 3-4 cm lateral to the linea semilunaris. The aponeurosis of the external oblique muscle was exposed around 1-2 cm laterally from the end of the rectus sheath (Fig.

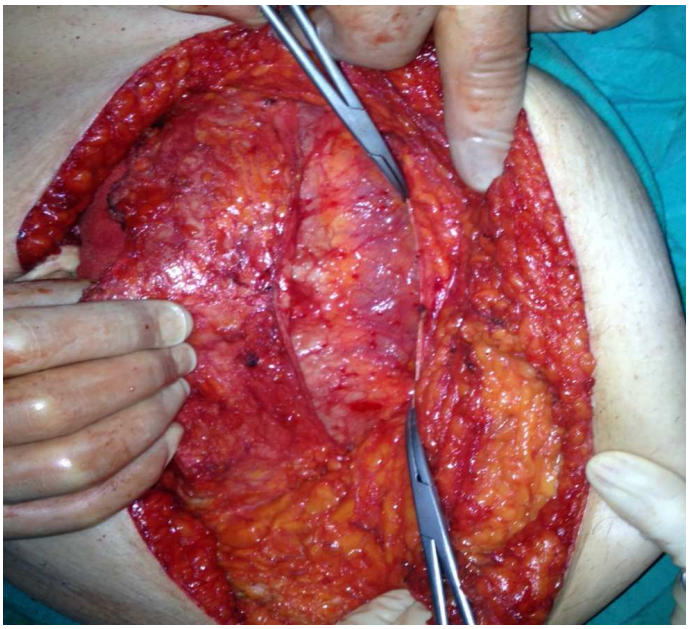

Fig. 1. Unilateral component separation.

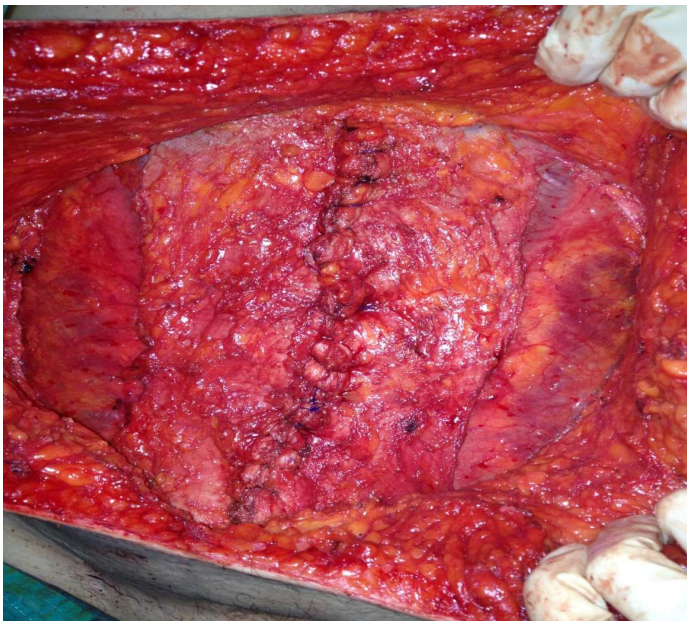

Fig. 2. Final component separation.

1). The myoaponeurosis of the external oblique muscle was transected longitudinally as far as the costa at the superior and the inguinal ligament at the inferior. The avascular area between the external oblique muscle and the internal oblique muscle was dissected. In this technique, the abdominal wall was unilaterally advanced to the midline by about 3-5 cm at the upper edge of the rectus muscle, 7-10 cm at the waistline and 1-3 cm at lower abdomen (Fig. 2). In the CSM group, a prolene mesh was placed on this area after closing the abdomen, while in the CS group, no mesh was used.

Perioperative Care

All surgeries were performed under general anesthesia. A urinary catheter was inserted into each patient and removed at the postoperative 2nd hour. Anti-embolism stockings were applied to every patient, and enoxaparin (Clexane, Sanofi Aventis) was administered to those with a BMI > 30 for embolism prophylaxis. All patients received prophylactic antibiotherapy prior to surgery. Wounds were monitored daily for hematoma, seroma and skin necrosis. Patients with wound site infections were administered antibiotic treatment based on culture results. Two aspirative drains were placed subcutaneously into the patients from all groups as routine. When the drainage amount decreased below 50 cc, the drains were removed. Patients were called for controls at 3, 6, 12 and 24 months, and checked with a physical examination. Cases suspected of recurrence during the physical examination were examined further with ultrasonography or computerized tomography.

Statistical Analysis

A Shapiro-Wilk test was used to assess whether the variables followed a normal distribution. Variables were reported as mean±standard deviation or median (minimum: maximum). Based on the results of the normality test, ANOVA or Kruskal Wallis tests were used for the comparison of the groups. A Dunn test was also performed after the Kruskal Wallis test for a pairwise comparison. Categorical variables were compared with Chi-square, Fisher's exact or Fisher-Freeman-Halton tests. To determine the independent risk factors affecting recurrence development, a binary lo-

Table 1. Patient's demographic data

	PPR (n = 30)	CSM (n = 30)	CS (n = 30)	*p*-value	Pairwise Comparisons		
					p_{1-2}	p_{1-3}	p_{2-3}
Age (year)	55.73 ± 12.06	57 ± 11.58	54.80 ± 12.20	0.775[a]	-	-	-
Gender (F/M)	17/13	16/14	17/13	0.956[b]	-	-	-
Weight (kg)	74.83 ± 8.22	75.63 ± 10.47	74.93 ± 12.73	0.951[a]	-	-	-
BMI	26.47 ± 2.46	26.34 ± 2.62	26.88 ± 2.82	0.712[a]	-	-	-
Defect (cm) (transverse diameter)	10 (7:17)	11.50 (7:24)	8 (7:23)	**0.003[c]**	0.942[e]	0.063[e]	**0.003[e]**
ASA, n (%)							
I	7 (23.30)	9 (30)	12 (40)	0.355[d]	-	-	-
II	12 (40)	11 (36.70)	14 (46.70)				
III	10 (33.30)	9 (30)	3 (10)				
IV	1 (3.30)	1 (3.30)	1 (3.30)				
Smoking, n (%)	6 (20)	5 (16.70)	7 (23.30)	0.812[b]	-	-	-
Recurrence/Primary, n (%)							
Recurrence	4 (13.30)	5 (16.70)	8 (26.70)	0.390[b]	-	-	-
Primary	26 (86.70)	25 (83.30)	22 (73.30)				

Data are shown as mean ± standard deviation or n (%) or median (minimum: maximum). PPR = Prosthetic repair, CSM = Component separation technique with mesh, CS = Component separation technique without mesh

[a]ANOVA test, [b]Chi-square test, [c]Kruskal Wallis Test, [d]Fisher-Freeman-Halton Test, [e]Dunn Test

gistic regression analysis was performed. SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) software was used for the statistical analyses. A p - value of ≤ 0.05 was considered statistically significant.

RESULTS

Demographic data of the patients from all groups were evaluated (Table 1). There was no difference in age, gender, weight and BMI between the groups. There was a statistically significant difference in transverse diameter of the defect between the groups (p = 0.003). Subgroup analyses revealed that the median transverse diameter was higher in CSM group compared to CS group (p = 0.003). No statistically significant difference was found in ASA score, smoking status and primary or recurrent nature of hernia between the groups ($p > 0.005$).

For the patients in all groups, the duration of surgery, postoperative morbidity, need for reoperation after morbidity, and recurrence rates on the day of hospitalization and during the two-year follow-up period were evaluated (Table 2). Other than wound site complications, no morbidities were detected in the patients. A statistical difference was noted in the duration of surgery ($p < 0.001$), with a subgroup analysis revealing that the duration of surgery was longer in the CSM group than in the PPR and CS groups (PPR-CSM; p = 0.008, CSM-CS; $p < 0.001$). There was no statistical difference in morbidity, length of hospital stay or recurrence in the two-year follow up between the groups. Yet, the recurrence rate was 20% in the CS group and 10% in CSM group (Fig. 3).

A logistic regression analysis was used to examine

Table 2. Follow up data

	PPR (n = 30)	CSM (n = 30)	CS (n = 30)	*p*-value	Pairwise Comparisons		
					p_{1-2}	p_{1-3}	p_{2-3}
Duration of surgery	122.50 (100:195)	140 (105:200)	120 (85:150)	**< 0.001**[c]	**0.008**[e]	0.431[e]	**< 0.001**[e]
Morbidity							
Yes	6 (20)	7 (23.70)	6 (20)	0.935[b]	-	-	-
No	24 (80)	23 (76.70)	24 (80)				
Morbidity							
Hematoma	1 (3.30)	0	0	< 0.99[d]	-	-	-
Seroma	5 (16.70)	6 (20)	6 (20)				
Skin Necrosis	0	1 (3.30)	0				
No	24 (80)	23 (76.70)	24 (80)				
Reoperation for wound complication							
Yes	-	2 (7.10)	0	-	-	-	0.229[f]
No	-	26 (92.90)	30 (100)				
Day of hospitalization	5 (3:13)	5 (3:18)	4 (3:12)	0.078[c]	-	-	-
Recurrence							
Yes	4 (13.30)	3 (10)	6 (20)	0.654[d]	-	-	-
No	26 (86.70)	27 (90)	24 (80)				

Data are shown as mean ± standard deviation or n (%) or median (minimum: maximum). Group 1 = Prosthetic repair, Group 2 = Component separation technique with mesh, Group 3 = Component separation technique without mesh
[b]Chi-square test, [c]Kruskal Wallis Test, [d]Fisher-Freeman-Halton Test, [e]Dunn Test, [f]Fisher's Exact Test

Table 3. Risk factors affecting recurrence

Factor	Wald	*p*-value	OR	95% CI for OR	
				Lower	Upper
Recurrent/Primary					
Primary (ref. cat.)	-	-	1	-	-
Recurrent	7.97	**0.005**	29.91	2.83	316.25
Smoking					
No (ref.cat)	-	-	1	-	-
Yes	9.48	**0.002**	39.73	3.81	413.94
Morbidity					
No (ref.cat)	-	-	1	-	-
Yes	13.10	**< 0.001**	147.58	9.88	220.54
Model χ^2= 98.01; ***p* < 0.001**					
Pseudo R^2= 89%					
N = 90					

OR = Odds ratio, Ref.cat = Reference category, CI = Confidence Interval

such potential risk factors as duration of surgery, BMI, transverse diameter of the hernia, wound complications, smoking status, ASA scoring, primary or recurrent nature of the hernia, age, gender and length of hospital stay, which were likely to affect recurrence development (Table 3). Recurrent incisional hernia, smoking and postoperative morbidity development were found to be statistically associated with recurrence ($p = 0.005$, $p = 0.002$, $p < 0.001$;respectively).

DISCUSSION

The use of tension-free techniques with prosthetic materials for incisional hernia repairs has decreased recurrence rates from 50% to 24% [11]. The risk factors for recurrence following incisional hernia reconstruction have been identified as hernia diameter (> 10 cm), BMI (> 30 kg/m2), history of previous repair, chronic obstructive pulmonary disease and diabetes,

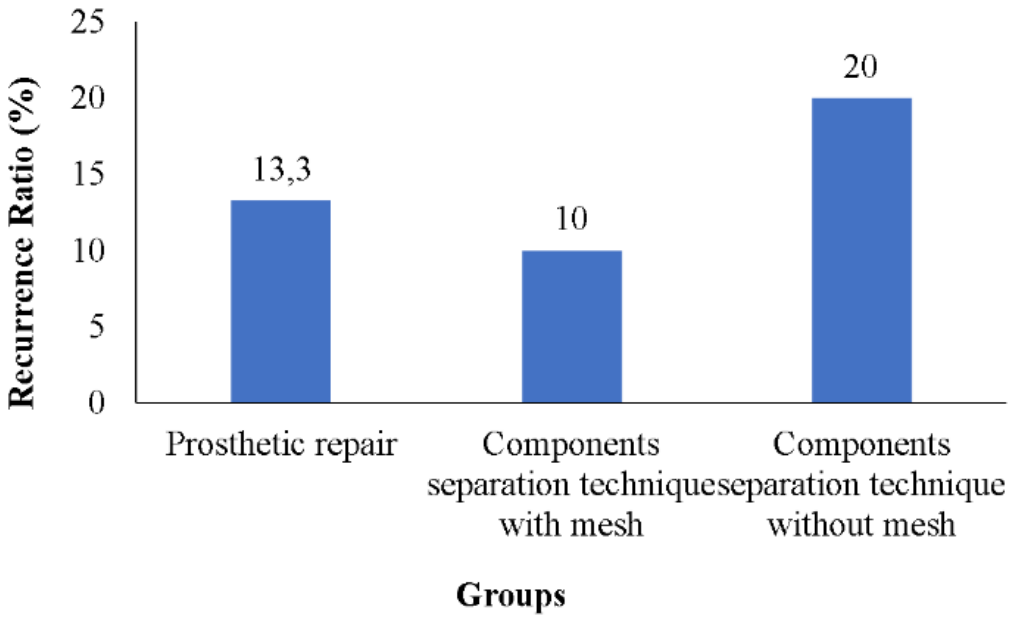

Fig. 3. Recurrence rates between groups during follow-up.

smoking and postoperative wound site complications (surgical site infection, hematoma and seroma) [12, 13] The present study also found that a history of previous repair, smoking and surgical site infection were statistically associated with recurrence development. The use of mesh is recommended as standard in incisional hernia reconstructions [14]. Repairs with mesh have been reported to significantly reduce recurrence rates in CS, as in the standard open ventral hernia repair technique [15, 16]. The goal of tension-free and anatomic repair is to create a neo-linea alba by approximating the rectus muscles again to the midline [17], which enables a tension-free closure of the fascia and its reinforcement with mesh, minimizing the risk of recurrence [18, 19]. In the present study, the recurrence rate during the postoperative two-year follow-up was 13.3% in PPR, 20% in CS and 10% in CSM, meaning no statistical difference in recurrence development between the surgical methods. That said, the recurrence rate was lower in patients with mesh, and lowest in the CSM group. We believe that the failure to identify a statistical difference was due to the low volume of patients, and that a statistical difference may be established in future studies with a larger patient groups.

Wound site complications (hematoma, seroma, skin necrosis and surgical site infection) following the repair of giant incisional hernias may occur in 12-67 % and 12-27 % of patients treated with CS and PPR, respectively [20, 21]. It is believed that wound complications increase with wide dissections, prolonged durations of surgery and ligation of the epigastric perforating arteries at the dissection site [20]. After ligating the epigastric perforating arteries, the supply of skin can only be provided through intercostal arteries and the branches of the pudental artery, leading to wound site perfusion and supply disorders. Although attention was paid to preserving the perforating arteries in the present study, the wound site complication rates were 20%, 23.7% and 20% in the PPR, CSM and CS groups, respectively. A direct association has been identified between wound complications and recurrence risk [12, 13]. The present study also identified a more frequent development of recurrence in patients with wound complications. We believe that termination of smoking, especially in the preoperative period, and taking care to preserve the perforating arteries in patients with recurrent incisional hernia may be helpful.

This study is the first in literature to compare three surgical methods (CS with mesh and without mesh, and primary prosthetic repair) in incisional hernias. Our study is limited by the relatively low number of cases included in the groups and the single-center retrospective design.

In addition, a statistically significant difference was found in the transverse diameter of the hernia defect between the groups (groups 2 and 3, $p = 0.003$). Accordingly, the CSM procedure was applied to hernias with larger diameters, which may be attributed to the non-randomized design of the study. Prospective randomized controlled studies with a larger number of patients are needed for the acquisition of better data.

CONCLUSION

In conclusion, in giant midline incisional hernias, the CS technique is an effective and safe method involving careful dissection and the preservation of perforating vascular structures as far as possible. Nevertheless, we believe that such procedures should be reinforced with a mesh in order to minimize the recurrence rates as the defect size increases. We also believe that there is a need for randomized studies involving larger numbers of patients and evaluating short-term and long-term outcomes in order to determine the place of CS in incisional hernia reconstructions.

Authors' Contribution

Study Conception: UA, UEE; Study Design: UA, UEE; Supervision: UA, UEE; Funding: UA, UEE; Materials: UA, UEE; Data Collection and/or Processing: UA, UEE; Statistical Analysis and/or Data Interpretation: UA, UEE; Literature Review: UEE; Manuscript Preparation: UA and Critical Review: UA, UEE.

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 2021;7(3):304-311 Original Article

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Posttransplant de novo donor specific HLA antibody monitoring and clinical outcomes: a single-center experience

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ABSTRACT

Objectives: Despite the improvements in early-term outcomes of kidney transplantation, late-term graft failure still remained as a critical problem. De novo donor specific antibodies (DSA) developing against direct human leukocyte antigens (HLA) are the significant risk factors for shortened graft survival in the previously non-sensitized cases. The purpose of this study is to evaluate the clinical outcomes of de novo DSA development in the kidney transplant cases.

Methods: The present study included 121 (alive/cadaver: 106/15) of 148 (alive/cadaver: 125/23) cases who were not previously sensitized (PRA and DSA negative) and undergone kidney transplantation between August 2012-January 2018. DSAs of the cases without expected declines in creatinine levels in the polyclinic follow-ups and postoperative early-term were evaluated. Renal biopsy was performed in the cases encountered with > 2000 mean fluorescence intensity (MFI) de novo DSA against HLA-A, HLA-B, HLA-DR. Treatment protocol of plasmapheresis+intravenous immunoglobulin (IVIG)+rituximab (in the cases without clinical response) was administered in the cases with antibody-mediated rejection (AMR) detected by renal biopsy. In addition, the presence of de novo non-DSA was also evaluated in the cases. The presence of de novo was encountered by identifying the specificities of anti-HLA antibody specificities using Luminex single antigen beads in the recipient serum.

Results: De novo DSA (antibodies against HLA-A, HLA-B, HLA-DR and HLA-DQ) were monitored in 23 cases. DQ positivity was detected in 10 cases. MFI values were > 4000 and 2000-4000 in 8 and 2 cases, respectively. De novo non-DSA was found in 19 cases. Biopsy was performed in 8 cases due to the development of MFI > 2000 de novo DSA against HLA-A, HLA-B and HLA-DR and the findings of acute humoral rejection (AHR) were encountered in 2 cases. Additionally, acute humoral rejection was diagnosed in 1 case that developed de novo non-DSA. Two cases were diagnosed with AHR by biopsy although no de novo DSA or non-DSA developed and renal graft loss occurred in these two cases.

Conclusions: The fact that routine DSA monitoring in all the cases provided no significant contribution to the outcomes of our study may contribute to the debates on the necessity of DSA monitoring in the patients with low immunological risk.

Keywords: De novo DSA, kidney, transplantation, monitoring

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Despite the improvements in early-term outcomes of kidney transplantation, late-term graft failure still remained as a critical problem [1]. Current studies demonstrated that antibody-mediated humoral tissue injury is responsible for more 60% of the late graft losses [2-4]. De novo donor specific antibodies (DSA) developing against direct human leukocyte antigens (HLA) are the significant risk factors for shortened graft survival in the previously non-sensitized cases. The presence of DSA may be associated with antibody-mediated rejection (AMR) and cause shortened graft survival [5-7]. That fact orientated the researchers to investigate the HLA antibodies [8, 9]. The purpose of the present study is to evaluate the clinical outcomes of de novo DSA development in the cases who underwent kidney transplantation.

METHODS

The present study included 121 (living/deceased: 106/15) of 148 (living/deceased: 125/23) caseswhowere not previouslysensitized (PRA and DSA negative) and undergone kidney transplantation between August 2012-January 2018. Ethics committee approval dated 17.01.2017 No:91 of the study was obtained from the Ethics Committee of University of Health Sciences Gazi Yaşargil Training and Research Hospital. All transplantations were performed after achieving negative T-cell crossmatch by flow cytometry and complement dependent cytotoxicity (CDC) methods. The cases without expected decline in the creatinine levels in the postoperative early term and those who received routine DSA assessment once at every 3 months for the first year and then once yearly were included in the study. The cases in whom this protocol could not be implemented were excluded from the study. Renal biopsy was performed in the cases encountered with > 2000 mean fluorescence intensity (MFI) de novo DSA against HLA-A, HLA-B and HLA-DR. Renal biopsies were evaluated according to the present Banff criteria at the time of biopsy. Treatment protocol of plasmapheresis+intravenous immunoglobulin (IVIG)+rituximab (in the cases without clinical response) was administered in the cases with humoral rejection detected by renal biopsy. In addition, the presence of de novo non-DSA was also evaluated in the cases. The presence of de novo DSAwas encountered by identifying the specificities of anti-HLA antibody specificities using Luminex single antigen beads in the recipient serum. The demographic and clinical characteristics of the patients were presented in Table 1.

Immunosuppression and Prophylaxis

Basiliximab (20 mg/day; at the day of operation and postoperative 4th day) and antithymocyteglobulin (ATG; for high-risk patients; 3 mg/kg during operation and 1.5 mg/kg at the postoperative 1st and 2nd days) were administered as the induction therapy. Methylprednisolone 1000 mg was administered intraoperatively. This dose was gradually tapered in the following days and switched to 20 mg oral prednisolone at the postoperative 6th day. Oral prednisolone dosage was reduced gradually to reach 5 mg a day at the first year after transplantation. Calcineurin inhibitors (CNI; tacrolimus: 0.1-0.15 mg/kg/day and cyclosporine: 6-8 mg/kg/day) and mycophenolate mofetil (MMF; 2g/day, by splitting into two doses) or Mycophenolate sodium (MMF; 1440 mg/day, by splitting into two doses) were administered for maintenance of the immunosuppression. MMF dose of 600 mg/m² was administered as split into two doses in the children. Everolimus (replaced by MMF at the 5th day) was added to the treatment protocol to be used together with tacrolimus in the cases with 2 ≥ mismatches. Target level of everolimus with tacrolimus was attempted to maintain between 4-8 mg/dL. However, everolimus was used instead of CNI in the cases supposed to develop thrombotic microangiopathy (TMA) because of use of CNIs and target level was attempted to maintain between 8-10 mg/dL. Trimethoprim/sulfamethoxazole (400 mg/day) and valganciclovir (900 mg/day) were administered for the prophylaxis of *Pneumocystis Jirovecii* (until the postoperative 6th month) and cytomegalovirus (CMV) (until the postoperative 3rd month), respectively. Delayed graft function (DGF) was defined as the need for dialysis in the posttransplant period. Graft loss was defined as return of the recipient to dialysis due to graft failure. Acute rejection was diagnosed by renal biopsy. Acute cellular rejection (ACR) was treated with intravenous pulse methylprednisolone and/or ATG therapy depending on the severity of rejection. The cases who were diagnosed or comorbid with AMR received the treatment of plasmapheresis+intra-

Table 1. Descriptive data of the kidney transplant cases

Characteristics	Data
Gender M/F	
Recipient	69/52 (57%/43%)
Donor	41/65 (39%/61%)
Age (years)	
Recipient	34.1 (11-68)
Donor	41 (10ay-71)
Follow-up period (months)	32.5 (1-68)
Living donor /deceased donor	106/15 (87.6%/12.4%)
Operation of donor (O/L)	
Open nephrectomy	81 (67%)
Laparoscopic nephrectomy	40 (33%)
Relationship	
Spouse	35 (33%)
First degree	41 (39%)
Second degree	19 (18%)
Third degree	3 (3%)
Fourth degree	2 (2%)
Unrelated	6 (5%)
Number of DSA studied patients	121 (81.7%)
Median DSA positive time	21 (4-56)
Preemptive	38 (36%)
Induction	
None	15 (13%)
ATG	67 (55%)
Basiliximab	39 (32%)
Incompatibility numbers	15 (12.3%)
1	4 (3.3%)
2	17 (14%)
3	42 (34.7%)
4	15 (12.4%)
5	17 (14%)
6	11 (9%)
Rejection	
Acute celluler	4 (2.7%)
Acute humoral	4 (2.7%)
Celluler + Humoral	1 (0.6%)
Graft loss	6 (4%)
CAN	1
Humoral rejection	2
BKN	1
RAP	1
FSGS recurrence	1
Death	2 (1.6%)
DGF	3 (2.4%)
Discharge creatinine (mg/dl)	1.14 (0.55-2.4)
Last creatinine level (mg/dl)	1.1 (0.49-4.34)
Length of hospital stay (days)	10.1 (5-42)

CAN = Chronic allograft nephropathy, BKN = BK nephropathy, RAP = Renal artery pseudoaneurysm, FSGS = Focal segmental glomerulosclerosis, ATG = Anti-tymocyte globülin, DGF = Delayed graftfunction M = Male, F = Female

venous immunoglobulin (IVIG) every other day.

Statistical Analysis

Statistical analysis was performed using SPSS Software Version 16. The probability of the variables for normal distribution was tested by analytic statistical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyses were given as median values for non-normally distributed variables. Since study data were non-normally distributed between the groups (DSA, Non-DSA and non-anti-HLA); creatinine values were compared using Mann-Whitney U test. A *p-value* less than 0.05 was accepted as statistically significant.

Table 2. De novo DSA and de novo Non-DSA data

	n (%)
De novo DSA (A, B, DR)	
DSA NEGATIVE	111 (91.7%)
1000 < CLASS 2 < 2000	2 (1.6%)
CLASS 1 >2000	5 (4.1%)
CLASS 2>2000	2 (1.6%)
CLASS 1 and 2 > 2000	1 (0.8%)
De novo DSA (DQ)	
De novo Non-DSA	3 (2.5%)
DQ CLASS 2 > 4000	2 (1.6%)
2000 < DQ CLASS 2 <4000	8 (6.6%)
1000 < DQ CLASS 2 < 2000	19 (15.7%)

DSA = Donor specific antibody

RESULTS

Mean follow-up duration ranged between 1 and 68 months in 121 cases included in the study. Median follow-up period was 32.5 months. HLA antibodies were encountered in 42 (34.7%; de novo DSA: 23, de novo Non-DSA: 19) cases. De novo DSA (DSA-A, DSA-B and DSA-DR) were detected in 10 cases. De novo DSA MFI value was > 2000 in 8 (6.6%) of those cases. We have determined DQ positivity in 13 (10.7%) cases. MFI values were > 4000, 2000-4000 and 1000-2000 in 8, 2 and 3 cases with DQ positivity, respectively (Table 2). In the postoperative term, de novo DSA and de novo non-DSA developed in 21th (a range of 4-56 months) and 24th (a range of 4-45 months) months, respectively. However, no statistically significant difference was present between the times of development of de novo DSA also in the postoperative term. In addition, no statistically significant correlation was detected between development of DSA and recipient age, recipient gender, DGF and number of donor-recipient matches. Except the cases with occurrence of graft loss, recent creatinine levels of the patients without anti-HLA antibodies (non anti-HLA), with de novo DSA and de novo non-DSA patients were 1.18 ± 0.51 (0.50-4.34), 1.30 ± 0.58 (0.89-2.75), and 1.01 ± 0.28 (0.49-1.6), respectively. No statistically significant difference was found between the creatinine levels of the patients with non anti-HLA compared with de novo DSA and de novo non-DSA ($p = 0.819$ and $p = 0.401$, respectively). No statistically significant difference was detected also between the creatinine levels of the patients with de novo DSA and de novo non-DSA ($p = 0.189$). The findings of AMRwas encountered in 2 of the 8 patients with de novo DSA by renal biopsy (Table 3) (Cases 3 and 6). These two cases became DSA negative after plasmapheresis+intravenous immunoglobulin (IVIG) therapy. However they were found DSA positive again during their follow-ups. In the follow-ups; 3 of 6 DSA positive cases became negative without implementation of any treatment. The rest 3 cases remained positive. Besides, one case with develoment of non-DSA was diagnosed with AMR. AMR developed in one patient without de novo DSA and one patient with de novo DSA DQ positivity (Table 3) (Cases A, B and C).

DISCUSSION

Although many studies have determined the association between development of de novo DSA after kidney transplantation and an immunological phenomenon such as AMR, there is no consensus on routine DSA monitoring in the posttransplantation period. Routine DSA monitoring is not performed in the postoperative follow-ups in many centers. In our study, we have evaluated posttransplant DSA outcomes of 121 non-sensitized cases (the cases that do not require implementation of desensitization protocol in the preoperative period) and the association between these outcomes and AMR. HLA-antibodies were encountered in 42 (34.7%) cases. De novo DSA was detected in 23 (17.4%; antibodies against HLA-A, HLA-B,

Table 3. De novo DSA/Non-DSA and acute humoral rejection relationship with cases

Cases	DSA type and MFI values	MM count	Induction	Biopsy result	De novo DSA/non-DSA process	Treatment
1	Class I 3213 Class II 7428	4	ATG	The patient did not give approval	56th month	Cr level is stable Outpatient clinic follow-up
2	Class I 11089	4	ATG	CAN	51th month	Outpatient clinic follow-up
3	Class II 20182	3	Basiliximab	AHR	24th month	PE + IVIG Outpatient clinic follow-up
4	Class II 3441	3	Basiliximab	CAN	12th month	Outpatient clinic follow-up
5	Class I 4336	4	ATG	No rejection	26th month	Outpatient clinic follow-up
6	Class I 6583	4	ATG	AHR	18th month	Outpatient clinic follow
7	Class I 2356	0	No induction	CAN	8th month	Outpatient clinic follow
8	Class I 9482	0	ATG	No rejection	4th month	Outpatient clinic follow
A	De novo DSA (-)	2	Basiliximab	AHR	De novo DSA (-)	PE + IVIG; Graft loss
B	Class II 9654	3	ATG	AHR	De novo DSA (+ DQ)	PE + IVIG Outpatient clinic follow-up
C	Class I 32227 Class II 37124	3	ATG	ACR (+) AHR (+)	De novo DSA (-) De novo non-DSA (+)	PE + IVIG Graft loss

AHR = Acute Humoral Rejection, DSA = Donor specific antibody, ATG = Anti-tymocyte globülin Cr = Creatinine, CAN = Chronic allograft nephropathy, ACR = Acute cellular rejection, PE = Plasma exchange, IVIG = Intravenous immunoglobulin, MFI = Mean Fluorescence Intensity

HLA-DR and HLA-DQ) cases. DQ positivity was determined in 13 (10.7%) of those cases. The findings of AMR was observed in 2 of 8 cases with de novo DSA development. In addition, a case with de novo non-DSA development was diagnosed with AMR. AMR was also diagnosed by biopsy in two cases despite absence of de novo DSA development and graft loss occurred in these cases. A significant association of de novo DSA development with graft loss and reduced graft survival has been found also in the literature. Li *et al*. [10] have determined that 1-, 3- and 5-year survival rates of the patients with de novo DSA development were 92%, 77% and 69%, respectively. Whereas, these rates were 100%, 100% and 96% in the cases without de novo DSA development, respectively. The same study has encountered that occurrence of de novo DSA was not correlated with development of AMR with in the posttransplant first

6 months whereas occurrence of de novo DSA was found significantly correlated with development of AMR after posttransplant 6th month [10]. Time interval between the occurrence of posttransplant de novo DSA and development of rejection still remained unclear. The previous studies have suggested that de novo DSA development has no negative effect on graft function [11, 12]. Terasaki *et al*. [12] have carried out a 1-year prospective follow-up study in 23 centers and found that the rates of graft failure in the cases with and without development of anti-HLA antibodies were 6.6% and 3.3%, respectively. In the same manner, Süsal *et al*. [13] have emphasized the importance of postoperative DSA monitoring in the patients with high immunological risk and impaired graft function. However, debates on DSA are still ongoing. Although, some studies have stated that DSA positivity in the absence of rejection has no impact on graft survival, there are also other studies which have noted that early and late developments of DSA have similar impact on graft injury [14, 15]. Prajuli *et al*. [14] has denoted in his study that DSA positivity in the absence of rejection has no impact on graft survival. In that study, post-biopsy follow-up period was shorter than 3 years. That period may be inadequate to draw reasonable conclusions. In our study, 2 cases with DSA development were diagnosed with biopsy-proven AMR. However, 2 cases without detection of DSA were also diagnosed with AMR by biopsy. Non DSA was present in one of those cases and graft loss occurred in both cases. Another case in our study was HLA-DQ DSA-positive and diagnosed with AMR by renal biopsy. Even though, there is no consensus on DSA positivity and graft survival with all aspects in the literature, our outcomes are not exactly consistent with general literature. That may be resulting from the fact that number of DSA positive patients is not high enough to present significant outcomes. Ginevri *et al*. [16] have identified de novo DSA and de novo non-DSA in respectively 19 (23%) and 24 (29%) patients in their 4.3-year follow-up study on 82 pediatric cases with kidney transplantation. Median DSA development duration was 24 months and DSAs were mostly against HLA-DQ antigens. Of the 82 cases; 8 and 4 were C4d+ AAR and C4d- AAR, respectively. The development of DSA and late AMR were correlated. Median time to development of AMR was 1 year [16]. In the present time, the association between HLA-DQ antibodies and AMR was investigated by many study groups and numerous articles have been reported on this issue [17-19]. Willicombo *et al*. [19] have detected de novo DSA in 92 (18.2%) of 505 cases in their study and 50 (54.3%) of those cases were found to have HLA-DQ DSA. That study has identified a significant association between the presence of HLA-DQ DSA andAMR [19]. DeVos *et al* [20] have obtained similar outcomes and detected rejection in 21 of the cases with HLA-DQ antibody. The rate of 3-year graft survival was found statistically significantly lower in those patients [20]. HLA-DQ antibody was identified in 13 cases in our study. Only one patient was diagnosed with biopsy-proven AMR. However, diagnosis of subclinical AMR could not be established in the cases with HLA-DQ positivity since we did not perform routine renal biopsy. In our study, we determined the MFI cut-off values as 1000, 2000 and 4000. In our study, the relationship between these MFI values and AMR was not significant. There is no consensus on the MFI cut-off values. This value varies from clinic to clinic. Morris *et al*. [21]. They stated in their study that cases with MFI < 2000 may not be an obstacle for transplantation. Also, in another study, a significant difference was observed between cases with MFI < 1500 and cases with > 1500 in terms of graft survive [22].

Postoperative routine DSA monitoring in the patients with low immunological risk is not performed because of high-cost. However, it is a recommended procedure in the patients with high immunological risk. We have aimed to present a contribution to the studies that evaluated the association between routine DSA monitoring performed in our country and AMR.

CONCLUSION

Although, retrospective design of our study is a limitation, nevertheless, the fact that routine DSA monitoring is a high-cost procedure and that routine DSA monitoring in all the cases in our study provided no contribution to the outcomes of our study may contribute to the debate on necessity of routine DSA monitoring in the patients with low immunological risk.

Authors' Contribution

Study Conception: NA; Study Design: NA, VA;

Supervision: NA, VA; Funding: NA, VA; Materials: NA, VA; Data Collection and/or Processing: NA, VA, ŞK; Statistical Analysis and/or Data Interpretation: NA, ŞK; Literature Review: NA; Manuscript Preparation: NA and Critical Review: NA, VA, ŞK.

Conflict of interest

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

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Investigation of the situations affecting vocational school students' anxiety levels and academic achievements

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ABSTRACT

Objectives: In this study, we aim to determine the prevalence of anxiety and evaluate its relationship with academic performance in a vocational school of health services students, which causes significant disability and loss of labor and is frequently seen with mood disorders in the society.

Methods: A sample was not selected for the research, it was aimed to reach all students. Of the 1093 students who are attending the school, 849 (77.7%) students participated in the study. In order to determine the level of anxiety in students, a questionnaire form consisting of the Beck Anxiety Inventory and descriptive features were applied by the online survey method.

Results: Of the students; 80.1% are female, 98.1% are single, 57.1% are in their first year, and the average age is 20.25 ± 1.81. The total scale score was found 9.42 ± 8.65 and it was 9.90 ± 8.69 for female students and 7.49 ± 8.24 for male students. Variable levels of anxiety were detected in 38.8% of the participants. There was no statistically significant relation found between anxiety level and academic performance, but both anxiety levels and academic performances were affected by the gender of participants.

Conclusions: Making psychological evaluations of students while they are starting their higher education and checking their statuses periodically using standard self-report tools by using technological instruments; would make it possible to make necessary interventions by noticing the situations that may adversely affect their academic success, social life, mental and cognitive development in the early stages.

Keywords: vocational school, students, anxiety, grades

Anxiety's lifetime prevalence is reported to be between 13.6% and 28.8%. It can cause significant disability and loss of labor and is frequently found in society along with mood disorders. It is a state of inquietude that can be observed as ranging from a mild level of uneasiness causing disquietude and tension to a state of apprehension that is severe enough to cause a sense of panic. It manifests itself with deteriorations in the physical, mental, somatic and cognitive areas of the person, with the expectation of a danger that may arise due to personal or environmental reasons [1-3].

If the anxiety of the person is within the ideal limits, support systems come into play and this mechanism provides an opportunity for the person to improve himself. It's a fact that if anxiety is not at the ideal level and increased, it can affect the mental and emotional state of the person and cause physical or psychological disorders, leading to negative experiences in the person's life [4]. This may lead to low performance in business life and it can also manifest itself

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as a decrease in lesson successes in school life as well. The relationship between increasing anxiety levels and academic performance needs to be examined extensively [5]. Because this relationship is important to provide appropriate medical and social supports in order to eliminate the low marks in students' grades, in case they exist.

In this study we planned to evaluate the prevalence of anxiety, relationship of anxiety levels and the academic performance in health services vocational school students.

METHODS

This descriptive and cross-sectional study was carried out at Erciyes University Halil Bayraktar Health Services Vocational School students during June 2020. All of the students studying in a total of ten programs in two different departments within the school were included in the study. The study was planned and carried out as voluntary participation in the online survey, as education and training activities were continued as distance education within the scope of Covid-19 epidemic preventive measures. Approval numbered 2020/322 from the ethics committee of Erciyes University along with permission from the directorate of the vocational school was obtained for the study. Information about the study was given to the participants on the online survey page and their informed consent was taken by their choosing the "I accept to participate in the study voluntarily" option on the same page. Students were asked to answer the participant information section consisting of six questions where socio-demographic information, school cumulative grade point average (CGPA), and the information about the department they were studying were collected; along with the Beck Anxiety Inventory (BAI), which consists of 21 questions that used to measure anxiety states. The BAI is defined as a reliable self-report tool for measuring participants' anxiety levels. The scale consists of querying 21 symptoms. Participants are asked to state to what extent they feel uncomfortable with regards to each item “during the past week, including today”. The answers are scored on a scale of 0 to 3 ranging from "not at all" to "severely", resulting in a total score of from 0 to 63. While the total scale score between 0 to 9 points is interpreted as normal anxiety level, from 10 to 18 points are evaluated as mild-moderate, from 19 to 29 points are moderate-severe and from 30 to 63 points are considered as serious anxiety levels. The developers of the scale reported a high level of internal consistency (Cronbach alpha = 0.92) and a good test-retest correlation (r = 0.75) [6-8]. The results of the validity and reliability study of the Turkish version of BAI also support its use as a reliable and valid measure of anxiety in the Turkish population [9]. In our study, Cronbach's alpha value was found to be 0.90.

Statistical Analysis

Statistical analyses of the collected data were done with the SPSS program. Descriptive statistics were presented as mean ± standard deviation, median (min, max), frequency distribution and percentages. The relationship between anxiety level and other independent variables were evaluated with Chi-square tests. Since the data did not match the normal distribution, Mann-Whitney and Kruskal-Wallis tests were used to compare the mean values of the anxiety score among different subgroups and to examine from which independent variables they were affected. The relationship between cumulative grade point averages and other independent variables were evaluated with Chi-square tests. For all statistical tests, values where p <0.05 were considered as being significant.

For post-hoc analysis, Chi-Square values were calculated by using residual (Z) values, p values were calculated from these Chi-Square values and Bonferroni correction was applied to these p values [10-11].

RESULTS

From 1093 students attending 10 different programs within the school, 849 (77.7%) students participated in the study. According to Table 1, of the participants; 80.1% were women, 98.1% were single, 57.1% were in the first year of their education. The average age of the participants was 20.25 ± 1.81 (min: 18, max: 30). While the total scale score was calculated as 9.42 ± 8.65 (min: 0, max: 60), varying levels of anxiety from mild-moderate to serious were detected in 38.8% of the participants. As it could also be seen from Table 1; the changes in the average scale score in relation to the gender of the participants, the

Table 1. Changes in the BAI total score according to the characteristics of the participants

n = 849	BAI total score					Kruskal-Wallis H / Mann-Whitney U	*p* value
	n	%	x̄	SD	Mean rank		
Genders						45327.000[a]	**< 0.001**
Female	680	80.1	9.90	8.69	442.84		
Male	169	19.9	7.49	8.24	353.21		
Years of education						87528.000[a]	0.834
First	485	57.1	9.30	8.35	426.53		
Second	364	42.9	9.59	9.05	422.96		
Cumulative grade point averages (CGPA)						4.008[b]	0.405
<=2.00	37	4.4	9.57	9.44	414.03		
2.01 - 2.50	119	14.0	10.42	10.68	432.49		
2.51 - 3.00	271	31.9	9.37	8.52	423.07		
3.01 - 3.50	342	40.3	8.77	7.82	413.85		
3.51 - 4.00	80	9.4	10.81	8.68	473.18		
Ages						10.132[b]	0.072
18	65	7.7	10.85	7.61	491.82		
19	220	25.9	9.36	8.71	425.14		
20	296	34.9	9.76	8.79	435.98		
21	160	18.8	8.54	7.98	399.76		
22	52	6.1	9.65	9.61	416.37		
23+	56	6.6	8.50	9.68	368.96		

[a]Mann Whitney U, [b]Kruskal Wallis H, BAI = Beck Anxiety Inventory

programs they studied, the number of years of their education, their CGPAs, and their ages were observed and they were tested for statistical significance. Accordingly, statistically significant relations were found in the change of total scale score with participants' genders and anxiety levels ($p < 0.001$).

When we looked at which of the participants' gender, school year, CPGA, age characteristics were related with the level of anxiety calculated; it is seen in Table 2 that there is no statistically significant relationship between the calculated anxiety levels and these independent variables ($p > 0.05$).

When we look at which independent variables CPGA is affected in Table 3, it is seen that only the differences regarding the gender of the participants are statistically significant. CPGA was calculated as 3.48 ± 0.94 in females and 2.89 ± 1.02 in male participants. Performed post-hoc analyses revealed that the aforementioned statistical significance between gender and CPGA was due to the 2.01-2.50 and 3.01-3.50 CPGA levels. While the CGPA is statistically significantly affected by the school programs that students were getting their education (x2 (36) = 101.309, $p < 0.001$); it was determined that there was no relationship between the level of anxiety and the school programs that students were getting their education ($p > 0.05$, Fisher's exact test).

DISCUSSION

The prevalence of anxiety, which was determined as 38.8% among the students participating in the study, was similarly found to be 40% in another recent study using the same scale. This rate is lesser than the previous studies conducted in different countries at dif-

Table 2. Changes in the anxiety level according to the characteristics of the participants

n = 849	Anxiety level								X^2	*p* value
	Normal		Mild-moderate		Moderate-severe		Serious			
	n	%	n	%	n	%	n	%		
Genders									6.656[a]	0.084
Female	403	59.3	181	26.6	70	10.3	26	3.8		
Male	117	69.2	38	22.5	10	5.9	4	2.4		
Years of education									1.487[a]	0.685
First	301	62.1	125	25.8	45	9.3	14	2.9		
Second	219	60.2	94	25.8	35	9.6	16	4.4		
Cumulative grade point averages (CGPA)									12.179[a]	0.431
<=2.00	22	59.5	10	27.0	3	8.1	2	5.4		
2.01 - 2.50	70	58.8	29	24.4	13	10.9	7	5.9		
2.51 - 3.00	170	62.7	68	25.1	23	8.5	10	3.7		
3.01 - 3.50	215	62.9	90	26.3	27	7.9	10	2.9		
3.51 - 4.00	43	53.8	22	27.5	14	17.5	1	1.3		
Ages									17.110[a]	0.312
18	37	56.9	15	23.1	12	18.5	1	1.5		
19	133	60.5	62	28.2	19	8.6	6	2.7		
20	172	58.1	86	29.1	24	8.1	14	4.7		
21	106	66.3	36	22.5	14	8.8	4	2.5		
22	33	63.5	11	21.2	6	11.5	2	3.8		
23+	39	69.6	9	16.1	5	8.9	3	5.4		
Total	521	61.4	219	25.8	79	9.3	30	3.5		

[a]Pearson's chi-squared test (X^2),, [b]Fisher's Exact

ferent times [5,12-18]. When the studies on the subject are examined, as the anxiety level of women is higher than that of men; in studies with a high rate of women participants, it is seen that the level of anxiety increases in the study population. But in our study, although four-fifths of the participants were women, the total anxiety level was found to be lower than in other studies [16, 19, 20]. This can be accepted as evidence that the only variable that affects the level of anxiety is not gender. There are other studies supporting this idea, reported that there is no statistically significant difference at the anxiety level that can be associated with gender [12, 21, 22].

As 98.1% of the participants in the study were single, there was not any statistical tests applied for making comparisons of changes with marital status to avoid statistically erroneous results. However in a study conducted with students, it was stated that the prevalence of anxiety was higher in singles. But in another research conducted with patients; while it was stated that anxiety disorders were found to be more common in divorced, widowed, or separated people in previous field studies, according to their own findings the diagnosis of anxiety disorder was reported to be significantly higher in married people than in singles [2, 18]. This suggests that the marital status of the participants does not alone affect the anxiety state and other factors may also have a role. There was no statistically significant difference between the year of study with the total anxiety scores and categorical anxiety levels. In the literature, some studies state a statistical relationship between the class studied and

Table 3. Changes in the cumulative grade point averages according to the characteristics of the participants

n = 849	Cumulative grade point average										X^2	*p* value
	<=2.00		2.01 - 2.50		2.51 - 3.00		3.01 - 3.50		3.51 - 4.00			
	n	%	n	%	n	%	n	%	n	%		
Genders											52.166[a]	**<0.001**
Female	21	3.1	76	11.2	210	30.9	300	44.1	73	10.7		
Male	16	9.5	43	25.4	61	36.1	42	24.9	7	4.1		
Years of education											2.159[a]	0.706
First	22	4.5	67	13.8	159	32.8	187	38.6	50	10.3		
Second	15	4.1	52	14.3	112	30.8	155	42.6	30	8.2		
Anxiety levels											11.591[c]	0.455
Normal	22	4.2	70	13.5	170	32.7	215	41.3	43	8.3		
Mild- moderate	10	4.6	29	13.2	68	31.1	90	41.1	22	10.0		
Moderate- severe	3	3.8	13	16.3	23	29.1	28.8	33.8	14	17.5		
Serious	2	6.7	7	23.3	10	33.3	10	33.3	1	3.3		
Ages											26.284[a]	0.157
18	1	1.5	9	13.8	23	35.4	26	40.0	6	9.2		
19	8	3.6	35	15.9	69	31.4	86	39.1	22	10.0		
20	14	4.7	34	11.5	88	29.7	131	44.3	29	9.8		
21	7	4.4	18	11.3	58	36.3	68	42.5	9	5.6		
22	2	3.8	9	17.3	20	38.5	16	30.8	5	9.6		
23+	5	8.9	14	25.0	13	23.2	15	26.8	9	16.1		
Total	37	4.4	119	14.0	271	31.9	342	40.3	80	9.4		

[a]Pearson's chi-squared test (X^2), [b]Fisher's Exact, [c]Monte Carlo

anxiety status, whereas in some studies there is no significant difference reported. In the studies that state that there is a relation between the class and anxiety level, while some researchers reported that the level of anxiety was higher in the first grades, the other researchers reported that in the final grades [16, 21, 23].

No significant relationship was found between the CPGAs of the participants with the total BAI and the anxiety levels. On the other hand, while we were observing the changes in independent variables and their effects on the students' academic achievements by looking at CPGAs; a statistically significant relationship was determined between the CPGAs with the gender of the participants, and the program in which they were educated. Accordingly, it could be said that being a woman has positive effects on academic success in students (Table 3). On the other hand, the relationship between the program studied and CPGA might be related to the ease or difficulty of the courses within the scope of the program, the simplicity or complexity of the applications carried out within the scope of education as well as other factors. In order for this to be understood, other investigations should be made examining the possible causalities.

While there was no significant difference in the change of total anxiety scores and categorical anxiety levels related to ages of participants in this study; it was reported that high anxiety scores were associated with increasing age and the prevalence of anxiety increased significantly at older ages in another study [18]. Again, there is information in the literature that anxiety disorders start especially in the 20s, and the

incidence increases with age [2].

Limitations

Studies examining the effects of various variables such as emotion and anxiety state and belief state, physical activity level, body mass index, familial features, etc. are present in the literature. The limitations observed in all cross-sectional studies are valid both for these other studies and as well for this study. Although it was carried out with a large number of participants from ten different programs, the information in the study was collected from students of the vocational school of health services. Different results can be obtained in studies conducted in other schools. Also, participation in the study was on a voluntary basis. And in the studies carried out in the form of the participation of volunteers; it is a known phenomenon that those who have the examined feature are not willing to participate in the study as much as those who do not [24]. In addition, the relationship of variables examined within the scope of the study with anxiety states of the individuals was only examined using a self-report questionnaire, without processes that make it possible to make a definitive diagnosis, such as clinical interviews. Despite all these limitations, it is important to carry out studies that make it possible to follow the emotional and anxiety states of the students throughout their education life. Because stress, emotion, and anxiety cases that were not diagnosed in the early stages during the studentship period; may negatively affect the quality of life and job performance of individuals when they get into professional life thereafter [25].

CONCLUSION

It is appropriate to make psychological evaluations of students while they are starting their higher education and then to check their statuses regularly during the education; within the periods determined by specialists, with standard self-report tools that are tested for reliability, and also by using technological instruments for evaluations whenever it is possible. In this way, it will be possible to make necessary interventions by noticing the situations that may adversely affect their academic success, social life, mental and cognitive development in the early stages.

Authors' Contribution

Study Conception: MB; Study Design: MB; Supervision: MB, MD; Funding: MB, MD; Materials: MB; Data Collection and/or Processing: MB, MD; Statistical Analysis and/or Data Interpretation: MB; Literature Review: MB; Manuscript Preparation: MB, MD and Critical Review: MB, MD.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript. Authors declare that they have no conflict of interest.

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The relationship between collapsibility index of inferior vena cava and hypotension after spinal anesthesia

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ABSTRACT

Objectives: Hypotension is a common complication of spinal anesthesia. Imaging of inferior vena cava (IVC) and measurement of the IVC-collapsibility index (IVC-CI) by ultrasonography (USG) has been a widely used non-invasive, easy and reliable method for measurement of the fluid imbalance. In the present study, we aimed to investigate the predictive ability of the maximum IVC diameter (dIVCmax) and IVC-CI for hypotension after spinal anesthesia.

Methods: The study was designed as prospective and observational. One hundred thirty-two patients aged 18-75 years with ASA I-II underwent inguinal hernia surgery with spinal anesthesia and recruited to the study. Maximum and minimum (dIVCmin) IVC diameters were measured. IVC-CI (%) was quantified according to the formula of [(dIVCmax-dIVCmin)/dIVKmax]×100%.

Results: The patients were grouped as hypotensive and non-hypotensive. In fifty-seven patients of 120 cases (47.5%), hypotension has emerged following spinal anesthesia. No significant differences in dIVCmax and IVC-CI were recorded between the study groups ($p > 0.05$). There were significant inverse correlation between age and IVC-CI. Significant positive correlation between the lowest values of the systolic arterial pressure, diastolic arterial pressure, mean arterial pressure and IVC-CI and significant positive correlation between dIVCmax and diastolic blood pressure, maximum and minimum values of the mean arterial pressure.

Conclusions: We found that dIVCmax and IVC-CI values measured before spinal anesthesia were not sufficient parameters enough to predict hypotension after spinal anesthesia. Further studies investigating the IVC measurements under spinal anesthesia together with dynamic hemodynamic monitorization modalities are needed.

Keywords: Hypotension, inferior vena cava, inferior vena cava collapsibility index, spinal anesthesia, ultrasonography

Hypotension is the most common complication of spinal anesthesia. In the literature, hypotension is reported at a ratio of 8.2-57.9%. The primary underlying cause of hypotension induced by spinal anesthe-

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sia (SA) is arterial, arteriolar and venous dilatation due to preganglionic sympathetic nerve blockage. The hypotension may aggravate in case of volume depletion in patients underwent spinal anesthesia [1-4].

Measurement of the inferior vena cava (IVC) diameter by ultrasound and IVC-collapsibility index (IVC-CI) by ultrasonography (USG) has been a widely used non-invasive, straightforward and reliable method for assessment of intravascular volume. IVC is a highly compliant vessel and the change in the collapsibility of the vessel can guide the clinicians about the clinical status of the patient. At each respiratory cycle the vessel contacts and expands. With negative pressure at each inspiration, the venous return to the heart increases and IVC collapse. The changes in the diameter of the vessel depends on the total body fluid status. As compared to the relatively higher intravascular volume status, lower volume within the vasculature increases the percentage of the IVC collapse. It has been demonstrated that IVC diameter can change even in healthy subjects however, the maximum diameter of IVC may decrease deeply in hypovolemic cases [5]. The collapsibility of IVC is efficient method for demonstrating the intravascular volume. IVC collapsibility can be calculated using he formula as follows: [(dIVCmax - dIVCmin) / dIVCmax] × 100%.

The aim of the current analysis is to investigate the relationship between IVC diameter, hypotension sourced from SA within the cases underwent an inguinal hernia operation and IVC -CI.

METHODS

The ethics committee of the local institution approved the protocol, and each patient gave written informed consent before inclusion. The study was a prospective observational implemented between 01.04.2017-01.10.2017. The subjects between 18-75 years old with American Society of Anesthesiologists (ASA) Score I, II those were planned to have inguinal hernia operation under spinal anesthesia recruited to the current study. The patient exclusion criteria were as follows; body mass index > 35, presence of hypertension, major peripheral artery disease, multiple vessel disease, unstable angina, left ventricle ejection fraction < 40%, respiratory disease, neurological disorder, increased intraabdominal pressure, cardiac pacemaker, using angiotensin receptor blocker. The cases with systolic arterial pressure > 150 mmHg and mean arterial pressure < 60 mmHg were excluded from the study.

The demographical data of the patients enrolled into the study were recorded. By a blinded physician,

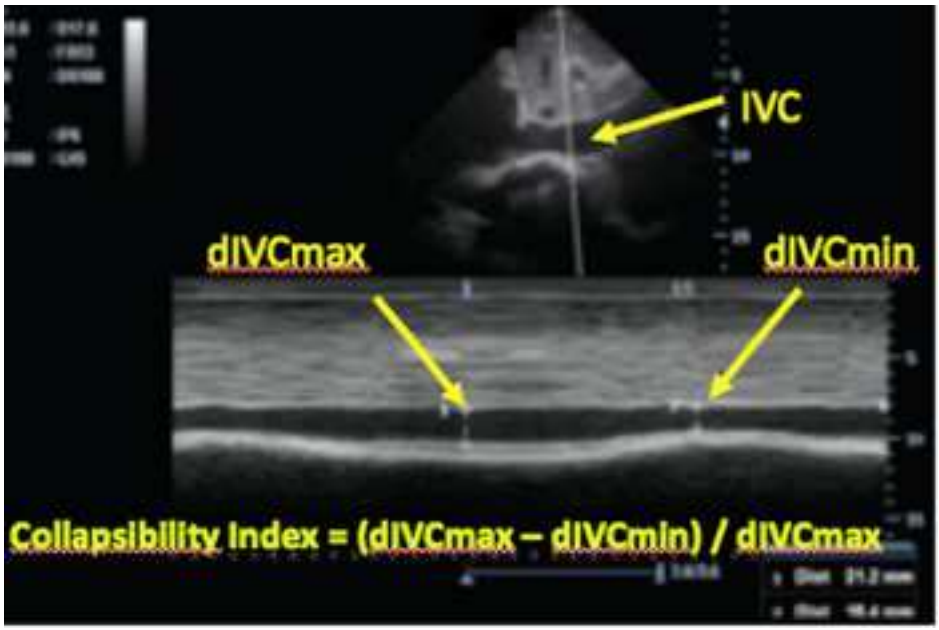

Fig. 1. Ultrasound measurements of inferior vena cava (IVC) and calculation of collapsibility index. Panel above shows two-dimensional scan of the IVC with right atrium to the left and panel below shows M-mode scan with respiratory variations in diameter. dIVCmax = maximum diameter of IVC, dIVCmin = minimum diameter of IVC.

five min prior to spinal anesthesia, the diameters of the IVC at inspiration (dIVCmin) and expiration (dIVCmax) were recorded at 2-3 cm subcostal location using 5-Mhz probe ultrasound (Esaote, MyLab 30gold cardiovascular, Florence, Italy) at M-mode with the patient in the supine position. This process were repeated 3 times and the mean of the 3 measurements were recorded. IVC collapsibility index (IVC-CI) were calculated using the formula of [(dIVCmax - dIVCmin)/dIVCmax × %100] (Fig. 1). The cases with >0.2 cm difference between the two sequential dIVCmax were excluded from the study.

Following the routine monitorization, premedication with intravenous (IV) midazolam 0.03-(0.05 mg/kg) (Dormicum®, Deva, Istanbul, Turkey) were implemented by an anesthetist outside the study. At the sitting position, sterilization was done over the skin zone of the spinal anesthesia and around the L4-5 or L3-4 intervertebral spaces with a 25G (gauge) Quincke spinal needle was introduced using mid-line approach. After observing the cerebrospinal fluid flow, 0.5% hyperbaric bupivacaine (Marcaine Heavy, AstraZeneca, Kırklareli, Turkey) was injected at a dosage according to the height of the patient (12-18 mg). The level of the sensorial block was determined using Pinprick test and the level of the motor block level was defined utilizing Bromage scale. As the block level was reached to T8 and Bromage 0, the operation started. Following spinal anesthesia, the subjects at whom vasoactive medication was implemented due to hypotension and the dosage of those vasoactive drugs were recorded. After the anesthesia till the surgical operation concluded, the heart beats per min and the blood pressures of the patients were recorded at every 2 min. Also, the maximal sensory levels of the cases were recorded.

No any patients received any fluid replacement therapy before the spinal anesthesia. The fluid therapy was planned calculating the preoperative starvation time and fluid maintenance and target fluid replacement was done during the surgical operation. Fluid replacement regime was implemented as follows; 4 mL/h for the first 10 kg body weight, 2 ml/h for the second 10 kg body weight and 1 ml/h for the rest body weight. Hypotension was defined as the starting mean arterial pressure decreases by > 30% and/or mean arterial pressure was < 60 mmHg. The patients were grouped according to the hypotension status. As hypotension was determined IV fluid infusion was increased. Ephedrine (Ephedrine hydrochloride, Osel, Beykoz, Istanbul) was utilized at a dosage of 5-10 mg. When heart beat per min was < 40, IV atropine (Atropine Sulfate, Biofarma, Sancaktepe, Istanbul) (0.5 mg) was administered.

Statistical Analysis

For calculating the sample size G power version 3.1.9.2 was used. The effect size for the independent study groups for the t-test was d = 0.57 and for α = 0.05 with power = 0.85, the minimum needed case number was 118. For statistical analysis SPSS 22.00 (Statistical Package for Social Sciences, Inc., Chicago,

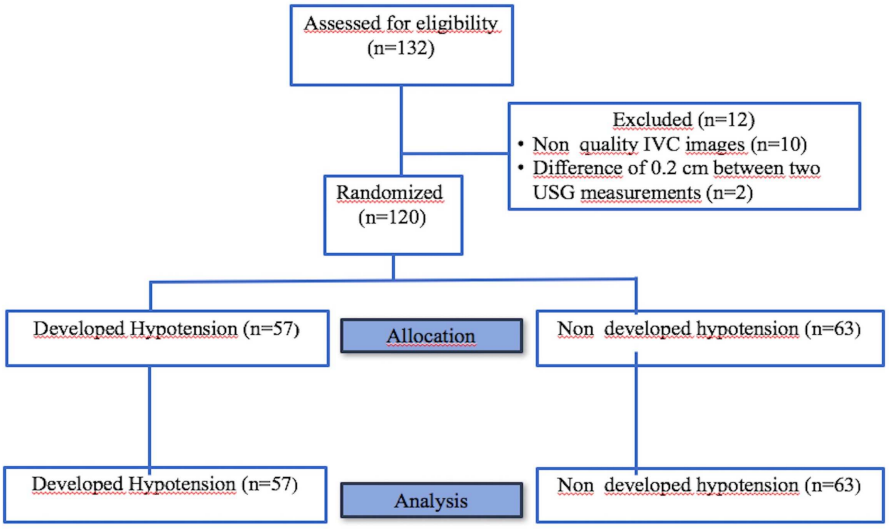

Fig. 2. Flow chart of the study.

IL) was used. Numerical data are expressed as mean ± standard deviation or median and inter-quartile range depending on their distribution which was tested by Kolmogorov-Smirnov test. Spearman correlation test was used for the correlation analysis. Continuous variables with normal and non-normal distributions were compared using Student's t-tests and Mann–Whitney U tests, respectively. Categorical variables were compared using the Pearson's chi-square test or Fischer's exact test, as appropriate.

RESULTS

A total of 132 patients who underwent inguinal hernia with spinal anesthesia were included in the study and statistical analysis was performed in 120 cases (Fig. 2).

The patient characteristics are shown in Table 1. Hypotension was recorded in 47.5% (n = 57) of the patients. No significant difference was noted for dIVCmax and IVC-CI between the study groups (Table 1). Sixty five percent of the cases have rendered dIVC < 15 cm and IVC-CI > 50% whereas in 2.5% of the subjects, IVC diameter was 15-25 mm and IVC-CI > 50%.

There was no meaningful correlation between dIVCmax and IVC-CI (r = 0.145, $p = 0.114$). No statistically significant negative correlation was recorded between age and IVC-CI ($p < 0.05$, r = 0.184) (Table 2). No significant correlation was noted between the percentage of the decrease in mean arterial pressure and IVC-CI and dIVCmax (Fig. 3).

DISCUSSION

The researchers investigated the impact of USG guided IVC measurement on the hypotension after spinal anesthesia in patients undergoing inguinal hernia operation with a prospective observational study. In 47.5% of the cases hypotension during the spinal anesthesia has been recorded. There was no statistically significant difference between the cases in terms of hypotension after spina anesthesia related with dIVCmax and IVC-CI. While there was a negative correlation between age and IVC-CI, no significant correlation was observed between the percentage of

Table 1. Comparison of patient characteristics, hemodynamic data, and preoperative inferior vena cava ultrasound measurements between patients who did and did not develop hypotension after spinal anesthesia

	Developed hypotension		
	Yes (n = 57)	No (n = 63)	*p value*
Age (year)	49.0 ± 13.5	46.7 ± 14.0	0.400
Sex, n (%)			0.101
Female	3(4.2)	6 (12.2)	
Male	68 (95.8)	43 (87.8)	
BMI, kg/m2	25 ± 3.9	25.2 ± 5.7	0.921
ASA, n (%)			0.322
I	21 (29.6)	19 (38.8)	
II	45 (63.4)	29 (59.2)	
Baseline HR, beats/min	79.9 ± 14.3	76.4 ± 16.1	0.170
MBP, mmHg	109.6 ± 19.0	108.2 ± 16.7	0.705
dIVCmax, cm	1.7 ± 0.5	1.7 ± 0.5	0.636
IVC-CI, %	41.7 ± 16.0	38.0 ± 12.3	0.213

ASA = American Society of Anesthesiologists, BMI = Body Mass Index, MBP = Mean Blood Pressure, dIVCmax = Inferior Vena Cava Maximum Diameter, IVC-CI = Inferior Vena Cava Collapsibility Index

Table 2. Comparison of patient characteristics between inferior vena cava maximum diameter and inferior vena cava collapsibility index

	dIVCmax (cm)		IVC-CI (%)	
	r	*p* value	r	*p* value
Age (year)	0.114	0.215	-0.184	0.044
Weight (kg)	-0.158	0.085	0.173	0.059
Height (cm)	-0.124	0.177	0.123	0.181
BMI (kg/m2)	-0.139	0.131	0.139	0.131

BMI = Body Mass Index, dIVCmax = Inferior Vena Cava Maximum Diameter, IVC-CI = Inferior Vena Cava Collapsibility Index

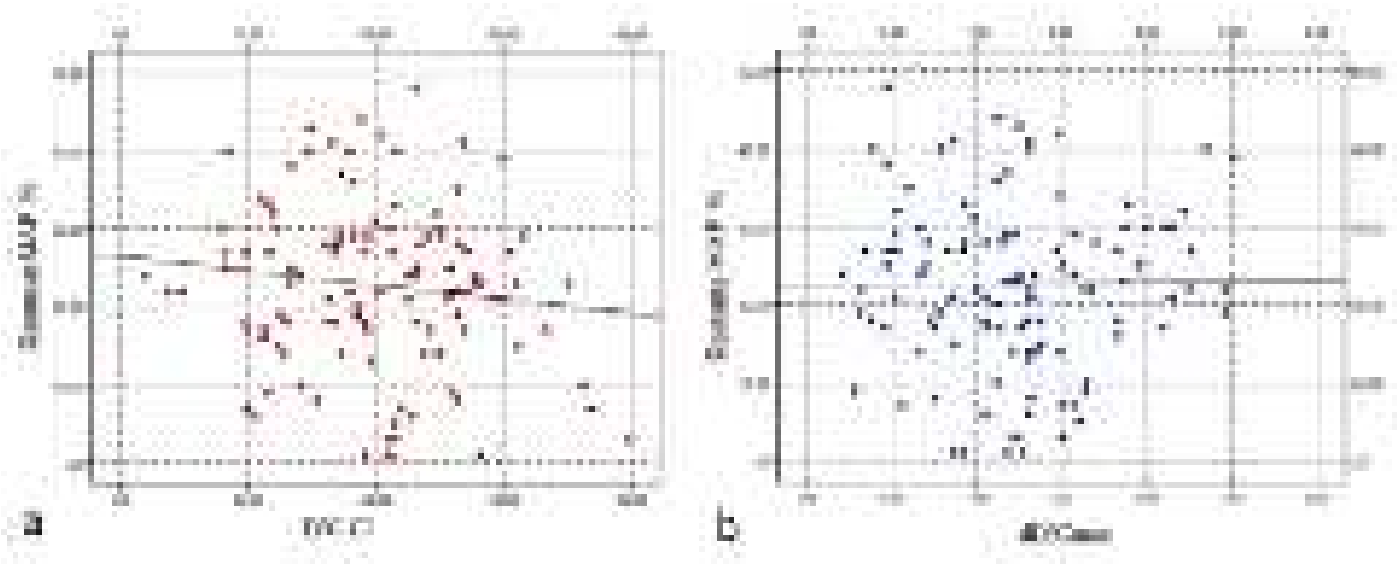

Fig. 3. (a) Correlation between the percentage of the decrease in mean arterial pressure (MAP) and inferior vena cava collapsibility index (IVC-CI), (b) Correlation between the percentage of the decrease in mean arterial pressure (MAP) and inferior vena cava maximum diameter (dIVCmax).

fall in MAP and IVC-CI and dIVCmax.

IVC ultrasound has been a frequent, easily doable and non-expensive method for assessment of intravascular volume status. Regarding the importance of determination of the pre-operative volume status, fast evaluation by ultrasonography may provide benefit in the treatment of critical patients [5]. While inspiration induces IVC collapse by enabling a negative pressure within the thorax, expiration allows an increment in venous return that yields the return of the IVC diameter to its original size. The decrease in the intravascular volume status may increase the percentage of the IVC collapse. In the children with dehydration needing volume supplement, the IVC diameter was decreased [6, 7]. Relatively higher IVC-CI, in particular with a small IVC diameter shows a decreased volume status [8] .According to the Society of Emergency Physicians, in adult patients with normal CVP, IVC dimeter and IVC-CI should be 15-25 mm and > 50% whereas in cases with volume deficient due to total compression the diameter of the IVC was less than 15 mm [9]. In our study, in 65% of the cases IVC diameter was < 15 mm and IVC-CI was > 50% while in 2.5% of the subjects the diameter of the IVC was 15-25 mm and IVC-CI was > 50%. By those results, it was assumed that there was volume deficit in most of our patients. However, since there was no monitorization of the CVP, no relation could be detected between the CVP and the

volume status.

Ceruti *et al*. [10] has reported the results of 160 cases about the IVC diameter and IVC collapsibility by ultrasound preceding spinal anesthesia. In one group within 15 min 500 ml fluid (Ringerfundine; B. Braun) was loaded and IVC-CI was evaluated and following 15 min volume replacement spinal anesthesia was implemented. Finally, before the spinal anesthesia, volume loading by the guidance of IVC USG decreased the incidence of arterial hypotension, provided the volume status optimization and decreased the interventions following arterial hypotension attacks. However, no any correlation has been demonstrated between the volume loading preceding the spinal anesthesia and IVC-CI [10]. Beside that study, no ant subject received pre-operative volume replacement. Calculating the pre-operative starvation time and hourly volume replacement requirement, crystalloid replacement was applied. There was no any significant relationship between the amount of volume loaded and hypotension, in the present study. In line with the study by Ceruti *et al*. [10], no any meaningful correlation was detected between the IVC-CI and the hypotension after spinal anesthesia, in the current study.

Zhang *et al*. [11] has demonstrated that for the hypotension after general anesthesia, IVC measurements before induction of general anesthesia, IVC-CI was more predictive than dIVCmax and in the same study the threshold value was 43% for IVC-CI. In the present study, there was no significant difference in IVC-CI between the study groups and IVC-CI was not found predictive for hypotension after spinal anesthesia. The underlying cause for such result might be multifactorial component of the hypotension after spinal anesthesia in which hypovolemia could be one of them. While IVC-CI is so determinant for the stats of intravascular volume, it doesn't seem the same as for hypotension after spinal anesthesia.

Intra-operative hypotension is one of the frequent adverse event for anesthesia, whereas the definition may change within the clinical trials. Bjiker *et al*. [12] [has found 140 definitions for hypotension in the literature. In our study, similar to the study of Zhang *et al*. [11] , hypotension was defined as > 30% decrease in mean arterial pressure and/or a value of < 60mmHg in mean arterial pressure. The sympathetic blockage following spinal anesthesia impacts of the regulation of the circulation both by decreasing the venous return and also decreasing the systemic vascular resistance. By the way, as the level of blockage reaches to T4, the cardioselective fibers also are impeded, heart rhythm and also the cardiac output may reduce [13] . Since the sympathetic fibers are within T1-L2, the blockages under the L2 don't have influence on arterial blood pressure [14] . In the present study, as the block level was T8, the surgical operation was initiated. The level of the blockage didn't reach to T4 in any patient within our study. There was no significant difference in the highest level of the blockage between the cases with and without hypotension after spinal anesthesia in the present study.

Limitations

The limitations of our study are as follows; one-center design of the study, the nature of the data came from only one type of surgical operation, no measurement of IVC during the hypotension and after the spinal anesthesia, no comparison of the IVC measurements with some dynamic tests such as CVP and cardiac output. Another limitation was several definitions of the hypotension. The cases with the history of hypertension were not included but the subjects with undiagnosed hypertensive subjects might be recruited.

CONCLUSION

IVC-CI and dIVCmax were not significantly associated with the hypotension after spinal anesthesia in the patients undergoing inguinal hernia operation with spinal anesthesia. Further studies investigating the IVC measurements under spinal anesthesia together with dynamic hemodynamic monitorization modalities are needed.

Authors' Contribution

Study Conception: ST, DK; Study Design: SBT, CY; Supervision: ST, ÇB; Funding: ÇB, DT; Materials: DT, CY; Data Collection and/or Processing: DK, CY; Statistical Analysis and/or Data Interpretation: ET, DK; Literature Review: ÇB, DT; Manuscript Preparation: ST, ET and Critical Review: ST, DT.

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 2021;7(3):326-331 Original Article

DOI: 10.18621/eurj.870267 *General Surgery*

Long-term outcomes of tension-free repair for the primary inguinal hernias

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ABSTRACT

Objectives: Mesh repair is the gold standard in inguinal hernia(IH) repair. If suture repair is to be performed, the common view is to apply tension-free repair. The aim of our study was to analyze retrospectively the changes in primary IH repair at our clinic in 24-years period with regard to the surgical techniques used, patient demographics, complications, and duration of hospital stay.

Methods: The study is based on retrospective analyses of IH repair in 1020 patients in two different periods. In the first period of the study, between 1997-1999 Modified Bassini (MB) method was used for suture repair and Lichtenstein (LH) method was used for mesh repair. In the second period of the study, between 2017-2019, LH method was used for mesh repair and Posterior Wall Darn (PWD) method was used for suture repair.

Results: The rates of postoperative complications were high and time to return to work was longer in suture repair with MB. Less postoperative complications, shorter time to return to work and less recurrence were observed in the PWD method compared to MB.

Conclusions: Suture repair is a preferable option only in relevant cases and these must be tension free repair techniques such as PWD. When required, suture repairs could be successfully performed with low complication and recurrence rates, similar to mesh repairs by experienced surgical teams.

Keywords: tension-free, posterior wall darn, hernia repair

Inguinal hernia (IH) repair is one of the most common performed operations worldwide. An average of 20 million people undergo IH surgery each year [1-3]. It is the most common abdominal wall hernia, accounting for approximately 75% of all hernias, and there is a 27% lifelong recurrence risk of IH in men and 3% in women [4]. Though performed so frequently, there is no consensus on which surgical method is the best in IH repair yet. Being the pioneer of the modern hernia surgery, Bassini suture repair is still applied in the world with many modifications [5, 6]. Mesh repair techniques in IH repair that started with the Liectenstein method have gradually decreased the preference of suture repairs, along with the facts that the availability of the mesh become easier and studies have shown that the recurrence rate in mesh repair is lower [7].

The aim of current study was to analyze the changes in IH repair at our clinic in 20-years period with regard to the surgical techniques used, patient demographics, complications, and duration of hospital stay retrospectively.

METHODS

The study is based on retrospective analyses of IH repair in 1020 patients at a single center in two differ-

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ent periods.

In the first period of the study, the results of unilateral primary inguinal hernia surgeries performed at our clinic between the years 1997-1999 were evaluated. The patients were divided into 2 groups as being performed suture and mesh repair. Modified Bassini (MB) method was used for suture repair and Lichtenstein (LH) method was used for mesh repair.

In the second period of the study, operations performed for unilateral primary inguinal hernia between the years 2017-2019 were analyzed. LH method was used for mesh repair and Posterior Wall Darn (PWD) method was used for suture repair.

In the first period, surgical methods were determined according to the surgeon's and patient's preferences and the mesh availability. In the second period, suture repair was used for patients who refused the mesh or patients younger than 45 years or patients with contaminated wounds. Standard LH repair was applied to the remaining patient group.

Exclusion criterias were as follows:

- Laparoscopic repairs (TAPP)
- Endoscopic repairs (TEP)
- Femoral hernias
- Obturator hernias
- Recurrent cases and
- Bilateral hernias

The demographic characteristics, post-operative length of stay, postoperative complications, and recurrence rates of the patients were analyzed.

Surgical Methods

Modified Bassini Technique (MB)

With an oblique inguinal incision, the skin, subcutaneous, superficial fascia, and external oblique aponeurosis were dissected. The medial leaf of the external oblique aponeurosis was dissected up to the rectus muscle. The lateral leaf was dissected until the Poubart ligament and the iliopubic tract were exposed. In indirect hernias, the hernia sac was dissected to the neck level, ligated and excised (high-ligation). In direct hernias, the protruded pouch was inverted into the abdomen with purse-string sutures. Reinforcement sutures were placed seperately, at intervals of one centimeter, starting from the pubis with prolene suture material, passing through the conjoint tendon and the poubart ligament. The inner ring has been narrowed up to allow the passage of finger pulp (Fig. 1).

Lichtenstein Technique (LH)

The dissection was performed until the Poubart ligament and iliopubic tract were exposed. The pubic bone was exposed up to approximately 2 cm medial of the pubic tubercle. A monofilament polypropylene mesh with 8×15 cm size was used for the repair. The medial side of the mesh was suture to the aponeurotic tissue above the pubic bone, covering the pubic bone 2-3 cm medial with 3-0 prolene suture. With the same suture, the lower edge of the mesh was suture to the poubart ligament continuously and not too tightly, and the procedure was continued up to lateral of the internal ring. An incision was made on the lateral edge of the mesh and 2 tails were created with the upper part wider than the lower side. The upper edge of the mesh was continuously suture with nonabsorbable suture to

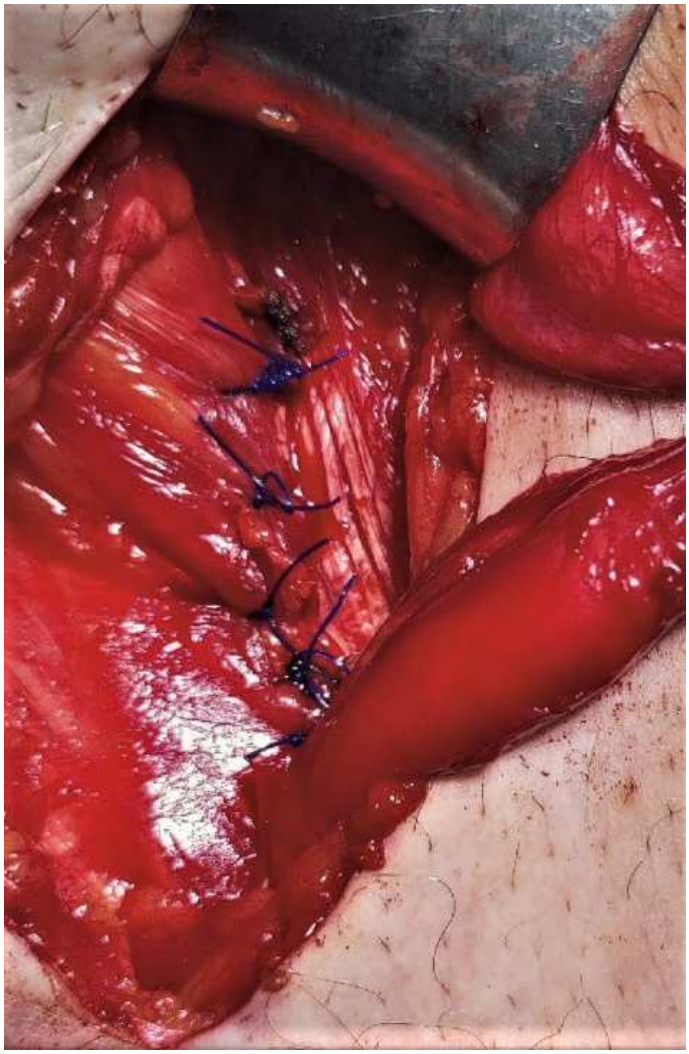

Fig. 1. MB repair with seperated sutures.

internal oblique aponeurosis, 2-3 cm beyond the borders of Hasselbach's triangle. The lower edges of both tails were attached to the inguinal ligament and just lateral to the underlying continuous suture with a few nonabsorbable sutures. An excess of 3-4 cm mesh that was left on the lateral edge of the mesh, was folded under the eksternal oblique aponeurosis which would cover the mesh (Fig. 2).

Posterior Wall Darn Method (PWD)

In this method, sutures were placed between the conjoint tendon and the iliopubic tract over 2 layers of polypropylene so that the stitches weren't be too tight, and rectus muscle and fascia were not stretched. Sutures were passed through both the iliopubic tract and the conjoint tendon at equal intervals of at least 6 mm and at most 12 mm length. Unlike the Bassini technique, the tissues were not tightly brought close to each other, only the repair line was attached tightly and the suture was left loose in accordance with the PWD technique. After narrowing the internal orifice of the inguinal canal, the suture is locked and tied (Fig. 3).

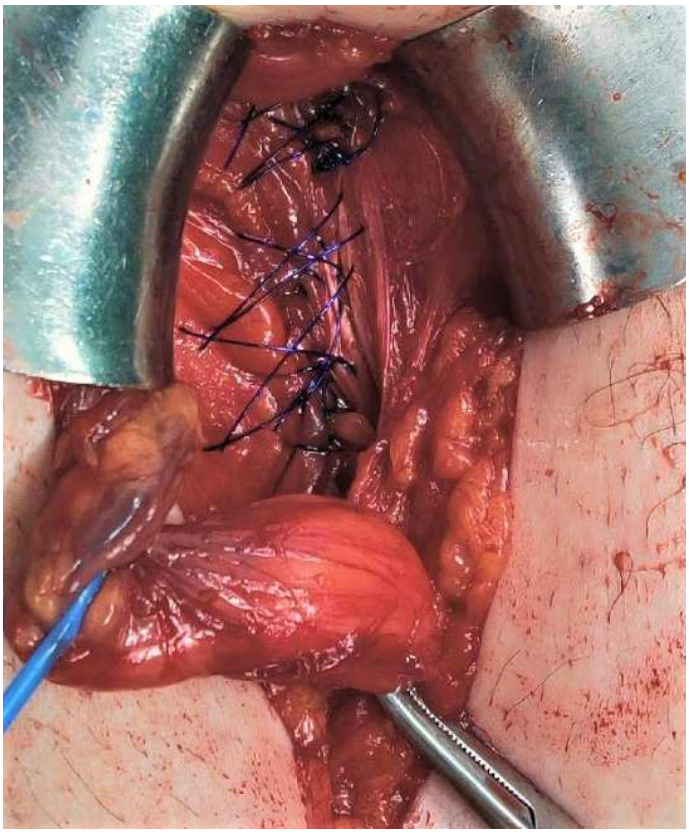

Fig. 3. PWD tension-free repair with continuous sutures.

Statistical Analysis

Statistical analysis was performed using the SPSS for Windows version 22.0 software (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to test the normal distribution of data. Descriptive data were expressed in mean ± standard deviation, medians (range) and number and frequency (%).

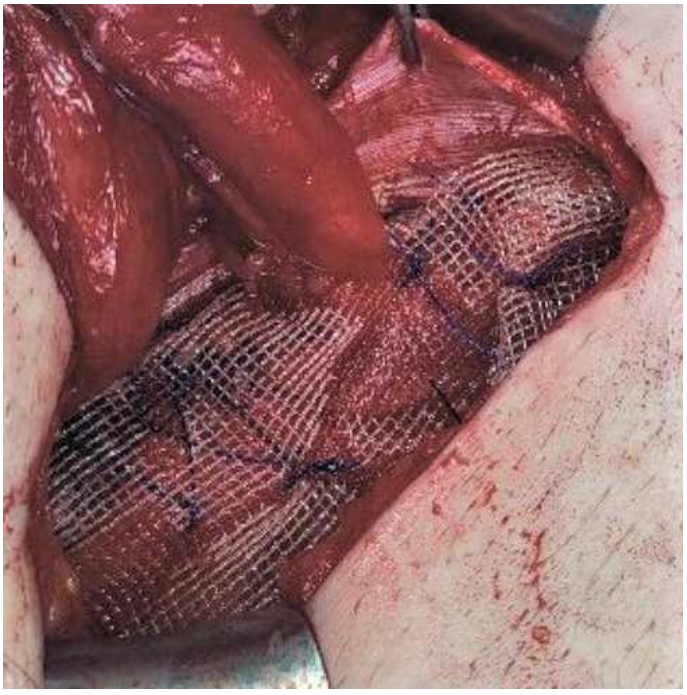

Fig. 2. LH repair with mesh.

RESULTS

At the first period, there were 150 primary unilateral inguinal hernia cases within 2-years time. LH technique was applied to 90 (60%) patients and MB technique was applied to 60 (40%) patients. 79 (88%) of the patients in the LH group and 52 (87%) of the patients in the MB group were male. Most of the patients (75%) were ≤ 45 years old. 67 (75%) of the patients who underwent LH repair and 45 (75%) of the patients in the MB group were ≤ 45 years old. After the LH repair performed at this period, the postoperative hospital stay was approximately 1 day (6-28 hours), and the average time to return to work was 10 days (7-16 days). Postoperative surgical site infection was developed in only 2 (2.2%) patients in the LH repair group and early recurrence was not observed. (Table 1). After the MB repair performed at this pe-

riod, the average postoperative hospital stay was 3 days (25-96 hours), and the average time to return to work was 22.5 days (17-30 days). In the MB group, 3 (5%) patients had developed surgical site infection; 2 (3.3%) had scrotal hematoma; and 2 (3.3%) had early recurrence.

At the second period, there were 870 primary unilateral inguinal hernia cases within 2 years. LH technique was applied to 792 (91%) and PWD technique was applied to 78 (19%) patients respectively. 811 (93%) patients were male and 59 (7%) were female. 665 (84%) of the patients who underwent LH repair are were > 45 years old, while 66 (85%) of the patients who underwent PWD repair were ≤ 45 years old. The mean postoperative hospital stay following the LH repair performed at this period was 1.01 days (11-172 hours), and the average time to return to work was 8.9 days (4-18 days). In the LH repair group, 17 (2.1%) patients developed post-operative seroma, 21 (2.7%) patients developed surgical site infection, and 13 (1.6%) patients developed scrotal hematoma. Early recurrence was observed in 11 (0.9%) patients in LH repair group. The mean postoperative hospital stay in PWD repair group was 1 day (7-49 hours), and the time to return to work was 9.2 days (3-19 days) on average. In the PWD repair group, post-operative complications were; seroma in 3 (3.8%) patients, surgical site infection in 4 (5.1%) patients, and scrotal hematoma in 4 (5.1%) patients. Early recurrence was observed in 1 (1.3%) patient in PWD repair group (Table 1).

DISCUSSION

With the Bassini method, an important milestone

Table 1. Demographic data and clinical outcomes of patients

	1st PERIOD (n = 150)		2nd PERIOD (n = 870)	
	Lichtenstein	Modified Bassini	Lichtenstein	Posterior Wall Darn
Number of patients (%)	90 (60%)	60 (40%)	792 (91.0%)	78 (9.0%)
Gender, n (%)				
Male	79 (87.8%)	52 (86.7%)	739 (93.3%)	72 (92.3%)
Female	11 (12.2%)	8 (13.3%)	53 (6.7%)	6 (7.7%)
Age, n (%)				
16-25 years	17 (18.8%)	9 (15.0%)	9 (1.1%)	22 (28.2%)
26-35 years	28 (31.1%)	17 (28.3%)	27 (3.4%)	35 (44.9%)
36-45 years	22 (24.4%)	19 (31.7%)	105 (13.3%)	9 (11.5%)
46-65 years	14 (15.5%)	9 (15.0%)	411 (51.9%)	10 (12.8%)
66-75 years	6 (6.6%)	4 (6.7%)	179 (22.6%)	1 (1.3%)
> 75 years	3 (3.3%)	2 (3.3%)	61 (7.7%)	1 (1.3%)
Postoperative hospital stay (h), median (range)	24.0 (6-28)	72.0 (25-96)	24.2 (11-172)	24.1 (7-49)
Time to turn to work (d), median (range)	10.0 (7-16)	22.5 (17-30)	8.9 (4-18)	9.2 (3-19)
Postoperative complications, n (%)				
Seroma	0 (0%)	0 (0%)	17 (2.1%)	3 (3.8%)
Surgical site infection	2 (2.2%)	3 (5%)	21 (2.7%)	4 (5.1%)
Scrotal hematoma	0 (0%)	2 (3.3%)	13 (1.6%)	4 (5.1%)
Recurrence	0 (0%)	2 (3.3%)	11 (0.9%)	1 (1.3%)

in the development of modern hernia surgery, suture repair has been preferred with modifications for years and continues to be a preferred technique in selected cases [8-10]. Currently available guidelines (EHS, the HerniaSurge Group, AHS etc.) hold the view that mesh repair is the gold standard in inguinal hernia repair [11-13]. If suture repair is to be performed, the common view is to apply tension-free repair [14]. Although, in the last guideline [12], only Shouldice repair is recommended as a suture repair, different suture repair techniques are still used in the world [15].

Mesh repair was performed mainly in our clinic between the years 1997-1999, the MB technique was also applied to a significant number of patients in these years. Although early recurrence rates after MB were low, the rates of post-operative complications were high and time to return to work was longer.

In the last 20 years, the suture repair method has evolved from Bassini to its modifications like PWD, which is based on "continued non-absorbable" sutures and repair without tension [16-19]. That applied to our clinic as well. Complications such as post-operative seroma, hematoma and surgical site infection are less common that makes this method advantageous especially in contaminated cases [20]. In our cases, less post-operative complications, shorter time to return to work and less recurrence were observed in the PWD group compared to MB group.

According to HerniaSurge Group guideline; suture repair can be applied in cases such as mesh allergy and the patient's refusal to repair with mesh[12]. There are publications in the literature showing that suture repair is superior to mesh repair in terms of recurrence, in young male population with indirect hernia [21]. There are also studies indicating that young men develop more chronic pain following mesh usage compared to elderly [22, 23]. During the past 20 years in our clinic, we have decreased using suture repair eventually, except for selected cases. In the second period; 85% of the patients who underwent PWD repair were ≤ 45 years old and 84% of the group in which LH was applied in the second period were > 45 years old. In the first period, the mean age was similar in the MB and LH groups. The selected case approach that we applied in our surgical routine is also have proved its effectiveness in achieving fewer complications, shorter hospital stays and shorter time to return to work in the suture repair group.

We have been using the PWD method, as a standard suture repair method in our clinic since 2000. In a study conducted by Ivanov *et al*. PWD was applied to 116 patients. The total complication rate was reported as 22.4% and the mean duration of hospital stay was 2.17 days [24]. In the PWD repairs that we performed in the second period in our study, our total complication rate was 10.2% and the hospital stay was around 1 day (7-49 hours). As a result of applying this method in selected cases, especially with the same experienced surgical team; the duration of hospitalization and time to return to work is shortened and post-operative complications are decreased in suture repairs.

Currently, LH repair is the standard treatment in open IH repair all over the world[11]. We perform LH repair, which we first started to apply in our clinic in 1997, more frequently today. There has been no change in the LH technique past 24 years. During this period, an important training standard has been achieved in the application of the method and the method has been a standardised procedure in our clinic. As a result of this, in the second period, a significant decrease was observed in the time to return to work.

The comparison of the two groups analysed at intervals of 24 years shows that the suture repair rates have been gradually reduced by applying to only selected cases in the second period. Thus today, recurrence rates and lenght of hospital stay are reduced and time to return to work is earlier. Furhermore, with performing suture repairs in selected cases, there are similar complication rates after mesh and suture hernia repair.

CONCLUSION

Mesh repair must be prefered in inguinal hernia treatment. Suture repair is a preferable option only in relevant cases and these must be tension free repair techniques such as PWD. When required, suture repairs could be successfully performed with low complication and recurrence rates, similar to mesh repairs by experienced surgical teams.

Authors' Contribution

Study Conception: FB, HB, ST; Study Design FB,

HB, ST; Supervision: FB, HB, ST; Funding: FB, HB, ST; Materials: FB, HB, ST; Data Collection and/or Processing: FB, HB, ST; Statistical Analysis and/or Data Interpretation: FB, HB, ST; Literature Review: FB, HB, ST; Manuscript Preparation: FB, HB, ST and Critical Review: FB, HB, ST.

Conflict of interest

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

Financing

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