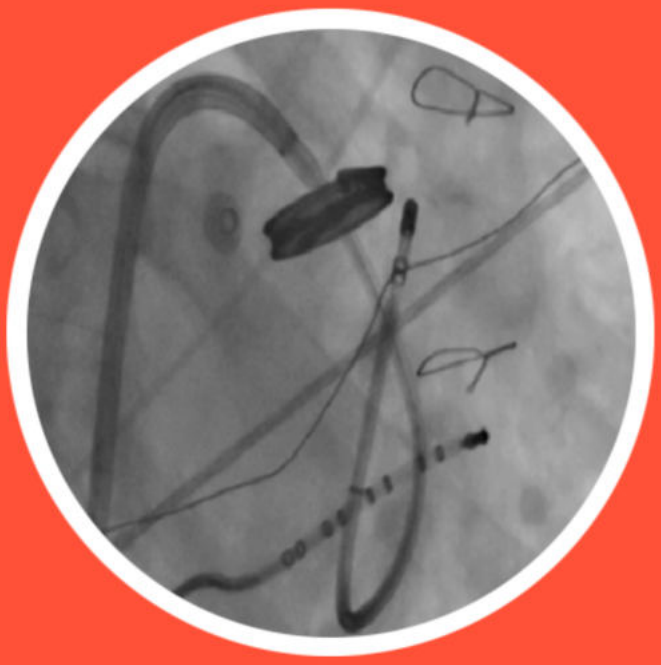
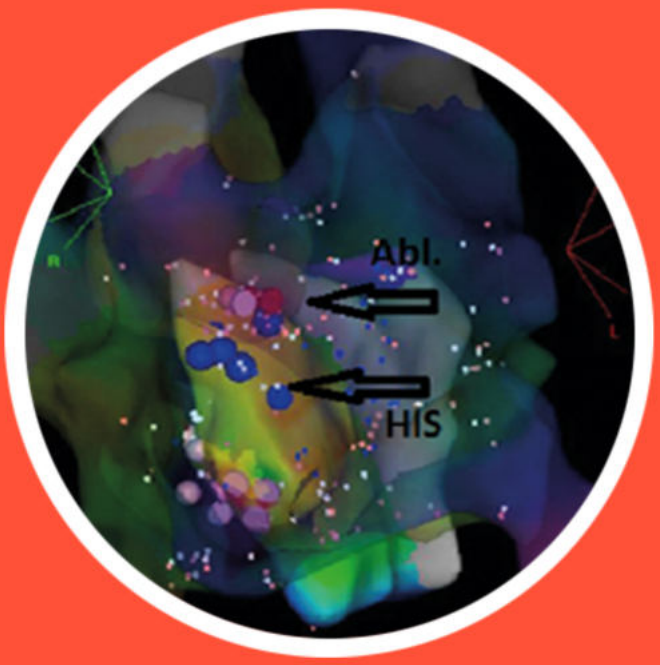
Volume 7 · Issue 2 · March 2021
e-ISSN: 2149-3189

The European Research Journal





Available at http://dergipark.org.tr/eurj

The European Research Journal

Aim and Scope

The European Research Journal (EuRJ) is an international, independent, double-blind peer reviewed, Open Access and online publishing journal, which aims to publish papers on all the related areas of basic and clinical medicine.

Editorial Board of the European Research Journal complies with the criteria of the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), and Committee on Publication Ethics (COPE).

The journal publishes a variety of manuscripts including original research, case reports, invited review articles, technical reports, how-to-do it, interesting images and letters to the editor. The European Research Journal has signed the declaration of the Budapest Open Access Initiative. All articles are detected for similarity or plagiarism. Publication language is English. The journal does not charge any article submission or processing charges.

EuRJ recommends that all of our authors obtain their own ORCID identifier which will be included on their article.

The journal is published bimonthly (January, March, May, July, September, and November).

Abstracting and Indexing

The journal is abstracted and indexed with the following: ULAKBIM TR Index (ULAKBİM TR DİZİN), NLM Catalog (NLM ID: 101685727), Google Scholar (h-index: 6), Index Copernicus (ICV 2019: 100), EMBASE, ProQuest Central, ROAD, SciLit, MIAR (ICDS 2020: 3.7), J-Gate, SHERPA/RoMEO, BASE, EZB, CrossRef, JournalTOCs, WorldCat, TURK MEDLINE, Turkish Citation Index, EuroPub, OpenAIRE, ResearhGate, SOBIAD, Publons (Clarivate Web of Science).

Publisher

The European Research Journal (EuRJ)
The Association of Health Research & Strategy
Kırcaali Mah. Fevziçakmak Cd. Göktaş İş Mrk.
Kat:3 No:62/12
Osmangazi/BURSA-TURKEY
www.dergipark.org.tr/eurj/

THE ASSOCIATION OF HEALTH RESEARCH AND STRATEGY

e-ISSN: 2149-3189

EDITORIAL BOARD

EDITORS

Omer SENORMANCI, MD

Associate Professor,
University of Health Sciences, Bursa Yuksek Ihtisas Training & Research Hospital,
Department of Psychiatry,
Bursa, Turkey

Rahmi DUMAN, MD,

Associate Professor,
Ankara LIV Hospital,
Department of Ophthalmology,
Ankara, Turkey

Ali ASAN, MD

Associate Professor,
University of Health Sciences, Bursa Yuksek Ihtisas Training & Research Hospital,
Department of Infectious Disease,
Bursa, Turkey

Meliha KASAPOGLU AKSOY, MD

Associate Professor,
University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital,
Department of Physical Therapy & Rehabilitation,
Bursa, Turkey

Sinem KIYICI, MD

Associate Professor,
University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital,
Department of Endocrinology & Metabolism
Bursa, Turkey

Soner CANDER, MD

Associate Professor,
Uludag University Medical School,
Department of Endocrinology & Metabolism
Bursa, Turkey

Metin GUCLU, MD

Associate Professor,
University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital,
Department of Endocrinology & Metabolism
Bursa, Turkey

Cuma Bulent GUL, MD

Associate Professor,
University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital,
Department of Nephrology
Bursa, Turkey

Sedat ONER, MD

Associate Professor,
University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital,
Department of Urology
Bursa, Turkey

Burcu METIN OKMEN, MD

Associate Professor,
University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital,
Department of Physical Therapy & Rehabilitation,
Bursa, Turkey

Arda ISIK, MD

Associate Professor,
Binali Yildirim University School of Medicine,
Department of General Surgery,
Erzincan, Turkey

Emin USTUNYURT, MD

Associate Professor,
University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital,
Department of Gynecology & Obstetrics,
Bursa, Turkey

Mehtap BULUT, MD

Professor,
University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital,
Department of Emergency Medicine,
Bursa, Turkey

Mete KAYA, MD

Professor,
University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital,
Department of Pediatric Surgery,
Bursa, Turkey

Melih CEKINMEZ, MD

Professor,
University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital,
Department of Neurosurgery,
Bursa, Turkey

Serhat YALCINKAYA, MD

Associate Professor,
Kutahya University of Health Sciences,
Department of Thoracic Surgery
Kutahya, Turkey

Korgun OKMEN, MD

Associate Professor,
University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital,
Department of Anesthesiology & Reanimation,
Bursa, Turkey

Derya KARASU, MD

Associate Professor,
University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital,
Department of Anesthesiology & Reanimation,
Bursa, Turkey

Hasan ARI, MD

Professor,
University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital,
Department of Cardiology,
Bursa, Turkey

Erhan TENEKECIOGLU, MD

Associate Professor,
University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital,
Department of Cardiology,
Bursa, Turkey

Kadir Kaan OZSIN, MD

Associate Professor,
University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital,
Department of Cardiovascular Surgery,
Bursa, Turkey

INTERNATIONAL EDITORIAL BOARD MEMBERS

Ozkan KANAT, MD,
Professor,
Acibadem University Hospital
Department of Medical Oncology,
Bursa, Turkey

Sait Ait BENALI, MD

Professor,
Cadi Ayyad University School of Medicine,
Department of Neurosurgery,
Marrakech, Morocco

Sedat ALTIN, MD

Professor,
University of Health Sciences,Yedikule Training & Research Hospital,
Department of Chest Diseases,
Istanbul, Turkey

Semih HALEZEROGLU, MD, FETCS

Professor,
Acibadem University School of Medicine,
Department of Thoracic Surgery,
Istanbul, Turkey

Veysel TAHAN, MD, FACP, FACG, FESBGH

Assistant Professor,
University of Missouri,
Division of Gastroenterology and Hepatology,
Columbia, Missouri, USA

Yenal DUNDAR, MD

University of Liverpool School of Medicine,
Department of Psychiatry,
Liverpool, UK

Table of Contents

Original Articles

Reviews

The European Research Journal 2021;7(2):107-115 Original Article

DOI: 10.18621/eurj.689738 *Radiology*

Pain assessment of ultrasound-guided liver biopsy for diffuse parenchymal diseases: a randomized trial comparing intercostal and subcostal techniques

Yaşar Türk[1,2], Banu Alıcıoğlu[2], İsmail Devecioğlu[3]

[1]*Department of Radiology, Tekirdağ Namık Kemal University School of Medicine, Tekirdağ, Turkey*
[2]*Department of Radiology, Zonguldak Bülent Ecevit University School of Medicine, Zonguldak, Turkey*
[3]*Department of Biomedical Engineering, Tekirdağ Namık Kemal University, Çorlu Engineering Faculty, Tekirdağ, Turkey*

ABSTRACT

Objectives: Percutaneous liver biopsy is widely used in diffuse liver parenchymal diseases. Comparison of the severity of pain is not properly studied. In this randomized study, pain intensity between the intercostal and subcostal techniques of US-guided Tru-Cut liver biopsy in diffuse liver diseases was compared.

Methods: Between March 2016 and May 2017, all potential study participants referred to the interventional radiology department for ultrasound-guided liver biopsy (n = 245), were assessed for enrollment. The pain intensity at 0, 2, and 4 h post-procedure was compared in two groups using a Numeric Rating Scale (NRS). Premedication was not used. After applying local anesthesia under US-guidance, 18-G automatic biopsy needle free-hand US-guided biopsy was performed.

Results: Immediately after the biopsy (p = 0.0024), and at the 2nd hour (p = 0.0298), NRS of the subcostal group was significantly less than the intercostal group. Furthermore, the need for oral (p = 0.0492) or intramuscular (p = 0.0094) analgesics after the biopsy in the subcostal group was significantly less than the intercostal group. At the evaluation of both groups together, 55.62% of the patients had a mild and 27.22% had a moderate pain score. NRS score decreased with time in each group.

Conclusions: The pain intensity and the need for analgesics were less in the subcostal biopsies. Since intense pain and anxiety may be the cause of loss of the patients after the first biopsy, a subcostal biopsy could be preferred primarily.

Keywords: Image-guided biopsy, liver, pain, ultrasound

Nowadays, despite the advanced imaging modalities, tru cut biopsy remains the gold standard in the diagnosis of liver parenchymal diseases [1, 2]. Percutaneous liver biopsy is fundamental for the histological diagnosis, staging, and assessment of response to therapy in diffuse liver parenchymal diseases. Ultrasonography (US)-guided biopsy is the most accurate and cost-effective method and provides more specimens with less pain to patients [3]. The incidence of serious complications is less than 1%, and the complications following percutaneous liver biopsy are well documented in a multicentre retrospective study on 68278 biopsies [4, 5]. Pain is known as the most frequent reason for patient discomfort following

Received: ***February 15, 2020;*** ***Accepted:*** ***June 18, 2020;*** ***Published Online:*** ***January 31, 2021***

How to cite this article: *Türk Y, Alıcıoğlu B, Devecioğlu İ. Pain assessment of ultrasound-guided liver biopsy for diffuse parenchymal diseases: a randomized trial comparing intercostal and subcostal techniques. Eur Res J 2021;7(2):107-115. DOI: 10.18621/eurj.689738*

Address for correspondence: *Yaşar Türk, MD., Assistant Professor, Zonguldak Bülent Ecevit University School of Medicine, Department of Radiology, Zonguldak, Turkey. E-mail: yasar.turk@beun.edu.tr*

e-ISSN: 2149-3189

biopsy. 20% of patients had moderate, 16% of patients had severe pain and about 10% of patients wouldn't tolerate another biopsy in the future [6]. The reported moderate and severe pain generally requires hospitalization and is observed in 1-5% of the patients [7, 8], but some studies revealed that more than 50% of patients had moderate and severe pain following the procedure [9-11]. Pain is a very subjective and complex sensation and difficult to analyze, it is located at the biopsy puncture, radiating to the right shoulder, with mild to moderate intensity, and relives gradually [6, 12].

Although liver biopsy is a frequently used procedure, a consensus has not been reached on the best approach subcostal versus intercostal [9, 13, 14]. Hepatitis C, younger age, the experience of the operator, the number of punctures were addressed as predisposing factors of pain. Severe pain sensation may induce anxiety that is another factor to increase pain intensity after percutaneous liver biopsy [11], it's, therefore, an outstanding matter to control the pain of the patients after the biopsies as well as to improve liver biopsy techniques worldwide. However, variances in biopsy techniques, preferred anesthesia/analgesia type, underlying liver disease of the patients of the studies may result in different conclusions. Comparison of severity of pain in subcostal and intercostal liver biopsy technique is not widely studied in the literature. This randomized study aims to compare pain intensity between the intercostal and subcostal techniques of US-guided liver biopsy in patients with diffuse liver disease.

METHODS

Study design

The study approval was obtained from the ethics committee. Comparing the pain intensity by a Numeric Rating Scale (NRS) between the intercostal and subcostal techniques of US-guided Tru-Cut liver biopsy in diffuse liver diseases was the main objective.

Patient selection

All liver patients referred for ultrasound-guided biopsy between March 2016 and May 2017 to the interventional radiology unit were assessed in a state hospital. All participants who have not inclusion criteria were excluded at the screening. All biopsies were performed by one board-certified interventional radiologist with 17 years of experience in US-guided biopsy. At a dedicated outpatient interventional radiology clinic, the screening and enrollment process was performed by analysis of medical records and if there are abdominal imaging studies. Any history of prior liver percutaneous core biopsy was explored by reviewing medical records. If there is, Ultrasound, CT, and MR images were reviewed at the hospital PACS system to identify the safest liver core biopsy approach. Selecting the participants who met the inclusion criteria were done by the interventional radiologist.

The study inclusion criteria were 1) age of > 18 years, 2) clinical indication of liver biopsy for a non-focal liver lesion, and 3) accepting the informed consent by the patients.

The exclusion criteria were as follows: 1) abnormal coagulation test results (with an international normalized ratio of > 1.5 and a low thrombocyte number (< 70,000/mm3)), 2) intrahepatic bile duct dilatation, 3) focal liver lesions, 4) hydatid cyst, 5) massive ascites, 6) previous liver transplantation, 7) patients who the biopsy can be done with only one of the two techniques, therefore, cannot be randomized. and 8) pregnancy.

Randomization

Two hundred forty-five patients were assessed for eligibility. After the exclusion of 37 patients, 208 cases were randomized into intercostal and subcostal groups. A computerized randomization system is used for patient selection. The assistant noted the pain score and, the patients were blind to the study method.

Procedure

Before the biopsy

All the study patients' liver biopsy indications were done clinically. They referred to the interventional radiologist. The indication of biopsy and complete blood count, and a coagulation profile including INR, APTT, platelets, and fibrinogen were re-analyzed and approved by the interventional radiologist. The patients were followed up daily following the biopsy. They were informed about the procedure and the possible complications and then asked to sign the consent form upon agreeing to participate in the study. The in-

travenous line was inserted after the blood pressure and heart rate were measured. Moreover, the State-Trait Anxiety Inventory was used to measure each participant's trait and state anxiety level before the biopsy [15].

During the biopsy

The patients were transferred to the biopsy room. To maintain their full cooperation, no oral or intravenous analgesics or intra-procedure conscious sedation were given. Under sterile conditions, 20 ml of 2% prilocaine hydrochloride (Pricain; Polifarma Pharmaceutical JSC. Tekirdag/Turkey) solution was injected ultrasound guided. Local anesthesia was done from the subcutaneous tissue to the liver capsule in the biopsy area by using a 25-gauge needle. To obtain the optimal cooperation of the patients during the procedure, premedication or intra-procedure conscious sedation was not used.

The intercostal approach was performed from the right hemithorax inferolateral, and the subcostal approach was performed from the right side. A small incision of < 5mm was made by a number 11 blade and the biopsy was done by an 18-gauge fully automated, biopsy needle (Bard MaxCore, Covington, GA) with the method of freehand US-guided biopsy. The cutting length of the needle was 22 mm. In all cases, only one sample with one pass was taken and needle penetration depth into the liver was 2 cm from the liver capsule. (In case of the inadequate biopsy sample, < 15 mm in length, the biopsy was repeated at the same entry side and the subject was excluded from the study. A simple wound dressing was applied after the procedure.

After the biopsy

Following the biopsy, all patients were transferred to the daycare unit and requested to lie on the biopsy side for 4 h. The patients were followed up every 15 min of the first 2 h and every 30 min of the following 2 h in terms of the vital findings. If necessary, 500 mg paracetamol (MİNOSET® 500 mg tablet, Bayer Turkish Chemical Industry, Ltd company Istanbul/Turkey) was administered. If the medication failed to control the pain, Diclofenac Sodium 75 Mg / 3 Ml (Dikloron, Deva Holding Ltd.) intramuscular analgesic would be ordered. The patients were discharged if there were no complications during the first 4 h after the biopsy. All the patients were instructed to contact a medical center immediately in case of any problems or complications. The electronic records and hospital referrals of all the patients were cross-checked for late complications upon completion of six months following the biopsy procedure.

Statistical Analysis

All statistical analyses were performed in MATLAB (R2016a, The MathWorks Inc., USA). Age and anxiety levels of patients in intercostal and subcostal groups were compared with Student's t-test. χ^2 test was used to test any differences between treatment groups in means of sex ratio, liver biopsy history, final pathology results, need for additional analgesics. Mann-Whitney U test was used to compare pain scores of patients in intracostal and subcostal groups. The same tests were used to compare the parameters of male and female patients. The relationship between age and pain scores was evaluated with the Spearman rank-order correlation test.

RESULTS

Between March 2016 and May 2017, 245 participants were screened, and 231 were interviewed for enrollment at an outpatient interventional radiology clinic. A total of 37 participants were excluded due to the focal liver lesion, massive ascites, abnormal coagulation test results, etc. A total of 208 participants (mean age, 43.13 years; age range, 19-81 years; 124 females, 84 males) was randomly assigned to either the subcostal (n = 104; mean age, 43.08 years; age range, 19-81 years; 58 females, 46 males) or intercostal (n = 104; mean age, 43.19 years; age range, 19-79 years; 66 females, 38 males) arm. Of these participants, 10 did not undergo treatment because of biopsy cancellation (n = 8) or withdrawal of consent (n = 2).

Liver biopsy was done in 198 of the 208 randomly assigned participants. Demographics of patients undergoing US-guided liver biopsy are shown in Table 1. Groups were matched on age, gender, liver biopsy history, and final pathology results.

The primary aim of this study was to compare the pain level of participants within 0, 2, and 4 hours after the ultrasound-guided percutaneous liver biopsy pro-

Table 1. Demographics and technical characteristics in per-protocol population

Characteristic	SC group n = 83 (49.11%)	IC group n = 86 (50.89%)	*p* value
Mean Age ± SD	43.60 ± 12.16	44.05 ± 11.84	0.810*
Sex ratio (female/male)	45/38	56/30	0.150**
Previous liver biopsy history, n (%)			0.419**
Yes	11 (0.13)	8 (0.09)	
No	72 (0.87)	78 (0.91)	
Final pathology result, n (%)			0.739**
Diagnostic	80 (0.96)	82 (0.95)	
Nondiagnostic	3 (0.04)	4 (0.05)	

IC = Intercostal, SC = Subcostal. SD = standard deviation, *Student's t-test, ** Mann–Whitney U test

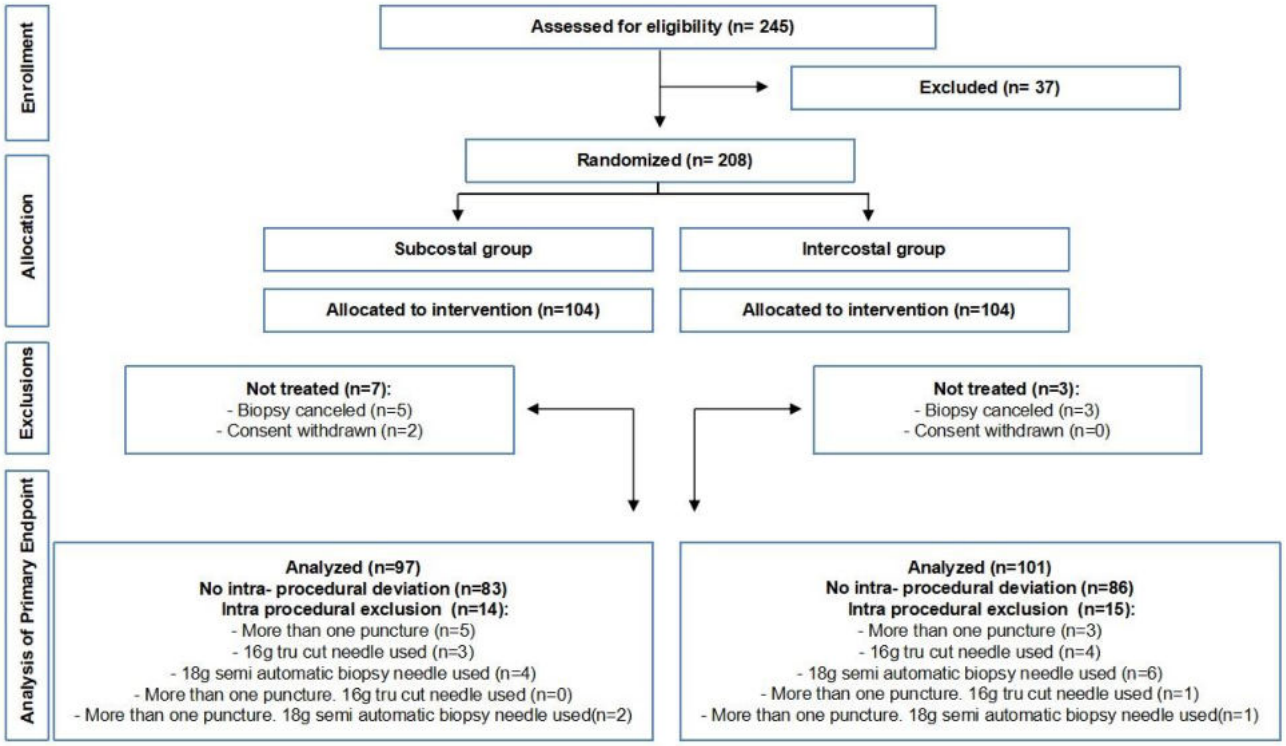


Fig. 1. Consort diagram.

cedure with either the subcostal or the intercostal approach.

The NRS was used to quantify pain. All patients declared that they would tolerate another biopsy if it was clinically required in the future. The median NRS scores, just after the procedure, 2 and 4 h later are summed up in Table 2.

Of the treated participants, fifteen patients in the intercostal group and fourteen patients in the subcostal group excluded due to more than one puncture, 16 g fully automated tru cut, or 18 g semi-automated tru cut needle use (because of different size and different sampling methods). The detail is seen in the consort diagram in Fig. 1.

Immediately after the biopsy ($p = 0.0024$), and at the 2nd hour ($p = 0.0298$), NRS of the subcostal group was significantly less than the intercostal group. No significant difference was found in the pain level between the intercostal and subcostal groups 4 hours after the procedure ($p = 0.0787$). No significant differ-

Table 2. Pain dissipation after US-guided percutaneous tru-cut liver biopsy.

	IC group (n = 86)	SC group (n = 83)	*p* value	M patients (n = 68)	F patients (n = 101)	*p* value
Anxiety level[a]	39.74 ± 9.86	37.47 ± 11.16	0.1617[b]	40.00 ± 10.54	37.70 ± 10.50	0.1657[b]
Just after the biopsy[c]	3 [1-5]	2 [1-3]	**0.0024**[d]	2	2	0.4673[d]
2nd-hour[c]	1.5 [0-3]	1 [0-2]	**0.0298**[d]	1	1	0.5692[d]
4th-hour[c]	0 [0-2]	0 [0-1]	0.0787[d]	0	0	0.3414[d]
Additional analgesics, n (%)						
Tablet	28 (0.326)	16 (0.193)	**0.0492**[e]	16	28	0.5424[e]
IM Amp	15 (0.174)	4 (0.048)	**0.0094**[e]	9	10	0.5010[e]

IC = Intercostal, SC = Subcostal, F = Female, M = Male, [a]Reported as mean ± standard deviation, [b]Student's t-test, [c]Reported as the median score [interquartile range, IQR], [d]Mann–Whitney U test; [e]χ^2 test

ence was found between male and female patients regarding pain level. The need for additional oral and intramuscular analgesics after the biopsy was 28 and 15 out of 86 patients in the intercostal group, respectively; 16 and 4 out of 83 patients in the subcostal group, respectively.

The requirement for additional analgesics was significantly less in the subcostal group than the intercostal group (oral analgesic: $p = 0.0492$; intramuscular analgesic: $p = 0.0094$). At the evaluation of both groups together, 55.62% of the patients had a mild and 27.22% had a moderate pain score. Median NRS decreased with time in each group. We did not find any correlation between NRS scores and age neither in different treatment groups nor post-operative times. Besides, there were no significant differences between intracostal and subcostal groups in anxiety levels ($p = 0.1617$). Finally, when male and female patients were compared, no significant differences were found in any parameter (see Table 2).

Minimal external hemorrhage due to compression failure of skin dress was observed in one patient in the subcostal study group, but no intervention was required. No late complications were observed in any of the patients.

DISCUSSION

We performed a randomized study to compare the pain level of percutaneous US-guided parenchymal liver biopsy within 0, 2, and 4 hours after biopsy when the intercostal or subcostal approaches were used. From March 2016 to May 2017, 245 potential study participants were assessed for enrollment. A total of 208 participants were randomly assigned to the subcostal (n = 104) or intercostal (n = 104) arm. A total of 169 participants underwent treatment without intraoperative exclusion (mean age, 43.83 years; age range, 19-81 years; 101 females, 68 males); subcostal (n = 83; mean age, 43.60 years; age range, 19-81 years; 45 females, 38 males) or intercostal (n = 86; mean age, 44.05 years; age range, 22-79 years; 56 females, 30 males). The results of our study showed that both intercostal and subcostal biopsies were less painful similar to previous studies [6, 10, 12, 14, 16, 17]. Moreover, pain intensity and the need for analgesics were more in the intercostal biopsies. The probable reasons are: (1) the intercostal approach may result in a pleural puncture, which is a sensitive epithelial layer; (2) the intercostal approach may traumatize the respiratory muscles; (3) respiratory movement during the intercostal approach acts in a contrary direction to the needle movement, which can cause more damage to the liver capsule. Conversely, in the subcostal approach, the needle versus respiratory movements is in the same direction, and this condition can cause less capsular damage; (4) injury of the periosteum of the ribs, which is sensitive to pain, and (5) intercostal nerve trauma are possible [6]. Both methods necessitate peritoneal puncture. Technically, the right subcostal liver biopsy can be relatively difficult because

of the oblique course of biopsy needles. However, the complications were not found to be different in the current study. Subcostal biopsies are technically successful, nevertheless, this approach might not be preferred for patients with Chilaiditi syndrome, which is a rare anomaly with a 0.025%-0.28% of incidence [11]. In such cases, the right intercostal or the left subcostal approach can be used.

Although, the combination of sedation and analgesia could have a synergistic effect on reducing the pain during the biopsy procedure, however, result in partial amnesia and loss of corporation [18, 19] that could be challenging during the local anesthesia and biopsy. In this mean, to maintain the full cooperation of the patients during local anesthesia and biopsy, no systemic sedation or analgesia was administered in this study. If local anesthesia is applied well and biopsy is performed in the same tract that is infiltrated with lidocaine, the procedure will be almost painless and thus eliminate premedication risks. The well-innervated liver capsule is sensitive to pain sensation. So, effective administration of local anesthetics to this area plays an essential role in reducing pain during the biopsy. In the current study, 55.62% of the patients had mild and 27.22% of the patients had moderate pain score levels following biopsy that was similar to the previous studies (Table 3). The variables affecting pain after biopsy remain mostly unknown. Because the same intervention could result in different pain intensities in different participants. Although a consensus

Table 3. Brief review of the literature studying of pain after percutaneous liver biopsies

Study (year)	Number of patients	Biopsy	Mean pain scale	Used analgesics/sedation	Size of the needle, technique	Predisposing factors of pain
Castera *et al.* [10] (1999)	30	parenchymal	28 (VAS)	LA 10 ml 1% lidocaine	Menghini Technique	Hepatitis C, young age
Cadranel *et al.* [9] (2000)	> 2000	mostly parenchymal	28 (VAS)	varied	varied	Female, hepatitis C; (Pain less in experienced physician, general anesthesia)
Riley *et al.* [14] (2002)	121	miscellaneous	Not given	LA 1% lidocaine	Not given	Hepatitis C, young age, history of iv drug use
Eisenberg *et al.* [11] (2003)	54	miscellaneous	42 (VAS)	5 mg diazepam (po, 1 h before) LA 10 ml 2% lidocaine	16 G automated trucut	Female, high anxiety level
Tan *et al.* [6] (2005)	70	parenchymal	Not given	1 mg midazolam+50 µgr fentanyl 5-10 ml 1% lidocaine	18 G	Female
Lindner *et al.* [16] (2014)	223	parenchymal (n =85) focal lesion (n =113)	2.98 (NRS)	LA scandicain 1%	Trucut (mostly subcostal)	Parenchymal biopsy had more pain compared to focal lesions, females, young age
Baig *et al.* [17] (2015)	50	not given	2.7 ± 1.11 (VAS[0-4])	10 ml 2% xylocaine +adrenaline	18/16 G automatic Trucut	Younger age, male
Pezeshki Rad *et al.* [12] (2018)	112	parenchymal and focal lesion	17.86 (VAS)	LA 10 ml 2% lidocaine	16G	Intercostal biopsy
Current study	169	parenchymal	1.68 (NRS)	LA 10 ml 1% lidocaine	18 G	Intercostal biopsy

LA = Local anesthesia, VAS = Visual analog scale, NRS = Numeric rating scale

does not exist [7], operators' manual skills and experience play a great role in reducing pain during and after the biopsy [4, 11, 20, 21]. Nonskilled hands could not finish the biopsy procedure in a single deep inspiration of the patient, and rebreathing of the patient during the biopsy may cause more trauma to the liver capsule and parenchyma, resulting in more pain. The reduction of the biopsy needle gauge and the number of biopsy and/or entries was reported to reduce complications and pain [9], on the other hand, the needle's size must be regulated to obtain enough sample size for histopathological analysis [22]. The use of Tru-cut needles as opposed to the Menghini-style aspiration needles was reported to be associated with higher pain intensity, but this finding was considered controversial [7]. In contradiction, neither number of the passes and the size of the needle, nor subcostal/intercostals biopsy were found to be different in Lindner *et al*.'s [16] study. To ensure that this conflict does not affect the results of the study, the cases with more than one puncture and also the cases with a different type or gauge of biopsy needles were excluded because of different size and different sampling methods.

Liver biopsies are found to be more painful in patients with Hepatitis C infection, younger age, or history of intravenous drug use [14]. However, Tan *et al*. [6] found no significant difference in terms of pain in Hepatitis B/C and biopsy pass numbers. Castera *et al*. [10], Eisenberg *et al*. [11], Riley [14], Lindner *et al*. [16], and Baig and Javed [17] showed that pain scores are related to patients' age. It has been detected less pain in patients older than 50 years of age as it was previously explained as an adaptation to stress and painful events [16]. While older patients have undergone liver biopsy more for focal liver lesions rather than a diffuse parenchymal disease, younger patients have undergone biopsy more for the parenchymal disease. Meanwhile, whether the young age or parenchymal disease or both play a part in the intensity of pain [6, 11, 13, 16] is a controversial point. Whereas, Baig and Javed [17] found men had more intense pain after a biopsy. However, our study, just like Pezeshki Rad *et al*. [12] found no gender or age predilection.

The assessment of pain poses a significant problem in clinical practice and clinical research because of the subjective nature of pain perception [23]. The measurement of pain severity with the visual analog scale (VAS), NRS, and verbal rating scale (VRS) are accepted as accurate and current, but VAS has lower rates of completion and success than NRS in older patients [24]. Similar difficulties were observed in patients having a high dose of opioids [25]. Moreover, both VAS and NRS showed better sensitivity than VRS, which has fewer categories for pain assessment [26].

The common conclusion reached in all studies is; the intensity of pain felt after the percutaneous liver biopsy may differ from mild to moderate. While it is felt most intensely right after the biopsy, the intensity of pain decreases in the following 2 to 4 hours [6, 12, 16].

Recently, Pezeshki Rad *et al*. [12] compared pain intensity in intercostal and subcostal biopsies in focal and diffuse parenchymal liver diseases, similar to our results, pain score was less in the subcostal group; 10% of the intercostals group, 3.33% of the subcostal group patients required intravenous analgesics. We did not administer intravenous analgesics but the need for oral or intramuscular analgesics was less in the subcostal group. Differently, to our study, pain intensity was similar just after the biopsy but significantly less in the 2nd and 4th hour. Tan *et al*. [6] used the VAS assessment score, compared the intercostal with the left subcostal method, and found no significant differences between the two groups; although they subjectively observed that the intercostals group seemed to have more pain and their post-procedural analgesic requirement was higher in the intercostal group (27% vs. 36.4%), it was not statistically significant (p = 0.64). In the study by Eisenberg *et al*. [11], 1 mg of intravenous midazolam and 50 mg of fentanyl was administered to all of their patients before biopsy unless they were contraindicated.

During parenchymal liver diseases, repeated biopsies may be needed. Severe pain and anxiety may be the cause of the loss of the patients after the first biopsy. From the patients' perspective, perception and compliance to liver biopsy are becoming a crucial issue for clinical management. The subcostal approach was found to be more suitable in US-guided liver biopsy.

Further randomized studies will be needed to evaluate the effectiveness of subcostal route versus intercostal regarding pain assessment. Despite advances in technology, there are potential gaps in our knowledge about pain perception in the liver biopsy.

Limitations

The subjective nature of pain and retrospective analysis which could have caused a possible selection bias is a limitation in our study. All the liver biopsies were done in a single-center and by the same interventional radiologist which is inferior to a multicenter randomized controlled trial.

CONCLUSION

In conclusion, we found a statistically significant difference in the pain score level and subsequent need for oral or intramuscular analgesics 0 and 2 h after percutaneous liver biopsy via the intercostal or subcostal approach. Our study suggests that a subcostal approach can be effective in reducing the pain score level and subsequent need for analgesics after a percutaneous needle biopsy.

Authors' Contribution

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

Conflict of interest

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

Financing

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

REFERENCES

1. Aribaş BK, Arda K, Çiledağ N, Aktaş E, Yakut F, Kavak S, et al. Accuracy and safety of percutaneous US-guided needle biopsies in specific focal liver lesions: comparison of large and small needles in 1300 patients. Panminerva Med 2012;54:233-9.
2. Howlett DC, Drinkwater KJ, Lawrence D, Barter S, Nicholson T. Findings of the UK national audit evaluating image-guided or image-assisted liver biopsy. Part I. Procedural aspects, diagnosticadequacy, and accuracy. Radiology 2012;265:819-31.
3. Papini E, Pacella CM, Rossi Z, Bizzarri G, Fabbrini R, Nardi F, et al. A randomized trial of ultrasound-guided anterior subcostal liver biopsy versus the conventional Menghini technique. J Hepatol 1991;13:291-7.
4. Piccinino F, Sagnelli E, Pasquale G, Giusti G. Complications following percutaneous liver biopsy. A multicentre retrospective study on 68,276 biopsies. J Hepatol 1986;2:165-73.
5. McGill DB, Rakela J, Zinsmeister AR, Ott BJ. A 21-year experience with major hemorrhage after percutaneous liver biopsy. Gastroenterology 1990;99:1396-400.
6. Tan KT, Rajan DK, Kachura JR, Hayeems E, Simons ME, Ho CS. Pain after percutaneous liver biopsy for diffuse hepatic disease: a randomized trial comparing subcostal and intercostal approaches. J Vasc Interv Radiol 2005;16:1215-9.
7. Janes CH, Lindor KD. Outcome of patients hospitalized for complications after outpatient liver biopsy. Ann Intern Med 1993;118:96-8.
8. Perrault J, McGill DB, Ott BJ, Taylor WF. Liver biopsy: complications in 1000 inpatients and outpatients. Gastroenterology 1978;74:103-6.
9. Cadranel JF, Rufat P, Degos F. Practices of liver biopsy in France: results of a prospective nationwide survey. For the Group of Epidemiology of the French Association for the Study of the Liver (AFEF). Hepatology 2000;32:477-81.
10. Castéra L, Nègre I, Samii K, Buffet C. Pain experienced during percutaneous liver biopsy. Hepatology 1999;30:1529-30.
11. Eisenberg E, Konopniki M, Veitsman E, Kramskay R, Gaitini D, Baruch Y. Prevalence and characteristics of pain induced by percutaneous liver biopsy. Anesth Analg 2003;96:1392-6.
12. Pezeshki Rad M, Abbasi B, Morovatdar N, Sadeghi M, Hashemi K. Pain in percutaneous liver core-needle biopsy: a randomized trial comparing the intercostal and subcostal approaches. Abdom Radiol 2019;44:286-91.
13. Mayoral W, Lewis JH. Percutaneous liver biopsy: what is the current approach? Results of a questionnaire survey. Dig Dis Sci 2001;46:118-27.
14. Riley TR 3rd. Predictors of pain medication use after percutaneous liver biopsy. Dig Dis Sci 2002;47:2151-3.
15. Spielberger, C. D. Anxiety as an emotional state. In: Spielberger C. D (editor). Anxiety: Current trends in theory and research Vol. 1, New York, NY, USA: Academic Press; 1972. pp. 3-19.
16. Lindner A, Frieser M, Heide R, Wildner D, Neurath MF, et al. Postinterventional pain and complications of sonographically guided interventions in the liver and pancreas. Ultraschall Med 2014;35:159-65.
17. Baig MA, Javed W. Pain associated with liver biopsies through percutaneous approach under sonographic guidance-a cross sectional pilot study in a tertiary care hospital. J Ayub Med Coll Abbottabad 2015;27:45-7.
18. Brouillette DE, Yoo YK, Chien MC, Rabinovitz M, Tarter RE, Van Thiel DH. Use of midazolam for percutaneous liver biopsy. Dig Dis Sci 1989;34:1553-8.
19. Alexander JA, Smith BJ. Midazolam sedation for percutaneous liver biopsy. Dig Dis Sci 1993;38:2209-11.
20. Menghini G. One-second needle biopsy of the liver. Gastroenterology 1958;35:190-9.
21. Froehlich F, Lamy O, Fried M, Gonvers JJ. Practice and complications of liver biopsy. Results of a nationwide survey in

Switzerland. Dig Dis Sci 1993;38:1480-4.
22. Scheuer PJ. Liver biopsy size matters in chronic hepatitis: bigger is better. Hepatology 2003;38:1356-8.
23. Jensen MP, Karoly P. Self-report scales and procedures for assessing pain in adults. In: Turk DC, Melzack R, eds., Handbook of Pain Assessment. New York, NY, USA: The Guilford Press; 2010: pp.19-44.
24. Lund I, Lundeberg T, Sandberg L, Budh CN, Kowalski J, Svensson E. Lack of interchangeability between visual analogue and verbal rating pain scales: a cross sectional description of pain etiology groups. BMC Med Res Methodol 2005;5:31.
25. Jensen MP, Turner JA, Romano JM. What is the maximum number of levels needed in pain intensity measurement? Pain 1994;58:387-92.
26. Cardella JF, Kundu S, Miller DL, Millward SF, Sacks D; Society of Interventional Radiology. Society of Interventional Radiology clinical practice guidelines. J Vasc Interv Radiol 2009;20(7 Suppl):S189-91.

The European Research Journal 2021;7(2):116-126 Original Article

DOI: 10.18621/eurj.774757 *Health Care Services*

The perception concerning the COVID-19 pandemic: case of Turkey

Haydar Hoşgör[1], Zeynep Aközlü[2], Derya Gündüz Hoşgör[3]

[1]Department of Medical Services and Techniques, Uşak University, Vocational School of Health Services, Uşak, Turkey
[2]Department of Medical Services and Techniques, Maltepe University, Vocational School, İstanbul, Turkey
[3]Department of Nursing Management, Doctorate Program Student, İstanbul University-Cerrahpaşa, Institute of Graduate Studies, İstanbul, Turkey

ABSTRACT

Objectives: This study aims to evaluate the level of knowledge and perception of the Turkish society about the COVID-19 pandemic.

Methods: This cross-sectional study whose sampling consists of 903 adults.

Results: About half (49.6%) of the participants' information sources about COVID-19 composed of printed and visual media tools such as television, radio, newspaper, etc. 57.5% of the participants stated that their self-knowledge levels about COVID-19 were at a good level, whereas 19.7% of them at a very good level. 64.4% of the participants stated that their health would be seriously damaged if they get this virus; 58.9% of them thinks that this virus will severely damage their place of the resident; 50.9% of them stated that they trust that this crisis will be handled effectively by the health authorities of Turkey. Participants rated themselves an average of 8.7 points on compliance with COVID-19 measures. It was found that the participants had a 55% confidence in the Coronavirus Scientific Advisory Board (Turkey) and the World Health Organization (WHO) regarding COVID-19.

Conclusions: Like all over the world, health authorities also in Turkey have taken several measures in the context of fighting against the pandemic and they expect society to comply with these measures. The fact that individuals in the society fulfill their individual responsibilities by confirming the accuracy of the information took place in printed/visual and social media from reliable sources is an important factor in reducing the effects of infectious diseases.

Keywords: COVID-19, coronavirus, pandemic, public health, perception

Novel coronavirus (COVID-19, SARS-CoV-2), which was first detected at the end of December 2019 in Wuhan, China, and spread across the world in a short time, was announced by the WHO as a public health emergency on 30 January 2020, and as a pandemic on 11 March 2020 [1]. Global public health campaigns have been launched to reduce the spread of the virus [2]. Health authorities and governments have begun to take serious measures to reduce the transmission of the disease [3]. Although it varies from country to country, domestic and international travel has been stopped, significant changes have come off in receiving education and manner of work, large events and worships were banned and houses of worships and shopping malls were shuttered.

Since it is a never-before-seen disease that is likely

Received: July 28, 2020; Accepted: August 27, 2020; Published Online: January 23, 2021

How to cite this article: Hoşgör H, Aközlü Z, Güzdüz Hoşgör D. The perception concerning the COVID-19 pandemic: case of Turkey. Eur Res J 2021;7(2):116-126. DOI: 10.18621/eurj.774757.

Address for correspondence: Zeynep Aközlü, MSc., Maltepe University, Vocational School, Department of Medical Services and Techniques, İstanbul, Turkey. E-mail: zeynepakozlu@maltepe.edu.tr, Tel: +90 216 6261050/2158, Fax: +90 216 6261070

e-ISSN: 2149-3189

to result in death, COVID-19 had the potential to lead to chaos and fear among the public [4]. On the other hand, slowing down of the transmission also required significant behavioral changes in individuals [2]. Because it was a known fact that the knowledge and attitudes obtained by individuals towards a disease greatly affect the degree of obedience to personal protective measures and, consequently, the course of the disease [4]. Therefore, as of the occurrence of COVID-19, health authorities and governments have started to take an active role in printed/visual and social media to inform people correctly and to report responsibilities to individuals in the fight against the pandemic. For example, the Ministry of Health of Turkey established the Coronavirus Scientific Advisory Board on January 10, 2020, even though there were no cases or deaths in Turkey in that period. Scientific Board members aimed to inform the public about the course of the disease and the ways of prevention, via TV channels and media transparently, and to survive the outbreak with less damage.

It is known that there is a relationship between the way people perceive disease and the reactions to the disease and adaptation to the disease [5]. Widespread and constant participation in health-protective behaviors proposed by health authorities during the pandemic is critical for the successful management of COVID-19. The evidence acquired from previous contagious disease outbreaks points to the role of perceived risk, anxiety, media interest and information on individuals' health-protective behavioral intentions [6]. Getting exact information from various sources such as public health professionals, government, and media may raise people's awareness of risk and may consequently enable them to adopt preventive measures [4]. Health risk perception of public plays an important role in the adoption of these actions, in the emotions and daily habits of people [3]. It is also known that when people realize that they are vulnerable to risk, they have a higher motivation to apply to preventive health behaviors [7].

This study examines what kind of perception COVID-19 creates in Turkish people and what kind of an attitude it causes. At the end of the study, the level of knowledge, risk perception, and trust levels of Turkish people about COVID-19 will be revealed and in addition, it will be determined from which information sources they learned COVID-19. It is possible to state that researching this subject, which is quite new as of now, in the sample of Turkey, will both contribute to the gap in the national and international literature and facilitate the comparison of the reactions of the societies about this pandemic. In this context, answers to the following questions were sought in this study:

i. How do the demographic characteristics of the participants distribute?

ii. What are the participants' COVID-19 sources of information?

iii. What is the level of knowledge of the participants about COVID-19?

iv. What are the measures taken by participants against COVID-19?

v. What are the participants' perceptions of COVID-19 risk?

vi. What are the levels of trust of the participants against individuals and institutions fighting against COVID-19?

METHODS

Design, Population & Sample Size and Setting

This study was designed in a cross-sectional design. The sampling of the study consists of adults aged over 18 years old, who agree to participate in the research, who live in Turkey and speak Turkish, who know how to use a mobile device or computer with internet access and who do not have any mental or physical disabilities. Bayesian sampling formula [8] was used to calculate the minimum sample size to participate in the research.

In the numerator of the formula, the value of (0.5 × 0.5 = 0.25), which has the highest (p.q) value, was taken as the basis. The population (N) of the research was taken as 83 million. In the denominator of the formula, the tolerance level (B) was taken as 5%. The fact that the studies conducted in the research are in a confidence interval is of great importance for the reliability of the research. The confidence interval generally accepted by the researchers is 95% (± 2.5). Accordingly, Z value was taken as 1.96. Thus, the minimum

$$n = \frac{N\,(p.q)}{\frac{(N-1).B^2}{Z^2}} + (p.q)$$

n:	Sample size
N:	Population
p:	Population rate or estimate
q:	1-p
B:	Tolerance level (acceptable margin of error)
Z:	Credible intervals

sample size of the study group was calculated as 384. The data of the study were collected between the dates of 01.05.2020-10.05.2020 by convenience sampling method and a total of 903 participants were reached.

Data Collection Tools

An electronic form was prepared by researchers through Google Forms as a data collection tool. This form was based on the survey form of McFadden *et al*. [9], whereas the survey was revised to make it more suitable for Turkish culture. The revised survey form includes a total of 7 chapters and 56 expressions as follows: demographic characteristics (10 expressions); the knowledge level of the society about COVID-19 (4 expressions); COVID-19 information sources (1 expression); the measures that can be taken against COVID-19 (20 statements); COVID-19 risk perception (11 expressions); the level of compliance with COVID-19 measures (1 statement); and trust (9 expressions).

Ethical Considerations

Ethics committee approval was obtained from the Social and Humanities Scientific Research and Publication Ethical Committee of the Uşak University (Decision no: E.15785) and Ministry of Health of Turkey, General Directorate of Health Services.

Statistical Analysis

The analysis of the data was carried out with SPSS. Within the scope of the study, basic descriptive statistics such as frequency, percentage, mean, standard deviation, minimum and maximum values were used.

Table 1. Descriptive characteristics of participants (n = 903)

	n	%		n	%
Gender			**Marital Status**		
Female	671	74.3	Married	348	38.5
Male	232	25.7	Single	555	61.5
Family Type			**Chronic Disease Status**		
Nuclear	800	88.6	Yes	159	17.6
Extended	103	11.4	No	744	82.4
Level of Education			**Place or Residence**		
≤ High School	213	24.0	Province	286	31.7
University	526	58.0	District	171	18.9
≥ University	164	18.0	Metropolitan	446	49.4
Economic Level			**Region of Residence**		
More than expense	218	24.1	West	728	80.6
Balanced	549	60.8	Central	152	16.8
Less than expense	136	15.1	East	23	2.5
Age			**Occupation**		
18-24	361	40.0	Student	347	38.4
25-34	206	22.8	Housewife	48	5.3
35-44	207	22.9	Retired	34	3.8
45 years and older	129	14.3	Civil servant	184	20.4
Min.	18		Private sector employee	165	18.3
Max.	67		Trades/self-employment	29	3.2
Mean.-SD.	31.2		Employer	19	2.1
SD.	± 11.4		Other	77	8.5

RESULTS

In terms of the socio-demographic characteristics of the participants, the following results were obtained: Of the participants, 74.3% (n = 671) were females; 61.5% (n = 555) was single; 58.0% (n = 526) were university graduates; 40.0% were aged between 18-24 years old (n = 361, mean = 31.2 ± 11.4 years); 60.8% (n = 549) had a balanced income-expense level; 88.6% (n = 800) had a nuclear family type; 82.4% (n = 744) had no chronic disease; 49.4% (n = 446) live in a metropolitan; 80.6% (n = 728) live in the western side of Turkey; and 38.4% (n = 347) were students (Table 1).

In terms of participants' sources of information about COVID-19; it was found that 49.6% (n = 448) of them get information via printed and visual media tools such as TV, radio, newspaper, etc.; while 30.7% (n = 277) of them use social media tools such as Facebook, Twitter, etc.; 19.4% (n = 175) of them use national and international official health authorities such as the WHO and the Ministry of Health; and 0.3% (n = 3) of them get information from their close circles like friends/neighbors/relatives. 57.5% (n = 519) of the participants evaluated their self-knowledge level about COVID-19 as good and 19.7% (n = 178) as very good. 98.9% (n = 893) of the participants correctly knew that COVID-19 was a respiratory disease caused by an infectious virus; while 98.2% (n = 887) of them correctly knew that the virus was transmitted by coughing or sneezing; and 68.4% (n = 581) of them correctly knew that there are no proven treatments or

Table 2. Participants' COVID-19 information sources and knowledge levels (n = 903)

	n	%
COVID-19 information sources		
Printed/visual media	448	49.6
Social media	277	30.7
State health authorities	175	19.4
Friend/neighbor/relatives	3	0.3
Knowledge level about COVID-19 (Self-assessment)		
Very weak	3	0.3
Weak	13	1.4
Medium	190	21.0
Good	519	57.5
Very good	178	19.7
Partial	5	0.6
Status of knowing the definition of COVID-19		
Correctly knows	893	98.9
Wrongly knows	6	0.7
Have no idea	4	0.4
Status of knowing the mechanism of transmission of COVID-19		
Correctly knows	887	98.2
Wrongly knows	12	1.3
Have no idea	4	0.4
Status of knowing the presence of vaccine and treatment for COVID-19		
Correctly knows	581	64.3
Wrongly knows	280	31.0
Have no idea	42	4.7

vaccines for COVID-19 at the moment (Table 2).

In terms of the measures taken by participants against COVID-19, the results were as follows respectively: to washhands (99.8%, (f = 901); to avoid close contact with patients with COVID-19 (99.3%, f = 897); to wear a mask (99.0%, f = 894); a balanced diet (98.9%, f = 893); to cover the cough or sneeze with a flexed elbow (98.8%, f = 892); to maintain the social distance (98.0%, f = 885); to use alcohol-based hand sanitizers (98.0%, f = 885); to ventilate home (97.9%, f = 884); to avoid touching eyes, nose, and mouth with unwashed hands (97.3%, f = 879); to stay home when sick (92.2%, f = 851); to use cologne (94.1%, f = 850); to be careful when opening a mail and cargo (93.7%, f = 846); to touch the frequently contacted places such as the door handle with elbows (90.2%, f = 815); to avoid using alcohol and smoking (90.1%, f = 814); to wear gloves (83.7%, f = 756); to do exercise regularly (81.1%, f = 732); to use herbal supplements (55.0%, f = 497); to wait for warmer weather (17.6%, f = 159); and to get the flu vaccine (11.6%, f = 105) (Fig. 1).

It was found that 36.9% (n = 333) of the participants ***"agree"*** with the expression of *"if I get COVID-19, my health will be seriously damaged"*; 63.7% (n = 576) of them ***"strongly agree"*** with the expression of *"I think COVID-19 is more serious than influenza in terms of risk"*; 30.2% (n = 273) of them were ***"undecided"*** about the expression of *"I wouldn't go to the hospital even if I got another disease due to the risk of getting COVID-19"*; 39.5% (n = 357) of them ***"agree"*** with the expression of *"COVID-19 will severely damage my place of resident"*; 38.9% of them (n = 352) ***"agree"*** with the expression of *"COVID-19 will spread widely in Turkey"*; 43.2% of them (n = 390) ***"disagree"*** with the expression of *"My risk of getting COVID-19 is higher than others"*; 51.5% of them (n = 465) ***"agree"*** with the expression of *"I believe I can protect myself better than others against the risk of COVID-19"*; 42.4% of them (n = 382) ***"agree"*** with the expression of *"I am very worried about the possible risks of this virus to my family and loved ones"*; 50.8% of them (n = 459) ***"strongly disagree"*** with the expression of *"I think the government is exaggerating this virus risk"*; 33.8% of them (n =

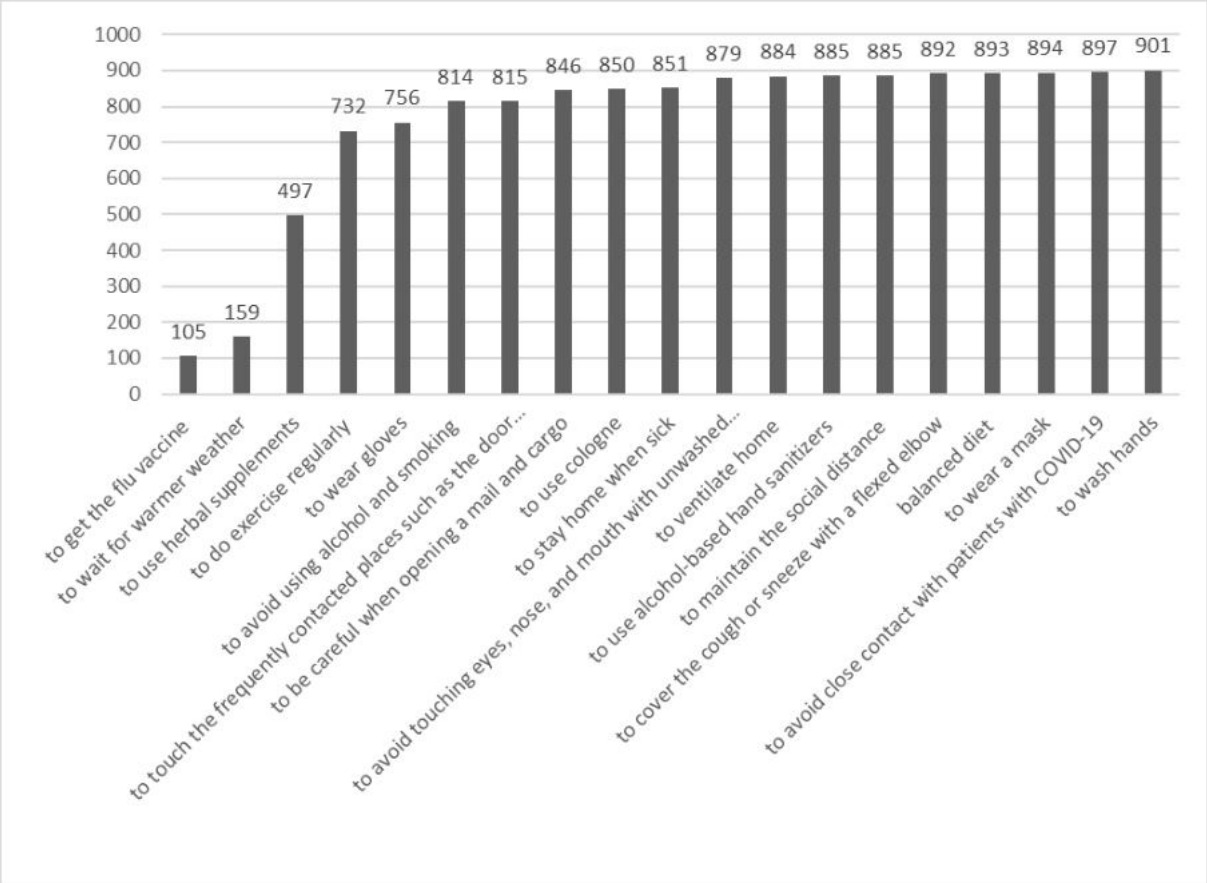


Fig. 1. Precautions against COVID-19.

305) ***"agree"*** with the expression of *"I trust that this crisis will be handled effectively by the health authorities of Turkey"*; and 65.3% of them (n = 90) ***"strongly agree"*** with the expression of *"Against this pandemic risk, quarantine should be imposed on people coming into Turkey from abroad, especially from China"* (Table 3).

In terms of the assessment to comply with COVID-19 measures, it was seen that 41.3% (n = 373) of the participants gave themselves 10 points, while 24.7% of them gave 9 points (n = 223), 19.3% of them gave 8 points (n = 174), and 7.2% of them gave 7 points (n = 65). It was determined that the mean score of all participants was 8.7 ± 1.7 (Table 4).

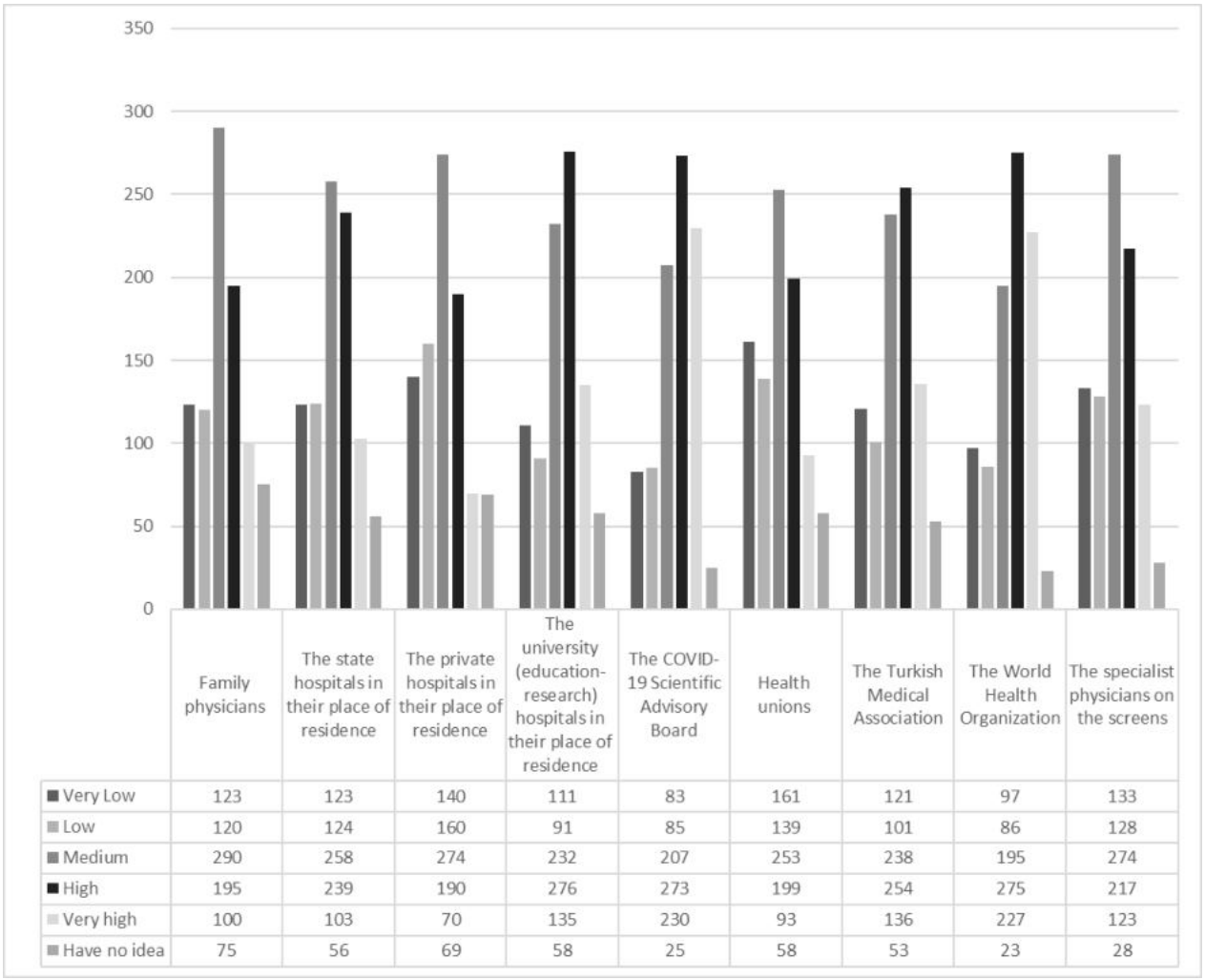
Table 3. Participants' risk perceptions concerning the COVID-19 pandemic (n = 903)

Risk perception statements	Strongly Disagree		Disagree		Undecided		Agree		Strongly Agree		I do not know	
	n	%	n	%	n	%	n	%	n	%	n	%
If I get COVID-19, my health will be seriously damaged	27	2.9	101	11.2	139	15.4	**333**	**36.9**	248	27.5	55	6.1
I think COVID-19 is more serious than influenza in terms of risk	35	3.9	18	2.0	19	2.1	251	27.8	**576**	**63.7**	4	0.4
I wouldn't go to the hospital even if I got another disease due to the risk of getting COVID-19	99	10.9	171	18.9	**273**	**30.2**	220	24.3	110	12.1	30	3.3
COVID-19 will severely damage my place of resident	17	1.9	88	9.7	199	22.1	**357**	**39.5**	176	19.4	66	7.3
COVID-19will spread widely in Turkey	13	1.5	73	8.1	167	18.5	**352**	**38.9**	253	28.0	45	4.9
My risk of getting COVID-19 is higher than others	114	12.6	**390**	**43.2**	159	17.6	98	10.8	65	7.2	77	8.5
I believe I can protect myself better than others against the risk of COVID-19	14	1.6	35	3.9	182	20.1	**465**	**51.5**	155	17.1	52	5.7
I am very worried about the possible risks of this virus to my family and loved ones	52	5.7	161	17.8	119	13.2	**382**	**42.4**	182	20.1	7	0.7
I think the government is exaggerating this virus risk	**459**	**50.8**	349	38.6	52	5.7	19	2.1	13	1.5	11	1.2
I trust that this crisis will be handled effectively by the health authorities in Turkey	89	9.8	117	13.0	219	24.2	**305**	**33.8**	155	17.1	18	2.0
Against this pandemic risk, quarantine should be imposed on people coming into Turkey from abroad, especially from China.	53	5.8	42	4.7	15	1.7	156	17.2	**590**	**65.3**	47	5.2

Table 4. Level of compliance (between 1-10) of the participants to COVID-19 measures (n = 903)

I never follow the measures									I strictly follow the measures
									10 pts
								9 pts	
							8 pts		
						7 pts			
					6 pts				
				5 pts					
			4 pts						
		3 pts							
	2 pts								
1 point									
n = 10	n = 3	n = 8	n = 7	n = 24	n = 16	n = 65	n = 174	n = 223	n = 373
1.1%	0.3%	0.9%	0.8%	2.7%	1.8%	7.2%	19.3%	24.7%	41.3%

Mean: 8.7 ± 1.7



	Family physicians	The state hospitals in their place of residence	The private hospitals in their place of residence	The university (education-research) hospitals in their place of residence	The COVID-19 Scientific Advisory Board	Health unions	The Turkish Medical Association	The World Health Organization	The specialist physicians on the screens
Very Low	123	123	140	111	83	161	121	97	133
Low	120	124	160	91	85	139	101	86	128
Medium	290	258	274	232	207	253	238	195	274
High	195	239	190	276	273	199	254	275	217
Very high	100	103	70	135	230	93	136	227	123
Have no idea	75	56	69	58	25	58	53	23	28

Fig. 2. Trust in people and institutions making a statement about COVID-19.

When the participants' level of trust in the people and institutions making a statement about COVID-19 is analyzed, the participants were found to trust in the health unions (32%, n = 253); in the state hospitals in their place of residence (28.6%, n = 258); in the private hospitals in their place of residence (30.3%, n = 274); and in family physicians (32.1%, n = 290) at a ***"medium-level"***; while 24% of them (n = 217) trust in the specialist physicians on the screens, 28.1% of them (n = 254) in the Turkish Medical Association (n = 254), 30.2% of them in the Coronavirus Scientific Advisory Board of the Ministry of Health of Turkey (n = 273), 30.4% of them in the WHO (n = 275), and 30.5% of them in the university (education-research) hospitals in their place of residence (n = 276) at a ***"high level"*** (Fig. 2).

DISCUSSION

In global crisis situations such as outbreaks, individuals desire to access fast and reliable information to be aware of the state of the world and of the country in which they live. The communication sources preferred by individuals to access information may be influenced by factors such as age, education level, and ability to use communication tools. The literature shows that the media can significantly affect public perception of risk issues. It was also stated that those who did not have any previous health hazard experience or knowledge are more likely to rely on media tools to learn about hazards [10]. Considering the mean age and education levels of the individuals participating in our study, it was an expected situation that printed/visual media and social media were used as a source of access to information. In a study carried out in India, similar to our research, it was found that individuals' sources of access to information in the COVID-19 process were printed/visual (44.19%) and social media (34.88%) [11]. In another study conducted in 2015 in Saudi Arabia to examine the MERS-CoV perceptions of 281 healthcare professionals, it was reported that the most important first source of information was the internet and social media, and the second was TV [12].

The result concerning the fact about 20% of the individuals participating in our study prefer national or international public health institutions such as the WHO and the Ministry of Health of Turkey as sources of information can be explained by the fact that the information received from these public health institutions are being broadcasted/shared quickly through printed/visual media tools such as TV, newspaper and social media platforms such as Twitter, and Facebook. In recent years, social media has become an increasingly important source of information for risk and crisis communication. Kırık and Özkoçak [13] state that the posts of social media users across the world exceeded 275 million in the period of 21 January-11 March 2020. In addition, the authors underline that the top 10 countries with the most social media posts about COVID-19 are Japan, the United States, South Korea, Britain, France, Brazil, People's Republic of China, Malaysia, Taiwan, and Italy, respectively; and they emphasize the importance of the Turkey taking the eleventh place with more than 6.5 million social media posts. In this context, although social media panic is known to be faster than COVID-19 spread [14], it is possible to address the fact that social media is an important source of information that is frequently used in terms of risk and crisis communication especially in terms of access to information.

It is believed that the fact that almost all of the individuals participating in our study correctly defined the definition of COVID-19 and the route of transmission was associated with the high access to information sources. However, although there is no specific antiviral treatment [15] or vaccine [16] with proven reliability and effectiveness for COVID-19 today, it was observed that the level of knowledge of the participants was not at the desired extent. Yet compared to the literature, the level of knowledge of our participants was higher [11]. On the other hand, in their study conducted with the participation of 240 medical faculty students in Iran, Taghrir *et al*. [17] revealed that about 87% of the participants answered the questions about COVID-19 correctly. Similarly, in another study on healthcare personnel, Elamin *et al*. [12] found this ratio as 87%. Of course, it can be mentioned that the educational levels of the participants and the field they were educated had an effect on attaining these results.

It can be said that this situation about medicines and vaccines is related to news in social media that has not been scientifically proven [18], like "some antimalarial drugs and pneumonia vaccine prevent

COVID-19". In this regard, it is possible to say that the evidence-based information provided by the media and other official sources and how this information was conveyed will play an important role in emergencies such as outbreaks. Hou *et al*. [19] found that the public responded quickly to government-related announcements about COVID-19 and adopted the recommended behavior according to the directives / guidelines provided. On the other hand, it was found that during the pandemic, informal authorities had put forward misinformation and rumors about some cures and treatments, but as a result of the timely clarification of all these myths by the competent authorities, there was a tendency to decrease in irrational behavior.

In a study conducted in Hong Kong, it was revealed that the most effective method of preventing the COVID-19 outbreak was to increase personal hygiene practices [20]. In our study, we found that the Turkish people have a high level of compliance with the measures proposed by authorities such as Center for Disease Control and Prevention (CDC), WHO, and the Ministry of Health of Turkey to protect against COVID-19, such as washing hands; avoiding contact with a patient with COVID-19; using masks in crowded areas; covering the cough/sneeze with the flexed elbows; maintaining the social distance; using alcohol-based hand sanitizers; and avoiding touching eyes, nose, and mouth with unwashed hands. Besides, they were found to act health-protective and improving behaviors such as balanced nutrition, frequent ventilation of the house, avoiding alcohol-smoking, and regular exercise. This result, on the other hand, is thought to be associated with the high level of printed/visual media and social media usage of the participants in our study and the information advertisements prepared by the Ministry of Health of Turkey. Aker and Mıdık [21], in parallel with our results, reported that 87% of the participants considered hand washing as the most effective measure to be taken against the virus.

In a study carried out in Germany, it was found that the hand washing rate of individuals was lower compared to our study [22]. In a study conducted in Turkey, on the other hand, it was determined that individuals had a high sensitivity to the pandemic and were not unconcerned with the pandemic, that they attach importance to the information provided by media channels and to the implementation of the decisions taken, and that they take measures such as hand hygiene seriously. Again in the same study, the rate of those who think that COVID-19 will lose its effect with the coming of summer months was 42.9% [23]. In another study, this rate was found to be 20.9% [11]. Warmer summertime air has not yet been proven to be effective in reducing the spread of COVID-19 [18]. The fact that the majority of the participants in our study did not believe in this myth can be interpreted as a positive result.

When the risk perceptions gainst COVID-19 are analyzed, it was seen that 64.4% of our participants think that if they get COVID-19, their health will be seriously damaged. In a study conducted in Italy, this rate was 57.0% [24]. The reason for this difference can be explained by the fact that the data collection dates of this study were about 50 days before the data collection dates of our study. The total number of cases and deaths in Turkey on the dates of our study was 122392 and 3268 respectively [25], while the total number of cases and deaths in Italy was 10149 and 631 [26] respectively during the dates of the study of Simione and Gnagnarella [24]. In the studies carried out by Taghrir *et al*. [17] in Iran and by McFadden *et al*. [9] in the United States, it was reported that the mean risk perception score of the participants was calculated at a moderate level of 51% and 50%, respectively. Also, in our study, it was observed that 62.5% of the participants had concerns for their families and their loved ones about getting the disease. These results were not similar to the study of Simione and Gnagnarella [24]. In addition, 91.5% of our participants thought that COVID-19 was more serious than influenza. Considering the effects of perceptions concerning the disease on the behavior change of individuals towards disease prevention, it is possible to interpret this result positively, too.

Another point that should be examined within the scope of the study is how much score the participants attributed to them about complying with COVID-19 measures. In this context, it was calculated that the mean score given by all participants in complying with COVID-19 measures was 8.7 ± 1.7. In other words, the level of compliance of the participants with the relevant measures reflects a high level of 87%. In parallel with our findings, Taghrir *et al*. [17] found this rate as 95%.

The fact that individuals in the community trust in

health authorities and the government in the fight against the pandemic and they follow these suggestions is important for the course of the pandemic. To carry out the pandemic process effectively in Turkey, a scientific advisory board with a total of 38 specialists in their fields such as microbiology, virology, infectious diseases, internal diseases, intensive care, chest diseases, public health, and pediatrics was established within the Ministry of Health of Turkey on January 10, 2020. This board is effective both in fighting against the pandemic and in informing the society with the most accurate and up-to-date information in printed/visual and social media. Based on the results obtained from our study, the rate of trust in the Coronavirus Scientific Advisory Board of the Ministry of Health of Turkey and the WHO was quite similar (~%55.0). McFadden *et al*. [9] reported that the institution they trusted in the first place was the Director of CDC and the second was the Director of the National Institutes of Health. In addition, half of our participants think that this crisis will be handled effectively by the health authorities in Turkey, while the vast majority of them (89.4%) think that the government is "not exaggerating" this virus risk. In a study conducted in Germany, on the other hand, the trust rate for health authorities was 71.0%, while the trust rate for government/politicians was 54.5% [22].

In our study, we found that the trust rate for private hospitals was quite low compared to state hospitals and university (education-research) hospitals. The reason for this is thought to be related to the fact that hospitals that have at least two specialist physicians in infectious diseases and clinical microbiology, chest diseases, internal diseases, and that hospitals with adult intensive care beds on level three were declared as Pandemic Hospital by the Scientific Advisory Board, moreover to the fact that state hospitals and university (education-research) hospitals have been converted to Pandemic Hospital in general. On the other hand, it can be stated that the fact that private hospitals are rather considered as health enterprises in the eyes of society has the potential to affect this situation.

CONCLUSION

The COVID-19 pandemic still continues with its globally unknown effects. Like all over the world, health authorities also in Turkey have taken several measures in the context of fighting against the pandemic and they expect society to comply with these measures. Risk perception is an important component of creating behavior change. To increase the risk perception of society in a way that will not cause concern and to encourage individuals to engage in health-protecting behaviors are the primary duties of governments and health authorities. Factors such as sharing up-to-date and accurate information with the society in all kinds of media tools in such crises and increasing the level of trust/compliance of individuals to health authorities will have an impact on minimizing irreversible conditions. The fact that individuals in the society fulfill their individual responsibilities by confirming the accuracy of the information took place in printed/visual and social media from reliable sources is an important factor in reducing the effects of infectious diseases.

Authors' Contribution

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

Conflict of interest

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

Financing

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

REFERENCES

1. World Health Organization. COVID-19 situation reports. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/. Accessed May 18, 2020.
2. Van Bavel JJ, Baicker K, Boggio PS, Capraro V, Cichocka A, Cikara M, et al. Using social and behavioural science to support COVID-19 pandemic response. Nat Hum Behav 2020;4:460-71.
3. Motta Zanin G, Gentile E, Parisi A, Spasiano D. A preliminary

evaluation of the public risk perception related to the COVID-19 health emergency in Italy. Int J Environ Res Public Health 2020;17:3024.
4. Roy D, Tripathy S, Kar SK, Sharma N, Verma SK, Kaushal V. Study of knowledge, attitude, anxiety & perceived mental healthcare need in Indian population during COVID-19 pandemic. Asian J Psychiatr 2020;51:102083.
5. Hekler EB, Lambert J, Leventhal E, Leventhal H, Jahn E, Contrada RJ. Commonsense illness beliefs, adherence behaviors, and hypertension control among African Americans. J Behav Med 2008;31:391-400.
6. Faasse K, Newby JM. Public perceptions of COVID-19 in Australia: perceived risk, knowledge, health-protective behaviours, and vaccine intentions. medRxiv 2020:20079996.
7. Oh S-H, Lee SY, Han C. The effects of social media use on preventive behaviors during infectious disease outbreaks: the mediating role of self-relevant emotions and public risk perception. Health Commun 2020 Feb 16;1-10.
8. Özdinç Ö. [The sentiments of Çukurova University students on sports and the sports participation – socialization relationship]. SPORMETRE Beden Eğitimi ve Spor Bilim Derg 2005;3:77-84. [Article in Turkish]
9. McFadden SAM, Malik AA, Aguolu OG, Willebrand KS, Omer SB. Perceptions of the adult US population regarding the novel coronavirus outbreak. PLoS One 2020;15:e0231808.
10. Oh S-H, Paek H-J, Hove T. Cognitive and emotional dimensions of perceived risk characteristics, genre-specific media effects, and risk perceptions: the case of H1N1 influenza in South Korea. Asian J Commun 2015;25:14-32.
11. Vadivu S, Annamuthu P. An awareness and perception of COVID-19 among general public-a cross sectional analysis. Int J Mod Trends Sci Technol 2020;6:49-53.
12. Elamin F, Nour MO, Babilghith AO, Natto HA, Al-Amin FO, Alawneh SM. Knowledge, attitude and practices of healthcare providers towards MERS-CoV infection at Makkah hospitals, KSA. Int Res J Med Med Sc 2020;3:103-12.
13. Kırık AM, Özkoçak V. [Social media and new coronavirus (Covid-19) pandemia in the context of the new world order]. J Soc Sci 2020;7:133-54. [Article in Turkish]
14. Depoux A, Martin S, Karafillakis E, Preet R, Wilder-Smith A, Larson H. The pandemic of social media panic travels faster than the COVID-19 outbreak. J Travel Med 2020:3;27:taaa031.
15. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. Int J Antimicrob Agents 2020,55:105924.
16. Sahin AR, Erdogan A, Agaoglu PM, Dineri Y, Cakirci AY, Senel ME, et al. 2019 novel coronavirus (COVID-19) outbreak: a review of the current literature. Eurasian J Med Oncol 2020;4:1-7.
17. Taghrir MH, Borazjani R, Shiraly R. Covid-19 and Iranian medical students; A survey on their related-knowledge, preventive behaviors and risk perception. Arch Iran Med 2020;23:249-54.
18. World Health Organization. Myth busters. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public/myth-busters?gclid=EAIaIQobChMIxOuG8vO96QIVE8ayCh15RgK_EAAYASACEgKzofD_BwE. Accessed May 18, 2020.
19. Hou Z, Du F, Jiang H, Zhou X, Lin L. Assessment of public attention, risk perception, emotional and behavioural responses to the COVID-19 outbreak: social media surveillance in China. Hyg Trop Med 2020:20035956.
20. Kwok KO, Li KK, Chan HHH, Yi YY, Tang A, Wei WI, et al. Community responses during early phase of Covid-19 epidemic, Hong Kong. Emerg Infect Dis 2020;26:1575-9.
21. Aker S, Mıdık Ö. The views of medical faculty students in Turkey concerning the COVID-19 pandemic. J Community Health 2020;45:684-8.
22. Gerhold L. Covid-19: risk perception and coping strategies. PsyArXiv Prepr 2020;1-11.
23. Bostan S, Erdem R, Öztürk YE, Kılıç T, Yılmaz A. The effect of Covid-19 pandemic on the Turkish society. Electron J Gen Med 2020;17:em237.
24.Simione L, Gnagnarella C. Differences between health workers and general population in risk perception, behaviors, and psychological distress related to COVID-19 spread in Italy. PsyArXiv Prepr 2020.
25. Worldometer. Turkey Coronavirus. Available at: https://www.worldometers.info/coronavirus/country/turkey/. Accessed May 18, 2020.
26. Worldometer. Italy Coronavirus. Available at: https://www.worldometers.info/coronavirus/country/italy/. Accessed May 18, 2020.

The European Research Journal 2021;7(2):127-135 Original Article

DOI: 10.18621/eurj.698967 *Nephrology*

Effect of the tunneled-cuffed central venous catheters on oxidative stress indices and inflammation in chronic hemodialysis patients

Berfu Korucu[1], Hacı Hasan Yeter[1], Elif Burcu Bali[2], Mehmet Kürşat Derici[3]

[1]*Department of Nephrology, Gazi University School of Medicine, Ankara, Turkey*
[2]*Department of Medical Services and Techniques, Gazi University Vocational School of Health Services, Ankara, Turkey*
[3]*Department of Pharmacology, Kırıkkale University School of Medicine, Kırıkkale, Turkey*

ABSTRACT

Objectives: The use of central venous catheters as hemodialysis (HD) vascular access is associated with worse morbidity and mortality in HD patients. This occasion is often attributed to comorbidities of the patients with central venous catheters. Studies reveal that a biofilm layer occurs on most of the tunneled-cuffed central venous catheters (TC-CVCs). This study aimed to determine the oxidative stress (OS) and systemic inflammation (SI) status in patients with TC-CVCs as HD vascular access without clinical signs and symptoms of infection.

Methods: The study is composed of eighty-five patients with a minimum HD vintage of one year. Patients with a history of infection or a cardiovascular event within six months, malignancy, systemic inflammatory diseases, or malnutrition were excluded. OS indices and SI markers were studied and compared in patients with arteriovenous fistula (AVF) and TC-CVCs.

Results: Mean native thiol/total thiol (NT/TT) ratio was significantly higher and mean disulphide/total thiol (DT/TT) ratio was significantly lower in AVF group comparing TC-CVC group (0.46 ± 0.17 and 0.36 ± 0.17, $p = 0.03$ for NT/TT; 0.27 ± 0.08 and 0.31 ± 0.08, $p = 0.04$ for DS/TT; respectively). Mean OS index was significantly lower in the AVF group comparing TC-CVC group (0.15 ± 0.14 and 0.24 ± 0.23, $p = 0.04$; respectively]. Median hs-CRP levels and median IL-6 levels were significantly lower in AVF group comparing TC-CVC group (5.8 [min: 3.0-max: 82.5] mg/L and 9.7 [min: 3.0-max: 45.4] mg/L, $p = 0.004$ for hs-CRP; 6.2 [min: 2.0-max:159.0] pg/mL and 12.2 [min: 2.6-max: 41.3) pg/mL, $p = 0.01$ for IL-6; respectively).

Conclusions: TC-CVCs inversely affect OS and systemic inflammatory status in HD patients, presumably due to foreign body reactions and biofilm layers.

Keywords: Arteriovenous fistula, central venous catheters, hemodialysis vascular access, oxidative stress, systemic inflammation

Hemodialysis (HD) is the most frequent renal replacement therapy (RRT) modality. HD requires a proper functioning vascular access (VA) such as arteriovenous fistula (AVF), arteriovenous graft (AVG), or central venous catheter (CVC). The use of CVCs is associated with worse morbidity and mortality in HD patients, which is usually attributed to patients' comorbidities, and these results are thought to be related to

Received: *March 5, 2020;* ***Accepted:*** *June 3, 2020;* ***Published Online:*** *January 31, 2021*

How to cite this article: *Korucu B, Yeter HH, Bali EB, Derici MK. Effect of the tunneled-cuffed central venous catheters on oxidative stress indices and inflammation in chronic hemodialysis patients. Eur Res J 2021;7(2):127-135. DOI: 10.18621/eurj.698967*

Address for correspondence: *Berfu Korucu, MD., Gazi University School of Medicine, Department of Nephrology, Bahçelievler, Ankara, Turkey. E-mail: berfukorucu@gmail.com, Mobile phone: +90 531 5262449*

e-ISSN: 2149-3189

selection bias [1-4].

CVCs are widely produced from polyurethane, which is shown to induce mild foreign body reactions, although it is one of the most biocompatible substances [5]. CVCs interact with proteins and cells in the circulatory system and form an adherent biological material. When microorganisms settle on this material, it is called a biofilm layer [6]. Studies using quite sensitive techniques, including electron microscopy have reported the incidence of the biofilm layers at rates ranging from 36% to 100% in removed catheters of HD patients [7-9]. Thus, there is an increasing number of attempts to make polyurethane catheters more compatible and lead to less bacterial colonization [10].

Cardiovascular diseases (CVDs) are the most frequent cause of mortality in patients under RRT [11]. The two of the most critical factors for CVDs are oxidative stress (OS), and systemic inflammation (SI). The HD procedure and kidney disease itself are triggers of OS and SI [12, 13]. On the other hand, in HD patients, smoking, serum uric acid levels, fluid overload, dialyzer type, dialysate purity, anemia, intravenous iron, and diabetes have also been associated with OS and SI [14]. However, this foreign substance in the vessel may be contributing to morbidity and mortality via triggering OS and SI as a potential biofilm carrier without any signs of infection.

This study aimed to determine the OS and SI status in patients with tunneled-cuffed CVCs (TC-CVCs) as HD VA without clinical signs and symptoms of infection comparing patients with AVF.

METHODS

Participants and Study Design

The study is composed of eighty-five patients with a minimum HD vintage of one-year. Informed consent was obtained from all patients. Patients with a history of infection or a cardiovascular event within six months were excluded. Patients with a history of malignancy, systemic inflammatory diseases, and malnutrition also excluded. Patients with AVGs, tunneled femoral or temporary catheters, patients treated with high-flux dialyzers or anticoagulated with citrate or low molecular weight heparin, and patients with catheters locked with antibiotics were also excluded for standardization (Fig. 1). Patients undergoing hemodialysis with TC-CVC were those with unfunctional AVF/AVG (68.2 %) and those who choose catheter use because of renal transplantation plan from a living donor in the near future (31.8 %).

All of the patients were under a standard HD procedure via AVF or polyurethane TC-CVC, thriceweekly (12 hours/week), using bicarbonate-containing dialysate and low-flux polysulfone membrane. All patients were anticoagulated with heparin. The blood flow rate ranged from 300 to 350 mL/min, and the dialysate flow rate was 500 mL/min. All tunneled-cuffed CVCs locked with heparinized saline after HD.

The average of ultrafiltration rate within the last month, cumulative intravenous iron and erythropoiesis-stimulating agent (ESA) doses applied within the last six months were calculated. Doses of darbepoetin were converted to equivalent doses of epoetin for standardization [15]. Patients with >100 ml/day urine output were considered to have a residual renal function (RRF) [16].

Blood Specimen Collection

Blood specimens were collected at the initiation of a mid-week session. Specimens were allowed to clot at room temperature for 30 minutes. Clot removed by centrifuging samples at 3500 rpm for 10 minutes. The serum immediately transferred into a polypropylene tube and stored at -80oC.

Materials and Measurements

The thiol measurements, OS indices, and inflammatory parameters were measured from freshly collected serum. Laboratory parameters (within three months for intact parathormone and two weeks for others) and demographic features were recorded from patients' files.

Single pool Kt/V calculated by Daugirdas' second-generation formula. Urea reduction ratio (URR) calculated by taking the difference between pre- and post-dialysis urea levels and divided by predialysis urea levels.

Biochemical study

Thiol/disulfide homeostasis measured using a novel automatic spectrophotometric method (Rel Assay Diagnostics, Turkey) [17]. Total oxidant status (TOS) and total antioxidant status (TAS) levels were measured using commercially available kits (Rel

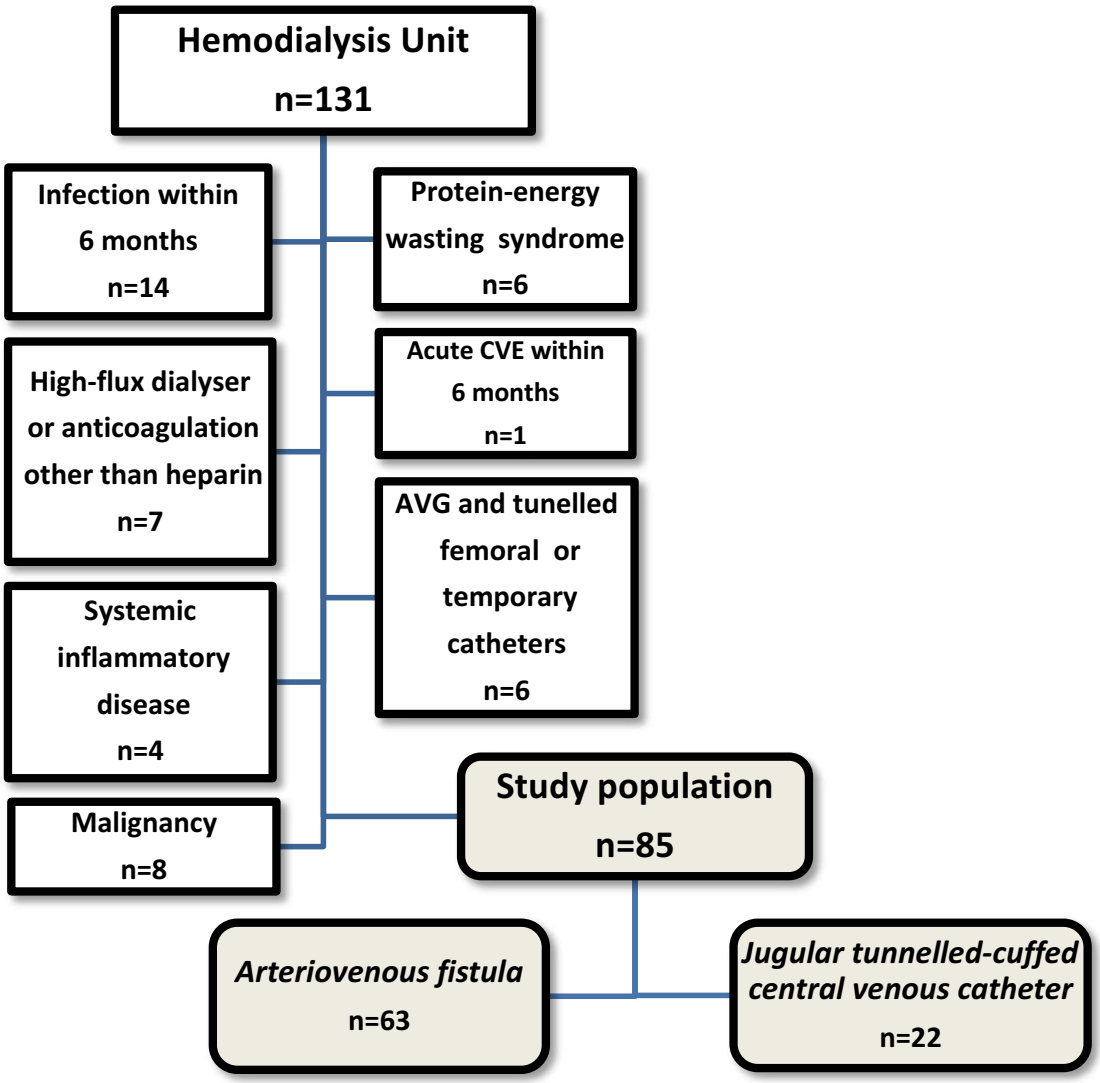


Fig. 1. Study design, study population, and groups. CVE = Cardiovascular event, AVG = Arteriovenous graft.

Assay Diagnostics, Turkey) [18]. The ratio of TOS to TAS accepted as the OS index (OSI). For calculation, the unit of TAS converted to μmol/L, and the OSI calculated according to the following formula: OSI (arbitrary unit) = TOS (μmol H2O2 equivalent/L) / TAS (μmol Trolox equivalent/L). For regression analysis, cases with a TOS > 5 μmol H2O2 equivalent/L were grouped as elevated score according to the manufacturer's recommendation.

Serum hs-CRP levels determined by a nephelometric technique using BNII/BN Pro-Spec (Siemens, Marburg, Germany); serum IL-6 levels determined by chemiluminescence immunoassay technique using Immulite 2000 (Siemens Diagnostics, Gwynedd, UK).

Ethical statements

The institute's committee (Kırıkkale University Clinical Research Ethics Committee) has approved the study protocol on human research (Decision No: 14/03, dated 27.6.2019).

Statistical Analysis

Data were expressed as mean ± standard deviation or medians with ranges. For data normally distributed; Student's t-test is used for comparison between two groups. Inflammatory markers were non-normal distributed, and the Kruskal-Wallis test performed. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Science (SPSS, Chicago, IL, USA) for personal computers, version 21.0.

RESULTS

Baseline characteristics

Demographic features, frequencies of comorbid diseases, frequency of smokers, laboratory parameters, HD adequacy indices, mean ultrafiltration rates, and cumulative doses of iron and ESAs were similar between groups. The frequency of patients with the RRF was higher in the TC-CVC group (Table 1).

Oxidative stress measurements

Mean TT and DS levels were significantly lower in the AVF group comparing the TC-CVC group (Fig. 2). The mean NT/TT ratio was significantly higher, and the mean DS/TT ratio was significantly lower in the AVF group comparing the TC-CVC group (Table 2, Fig. 3).

Mean TOS levels were significantly lower in the AVF group comparing the TC-CVC group. Mean TAS levels were similar between groups. Mean OSI was significantly lower in the AVF group comparing TC-CVC group (Table 2, Figs. 3 and 4).

Table 1. Baseline characteristics and health parameters

	AVF (n = 63)	TC-CVC (n = 22)	*p* value
Female/male	22/41	12/10	0.07
Age (years)	55.2 ± 17.0	63.9 ± 18.7	0.28
BMI (kg/m^2)	24.9 ± 5.5	24.9 ± 4.8	0.97
DM, n (%)	13 (20.6)	3 (13.6)	0.50
CAD, n (%)	17 (26.9)	7 (31.8)	0.61
PAD/CVD, n (%)	8 (12.6)	3 (13.6)	0.87
Smoking, n (%)	10 (15.8)	4 (18.1)	0.56
Urea nitrogen (mg/dL)	62.8 ± 14.8	61.6 ± 15.8	0.59
Creatinine (mg/dL)	8.4 ± 1.9	7.1 ± 2.5	0.15
Sodium (mEq/L)	139.5 ± 2.3	138.8 ± 2.0	0.42
Potassium (mEq/L)	4.9 ± 0.7	4.7 ± 0.6	0.39
Uric acid (mg/dL)	5.3 ± 0.9	5.2 ± 1.0	0.80
Hemoglobin (g/dL)	11.2 ± 1.5	10.5 ± 1.6	0.09
Albumin (g/dL)	3.8 ± 0.3	3.6 ± 0.4	0.13
Calcium (mg/dL)	8.8 ± 0.8	8.7 ± 0.7	0.85
Phosphorus (mg/dL)	4.9 ± 1.2	4.7 ± 1.3	0.49
iPTH (pg/mL)	452.7 ± 422.9	349.3 ± 336.8	0.31
Kt/V	1.6 ± 0.2	1.6 ± 0.3	0.85
URR (%)	73.7 ± 6.8	74.2 ± 8.0	0.80
HD vintage (months)	76.0 ± 67.1	71.1 ± 47.8	0.61
Mean UF (mL)	2400 (500-3500)	2300 (1700-3000)	0.08
RRF n (%)	17 (26.9)	9 (40.9)	0.05
Cum. IV Iron (mg)	749.2 ± 434.7	713.6 ± 425.7	0.71
Cum. ESA (IU)	60000 (0-180800)	64000 (0-176000)	0.82

Data are shown as mean±standard deviation or n (%) or median (minimum-maximum). AVF = Arteriovenous fistula, TC-CVC = Tunneled cuffed central venous catheter, BMI = Body mass index, DM = Diabetes mellitus, CAD = Coronary artery disease, PAD/CVD = Peripheral artery disease/cerebrovascular disease, iPTH = intact Parathormone, URR = Urea reduction ratio, HD = Hemodialysis, UF = Ultrafiltration, RRF = Residual renal function, Cum. IV Iron = Cumulative intravenous iron, Cum. ESA = Cumulative erythropoiesis-stimulating agents

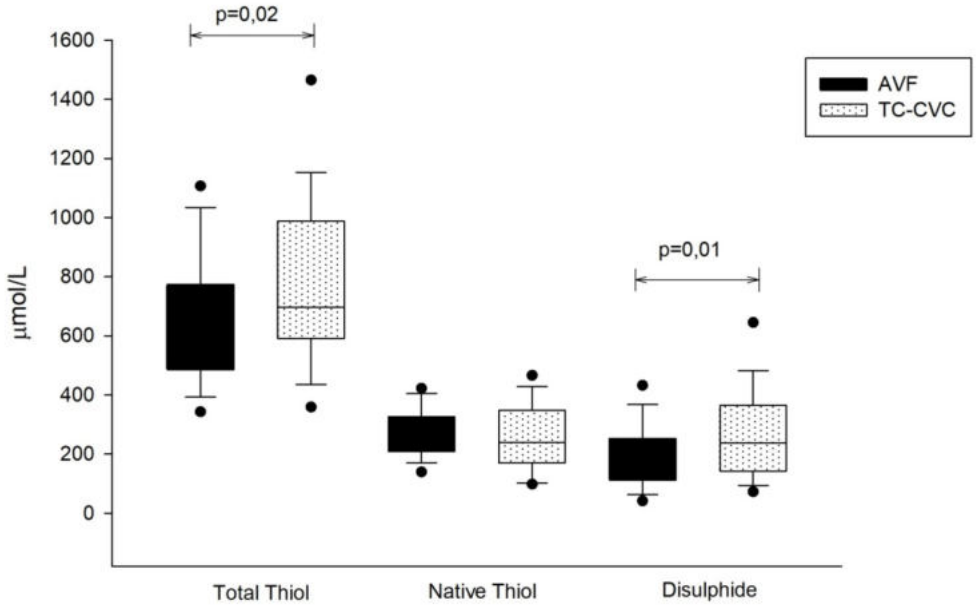


Fig. 2. Thiol measurements of the groups. AVF = Arteriovenous fistula, TC-CVC = Tunneled cuffed central venous catheter.

Table 2. Oxidative stress indices and inflammatory markers of the groups

	AVF (n = 63)	TC-CVC (n = 22)	*p* value
TT (µmol/L)	647 ± 233.5	788.2 ± 285.1	**0.02**
NT (µmol/L)	272.2 ± 86.6	256.2 ± 110.3	0.49
DS (µmol/L)	187.5 ± 112.9	265.9 ± 152.9	**0.01**
NT/TT	0.46 ± 0.17	0.36 ± 0.17	**0.03**
DS/TT	0.27 ± 0.08	0.31 ± 0.08	**0.02**
TOS (µmol/L)	3.4 ± 3.2	5.5 ± 5.7	**0.04**
TAS (mmol/L)	2.3 ± 0.2	2.2 ± 0.2	0.29
OSI)	0.15 ± 0.14	0.24 ± 0.23	**0.04**
hs-CRP (mg/L)	5.8 (3.0-82.5)	9.7 (3.0-45.4)	**0.004**
IL-6 (pg/mL)	6.2 (2.0-159.0)	12.2 (2.6-41.3)	**0.01**

Data are shown as mean±standard deviation or median (minimum-maximum). AVF = Arteriovenous fistula, TC-CVC = Tunneled cuffed central venous catheter, TT = Total thiol, NT = Native thiol, DS = Disulphide, TOS = Total oxidant status, TAS = Total antioxidant status, OSI = Oxidative stress index, hs-CRP = high sensitive C-reactive protein, IL-6 = Interleukin-6.

Inflammatory markers

Median hs-CRP levels and median IL-6 levels were significantly lower in the AVF group comparing the TC-CVC group (Table 2, Fig. 4).

Logistic regression analysis of risk factors for elevated total oxidative status

When corrected for all possible risk factors, TC-CVC significantly increases the risk of elevated TOS scores [OR: 6.90 (min: 1.09 – max: 43.6), $p = 0.04$] (Table 3).

DISCUSSION

CVCs are recommended to be the last choice for

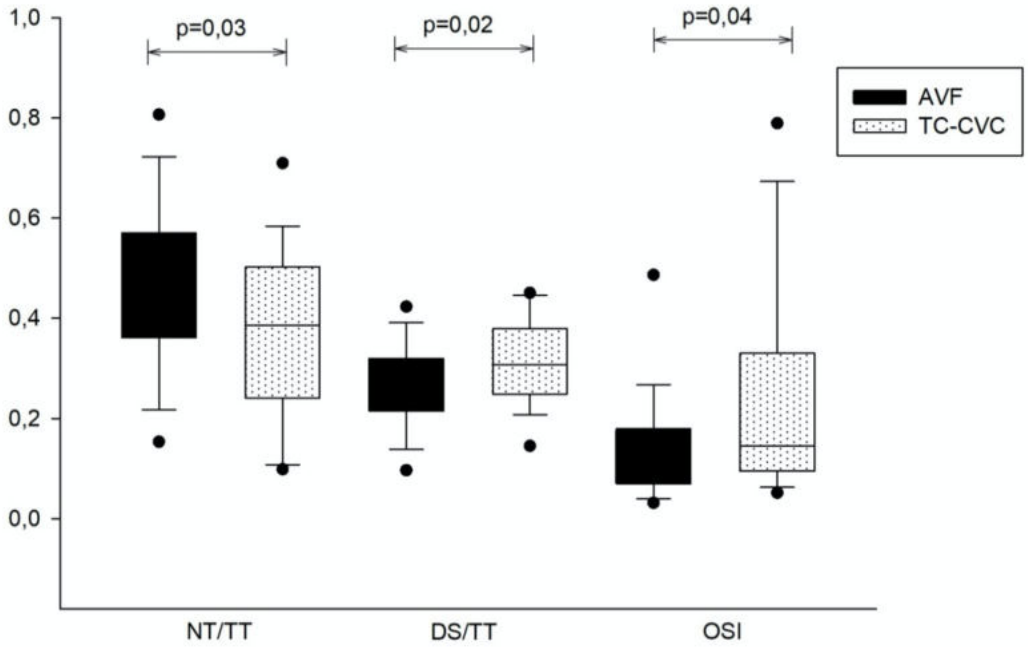


Fig. 3. Thiol balances of the groups. AVF = Arteriovenous fistula; TC-CVC = Tunneled cuffed central venous catheter.

Table 3. Logistic regression analysis of risk factors for elevated total oxidative status

	OR (95% CI)	*p*-value
Age	1.10 (0.95-1.08)	0.17
BMI (kg/m^2)	1.78 (0.59-1.20)	0.93
DM	3.24 (0.24-42.6)	0.37
Vascular disease*	5.68 (0.40-80.7)	0.19
Smoking	6.16 (0.44-85.8)	0.17
Cum. IV iron (mg)	0.99 (0.99-1.00)	0.07
Mean UF (mL)	0.65 (0.99-1.00)	0.65
hs-CRP (mg/L)	0.34 (0.96-1.11)	0.34
TC-CVC	**6.90 (1.09-43.6)**	**0.04**

BMI = Body mass index, DM = Diabetes mellitus, Cum. IV Iron = Cumulative intravenous iron, UF = Ultrafiltration, hs-CRP = high sensitive C-reactive protein, TC-CVC = Tunneled cuffed central venous catheter

*Coronary artery disease, peripheral artery disease and/or cerebrovascular disease

HD VA by current guidelines. This approach is due to the observed higher mortality in patients with CVCs [1-3, 19, 20]. Most of these studies have not reported the causes of death. A recent well-designed study revealed a discordance in mortality rates and reported acute catheter complications [21].

Following the placement of the CVC, a layer of macromolecules, cells, and fibrinogen are rapidly deposited on the surface [6]. Microbial contamination of the layer can be as short as 24 hours. Intraluminal colonization, in particular, is reported to be detected in 49-75% of patients with chronic HD catheters [9]. Bacteriae adhered to the biofilm produces an extracellular matrix that facilitates the adhesion of other pathogens and forms resistance to antibiotics and the host immune system [22]. The planktonic bacteriae can spread in circulation and cause bloodstream infections. However, there are emerging suspicions that this biofilm layer can also lead to OS and a silent SI [23].

OS is a risk factor for cardiovascular mortality

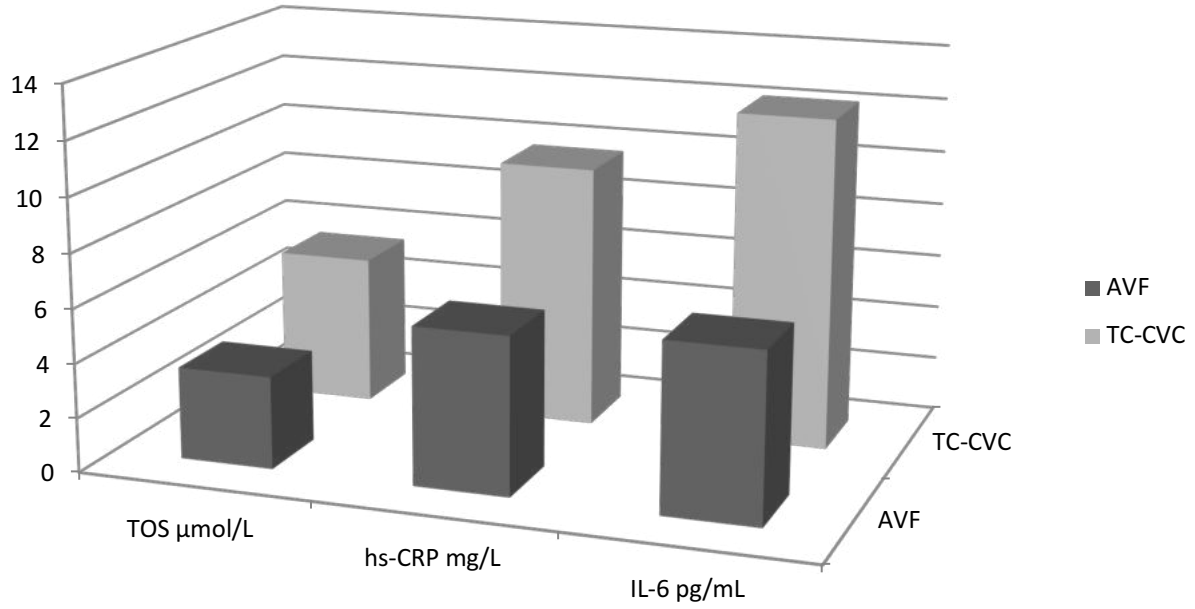


Fig. 4. Thiol balances of the groups. AVF = Arteriovenous fistula; TC-CVC = Tunneled cuffed central venous catheter.

preferentially via oxidation of low-density lipoprotein in endothelium forming plaques [24]. SI is also a plaque trigger and a risk factor for CVDs [25]. The increased OS and SI have also been demonstrated in HD patients and associated with CVDs [26]. In our study, considering the proven OS factors in HD patients, we investigated the relationship between the presence of TC-CVC and the relationship between OS and SI using novel and sensitive markers.

Reactive oxygen species results in oxidation between two electrons or redox modification of radical-based amino acid residues. In this redox reaction, the –SH groups of organosulfur compounds (thiols) such as cysteine oxidized and form a disulfide [27]. Thus, the dynamic thiol/disulfide homeostasis moves towards the disulfide form, which is the first sign of radical-mediated protein oxidation. This shift is the reflection of increased OS. Together with thiol-disulfide equilibrium, TAS and TOS measurements were made, and the OSI was calculated. Hs-CRP and IL-6 levels were used to determine SI.

The TC-CVC group had higher TT levels and DS levels, and more importantly, had lower NT/TT ratios that reflect superior antioxidant capability and higher DT/TT ratios that reflect oxidant stress. TOS levels and calculated OSI were also significantly higher in the TC-CVC group comparing the AVF group. On the other hand, the TC-CVC group had significantly higher hs-CRP and IL-6 levels.

The study revealed a clear difference between AVF and TC-CVC groups in terms of SI, consonant to the literature [28]. Furthermore, this is the first study to demonstrate the relationship between TC-CVC and OS with novel sensitive markers. All possible factors that may interact with these parameters such as, diabetes prevalence, vascular diseases, smoking, iron, and ESA therapies were similar between the groups. Also, TC-CVC was found to be an independent risk factor for elevated TOS. Moreover, patients who had an infectious disease and had any vascular event within the last six months were excluded from the study.

A meta-analysis composed of 62 studies reported that the proportion of access-related fatal infections in available studies was not precise, and in one study, only 23% of all infection-related hospitalizations were caused by access infection, suggesting that infections do not entirely explain the increased mortality associated with access types. In this meta-analysis, patients with CVCs had higher risks for all-cause mortality and cardiovascular events [29]. In a study of 4854 patients, AVF use 90 days after dialysis initiation was found to be associated with lower cardiovascular mortality compared with CVC use. The authors hypothesized that the biofilm in synthetic CVCs might increase the risk of CVD in HD patients via systemic inflammation [30].

Clinicians should bear in mind that OS and SI further increased by the use of TC-CVC may be a cause of worsening cardiovascular outcomes in HD patients. AVGs should be applied when AVF is not possible due to the patient's vascular structure. However, it should be remembered that peritoneal dialysis (PD) is an equivalent method applicable in almost all patients. PD should be introduced to every dialysis patient and encouraged to be used more frequently. For a small number of patients with no AVF or AVG chance and contraindications for PD, more biocompatible, less biofilm-producing CVCs with added antimicrobial properties may be used.

CONCLUSION

In HD patients, TC-CVCs inversely affect OS and SI status, presumably due to foreign body reactions and biofilm layers. However, VA through AVF is associated with a less oxidant state, and it is practically predictable that these more favorable effects will have ameliorating effects on adverse cardiovascular outcomes in these patients.

Authors' Contribution

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

Conflict of interest

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

Financing

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

REFERENCES

1. Pastan S, Soucie JM, McClellan WM. Vascular access and increased risk of death among hemodialysis patients. Kidney Int 2002;62:620-6.
2. Astor BC, Eustace JA, Powe NR, Klag MJ, Fink NE, Coresh J; CHOICE Study. Type of vascular access and survival among incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study. J Am Soc Nephrol 2005;16:1449-55.
3. Polkinghorne KR, McDonald SP, Atkins RC, Kerr PG. Vascular access and all-cause mortality: a propensity score analysis. J Am Soc Nephrol 2004;15:477-86.
4. Brown RS, Patibandla BK, Goldfarb-Rumyantzev AS. The survival benefit of "Fistula First, Catheter Last" in hemodialysis is primarily due to patient factors. J Am Soc Nephrol 2017;28:645-52.
5. Sheikh Z, Brooks P, Barzilay O, Fine N, Glogauer M. Macrophages, foreign body giant cells and their response to implantable biomaterials. Materials 2015;8:5671-701.
6. Murga R, Miller J, Donlan R. Biofilm formation by gram-negative bacteria on central venous catheter connectors: effect of conditioning films in a laboratory model. J Clin Microbiol 2001;39:2294-7.
7. Perez E, Williams M, Jacob JT, Reyes MD, Tejedor SC, Steinberg JP, et al. Microbial biofilms on needleless connectors for central venous catheters: comparison of standard and silver-coated devices collected from patients in an acute care hospital. J Clin Microbiol 2014;52:823-31.
8. Kanaa M, Wright M, Sandoe J. Examination of tunnelled haemodialysis catheters using scanning electron microscopy. Clin Microbiol Infect 2010;16:780-6.
9. Mermel LA. What is the evidence for intraluminal colonization of hemodialysis catheters? Kidney Int 2014;86:28-33.
10. Francois P, Vaudaux P, Nurdin N, Mathieu H, Descouts P, Lew DP. Physical and biological effects of a surface coating procedure on polyurethane catheters. Biomaterials 1996;17:667-78.
11. Fox CS, Matsushita K, Woodward M, Bilo HJ, Chalmers J, Heerspink HJL, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet 2012;380:1662-73.
12. Cristol J, Canaud B, Rabesandratana H, Gaillard H, Serre A, Mion C. Enhancement of reactive oxygen species production and cell surface markers expression due to haemodialysis. Nephrol Dial Transplant 1994;9:389-94.
13. Modlinger PS, Wilcox CS, Aslam S. Nitric oxide, oxidative stress, and progression of chronic renal failure. Semin Nephrol 2004;24:354-65.
14. Liakopoulos V, Roumeliotis S, Gorny X, Dounousi E, Mertens PR. Oxidative stress in hemodialysis patients: a review of the literature. Oxid Med Cell Longev 2017;2017:3081856.
15. Scott SD. Dose conversion from recombinant human erythropoietin to darbepoetin alfa: recommendations from clinical studies. Pharmacotherapy 2002;22(9P2):160S-5S.
16. Shemin D, Bostom AG, Laliberty P, Dworkin LD. Residual renal function and mortality risk in hemodialysis patients. Am J Kidney Dis 2001;38:85-90.
17. Erel O, Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem 2014;47:326-32.
18. Erel O. A new automated colorimetric method for measuring total oxidant status. Clin Biochem 2005;38:1103-11.
19. Moist LM, Trpeski L, Na Y, Lok CE. Increased hemodialysis

catheter use in Canada and associated mortality risk: data from the Canadian Organ Replacement Registry 2001-2004. Clin J Am Soc Nephrol 2008;3:1726-32.
20. Dhingra RK, Young EW, Hulbert-Shearon T, Leavey SF, Port FK. Type of vascular access and mortality in US hemodialysis patients. Kidney Int 2001;60:1443-51.
21. Quinn RR, Oliver MJ, Devoe D, Poinen K, Kabani R, Kamar F, et al. The effect of predialysis fistula attempt on risk of all-cause and access-related death. J Am Soc Nephrol 2017;28:613-20.
22. Flemming H-C, Wingender J, Szewzyk U, Steinberg P, Rice SA, Kjelleberg S. Biofilms: an emergent form of bacterial life. Nat Rev Microbiol 2016;14:563-75.
23. Cappelli G, Tetta C, Canaud B. Is biofilm a cause of silent chronic inflammation in haemodialysis patients? A fascinating working hypothesis. Nephrol Dial Transplant 2005;20:266-70.
24. Aviram M, Dornfeld L, Rosenblat M, Volkova N, Kaplan M, Coleman R, et al. Pomegranate juice consumption reduces oxidative stress, atherogenic modifications to LDL, and platelet aggregation: studies in humans and in atherosclerotic apolipoprotein E-deficient mice. Am J Clin Nutr 2000;71:1062-76.
25. van Leuven SI, Franssen R, Kastelein J, Levi M, Stroes ES, Tak PP. Systemic inflammation as a risk factor for atherothrombosis. Rheumatology 2007;47:3-7.
26. Cachofeiro V, Goicochea M, De Vinuesa SG, Oubiña P, Lahera V, Luño J. Oxidative stress and inflammation, a link between chronic kidney disease and cardiovascular disease. Kidney Int Suppl 2008;(111):S4-S9.
27. Cremers CM, Jakob U. Oxidant sensing by reversible disulfide bond formation. J Biol Chem 2013;288:26489-96.
28. Banerjee T, Kim SJ, Astor B, Shafi T, Coresh J, Powe NR. Vascular access type, inflammatory markers, and mortality in incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study. Am J Kidney Dis 2014;64:954-61.
29. Ravani P, Palmer SC, Oliver MJ, Quinn RR, MacRae JM, Tai DJ, et al. Associations between hemodialysis access type and clinical outcomes: a systematic review. J Amn Soc Nephrol 2013;24:465-73.
30. Wasse H, Speckman RA, McClellan WM. Arteriovenous fistula use is associated with lower cardiovascular mortality compared with catheter use among ESRD patients. Semin Dial 2008;21:483-9.

The European Research Journal 2021;7(2):136-141 Original Article

DOI: 10.18621/eurj.584619 *Anesthesiology and Critical Care Medicine*

Comparison of ultrasonography-guided pectoral nerve block with patient-controlled analgesia for breast surgery patients

Gökhan Işık Serçe, Evrim Kucur Tülübaş

Department of Anesthesiology and Critical Care Medicine, Bakırköy Dr. Sadi Konuk Training and Research Hospital, İstanbul, Turkey

ABSTRACT

Objectives: Pectoral nerve block is an effective method that can be applied for analgesic purposes in breast surgery. In this prospective study we aimed to compare the postoperative analgesic efficacy of pectoral nerve block for postoperative analgesia and patient-controlled analgesia (PCA) for patients undergoing breast surgery in terms of the incidence of nausea and vomiting.

Methods: The study included 93 patients who underwent ASA I-II anesthesia and breast surgery. Group 1 was PCA group, group 2 was PECS (Pectoral Nerves) block group. PECS block was administered as PECS-1 and PECS-2 block under the guidance of ultrasonography. Patients investigated in the study had postoperative monitoring forms examined for vital signs and visual analog scale (VAS) scores in the 1st, 6th and 24th hours.

Results: When the pectoral nerve block with bupivacaine under ultrasound guidance was compared with PCA device, there were significant reductions in VAS score at 24 hours.(1.53 vs 4.27, 1.10 vs 3.27 and 0.90 vs 1.93, respectively; $p = 0.0001$). Although there was no significant difference in terms of vomiting, there was a difference in favor of pectoral nerve block especially at the postoperative 6th hour in terms of nausea.

Conclusions: Pectoral nerve block can be used in the patients undergoing breast surgery due to the lower visual analog score and nausea incidence in the postoperative period.

Keywords: Breast surgery, pectoral nerve block, ultrasonography, patient-controlled analgesia

Breast cancer is the most common cancer type among women. In the United States of America, 1 out of every 8 women will be diagnosed with breast cancer [1]. All breast surgeries, led by modified radical mastectomy, are limited by severe acute postoperative pain and painful shoulder movements [2].

Thoracic paravertebral block is the most commonly used block to ensure analgesia among patients operated for breast cancer. However, patients administered thoracic paravertebral block feel pain after surgery in both the axilla and upper extremities. This is because this block does not effectively block the medial and lateral pectoral nerves [3-10]. Pectoral nerve block enters the scenario to solve these problems. Pectoral nerve block administers local anesthetic between the muscles of the anterior wall of the chest; the pectoralis major, pectoralis minor and serratus anterior muscles; and provides very effective analgesia for breast surgery.

In the postoperative period vomiting may cause many unwanted results such as fluid electrolyte loss, aspiration of vomited material in the airway, straining of suture lines and increased intraocular and intraabdominal pressure [11]. All of these results disrupt the patient's comfort and may increase the duration of hospital stay and involve serious costs. After these sur-

Received: ***June 30, 2019;*** *Accepted:* ***June 15, 2020;*** *Published Online:* ***January 25, 2021***

How to cite this article: *Serçe GI, Kucur Tülübaş E. Comparison of ultrasonography-guided pectoral nerve block with patient-controlled analgesia for breast surgery patients. Eur Res J 2021;7(2):136-141. DOI: 10.18621/eurj.584619*

Address for correspondence: *Evrim Kucur Tülübaş, MD., Bakırköy Dr. Sadi Konuk Training and Research Hospital, Department of Anesthesiology and Critical Care Medicine, Zuhuratbaba Mah., Tevfik Sağlam Cad., No: 11, 34147, Bakırköy, İstanbul, Turkey. E-mail: evrim.kucurtulubas@saglık.gov.tr*

e-ISSN: 2149-3189

geries the use of high-dose opioids for analgesic purposes increases the incidence of nausea and vomiting. When pectoral nerve block is correctly administered, it reduces opioid requirements to a minimum due to strong analgesic effect and reduces the incidence of nausea-vomiting. In this prospective study we aimed to compare the postoperative analgesic efficacy of pectoral nerve block for postoperative analgesia and patient-controlled analgesia (PCA) for patients undergoing breast surgery in terms of the incidence of nausea and vomiting.

METHODS

After this study received permission from University of Health Sciences, Bakırköy Dr. Sadi Konuk Traning and Research Hospital Local Ethics Committee numbered 2016-02-06, the records of a total of 93 patients who underwent modified radical mastectomy with general anesthesia at Bakırköy Dr. Sadi Konuk Education and Research Hospital General Surgery Clinic from 01.03.2016 to 01.07.2016 were investigated. After the approval of the ethics committee, the study was applied prospectively. The patients investigated had general 3 anesthesia induction with fentanyl 2 mcg/kg (according to ideal body weight [IBW]) and propofol 2-3 mg/kg with muscle relaxant of rocuronium 0.6 mg/kg (according to true body weight [TBW]). Anesthesia maintenance used 40% O2 + 60% air with 2% sevoflurane and remifentanil (0.1-0.3 mcg/kg/min) infusion. All patients were administered 1 g paracetamol + 100 mg tramadol and 8 mg ondansetron before the start of the surgical procedure.

We included ASA I and II female patients between the ages of 18 and 65 years undergoing modified radical mastectomy for carcinoma breast after obtaining of participants. Patients with local anesthetic allergy, locally advanced breast malignancies with skin ulceration or infiltration of chest wall, patients on anticoagulants, bleeding dyscrasias and anormaly liver function tests were excluded from the study.

Accidental numbers were produced in order to prevent selection bias. Group 1 was PCA group, group 2 was PECS group. Random numbers made MedCalc 18.2.1. Breast surgery team consists of 3 surgical specialists and 1 anesthesiologist. Patients who underwent only radical mastectomy were included in this study.

The pectoral nerve block was performed both as PECS-1 and PECS-2 blocks between the 3rd and 4th intercostal spaces, in the midclavicular line, accompanied by ultrasonography. It was performed before incision, after intubation. For PECS-1 block, 10 ml of 0.25% bupivacaine was administered between the pectoralis major and pectoralis minor muscles. For PECS-2 block, in the same plane, 20 ml 0.25% bupivacaine was administered between the serratus anterior and pectoralis minor muscles. A LOGIQE GE Healthcare brand (GE Medical Systems, Phoenix – USA) USG device and USG probe (12 MHz, Linear) were used with a Pajunk brand 50 mm blunt-tipped peripheral nerve block needle (Stimuplex A®B. Braun 82 Melsungen AG, JAPAN).

Patients using a patient-controlled analgesia (PCA) device for postoperative analgesia had the device set up after extubation at the end of the operation with IV. The medication solution used in the PCA device is standard for our clinic and is set with tramadol 300 mg/100 ml, bolus 5 mg, lock time 15 minutes and basal infusion 10 mg/hour. When the VAS score was above 4, 0,1 mg/kg of morphine IV was administered.

Patients investigated in the study had postoperative monitoring forms examined for vital signs [systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP)], vomiting presence/absence, nouse presence/absence and visual analog scale 4 (VAS) scores in the 1st, 6th and 24th hours. Clinical nurses were evaluated for nausea and vomiting and the presence / absence of nausea and vomiting was recorded. VAS scores of the patients were evaluated by the anesthesiologist and the checked by the authors. PCA use of the patients was evaluated by the anesthesiologist.

Statistical Analysis

Statistical analysis of data used the SSPS 23 program. Normal distribution of data was tested with the Kolmogorov-Smirnov test. Mean, standard deviation, median, minimum and maximum values were used for descriptive statistics. Frequency and percentage values were calculated for categorical variables. The Mann Whitney U test was used to compared to groups with non-normal distribution, while the chi-square or Fisher exact probability test was used to compare categorical variables. The Cochran Q test and the Friedman test for variation over time was used. $P < 0.05$ was ac-

cepted as statistically significant. For the analysis results with 80% power and moderate effect levels, the necessary sample number for each group was identified as 30, for a total of 60 people (PECS and PCA groups). Power analysis used the PASS 15 (Power Analysis and Sample Size Software, 2017) program.

RESULTS

The study included 93 patients operated modified radical mastectomy the General Surgery Clinic of Bakırköy Dr. Sadi Konuk Education and Research Hospital. The 93 patients determined by screening were all women. Five patients in ASA III risk group and 5 patients above the age of 65 years were excluded from the study. Our prostective study investigated the pectoral nerve block (PECS) and patient-controlled analgesia (PCA) methods for postoperative analgesia in terms of analgesic efficacy and postoperative nausea-vomiting. Of the 43 patients with pectoral nerve block administered, 10 had insufficient monitoring and 3 patients were transferred to the intensive care unit and were excluded from the study. Of the 40 patients with patient-controlled analgesia device, 6 patients had the device removed due to severe nausea and vomiting in the early postoperative period, and 4 had insufficient postoperative monitoring and were excluded from the study. Finally, patient data of 30 cases in the PECS group and 30 cases in the PCA group for a total of 60 patients were investigated statistically.

The mean age in the PCA group was 48 years, while it was 53 years in the PECS group. The PCA comprised 11 patients in ASA I and 19 patients in ASA II. The PECS group comprised 8 patients in ASA I and 22 patients in ASA II. There was a statistically significant difference identified between the groups in terms of mean SAP in the 1st hour ($p < 0.05$). In the PCA group the systolic blood pressure in the 1st hour was significantly higher compared to the PECS group. There was no statistically significant difference between the groups for mean SAP in the 6th and 24th hours ($p > 0.05$). There was no statistically significant difference identified between the groups in terms of mean DAP in the 1st, 6th and 24th hours ($p > 0.05$) (Table 1).

PCA group received 30 mg of the first hour, 110 mg at 6 hours and 315 mg of tramadol at 24 hours.

There was no significant difference identified between the nausea rates in the block and PCA groups in the 1st hour ($p = 1.000$). The nausea rates all patients were similar in the first hour. In the 6th hour there was no nausea among the block patients. Among 30 patients with PCA, 18 (60% of patients) had nausea. When examined in terms of nausea in the 6th hour, pectoral nerve block effectively prevented nausea after breast surgery. PCA administration was understood to be deficient in this regard. There was no nausea in both the PECS group and PCA group in the 24th hour. *P* value could not be calculated as there was no patient with nausea in either group (Table 2). There was no significant difference identified between the PECS and PCA groups in terms of vomiting in the 1st hour ($p = 1.000$). The vomiting rates in the patient and PCA

Table 1. Assessment of SPB and DBP measurements

	PCA (Mean ± SD)	PECS (Mean ± SD)	*p value*
SAP (mm/Hg)			
1st hour	148.67 ± 19.61	133.33 ± 19.49	**0.048**
6th hour	137.33 ± 17.60	135.17 ± 18.31	0.454
24th hour	131.00 ± 16.89	137.17 ± 17.89	0.410
DAP (mm/Hg)			
1st hour	83.67 ± 7.06	78.17 ± 10.79	0.227
6th hour	77.50 ± 6.40	79.67 ± 7.87	0.917
24th hour	76.67 ± 15.72	80.17 ± 7.20	0.408

*Fisher exact probability test, **Mann Whitney U test, PCA = Patient-Controlled Analgesia, PECS = Pectoral Nerves block, SBP = Systolic blood pressure, DAP = Diastolic blood pressure

Table 2. Comparison of nausea, vomiting and VAS scores between groups

	Nausea 1st hour	Nausea 6th hour	Nausea 24th hour
PCA	9	18	0
PECS	5	0	0
p* value	1.00	**0.01**	-
	Vomiting 1st hour	**Vomiting 6th hour**	**Vomiting 24th hour**
PCA	9	0	0
PECS	3	0	0
p* value	0.143	-	-
	VAS 1st hour	**VAS 6th hour**	**VAS 24th hour**
PCA (mean)	4.27	3.27	1.93
PECS (mean)	1.53	1.10	0.90
P**	**0.0001**	**0.0001**	**0.0001**

*Fisher exact probability test, **Mann Whitney U test, PCA = Patient-Controlled Analgesia, PECS = Pectoral Nerves block

groups were similar in the 1st hour. There was no vomiting in the PECS and PCA groups in the 6th and 24th hours. As a result *p* values could not be calculated. According to analysis to identify differences in the VAS scores for the PECS and PCA groups in the 1st, 6th and 24th hours, there were significant differences identified in the 1st hour ($p = 0.0001$), 6th hour ($p = 0.0001$) and 24th hour ($p = 0.0001$). For all measurements the PECS group were observed to have lower VAS scores (Table 2).

DISCUSSION

In the present study, when the PECS and PCA were compared, the VAS score in the PECS group was statistically significantly lower at the 1st, 6th and 24th hours. In this case, the use of PECS for postoperative analgesia seems to be effective. Another result is that the nausea is significantly higher in the PCA group than the PECS group at the 6th hour. There 6 was no significant difference in term of vomiting in the 1 st, 6th and 24th hours between the groups.

Postoperative pain is an acute pain beginning with surgical trauma, and ideally will gradually reduce to end with wound healing. If postoperative pain is not treated, it may cause serious systemic side effects like atelectasis, hypoxemia and pneumonia in the pulmonary system; tachycardia, mainly, along with cardiac arrhythmia, hypertension, myocardial ischemia and thromboembolic events in the cardiovascular system; gastric stasis, paralytic ileus, nausea and vomiting in the gastrointestinal system; urinary retention in the genitourinary system; increased catabolism and hyperglycemia in the endocrine system; immunosuppression and tendency for infections in the immune system; delayed wound healing and muscle spasms [12-14]. The occurrence of these negative effects of postoperative pain mentioned above have led to approaches to postoperative pain treatment becoming important in anesthesia practice.

However, in spite of the latest developments in analgesia administration methods and production of analgesic mediations with new pharmacokinetic profiles, current evidence shows that postoperative pain is not sufficiently treated [13].

Together with a variety of conservative methods for analgesia management for breast cancer operations, thoracic paravertebral block used to be ensure analgesia. However, as thoracic paravertebral block does not effectively block the medial and lateral pectoral nerves, its use for analgesic aims in breast sur-

gery is limited. Additionally, thoracic paravertebral block administration includes the risk of serious pneumothorax, spinal cord trauma, sympathetic block and linked hypotension [3-8]. Due to these complications and insufficient analgesic power, paravertebral block administration is avoided. Pectoral nerve block began as an alternative.

Similar to the present study, the study by Bashandy *et al*. [14], in which PECS block was compared with the PCA group, it was reported that, in the post-anesthesia care unit, nausea and vomiting as well as sedation scores were lower in the PECS group when compared to the control group and the VAS score significantly decreased in the PECS group. In addition, the combined Pecs I and II block is a simple, easy-to-learn technique that produces good analgesia for radical breast surgery. Unfortunately, even if nausea and vomiting decreased in the PECS group also in the present study, not to evaluate them with PONV, which is more specific, remains as a limitation in this study. In another publication, Neeth *et al*. [17] compared PECS block with general anesthesia and reported that PECS block reduced the need for postoperative analgesia and led to a decrease in the VAS score. However, unlike the present study, they did not find any difference in terms of nausea and vomiting in the postoperative evaluation performed with PONV. Another study that supports the results obtained in this study and reported no difference in nausea and vomiting, but reported a decrease in VAS value, is the study by Morioka *et al*. [16]. In the present study, however, nausea was significantly higher in the PCA group at 6th hour. Kulhari *et al*. [17] compared the PECS block with thoracic vertebral block. Although it does not have the same characteristics with the present study, given the evaluation in terms of PONV, the vomit and nausea incidence was found to be low in both groups for block suitability and the decrease in the use of opioids was seen to be directly associated with the low incidence of vomit and nausea.

Contrary to the results obtained in the present study, Cros *et al*. [18] reported that PECS I was not better than a saline placebo in the presence of multimodal analgesia for breast cancer surgery in the breast surgery group that underwent only in the PEC 1 block. However, in addition to PECS 1 block, PEC 2 block was also implemented in the patient group in the present study. Since the PECS 1 block is insufficient in mastectomies where axillary dissection is implemented alone, the block of thoracicus longus nerve was described as the added PECS 2 block [19, 20].

Limitations

There are some limitations when evaluating these results. The most important of these is that the results are not prospective. In others, however, we did not measure the total amount of tramadol consumed by patients in PCA, we should have used PONV score for vomiting and nausea. The high systolic arterial pressure in the PCA group at the first hour depended on the VAS score being above 4. In this case, we could not give enough analgesia within 1 hour. Therefore, we administered the rescue dose.

CONCLUSION

In conclusion, we believe pectoral nerve block within a multimodal approach especially using USG guidance provides reliable and effective postoperative analgesia for patients undergoing breast surgery.

Authors' Contribution

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

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.

Financing

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

REFERENCES

1. Desroches J, Grabs U, Grabs D. Selective ultrasound guided pectoral nerve targeting in breast augmentation: How to spare the

brachial plexus cords? Clin Anat 2013;26:49-55.
2. Fecho K, Miller NR, Merrit SA, Klauber-Demore N, Hultman CS, Blau WS. Acute and persistent postoperative pain after breast surgery. Pain Med 2009;10:708-15.
3. Perlas A, Niazi A, McCartney C, Chan V, Xu D, Abbas S. The sensitivity of motor response to nerve stimulation and paresthesia for nerve localization as evaluated by ultrasound. Reg Anesth Pain Med 2006;31:445-50.
4. Ono K, Danura T, Koyama Y, Hidaka H. [Combined use of paravertebral block and general anesthesia for breast cancer surgery]. Masui 2005;54:1273-6. [Article in Japanese]
5. Kairaluoma PM, Bachmann MS, Korpinen AK, Rosenberg PH, Pere P. Single-injection paravertebral block before general anesthesia enhances analgesia after breast cancer surgery with and without associated lymph node biopsy. Anesth Analg 2004;99:1837-43.
6. Moskowitz AS, Goodman RR. Autoradiographic analysis of mu1, mu2, and delta opioid binding in the central nervous system of C57BL/6BY and CXBK (opioid receptor-deficient) mice. Brain Res 1985;360:108-16.
7. Arunakul P, Ruksa A. General anesthesia with thoracic paravertebral block for modified radical mastectomy. J Med Assoc Thai 2010;93.Suppl 7: S149-53.
8. Boughey JC, Goravanchi F, Parris RN, Kee SS, Kowalski AM, Frenzel JC, et al. Prospective randomized trial of paravertebral block for patients undergoing breast cancer surgery. Am J Surg 2009;198:720-5.
9. Moller JF, Nikolajsen L, Rodt SA, Ronning H, Carlsson PS. Thoracic paravertebral block for breast cancer surgery: a randomized double-blind study. Anesth Analg 2007;105:1848-51.
10. Schnabel A, Reichl SU, Kranke P, Pogatzki EM, Zahn PK. Efficacy and safety of paravertebral blocks in breast surgery: a meta-analysis of randomized controlled trials. Br J Anaesth 2010;105:842-52.
11. Dinges HC, Otto S, Stay DK, Bäumlein S, Waldmann S, Kranke P, et al. Effect rates of opioids in equianalgesic doses via intravenous patient-controlled analgesia: a systematic review and network meta-analysis. Anesth Analg 2019;129:1153-62.
12. Nathanson SD, Wachna DL, Gilman D, Karvelis K, Havstad S, Ferrara J. Pathways of lymphatic drainage from the breast. Ann Surg Oncol 2001;8:837-43.
13. Kenny GNC. Ketorolac trometamol--a new non-opioid analgesic. Br J Anaesth 1990;65:445-7.
14. Bashandy GMN, Dina NA. Pectoral nerves I and II blocks in multimodal analgesia for breast cancer surgery: a randomized clinical trial. Reg Anesth Pain Med 2015;40:68-74.
15. Neethu M, Pandey RK, Sharma A, Darlong V, Punj J, Sinha, et al. Pectoral nerve blocks to improve analgesia after breast cancer surgery: a prospective, randomized and controlled trial. J Clin Anesthesia 2018;45:12-7.
16. Morioka H, Kamiya Y, Yoshida T, Baba H. Pectoral nerve block combined with general anesthesia for breast cancer surgery: a retrospective comparison. JA Clin Rep 2015;1:5.
17. Kulhari S, Bharti N, Bala I, Arora S, Singh G. Efficacy of pectoral nerve block versus thoracic paravertebral block for postoperative analgesia after radical mastectomy: a randomized controlled trial. Br J Anaesth 2016;117:382-6.
18. Cros J, Senges P, Kaprelian S, Desroches J, Gagnon C, Labrunie A, et al. Pectoral I block does not improve postoperative analgesia after breast cancer surgery: a randomized, double-blind, dual-centered controlled trial. Reg Anesh Pain Med 2018;43:596-604.
19. Guzzetti L, Danelli G, Ricci B, Torrano V, Russo G, Fusco P, et al. An observational analysis about novel chest wall blocks (PECS and SERRATUS) during breast surgery. Austin J Surg 2016;3:1-5.
20. Eldeen HMS. Ultrasound guided pectoral nerve blockade versus thoracic spinal blockade for conservative breast surgery in cancer breast: a randomized controlled trial. Egypt J Anaesth 2016;32:29-35.

The European Research Journal 2021;7(2):142-151 Original Article

DOI: 10.18621/eurj.648843 *Anesthesiology and Reanimation*

Comparison of the effects of isoflurane and sevoflurane on surgical stress in intracranial tumor surgery

Vuslat Muslu Erdem[1], Halil Erkan Sayan[2], Şefika Gülsen Korfalı[3]

[1]Department of Anesthesiology and Reanimation, Lütfiye Nuri Burat State Hospital, İstanbul, Turkey
[2]Department of Anesthesiology and Reanimation, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey
[3]Department of Anesthesiology and Reanimation, Uludağ University School of Medicine, Bursa, Turkey

ABSTRACT

Objectives: Surgeries can trigger stress responses including metabolic and hormonal changes. It is important to suppress stress response during surgery. We compared the effects of isoflurane and sevoflurane on surgical stress in intracranial tumor surgery.

Methods: Thirty ASA physical status I, II, III patients, scheduled for elective craniotomies, were enrolled in this prospective, randomized study. Anesthesia was induced with sodium thiopental fentanyl and vecuronium bromide and maintained with a 50% oxygen-air mixture along with isoflurane or sevoflurane. Venous blood was sampled to measure cortisol, ACTH and prolactin levels 24 hours before surgery, 1 min before anesthesia induction, during tumor removal, 1 min after extubation, at 3, 6, 12, 24, 48 hours.

Results: There was no statistically significant difference between two groups regarding demographic characteristics of patients. In group I, ACTH levels were significantly higher 1 min after extubation, at 3 and 6 hours. In Group S, significant increases were observed during tumor removal, 1 min after extubation, at 3 and 6 hours. Cortisol levels were significantly higher in both group after tumor removal, 1 min after extubation, at 3, 6, 12 and 24 hours. Prolactin levels were significantly higher in Group I during tumor removal, after extubation, at 3 and 6 hours. In group S, significant increase in prolactin level was observed only during tumor removal and 1 min after extubation. There were no significant differences in ACTH, cortisol and prolactin values between the two groups.

Conclusions: Using isoflurane or sevoflurane for anesthesia during intracranial tumor surgery are not superior to each other regarding hemodynamic and hormonal stress response.

Keywords: surgical stress, isoflurane, sevoflurane, catecholamines, ACTH, cortisol

General anesthetic agents, opioids, local anesthetics and various regional anesthesia techniques have been tried to suppress the excessive stress response which may be caused by surgical intervention [1, 2]. One of the important aims of the search for new anesthetic agents is to find the ideal anesthetic agent that suppresses stress response and limits the neuroendocrine, inflammatory and immune response [3]. It is stated that an anesthetic agent with these properties may contribute to the improvement of the postoperative period and the shortening of hospital stay [3].

The potent volatile anesthetics all induce myocardial depression with dose-dependent reductions in blood pressure and cardiac output, although the mech-

Received: ***November 20, 2019;*** *Accepted:* ***January 30, 2020;*** *Published Online:* ***January 30, 2020***

How to cite this article: *Muslu Erdem V, Sayan HE, Korfalı ŞG. Comparison of the effects of isoflurane and sevoflurane on surgical stress in intracranial tumor surgery. Eur Res J 2021;7(2):142-151. DOI: 10.18621/eurj.648843*

Address for correspondence: *Halil Erkan Sayan, MD., Assistant Professor, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Department of Anesthesiology and Reanimation, Bursa, Turkey. E-mail: erkansayan@hotmail.com, Tel: +90 224 2955000*

e-ISSN: 2149-3189

anisms for decline in blood pressure and the degree of myocardial depression [4].

Isoflurane is suppress the excessive stress response mechanisms include metabolic suppression, inhibition of sympathetic activity, reduction of glutamate receptors which are prevent calcium flow and suppression of excitotoxicity of calcium cascade [5]. Isoflurane and sevoflurane have primary vasodilatory properties, thereby reducing systemic vascular resistance with relatively little initial effect on cardiac inotropy [4].

Most elective neurosurgical interventions are performed because of intracranial mass lesions. Although pathological reasons for these lesions are different, anesthesia applications are similar [6].

In this study, we aimed to assess the effects of isoflurane and sevoflurane on hemodynamics and hormonal responses to elective intracranial tumor surgery. The secondary objective was the investigate suppression of the adrenergic response by monitoring hemodynamic parameters: systolic and diastolic arterial pressure and heart rate.

METHODS

After the approval of the Ethics Committee of Uludag University School of Medicine (Decision number: 04.04.2003-2783); thirty American Society of Anesthesiologists (ASA) classification I-II-III, patients were enrolled, for an intracranial intracranial tumor surgery under elective conditions. Written informed consents were obtained from all patients.

The exclusion criteria were as follows: Patients who were previously had an operation for the same tumor, whom had pituitary adenomas, have allergies to anesthetic drugs, developed an air embolism during the operation, were taken into the surgery within 48 hours after the operation and pregnancy.

The patients were randomly divided into two groups. Isoflurane (Group I; n = 15) and sevoflurane (Group S; n = 15) group by sealed envelope (Fig. 1). Prior to induction arterial catheter was inserted for continuous blood pressure monitoring and blood sampling. Three-lead electrocardiogram (ECG), peripheral oxygen saturation (SpO_2), the end-tidal concentrations of the volatile anesthetics and the $ETCO_2$ were monitored continuously.

Before the induction of anesthesia, 1 mg. kg^{-1} lidocaine was given intravenously to reduce hemodynamic response to the intubation. All patients were induced with sodium thiopental according to ideal body weight (3-5 mg. kg^{-1}), fentanyl (2 µg. kg^{-1}) and vecuronium bromide (0.1 mg. kg^{-1}). In the maintenance, the volatile anaesthetic (0.8-1.2 MAC) was given in a mixture of 50% oxygen-air according to the study group. Ventilation was controlled mechanically in order to achieve an end-tidal CO_2 between 30-35 mmHg.

Each patient was treated with fentanyl 2µg. kg^{-1} 5 min prior to placement of the skull clamp. The vecuronium bromide (0.02 mg. kg^{-1}) was administered as the neuromuscular blocking drug according to train -of - four monitoring. Hemodynamic response of at least one minute in duration were defined as hypertension (mean arterial pressure > 20% from the baseline measurement), tachycardia (heart rate > 20% from the base line measurement), and bradycardia (heart rate < 45/minute). Hypertension and tachycardia were treated with bolus fentanyl (1µg. kg^{-1}) as arescue drug to prevent pain and increased hemodynamic response. Hypotension was treated fluid bolus. Hypotension unresponsive to a fluid bolus was treated by ephedrine sulfate 5-10 mg intravenous bolus injection. For bradycardia, anticholinergic drugs were administered. After the operation, patients were extubated and transferred to Neurosurgical Intensive Care Unit.Pain requiring rescue medication (Visual Analog Scale above 5) were treated with non-steroidal anti-inflammatory agent.

Hemodynamic data were monitored throughout the operation. Heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and mean arterial pressure (MAP) were recorded in 12 different times: one minute before anesthesia induction (T1), one minute after intubation (T2), during skull clamping (T3), skin incision (T4), craniotomy (T5), dura incision (T6), tumor removal (T7), dural closure (T8), bone closure (T9), skin closure (T10), one minute before extubation (T11) and one minute after extubation (T12). Peripheral blood samples were collected 24 hours before surgery (P1), one min before anesthesia induction (P2), during tumor removal (P3), one minute after extubation (P4), at 3 hours (P5), at 6 hours (P6), at 12 hours (P7), at 24 hours (P8), and at 48 hours (P9) (Fig. 1).

Five cc peripheral blood samples were taken and

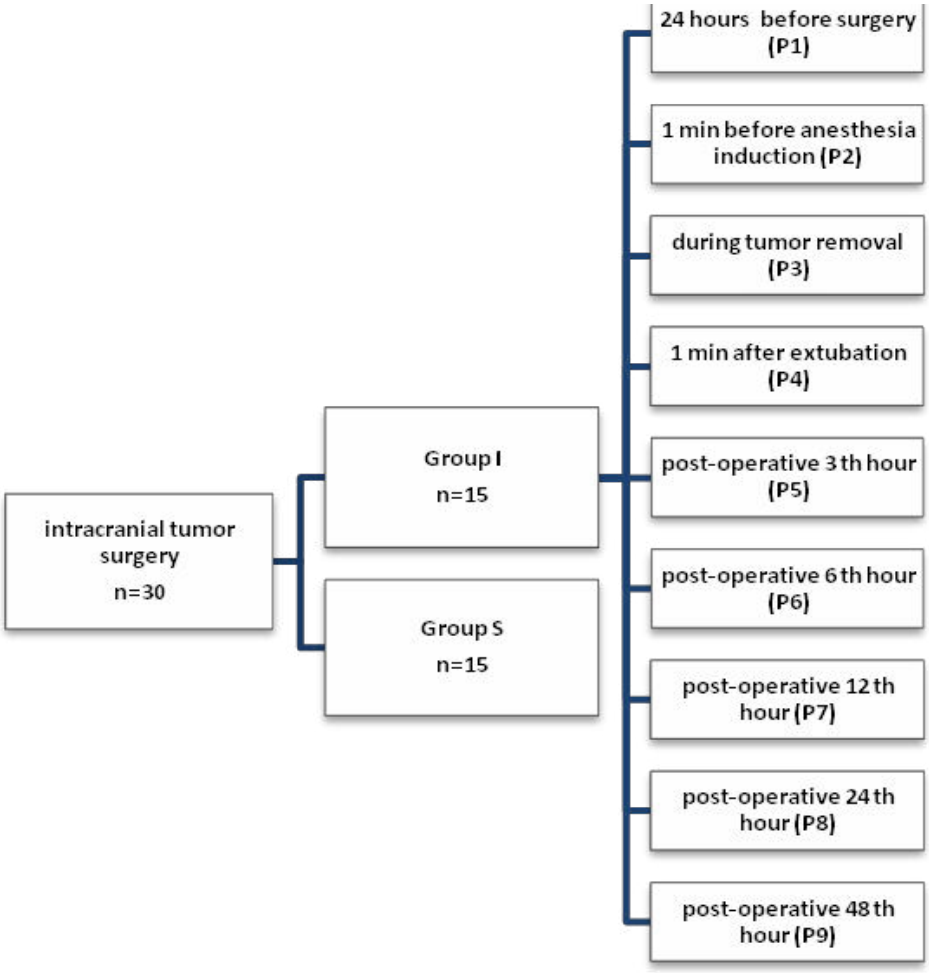


Fig. 1. Flow diagram and peripheral blood samples. P = period, min = minute, I = isoflurane, S = sevoflurane

placed into 2.5 cc. dry tubes and 2.5 cc. citrated tubes. Samples were centrifuged at 5000 rpm for 10 minutes and separated from their shaped components as plasma and serum. Plasma and serum samples were taken with an automatic pipette and placed in separate plastic ependymoma tubes and coded. It was frozen at – 500 °C for further processing.

After all samples were collected, serum samples were brought to room temperature to measure Prolactin, Cortisol and ACTH levels. The measurements were made at the Uludag University School of Medicine Central Laboratory. For ACTH measurements, IMMULITE®ACTH (Siemens, Germany) measurement kit was used. Quantitative ACTH measurements were performed on plasma samples with this kit. The ADVIA®Centaur™ (Siemens, Germany) system was used to measure the prolactin levels. In this system, prolactin levels in serum samples were detected by two-stage immuno analysis technique. For cortisol measurement, COAT-A-COUNT® (Siemens, Germany) Cortizol measurement kit was used. Using this kit, radioimmune analysis technique was used for the quantitative determination of cortisol level in serum. COAT-A-COUNT®Cortisol measurement kit is 98% sensitive and highly specific.

Statistical Analysis

A power analysis was performed prior to the study. According to the power analysis 15 patient per group should be enrolled to detect at least 20% difference in MAP measurement among the groups. The α error was set a 0.05 and the type II error was set at 0.20. All data was coded and evaluated on a computer and statistical analyzes were obtained from the SPSS for Windows Version 22.0 Statistics module. Continuous values were presented in the form of mean and standard deviation or median (minimum - maximum). Categorical data were presented as frequency (n, %). The normal

Table 1. Demographic characteristics of thepatients and duration of the operation

	Isofluran Group (n = 15)	Sevofluran Group (n = 15)	*p* value
Gender (M/F)	5 /10	5 /10	
Age (year)	53.2 ± 17.2	44.4 ± 14.1	0.57
Weight (kg)	67.9 ± 10.7	72.4 ± 12.5	0.20
Height (cm)	165.5 ± 9.5	168.2 ± 7.6	0.50
Duration of the operation(min)	352.6 ± 92	300.0 ± 87.6	0.64

Data are shown as mean ± standartd deviation or number. M = Male, F = Female

distribution of continuous data was primarily tested using the Kolmogorov-Smirnov test. Kruskal-Wallis test was used for comparisons not normal distribution. Bonferroni test was used for pairwise comparisons when their significance. Pearson chi- square test was used to compare the ratios in the groups. The t-test was used to compare group ratios and the Mann-Whitney U test was used to compare group percent changes. The measurement averages over time in the drug groups were compared with the Variance Analysis in Repeated Measurements. The significance of the changes over time was investigated by paired t-test and Wilcoxon rank sum tests. In all statistical analyzes, $p < 0.05$ significance level was accepted.

RESULTS

There was no significant difference between two groups in terms of age, sex, weight, height. Duration of operation in isoflurane group was 352.6 ± 92 minutes and operation time in sevoflurane group was 300.0 ± 87.6 minutes. There was no significant differences in operation time between two groups ($p = 0.642$) (Table 1).

There was no significant differences regarding MAP between the two groups. However, in within groups comparison, MAP were statistically lower one minute after intubation, during skin incision, craniotomy, dural incision, tumor removal, dural closure, bone closure and skin closure (p - values are $p < 0.05$, $p < 0.01$, $p < 0.01$, $p < 0.01$, $p < 0.01$, $p < 0.01$, $p < 0.01$) (Fig. 2).

Heart rates were significantly lower one minute after intubation, during skin incision, craniotomy, dural incision, tumor removal, dural closure, and skin closure. (p - values are $p < 0.05$, $p < 0.01$, $p < 0.01$, $p < 0.01$, $p < 0.01$, $p < 0.01$, $p < 0.01$, $p < 0.05$) (Fig. 3).

ACTH levels were significantly increased one minute after extubation, at 3 and 6 hours in group I ($p < 0.01$). In Group S, significant increases were observed during tumor removal, one minute after extubation, at 3 and 6 hours. ($p < 0.05$, $p < 0.01$, $p < 0.01$, $p < 0.01$) (Fig. 4).

Cortisol levels were significantly higher in both groups during tumor removal, one minute after extubation, at 3, 6, 12 and 24 hours. (Group I: $p < 0.01$, $p < 0.01$, $p < 0.01$, $p < 0.01$, $p < 0.01$, $p < 0.01$; Group S: $p < 0.01$, $p < 0.01$, $p < 0.01$, $p < 0.01$, $p < 0.01$, $p < 0.05$) (Fig. 5).

Prolactin levels significantly increased in Group I during tumor removal, one minute after extubation, at 3 and 6 hours. ($p < 0.01$, $p < 0.01$, $p < 0.05$, $p < 0.05$). In group S, significant increases in prolactin level were observed only during tumor removal and one minute after extubation ($p < 0.01$, $p < 0.01$) (Fig. 6). No significant differences were found between the two groups in ACTH, cortisol and prolactin levels.

DISCUSSION

It has been reported that response to surgical stress, increased metabolism, catabolism, and other physiological changes predispose to severe post-operative complications such as myocardial infarction, pulmonary infection, thromboembolism [7]. Suppression of surgical stress responses can lead to shorter healing duration, shorter hospitalization duration after the surgery and reduce the hospital costs especially for patients with malnutrition, suppressed immune system, elderly patients and ASA III-IV patients. For these rea-

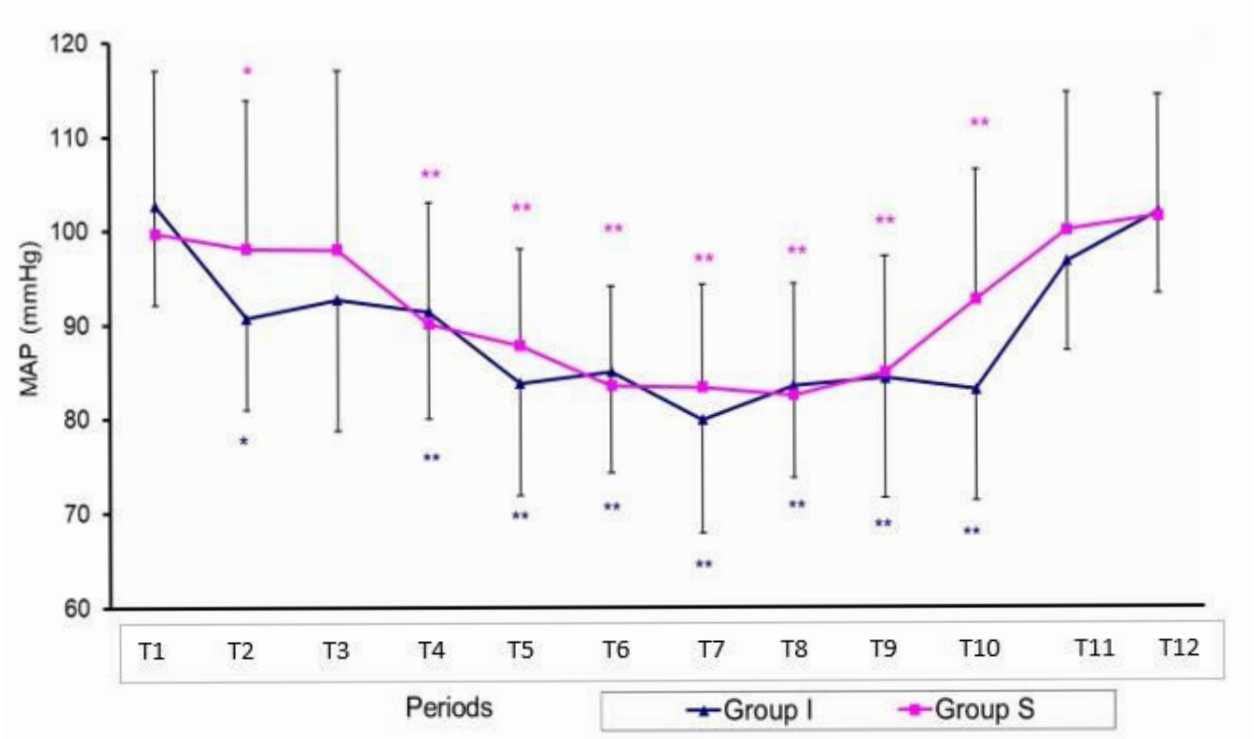


Fig. 2. Mean arterial pressure (MAP) (mean ± SD). Within group *$p < 0.05$, **$p < 0.01$. SD = Standard deviation. Periods: T1 = one minute before induction, T2 = one minute after intubation, T3 = during skull clamping, T4 = skin insicion, T5 = craniotomy, T6 = dural incision, T7 = tumor removal, T8= dural closure, T9= bone closure, T10 = skin closure, T11 = one minute before extubation, T12 = one minute after extubation.

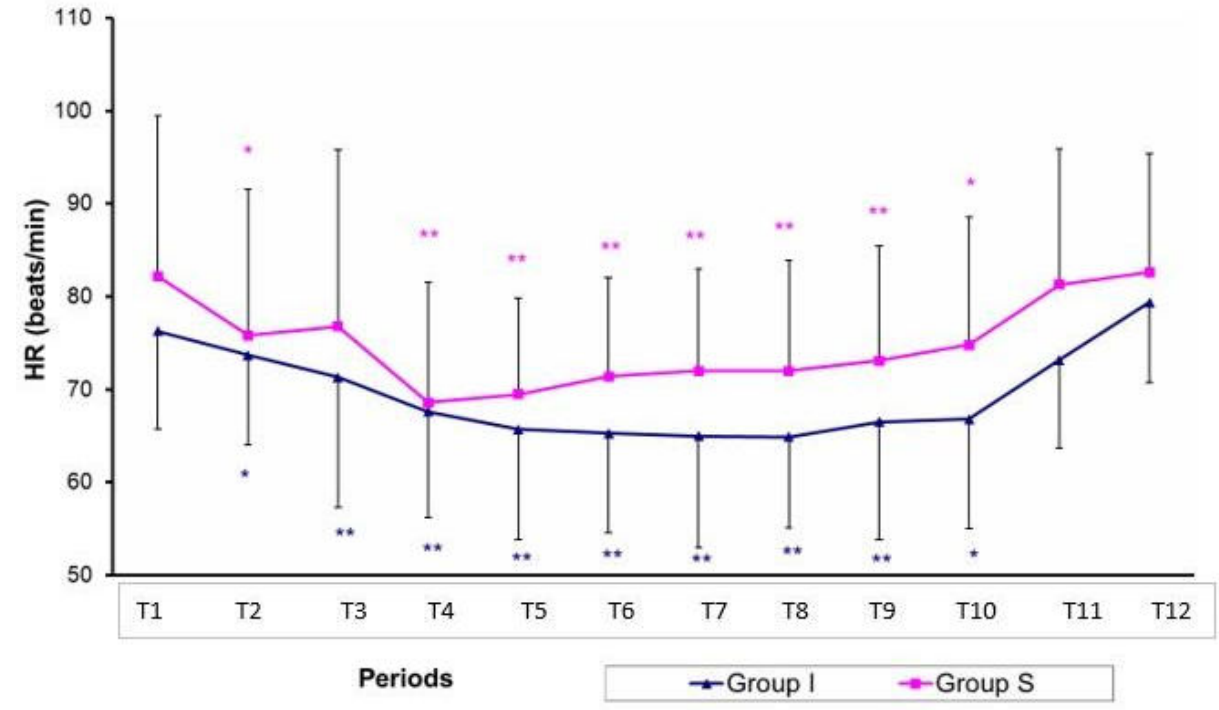


Fig. 3. Heart rate (HR) (mean±SD). Within group *$p < 0.05$, **$p < 0.01$. SD = Standard deviation. Periods: T1 = one minute before induction, T2 = one minute after intubation, T3 = during skull clamping, T4 = skin insicion, T5 = craniotomy, T6 = dural incision, T7 = tumor removal, T8= dural closure, T9= bone closure, T10 = skin closure, T11 = one minute before extubation, T12 = one minute after extubation.

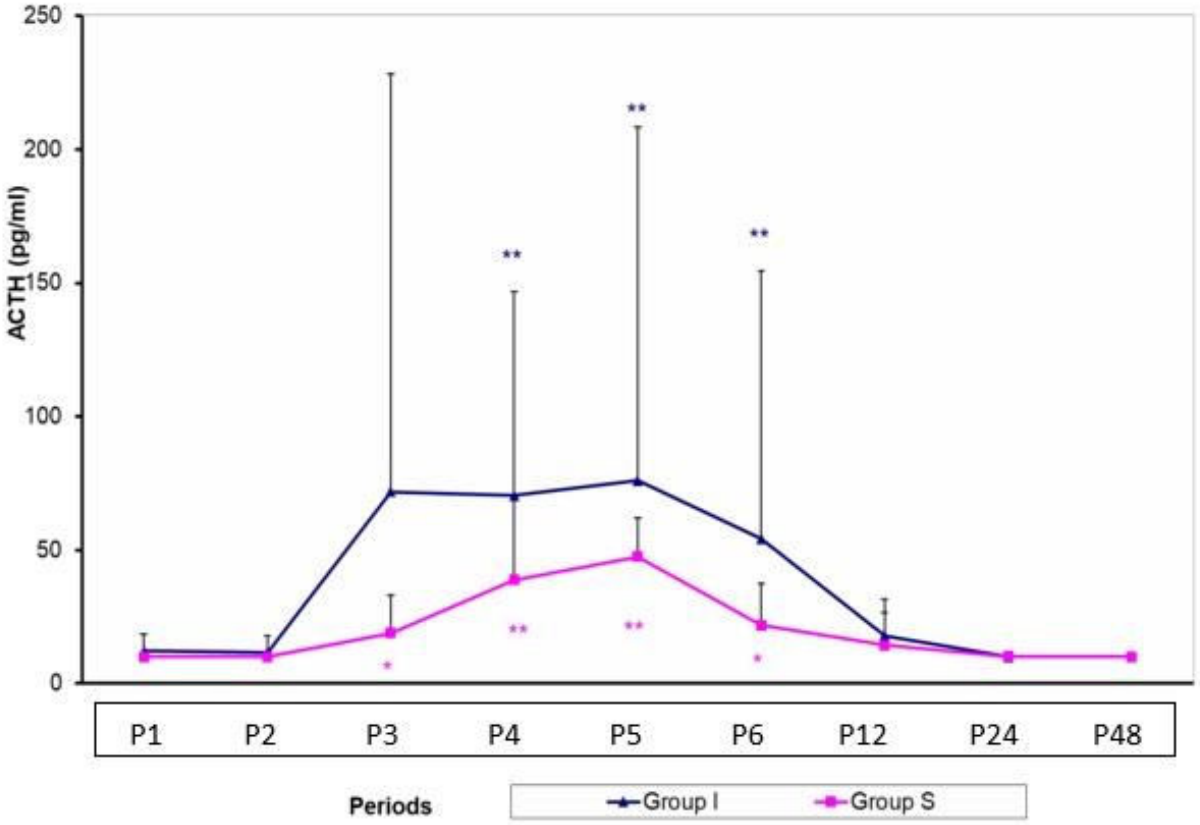


Fig. 4. ACTH levels (mean ± SD). Within group *$p < 0.05$, **$p < 0.01$. SD = Standard deviation. Periods: P1 = 24 hours before surgery, P2 = one minute before induction, P3 = during tumor removal, P4 = one minute after extubation, P5 = at 3 hours, P6 = at 6 hour, P12 = at 12 hours, P24 = at 24 hours. P48 = at 48 hours.

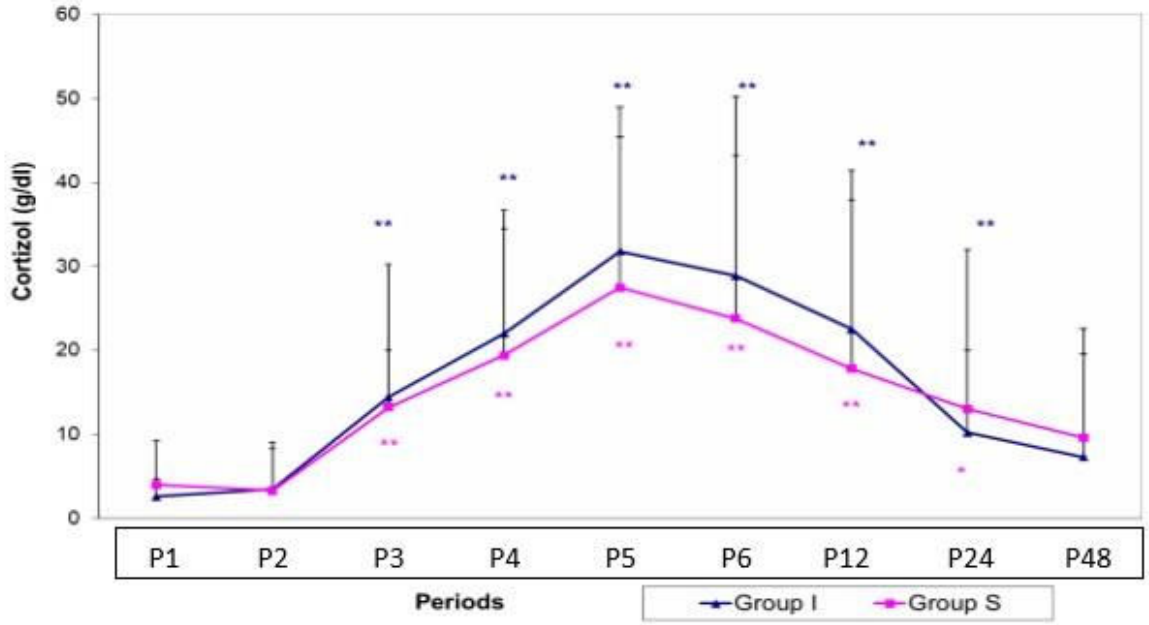


Fig. 5. Cortizol levels (mean±SD). Within group *$p < 0.05$, **$p < 0.01$. SD = Standard deviation. Periods: P1 = 24 hours before surgery, P2 = one minute before induction, P3 = during tumor removal, P4 = one minute after extubation, P5 = at 3 hours, P6 = at 6 hour, P12 = at 12 hours, P24 = at 24 hours. P48 = at 48 hours.

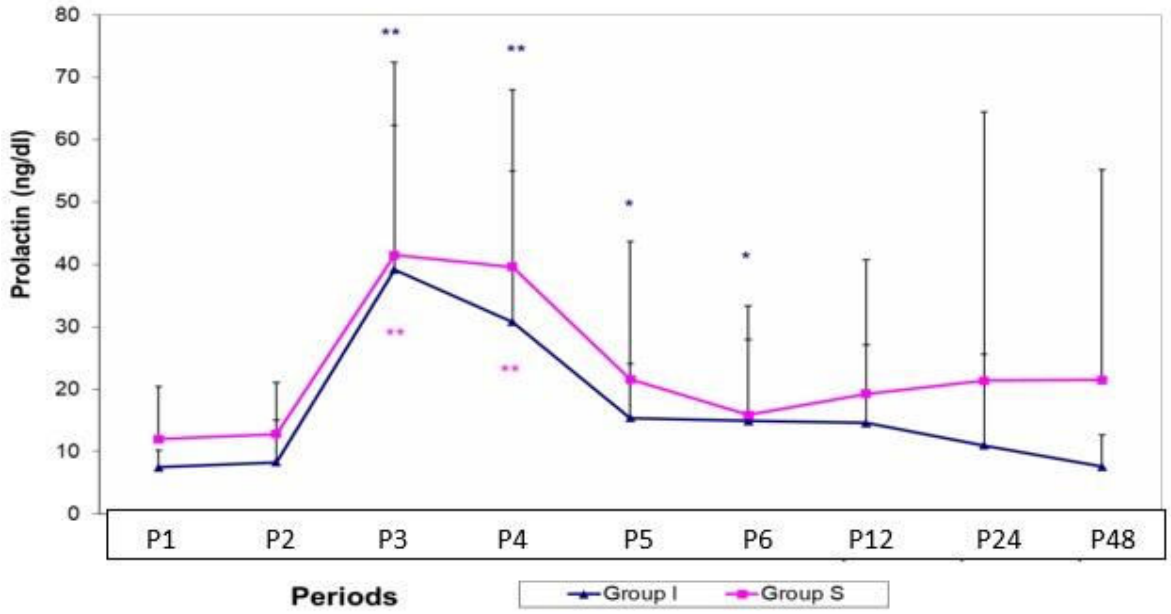


Fig. 6. Prolactin levels (mean±SD). Within group *$p < 0.05$, **$p < 0.01$. SD = Standard deviation. Periods: P1 = 24 hours before surgery, P2 = one minute before induction, P3 = during tumor removal, P4 = one minute after extubation, P5 = at 3 hours, P6 = at 6 hour, P12 = at 12 hours, P24 = at 24 hours. P48 = at 48 hours.

sons, suppression of stress responses has critical importance [8].

It has been shown that the hypothalamic–pituitary–adrenal axis can be depressed with high dose opioids during the surgical procedure and the stress response can be partially controlled [9-11]. There are also other studies that show that regional anesthesia techniques and local anesthetics are successful in suppressing stress response [9, 12-17].

In the post-surgical period, the stress responses can be controlled with a good pain therapy. It has also been suggested that β-blocker, α-2 agonist, Ca+2 channel blockers may be used to reduce stress hormone secretion and the effects of these hormones on target organs in some cases [1, 18, 19].

A few experimental studies have investigated the effects of volatile anesthetic agents such as isoflurane and sevoflurane on the hormonal and immunological responses [20, 21]. The effects of usage of isoflurane and sevoflurane during anesthesia on the hormonal stress responses which develop as a result of surgical traumas are still unclear [12].

Sympathetic adrenergic response to surgical stimuli clinically manifests itself as hypertension, increased heart rate and body temperature [1]. Opioids suppress sympathetic adrenergic response [1, 10]. However, intravenous or volatile anesthetic agents have not been able to suppress this response [22]. Segawa *et al*. [22] investigated the effects of sevoflurane and isoflurane at different concentrations on adrenaline and noradrenalin levels in blood during liver transplantations. The reduction of blood pressure increase due to surgical stimulation with volatile anesthetic agents was reported to be the result of suppression of the effects of catecholamines on vascular smooth muscles and myocardium [22].

Ura *et al*. [23] studied serum noradrenalin levels in patients who received sevoflurane anesthesia at different concentrations to determine the concentration of sevoflurane that could prevent the adrenergic response to surgical incision and the increase in mean arterial pressure.

Stress hormone levels in blood have been reported to suddenly increase up to 10 to 100 times of normal levels due to endotracheal intubation and surgical stimulation and gradually decrease to baseline levels within hours or days [24, 25]. Murakawa *et al*. [26] investigated the effects of sevoflurane anesthesiaon serum cortisol levels in gastrointestinal and gynecological surgeries. They found that there was no change in serum cortisol levels after anesthesia induction with sevoflurane, but cortisol levels increased 2-3 times of the pre- anesthetic levels during and after surgery [26]. We also found a rapid increase in ACTH, cortisol, and

prolactin levels during surgery, reaching 6-7 times of pre-anesthetic levels in both groups in our study.

Roth-Isigkeit *et al*. [27] reported that plasma ACTH and cortisol levels increased during the study in patients who underwent coronary artery bypass graft surgery. They found that while ACTH levels decreased to baseline levels after 24 to 48 hours postoperatively, cortisol levels remained significantly higher at 72 hours in postoperative period compared to preoperative period. In our study, we also found that cortisol levels were significantly higher at the 24th postoperative hour compared to baseline levels in both groups. However, ACTH levels were returned to their baseline levels at the 12th postoperative hour in both groups.

Hase *et al*. [25] studied the effects of isoflurane and sevoflurane, with combination of epidural anesthesia during the gastric surgery in elderly patients. They looked at the ACHT, cortisol, adrenaline and noradrenaline levels during and after surgery. They found that there was no statistically significant difference between the two groups. Marana *et al*. [28] compared TIVA with propofol versus sevoflurane anesthesia. TIVA inhibited ACTH-cortisol axis and reduced NE, E and GH levels but it enhanced prolactin as compared with sevoflurane.

Marane *et al.* [29] compared the effects of desflurane versus sevoflurane anesthesia on intra and postoperative release of the stress hormones and inflammatory cytokines in laparoscopic surgery. Although a decrease in cortisol concentration level was observed in both groups, only in the DES group there was a significant difference in intraoperative cortisol levels as compared to the baseline levels. The consequent increase of ACTH level was significantly higher in the SEVO group at 30 minutes after the beginning of surgery and at 4 hours after the end of surgery. They concluded that desflurane and sevoflurane produced a different stress response in the setting of laparoscopic surgery [29]. In our study, there was no statistical differencebetween isoflurane and sevoflurane group in terms of hormone levels. The surgical stress levels are known to be relatively lower in laparoscopic surgeries compared to intracranial tumor surgeries.

Krog's study [30] showed that Cortisol and ACTH levels are statistically lower in laparoscopic aorta-bifemoral bypass group than open aorta-bifemoral bypass group. The patients operated with a laparoscopic aorta-bifemoral bypass achieved earlier hormonal homeostasis after surgery compared to open group [30]. Minimally invasive surgery seems to reduce hormonal stress response to surgery.

There are few comparative studies of stress hormone changes during long surgeries under general anesthesia. Nishiyama *et al*. [31] showed that isoflurane-nitrous oxide and sevoflurane-nitrous oxide had the same effects on stress hormone changes except for epinephrine, norepinephrine, and ADH levelsduring inhalation anesthesia with the duration of more than 10 hours. We also found that there were no statistically significant differences in ACTH, cortisol and prolactin levels in blood; before, during and after the surgery between the two groups. We think that our results might have been affected because intracranial tumor surgery are longer and highly stressful operations.

Miura *et al*. [24] administered isoflurane, ketamine and fentanyl - N_2O anesthesia to the rats with incomplete cerebral ischemia and looked at noradrenalin levels in the carotid and hippocampus. They found that the noradrenalin levels in blood and brain were changed independently of each other and the anesthesia method [24]. Partial ischemia may occur during intracranial mass surgery. Depending on the localization of the tumor, this can lead to changes in the secretion of the hypophyseal hormones. In our study, we found a very high ACTH level in one patient during tumor removal in sevoflurane group (Fig. 4). We attributed this to the tumor localization and therefore the surgical field's closeness to the pituitary gland.

Mustolo *et al*. [32] compared the effects of sevoflurane-fentanyl and isoflurane-fentanyl on the surgical stress index. They found that surgical stress index was higher in sevoflurane-fentanyl group.

Limitations

The limitation of our study was relatively small number of patients the power analyze. In our study we used special laboratory kit. Because of our limited financial resource we could not Increase the number of patients. Thus more patients needed in future studies to confirm our results.

CONCLUSION

As a result, isoflurane or sevoflurane anesthesia

has similar effects in terms of hemodynamic and hormonal stress response during intracranial tumor surgery.

Authors' Contribution

Study Conception: ŞGK; Study Design: ŞGK; Supervision: ŞGK; Funding: ŞGK; Materials: HES; Data Collection and/or Processing: VME; Statistical Analysis and/or Data Interpretation: HES; Literature Review: HES; Manuscript Preparation: VME and Critical Review: HES.

Conflict of interest

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

Financing

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

REFERENCES

1. Breslow MJ. Clinical Implications of the stress response to surgery. In: Rogers, MC., Tinker, JH., Covino, BG., Longnecker D, ed. Principles and Practice of Anesthesiology. 2nd. Mosby; 1998:103-120.
2. Chi OZ, Choi YK, Lee DI, Kim YS, Lee I. Intraoperative mild hypothermia does not increase the plasma concentration of stress hormones during neurosurgery. Can J Anaesth 2001;48:815-8.
3. Galley HF, DiMatteo MA, Webster NR. Immunomodulation by anaesthetic, sedative and analgesic agents: does it matter? Intensive Care Med 2000;26:267-74.
4. Torri G. Inhalation anesthetics: a review. Minerva Anestesiol 2010;76:215-28.
5. Milde LN. Cerebral protection. In: Cucchiara RF, Black S, Mchenfelder JD (eds.). Clinical Neuroanesthesia. New York: Churchill Livingstone, 1998: pp.177-228.
6. Yörükoğlu D. Tümör cerrahisinde anestezi. In: Kecik Y, ed. Nöroanestezi. 1. Baskı. Ankara: Atlas Yayıncılık; 2000:171-198.
7. Kehlet H. The surgical stress response: should it be prevented? Can J Surg 1991;34:565-7.
8. Chrousos GP. The role of stress and the hypothalamic–pituitary–adrenal axis in the pathogenesis of the metabolic syndrome: neuro-endocrine and target tissue-related causes. Int J Obes 2000;24:S50-5.
9. Aono H, Takeda A, Tarver SD, Goto H. Stress responses in three different anesthetic techniques for carbon dioxide laparoscopic cholecystectomy. J Clin Anesth 1998;10:546-50.
10. Desborough JP. The stress response to trauma and surgery. Br J Anaesth 2000;85:109-17.
11. Besnier E, Clavier T, Compere V. The hypothalamic-pituitary-adrenal axis and anesthetics: a review. Anesth Analg. 2017;124:1181-9.
12. Marana E, Annetta MG, Meo F, Parpaglioni R, Galeone M, Maussier ML, et al. Sevoflurane improves the neuroendocrine stress response during laparoscopic pelvic surgery. Can J Anesth 2003;50:348-54.
13. Naito Y, Tamai S, Shingu K, Shindo K, Matsui T, Segawa H, et al. Responses of plasma adrenocorticotropic hormone, cortisol, and cytokines during and after upper abdominal surgery. Anesthesiology 1992;77:426-31.
14. Liu S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia: their role in postoperative outcome. Anesthesiology 1995;82:1474-506.
15. Weissman C. The metabolic response to stress: an overview and update. Anesthesiology 1990;73:308-27.
16. Geze S, Yilmaz AA, Tuzuner F. The effect of scalp block and local infiltration on the haemodynamic and stress response to skull-pin placement for craniotomy. Eur J Anaesthesiol 2009;26:298-303.
17. Kendrišić M, Šurbatović M, Djordjević D, Trifunović B, Jevdjić J. Analgesic efficacy and safety of four different anesthesia/postoperative analgesia protocols in patients following total hip arthroplasty. Vojnosanit Pregl 2017;74:814-20.
18. Scherpereel P. Endocrine, Immune and Metabolic stress responses to surgery. In: XXXVIII.Türk Anesteziyoloji ve Reanimasyon Kongresi-2004 Özet Kitabı. 2004:234-235.
19. Wang XW, Cao JB, Lv BS, Mi W, Wang Z, Zhang C, et al. Effect of perioperative dexmedetomidine on the endocrine modulators of stress response: a meta-analysis. Clin Exp Pharmacol Physiol 2015;42:828-36.
20. Kain ZN, Zimolo Z, Heninger G. Leptin and the perioperative neuroendocrinological stress response. J Clin Endocrinol Metab 1999;84:2438-42.
21. Goto Y, Ho SL, McAdoo J, Fanning NF, Wang J, Redmond HP, et al. General versus regional anaesthesia for cataract surgery: effects on neutrophil apoptosis and the postoperative pro-inflammatory state. Eur J Anaesthesiol 2000;17:474-80.
22. Segawa H, Mori K, Murakawa M, Kasai K, Shirakami G, Adachi T, et al. Isoflurane and sevoflurane augment norepinephrine responses to surgical noxious stimulation in humans. Anesthesiology 1998;89:1407-13.
23. Ura T, Higuchi H, Taoda M, Sato T. Minimum alveolar concentration of sevoflurane that blocks the adrenergic response to surgical incision in women: MAC(BAR). Eur J Anaesthesiol 1999;16:176-81.
24. Miura Y, Mackensen GB, Nellgård B, Pearlstein RD, Bart RD, Dexter F, et al. Effects of isoflurane, ketamine, and fentanyl/N2O on concentrations of brain and plasma catecholamines during near-complete cerebral ischemia in the rat. Anesth Analg 1999;88:787-92.
25. Hase K, Meguro K. Perioperative stress response in elderly patients for elective gastrectomy -The comparison between isoflurane anesthesia and sevoflurane anesthesia both combined with epidural anesthesia. Japanese J Anesthesiol 2000;49:128-9.
26. Murakawa T, Tsubo T, Ogasawara H, Takahashi S, Kudo T, Matsuki A. Plasma cortisol levels during abdominal surgery under sevoflurane anesthesia: comparison between gastrointesti-

nal and gynecological surgery. Japanese J Anesthesiol 1990;39:723-7.
27. Roth-Isigkeit AK, Schmucker P. Postoperative dissociation of blood levels of cortisol and adrenocorticotropin after coronary artery bypass grafting surgery. Steroids 1997;62:695-9.
28. Marana E, Colicci S, Meo F, Marana R, Proietti R. Neuroendocrine stress response in gynecological laparoscopy: TIVA with propofol versus sevoflurane anesthesia. J Clin Anesth 2010;22;250-5.
29. Marana E, Russo A, Colicci S, Polidori L, Bevilacqua F, Viviani D, et al. Desflurane versus sevoflurane: a comparison on stress response. Minerva Anestesiol 2013;79:7-14.
30. Krog AH, Thorsby PM, Sahba M, Pettersen EM, Sandven I, Jørgensen J, et al. Perioperative humoral stress response to laparoscopic versus open aortobifemoral bypass surgery. Scand J Clin Lab Invest 2017;77:83-92.
31. Nishiyama T, Yamashita K, Yokoyama T. Stress hormone changes in general anesthesia of long duration: Isoflurane-nitrous oxide vs sevoflurane-nitrous oxide anesthesia. J Clin Anesth 2005;17:586-91.
32. Mustola S, Parkkari T, Uutela K, Huiku M, Kymäläinen M, Toivonen J. Performance of surgical stress index during sevoflurane-fentanyl and isoflurane-fentanyl anesthesia. Anesthesiol Res Pract 2010;2010:810721.

The European Research Journal 2021;7(2):152-158 Original Article

DOI: 10.18621/eurj.603491 *Microbiology*

Optimization of culture conditions for antibacterial substance production from newly isolated *Brevibacillus laterosporus* EA62

Elif Demirkan, Aynur Aybey, Alev Usta Ak

Department of Biology, Bursa Uludağ University, Faculty of Arts and Sciences, Bursa, Turkey

ABSTRACT

Objectives: In the present study, it was reported the effects of some nutritional (amino acid, carbon, nitrogen and metal sources) and physical factors (pH and temperature) on antibacterial substance activity of *Brevibacillus laterosporus* EA62.

Methods: The agar well diffusion assay was performed to evaluate the antibacterial activity of the substance. The antibacterial activity of the new substance was examined against four pathogenic bacteria under different nutritional and physical conditions.

Results: The best antibacterial activity was obtained in modified medium consists of the 5% glucose, 0.1% tryptone, 0.05% MgSO4 + CaCO3 and 0.5% glutamic acid. For physical parameters, maximal activity was observed after 72 h when incubated at 37°C, pH 7.0.

Conclusions: This study indicates that Brevibacillus laterosporus EA62 could be an important source of antibacterial substances under this medium optimization.

Keywords: This study indicates that *Brevibacillus laterosporus* EA62 could be an important source of antibacterial substances under this medium optimization.

Antibiotics are chemicals which kill or inhibit the growth of bacteria or fungi, and can be used to treat infections by these organisms. Antibiotics are the one of the most important commercially exploited secondary metabolites produced by bacteria, fungi and Streptomyces and employed in a wide range. In recent years, soil bacteria have been investigated in terms of antibiotic production potential. The soil is a natural source for microorganisms and their antimicrobial products [1]. Soil bacteria and fungi have played a significant and an important role in antimicrobial product discovery. The selection of natural antimicrobial products from soil microorganisms is considered as analternative method for the disease control and plant protection. Considerable research is being done in order to find new antimicrobial producing bacteria isolated from soil and their active substances [2, 3]. Several classes of antimicrobial substances that inhibit the growth of fungi and bacteria in vitro assays have been identified in the last decades [4].

Brevibacillus is omnipresent in agricultural soils, and it can secrete structurally diverse secondary metabolites with broad antibiotic spectra. Some of these metabolites, such as chitinaseand gramicidin S, have been extensively studied, and numerous *Brevibacillus* species, which have the potential as antimicrobial agents, have become research hotspots in the recent years [5]. *Brevibacillus laterosporus* can pro-

Received: ***August 7, 2019;*** *Accepted:* ***September 26, 2020;*** *Published Online:* ***January 5, 2021***

How to cite this article: *Demirkan E, Aybey A, Usta A. Optimization of culture conditions for antibacterial substance production from newly isolated Brevibacillus laterosporus EA62. Eur Res J 2021;7(2):152-158. DOI: 10.18621/eurj.603491*

Address for correspondence: *Elif Demirkan, PhD., Professor, Bursa Uludağ University, Faculty of Arts and Sciences, Department of Biology, Bursa, Turkey. E-mail: edemirkan@uludag.edu.tr*

e-ISSN: 2149-3189

duce different virulence factors: parasporal crystalline [6], extracellular protease [7] and lipopeptide antibiotics [8]. Additionally, *B. laterosporus* also secretes short sequencepeptides with broad antibiotic spectra, such as loloatin A [9]; however, these metabolites have not been extensively studied.

The number of multi-drug resistant bacterial strains has increased, partly due to the misuse of antibiotics, resulting in serious health challenges in hospital settings. Thus, the discovery of new potential antibacterial substance producing microorganisms has become an important goal. Many species, such as *Streptomyces, Bacillus* and *Penicillium* have been studied continuously for their ability to produce antibiotics [10]. Environmental factors such as pH, temperature and medium composition can influence the production of antagonistic substances from bacteria. Several reports have been discussed regarding antibacterial components, its optimizing by altering several physical factors and medium composition [11-13]. In the present study, it has been optimized nutritional and physical parameters to produce for antibacterial substance of *B. laterosporus* EA62.

METHODS

Bacterial Strains and Growth Conditions

B. laterosporus EA62 which was isolated and identified by 16S rRNA gene analysis in the previous study, was used in the current study [14]. Basal growth medium was consisted of 15 g/L glucose, 1 g/L yeast extract, 0.5 g/L MgSO4, 3 g/L CaCO3 and 0.5 g/L (NH4)2HPO4 at pH 7.0. The overnight cultures adjusted 108 CFU/ml were inoculated at 10% in 150 mL of basal media and incubated at 37 °C at 150 rpm for 72 h [14]. After incubation, samples were filtered through a 0.22 µm filter, and the filtrate as antibacterial substance was subsequently used to determine the effects of nutritional and physical parameters on antibacterial substance activity against some pathogenic Gram-negative *Yersinia enterocolitica* (ATCC 9610) and *Salmonella typhimurium* (ATCC 14028) the Gram-positive bacteria, *Staphylococcus aureus* (ATCC 25923) and *Enterococcus faecalis* (ATCC 29212) by using agar well diffusion assay [15].

Effects of Different Nutritional and Physical Parameters on Production of Antibacterial Substance

Carbon sources including sucrose, maltose, potato starch and wheat bran (1.5% w/v), nitrogen sources including organic (corn step liquor, tryptone and skim milk at 0.1% w/v) and inorganic sources ((NH4)2NO3 and (NH4)2SO3 at 0.05% w/v) were evaluated for their effect of antibacterial substance activityin basal medium. In addition, amino acids including alanine, phenylalanine, valine, tyrosine, lysine, histidine, cystine, arginine, glutamic acid (0.5% w/v) were tested to obtain the best amino acid. The culture medium was supplemented with metal ions such as CaCl2, FeSO4, LiSO4, NaCl, CaCO3, MgSO4, and MnSO4 (0.05% w/v)in basal medium.

Antibacterial substance (grown in basal medium for 72 h) was exposed to various temperatures. Sterile filtered antibacterial substances were incubated for 15-30 min at 30, 40, 45, 50 and 55 °C at the optimal pH of 7.0 and then immediately cooled in ice water. A control was maintained by incubating antibacterial substances at 37 oC. For optimizing pH, different pH was estimated by adjusting pH of antibacterial substances to the 4.0 to 9.0. After incubation for 1 h and before plating for antibacterial activity, pH treated samples were neutralized pH 6.5-7 to determine the antibacterial substance activity.

Statistical Analysis

For statistical analysis, the standard deviation for each experimental result and student's t-test were calculated using Microsoft Excel. All of the assays were carried out in triplicate. The bars correspond to standard deviation [16].

RESULTS

In this study, it was carried out to determine the antibacterial substance activity of *B. laterosporus* EA62 by assessing the effect of nutritional and physical conditions. The isolate was inoculated in basal medium and incubated at 37oC for 72 h; the filtered supernatant as antibacterial substance wasused to determine the antibacterialactivity against *Y. enterocolitica, S. typhimurium, S. aureus* and *E. faecalis* under various nutritional and physical conditions.

The basal medium was optimized with different carbon and nitrogen sources, metal ions and amino acids.

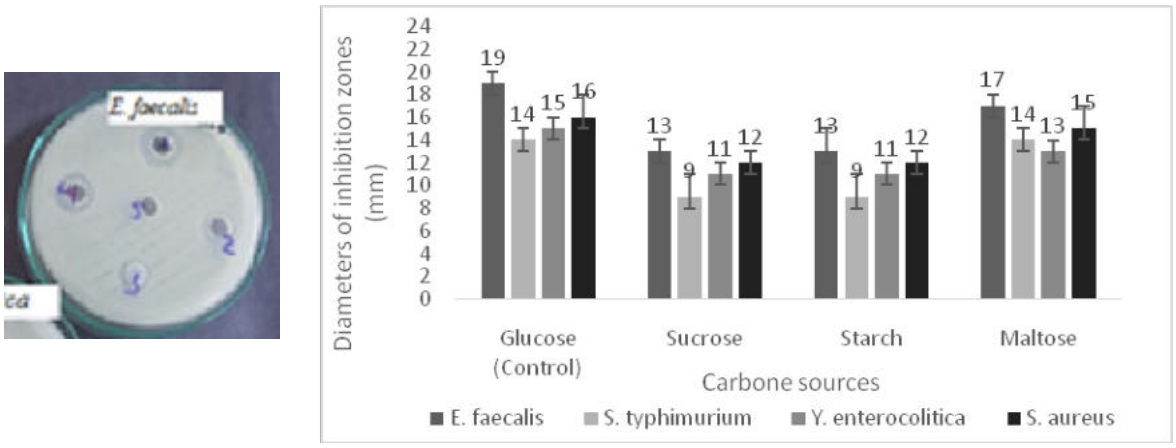


Fig. 1. Effect of different carbon sources on the production of antibacterial substance against pathogens. 1-Glucose, 2-Sucrose, 3-Starch, 4-Maltose, 5-Wheat bran on petri dish.

Among the different carbon and nitrogen sources studied, addition of glucose (Fig.1) and tryptone (Fig. 2) to the basal medium showed highest antibacterial activity against *E. faecalis*. Our data showed that glucose (19 mm) followed maltose (17 mm) against *E. faecalis* and glucose (16 mm) followed maltose (15 mm) against *S. aureus* enhanced the antimicrobial activity. No antibacterial activity was observed using wheat bran (Fig. 1). The production of antibacterial substance was repressed by wheat bran.

Among nitrogen sources, higher antibacterial activity was achieved when tryptone (20 mm) and yeast extract (19 mm) against *E. faecalis* used as a nitrogen source followed tryptone (17 mm) and yeast extract (17 mm) against *S. typhimurium*. In this study, yeast extract and tryptone alone appeared more efficient at the activity of the antibacterial substance and antibacterial activity was not observed in the presence of skim milk as organic nitrogen source.

Some amino acids were tested in the basal medium to determined inhibitory effects of the antibacterial substance in this study. Glutamic acid has the most effective amino acid on antibacterial substance activity against all bacteria tested, while valine and arginine has the least, phenylalanine and cysteine resulted in no antibacterial substance activity (Fig. 3). Maximum zone of inhibition in basal medium containing glutamic acid was observed against *S. aureus* (19 mm) followed bylisine (17 mm) and alanine (17 mm) against *E. faecalis*.

In this study, a small effect was only observed for MgSO4 and MgSO4+CaCO3 combination among the metal ions, no antibacterial activity was obtained in the presence of the others (Fig. 4). Results showed that a synergistic effect of MgSO4 and CaCO3 on the antibacterial substance activity occurred and antibacter-

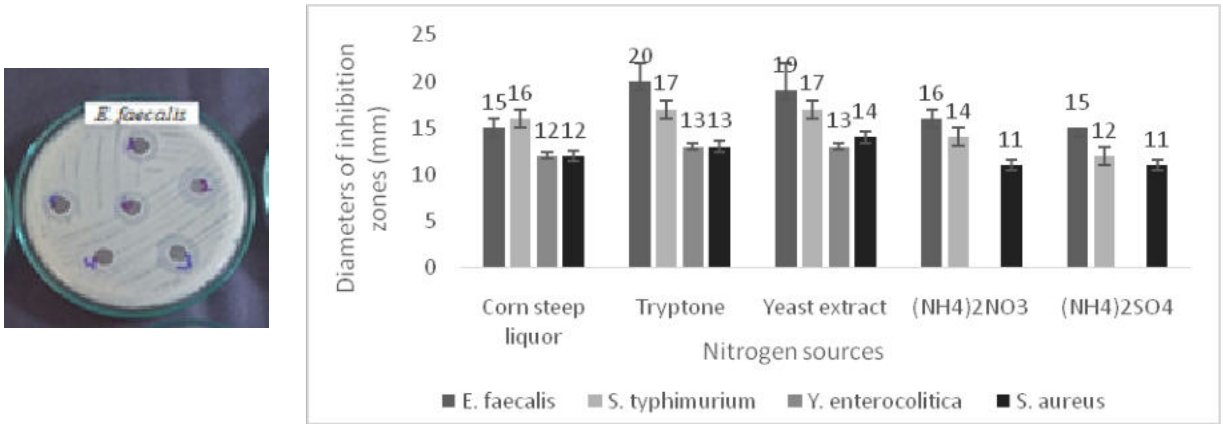


Fig. 2. Effect of different nitrogen sources on the production of antibacterial substance against pathogens. 1-Corn steep Liquor, 2-Tryptone, 3-Yeast extract, 4-Skim milk, 5-(NH4)2NO3, 6-(NH4)2SO3on petri dish.

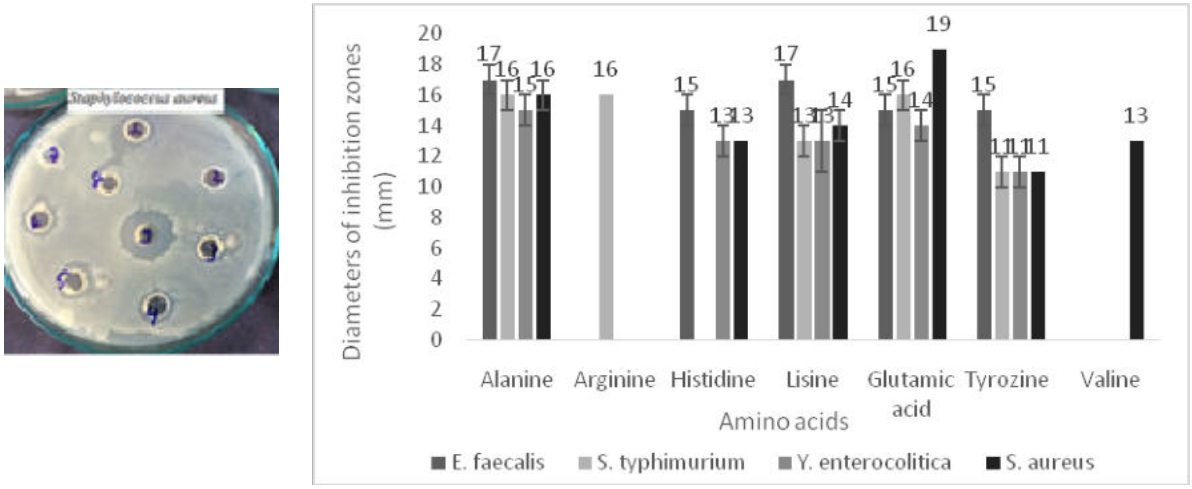


Fig. 3. Effect of different amino acid sources on the production of antibacterial substance against pathogens. 1-Alanine, 2-Phenylalanine, 3-Valine, 4-Tyrosine, 5-Lysine, 6-Histidine, 7-Cystine, 8-Arginine, 9-Glutamic acid on petri dish.

ial activity was considerably decreased when metal ion sources alone were used. Maximal inhibitory zones were determined in presence of MgSO4 (15 mm) against *E. faecalis* and combination with CaCO3 (19 mm) was increased the antibacterial activity against all tested pathogens while CaCO3 alone had no effect.

The effect of different temperature and pH on antibacterial substance activity have been outlined in Figure 5. Treatment of antibacterial substance at 30, 37, 40, 50, 55°C did not show significant from the control. The maximum antibacterial substance activity was obtained at 37 °C as control against *Y. enterocolitica* (17 mm), although 40 °C was also effective at promoting antibacterial activity, as the observed inhibition zone was 15 mm against *S. typhimurium.*

Generally, the maximum activity was obtained at an initial pH of 7.0. At lower and higher pH values were reduced the antibacterial substance activity. The highest zone of inhibition was obtained for *Y. enterocolitica* (17 mm) at pH 7.0 and the lowest *E. faecalis* and *Y. enterocolitica* (11 mm) at pH 4.0, *E. faecalis* and *Y. enterocolitica* (10 mm) at pH 9.0. No zone of inhibition was recorded below pH 4.0 and above pH 9.0.

Modified medium determined for each bacterial strainswas found different. But the best results for each parameters were selected to determine modified medium. According to these results, the maximum production of antibacterial substance was obtained in-optimized medium (consisted of 1.5% glucose, 0.1% of tryptone, 0.05% of MgSO4 +CaCO3 and 0.5% glutamic acid at pH 7.0).

The production of antimicrobial substance in the modified medium showed a slight increase compared to each test bacteria according to the control medium (Table 1). An increase of 17% for *S. typhimurium,* 5%

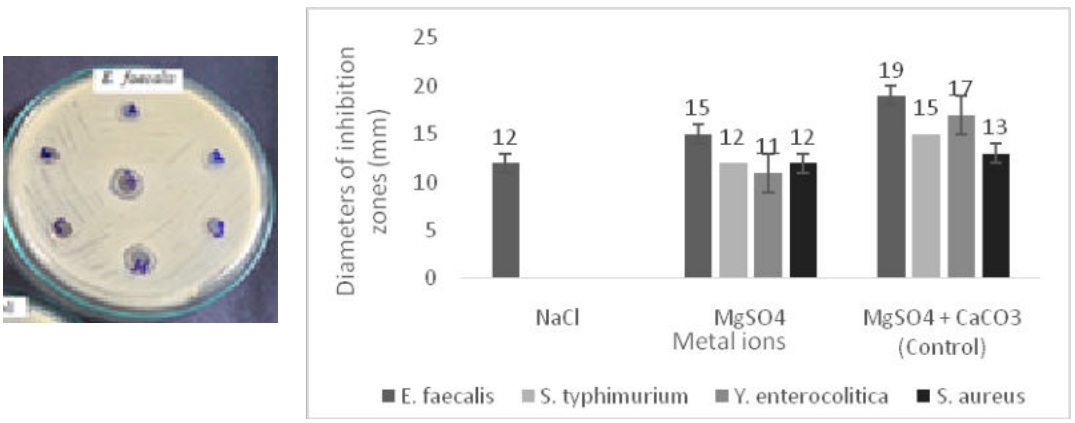


Fig. 4. Effect of different metal ions on the production of antibacterial substance against pathogens. 1-CaCl2, 2-FeSO4, 3.LiSO4, 4-NaCl, 5-KCl,6.MnSO4, 7-MgSO4 on petri dish.

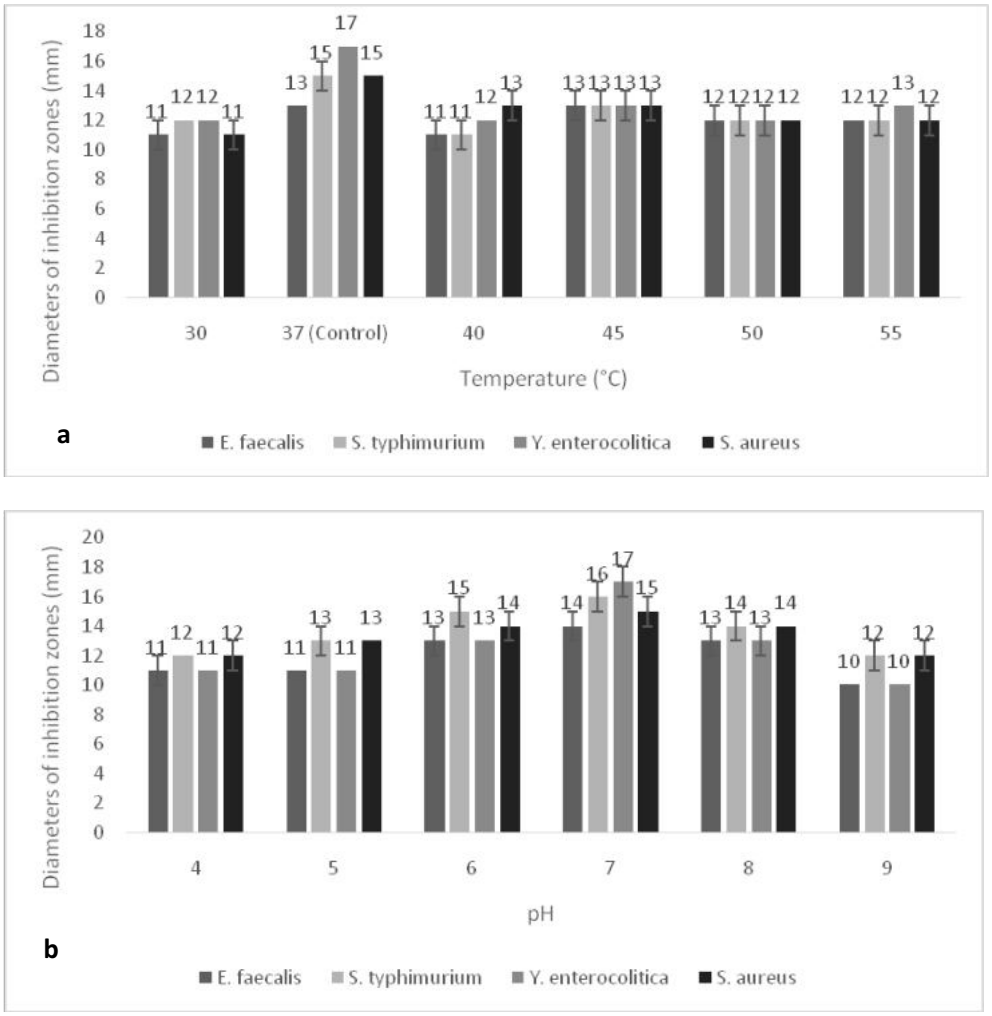


Fig. 5. Effect of temperatures (a) and pH (b) on antibacterial substance activity against pathogens.

for *Y. enterocolitica*, 6% for *S. aureus,* and 7% for *E. faecalis* was found.

DISCUSSION

Prior knowledge and experience in developing a suitable basal medium play a significant role in the further media optimization [17]. The optimization of various physical and nutritional growth parameters caused an increase in the antibacterial substance activity; the important physical factors that determine the bioprocess are temperature, pH, agitation, inoculum size and inoculum age [18]. In a previous study,

Table 1. Comparison of antibacterial substance acitivity in modified and basal medium against bacteria tested

Bacterial Strains	Inhibition zones in control medium (mm)	Inhibition zones in modified medium (mm)
Salmonella typhimurium	17 ± 2	20 ± 1
Yersinia enterocolitica	17 ± 1	18 ± 2
Staphylococcus aureus	15 ± 2	16 ± 1
Enterococcus faecalis	13 ± 1	14 ± 2

Data are given as mean ± standard deviation

it was observed that the antibacterial substance showed inhibitory activity against the test pathogens (Gram-negative Y. enterocolitica (ATCC 9610) and S. *typhimurium* (ATCC 14028) the Gram-positive bacteria, *S. aureus* (ATCC 25923) and *E. faecalis* (ATCC 29212). Maximum zone of inhibition was observed against *S. aureus* (19 mm) followed by *Y. enterocolitica* (17 mm) [14]. Therefore, in this study, the effects of nutritional and physical parameters were investigated for the production of antibacterial substance from *B. laterosporus* EA62.

Different carbon sources, such as maltose [19], dextrose [20], arabinose [21], fructose [22], and mannitol [23] have been reported to be suitable for the activity of antibiotic substances in different microorganisms. In this study, among the different carbon sources studied, addition of glucose to the basal medium showed highest antibacterial activity against all bacteria tested. In addition, the antagonistic activity of bacteriocinas an antimicrobial substance was also increased when glucose was added to the medium in a previous studies [24, 25]. Some studies have reported that organic or inorganic nitrogen sources influence enzyme activity. It was previously reported that antimicrobial activity was considerably decreased when nitrogen sources alone were used in the fermentation media [22]. In present study, higher antibacterial substance activity was achieved when tryptone and yeast extract against all bacteria tested used as a nitrogen source. Similar results were observed for antibiotic activity in batch cultures of *Bacillus laterosporus* ST-1 when grown in the presence of yeast extract in glucose broth [26]. In addition, inhibitory effect of antibacterial substance was only observed for MgSO4 and MgSO4 + CaCO3 combination among the metal ions, no antibacterial activity was obtained in the presence of the others. The addition of MgSO4increased iturin A activity by *Bacillus amyloliquefaciens* B128 [27, 28], indicating that that rare earth metals and trace metals, notably manganese, zinc and iron, may trigger the activity of various secondary metabolic pathways.The use of amino acids as nitrogen sources can inhibit the synthesis of secondary metabolites [29]. Therefore, some amino acids were tested in the basal medium to determined inhibitory effects of the antibacterial substance in this study and glutamic acid has found as the most effective amino acid on antibacterial substance activity against all bacteria tested while phenylalanine and cysteine showed no inhibitory effects on antibacterial substance production.

The effect of different temperature and pH on antibacterial substance activity was also determined and maximum antibacterial substance activity was found at 37 °C and pH 7.0 against all bacteria tested. A similar result for temperature was previously reported, but the antibiotic showed maximum activity at pH 8.0 [30]. Although the maximum antibiotic activity occurred at a low temperature (30 °C) and at pH 7.0 [26], antibiotic activity was achieved at temperatures as high as 40 °C and at pH 7.0 [31].

CONCLUSION

In summary, this is a novel antibacterial substance from the soil microorganism, *Brevibacillus laterosporus* EA62, and it is active against some important gram negative and positive pathogens. The effects of nutritional and physical parameters on antibacterial substance activity were examined. The amtibacterial substance produced by EA62 may be potential applications for the pharmaceutical industry and could be a promising candidate for infection diseases after purified and characterized in the near future.

Authors' Contribution

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

Conflict of interest

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

Financing

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

REFERENCES

1. Dancer SJ. How antibiotics can make us sick: The less obvious

adverse effects of antimicrobial chemotherapy. Lancet Infect Dis 2004;4:611-9.
2. Courtis S, Cappellano C, Ball M, Francois F, Helynck F, Martizez A, et al. Recombinant environmental libraries provide access to microbial diversity for drug discovery from natural products. Appl Environ Microbiol 2003;69:49-55.
3. Viscardi M, Perugini AG, Auriemma C, Capuano F, Morabito S, Kim KP, et al. Isolation and characterisation of two novel coliphages with high potential to control antibiotic-resistant pathogenic Escherichia coli (EHEC and EPEC). Int JAntimicrob Agents 2008;31:152-7.
4. Wang J, Haddad NI, Yang SZ, Mu BZ. Structural characterization of lipopeptides from Brevibacillus brevis HOB1. Appl Biochem Biotechnol 2010;160:812-21.
5. Mogi T, Kita K. Gramicidin S and polymyxins: the revival of cationic cyclic peptide antibiotics. Cell Mol Life Sci 2009;66:3821-6.
6. Smirnova TA, Minenkova IB, Orlova MV, Lecadet MM, Azizbekyan RR. The crystal-forming strains of Bacillus laterosporus. Res Microbiol 1996;147:343-50.
7. Huang X, Tian B, Niu Q, Yang J, Zhang L, Zhang K. An extracellular protease from Brevibacillus laterosporus G4 without parasporal crystals can serve as a pathogenic factor in infection of nematodes. Res Microbiol 2005;156:719-27.
8. Desjardine K, Pereira A, Wright H, Matainaho T, Kelly M, Andersen RJ. Tauramamide, a lipopeptide antibiotic produced in culture by Brevibacillus laterosporus isolated from a marine habitat: structure elucidation and synthesis. J Nat Prod 2007;70:1850-3.
9. Krachkovskii SA, Sobol AG, Ovchinnikova TV, Tagaev AA, Yakimenko ZA, et al. Isolation, biological properties, and spatial structure of antibiotic loloatin A. Russ J Bioorg Chem 2002;28:269-73.
10. Usta Ak A, Demirkan E. The effect of growth parameters on the antibiotic activity and sporulation in Bacillus spp. isolated from soil. J Microbiol Biotech Food Sci 2013;2:2310-3.
11. Parente E, Ricciardi A, Addario G. Influence of pH on growth and bacteriocin production by Lactococcuslactis subsp. lactis 140NWC during batch fermentation. Appl Microbiol Biotechnol 1994;41:388-94.
[12] Moortvedt-Abildgaard CI, Nissen-Meyer J, Jelle B, Grenov B, Skaugen M, Nes IF. Production and pH-dependent bactericidal activity of lactocin S, a lantibiotic from Lactobacillus sake L45. Appl Environ Microbiol 1995;61:175-9.
13. Jose PA, Sivakala KK, Jebakumar SRD. Formulation and statistical optimization of culture medium for improved activity of antimicrobial compound by Streptomyces sp. JAJ06. Int J Microb 2013;1-9.
14. Usta Ak A, Demirkan E, Cengiz M, Sevgi T, Zeren B, Abdou M. Optimization of culture medium for the production and partial purification and characterization of an antibacterial activity from Brevibacillus laterosporus Strain EA62. Rom Biotechnol Lett 2019;24:705-13.
15. Wang H, Lu Y, Zhang X, Hu Y, Yu H, Liu J, et al. The novel antimicrobial peptides from skin of Chinese broad-folded frog, Hylaranalatouchii (Anura:Ranidae). Peptides 2009;30:273-82.
16. Kavanagh F. Analytical Microbiology. Vol. 2. New York: Ahead Press, 1972.
17. Jia B, Jin ZH, Mei LH. Medium optimization based on statistical methodologies for pristinamycins production by Streptomyces pristinaespiralis. Appl Biochem Biotechnol 2008;144:133-43.
18. Ashokkumar B, Kayalvizhi N, Gunasekaran P. Optimization of media for β fructofuranosidase production by Aspergillus nigerin submerged and solid state fermentation. Process Biochem 2001;37:331-8.
19. Singha P,Roymon MG. Antibiotic potential of soil actinomycetes under influence of physical and nutritioial parameters. Indian J Sci Res 2017;13:203-7.
20. Linda H, Al-Ghazali R. Omran. Optimızation of medium composition for antibacterial metabolite activity from Streptomyces sp.Asian J Pharm Clin Res 2017;10:381-5.
21. Kadiri SK,Yarla NS. Optimization of antimicrobial metabolites activity by Streptomyces fradiae. Int J Pharm Sci 2016;7:223-5.
22. Kumar SN, Siji JV, Ramya R, Nambisan B, Mohandas C. Improvement of antimicrobial activity of compounds produced by Bacillus sp. associated with a Rhabditid sp. (entomopathogenıc nematode) by changing carbon and nitrogen sources in fermentation media. J Microbiol Biotech Food Sci 2012;1:1424-38.
23. Abdelghani T. Activity of antibacterial and antifungal metabolites by (S.albovinaceus) strain no.10/2 and media optimization.AmInt J Bio 2017;5:1-24.
24. Ekhay O, Ouhsassi M, Abdeltif EH, Idaomar M, Abrini J. Optimization of bacteriocin-like production by Enterococcus durans E204 isolated from camel milk of Morocco. Curr Res Microbiol Biotechnol 2013;1:155-9.
25. Todorov SD. Bacteriocin production by Lactobacillus plantarum AMA-K isolated from Amasi, a zimbabwean fermented milk product and study of the adsorption of bacteriocin AMA-K to Listeria sp. Braz J Microbiol 2008;39:178-87.
26. Kalpana S, Bagudo AI, Aliero AA. Effect of inhibitory spectrum and physical conditions on the activity of antibiotic substance from B. laterosporus ST-1. Niger J Microbiol 2010;24:2134-9.
27. Lin HY, Rao YK, Wu WS, Tzeng YM. Ferrous ion enhanced lipopeptide antibiotic iturin A activity from Bacillus amyloliquefaciens B128. Int J Appl Sci Eng 2007;5:123-32.
28. Ochi K, Hosaka T. New strategies for drug discovery: activation of silent or weakly expressed microbial gene clusters. Appl Microbiol Biotechnol 2013;97:87-98.
29. Martin JF, Demain AL. Fungal development and metabolite formation. In: The Filamentous Fungi. Eds. Smith JE, Berry DR, Arnold, London. 1978;3:426-50.
30. Bisht SS, Praveen B, Panda A, Rajakumar V. Isolation, purification and characterization of bacitracin from Bacillus sp. Int J Pharm Sci 2011;3:136-8.
31. Joshi RD, Hamde VS, Umrikar AM, Kulkarni SS, Bhate MA. Studies on activity of peptide antibiotic by thermotolerant Bacillus sp. Int Multidis Res J 2012;2:30-3.

The European Research Journal 2021;7(2):159-169 Original Article

DOI: 10.18621/eurj.775245 *Cardiology*

Features of patients with premature ventricular complex ablation: a tertiary referral center experince

Ahmet Tütüncü[1], Erhan Yılmaz[2]

[1]Department of Cardiology, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey
[2]Department of Cardiology, Bursa Orhangazi State Hospital, Bursa, Turkey

ABSTRACT

Objectives: In patients who do not respond to medical treatment with idiopathic premature ventricular complex (PVC), catheter ablation is performed using the electroanatomic mapping (3D EAM) system for ablation. The aim of this study is to evaluate the acute and long-term success of patients and the procedural features and complication results associated with PVC localization in patients who underwent catheter ablation in our center.

Methods: Two hundred seventeen patients who underwent activation mapping and ablation using 3D EAM for PVC were included in the study. Patients were followed up for acute procedure success, periprocedural complications, and six-month long-term recurrence. In addition, these parameters, PVC's were evaluated in three groups as right ventricular outflow tract (RVOT), coronary cusp and rare localized origin, and clinical outcomes and interventional variables related to the success of the PVC's location were compared.

Results: In our study, the mean age of the patients was 43 ± 12.1 years and the female gender ratio was 37.8%. When catheter ablated PVC foci were evaluated, it is seen that 81 (37.3%) were from RVOT and 56 (25.8%) were from coronary cusp. In addition, 6 (2.8%) were aortomitral continuity, 22 (10.1%) were left ventricular summit/epicardial, 17 (7.8%) were parahisian, and total 80 (36.8%) were rare localized PVCs. Acute procedure success was 92.6% and long-term procedure success was 83% in all cases. When the patients in our study were analyzed according to their PVC locations and procedure successes, those with rare localization compared to those with RVOT and coronary cusp origin were 66 (87.5%), 79 (96.3%), and 53 (94.6%); respectively (p = 0.03) and long-term successes were 58 (72.5%), 73 (90.1%), and 49 (87.5%); respectively (p <0.05). Long-term transaction success was lower.

Conclusions: Frequent PVCs can be treated with electroanatomic mapping and radiofrequency ablation with high success rate and low complication rate. Patients with RVOT and coronary cusp-derived PVC had a high acute and long-term success rate, while success rates were lower in rare localized PVCs from epicardial/summit, papillary muscle, parahisian and tricuspid-mitral anulus.

Keywords: premature ventricular complexes, catheter ablation, electroanatomic mapping

Ventricular ectopic beats or premature ventricular complexes (PVCs) are caused by early depolarizations originating from ventricular myocardial cells. While most PVC originates from the ventricular myocardium, the bifurcation distal conduction tissue of the His bundle, such as bundle branches, fascicles or Purkinje fibers, are also potential source sites for these arrhythmias.

Received: *August 1, 2020;* ***Accepted:*** *September 30, 2020;* ***Published Online:*** *February 8, 2021*

How to cite this article: *Tütüncü A, Yılmaz E. Features of patients with premature ventricular complex ablation: single center case series. Eur Res J 2021;7(2):159-169. DOI: 10.18621/eurj.775245*

Address for correspondence: *Ahmet Tütüncü, MD., University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Department of Cardiology, Bursa, Turkey. E-mail: tutuncuahm@yahoo.com*

e-ISSN: 2149-3189

PVCs are common in clinical practiceIt is mainly seen in structural heart diseases such as ischemic heart disease (IHD) [1], heart valve disease [2], cardiomyopathy [3] and ventricular hypertrophy [4]. In patients with a normal heart angiographically and echocardiographically, more than 100 PVCs are seen daily in 4% [5].

PVCs are associated with poor prognosis in those with structural heart disease. The presence of frequent or complex PVCs after myocardial infarction increases cardiovascular mortality of 3-5 years [1]. Similarly, in those with left ventricular hypertrophy, PVCs are associated with an increase in all-cause mortality [4].

Current studies have shown that the possible negative effects of frequent PVCs and the development and reversibility of PVC-induced cardiomyopathy (CMP) in patients with a structurally normal heart [6, 7]. It has been suggested that the highest sensitivity and specificity (100% and 87%, area under the curve 0.96 respectively) in predicting PVC-induced CMP formation is more than 16% PVC load [7]. However, there are patients who have high PVC load but do not develop CMPOther situations that cause the development of PVC-related CMP; PVC QRS duration is over 140 ms, presence of interpolated PVC, PVC coupling interval < 300 ms, being asymptomatic and being epicardial origin PVC [8-10]. Singh *et al*. [9] stated that frequent PVC is one of the reversible causes of dilated cardiomyopathy (DCM) and showed an improvement in left ventricular (LV) function after suppression of PVCs with idiopathic DCM patients.

Today, catheter ablation is considered as a first-line treatment for patients with PVC-induced CPM. Recent publications have shown that catheter ablation of outflow-induced PVC is more effective than pharmacotherapy, in addition, catheter ablation provides a higher LVEF normalization compared to antiarrhythmic drug (AAD) [9, 11]. Indications for catheter ablation are PVCs that cause ventricular dysfunction [12] and the presence of serious symptoms and AADs are not desired by the patient, have side effects, or are not effective [13]. In PVC ablation, the complication rate is acceptable and the major complication rate is approximately 2.4% [14]. The success rate in experienced centers is more than 90%, and the complication rate is 1%.

The aim of this study is to report the baseline demographic and echocardiographic features of 217 patients with frequent PVC, in which we performed catheter ablation in our 3-year period, clinical results related to the success of the ventricular extra beats, and complication rates with interventional variables.

METHODS

Patient Selection

In our study; 217 patients who were successfully treated with PVC ablation between January 2016 and January 2019 at Bursa Yüksek İhtisas Training and Research Hospital were examined. Informed consent form was obtained from all patients before the procedure. At least once 24-hour ECG Holter monitoring was performed before catheter ablation. Patients with low (< 50%) LVEF were evaluated as PVC-CMP. According to Framingham coronary artery risk classification, coronary angiography was performed through femoral artery in addition to patients who were found to be moderate and high. Whether patients were diabetic, hypertensive or hyperlipidemic was recorded. The results from the routine blood sample taken from the antecubital vein were recorded. In routine echocardiographic evaluation (Vivid-7, GE Wingmed sound Horten, Norway); left atrial diameter (LAD), left ventricular systolic and diastolic diameters, left ventricular wall thickness and ejection fraction were calculated. Interventional variables such as the clinical results and complication rates, and the duration of the procedure and fluoroscopy were recorded according to the PVC locations.

The study was approved by the Bursa Yüksek İhtisas Training and Research Hospital Ethics Committee. Written consent was obtained from all patients before participating in the study, and this study was conducted according to the Helsinki Declaration.

Electrophysiological Study and Catheter Ablation

Patients were allowed to stop AADs five half-lives before planned ablation procedures. Electrophysiological study was performed under local anesthesia in a fasted state. Sedation was not applied to the patients before the procedure to avoid the risk of suppressing automaticity. If clinical PVCs were not initially available, isoproterenol infusion and electrical stimulation techniques were used to induce arrhythmia. Intra-

venous isoproterenol 1-5 µg/min infusion was given to provide at least 20% heart rate increase. Electrical stimulation was performed using the right ventricular apex or right ventricular outflow tract (RVOT) using burst pacing and triple extra stimuli pacing.

Electroanatomical mapping was done with EnsiteTM Precision (Abbott, Chicago, IL, USA) or CARTO3 (Biosense Webster, USA) (Fig. 1). Using fluoroscopic guidance, a decapolar diagnostic catheter was inserted through the right femoral vein into the coronary sinus. Ablation catheter 8F quadripolar irrigation ablation catheters used for mapping and ablation Thermocool Smarttouch CF (Biosense Webster Inc., Diamond Bar, California, USA) and FlexAbility (Endosense / Abbott, St) with 3.5 mm tip and 2-5-2 mm electrode range. Paul, MN, USA) was used. For left-sided access, a transaortic retrograde pathway or trans-septal puncture was performed, and an additional intravenous unfractionated heparin intravenously was given to provide an active clotting time of 300-350 seconds.

Firstly, an activation map was applied using the

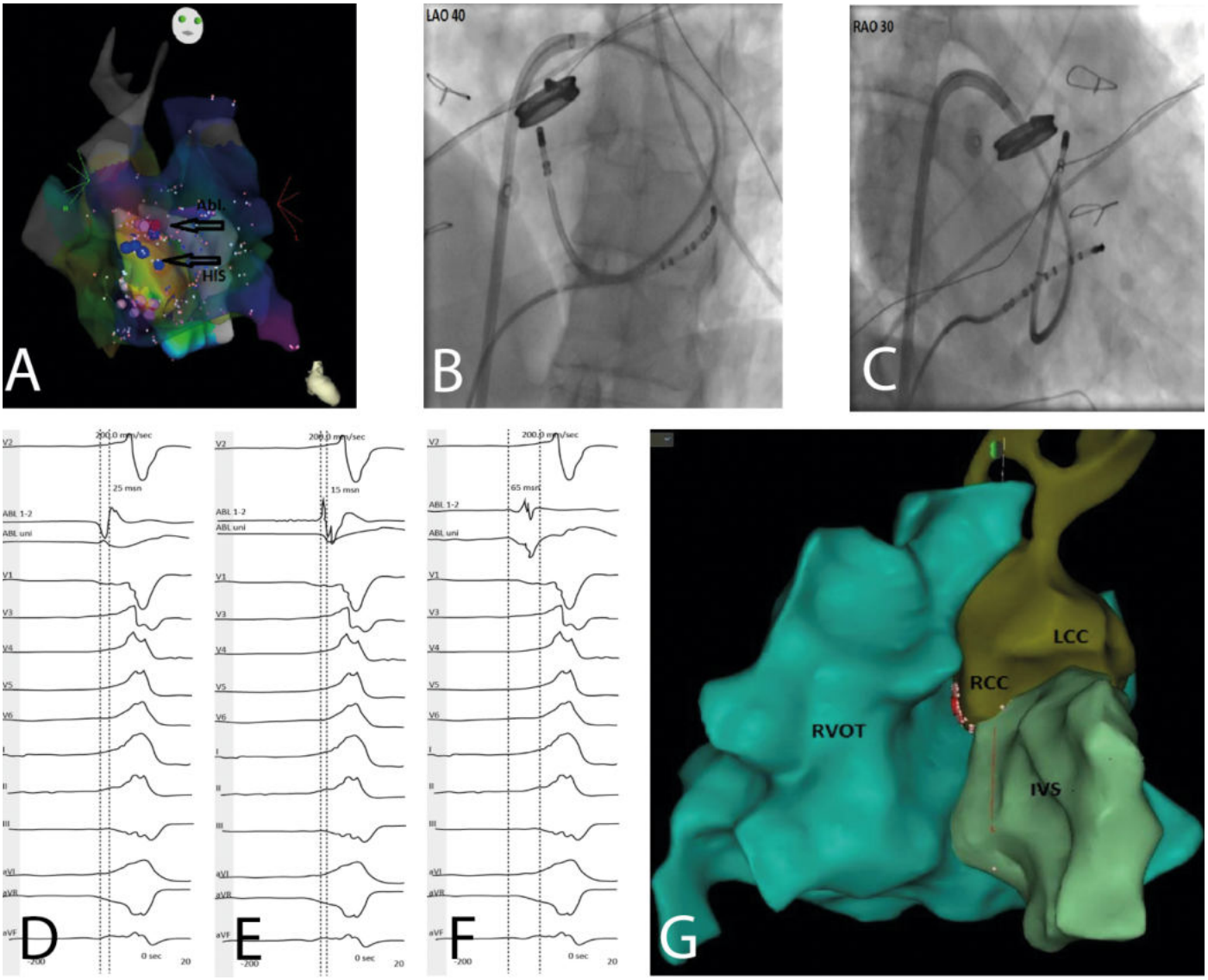


Fig. 1. 3D Electro anatomical mapping (EAM) and catheter ablation of Parahisian PVC with Carto system. (A) The earliest activation in the mapping is seen in the interventricular septum and the parahisian region. The red dot is a successful ablation site. Blue dots his sensation zone. (B-C) Fluoroscopic images of ablated areas. (D-E-F) Respectively, unipolar and bipolar recordings of RVOT, coronary cusp and interventricular septum. The earliest recording is seen in IVS, which received a signal 65 ms ahead. (G) Carto 3D EAM image. RVOT = Right ventricular outflow tract, LCC = left coronary cusp, RCC = right coronary cusp, IVS = interventricular septum.

mapping catheter. The PVC focus was evaluated by bipolar recordings, with the earliest local activation timing detected, and the presence of the QS complex formed in the case of radial spreading away from the PVC focus with unipolar electrograms. The purpose of the activation mapping was to identify the region that was recorded 30 ms or earlier from the start of the reference surface PVC QRS. In addition, the pace mapping technique was used to determine the source of the PVCs and the most suitable ablation site. The aim of pace mapping was to provide similarity in at least 11 of the 12 ECG morphologies. Irrigation ablation was performed in a 30-35 W power controlled mode in the appropriate ablation zone and a 10 Ω impedance drop was targeted. After ablation, electrophysiological study with or without isoproterenol was repeated and programmed electrical stimulation (PES) was performed. When tachycardia or PVCs with the same morphology were not induced after 30 minutes of waiting time after ablation, ablation was considered successful.

Statistical Analysis

Statistical study was done using SPSS 17 (SPSS Inc., Chicago, IL, United States) package computer program. Variables with normal distribution were expressed as mean ± standard deviation, and variables without normal distribution were expressed as median (interquartile range: IQR). Categorical variables were given as frequency and percentage (%). Student's t test was used to compare normally distributed numeric variables in two different groups, while Mann Whitney U test was used for non-normally distributed numeric variables. Chi-square or Fisher's exact tests were used to compare nominal data. In our study, Bonferroni multiple comparison test was used to determine the difference between the three groups. A p value < 0.05 was considered significant.

RESULTS

In our study, the mean age of the patients was 43 ± 12.1 yeras and the female gender ratio was 37.8%. The study population was found to have hypertension (n = 45, 20.7%), hyperlipidemia (n = 45, 20.7%), diabetes mellitus (n = 31, 14.3.7%) and smoking (n = 60, 27.6%). In echocardiographic evaluation of patients, LVEF was 45.9 % ± 8.2%. VEB load was determined as 22.4% in 24-hour Holter monitoring. Demographic, laboratory, electrocardiographic and echocardiographic features of the study population are shown in Table 1.

Considering the characteristics of the catheter ablation procedure of the patients included in the study population; When catheter ablated PVC foci were evaluated, it was seen that 81 (37.3%) originated from right ventricular outlet (RVOT), 56 (25.8%) originated from coronary cusp. In addition, a total of 80 (36.8%), 6 (2.8%) aortomitral continuity, 22 (10.1%) left ventricular summit/epicardial, 17 (7.8%) parahisian, are of rare localization. In addition, 6 (2.8%) of the cases were due to multiple foci.

Table 1. Demographic and echocardiographic features of patients

	All patients (n = 217)
Age (year)	43 ± 12.1
Female gender, n (%)	82 (37.8)
Tobacco, n (%)	60 (27.6)
Hypertension, n (%)	45(20.7)
Hyperlipidemia, n (%)	45 (20.7)
Diyabetes mellitus, n (%)	31 (14.3)
LVEF (%)	45.9 ± 8.2
Septal thickness (mm)	0.92 ± 0.21
Posterior wall thickness (mm)	0.90 ± 0.24
Left ventricular diastolic diameter (mm)	50 ± 5.4
Left ventricular systolic diameter (mm)	36 ± 3.5
Left atrial diameter (mm)	37 ± 5.1
LDL (mg/dL)	139 ± 49
HDL (mg/dL)	44 ± 12
Triglycerides (mg/dL)	171 ± 72
Glucose (mg/dL)	110 ± 34
Creatinine (mg/dL)	1.18 ± 0.61
Sodium (mg/dL)	137 ± 3.9
Potassium (mg/dL)	4.0 ± 2.2
Hemoglobin (g/dL)	12.7 ± 1.6
WBC ($\times 10^9$/L)	7.1 ± 1.9
Thyroid stimulating hormone (mU/L)	1.75 ± 1.7

LVEF = Left ventricular ejection fraction, LDL = Low density lipoprotein, HDL = High density lipoprotein

Table 2. Procedural features and complications

	All patients ((n = 217))
Ventricular extra beat distribution, n (%)	
Right ventricular outflow tract VEA	81(37.3)
Coronary cuspıs VEA	56(25.8)
Rare localized VEA, n (%)	80 (36.8)
Aorto-mitral continuity	6 (2.8)
Parahisian	17 (7.8)
Left ventricular summit/ Epicardial	22 (10.1)
Papillary muscle	10 (4.6)
Tricuspi annulus	7 (3.2)
Mitral annulus	8 (3.7)
Fascicles	4 (1.8)
Multiple focus	6 (2.8)
The presence of concomitant cardiomyopathy, n (%)	
Yes	77 (35.5)
No	140 (64.5)
Anti arrhythmic drug use (%)	208 (95.9)
VEA burden (%)	22.4
VEA QRS duration (ms)	135± 37
VEA coupling interval, msn	17 (7.8)
Interpolated VEA, n (%)	22 (10.1)
Asymptomatic, n (%)	355± 115
Coronary angio intervention, n (%)	80 (36.9)
Mapping and ablation 3D-Electroanatomic mapping system	
CARTO, n (%)	121 (55.8)
EnSite Precision, n (%)	83 (38.2)
Columbus, n (%)	13 (6)
Irrigated ablation catheter, n (%)	210 (96.8)
Acute procedure success, n (%)	201 (92.6)
Long-term procedure success, n (%)	180 (83)
Procedure time (min)	81 ± 31
Ablation time (s)	466 ± 117
Fluoroscopy time (min)	19 ± 8.7
Death, n (%)	0(0)
Vascular access hematoma, n (%)	9 (4.1)
AV Complete block, n (%)	1(0.4)
Tamponade, n (%)	2 (0.9)

VEA = Ventricular extra beat

Radiofrequency (RF) catheter ablation procedure time, scope duration and RF application time of the patients included in the study population are 81 ± 31 minutes, 19 ± 8.7 minutes and 466 ± 117 seconds, respectively. It was observed that procedure success was 92.6% in the acute period and 83% of long-term procedure success. Coronary angiography was performed in 36.9% of the patients in the study. In addition, when the complication rates were examined, the most common complication site was hematoma 9 (4.1%). In addition, AV block was observed in 1 (0.4%) patient with Parahisian origin and tamponade was observed in 2 (0.9%) patients, but no procedure-related death occurred. Considering the PVC localizations of patients with tamponade, the first was RVOT free wall and the second was LV summit-induced and was observed during the ablation procedure through the coronary sinus. The procedural features and complications of the study population are shown in Table 2.

When the patients in our study were analyzed according to their PVC locations and procedure successes, those with rare localization compared to those with RVOT and coronary cusp origin were 66 (87.5%), 79 (96.3%), and 53 (94.6%); respectively (p = 0.03) and long-term successes were 58 (72.5%), 73 (90.1%), and 49 (87.5%); respectively (p <0.05). Long-term transaction success was lower. In addition, it was observed that the procedure, fluoroscopy and RF ablation times (101 ± 32.7 minutes, 27.2 ± 7.9 minutes, and 812 ± 96 seconds, respectively) were longer in those with rare localization. Interventional variables according to the clinical results related to ventricular extra beat locations and process successes of the study population are shown in Table 3.

DISCUSSION

With this study, we determined the demographic characteristics of the patients undergoing PVC ablation and the success and complication rates of the catheter ablation procedure in a high-volume center where catheter ablation was performed. Most of our patients were under 50 years old and 37.8% were females. This rate is Nakagawa *et al*. [15] compared to his study, it is seen that he has similar age and gender ratios. In addition, 85.2% of our patients were non-diabetic and 72.4% were non-smokers. When analyzed by PVC foci, most of the study population was non-RVOT (62.7%) originated group. Acute and long-term success rates of patients with PVC ablation were 92.6% and 83%, respectively. When the PVC foci were examined in detail, it was seen that the patients with rare localized PVC had low acute and long-term success rates, and longer procedure, fluoroscopy and RF ablation times.

Table 3. Clinical results and interventional variables related to the success of the procedure according to the locations of ventricular extra beats

Variables	RVOT (n = 81)	Coronary cuspıs (n = 56)	Rare Localization (n = 80)	*p* value
Age (year)	42.8 ± 16.8	41.6 ± 15.1	45.2 ± 13.9	0.58
Sex (female)	36.9%	39.8%	37.2%	0.77
Hypertension	20.4%	20.1%	15.1%	0.87
Diyabetes mellitus	14.4%	12.6%	15.4%	0.80
Acute procedure success	79 (96.3%)[b]	53 (94.6%)[b]	66 (87.5%)[a]	**0.03**
Long-term procedure success	73 (90.1%)[b]	49 (87.5%)[b]	58 (72.5%)[a]	**< 0.05**
Procedure time (minute)	71 ± 13.4[b]	64 ± 11.9[b]	101 ± 32.7[a]	**< 0.05**
Fluoroscopy time (minute)	15.8 ± 12.7[b]	16,7 ± 11.7[b]	27,2 ±7.9[a]	**< 0.05**
Total ablation time (second)	407 ± 76[b]	391 ± 48[b]	812 ± 96[a]	**< 0.05**
Total complication rate	3.7%	3.6%	5%	0.18

Data are shown as mean±standard deviation or n (%) or %. [a,b,c] the same letters show no significant difference between groups based on Bonferroni multiple comparison tests. RVOT = Right ventricular outflow tract. $p < 0.05$ was considered statistically significant.

The incidence of PVC in healthy subjects was examined by various researchers and PVC was detected in 1-4% of healthy people without asymptomatic and structural heart disease in standard twelve-lead ECG recordings. This rate increased to 39-67% when subjects were monitored for 24 hours with Holter monitoring [16]. The first step in the treatment of patients with PVC with mild symptoms without structural heart disease is the education of the benign nature of this arrhythmia. Beta-blockers or non-dihydropyridine calcium channel blockers may be considered in patients whose symptoms cannot be managed effectively, but these agents are effective only in a very limited proportion of 10-15% of patients [17, 18]. Although membrane active anti-arrhythmic drugs are more effective in PVC suppression, risk-benefit rates have not been carefully evaluated in those without structural heart disease. In patients with severe structural heart disease, these drugs (except amiodarone) should be used carefully in PVC suppression due to increasing mortality [17-19]. Although suppression can be achieved with pharmacological agents, a prospective study has shown that the effectiveness of drugs alone is poor in PVC suppression. Although the goal of medical therapy is to improve symptoms with a decrease in PVC load, catheter ablation is potentially curative by directly targeting abnormal cells where clinical PVCs appear. In a randomized study involving 330 patients with RVOT PVC, the 1-year recurrence rate of PVCs (defined as > 300 beats/day) was significantly lower in patients undergoing radiofrequency ablation (RFA) than medically treated with propafenone or metoprolol (19.4 vs 88.6%, $p < 0.001$) [20]. Similarly, in a retrospective study of 510 patients by Zhong *et al*. [21], catheter ablation showed a greater reduction in PVC load compared to class I/III antiarrhythmic drugs (93% vs 82%, $p = 0.04$). As a result, catheter ablation is an important option in the management of these patients.

Premature ventricular complexes are considered benign when there is no structural heart disease. There is a clear relationship between frequent premature ventricular contractions and cardiomyopathy and is reversible with catheter ablation in selected patients [22-24]. In our study, we evaluated those with LVEF < 50% as PVC related cardiomyopathy. The number of patients with PVC-related cardiomyopathy in our study was 77 (35.5%). The number of PVCs /24h associated with impaired LV function is usually reported at loads above 15-25% of total cardiac beats, but this rate may even be below 10% [6, 25, 26]. Many studies have reported PVC burden as an important predictor of the development of left ventricular (LV) systolic dysfunction. However, no exact cut-off value related to this load was found [27, 28]. Baman *et al*. [25] showed that more than 24% PVC load was associated with PVC-induced cardiomyopathy in 24-hour Holter monitoring. When the results of our study are evaluated, it is seen that the PVC load is 22.4% and the rate of PVC-related cardiomyopathy is 35.5%. In addition, PVC morphology, origin and PVC duration are other factors associated with cardiomyopathy [29].

Idiopathic PVCs generally originate from the exit path of the right and left ventricles, mitral and tricuspid annulus, His-Purkinje system, left ventricular summit and papillary muscles [30]. In our study, the majority of PVC localizations constitute 81 (37.3%) PVCs originating from RVOT. In addition, as a rare localized source of PVC, aorta-mitral continuity 6 (2.8%), parahisian 17 (7.8%), left ventricular summit/epicardial 22 (10.1%), papillary muscle 10 (4.6%), tricuspid 7 (3.2%) and mitral. annulus 8 (3.7%), fascicular 4 (1.8%) and multiple focus 6 (2.8%) were detected. In addition, the rate of PVC from coronary cusp is 56 (25.8%). In Lee *et al*.'s study [31], catheter ablation was performed in 152 patients, 54 of whom had CMP. In this study, those with and without CMP were 6 (11%) - 15 (15%) and those with papillary muscle were 9 (17%) -7 (7%), respectively. In a study by Tada *et al*. [32], catheter ablation was applied to 454 patients in total. According to this study, the majority of the patients were 223 (49%) patients with RVOT. Again, in this study, the rare localizations of PVC are mitral 24 (5%) and tricuspid 38 (8%) annulus and LV epicardial 93 (21%) origin [35]. Latchamsetty *et al*. [14] were included 1185 idiopathic PVC patients who underwent ablation therapy in their study, and 45% of the cases were shown to be RVOT, 15% were coronary cube and 40% were other rare origin PVCs. When the single central case series we have published is compared with other studies, it is seen that the rate of RVOT-induced PVC is lower and the rate of PVC with coronary cuspis is higher.

In our study, we compared the acute and long-term

success rates of RF ablation applied to rare localized foci with RVOT and coronary cusp-derived foci. According to this, acute procedure and long-term success rates of rare localized foci were found to be lower than other foci. Acute procedure success in our study was 92.6%. When evaluated as RVOT, coronary cusp and rare localizations according to PVC origins, this rate was 96.3%, 94.6% and 87.5%, respectively. The detection of PVC load lower than 80% in holter monitoring of the 6th month and 24 hours after catheter ablation treatment was evaluated as a long-term success. In our study, the long-term process success was 83%, when it was evaluated as RVOT, coronary cusp and rare localizations according to PVC origins, this rate was found to be 87.5%, 90.1%, and 72.5%, respectively. It has been observed that these rates overlap with many studies in the literature. In a study by Wang *et al*. [33], when RF ablation success rates were examined, it was seen that the highest rate was RVOT and the lowest rate was epicardially sourced PVCs. Latchamsetty *et al*. [14], in their study, it was observed that the focal points in which RF ablation applied was the highest and the lowest in terms of acute procedure success were RVOT and epicardial, respectively (93% and 67%, respectively). When long term procedure successes were examined, it was determined that the highest and lowest foci were RVOT and papillary muscle. (82% and 60%, respectively).

In another case series evaluating 815 patients who underwent idiopathic PVC/VT ablation, the success of acute procedure ranged from 76% to 100% and the recurrence rate was 0 - 23%. Acute procedure successes vary between 85% and 100% in fascicular and RVOT-induced VTs, and recurrence rates have been shown to range from 0 to 25% in this group of patients. In addition, acute period success was observed in 89 patients in the intracavitary PVC/VT group (96 patients). High recurrence rates such as 0-58% and 40% were found after a single ablation in papillary muscle and moderator band VT, respectively. In PVC / VT (81 patients) originating from tricuspid and mitral rings, the acute success of catheter ablation varies between 66% and 100%, and the lowest success rate in those originating from septal tricuspid rings has been observed [32].

Acute treatment success was achieved in 17 of 22 PVCs with epicardial and summit origin, and 6 of these patients were subxiphoid. Previous studies have reported similar success rates for epicardial regions of PVC origin (via the coronary sinus) even without using an epicardial subxiphoid approach [34, 35]. The subxiphoid approach was further questioned when the additional complication deficit and higher complication rate were considered when compared with the ablation approach of the coronary venous system and surrounding structures (coronary cusp or subcuspus). Unless medical treatment is desired or if there is no cardiomyopathy caused by PVC, medical treatment may be preferred as the first treatment in patients with epicardial PVC [36].

Acute treatment success was achieved in 8 of 10 PVCs of papillary muscle origin in our single center case series, and this number decreased to 7 in the long term. PVCs from papillary muscles also tend to be associated with a lower ablation success rate. Papillary muscle PVCs have a high recurrence rate and require longer procedure times and greater radiofrequency energy delivery [37]. For these arrhythmias, intracardiac echocardiography (ICE) has been shown to assist in guiding the procedure [38]. However, it was performed without using ICE in our cases.

In addition, we found in our study that rare localized PVC foci have longer RF ablation, fluoroscopy and processing times compared to other foci. These relatively long periods of time, Latchamsetty *et al*. [14], in their study, it was observed that rare localized PVC foci overlapped with the length of the procedural duration.

Complications of catheter ablation procedures of idiopathic PVC are rare, and the reported complication rate is 3-5%. The most common is the site of vascular complications. Less common complications include cardiac tamponade/hemopericardium, thromboembolic events, AV block and coronary artery injury [39]. When the complication rates in our study were evaluated, vascular complications were the most common intervention site and percutaneous intervention due to pseudo aneurysm was performed in one patient. Cardiac tamponade was observed in 2 patients and evacuated without surgical need. In addition, in 1 patient with parahisian PVC, AV block was observed 2 days after the procedure. No mortality was observed after the procedure. Comparing the complication rates in all three groups, this rate was higher in those with rare lo-

calization and was not statistically significant. These rates are observed to be compatible with the data of other studies.

Limitations

The primary limitation of our study is that the patients included in our study are from our clinic, a tertiary referral center, and may not reflect other patient populations. Second, the PVC load before and after ablation was assessed by 24-hour rhythm Holter monitoring. Since the frequency of PVCs is variable, one-time rhythm Holter follow-up may not accurately show the true load of PVCs, but in similar studies, the PVC load was also evaluated by a 24-hour Holter [40]. Third, in this study, the sample size was relatively small. Larger sampling sizes are needed to obtain more precise results regarding the parameters we examine after PVC ablation.

CONCLUSION

Frequent PVCs can be treated with electroanatomic mapping and radiofrequency ablation with high success rate and low complication rate. Patients with RVOT and coronary cusp-derived PVC had a high acute and long-term success rate, while success rates were lower in rare localized PVCs from epicardial / summit, papillary muscle, parahisian and tricuspid-mitral anulus. In addition, process, fluoroscopy and RF ablation times were determined longer in rare localized PVCs.

Authors' Contribution

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

Conflict of interest

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

Financing

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

REFERENCES

1. Ruberman W, Weinblatt E, Goldberg JD, Frank CW, Shapiro S. Ventricular premature beats and mortality after myocardial infarction. N Eng J Med 1977;297:750-7.
2. DeMaria AN, Amsterdam EA, Vismara LA, Neumann A, Mason DT. Arrhythmias in the mitral valve prolapsed syndrome. Prevalence, nature and frequency. Ann Intern Med 1976;84:656-60.
3. Savage DD, Seides SF, Maron BJ, Myers MJ, Epstein SE. Prevalence of arrhythmias during 24 hour electrocardiographic monitoring and exercise testing in patients with obstructive and nonobstructive hypertrophic cardiomyopathy. Circulation 1979;59:866-75.
4. Bikkina M, Larson MG, Levy D. Asymptomatic ventricular arrhythmias and mortality risk in subjects with left ventricular hypertrophy. J Am Coll Cardiol 1993;22:1111-16.
5. Kostis JB, McCrone K, Moreyra AE, Gotzoyannis S, Aglitz NM, Natarajan N, et al. Premature ventricular complexes in the absence of identifiable heart disease. Circulation 1981;63:1351-6.
6. Hasdemir C, Ulucan C, Yavuzgil O, Yuksel A, Kartal Y, Simsek E, et al. Tachycardia-induced cardiomyopathy in patients with idiopathic ventricular arrhythmias: the incidence, clinical and electrophysiologic characteristics, and the predictors. J Cardiovasc Electrophysiol 2011;22:663-8.
7. Taieb JM, Maury P, Shah D, Duparc A, Galinier M, Delay M, et al. Reversal of dilated cardiomyopathy by the elimination of frequent left or right premature ventricular contractions. J Interv Card Electrophysiol 2007;20:9-13.
8. Latchamsetty R, Bogun F. Premature ventricular complex induced cardiomyopathy. Rev Esp Cardiol (Engl Ed) 2016;69:365-9.
9. Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival trial of antiarrhythmic therapy in congestive heart failure. N Engl J Med 1995;333:77-82.
10. Peichl P, Wichterle D, Pavlu L, Cihak R, Aldhoon B, Kautzner J. Complications of catheter ablation of ventricular tachycardia: a single-center experience. Circ Arrhythm Electrophysiol 2014;7:684-90.
11. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Heart disease and stroke statistics -- 2014 update: a report from the American Heart Association. Circulation 2014;129: e28-e292.
12. Aliot EM, Stevenson WG, Almendral-Garrote JM, Bogun F, Calkins CH, Delacretaz E, et al. EHRA/HRS Expert Consensus on Catheter Ablation of Ventricular Arrhythmias: developed in a partnership with the European Heart Rhythm Association (EHRA), a Registered Branch of the European Society of Cardiology (ESC), and the Heart Rhythm Society (HRS); in collaboration with the American College of Cardiology (ACC) and the American Heart Association (AHA). Heart Rhythm 2009;6:886-933.
13. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, et al. ACC/AHA/ESC 2006 guidelines for manage-

ment of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol 2006;48:e247-e346.
14. Latchamsetty R, Yokokawa M, Morady F, Kim HM, Mathew S, Tilz R, et al. Multicenter outcomes for catheter ablation of idiopathic premature ventricular complexes. JACC Clin Electrophysiol 2015;1:116-23.
15. Nakagawa M, Takahashi N, Nobe S, Ichinose M, Ooie T, Yufu F, et al. Gender differences in various types of idiopathic ventricular tachycardia. J Cardiovasc Electrophysiol 2002;13:633-8.
16. Spesific Arrhythmias: Diagnosis and Treatment in Braunwald's Heart Disease A textbook of cardiovascular medicine. 10th Ed.. Philadelphia 2015: p.771-3.
17. Stec S, Sikorska A, Zaborska B, Krynski T, Szymot J, Kulakowski P. Benign symptomatic premature ventricular complexes: short-and long-term efficacy of antiarrhythmic drugs and radiofrequency ablation. Kardiol Pol 2012;70:351-8.
18. Krittayaphong R, Bhuripanyo K, Punlee K, Kangkagate C, Chaithiraphan S. Effect of atenolol on symptomatic ventricular arrhythmia without structural heart disease: a randomized placebo-controlled study. Am Heart J 2002;144:e10.
19. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The cardiac arrhythmia suppression trial. N Engl J Med 1991;324:781-8.
20. Ling Z, Liu Z, Su L, Zipunnikov V, Wu J, Du H, et al. Radiofrequency ablation versus antiarrhythmic medication for treatment of ventricular premature beats from the right ventricular outflow tract: prospective randomized study. Circ Arrhythm Electrophysiol 2014;7:237-43.
21. Zhong L, Lee YH, Huang XM, Asirvatham SJ, Shen WK, Friedman PA, et al. Relative efficacy of catheter ablation vs antiarrhythmic drugs in treating premature ventricular contractions: a single-center retrospective study. Heart Rhythm 2014;11:187-93.
22. Wang Y, Eltit JM, Kaszala K, Tan A, Jiang M, Zhang M, et al. Cellular mechanism of premature ventricular contraction-induced cardiomyopathy. Heart Rhythm 2014;11:2064-72.
23. Mountantonakis SE, Frankel DS, Gerstenfeld EP, Dixit S, Lin D, Hutchinson MD, et al. Reversal of outflow tract ventricular premature depolarization-induced cardiomyopathy with ablation: effect of residual arrhythmia burden and preexisting cardiomyopathy on outcome. Heart Rhythm 2011;8:1608-14.
24. Ban JE, Park HC, Park JS, Nagamoto Y, Choi JI, Lim HE, et al. Electrocardiographic and electrophysiological characteristics of premature ventricular complexes associated with left ventricular dysfunction in patients without structural heart disease. Europace 2013;15:735-41.
25. Baman TS, Lange DC, Ilg KJ, Gupta SK, Liu TY, Alguire C, et al. Relationship between burden of premature ventricular complexes and left ventricular function. Heart Rhythm 2010;7:865-9.
26. Kanei Y, Friedman M, Ogawa N, Hanon S, Lam P, Schweitzer P. Frequent premature ventricular complexes originating from the right ventricular outflow. Ann Noninvasive Electrocardiol 2008;13:81-5.
27. Sheldon SH, Gard JJ, Asirvatham SJ. Premature ventricular contractions and non-sustained ventricular tachycardia: association with sudden cardiac death, risk stratification, and management strategies. Indian Pacing Electrophysiol J 2010;10:357-71.
28. Duffee DF, Shen WK, Smith HC. Suppression of frequent premature ventricular contractions and improvement of left ventricular function in patients with presumed idiopathic dilated cardiomyopathy. Mayo Clin Proc 1998;73:430-3.
29. Sohn DW, Chai IH, Lee DJ, Kim HC, Kim HS, Oh BH, et al. Assesment of mitral annulus velocity by Doppler tissue imaging in the evalution left ventricular diastolic function. J Am Coll Cardiol 1997;30:474-80.
30. Stevenson WG. Current treatment of ventricular arrhythmias: state of the art. Heart Rhythm 2013;10:1919-26.
31. Lee A, Denman R, Haqqani HM. Ventricular ectopy in the context of left ventricular systolic dysfunction: risk factors and outcomes following catheter ablation. Heart Lung Circ 2019;28:379-88.
32. Tada H, Tadokoro K, Ito S, Naito S, Hashimoto T, Kaseno K, et al. Idiopathic ventricular arrhythmias originating from the tricuspid annulus: prevalence, electrocardiographic characteristics, and results of radiofrequency catheter ablation. Heart Rhythm 2007;4:7-16.
33. Wang JS, Shen YG, Yin RP, Thapa S, Peng YP, Ji KT, et al. The safety of catheter ablation for premature ventricular contractions in patients without structural heart disease. BMC Cardiovasc Disord 2018;18:177.
34. Baman TS, Ilg KJ, Gupta SK, Good E, Chugh A, Jongnarangsin, et al. Mapping and ablation of epicardial idiopathic ventricular arrhythmias from within the coronary venous system. Circ Arrhythm Electrophysiol 2010;3: 274-9.
35. Yokokawa M, Latchamsetty R, Good E, Chugh A, Pelosi F, Jr, Crawford T, et al. Ablation of epicardial ventricular arrhythmias from nonepicardial sites. Heart Rhythm 2011;8:1525-9.
36. Carrigan T, Patel S, Yokokawa M, Swanson S, Morady F, Bogun F. Anatomic relationships between the coronary venous system, surrounding structures, and the site of origin of epicardial ventricular arrhythmias. J Cardiovasc Electrophysiol 2014;25:1336-42.
37. Yokokawa M, Good E, Desjardins B, Crawford T, Jongnarangsin K, Chugh A, et al. Predictors of successful catheter ablation of ventricular arrhythmias arising from the papillary muscles. Heart Rhythm 2010;7:1654-9.
38. Good E, Desjardins B, Jongnarangsin K, Oral H, Chugh A, Ebinger M, et al. Ventricular arrhythmias originating from a papil- lary muscle in patients without prior infarction: a comparison with fascicular arrhythmias. Heart Rhythm 2008;5:1530-7.
39. Peichl P, Wichterle D, Pavlu L, Cihak R, Aldhoon B, Kautzner J. Complications of catheter ablation of ventricular tachycardia: a single-center experience. Circ Arrhythm Electrophysiol 2014;7:684-90.
40. Capucci A, DiPasquale G, Boriani G, Carini G, Balducelli M, Frabetti L, et al. A double-blind cross over comparison of fle-

cainide and slow-release mexiletine in thetreatment of stable premature ventricular complexes. Int J Clin Pharmacol Res 1991;11:23-33.

The European Research Journal 2021;7(2):170-176 Original Article

DOI: 10.18621/eurj.645582 *Otorhinolaryngology*

The relationship between nasal septal deviation and anatomical variations of the paranasal sinus

Oğuzhan Dikici, Osman Durgut

Department of Otorhinolaryngology, University of Health Sciences, Bursa Yüksek Ihtisas Training and Research Hospital, Bursa, Turkey

ABSTRACT

Objectives: The aim of this study was to determine the relationship between septum deviation and anatomic variations of the paranasal sinus.

Methods: A total of 157 (79 males, 78 females) patients between the ages of 17 and 77 years (mean age: 33.7 ± 14.9 years) were included in the study. Using paranasal sinus computed tomography imaging, anatomical variations including nasal septal deviation, Agger nasi cells, Haller cells, Onodi Cells, sphenoid sinus pneumatisation, paradoxical middle turbinates, middle turbinate pneumatisation, maxillary sinus septa,vertical septa in the sphenoid sinus, optic nerve dehiscenceand cribriform plate lamina lateralis height were evaluated.

Results: Agger nasi cells were present in 47.1% of cases, Haller cells were seen in 5% of cases and Onodi cells were observed in 23.6% of cases. In 70.1% of cases, one vertical septa in the sphenoid sinus was observed. Maxillary sinus septa was observed in 16.5% of cases. There was a significant negative correlation between the female gender and increased sphenoid sinus pneumatisation ($p = 0.035$). There was a positive correlation between maxillary sinus septa and the presence of Onodi cells ($p^{right} = 0.045$, $p^{left} = 0.017$). There was also a negative correlation between maxillary sinus septa and sphenoid sinus pneumatisation ($p^{right} = 0.001$, $p^{left} = 0.005$).

Conclusions: In our study, we found that maxillary sinus septa, Agger nasi, Haller cells, cribriform plate lamina lateralis height, sphenoid sinus septation and Onodi cells were interrelated. We recommend that surgeons evaluate patients with these variations to prevent complications.

Keywords: Agger nasi, Haller cells, Onodi cells, sinus surgery, maxillary sinus septa

Functional endoscopic sinus surgery (FESS), commonly used in the surgical treatment of pathologies of the sinuses, is often performed to improve the patient's comfort. To avoid complications during this procedure, all anatomic variations in the patient must be known and well described [1]. The anatomical layout of paranasal sinuses has been well established since the 19th and early 20th centuries [2]. Variations of anatomical structures within the ostiomeatal region can predispose individuals to paranasal sinus pathologies. Several sinonasal anatomical variations can be observed via paranasal sinus computed tomography (PSCT) [3]. The introduction of computed tomography (CT) as a diagnostic tool has improved the definition of these anatomical variations [1], and advances in FESS and imaging technology have increased the importance of understanding the anatomical structure of the paranasal sinus [2]. Multiplanar high resolution CT of the paranasal sinuses provides a precise and reliable preoperative roadmap for endoscopic sinus sur-

Received: ***November 11, 2019;*** *Accepted:* ***September 8, 2020;*** *Published Online:* ***January 27, 2021***

How to cite this article: *Dikici O, Durgut O. The relationship between nasal septal deviation and anatomical variations of the paranasal sinus. Eur Res J 2021;7(2):170-176. DOI: 10.18621/eurj.645582*

Address for correspondence: *Oğuzhan Dikici, MD., University of Health Sciences, Bursa Yüksek Ihtisas Training and Research Hospital, Mimarsinan Mah., Emniyet Cad., No:35, 16310, Yıldırım,Bursa, Turkey. E-mail: oguzhandikici@yahoo.com.tr, Tel: +90 224 2955000, Fax: +90 224 2955497*

e-ISSN: 2149-3189

geons[2]. CT is an imaging modality recognised as the gold standard for evaluating patients before FESS. The evaluation of anatomic variations using CT is important in both preoperative and intraoperative periods to avoid complications and improve operative success [1].

Anatomical variations in the anterior ethmoid sinus that result in a narrowing of the middle meatus include the presence of a large ethmoid bulla, a large concha bullosa, a paradoxical middle turbinate, an uncinate process bulla and a nasal septal deviation. Lateral deviation ofHaller cells and the uncinate process narrow the infundibulum. Septal pneumatisation in the form of an anterior extension of the sphenoid sinus can narrow the sphenoethmoid recess, which may contribute to the occurrence of posterior ethmoid and sphenoid sinus diseases and increase the chances of future surgical complications at these sites [4]. CT is the preferred method of examination for chronic sinusitis cases, as it enhances the surgeon's vision of the sinonasal cavity and provides a roadmap for surgery. It can enhancelocalisation of the sinus pathology when taken coronally or axially at 3-5 mm intervals. CT imaging performed in the coronal plane provides the most information for an endoscopic sinus surgery [5].

The aim of this study was to determine the relationship between septum deviation and anatomic variations of the paranasal sinus.

METHODS

This retrospective study was conducted at the Department of Otorhinolaryngology of Health Sciences University Bursa Yüksek Ihtisas Training and Research Hospital. The study was approved by the ethics committee of the same hospital with number 2011-KAEK-25 2019/02-12.

PSCT scans were examined retrospectively and evaluated by otorhinolaryngologists at the Department of Otorhinolaryngology of our hospital. A total of 157 (79 males, 78 females) patients aged between 17 and 77 years old (mean age: 33.7 ± 14.9 years) were included in the study. Exclusion criteria for this study were previous history of skull base or paranasal sinus surgery and congenital facial anomaly. In PSCT images, variations such as Agger nasi, Haller cells, Onodi Cells, (Fig. 1a-c) sphenoid sinus pneumatisation types, middle turbinate pneumatisation, cribriform plate lamina lateralis height (Fig. 2), paradoxical middle turbinate (Fig. 3), maxillary sinus septa (Fig. 4),vertical septa in sphenoid sinus, optic nerve dehissance and nasal septal deviation,were evaluated.

We classified sphenoid sinus pneumatisation in the coronal plane into three types, based on the classification described by Vaezi *et al*. [6]. In the coronal type 1 or previdian, the pneumatisation extends from the midline to the medial edge of vidian canal. In the coronal type 2 or prerotundum, pneumatisation extends to the lateral edge of foramen rotundum; and in the coronal type 3 or postrotundum, the pneumatisation extends laterally to the foramen rotundum [6].

Cribriform plate lamina lateralis height was evaluated and classified into three types. Measurements between 1 and 3 mm were classified as type 1, between 4 and 7 mm as type 2 and between 8 and 16 mm as type 3 [7].

The location of any deviation was classified as anterior, posterior or anteroposterior. The deviation side was either right or left. Septal deviation was divided

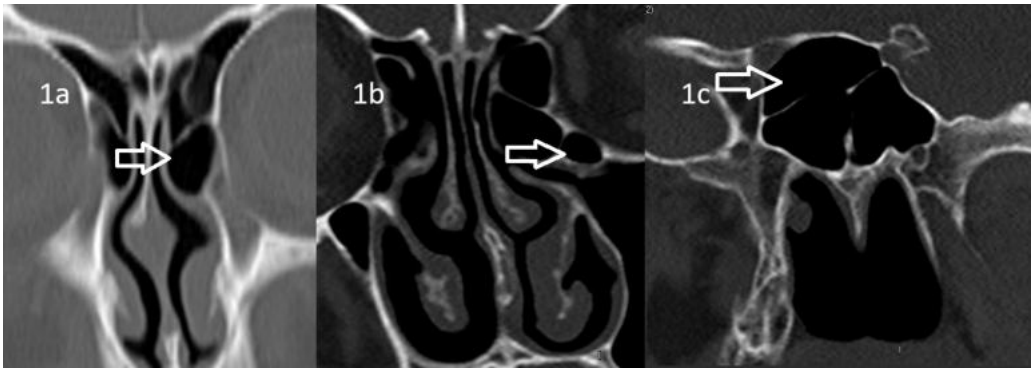


Fig. 1. (a) In coronal section of the PSCT, Agger nasi cell (arrow). (b) In coronal section of the PSCT, Haller cells (arrow) and (c) In coronal section of the PSCT, Onodi cell (arrow). PSCT = paranasal sinus computed tomography

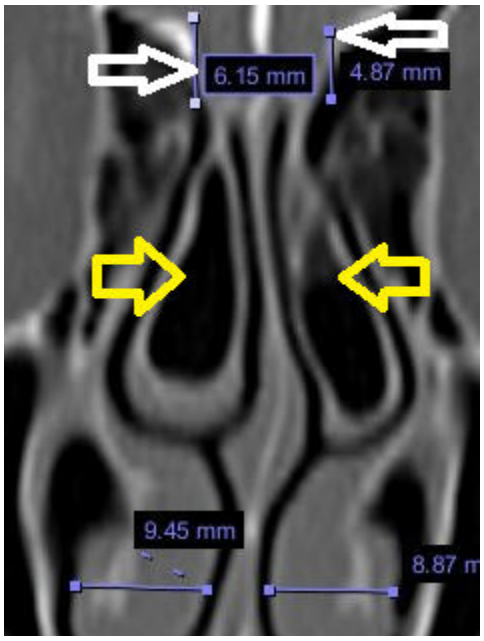


Fig. 2. In coronal section of the PSCT, Concha bullosa (yellow arrows) and measurement of crybriform plate lamina lateralis depth (white arrows). PSCT = paranasal sinus computed tomography

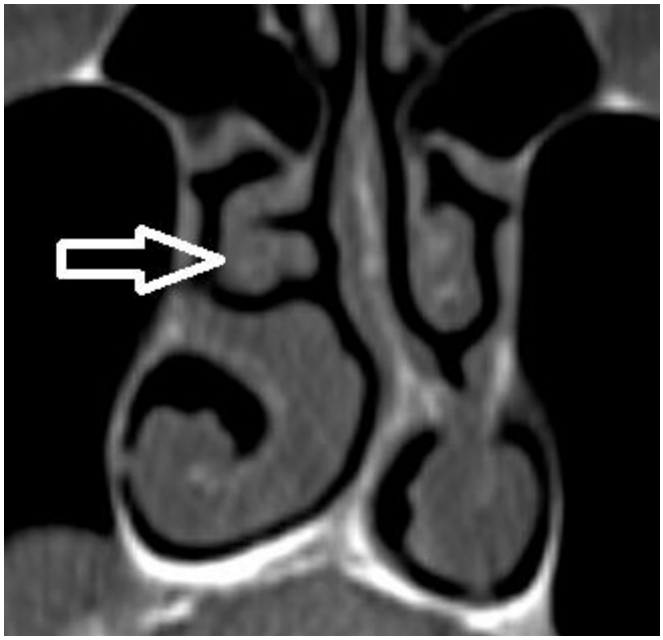


Fig. 3. In coronal section of the PSCT, right paradoxical middle turbinate (arrow). PSCT = paranasal sinus computed tomography tomography

into seven types according to the Mladina classification [8].

Statistical Analysis

The SPSS software (ver. 23.0) was used for statistical calculations. Both Pearson'scorrelation test and the Kruskal–Wallis test were used. A p value of < 0.05 was considered to indicate statistical significance.

RESULTS

The deviation was located on the right side in 72 (45.9%) patients and on the left side in 83 (52.9%) patients. There was deviation on both sides in 1 (0.6%) patient. The deviation was located in the anterior part in 35 (22.3%) patients, in the posterior part in 46 (29.3%) patients and the anteroposterior part in 73

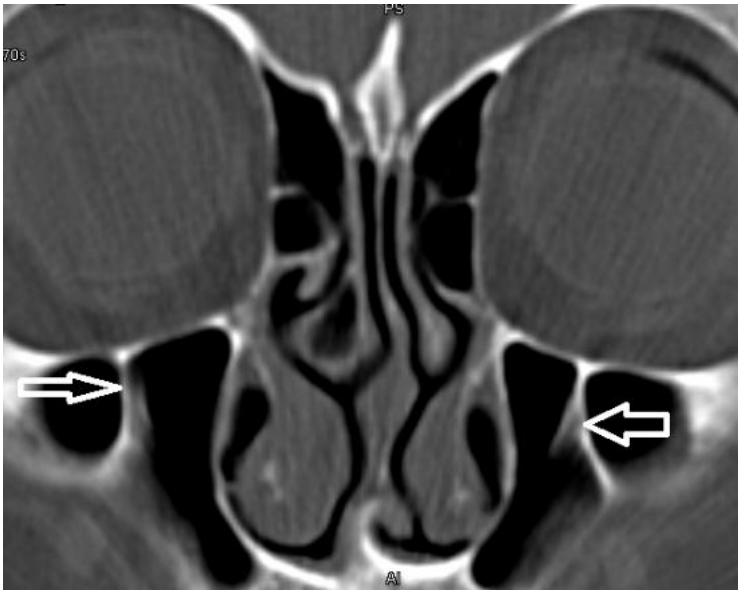


Fig. 4. In coronal section of the PSCT, maxillary sinus septa (arrows). PSCT = paranasal sinus computed tomography

(46.5%) patients. The Mladina classification results were as follows: Type 1 in 61 (38.9%) patients, type 2 in 62 (39.5%) patients, type 3 in17 (10.8%) patients, type 4 in3 (1.9%) patients, type 5 in 8 (5.1%) patients and type 6 in 5 (3.2%) patients.

Agger nasi cells were found on the right side in 80 (51%) patients, on the left side in 80 (51%) patients and on both sides in 74 (47.1%) patients. Haller cells were found on the right side in 13 (8.1%) patients, on the left side in 15 (9.6%) patients and on both sides in 8 (5%) patients. Onodi cells were found in 37 (23.6%) patients. There was no sphenoid sinus septum in 6 (3.8%) patients, 1 vertical septum in the sphenoid sinus in 110 (70.1%) patients, 2 vertical septa found in the sphenoid sinus of 30 (19.1%) patients and 3 vertical septa found in the sphenoid sinus of 11 (7%) patients. Sphenoid sinus pneumatisation classification results were as follows: Type 1 in 74 (47.1%) patients, type 2 in 58 (36.9%) patients and type 3 in 25 (15.9%) patients. There was optic nerve protrusion in to sphenoid sinus in 42 (26.8%) patients. Maxillary sinus septa was located on the right side in 30 (19.1%) patients, on the left side in 34 (21.7%) patients and on both sides in 26 (16.5%) patients. Paradoxical middle turbinate was present on the right side in 19 (12.1%) patients, on the left side in 13(8.3%) patients and on both sides in 9(5.7%) patients. A secondary middle turbinate was found in 1 (0.6%) patient.

Concha bullosa was found on the right side in 88 (56.1%) patients, on the left side in 84 (53.5%) patients and on both sides in 69 (43.9%) patients. Concha bullosa found on the right side was lamellar in 46 (26.3%) patients, bullous in 7 (4.5%) patients and bullolamellar in 35 (22.3%) patients. Concha bullosa found on the left side was lamellar in 47 (29.9%) patients, bullous in 4 (2.5%) patients and bullolamellar in 35 (22.3%) patients.

Cribriform plate lamina lateralis height was 6.1 ± 2.18 mm on the right side and 5.88 ± 2.39 mm on the left side. Keros classification results on the right side were type 0 in 1 (0.6%) patient, type 1in 19 (12.1%) patients, type 2 in 92 (58.6%) patients and type 3 in 45 (28.7%) patients. Keros classification results on the left side were type 0 in 3 (1.9%) patients, type 1 in 23 (14.6%) patients, type 2 in 82 (52.2%) patients and type 3 in 49 (31.2%) patients.

There was a significant negative correlation between the female gender and increased sphenoid sinus pneumatisation ($p = 0.035$). There was a positive correlation between maxillary sinus septa and the presence of Onodi cells ($p^{right} = 0.045$, $p^{left} = 0.017$). There was also a negative correlation between presence of maxillary sinus septa and sphenoid pneumatisation classification ($p^{right} = 0.001$, $p^{left} = 0.005$). There was a positive correlation between the presence of maxillary sinus septa on the right side with presence of right ($p = 0.007$) and left sided Haller cells ($p < 0.001$). However, presence of maxillary sinus septa on the left side was positively correlated with the presence of only left Haller cells ($p = 0.010$). The presence of right sided bullous turbinate was positively correlated with right sided maxillary septation ($p = 0.020$), as well as with left sided maxillary septation ($p = 0.004$). Likewise, there was a positive correlation between the presence of maxillary septa and bullolamellar type concha bullosa on the right side ($p^{right} = 0.024$, $p^{left} = 0.046$).

There was a positive correlation between the presence of Agger nasi cell on the right side and the presence of right sided and left sided maxillary septa ($p^{right} = 0.010$, $p^{left} = 0.014$). Similarly, there was a positive correlation between the presence of Agger nasi cells on the right side and the presence of Haller cells ($p^{right} = 0.002$, $p^{left} = 0.018$) on both sides. There was a correlation between the presence of Agger nasi cells on the left side and the presence of Haller cells on the right side ($p = 0.002$). There was a significant correlation between an increase in septation within the sphenoid sinus and increase in lateral lamellar height ($p = 0.004$). The presence of concha bullosa on both sides was positively correlated with the presence of Haller cells on the left side ($p^{right} = 0.050$, $p^{left} = 0.007$).
There was no significant relationship between septal deviation and the presence or type of concha bullosa, Agger nasi, Haller cells, Onodi Cells, sphenoid sinus pneumatisation, paradoxical middle turbinate, maxillary sinus septa,vertical septa in the sphenoid sinus, optic nerve dehiscence and cribriform plate lamina lateralis height ($p > 0.05$).

DISCUSSION

The development of minimally invasive surgical techniques has made it essential to understand the anatomy of the paranasal sinus. Anatomic variations must be well understood to ensure patient safety and

prevent surgical complications. Prior to performing FESS, PSCT is the gold standard imaging modality for the evaluation of patients [9]. Anatomical variations of the paranasal sinuses can cause various sinus pathologies and complicate surgeries. These variations include nasal septum deviations, concha bullosa, Agger nasi cells and Haller cells [10, 11].

Nasal septum deviationsare found in 20%-79% of the population [2, 4]. Nasal septum deviations are usually observed in the lower part of the septum, near the chondrovomeral region. Severe septal deviations may lateralise the middle turbinate and make it difficult to access pathologies within the middle meatus during surgery. Septal deviations should be carefully evaluated to improve surgical vision in FESS [2].

Koo *et al*. [3] found that deviations towards the left side were slightly more common than deviations towards the right side (43.9% and 36.4%, respectively). At 52.9% of cases, deviation towards the left side was also more common in our study.In addition, according to the Mladina classification, class 5 deviations were the most common class of deviations with 55.1% of cases. At 46.5% of observed cases, anteroposterior deviations constituted the most common of the three locations for deviations. In our study, the chondrovemoral region was the most common site for deviations.

Agger nasi cells are the most anterior ethmoid air cells. Anterior ethmoid cells, particularly Agger nasi cells, can cause constriction or obstruction of the nasofrontal canal [12]. In several studies, the prevalence of Agger nasi cells varied between 61.4% and 98.5%. However, in 90.6% of cases, the presence of agger nasi cells was bilateral [4, 13]. Unlike other studies, agger nasi cells were found on the right side in 51% patients, on the left side in 51% of patients and on both sides in 47.1% of patients.In addition, patients with agger nasi cell had a higher incidence of Haller cells and maxillary septa.

Haller cells, first identified by Albrecht Von Haller in 1756 and named after him, are infraorbital ethmoid cells [10, 14]. Zinreich and Kennedy described Haller cells as ethmoid air cells that adhere to the maxillary sinus ceiling and form part of the lateral wall of the infundibulum, inferior to the ethmoid bulla [4]. Khojastepour *et al*. [13] found a significant relationship between maxillary sinusitis and the presence of Haller cells. The presence of Haller cells may increase the risk of orbital injury during ethmoidectomy [10, 15]. Bolger *et al*. [16] reported that they found Haller cells in 45% of cases examined via CT. Yücel *et al*. [4] found Haller cells in 18.5%of cases in their studies. The incidence of Haller cells reported in different studies range between 5.5% and 45.9% [10, 14]. In our study, Haller cells were found on the right side in 8.1% of patients, on the left side in 9.6% of patients and on both sides in 5% of patients. In addition, patients with maxillary sinus septa and agger nasi cell had a higher incidence of Haller cells.

The presence of Onodi cells reported in previous studies range between 0.4% and 14% [2, 17]. Onodi cells may predispose the optic nerve and the internal carotid artery to injury during surgery [1]. In our study, Onodi cell was observed in 23.6% of patients. While septation was not observed in the sphenoid sinus in 3.8% of patients, 70.1% of patients had 1 vertical septum, 19.1% of patients had 2 vertical septa and 7% of patients had 3 vertical septa.Type 1 sphenoid sinus pneumatisation was found in 47.1% of patients, 36.9% of patients had type 2 and 15.9% of patients had type 3 sphenoid sinus pneumatisation. Sphenoid sinus agenesis was not detected in our study. Female patients and patients with maxillary sinus septa had less sphenoid sinus pneumatisation. Onodi cells were found more frequently in patients with maxillary sinus septa. Both Onodi cells and septation in the sphenoid sinus occurred frequently in our study. We concluded that especially in FESS, caution should be taken to prevent complications due to regional proportional differences.In addition, we concluded that caution should be taken in patients with maxillary sinus septation, as there is a high rate probability of Onodi cells within the low pneumatised sphenoid sinus.

The optic nerve can be exposed on the roof of the sphenoid sinus up to 24% [2]. The optic nerve is often exposed in the superior-lateral wall of the sphenoid sinus between 8 to 100% rate [14]. In our study, optic nerve protrusion was detected in the sphenoid sinus at a rate of 26.8%, comparable to figures in literature.Visual loss due to optic nerve injury is one of the most feared complications of endoscopic sinus surgery. Therefore, it is important to fully evaluate the radiological anatomy of the optic nerve before FESS [15].

Concha bullosa refers to the pneumatisation of the lower bulbous part of the middle turbinate. Concha bullosa occurs due to changes in the development of

ethmoid air cell system. Concha bullosa can be unilateral or bilateral and can be classified into three types based on the site of pneumatisation. They are the lamellar type; pneumatised vertical lamellae of the middle turbinate, the bulbous type; pneumatised lower part of the middle turbinate and thetrue type; vertical lamella and pneumatised bottom of middle turbinate [18]. Concha bullosa occurs in approximately 13%-55% of the population and is usually bilateral [2, 3, 19]. The incidence of bilateral concha bullosa has been reported between 36.4% and 54.7% [3, 18]. It is a possible aetiological factor in recurrent chronic sinusitis [3]. In our study, the incidence of concha bullosa was 56.1% on the right side, 53.5% on the left side and 43.9% on both sides. In patients with right sided concha bullosa, 26.3% of them were lamellar, 4.5% of them were bullous and 22.3% of them were true. In patients with left-sided concha bullosa, 29.9% of them were lamellar, 2.5% were bullous and 22.3% of them were true.

The paradoxical middle turbinate is the convex side of the middle turbinate facing the lateral direction [4]. In the literature, the frequency of paradoxical middle turbinates ranges between 2.8% and 32% [1, 4, 17]. The paradoxical middle turbinate is thought to cause recurrent rhinosinusitis and prevent access to the ostiomeatal unit during surgery [2]. Paradoxical middle turbinate can cause recurrent infundibular disease and sometimes headache [13, 20]. In our study, the paradoxical middle turbinate occurred on the right side 12.1% of the time, on the left side 8.3% of the time and on both sides 5.7% of the time.

Secondary middle turbinate is an extra turbinate between the upper turbinate and the middle turbinate, with a projection between the lateral nasal wall and the middle meatus [5]. In their studies, Kaplan *et al*. [5] found that secondary middle turbinate occurred at a rate of about 6%. Secondary middle turbinate was observed in 0.6% of patients in our study.

Septa in the maxillary sinus occur commonly and may be fibrous or bony. They usually extend from the infraorbital nerve canal to the lateral wall and may affect drainage of the maxillary sinuses [2]. In our study, maxillary sinus septation was seen on the right side 19.1% of the time, on the left side 21.7% of the time and in both sides 16.5% of the time. In addition, we found that the incidence of Agger nasi cells, Onodi cells, Haller cells and true type concha bullosa were higher in the presence of maxillary sinus septa. We also found that sphenoid sinus pneumatisation decreased in the presence of maxillary sinus septa. Abnormalities that may cause chronic sinusitis are more common in cases with maxillary sinus septa.

As described by Keros [7], there are three types of olfactory fossa, depending on the height of the lateral lamella of the cribriform plate. Type 1 refers to the shallow or flat olfactory fossa seen in 30% of cases and ranges between 1 mm and 3 mm. Type 2, which indicates a moderate deep olfactory fossa and occurs in 49% of cases,ranges between 4 mm and 7 mm. Type 3 ranges between 8 mm and 16 mm and is observed in 21% of cases [2]. Nouraei *et al*. [10] found Keros type 1 in 3.5%, Keros 2 in 74% and Keros 3 in 22.5% of their cases. In our study, the mean height of the cribriform plate lamina lateralis was 6.1 ± 2.18 mm on the right side and 5.88 ± 2.39 mm on the left side. Given that the lateral lamella of the cribriform plate is the thinnest bone in the anterior skull base and is dehiscenced in 14% of patients, the risk of intraoperative injury and iatrogenic cerebrospinal fluid leakage is higher in this region [2]. Anterior skull base examination using CT should be performed by every surgeon before FESS to reduce risk ofcomplications [21]. In our study, we found that an increase in the height of the olfactory fossa was positively correlated withincreases in sphenoid septation. Both of these factors are risky anomalies during the FESS procedure. We though that these relationships should be considered during CT evaluation before FESS.

CONCLUSION

Several studies have shown a relationship between chronic sinusitis and paranasal sinus anomalies. Before endoscopic sinus surgery, evaluation of patients for anomaliesusing CT can reduce the intraoperative complications and increase procedural success. In our study, we found that maxillary sinus septa, Agger nasi cells, Haller cells, Onodi cells, cribriform plate lamina lateralis height and sphenoid sinus septation were interrelated. However, nasal septum deviation was not related to the aforementioned anomalies. We recommend that surgeons evaluate patients for these variations to prevent procedural complications.

Author contributions

O.D. = Literature survey, design, planning, data collection, intellectual review of the results, writing, approving the final manuscript. O.D. = Literature survey, intellectual review of the results, writing, approving the final manuscript

Conflict of interest

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

Financing

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

REFERENCES

1. Şahin C, Yilmaz YF, Titiz A, Özcan M, Özlügedik S, Ünal A. [The Anatomic Variations of Paranasal Sinuses : Computerized Tomography Study]. KBB ve BBC Dergisi 2007;15:71-3. [Article in Turkish]
2. Vaid S, Vaid N. Normal anatomy and anatomic variants of the paranasal sinuses on computed tomography. Neuroimaging Clin N Am 2015;25:527-48.
3. Koo SK, Kim JD, Moon JS, Jung SH, Lee SH. The incidence of concha bullosa, unusual anatomic variation and its relationship to nasal septal deviation: a retrospective radiologic study. Auris Nasus Larynx 2017;44:561-70.
4. Yücel A, Dereköy FS, Yılmaz MD, Altuntaş A. [Effects of sinonasal anatomical Variations on paranasal sinus infections]. Kocatepe Tıp Dergisi 2004;5:43-7. [Article in Turkish]
5. Kaplan Y, Müderris S, Kunt T. [Tomographic analysis of sinonasal variations and relationship with sinusitis]. C Ü Tıp Fakültesi Derg 2004;26:29-36. [Article in Turkish]
6. Vaezi A, Cardenas E, Pinheiro-Neto C, Paluzzi A, Branstetter IV BF, Gardner PA, et al. Classification of sphenoid sinus pneumatization: relevance for endoscopic skull base surgery. Laryngoscope 2015;125:577-81.
7. Keros P. On the practical value of differences in the level of the lamina cribrosa of the ethmoid. Z Laryngol Rhinol Otol 1962;41:809-13.
8. Mladina R. The role of maxillar morphology in the development of pathological septal deformities. Rhinology 1987;25:199-205.
9. Yılmazsoy Y, Arslan S. Med HS. [Assessment of the prevalence of Haller cell variation and the relation between Haller cell variation and maxillary sinusitis]. J Health Sci Med 2018;1:54-8. [Article in Turkish]
10. Nouraei SAR, Elisay AR, Dimarco A, Abdi R, Majidi H, Madani SA, et al. Variations in paranasal sinus anatomy: implications for the pathophysiology of chronic rhinosinusitis and safety of endoscopic sinus surgery. J Otolaryngol Neck Surg 2009;38:32-7.
11. Daghighi M, Daryani A, Nejad KC, Daghighi M, Daryani A, Nejad KC, et al. Evaluation of anatomic variations of paranasal sinuses. Internet J Otorhinolaryngol 2012;7:7-11.
12. Lebowitz RA, Brunner E, Jacobs JB. The agger nasi cell: radiological evaluation and endoscopic management in chronic frontal sinusitis. Oper Tech Otolaryngol Head Neck Surg 1995;6:171-5.
13. Khojastepour L, Haghnegahdar A, Khosravifard N. Role of sinonasal anatomic variations in the development of maxillary sinusitis: a cone beam CT analysis. Open Dent J 2017;11(Suppl-1, M5):367-74.
14. Efendić A, Muharemović E, Skomorac R, Bečulić H, Šestić S, Halilović B, et al. Anatomic variations of posterior paranasal sinuses and optic nerve. Med Glas 2017;14:49-54.
15. Özer F, Çağıcı CA, Özer C, Kızılkılıç O, Yılmazer C, Özlüoğlu LN. [The progress of the optic nerve in the coronal paranasal sinus tomography]. Turk Otolarengoloji Ars 2013;47:15-20. [Article in Turkish]
16. Bolger WE, Butzin CA, Parsons DS. Paranasal sinus bony anatomic variations and mucosal abnormalities. Laryngoscope 1991;101:56-64.
17. Birkin T, Acar T, Esen Ö. [The anatomical variations of the sinonasal region and its relationship with sinus diseases]. Tepecik Eğit Hast Derg 2017;27:236-42. [Article in Turkish]
18. Kalaiarasi R, Ramakrishnan V, Poyyamoli S. Anatomical variations of the middle turbinate concha bullosa and its relationship with chronic sinusitis: a prospective radiologic study. Int Arch Otorhinolaryngol 2018;22:297-302.
19. Caversaccio M, Boschung U, Mudry A. Historical review of Haller's cells. Ann Anat 2011;193:185-90.
20. Shpilberg KA, Daniel SC, Doshi AH, Lawson W, Som PM. CT of anatomic variants of the paranasal sinuses and nasal cavity: poor correlation with radiologically significant rhinosinusitis but importance in surgical planning. Am J Roentgenol 2015;204:1255-60.
21. Kara A, Güven M, Yılmaz MS, Elden H, Demir D. [Keros classification and evaluation of cribriform plate depth asymmetry of the population in Marmara region]. Sakarya Med J 2018;8:352-8. [Article in Turkish]

The European Research Journal 2021;7(2):177-183 Original Article

DOI: 10.18621/eurj.752504 *General Surgery*

Outcomes of thyroid operations in patients of different age groups

Ali Çiftçi[1], Çağrı Tiryaki[2]

[1]Department of General Surgery, University of Health Sciences, Kocaeli Derince Training and Research Hospital, Kocaeli, Turkey
[2]Department of General Surgery, Buhara Hospital, Erzurum, Turkey

ABSTRACT

Objectives: To determine the effects of age on preoperative findings and on outcomes of thyroid surgeries.
Methods: In this retrospective study, we analyzed the demographics, surgical and pathological data, postoperative complications and biochemical results including calcium, phosphorus and parathyroid hormone (PTH) levels of patients who undertaken thyroid operations.
Results: Totally 288 consecutive patients operated for thyroid diseases were included in the study. The patients were grouped regarding their ages as patients in the 3rd decade (n = 26), 4th decade (n = 60), 5th decade (n = 81), 6th decade (n = 77) and 7th decade (n = 44). There was not any significant difference between groups regarding the preoperative diagnoses (p = 0.09). With an advance in age, the presence of multiple nodules in preoperative period was increasing (p = 0.015). On postoperative period, the pathological diagnosis was malignant in 46 (15.9%) patients. There was not any significant difference between groups regarding the tumor type (p = 0.80). The most common tumor type was papillary carcinoma in all age groups. Postoperative complications were determined in 68 (23.6%) patients and there was not any significant difference regarding the presence of postoperative complications in all age groups (p = 0.26).
Conclusions: In conclusion, there was not any significant difference regarding postoperative outcomes in patients operated for thyroid diseases who were in the different decades of their lives. We can suggest that, thyroid surgeries are as safe in elderly patients as in younger patients.
Keywords: thyroid surgery, age, complications

The incidence of thyroid diseases, especially cancers requiring surgery is increasing every day, most probably with the advances in diagnostic methods [1, 2]. Thyroidectomy is the most commonly performed endocrine surgery and for that reason, the patients requiring surgical treatment for thyroid diseases at different age groups are also augmenting [3].

Although thyroid surgeries are reported to have low rates of mortality and morbidity with advances in surgical techniques; in clinical practice, it was reported that, especially elderly patients with some thyroid diseases are less likely to receive specified therapies [4-6].

In this study, we aimed to determine the effects of age on preoperative findings and on outcomes of thyroid surgeries.

METHODS

In this retrospective study, we analyzed the demographics, surgical and pathological data, postoperative

Received: ***June 13, 2020;*** *Accepted:* ***November 1, 2020;*** *Published Online:* ***January 22, 2021***

How to cite this article: *Çiftçi A, Tiryaki Ç. Outcomes of thyroid operations in patients of different age groups. Eur Res J 2021;7(2):177-183. DOI: 10.18621/eurj.752504*

Address for correspondence: *Ali Çiftçi, MD., University of Health Sciences, Kocaeli Derince Training and Research Hospital, Department of General Surgery, Kocaali, Turkey. E-mail: draliciftci@hotmail.com*

e-ISSN: 2149-3189

complications and biochemical results including calcium, phosphorus and parathyroid hormone (PTH) levels of patients who undertaken thyroid operations between 2010 and 2017 in the University of Health Sciences, Kocaeli Derince Training and Research Hospital. The hospital records of patients operated for any thyroid diseases were retrospectively investigated and patients with missing records were not included in the study. The patients were grouped into decades regarding their ages to determine the effects of age on outcomes of thyroid operations. The indications for thyroid surgeries, preoperative ultrasonographic findings, the results of fine needle aspiration biopsy (FNAB) in preoperative period if present; histological findings, complications and laboratory data after operation were recorded. All surgeries were performed by the same operation team. Ethical committee approval was not obtained because the study was done retrospectively by evaluation of patients' data's.

Statistical Analysis

The data analysis was performed using the Statistical Package for the Social Sciences for Windows version 21.0 (SPSS Inc.; Chicago, IL, USA). Regarding descriptive statistics, the categorical variables were expressed as number and percentage and the numerical variables were expressed as mean, and standard deviation. In comparison of categorical variables, Chi-square test was performed. The numerical data were compared with the one way ANOVA. A $p < 0.05$ was considered statistically significant.

RESULTS

In this study, we analyzed the general characteristics and outcomes of 288 consecutive patients operated for thyroid diseases regarding their ages (Table 1). Concurrent parathyroid operations were performed in 13 (4.5%) patients. Among study participants, 247 (85.7%) were female but there was not any significant difference regarding gender between patients at different decades during operation ($p = 0.77$). Preoperative indication was analyzed in all decades. There was not any significant difference between groups regarding the preoperative diagnoses ($p = 0.09$). Number of nodules in preoperative period was significantly different between groups ($p = 0.015$). With an advance in age, the presence of multiple nodules was increasing.

In preoperative period, the suspicion of neoplasm was present in 42 patients while in postoperative period, the pathological diagnosis was malignant in 46 (15.9%) patients. There was not any significant difference between groups regarding the tumor type ($p = 0.80$). The most common tumor type was papillary carcinoma in all age groups. Substernal goiter was significantly more common in the 6th decade ($p = 0.01$). Location of tumor was significantly more commonly right lobe in patients in the 5th decade while it was significantly more commonly left lobe in patients in the 7th decade ($p = 0.009$). There was not any significant difference regarding the presence of postoperative complications in all age groups ($p = 0.26$).

In preoperative period, 14 patients were diagnosed with atypia with undefined significance and the postoperative diagnosis of these patients were papillary carcinoma (n = 3), follicular adenoma (n = 2), nodular goutier (n = 7), hurtle cell carcinoma (n = 1) and granulomatous thyroiditis (n = 1). On the other hand, fine needle aspiration biopsy (FNAB) was performed to the 34 of the patients diagnosed with any type of carcinomas in postoperative period. The results of those FNAB were as follows; adenomatous hyperplasia (n = 9), follicular neoplasm (n = 1), hyperplastic colloid nodule (n = 2), papillary carcinoma (n = 10), atypia with undefined significance (n = 3), hurtle cell carcinoma (n = 3), degenerated nodule (n = 1) in papillary carcinoma group; follicular neoplasia (n = 2) in follicular carcinoma group; and hurtle cell neoplasm (n = 2) in hurtle cell carcinoma group.

Bilateral total thyroidectomy was the most commonly performed operation in all age groups (Table 2). Right lobectomy + isthmectomy was significantly more commonly performed in patients in the 3rd decade compared with other age groups. Neck dissection was performed in 15 patients and there was not any significant difference between groups regarding the requirement of neck dissection.

There was not any significant difference regarding the presence of postoperative complications between groups. Transient hypocalcaemia was more common in patients in the 5th decade. (Table 3).

In postoperative period, calcium, phosphorus and parathyroid hormone levels were compared between groups (Table 4) and PTH levels were determined to be significantly higher in patients in the 6th and 7th

Table 1. General characteristics of study participants

	3rd decade (n = 26)	4th decade (n = 60)	5th decade (n = 81)	6th decade (n = 77)	7th decade (n = 44)	*p* value
Female (%)	23 (88.5)	51 (85.0)	71 (87.6)	67 (87.0)	35 (79.5)	0.77
Preoperative indication (%)						0.09
Toxic MNG	4 (15.4)	16 (26.7)	30 (37.0)	33 (42.8)	22 (47.7)	
Non-toxic MNG	12 (46.2)	23 (38.3)	31 (38.3)	31 (40.2)	13 (29.5)	
Neoplasm	5 (19.2)	13 (21.7)	12 (14.8)	7 (9.0)	5 (11.3)	
Atypia with undefined significance	0	4 (6.7)	5(6.2)	3 (3.9)	2 (4.5)	
Graves' Disease	2 (7.7)	1 (1.7)	1 (1.2)	1 (1.3)	0	
Non-toxic nodular adenoma	3 (11.5)	3 (5.0)	2 (2.4)	2 (2.6)	1 (2.3)	
Number of nodules						**0.015**
No	3 (11.5)	1 (1.7)	5 (6.2)	2 (2.6)	0	
One	5 (19.2)	10 (16.6)	5 (6.2)	4 (5.2)	2 (4.5)	
Multiple	18 (69.2)	49 (81.7)	71 (87.6)	71 (92.2)	42 (95.5)	
Dominant nodule size	25.32 ± 11.87	26.72 ± 12.36	26.70 ± 14.92	27.69 ± 13.25	30.77 ± 13.49	0.44
Postoperative tumor type (%)						0.80
Papillary	4 (15.4)	6 (10.0)	14 (17.3)	7 (9.0)	8 (18.2)	
Follicular	0	0	2 (2.4)	1 (1.3)	0	
Hurtle Cell	0	0	1 (1.2)	1 (1.3)	0	
Medullary	0	0	1 (1.2)	0	1 (2.3)	
Plonjan goiter (substernal)	0	2 (3.3)	7 (8.6)	12 (15.6)	2 (4.5)	**0.01**
Location of tumor						**0.009**
Right lobe	2 (7.7)	3 (5.0)	13 (16.0)	4 (5.2)	2 (4.5)	
Left lobe	1 (3.8)	2 (3.3)	4 (4.9)	0	6 (13.6)	
Bilateral	0	0	1 (1.2)	5 (6.5)	0	
Isthmus	1 (3.8)	1 (1.7)	0	0	0	
Neck dissection	0	4(6.7)	4(4.9)	6 (7.8)	1(2.3)	0.29
Postoperative complications	4 (15.4)	13 (21.7)	26 (32.1)	18 (23.4)	7 (15.9)	0.26

Data are shown as n (%). MNG = multi-nodular goiter

Table 2. Operation type

	3rd decade (n = 26)	4th decade (n = 60)	5th decade (n = 81)	6th decade (n = 77)	7th decade (n = 44)	*p* value
Right lobectomy +Isthmectomy	6 (23.1)	7 (11.7)	6 (7.4)	1 (1.3)	1 (2.3)	**0.011**
Left lobectomy +Isthmectomy	1 (3.8)	5 (8.3)	3 (3.7)	1 (1.3)	0	
Bilateral total thyroidectomy	18 (69.2)	46 (76.7)	72 (88.9)	74 (96.1)	40 (90.9)	
Right total left near total thyroidectomy	1 (3.8)	2 (3.3)	0	1 (1.3)	1 (2.3)	
Left total right near total thyroidectomy	0	0	0	0	2 (4.5)	

Data are shown as n (%).

Table 3. Postoperative complications

	3rd decade (n = 26)	4th decade (n = 60)	5th decade (n = 81)	6th decade (n = 77)	7th decade (n = 44)
Transient hypocalcemia (%)	1 (3.8)	8 (13.3)	18(22.2)	8 (10.4)	5(11.4)
Hematoma (%)	1(3.8)	0	0	0	0
Wound Infection (%)	1(3.8)	1(1.7)	2(2.4)	1(1.3)	0
Transient RLN paralysis (%)	0	1(1.7)	3(3.7)	3(3.9)	0
Permanent RLN paralysis (%)	0	0	1(1.2)	2(2.6)	0
Trachea injury (%)	0	0	0	1(1.3)	2(4.5)
Permanent hypocalcemia (%)	1(3.8)	2(3.3)	2(2.4)	3(3.9)	0
Esophagus injury (%)	0	1(1.7)	0	0	0

Data are shown as n (%).

decade compared with the younger patients while there was not any significant difference in postoperative calcium or phosphorus levels.

DISCUSSION

In this study, we analyzed the general characteristics of patients who were operated for any type of thyroid diseases and determined that most of the patients were female at all age groups; there was not any significant difference regarding the preoperative diagnoses between different age groups; with an advance in age, presence of multiple nodules was increasing. The pathological diagnosis was malignant in 46 (15.9%) patients and there was not any significant difference regarding the tumor type between patients at different age groups. The most common tumor type was papillary carcinoma in all age groups. Interestingly, substernal goiter was significantly more commonly determined in patients in the 6th decade. There was not any significant difference regarding the presence of postoperative complications in different age groups.

The data about the thyroid surgeries is accumulating in recent literature with an increase in the incidence of thyroid diseases [7-9]. In a retrospective study Grubey *et al*. [10] reported that, among 1207 outpatient thyroidectomy operations; 85.2% of the patients were female. They reported that there was not any significant difference between patients aged between 21 and 40 years, patients > 65 years and patients

Table 4. Postoperative calcium, phosphorus and parathyroid hormone levels

	3rd decade (n = 26)	4th decade (n = 60)	5th decade (n = 81)	6th decade (n = 77)	7th decade (n = 44)	*p* value
Calcium	8.42 ± 0.63	8.22 ± 0.63	8.30 ± 0.64	8.42 ± 0.62	8.41 ± 0.63	0.32
Phosphorus	3.73 ± 0.74	3.87 ± 0.76	4.10 ± 0.79	4.03 ± 0.76	3.91 ± 0.83	0.16
PTH	40.73 ± 29.75	41.32 ± 31.78	40.08 ± 31.45	54.91 ± 36.24	54.77 ± 42.25	**0.02**

Data are shown as mean±standard deviation. PTH = Parathyroid hormone

> 80 years regarding the complication and re-admission rates. Kovacic and Kovacic [11] investigated the outcomes of thyroid surgeries in 183 elderly patients and reported that patients ≥ 70 years of age were having higher rates of malignant diseases. However they also reported that the complication rates were not high after thyroid surgeries in those patients with ≥ 65 years of age. Similarly, Diaconescu *et al*. [12] also reported that despite some additional risks related to comorbidities in patients over 65 years, patients may benefit of all types of conservative or radical thyroidectomies. Canonico *et al*. [13] also reported that age did not increase the incidence of worse outcomes in patients who underwent thyroid surgery. On the other hand, in a population-based study on patients who underwent surgery for thyroid neoplasms, the rate of general postoperative complications was 6.5% and the rate of thyroid surgery-specific complications was 12.3%. In that study, the authors determined that older age and more comorbidities were risk factors for postoperative complications [14]. Caulley *et al*. [15] reported that the 30-day complication rate for total thyroidectomies was 7.74% and age ≥7 0 was a risk factor for postoperative complications. Similarly Liu *et al*. [16] also determined that older age was a risk factor for post-thyroidectomy bleeding in their meta-analysis. In our study, we did not determine any significant difference regarding postoperative complication rates in patients at different age groups. Postoperative hematoma was determined in only one patient and she was 26 years old.

The most common complication reported after thyroid surgeries is transient hypocalcaemia which may be seen in as much as 70% of patients, while permanent hypocalcaemia is exceedingly rare [17]. In our study, the most common complication was also transient hypocalcaemia determined in 40 (13.9%) patients while permanent hypocalcaemia was determined in only 8 (2.7%) patients.

The most common indications for thyroid surgeries include goitre, Grave's disease, toxic nodules and thyroid neoplasms [9, 18, 19]. In this study the most common indications for thyroid surgeries were also toxic and non-toxic multi-nodular goiter followed by thyroid neoplasms and there was not any significant difference regarding the preoperative indications in patients at different age groups.

In recent years, with an advance in diagnostic methods, the incidence of thyroid nodules is increasing and FNAB is the main initial diagnostic test in evaluation of thyroid nodules [20, 21]. However, the diagnostic accuracy of FNAB in malignant thyroid nodules is controversial. Recently, Kavanagh *et al*. [22] reported that, although FNAB is a safe and reliable method for cytological assessment of thyroid nodules, older patients were more likely to have non-diagnostic samples. However, we did not determine any significant differences regarding the cytological diagnoses of FNAB in patients at different age groups. Chiu *et al*. [23] retrospectively reviewed 1040 consecutive primary thyroid operations and reported that 380 of those patients were having cytologically indeterminate thyroid nodules. Among those 66% had follicular neoplasm, 12% had Hurthle cell neoplasm, 12% had papillary carcinoma and 7% had neoplasms with cellular atypia. In our study, although the number of patients with FNAB diagnosis of atypia with undefined significance was low (4.8%), among those patients the most common postoperative diagnoses were nodular goutier, papillary carcinoma, and follicular adenoma.

In a recent study, Liu *et al*. [24] investigated the characteristics of thyroid carcinoma in time and reported that papillary thyroid carcinoma was the most common type counting 86.4% of all thyroid carcinomas. In our study we also determined that papillary

carcinomas were the most common type accounting for 84.5% of all thyroid carcinomas in all decades. Nieman *et al*. [25] reported that patients with papillary thyroid cancer aged younger than 25 years of age or older than 75 years, exhibit higher rates of aggressive histopathologic features compared to patients aged between 25-75 years. However, we did not determine any significant differences between groups regarding outcomes of thyroid operations including patients with papillary carcinomas.

Substernal goiter may be regarded as a challenging indication for thyroid surgeons. In a recent study it was reported that among 1145 patients who underwent thyroid surgery, 60 (5.2%) patients were having substernal goiter. In that study also, similar with our results, 88% of patients were female [26]. Moten *et al*. [27] reported that Substernal thyroidectomy patients were older compared with the non-substernal cases. In our study the ratio of substernal goiter was 7.9% and we determined that substernal goiter was significantly more common in patients in the 6th decade of their life.

Limitations

There are some limitations of this study that should be mentioned. This is a retrospective study based on hospital records and performed in a single center. The number of patients with complications was low and follow-up data was not present in all patients.

CONCLUSION

In conclusion, we determined that, there was not any significant difference regarding postoperative outcomes in patients operated for thyroid diseases who were in the different decades of their lives. We can suggest that, thyroid surgeries are as safe in elderly patients as in younger patients. Larger prospective studies are required to determine the effects of age on outcomes of thyroid surgeries.

Authors' Contribution

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

Ethics statement

This study was designed as retrospective research, so that informed consent was obtained from all individual participants included in the study, but we have no ethical approval for this article. However, this article does not contain any studies with human participants or animals performed by any of the authors.

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.

Financing

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

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.
2. Lee YS, Lee BJ, Hong HJ, Lee KD. Current trends of practical issues concerning micropapillary thyroid carcinoma: The Korean Society of Thyroid-Head and Neck Surgery. Medicine 2017;96:e8596.
3. Sun GH, DeMonner S, Davis MM. Epidemiological and economic trends in inpatient and outpatient thyroidectomy in the United States, 1996-2006. Thyroid 2013;23:727-33.
4. Cernea CR, Brandão LG, Hojaij FC, Carlucci DD, Montenegro FLM, Plopper C, et al. How to minimize complications in thyroid surgery? Auris Nasus Larynx 2010;37:1-5.
5. Narayanan S, Arumugam D, Mennona S, Wang M, Davidov T, Trooskin SZ. An evaluation of postoperative complications and cost after short-stay thyroid operations. Ann Surg Oncol 2015;23:1440-5.
6. Shevchyk IV, Cobian BA, Martinez SR. Age-based disparities in the use of total thyroidectomy for papillary thyroid carcinoma. Clin Transl Oncol 2017;19:1253-9.
7. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid 2016;26:1-133.
8. Molinari AS, Treiguer A, Gava, VG, Rojas JL, Evangelista PE, Gonçalves I, Treiguer A, Gava VG, et al. Thyroid surgery performed on an overnight basis: a 17 years of experience. Arch En-

docrinol Metab 2015;59:434-40.
9. Isik A, Firat D, Yilmaz I, Peker K, Idiz O, Yilmaz B, et al. A survey of current approaches to thyroid nodules and thyroid operations. Int J Surg 2018;54:100-4.
10. Grubey JS, Raji Y, Duke WS, Terris DJ. Outpatient thyroidectomy is safe in the elderly and super-elderly. Laryngoscope 2018;128:290-4.
11. Kovačić I, Kovačić M. Surgical treatment of thyroid gland in elderly patients: our experiences. Acta Med Croatica 2016;70:185-90.
12. Diaconescu MR, Glod M, Costea I. Clinical features and surgical treatment of thyroid pathology in patients over 65 years. Chirurgia 2016;111:120-5.
13. Canonico S, Pellino G, Pameggiani D, Sciaudone G, Candilio G, De Fatico GS, et al. Thyroid surgery in the elderly: a comparative experience of 400 patients from an Italian university hospital. Int Surg 2014;99:523-7.
14. Papaleontiou M, Hughes DT, Guo C, Banerjee M, Haymart MR. Population-based assessment of complications following surgery for thyroid cancer. J Clin Endocrinol Metab 2017;102:2543-51.
15. Caulley L, Johnson-Obaseki S, Luo L, Javidnia H. Risk factors for postoperative complications in total thyroidectomy: a retrospective, risk-adjusted analysis from the National Surgical Quality Improvement Program. Medicine 2017;96:e5752.
16. Liu J, Sun W, Dong W, Wang Z, Zhang P, Zhang T, et al. Risk factors for post-thyroidectomy haemorrhage: a meta-analysis. Eur J Endocrinol 2017;176:591-602.
17. Puzziello A, Rosato L, Innaro N, Orlando G, Avenia N, Perigli G, et al. Hypocalcemia following thyroid surgery: incidence and risk factors. A longitudinal multicenter study comprising 2,631 patients. Endocrine 2014;47:537-42.
18. Liao S, Shindo M. Management of well-differentiated thyroid cancer. Otolaryngol Clin North Am 2012;45:1163-79.
19. Yano Y, Sugino K, Akaishi J, Uruno T, Okuwa K, Shibuya H, et al. Treatment of autonomously functioning thyroid nodules at a single institution: radioiodine therapy, surgery, and ethanol injection therapy. Ann Nucl Med 2011;25:749-54.
20. Gharib H, Papini E. Thyroid nodules: clinical importance, assessment, and treatment. Endocrinol Metab Clin North Am 2007;36:707-735.
21. Caleo A, Vigliar E, Vitale M, Crescenzo VD, Cinelli M, Carlomagno C, et al. Cytological diagnosis of thyroid nodules in Hashimoto thyroiditis in elderly patients. BMC Surg 2013;13:S2-S41.
22. Kavanagh J, McVeigh N, McCarthy E, Bennett K, Beddy P. Ultrasound-guided fine needle aspiration of thyroid nodules: factors affecting diagnostic outcomes and confounding variables. Acta Radiol 2017;58:301-6.
23. Chiu CG, Yao R, Chan SK, Strugnel SS, Bugis S, Irvine R, et al. Hemithyroidectomy is the preferred initial operative approach for an indeterminate fine needle aspiration biopsy diagnosis. Can J Surg 2012;55:191-8.
24. Liu X, Zhu L, Wang Z, Cui D, Chen H, Duan Y, et al. Evolutionary features of thyroid cancer in patients with thyroidectomies from 2008 to 2013 in China. Sci Rep 2016;22;6:28414.
25. Niemann AC, Reid AT, Smith J, James Hammond J, DeBolle AS, Wei I, et al. Association of patient age with high-risk pathologic features in papillary thyroid cancer. J Surg Res 2017;211:228-32.
26. Chávez Tostado KV, Velázquez-Fernandez D, Chapa M, Pantoja Millán JP, Salazar MS, Herrera MF. Substernal goiter: correlation between grade and surgical approach. Am Surg 2018;84:262-6.
27. Moten AS, Thibault DP, Willis AW, Willis AI. Demographics, disparities, and outcomes in substernal goiters in the United States. Am J Surg 2016;211:703-9.

The European Research Journal 2021;7(2):184-191 Original Article

DOI: 10.18621/eurj.678454 *Emergency Medicine*

Is the neutrophil/lymphocyte rate as effective as CURB-65 in the patient management of the community-acquired pneumonia patients admitted to the Emergency Medicine?

İlker Barut, Melih Yüksel, Halil Kaya, Zülfi Engindeniz

Department of Emergency Medicine, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey

ABSTRACT

Objectives: The aim of this study was to identify the patients with community-acquired pneumonia (CAP) in emergency departments, and to compare CURB-65 scoring system and Netrofil/Lymphocyte Ratio (NLO) which are some of the commonly used blood parameters to make an inpatient or outpatient decision quickly and effectively.

Methods: This study was performed retrospectively by examining the files of 442 patients who were admitted to the adult emergency department of Bursa Yüksek İhtisas Training and Research Hospital between September 1, 2017 and October 31, 2018. The demographic characteristics, physical examination findings, laboratory results, hospitalizations, and CURB-65 scores of the patients included in the study were recorded on a pre-prepared paper and electronic form and statistical analyzes of these data were conducted.

Results: Two hundred and fifty-five (57.69%) patients were male and the mean age was 70.93 years. The mean NLO value was 9.85, the mean MPV value was 8.62, the mean eosinophil value was 0.15 and the mean CURB-65 score was 1.85. When the post hoc paired group comparison was conducted for the mean NLR, it was found that the other groups differed from each other except the groups admitted to the intensive care unit and the service. Glasgow Coma Scale score and CURB-65 score were found to be significant predictors for hospitalization to service and intensive care unit ($p < 0.05$).

Conclusions: We think that NLR may be useful in decision-making process, especially in prospective studies, although the use of NLR in patients with CAP is not statistically significant. In this study, we also examined that CURB-65 is an effective scoring system in the management of this patient group.

Keywords: Emergency department, community-acquired pneumonia, CURB-65, Netrofil/lymphocyte ratio

Pneumonia is an acute infection of the lung parenchyma and is one of the major causes of morbidity and mortality [1]. According to World Health Organization data, it is the 4th most common cause of death worldwide [2]. Pneumonia is the third most common cause of hospitalization in the USA and causes an average of 544,000 hospitalizations from the emergency departmentper year [3]. Community-acquired pneumonia (CAP) is defined as an acute lung infection involving alveoli in patients who have not recently received medical care [4]. CAP causes significant morbidity and mortality, especially in the elderly patients and patients with significant comorbidity. CAP is affected by the patient's comorbidities and

Received: ***January 22, 2020;*** *Accepted:* ***April 23, 2020;*** *Published Online:* ***June 22, 2020***

How to cite this article: *Barut İ, Yüksel M, Kaya H, Engindeniz Z. Is the neutrophil/lymphocyte rate as effective as CURB-65 in the patient management of the community-acquired pneumonia patients admitted to the Emergency Medicine?. Eur Res J 2021;7(2);184-191. DOI: 10.18621/eurj.678454*

Address for correspondence: *Melih Yüksel, MD., Assistant Professor, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Department of Emergency Medicine, Bursa, Turkey. E-mail: melihdr@gmail.com*

e-ISSN: 2149-3189

may alter the course of existing diseases and decompensate them. Therefore, the main problem for CAP in the emergency department is to define the patient who will experience acute respiratory failure or multiple organ failure [5-7].

Various decision support systems are being developed to evaluate the pneumonia clinic. Pneumonia Severity Index (PSI), which emerged in 1997, and CURB-65, a scale of confusion, uremia, respiratory rate, blood pressure and parameters above 65 years of age,proposed in 2003, are two current and frequently used examples [8, 9].

Neutrophil/lymphocyte Ratio (NLR) is a simple parameter used to easily assess a person's inflammatory state. NLR has been recognized not only as an indicator of acute viral or bacterial infection but also as a marker of the systemic inflammatory response in some studies [10]. It has been shown to be used as a risk factor in determining the prognosis and mortality of sepsis, pulmonary embolism, cardiovascular system and neurovascular diseases [11-14].

The aim of this study was to define the patients with CAP in the emergency department and to compare NLR and CURB-65 scoring system, which aresome of the commonly used blood parameters to decide the inpatient or outpatient treatment quickly and effectively.

METHODS

Patients who were admitted to the adult emergency department of Bursa Higher Specialization Training and Research Hospitalbetween September 2017 and October 2018 and diagnosed as CAP were included in this retrospective single-center study. A total of 2,000 patients were diagnosed as CAP and 442 patients were included in the study with the exclusion of patients who could not provide data adequacy, who had recently received major trauma, malignancy treatment or subsequent malignancy diagnosis. Demographic characteristics, comorbidities, blood pressure, pulse rate, peripheral saturation, electrocardiogram (ECG) findings, CURB-65 scores, Glasgow Coma Scale (GCS), white cell count, neutrophil, lymphocyte, NLR and eosinophil values, mean platelet volume (MPV), emergency room discharge, service and intensive care unit hospitalization were examined.

Statistical Analysis

Data were analyzed via SPSS 21.0 (SPSS Inc., Chicago, IL, USA) software. Results were expressed as number, percentage, mean, median, minimum-maximum values, and standard deviation. The “Outcome” variable (Discharge / Admission to the service / Admission to the Intensive Care unit) was used in the analyzes. The suitability of the numerical variables to

Table 1. Descriptive statistics regarding the numerical variables

	Mean	SD	Median	Lowest	Highest
Age	70.93	16.32	75.00	18.00	105.00
Systolic blood pressure (mmHg)	129.36	29.52	126.50	50.00	242.00
Diastolic blood pressure (mmHg)	77.82	17.00	78.50	29.00	163.00
Pulse/min	101.79	21.04	100.00	41.00	170.00
Peripheral oxygen saturation (%)	90.52	7.26	92.00	54.00	100.00
GCS score	13.89	2.00	15.00	5.00	15.00
CURB 65 score	1.85	1.10	2.00	0.00	4.00
White blood cell	12.84	6.58	11.60	2.35	54.90
Neutrophil	9.89	6.17	8.30	0.40	50.50
Lymphocyte	1.91	2.18	1.40	0.20	19.90
NLO	9.58	10.76	5.65	0.06	73.00
MPV	8.62	1.29	8.60	5.70	14.10
Eosinophil	0.15	0.82	0.01	0.00	14.70

SD = Standard deviation, GCS = Glasgow Coma Scale, NLO = Neutrophil/Lymphocyte Ratio

Table 2. Distribution of numerical variable sex a mined according to out come of patients

	Outcome							
	Discharged		Admission to the service		Admission to the intensive care unit			
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	H*	*p* value
Age (years)	67.13 ± 17.81	71.5 (18-93)	70.85 ± 14.73	74.00 (22-94)	77.68 ± 13.10	80 (30-105)	31.627	**< 0.001**
SBP (mmHg)	134.48 ± 26.02	130 (50-242)	131.87 ± 28.97	128.00 (57-216)	117.30 ± 32.69	110 (52-242)	32.240	**<0.001**
DBP (mmHg)	82.13 ± 14.43	80 (60-156)	78.36 ± 17.08	77.00 (45-140)	69.61 ± 18.22	68 (29-163)	49.080	**< 0.001**
Pulse/min	96.37 ± 19.32	95 (55-164)	106.76 ± 18.28	104.50 (70-158)	105.07 ± 24.79	105 (41-170)	26.892	**< 0.001**
SPO2 (%)	92.75 ± 6.34	94 (54-100)	90.05 ± 6.47	90.00 (56-100)	87.22 ± 8.32	88.5 (62-100)	53.567	**< 0.001**
GKS score	14.85 ± 0.55	15 (10-15)	14.59 ± 0.76	15.00 (11-15)	11.30 ± 2.44	12 (5-15)	200.916	**< 0.001**
CURB 65 score	0.98 ± 0.72	1 (0-4)	2.01 ± 0.46	2.00 (0-4)	3.15 ± 0.78	3 (0-4)	291.202	**< 0.001**
WBC	11.03 ± 4.72	10.2 (3.6-29.1)	14.06 ± 6.81	13.00 (2.90-40.86)	14.52 ± 8.16	13.2 (2.35-54.9)	25.039	**< 0.001**
Neutrophils	7.99 ± 4.49	7.1 (0.5-27.1)	11.04 ± 6.33	9.70 (0.40-38.58)	11.80 ± 7.50	10.5 (1-50.5)	35.164	**< 0.001**
Lymphocytes	2.13 ± 2.39	1.61 (0.3-19.9)	2.00 ± 2.42	1.30 (0.20-16.10)	1.42 ± 1.18	1 (0.2-7.4)	24.595	**< 0.001**
Neutrophil / lymphocyte	6.42 ± 7.38	4 (0.11-44.33)	10.76 ± 11.31	6.89 (0.06-59.35)	13.61 ± 13.20	9.04 (0.16-73)	57.410	**< 0.001**
MPV	8.50 ± 1.27	8.35 (5.8-12.1)	8.64 ± 1.22	8.60 (5.70-12.10)	8.83 ± 1.41	8.7 (6-14)	3.431	0,180
Eosinophil	0.13 ± 0.23	0.10 (0-2.3)	0.19 ± 1.26	0.02 (0.00-14.70)	0.15 ± 0.80	0 (0-7.2)	30.956	**< 0.001**

SBP = systolic blood pressure, DBP =diastolic blood pressure, SPO2 = Peripheral oxygen saturation, MPV = mean platelet volume, GCS = Glasgow coma scale, WBC = White blood cell, *Kruskal-Wallis

normal distribution was examined by the Kolmogorov-Smirnov test. The Chi-square test, Spearman correlation analysis and Kruskal-Wallis analysis were used in pairwise comparisons. Tamhane T2 test was used as post hoc analysis. Multinomial logistic regression analysis was used to answer the question "Can the clinical judgment be measured during hospitalization decision-making?".The statistical significance level was considered as $p < 0.05$.

RESULTS

A total of 442 patients were included in the study. Two hundred and fifty-five (57.69%) of the patients were male and 187 (42.31%) were female. The mean age of the patients was 70.93, the mean GCS score was 13.89, the mean CURB-65 score was 1.85 and the mean NLR rate was 9.58 (Table 1). When the outcome of the patients was examined, it was found that 43.9%

Table 3. Pairwise comparison of the mean CURB 65 scores between the groups

(I) Outcome	(J) Outcome	Difference (I-J)	*p* value	95% Confidence Interval	
				Lower	Upper
Discharged	Admission to the service	- 1.023	**< 0.001**	- 1.18	- 0.87
	Admission to the intensive care unit	- 2.169	**< 0.001**	- 2.38	- 1.95
Admission to the service	Discharged	1.023	**< 0.001**	0.87	1.18
	Admission to the intensive care unit	- 1.146	**< 0.001**	- 1.35	- 0.94
Admission to the intensive care unit	Discharged	2.169	**< 0.001**	1.95	2.38
	Admission to the service	1.146	**< 0.001**	0.94	1.35

Table 4. Pairwise comparison of the mean neutrophil / lymphocyte ratio between the groups

(I) Outcome	(J) Outcome	Difference (I-J)	*p* value	95% Confidence Interval	
				Lower	Upper
Discharged	Admission to the service	- 4.34028	**< 0.001**	- 6.9944	- 1.6862
	Admission to the intensive care unit	- 7.19192	**< 0.001**	- 10.4775	- 3.9063
Admission to the service	Discharged	4.34028	**< 0.001**	1.6862	6.9944
	Admission to the intensive care unit	- 2.85164	0.203	- 6.6590	0.9557
Admission to the intensive care unit	Discharged	7.19192	**< 0.001**	3.9063	10.4775
	Admission to the service	2.85164	0.203	- 0.9557	6.6590

were discharged, 31.0% were hospitalized in the service and 25.1% were hospitalized in the intensive care unit. On the other hand, when the outcome of the patients and numerical variables were compared, it was seen that all variables except MPV differed between the groups (Table 2).

When post hoc paired group comparisons were conducted for CURB 65 mean scores, it was found that all groups differed from each other (Table 3). When the post hoc paired group comparison was conducted for the mean NLR, it was found that the other groups differed from each other except the groups that were admitted to the intensive care unit and the service (Table 4).

When the pairwise correlations between numerical variables are examined, it is considered that many variables are related to each other (Table 5).

A multinomial logistic regression analysis was performed to investigate the independent factors affecting the outcome of the emergency department of the patients, which is the main outcome measure of the study. Among the variables that were found significant in pairwise comparisons, age, systolic blood pressure, diastolic blood pressure, pulse, peripheral oxygen saturation, GCS score, CURB-65 score, BK, NLR and Eosinophil were taken ascovarianceto the regression model. Discharge status was taken as the reference category. In the regression analysis, a Nagelkerke R square value of 82.0% was obtained. GCS score and CURB-65 score were found to be significant predictors for hospitalization and intensive care unit admission (Table 6).

DISCUSSION

CAP increases the number of hospital admissions and treatment costs worldwide. It is also responsible for a significant portion of labor losses and mortality [15, 16]. Annual incidence in Europe is reported to be 0.5-1.1% [17]. In a study conducted in Finland, the frequency of pneumonia was11.6 / 1000 persons annually, and hospitalization rates werefound to be 2.67/1,000 for males and 1.10/1,000 for females [18]. In the USA, there were 107-370 cases per 100,000 between the ages of 18-64, whereas there were 630-5,697 cases per 100,000 over 65 years [19]. In our country, according to the results of a project carried out by the Ministry of Health, RefikSaydam National Public Health Agency and Baskent University, pneumonia was the 15th with a frequency of 1.15% among the first 20 acute and chronic diseases diagnosed by physicians [20]. In our study, the incidence of CAP was 0.4%, which is contrary to the literature. This may be due to the presence of a Chest Diseases Hospital in a location that is very close to our hospital, and thus,

Table 5. Correlations between numerical variables

		SBP	DBP	Pulse	POS	GKS	CURB 65	WB	Neutrophil	Lymphocyte	N/L	MPV	Eosinophil
Age	r	- 0.008	- 0.069	- 0.010	- 0.115	- 0.182	0.357	- 0.045	- 0.001	- 0.126	0,107	-0,014	- 0,070
	p	0.860	0.147	0.832	0.016	**< 0.001**	**< 0.001**	0.343	0.979	**0.008**	**0,025**	0,773	0,144
SBP	r		0.680	- 0.066	0.014	0.309	- 0.229	- 0.171	- 0.183	0.075	-0,187	-0,008	0,135
	p		**< 0.001**	0.169	0.769	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	0.114	**< 0.001**	0,860	**0,005**
DBP	r			- 0.020	0.047	0.282	- 0.301	- 0.139	- 0.159	0.066	- 0,154	-0,022	0,098
	p			0.675	0.325	**< 0.001**	**< 0.001**	**0.003**	**0.001**	0.169	**0,001**	0,643	**0,040**
Pulse	r				- 0.156	- 0.141	0.181	0.204	0.203	- 0.059	0,175	0,089	- 0,130
	p				**0.001**	**0.003**	**< 0.001**	**< 0.001**	**< 0.001**	0.221	**< 0.001**	0,064	**0,006**
SPO2	r					0.280	- 0.336	- 0.098	- 0.106	0.108	- 0,146	0,027	0,122
	p					**< 0.001**	**< 0.001**	**0.040**	**0.026**	**0.023**	**0,002**	0,577	**0,010**
GKS	r						- 0.615	- 0.137	- 0.154	0.172	- 0,243	-0,117	0,220
	p						**< 0.001**	**0.004**	**0.001**	**< 0.001**	**< 0.001**	**0,014**	**< 0.001**
CURB 65	r							0.182	0.224	- 0.233	0,328	0,066	- 0,253
	p							**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	0,166	**< 0.001**
WB	r								0.924	0.148	0,448	0,038	- 0,102
	p								**< 0.001**	**0.002**	**< 0.001**	0,427	**0,031**
Neutrophil	r									- 0.041	0,633	0,060	- 0,162
	p									0.390	**< 0.001**	0,211	**0,001**
Lymphocyte	r										-0,764	0,054	0,404
	p										**< 0.001**	0,261	**< 0.001**
NLR	r											0,002	- 0,405
	p											0,967	**< 0.001**
MPV	r												0,107
	p												**0.024**

SBP = Systolic blood pressure, DBP = Diastolic blood pressure, SPO2 = Peripheral oxygen saturation, GCS = Glasgow coma scale, WB = White blood cell, NLR = Neutrophil/lymphocyte ratio, MPV = Mean platelet volume

the majority of patients go to this center.

According to insurance companiesdata in Germany, 46.5% of 660,000 CAP cases were hospitalized per year and the majority of these patients are over 60 years of age [21, 22]. In another study conducted in Germany, the mean age was 76 for hospitalized patients [23]. Another study conducted in Australia found the rate of hospitalizations as 563 per 100,000 in the 65 to 74 age group [24]. In our study, the mean age of the patients who were discharged was 67.17, the mean age of the patients who were hospitalized in the service was 70.85 and the mean age of the patients who were admitted to the intensive care unit was 77.68. The mean age of the hospitalized patients in our study was consistent with other studies in the literature.

In a study conducted in the UK, approximately 1/3 of CAP patients were treated as inpatient and 2/3 of them were treated as outpatients. In that study, hospital-acquired pneumonia and aspiration pneumonia were excluded [25]. In another study, the incidence of pneumonia was 567/100,000 per year, and 48% of patients with pneumonia were hospitalized [26]. In a study conducted in the United States, the rate of hospitalization was identified as 24.8 per 10,000 adults [19]. In our study, 56% of the patients were hospitalized. Correlation with mean and median age increase in patients with intensive care and service hospitalization is a general result that was found in our study and consistent with the literature. As the age increases, the physical capacity decreases and the decompensation rates due to the comorbidities also increase, which has a negative effect on recovery times and the intensity of the health services [27].

While CURB -65 is recommended in European countries such as England and Sweden, PSI is mostly used in the US and Australia. It is observed that CURB-65 and PSI scoring systems have negative pre-

Table 6. Multinomial logistic regression analysis

Outcome		B	Wald	*p* value	Exp(B)	95% confidence interval	
						Lower	Upper
Admission to the service	Constant	4.720	1.383	0.240			
	Age	- 0.014	1.567	0.211	0.987	0.966	1.008
	Systolic blood pressure	0.012	2.029	0.154	1.012	0.996	1.028
	Diastolic blood pressure	- 0.024	2.826	0.093	0.976	0.950	1.004
	Pulse	0.024	7.757	**0.005**	1.024	1.007	1.041
	Peripheral oxygen saturation	- 0.043	3.265	0.071	0.958	0.914	1.004
	GKS score	- 0.470	4.727	**0.030**	0.625	0.409	0.955
	CURB 65 score	2.550	73.891	**< 0.001**	12.812	7.163	22.917
	WB	0.047	2,198	0.138	1.048	0.985	1.114
	Neutrophil/lymphocyte	0.025	1.425	0.233	1.025	0.984	1.067
	Eosinophil	0.092	0.130	0.719	1.096	0.665	1.809
Admission to the intensive care unit	Constant	21.654	15.489	**< 0.001**			
	Age	0.014	0.384	0.536	1.014	0.971	1.058
	Systolic blood pressure	0.013	0.887	0.346	1.013	0.986	1.040
	Diastolic blood pressure	- 0.037	2.725	0.099	0.964	0.923	1.007
	Pulse	0.008	0.360	0.549	1.008	0.981	1.037
	Peripheral oxygen saturation	- 0.073	3.350	0.067	0.930	0.860	1.005
	GKS score	-1.919	55.439	**< 0.001**	0.147	0.089	0.243
	CURB 65 score	4.843	87.966	**< 0.001**	126.814	46.096	348.878
	WB	0.037	0.520	0.471	1.038	0.939	1.147
	Neutrophil/lymphocyte	0.020	0.388	0.533	1.020	0.958	1.086
	Eosinophil	0.205	0.528	0.467	1.228	0.706	2.136

Reference category = Discharged

dictive values but relatively low positive predictive values [28]. The increase in hospitalization rates with CURB-65 is an expected result since it is the standard criterion in the study. In our study, CURB-65 score was found to be significant predictors for both hospitalizations to service and intensive care unit.

NLR, MPV and eosinophil values that we usedas blood parameters have been investigated in various studies to confirm the presence of infection and to evaluate clinical progression [29, 30]. In a previous study in our country, the NLR value in healthy population was found to be 1.7. In other studies, values were determined as 1.68 to 1.9 [31]. The NLR value gradually increases until the age of 20, a plateau period is reached and the NLR value increasesover the age of 60. This increase, especially over the age of 60, can be due to physiological conditions such as menopause and andropause. The mean NLR was found to be 2.96 in males and 2.49 in females over the age of 70 years [31]. It was reported that the NLR values in CAP were over 13 in inpatients and 18in the patients who were followed up in the intensive care unit. The mortality rate was higher in patients with NLR values of 23 and over [32]. NLR has been previously described as a predictor of bacteremia [33]. A value of < 3.0 for NLR may be used to prove the absence of infection, while a value of > 10, when taken as a cut off value, is efficient enough to be considered equivalent to other infection predictors such as CRP, PCT [29, 34]. The decrease in lymphocyte value was found to be determinant in the decision of hospitalization in the intensive care unit.

Even though there are favorable or unfavorable studies regarding the effectiveness of their individual use, it was stated even in th eunfavorable studies that they should be considered when deciding discharge / outpatient treatment or hospitalization [32]. In our study, the mean NLR value was found to be 10.76 in the inpatients and 13.61 in the intensive care unit patients. Although NLR value was significantly different in pairwise comparisons, it did not become statistically significant when evaluated as a whole.

Limitations

As the study was performed retrospectively, history, some of the vital signs and comorbidities were not examined sufficiently. In addition, short, medium and long-term morbidity and mortality rates could not be determined in this study, which is a limitation of the study. A prospective study may investigate this issue.

CONCLUSION

In conclusion, we think that NLR may be useful in decision-making process, especially in prospective studies, although the use of NLR in patients with CAP is not statistically significant. In this study, we also examined that CURB-65 is an effective scoring system in the management of this patient group.

Authors' Contribution

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

Conflict of interest

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

Financing

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

REFERENCES

1. Lanks CW, Musani AI, Hsia DW. Community-acquired pneumonia and hospital-acquired pneumonia. Med Clin North Am 2019;103:487-501.
2. The 10 leading causes of death in the world: World Health Organization 2018. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
3. Rider AC, Frazee BW. Community-acquired pneumonia. Emerg Med Clin North Am 2018;36:665-83.
4. Musher DM, Thorner AR. Community-acquired pneumonia. N Eng J Med 2014;371:1619-28.
5. Janssens JP, Krause KH. Pneumonia in the very old. Lancet Infect Dis 2004;4:112-24.
6. Bellelli G, Guerini F, Cerri AP, Trabucchi M. A sudden decline in mobility status as an early sign of acute infection in elderly patients: evidence from three case reports. Aging Clin Exp Res 2012;24:281-4.
7. Khokhar SR, Stern Y, Bell K, Anderson K, Noe E, Mayeux R, et al. Persistent mobility deficit in the absence of deficits in activities of daily living: a risk factor for mortality. J Am Geriatr Soc 2001;49:1539-43.
8. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003;58:377-82.
9. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Eng J Med 1997;336:243-50.
10. Li J, Chen Q, Luo X, Hong J, Pan K, Lin X, et al. Neutrophil−to−lymphocyte ratio positively correlates to age in healthy population. J Clin Lab Anal 2015;29:437-43.
11. Hwang SY, Shin TG, Jo IJ, Jeon K, Suh GY, Lee TR, et al. Neutrophil-to-lymphocyte ratio as a prognostic marker in critically-ill septic patients. Am J Emerg Med 2017;35:234-9.
12. Jia D, Liu F, Zhang Q, Zeng GQ, Li XL, Hou G. Rapid onsite evaluation of routine biochemical parameters to predict right ventricular dysfunction in and the prognosis of patients with acute pulmonary embolism upon admission to the emergency room. J Clin Lab Anal 2018;32:e22362.
13. Wang X, Zhang G, Jiang X, Zhu H, Lu Z, Xu L. Neutrophil to lymphocyte ratio in relation to risk of all-cause mortality and cardiovascular events among patients undergoing angiography or cardiac revascularization: a meta-analysis of observational studies. Atherosclerosis. 2014;234:206-13.
14. Gokhan S, Ozhasenekler A, Mansur Durgun H, Akil E, Ustundag M, Orak M. Neutrophil lymphocyte ratios in stroke subtypes and transient ischemic attack. Eur Rev Med Pharmacol Sci 2013;17:653-7.
15. Pinner RW, Teutsch SM, Simonsen L, Klug LA, Graber JM, Clarke MJ, et al. Trends in infectious diseases mortality in the United States. JAMA 1996;275:189-93.
16. Acute respiratory infections in under-fives: 15 million deaths a year. Lancet (London, England). 1985;2:699-701.
17. BTS Guidelines for the Management of Community Acquired Pneumonia in Adults. Thorax 2001;56 Suppl 4:Iv1-64.
18. Jokinen C, Heiskanen L, Juvonen H, Kallinen S, Karkola K, Korppi M, et al. Incidence of community-acquired pneumonia in the population of four municipalities in eastern Finland. Am J Epidemiol 1993;137:977-88.
19. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, et al. Community-acquired pneumonia requiring hospitalization among US adults. N Eng J Med 2015;373:415-27.
20. Başkent Üniversitesi Ulusal Hastalık Yükü ve Maliyeti Etkinlik Projesi.TC Sağlık Bakanlığı Sağlık İstatistikleri Yıllığı.Refik Saydam Hıfzıssıhha Merkezi Başkanlığı Hıfzıssıhha Mektebi

Müdürlüğü.2004.
21. Breitling LP, Saum KU, Schottker B, Holleczek B, Herth FJ, Brenner H. Pneumonia in the noninstitutionalized older population. Dtsch Arztebl Int 2016;113:607-14.
22. Kolditz M, Tesch F, Mocke L, Hoffken G, Ewig S, Schmitt J. Burden and risk factors of ambulatory or hospitalized CAP: A population based cohort study. Respir Med 2016;121:32-8.
23. Kolditz M, Ewig S. Community-acquired pneumonia in adults. Dtsch Arztebl Int 2017;114:838.
24. Dirmesropian S, Liu B, Wood JG, MacIntyre CR, McIntyre P, Karki S, et al. Pneumonia hospitalisation and case-fatality rates in older Australians with and without risk factors for pneumococcal disease: implications for vaccine policy. Epidemiol Infect 2019;147:e118.
25. Guest JF, Morris A. Community-acquired pneumonia: the annual cost to the National Health Service in the UK. Eur Respir J 1997;10:1530-4.
26. Cataudella E, Giraffa CM, Di Marca S, Pulvirenti A, Alaimo S, Pisano M, et al. Neutrophil-to-lymphocyte ratio: an emerging marker predicting prognosis in elderly adults with community-acquired pneumonia. J Am Geriatr Soc 2017;65:1796-801.
27. Rozenbaum MH, Mangen MJ, Huijts SM, van der Werf TS, Postma MJ. Incidence, direct costs and duration of hospitalization of patients hospitalized with community acquired pneumonia: a nationwide retrospective claims database analysis. Vaccine 2015;33:3193-9.
28. Marrie T, Lau C, Wheeler S, Wong C, Vandervoort M, Feagan B, et al. A controlled trial of a critical pathway for treatment of community-acquired pneumonia. Community-Acquired Pneumonia Intervention Trial Assessing Levofloxacin. JAMA 2000;283:749-55.
29. Karakonstantis S, Kalemaki D, Tzagkarakis E, Lydakis C. Pitfalls in studies of eosinopenia and neutrophil-to-lymphocyte count ratio. Infect Dis 2018;50:163-74.
30. Rodriguez-Fernandez A, Andaluz-Ojeda D, Almansa R, Justel M, Eiros JM, Ortiz de Lejarazu R. Eosinophil as a protective cell in S. aureus ventilator-associated pneumonia. Mediators Inflamm 2013;2013:152943.
31. Aydın İ, Ağıllı M, Aydın FN, Kurt YG, Çaycı T, Taş A, et al. [The reference ranges of neutrophil-lymphocyte ratio in different age groups]. Gülhane Tıp Derg 2015;57:414-8. [Article in Turkish]
32. De Jager CP, Wever PC, Gemen EF, Kusters R, van Gageldonk-Lafeber AB, van der Poll T, et al. The neutrophil-lymphocyte count ratio in patients with community-acquired pneumonia. PloS One 2012;7:e46561.
33. Zahorec R. Ratio of neutrophil to lymphocyte counts--rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy 2001;102:5-14.
34. Ljungstrom L, Pernestig AK, Jacobsson G, Andersson R, Usener B, Tilevik D. Diagnostic accuracy of procalcitonin, neutrophil-lymphocyte count ratio, C-reactive protein, and lactate in patients with suspected bacterial sepsis. PloS One 2017;12:e0181704.

The European Research Journal 2021;7(2):192-195 Original Article

DOI: 10.18621/eurj.672787 *Nephrology*

The effectiveness of oral protein supplementation in malnourished peritoneal dialysis patients

Mehmet Usta[1], Alparslan Ersoy[2], Yavuz Ayar[1]

[1]*Department of Nephrology, Bursa City Hospital, Bursa, Turkey*
[2]*Department of Nephrology, Bursa Uludağ University School of Medicine, Bursa, Turkey*

ABSTRACT

Objectives: Malnutrition is a common problem in chronic renal disease patients during pre-dialysis and dialysis, leading to increased cardiovascular diseases and mortality. This study aimed to evaluate the efficacy of supplemental protein supplementation on malnutrition in peritoneal dialysis patients.

Methods: Eighty-four stable adult peritoneal dialysis patients included in this study. In addition to the standard diets, oral nutritional product (372 calories, 61 g protein, 30 g glutamine, and 30 g arginine/100 g powder sachet twice a day) gave to patients. Before the study and after three months from the supportive therapy; anthropometric measurements with serum urea, creatinine, total protein, albumin, cholesterol, KtV, body mass index was analyzed.

Results: The mean age of peritoneal dialysis patients was 60 (46-78) years. Serum urea levels from 96 ± 44 to 109 ± 42 mg/dL (p = 0.007), total protein levels from 5.85 ± 0.68 to 6.18 ± 0.66 g/dL (7.8%, p = 0.007), albumin levels increased from 3.02 ± 0.27 to 3.32 ± 0.34 g/dL (11.7%, p = 0.003) increased significantly after an average of 0.43 g/kg protein and 178 cal/day energy support.

Conclusions: Albumin is an indicator of malnutrition related mortality. Therefore, using of protein nutritional products in addition to standard treatment may be beneficial for malnourished peritoneal dialysis patients.

Keywords: Peritoneal dialysis, malnutrition, albumin, protein supplementation

Nutrition plays an important role in chronic kidney diseases (CKD). The most important reason of protein- energy malnutrition is nutritional deficiency. It is directly related to mortality and morbidity. Inadequate oral intake, metabolic acidosis, chronic inflammation, hormonal and enzymatic changes (such as leptin, parathyroid hormone [PTH], insulin), dietary restriction, gastrointestinal diseases are the main causes of protein energy malnutrition in CKD (Table1). In addition, peritoneal dialysis (PD) patients with abdominal distention and reflux due to the pressure of intraabdominal fluid are the most important causes of nutritional disorders. Insulin resistance, metabolic acidosis, vitamin D deficiency, hypercalcemia-hypocalcemia, secondary hyperparathyroidism, hyperphosphatemia, renal anemia, uremic bone diseases, chronic inflammation, intermittent acute diseases should be taken into consideration to prevent malnutrition that affects mortality and morbidity [1-9].

Therefore, nutritional status and disorders in dialysis patients should be followed carefully and closely.

Received: ***January 9, 2020;*** ***Accepted:*** ***December 8, 2020;*** ***Published Online:*** ***January 5, 2021***

How to cite this article: *Usta M, Ersoy A, AyarY. The effectiveness of oral protein supplementation in malnourished peritoneal dialysis patients. Eur Res J 2021;7(2):192-195. DOI: 10.18621/eurj.672787*

Address for correspondence: *Yavuz Ayar, MD., Associate Professor, Bursa City Hospital, Department of Nephrology, Bursa, Turkey*
E-mail: yavuzayar@hotmail.com

e-ISSN: 2149-3189

In this study, we investigated the presence of protein energy malnutrition in peritoneal dialysis patients and detect it early and correct with short term supportive therapy.

METHODS

Patients

Eighty-four stable adult peritoneal dialysis patients evaluated. Patients with malignancy, acute-chronic infection or inflammatory disease and patients with normal serum albumin values (over 3.5 g/dL) excluded from the study. Malnutrition detected in 17 patients. Malnutrition assessed by serum albumin and creatinine levels, dietary protein and energy intake and obtained from interviews and follow-up. Serum albumin value below 3.5 g/dL or patients with insufficient of oral intake considered to be malnourished. Protein nitrogen appearance, subjective general evaluation and anthropometric measurements used to evaluate nutritional status in patients receiving PD treatment. Oral nutritional product (372 calories, 61 g protein, 30 g glutamine, and 30 g arginine/100 g powder sachet twice a day) gave to patients who detected malnutrition in addition to the standard diets. Before the study and after three months from the supportive therapy; anthropometric measurements with serum urea, creatinine, total protein, albumin, periton equilibrium test (PET), cholesterol, peritoneal dialysis adequacy test (Kt/V) and body mass index (BMI) evaluated.

Statistical Analysis

Data analyzed using Statistical Package for the Social Sciences (SPSS) version 21 (IBM Acquires SPSS Inc., Somers, NY, USA). Descriptive statistical methods (mean, median, frequency, standard deviation, ratio) compared with Pearson Chi-square, paired t and Mann Whitney U test used to compare two groups of variables that did not show normal distribution. Differences considered significant if $p < 0.05$.

RESULTS

Mean age of peritoneal dialysis patients was 60 years (46-78). Patients with malnutrition were examined for urea, creatinine, Kt/V, PET, total protein, albumin, cholesterol, phosphorus, transferrin saturation, BMI, thickness of triceps skin before and after 3 months of supportive therapy. As a result of the PET, 19 patients had high permeability, 25 patients were near high medium permeability, 27 patients were near low medium permeability, and 13 patients were low permeability. In malnourished patients, 11 had low permeability, 4 had near low medium and 1 patient had near high medium and high permeability. In addition to the standard dietary intake, patients evaluated and tested 3 months after supplementation. On average of 0.43 g/kg protein and 178 cal/day energy supplementation which results were significant recorded after the support. Serum urea levels from 96 ± 44 to 109 ± 42 mg/dL ($p = 0.007$), total protein levels from 5.85 ± 0.68 to 6.18 ± 0.66 g/dL (7.8%, $p = 0.007$), albumin levels from 3.02 ± 0.27 to 3.32 ± 0.34 g/dL (11.7%, $p = 0.003$) increased significantly. There was no significant change in other parameters. The clinical and laboratory results are summarized in Table 2.

Table 1. Causes of protein energy malnutrition in CKD patients

Reduction in oral intake
Diet restriction
Metabolic acidosis
Inflammation
Hormonal and enzymatic disorders Erythropoietin, PTH, leptin, insulin, etc.
Gastrointestinal disorders

CKD = Chronic kidney disease, PTH = Parathormone

DISCUSSION

PD, HD and renal transplantation are the renal replacement therapies used for end-stage renal disease patients. The incidence of malnutrition in PD is high [2]. In a study, the prevalence of malnutrition was 42% in patients receiving with PD treatment, while the prevalence in HD patients was 32% [3]. In this study, serum total protein and albumin levels were low. Negative nutritional parameters in PD patients are directly related to increased morbidity and mortality as well as

Table 2. Laboratory and clinical features

	Beginning	After 3 months	*p* value
Kt/V	1.96 ± 0.32	2.01 ± 0.35	0.224
Serum urea (mg/dL)	96 ± 44	109 ± 42	**0.007**
Serum creatinine (mg/dL)	7.5 ± 1.76	7.6 ± 1.96	0.835
Serum total protein (mg/dL)	5.85 ± 0.68	6.18 ± 0.66	**0.007**
Serum albumin (g/dL)	3.02 ± 0.27	3.32 ± 0.34	**0.003**
Serum phosphorus (mg/dL)	3.98 ± 1.54	3.58 ± 1.32	0.186
Total cholesterol (mg/dL)	152 ± 34.8	160 ± 39.2	0.311
Body mass index (kg/m^2)	21.6 ± 3.96	21.8 ± 4.12	0.794
Triceps skinfold (mm)	10.14 ± 4.81	10.89 ± 4.76	0.528

Kt/V = peritoneal dialysis adequacy test.

HD. These include low serum albumin, creatinine, body mass index, blood urea nitrogen, subjective global evaluation and nutritional scores. Allow value of serum albumin is considered to be 3.5-4.0 g/dl, which may increase the relative risk of death as compared to 4.0 g/dl or higher. On the other hand, decline in creatinine (an indicator of muscle mass) and ideal weight have also associated with increased risk of death in the patient population [8, 10, 11]. However, it is not clear whether nutritional support is beneficial for PD patients with improvement in these parameters. There are no multicenter and large studies on this subject. In our single-center study, we detected 17 malnutrition patients in total of 84 PD patients (19.5%). In particular, the main causes of malnutrition in PD patients are malnutrition, insufficient dialysis, hormone abnormalities and inflammation [12]. Nutritional education should be given to the patients. Treatment of abnormal hormone levels, inflammation and effective dialysis are important in PD patients. When we analyze the daily protein loss in PD, it is about 10 g. Thirty percent of this protein loss is essential amino acids [13-16]. In severe cases of peritonitis, protein loss may increase up to 100 g per day. Especially infection, inflammation and fluid overload detected in cases with low albumin as a biochemical predictor for malnutrition. These results progress to mortality [17-21]. Similarly, in a study evaluating peritoneal dialysis patients who received protein supplements for six months, malnutrition decreased between 6% and 28%. In another study, protein catabolism rate was lower and albumin level was higher in malnourished patients receiving oral protein supplementation for three months [20, 21]. Therefore, as in our study, PD patients should be closely monitored for malnutrition and supportive treatment. Total protein and albumin increased significantly with supportive treatment in our patients. We did not detect any peritonitis attacks during the study period. Data on oral nutritional support in PD patients are limited. Patient compliance observed important in oral nutrition therapy. Non-compliance and intolerance found to adversely effect on supportive therapy. In our study, we detected three non-compliance of 17 patients (17.6%). This data was equivalent to current studies.

CONCLUSION

Finally; malnutrition is common in peritoneal dialysis patients. PD patients should be followed up frequently and regularly for malnutrition. Particularly at high risk patients with low food intake, infection or inflammation, cardiac overload and anuric status should be monitored more frequently and carefully. In our study, we found significant increase in nutritional indicators, especially albumin, directly related to mortality when supportive therapy was given in addition to patients with malnutrition. But we need more large-scale studies.

Authors' Contribution

Study Conception: MU; Study Design: YA; Supervision: AE; Materials: AE; Data Collection and/or

Processing: MU, YA; Statistical Analysis and/or Data Interpretation: MU; Literature Review: MU; Manuscript Preparation: MU, YA and Critical Review: AE, YA.

Conflict of interest

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

Financing

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

Ethics committee approval

Ethics committee approval was received. Informed consent obtained from the patients.

REFERENCES

1. Ma L, Zhao S. Risk factors for mortality in patients undergoing hemodialysis: a systematic review and metaanalysis. Int J Cardiol.2017;238:151-8.
2. Stenvinkel P, Heimbürger O, Lindholm B. Wasting, but not malnutrition, predicts cardiovascular mortality in end-stage renal disease. Nephrol Dial Transplant 2004;19:2181-3.
3. Kopple JD. National Kidney Foundation K/DOQI Work Group. The National Kidney Foundation K/DOQI clinical practice guidelines for dietary protein intake for chronic dialysis patients. Am J Kidney Dis 2001;38(4Suppl1):S68-73.
4. Uhlig K, Macleod A, Craig J, Lau J, Levey AS, Levin A, et al. Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2006;70:2058-65.
5. LeveyAS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2005;67:2089-100.
6. Mak RH, CheungW. Energy homeostasis and cachexia in chronic kidney disease. Pediatr Nephrol 2006;21:1807-14.
7. LindholmB, Heimbürger O, Stenvinkel P. What are the causes of protein-energy PEW in chronic renal insufficiency? Am J Kidney Dis 2002;39:422-5.
8. Canada-USA (CANUSA) Peritoneal Dialysis Study Group. Adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcomes. J Am Soc Nephrol 1996;7:198-207.
9. Yan X, Yang X, Xie X, Xiang S, Zhang X, Shou Z, et al. Association between comprehensive nutritional scoring system (CNSS) and outcomes of continuous ambulatory peritoneal dialysis patients. Kidney Blood Press Res 2017;42:1225-37.
10. Chung SH, Linholm B, Lee HB. Influence of initial nutritional status on continuous ambulatory peritoneal dialysis patient survival. Perit Dial Int 2000;20:19-26.
11. Nazar CM. Significance of diet in chronic kidney disease. J Nephropharmacol 2013;2:37-43.
12. Wang AY, Sea MM, Ho ZS, Lui SF, Li PK, Woo J. Evaluation of handgrip strength as a nutritional marker and prognostic indicator in peritoneal dialysis patients. Am J Clin Nutr 2005;81:79-86.
13. Mehrotra R, Kopple J. Nutritional management of maintenance dialysis patients: why aren't we doing better? Annu Rev Nutr 2001;21:343-79.
14. Olivares-Gandy HJ, Domínguez-Isidro S, López-Domínguez E, Hernández-VelázquezY, Tapia McClung H, Jorge de-la-Calleja. A telemonitoring system for nutritional intake in patients with chronic kidney disease receiving-peritoneal dialysis therapy. Comput Biol Med 2019;109:1-13.
15. Dombros N, Dratwa M, Feriani M, Gokal R, Heimbürger O, Krediet R, et al; EBPG Expert Group on Peritoneal Dialysis. European best practice guidelines for peritoneal dialysis. 8 Nutrition in peritoneal dialysis. Nephrol Dial Transplant 2005;20 Suppl 9:ix28-ix33.
16. Toigo G, Aparicio M, Attman PO, Cano N, Cianciaruso B, Engel B, et al. Expert working group report on nutrition in adult patients with renal insufficiency (Part 2 of 2). Clin Nutr 2000;19:281-91.
17. Clinical practice guidelines for nutrition in chronic renal failure. K/DOQI, National Kidney Foundation. Am J Kidney Dis 2000;35(6Suppl2):S1-140.
18. Ikizler TA, Cano NJ, Franch H, Fouque D, Himmelfarb J, Kalantar-Zadeh K, et al. Preventionand treatment of protein energy wasting in chronic kidney disease patients. International Society of Renal Nutrition and Metabolism. Kidney Int 2013;84:1096-107.
19. Eustace JA, Coresh J, Kutchey C, Te PL, Gimenez LF, Scheel PJ, et al. Randomized double- blind trial of oral essential amino acids for dialysis-associated hypoalbuminemia. Kidney Int 2000;57:2527-38.
20. González-Espinoza L, Gutiérrez-Chávez J, del Campo FM, Martínez-Ramírez HR, Cortés-Sanabria L, Rojas-Campos E, et al. Randomized, open label, controlled clinical trial of oral administration of an egg albumin-based protein supplement to patients on continuous peritoneal dialysis patients. Perit Dial Int 2005;25:173-80.
21. Moretti HD, Johnson AM, Keeling-Hathaway TJ. Effects of protein supplementation in chronic hemodialysis and peritoneal dialysis patients. J Ren Nutr 2009;19:298-303.

The European Research Journal 2021;7(2):196-202 Original Article

DOI: 10.18621/eurj.607628 PSYCHIATRY

An investigation of the eating attitudes and coping ways with stress among medical students

Esra Doğruel, Selçuk Kırlı

Department of Psychiatry, Bursa Uludağ University School of Medicine, Bursa, Turkey

ABSTRACT

Objectives: The purpose of the current study is to investigate the eating attitudes, coping ways and their relationships among medical students.

Methods: A total of 100 medical students from all class levels of the medical school (except first and final year undergraduates) consisted of the research sample. Demographic Information Form, Eating Attitude Test and Coping with Stress Scale were filled by participants. SPSS 21.0 was used to analyze the data obtained.

Results: Findings of the study showed no significant differences between abnormal and normal eating attitude groups in terms of demographic variables (gender, age and body mass index, class levels). In addition, there was no significant difference between the groups with regard to avoidance coping score and problem focused coping score. However, there was a significant difference between eating attitude groups in terms of seeking social support score. The mean of social support score is higher in the abnormal eating attitude group.

Conclusions: According to our results, abnormal eating attitude group uses more seeking social support coping than normal eating attitude group.

Keywords: Eating attitude, coping ways with stress, medical students

Eating is one of the most important needs for the continuity of life in both humans and animals. Energy needs, social setting, time of day and stress can be counted as an answer of why animals and humans eat [1]. External and internal factors which influence appetite determine what types of food and how much amount of food is consumed by people. Internal factors contain physiological mechanisms of humans affecting appetite and they also include hormones. While food intake is stimulated by neuropeptide-Y, it is reduced by leptin. In addition, various external factors can affect food intake such as social factors (e.g., presence of others) and environmental factors (e.g., food prices) [2].

Alvarenga *et al*. [3] described eating attitudes as "beliefs, thoughts, feelings, behaviors and relationship with food". Various factors play a role in eating attitudes and also in disturbed eating attitudes which are seen as pioneer of eating disorders [4]. Eating disorders are one of the quite common psychiatric disorders in both Turkey and all around the world [5].

Stress is ineluctable phenomena in modern life [6]. It is prevalently believed that stress can have an impact on eating patterns [7]. Even though the nature of the association between eating disorders and stress is not obviously explained, several empirical researches and clinical observations show the relationship between stress and abnormal eating behavior [8, 9]. Moreover, findings about the impact of severity of stress on the eating behavior are controversial. The severity of

Received: ***August 20, 2019;*** *Accepted:* ***October 23, 2019;*** *Published Online:* ***January 7, 2020***

How to cite this article: *Doğruel E, Kırlı S. An investigation of the eating attitudes and coping ways with stress among medical students. Eur Res J 2021;7(2):196-202. DOI: 10.18621/eurj.607628*

Address for correspondence: *Esra Doğruel, MS., Bursa Uludağ University School of Medicine, Department of Psychiatry, Bursa, Turkey*
E-mail: esra.dgrl2@gmail.com

e-ISSN: 2149-3189

stress can be related with both decreased and increased eating behavior. The researchers have conducted a retrospective survey in United States Marines during combat in order to examine eating attitude of marines in this highly stressful situation. The results showed that when they experienced particularly their initial combat, their food intake decreased [10]. On the other hand, the influence of school examination which is a highly stressful event on eating attitude was investigated [8]. The results have indicated that there was a significant difference between examination day and stress-free day in terms of students' total energy intake. This study revealed that the energy intake increases in the major stressful circumstance.

Studies from different samples have reported that some certain groups of people are at higher risk for eating disorders, such as young adults [11]. Previous studies have suggested that eating disorders among college students in Western countries increase [12, 13]. A research conducted in Turkish sample has also revealed that eating disorders are quite prevalent in university students [14].

Coping is defined as "the cognitive and behavioral efforts made to master, tolerate, or reduce external and internal demands and conflicts among them" by Folkman and Lazarus [15]. Indeed, it is a factor determining the effect of stress on health [16]. Thus, it is crucial to apprehend individual's coping ways when under stressful life situation. Folkman and Lazarus [15] suggested two ways of coping: problem-focused coping which refers to focusing on managing and changing what the stressor is in person-environment relationship, and emotion-focused coping which refers to focusing on regulating emotional state regarding some stressful circumstance. Additionally, avoidance coping (getting away from stressor) and approach coping (going towards stressor) is another categorization in the literature [17, 18].

Although there are a lot of studies examining eating disorders, there have been a few studies investigating the relationship between eating attitude and coping ways with stress so far, especially on medical students whose education is pretty stressful. Several stress such as inability to cope were revealed among medical students in the earlier study [19]. Moreover, the transitional period from pre-clinical training to clinical training was also reported as critical phase creating stress among medical students [20]. This paper attempts to investigate eating attitudes which are indicative factor for eating disorders instead of diagnosing participants with a particular disorder and also to examine coping ways with stress. Additionally, the relationship between eating attitudes and coping ways with stress is examined.

METHODS

Participants

The participants were undergraduate medical students in Bursa Uludag University in the 2018-2019 academic year. Participation was based on voluntary. Research inclusion criteria were the absence of any psychiatric disorder and not being international students due to probable cultural differences in eating attitudes. In addition, first year and final year students were excluded from the study. It was considered that first year undergraduates could be stressful because of difficulties in adjustment to the university life such as being away from the home for the first time and final year undergraduates also could be stressful due to preparing Specialty Exam in Medicine (TUS) at the end of the year.

Initially, data was collected from a total of 200 students (110 females and 90 males). The number of participants from each class taking part in the study was determined according to the number of students in the classes. Among these participants, 49 of them were 2nd year, 44 of them were 3rd year, 56 of them were 4th year and 51 of them were 5th year. Thereafter, because the sample was nonclinical and cut off point is not determined for Turkish sample, the students who got 25% highest score in Eating Attitude Test (comparatively abnormal eating attitudes) and who got 25% lowest score in Eating Attitude Test (comparatively normal eating attitudes) were determined as research participants as it was done in the past studies [21-23]. Thus, the certain sample size included 100 students (27 of them were from 2nd year, 21 of them were from 3rd year, 26 of them were from 4th year and 26 of them were from 5th year) in the current study. Their age range was between 18 and 27 years.

Measures and Procedure

The researcher gave a brief introduction about the

present study to the participants and ensured confidentiality to them. Besides the Demographic Information Form, two questionnaires were administered, respectively: Eating Attitude Test and Coping with Stress Scale. Participants were asked to fill all items of these questionnaires and they were encouraged to feel free to ask any question. The tests were lasted approximately 15 minutes by each participant. The study was approved by Bursa Uludag University Faculty of Medicine Clinical Research Ethics Committee.

Demographic Information Form

The researchers developed the form to collect the data describing participants (e.g. sex, age, class level, and so on).

Eating Attitude Test (EAT-40)

It was developed by Garner and Garfinkel [24]. In the present study, it was used to assess eating attitudes and behaviors of participants. It is a self administered scale consisting of 40 items. Validity and reliability study in Turkey was run by Savaşır and Erol [25]. The cut off score was 30 in the original form, whereas it was not calculated for Turkish sample.

Coping with Stress Scale (CSS)

This scale was developed based on Folkman and Lazarus' model by Türküm [26]. It is a 5-point Likert type scale and comprises 23 items. Additionally to a single score which is minimum 23 and maximum 115, there are three subscales: Seeking social support, Problem focused coping and Avoidance. The score obtained from the subscales reflects which coping way is mostly used by individual.

Statistical Analysis

SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version21.0. Armonk, NY: IBM Corp.) was used to analyze data statistically and $p < 0.05$ was considered statistically significant. Shapiro Wilk test was used to determine the conformity of the variables to normal distribution. Continuous variables were expressed with median (minimum: maximum) and mean ± standard deviation or mean ± standard deviation (minimum: maximum) values. In order to express categorical variables, n (%) was used. According to the outcomes of normality test, Mann Whitney U test and Independent samples t test were used to compare two groups. Also, Pearson chi-square test was used to compare categorical variables among groups. The relationship between EAT score and CSS subscale scores were examined by correlation and also Spearman correlation coefficient (rs) was calculated.

RESULTS

Table 1 shows the distribution of participants in terms of EAT cut off score and Table 2 indicates the distribution of eating attitudes divided into two groups as normal and abnormal eating attitude groups.

Table 3 describes the comparisons of normal and abnormal eating attitude groups in terms of some demographic characteristics. There was no significant difference in terms of gender ($p = 0.062$), age ($p = 0.950$) and BMI ($p = 0.877$).

Table 4 shows that no significant differences in eating groups in terms of class level ($p = 0.782$) and whether to be in the period of pre-clinical and clinical trainig ($p = 0.423$).

Table 1. Distribution of participants according to EAT cut off score

	(n = 200)
Lower than EAT cut off score	183 (91.5%)
Higher than EAT cut off score	17 (8.5%)
EAT total score	15.42 ± 8.79 (3-47)

Data are expressed as n (%) and mean ± standard deviation (minimum -maximum). EAT = Eating Attitude Test

Table 2. Distribution of participants as normal and abnormal eating attitudes in terms of EAT scores

	(n =100)
Normal eating attitude	50 (50%)
Abnormal eating attitude	50 (50%)
EAT total score	17.59 ± 11.81 (3-47)

Data are expressed as n (%) and mean ± standard deviation (minimum -maximum). EAT = Eating Attitude Test

Table 3. Comparisons of eating attitude (EA) groups in terms of gender, age and body mass index (BMI)

	Normal EA (n = 50)	Abnormal EA (n = 50)	*p*-value
Gender (F/M)			
Female	27 (54.0%)	36 (72.0%)	0.062[a]
Male	23 (46.0%)	14 (28.0%)	
Age	22 (19-27)	21 (19-24)	0.950[b]
	21.34 ± 1.85	21.20 ± 1.56	
BMI	21.80 (17-30)	21.90 (16-32)	0.877[b]
	22.35 ± 3.20	22.45 ± 3.49	

Data are expressed as n (%) and mean ± standard deviation (minimum - maximum).
[a]Chi square test, [b]Mann-Whitney U test

Table 4. Comparisons of eating attitude (EA) groups in terms of their class levels

	Normal EA (n = 50)	Abnormal EA (n = 50)	*p*-value
Class level			
2nd year	13 (26.0%)	14 (28.0%)	0.782[a]
3rd year	9 (18.0%)	12 (24.0%)	
4th year	15 (30.0%)	11 (22.0%)	
5th year	13 (26.0%)	13 (26.0%)	
Pre-clinical training	22 (44.0%)	26 (52.0%)	0.423[a]
Clinical training	28 (56.0%)	24 (48.0%)	

Data are expressed as n (%).
[a]Chi square test

Table 5. Comparisons of eating attitude (EA) groups in terms of CSS subscale scores

	Normal EA (n = 50)	Abnormal EA (n = 50)	*p*-value
Avoidance	26.50 (17-36)	27(15-36)	0.279[b]
	26.48 ± 4.55	27.32 ± 5.35	
Problem focused coping	30 (13-37)	31 (12-40)	0.155[b]
	28.38 ± 5.50	29.54 ± 5.95	
Seeking social suppport	22.60 ± 4.64	25.26 ± 6.14	**0.016[e]**
	(10-33)	(7-35)	

Data are expressed as median (minimum:maximum and mean ± standard deviation and mean ± standard deviation (minimum:maximum). CSS = Coping with Stress Scale
[b]Mann-Whitney U test, [e]Independent samples t-test

Table 6. The correlation between CSS subscales' scores and EAT score

	EAT	
	r_s	p
Avoidance	0.19	0.058
Problem focused coping	0.17	0.100
Seeking social support	0.17	0.085

CSS = Coping with Stress Scale, EAT = Eating Attitude Test, r_s = Spearman correlation coefficient

Table 5 shows that there was not a significant difference between eating attitude groups in terms of avoidance coping score (p = 0.279) and problem focused coping score (p = 0.155). However, there was a significant difference between eating attitude groups in terms of seeking social support score. The mean of social support score is higher in the abnormal eating attitude group (p = 0.016).

Table 6 indicates that no relationship between CSS subscales' scores and EAT score.

DISCUSSION

Eating attitude is one of the common topics studied by contemporary clinical psychology and psychiatry. In the current study, the objectives were to examine the eating attitudes, to determine coping ways with stress and to reveal the associations between these variables among medical students.

Results of the study indicated no significant differences with regard to demographic variables between abnormal and normal eating attitude groups. Our findings did not offer differences between eating attitude groups in terms of gender and age. Similar to our findings, Khalid *et al*. [27] reported that there was no significant difference between male and female in terms of the prevalence of disturbed eating attitudes and age. On the other hand, contrary to our findings, there exist some studies suggesting that female students have higher risk of eating disorders than male students [28].

In the current study, no significant difference was found in BMI. This finding is consistent with previous study that has suggested that BMI may be a more significant predictor for risk of eating disorder in younger adolescents compared to young adult women [29]. Also, symptomatic behavior might not be a direct indicator of pathology, especially bulimia nervosa [30], it might explain why abnormal and normal eating attitude groups did not differ from one another in terms of BMI. In addition, abnormal and normal eating attitude groups did not differ from one another according to their class levels and whether to be clinical or pre-clinical training.

Finding from our study suggests that there is significant difference between abnormal eating attitude group and normal eating attitude group in terms of coping ways used under stressful circumstances. Abnormal eating attitude group use more seeking social support than normal eating attitude group. Contrary to our finding, Ball and Lee [31] revealed that eating disordered individuals use less active coping ways including seeking social support. On the other hand, Odacı and Çıkrıkçı [32] found that medical students got the highest score for the seeking social support in the all faculties included in their study. They suggested that it might be due to the fact that their practical classes and more intense curricula can contribute to improve one to one sharing with others among medical students. In this sense, when we consider these two studies' results together, our finding may be interpreted as because abnormal eating attitude group in medical students have difficulties to cope with stress, they try to get benefit from their improved skills during education process and they seek social support.

Results showed that abnormal eating attitude group did not differ from normal eating attitude group in terms of problem-focused coping. Similar to our findings, early study revealed no significant difference in problem-focused coping between eating disorder patients and control subjects [33]. As an alternative explanation for these findings, Odacı and Çıkrıkçı [32] have reported that medical students use more the problem-focused coping way than students in other faculties. They suggested that this may be due to medical students are more resistant than other faculty members.

In the present study, no significant difference was found in avoidant coping between the groups. Odacı and Çıkrıkçı [32] indicated that medical and dental students use more avoidance strategy compared to the students in other faculties. In this sense, because

medical students use more avoidance strategy and our research groups comprised of medical students, abnormal and normal eating attitude groups did not differ from one another. In addition, although our finding did not accord with those of Mayhew and Edelmann [34] who reported that avoidant coping is found associated with eating pathology in nonclinical sample; similar to our findings, a study carried out 149 undergraduate students [35] did not reveal association between binge eating and avoidance coping.

After medical students complete their education, they will work to improve human health. Therefore, they should protect primarily their own mental and physical health. Stress is inevitable part of life, but stress management can be improved. Hence, we recommend that stress management workshops can be carried out medical students.

Limitations

There are also several certain limitations in the current study. Since nonclinical sample was used and EAT scores' range was relatively narrow, findings should be interpreted with these potential limitations in mind. Another limitation was that the research sample consisted of medical students from one university. This makes difficult to generalize the findings to all medical student population. In future study, it will be important to acquire data from different medical faculty students.

Further research should replicate the findings with increased sample size. In addition, students may be rewarded in an effective way to increase their motivation to participate study. For instance, extra credits for their courses can be given.

CONCLUSION

We concluded that individuals with normal eating attitude group and individuals with abnormal eating attitude do not differentiate in terms of demographic characteristics. Also, abnormal eating attitude group uses more seeking social support coping than normal eating attitude group. Because our research sample involved medical students who are in cooperation regarding to their practical classes, they seek social support to cope with stressors.

Authors' Contribution

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

Conflict of interest

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

Financing

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

REFERENCES

1. Levine AS, Billington CJ. Why do we eat? A neural systems approach. Annu Rev Nutr 1997;17:597-619.
2. Popkin BM, Duffey K, Gordon-Larsen P. Environmental influences on food choice, physical activity, and energy balance. Physiol Behav 2005;86:603-13.
3. Alvarenga MS, Scagliusi FB, Philippi ST. Development and validity of the disordered eating attitude scale (DEAS). Percept Mot Skills 2010;110:379-95.
4. Leichner P, Arnett J, Rallo JS, Srikameswaran S, Vulcano B. An epidemiologic study of maladaptive eating attitudes in a Canadian school age population. Int J Eat Disord 1986;5:969-82.
5. Kumcağız H, Şahin C, Alakuş K, Akbaş M. The role of hope and negative thoughts in predicting eating attitudes. IJOESS 2017;8:939-54.
6. Hung C. Coping strategies of primary school teachers in Taiwan experiencing stress because of teacher surplus. Soc Behav Pers 2011;39:1161-74.
7. Wardle J, Gibson EL. Impact of stress on diet: process and implications. In: Stansfield S, Marmot M, editors. Stress and the heart. Psychosocial pathways to coronary heart disease. London: BMJ Publishing Group; 2002:124-49.
8. Michaud C, Kahn JP, Musse N, Burlet C, Nicolas JP, Mejean L. Relationships between a critical life event and eating behavior in high-school students. Stress Med 1990;6:57-64.
9. Strober M. Stressful life events associated with bulimia in anorexia nervosa: empirical findings and theoretical speculations. Int J Eat Disord 1984;3:3-16.
10. Popper R, Smits G, Meiselman HL, Hirsch E. Eating in combat: a survey of U.S. Marines. Mil Med 1989;154:619-23.
11. Seymeur M, Hoerr SL, Huang Y. Inappropriate dieting behaviors and related lifestyle factors in young adults: are college students different? J Nutr Educ 1997;29:21-5.
12. Thorsteinsdottir G, Ulfarsdottir L. Eating Disorders in

College Students in Iceland. Eur J Psychiat 2008;22:107-15.
13. Hoerr SL, Bokram R, Lugo B, Bivins T, Keast DR. Risk for disordered eating relates to both gender and ethnicity for college students. J Am Coll Nutr 2002;21:307-14.
14. Işık B. [Determining the Eating Disorders in the Students of Uludag University]. Published doctoral dissertation. Uludag University, Bursa, Turkey. 2009. [Article in Turkish]
15. Folkman S, Lazarus RS. An analysis of coping in a middle-aged community sample. J Health Soc Behav 1980;21:219-39.
16. Tobin DL, Holroyd KA, Reynolds RV, Wigal JK. The Hierarchical factor structure of the coping strategies inventory. Cogn Ther Res 1989;13:343-61.
17. Billings AG, Moos RH. The role of coping responses and social resources in attenuating the stress of life events. J Behav Med 1981;4:139-57.
18. Roth S, Cohen LJ. Approach, avoidance, and coping with stress. American Psychologist 1986;41:813-9.
19. Shaikh BT, Kahloon A, Kazmı M, Khalid H, Nawaz K, Khan N, et al. Students, stress and coping strategies: a case of Pakistani medical school. Educ Health 2004;17:346-53.
20. Helmers KF, Danoff D, Steinert Y, Leyton M, Young SN. Stress and depressed mood in medical students, law students, and graduate students at McGill University. Acad Med 1997;72:708-14.
21. Aytin N. [Examining the relationship between eating attitude, social problem solving and parental bonding in adolescents]. Unpublished master's thesis. Adnan Menderes University, Aydın, Turkey. 2014. [Article in Turkish]
22. Çakırlı Alşan Z. [The relationship between abnormal eating attitudes and behaviors and family environment self-esteem and perfectionism]. Published master's thesis. Istanbul University, İstanbul, Turkey. 2005. [Article in Turkish]
23. Meyer C, Waller G. The impact of emotion upon eating behavior: the role of subliminal visual processing of threat cues. Int J Eat Disord 1999;25:319-26.
24. Garner DM, Garfinkel PE. The eating attitudes test: an index of the symptoms of anorexia nervosa. Psychol Med 1979;9:273-9.
25. Savaşır I, Erol N. Yeme Tutum Testi: Anoreksiya nervoza belirtiler endeksi. Turk Psikoloji Dergisi 1989;7:19-25. [Article in Turkish]
26. Türküm AS. Stresle Başa Çıkma Ölçeğinin Geliştirilmesi: Geçerlik ve Güvenirlik Çalışmaları, Türk Psikolojik Danışma ve Rehberlik Dergisi 2002;2:25-34. [Article in Turkish]
27. Khalid S, Razia ET, Raza MH, Sheikh H, Salman M, Shehzadi N, et al. It's not just a "female issue": eating attitudes and behaviors of Pakistani male and female pharmacy students. Russ Open Med J 2017;6:e0406.
28. Memon AA, Adil SE, Siddiqui EU, Naeem SS, Ali SA, Mehmood K. Eating disorders in medical students of Karachi, Pakistan-a cross-sectional study. BMC Res Notes 2012;5:84.
29. Huon G, Lim J. The emergence of dieting among female adolescents: age, body mass index, and seasonal effects. Int J Eat Disord 2000;28:221-5.
30. Wilson G, Eldredge K. Frequency of binge eating in bulimic patients: diagnostic validity. Int J Eating Disord 1991;10:557-61.
31. Ball K, Lee C. Relationships between psychological stress, coping and disordered eating: a review. Psychol Health 2000;14:1007-35.
32. Odacı H, Çıkrıkçı Ö. University students' ways of coping with stress, life satisfaction and subjective well-being. TOJCE 2012;1:117-30.
33. Troop NA, Holbrey A, Trowler R, Treasure JL. Ways of coping in women with eating disorders. J Nerv Ment Dis 1994;182:535-40.
34. Mayhew R, Edelmann R. Self-esteem, irrational beliefs, and coping strategies in relation to eating problems in a nonclinical population. Pers Indiv Diff 1989;10:581-4.
35. Paxton SJ, Diggens 1. Avoidance coping, binge eating, and depression: an examination of the escape theory of binge eating. Int J Eat Disord 1997;22:83-7.

The European Research Journal 2021;7(2):203-208 Original Article

DOI: 10.18621/eurj.809340 *General Surgery*

The use of vacuum-assisted closure in Fournier's gangrene

Özer Özlü[1], Abdulkadir Başaran[1], Feyzi Kurt[2]

[1]*Department of General Surgery, Adana City Training and Research Hospital, Adana, Turkey*
[2]*Department of General Surgery, Seyhan State Hospital, Adana, Turkey*

ABSTRACT

Objectives: Fournier's gangrene is an emergency surgical disease which develops and progresses rapidly and there is high risk of mortality with a delay in diagnosis and treatment. The objective of this study is to investigate the impact of vacuum-assisted closure on the clinical outcome in the treatment of Fournier's gangrene.

Methods: A total of 28 patients diagnosed as Fournier's gangrene and admitted to our hospital from January 2010 to December 2018 are included in this retrospective study. The diagnosis was established on the basis of physical examination. Epidemiological data including gender, age, and presence of diabetes mellitus, clinical outcomes including use of vacuum-assisted closure, length of admittance, the number of debridement and other surgical procedures were evaluated retrospectively from the medical records and the hospital treatment registry.

Results: There were 16 (57.1%) male and 12 (42.9%) female patients and the mean age of the patients was 59.54 ± 16.76 years. The mean number of debridement was 3.67 ± 1.5 times and the total hospital stay was 26.67 ± 7.7 days for vacuum-assisted closure group (n = 9). The average number of debridement was 4.11 ± 0.94 times and the total hospital stay was 31.58 ± 6.33 days for the rest of the patients (n = 19).

Conclusions: The average number of debridement and hospital stay were lower in patients treated with vacuum-assisted closure. We also observed an increase in patient comfort and the workload of the stuff is decreased as there was less exudate in the vacuum-assisted closure group.

Keywords: Fournier's gangrene, vacuum-assisted closure, diabetes, hospital stay

Fournier's gangrene (FG) is an emergency surgical disease that quickly develops and progresses. There is high risk of mortality with a delay in diagnosis and treatment. FG is an obliterating endarteritis of the subcutaneous arteries resulting with gangrene and fasciitis of the external genitalia. Although FG often involves genital and perianal region, it can also be seen in lower extremities and other parts of the body. The disease was named after Jean Alfred Fournier who was the first to describe it [1]. However several sources state that the disease was first described by Bauriene in 1764 [2, 3]. Fournier's disease is defined as a gangrene that has a fulminant course in specific focus of scrotum. Most of these infections were initially divided into subgroups such as necrotizing fasciitis, clostridial gangrene, and streptococcal gangrene. FG was then defined as scrotal gangrene, periurethral flegman, or synergistic necrotizing cellulitis [3, 4].

The disease affects mostly men. However, it is also observed in women and children. FG often occurs in

Received: *October 12, 2020;* ***Accepted:*** *November 13, 2020;* ***Published Online:*** *March 4, 2021*

How to cite this article: *Özlü Ö, Başaran A, Kurt F. The use of vacuum-assisted closure in Fournier's gangrene. Eur Res J 2021;7(2):203-208. DOI: 10.18621/eurj.809340*

Address for correspondence: *Özer Özlü, MD., Adana City Training and Research Hospital, Department of General Surgery, Adana, Turkey*
E-mail: ozerozlu5757@yahoo.com, GSM: +90 506 6285426

e-ISSN: 2149-3189

colorectal (30-50%) or urogenital (20-40%) regions and other areas of skin (20%) [3]. FG is more often seen with several systematic diseases. 20-70% of patients have diabetes mellitus (DM) [5]. The primary cause for development of disease is the reduced cellular immunity. Any condition reducing cellular immunity may lead to development of FG. The bacterial infections observed in anorectal, perianal and genitourinary regions thrombose small subcutaneous veins, resulting in development of gangrene in the skin. The bacteria found in those regions usually causes rapid and severe tissue damage. In case of local trauma or infection the high virulence causes the disease to develop. FG is a polymicrobial disease that often develops with aerobic and anaerobic microorganisms [4].

The treatment of disease includes aggressive surgical debridement in combination with the use of broad spectrum antibiotics [6]. Despite advances in treatment, the mortality and morbidity of the disease remains still high [7]. There are different methods attempted to reduce morbidity and mortality of this disease. The Vacuum-Assisted Closure (VAC) is one of these methods. The objective of this study is to review the efficacy of VAC on the clinical outcomes of patients with FG. VAC covers the wound with a foam dressing and mechanically brings the skin edges closer by applying negative pressure to the wound bed. The formation of micro-deformation in the tissue and the increase in the capillary flow stimulates the formation of granulation tissue. The removal of wound exudate and its enzymes prevents further tissue damage and reduces the wound dressing changes by keeping the surrounding skin dry [8].

METHODS

Study Design and Participants

The data of 28 patients diagnosed as Fournier's gangrene and admitted to our hospital between January 2010 and December 2018 were reviewed retrospectively. This study was approved by the local Clinical Research Ethical Committee of the Training and Research Hospital in our city (Decision no: 490/2019). Written informed consent was obtained from a patient for imaging the lesions.

Treatment

The diagnosis was established based on physical examination (Fig. 1a). Surgical debridement was performed as soon as possible. The patients received double parenteral antibiotics until the culture and sensitivity results were available. The wound dressings were changed daily and the surgical debridement was performed depending on the nature of the wound and necrosis as the standard procedure. After the acute phase VAC was used in some patients mainly depending on extension of the necrosis and presence of DM. The use of VAC device (Renasys EZ Max, Smith and Nephew Inc., St. Petersburg, Florida, USA) starts with placing foam-based sponges with small pores on the wound. Suction tubing is then placed on top of the sponge and the area is sealed with adhesive tapes (Fig. 1b). The tube is connected to the vacuum pump and a pressure between 80-120 mm is applied [9]. The dressing was changed every 48-72 hours depending on the amount of exudate. The closure of the wound or the continuation of VAC therapy was decided by the formation of granulation tissue, the presence of exudate or necrotic tissue in the wound (Fig. 1c).

Fig. 1. a) Fournier's gangrene, b) Application of VAC, c) The wound after one week

Table 1. Demographic and clinical data of patients based on treatment

	Group 1 (n = 9)	Group 2 (n = 19)	*p value*
Gender (M/F)	5/4	11/8	
Age	65.0 ± 17.8	56.95 ± 16.1	0.054
DM (-/+)	1/8	13/6	**0.01**
Lesion size (cm)	24.4 (12-44.5)	22.6 (10-42)	0.825
Debridement	3.67 ± 1.5	4.11 ± 0.94	0.48
Hospital Stay (days)	26.67 ± 7.7	31.58 ± 6.3	0.114

Data are shown as mean ± standard deviation or number. M/F: Male/Female

Data collection

Epidemiological data including gender, age and presence of diabetes mellitus, clinical outcomes including use of vacuum-assisted closure, length of admittance, the number of debridement and other surgical procedures were evaluated from the medical records and the hospital treatment registry.

Statistical Analysis

The data were analyzed using SPSS (Statistical Package for Social Sciences) 20.0 for Windows. The distribution of the variables was checked with normality tests. The t-test was used for normally distributed continuous variables, and Mann-Whitney U Test was used for non-normally distributed variables. The results were expressed in ± standard deviation, n, and percent (%). A p value of < 0.05 was considered statistically significant.

RESULTS

A total of 28 patients were included in the study. Sixteen (57.1%) patients were males and 12 (42.9%) patients were females. The mean age of the patients was 59.54 ± 16.76 years (27-78 years). There were 14 (50%) patients with DM and 8 (57.15%) of them were females and 6 (42.85%) of them were males. The mean number of debridement was 3.96 ± 1.14 (2-7) and the total hospital stay was 30.0 ± 7.05 (15-39) days.

Further analyses were performed according to groups based on treatment as; group 1 = VAC group, group 2 = conservative treatment group. In group 1 55.55% of patients were male (n = 5) and 44.44% (n = 4) were female. The mean number of debridement was 3.67 ± 1.5 and the total hospital stay was 26.67 ± 7.7 days for group 1 (n = 9). The average number of debridement was 4.11 ± 0.94 and the total hospital stay was 31.58 ± 6.33 days for group 2 (n = 19). The difference between these groups was not statistically significant. The demographic and clinical data of treatment groups are summarized in Table 1.

Half of the patients (n = 14) had DM. For the patients with DM the mean number of debridement and the duration of hospital stay were higher than the patients who did not have DM but the difference between the groups was not statistically significant. The data concerning DM is summarized in Table 2.

In group 1 secondary wound healing was achieved in 7 patients. Whereas one patient healed with a flap and the other one with skin grafting. In group 1 there

Table 2. Data of patients based on presence of diabetes

	DM (+)	DM (-)	*p value*
Gender (M/F)	6/8	10/4	
Age	61.9 ± 14.9	57.2 ± 18.7	0.58
Debridement	3.93 ± 1.27	4.0 ± 1.04	0.73
Hospital stay	31.07 ± 7.93	28.93 ± 6.16	0.231

Data are shown as mean ± standard deviation or number. M/F: Male/Female

Table 3. Clinical outcomes of patients

	Group 1 (n = 9)	Group 2 (n = 19)
Secondary healing, n (%)	7 (77.8)	11 (57.9)
Flap, n (%)	1 (11.1)	4 (21.05)
Skin graft, n (%)	1 (11.1)	4 (21.05)
Colostomy, n (%)	0 (0)	2 (10.5)
Mortality, n (%)	0 (0)	1 (5.26)

was no mortality and none of the patients underwent colostomy. Whereas in group 2 two patients underwent colostomy and one patient died due to sepsis and multiple organ failure. The kind of healing and the clinical outcomes are summarized in Table 3.

There was no problem with the flap and graft performed in group 1 but in group 2 local necrosis was developed in one flap. The necrotic area was healed after the debridement and the wound is closed with fibrosis.

DISCUSSION

The earlier the diagnosis of FG is established and treated, the better the prognosis is. The radiological methods, such as ultrasonography, computed tomography, and magnetic resonance imaging can be used for diagnosis. However, the primary diagnosis of FG is based on the findings of physical examination [7, 10]. The signs of inflammation, presence of edema, necrosis, subcutaneous crepitation and pain are important for diagnosis. We also established the diagnosis on the basis of physical examination findings. Although the FG is seen in both genders and at any age, it mostly affects elderly men [11-13]. Most of the patients in our study were also elderly men. The reason for high incidence of FG in elderly is that a number of chronic diseases are common at older ages. Other than older age, obesity, DM, alcoholism, respiratory system diseases, diseases of liver, malnutrition, and other immunosuppressive diseases play a role in development of FG [14, 15]. DM is the most critical and common disease among these conditions with an incidence of 70% in the literature [16, 17]. In our study 50% of the patients had diabetes mellitus.

FG is more common in the perineal, urogenital and anorectal regions. However, it can be seen in other parts of the body including abdomen and lower extremities. It can also be observed in perineum of women during postpartum period [5, 13]. All of our patients had FG at the perineal, urogenital or anorectal regions. The treatment of FG includes broad aggressive surgical debridement and use of appropriate broad spectrum antibiotics [7, 18]. During the debridement, the entire necrotic tissue must be removed until the living tissue is reached. The debridement must be repeated until the infection is controlled. The mean number of debridement ranges from 3 to 7 for each patient in the literature [19]. The mean number of debridement was 2-7 (3.96 ± 1.14) and the total hospital stay was 30.0 ± 7.05 (15-39) days in our study. The duration of hospital stay was 31.07 ± 7.93 days for patients with DM and 28.93 ± 6.16 days for rest of the patients and the difference between the groups was not statistically significant. The mean number of debridement and the total hospital stay was less in group 1 compared to group 2 and the difference between the groups was also not statistically significant. There were more patients with DM in group 1 (88.9% to 31.6%) and the difference between the groups was statistically significant (p = 0.01). The patients in group 1 were also older and the lesion size was bigger. In a randomized study a significant difference could be observed considering above mentioned conditions.

The Negative Pressure Wound Treatment (NPWT) is based on continuous or intermittent application of negative pressure on the wound surface to remove the fluid material from the wound site and we know that NPWT has been used for decades. Today, advanced systems have been developed for NPWT with the use of technology. Recently, the VAC has been widely used for the pressure sores in particular and its use for patients with chronic wound increased as well. The need for debridement of patients is reduced with the use of VAC [20]. This also improves the comfort of patients and decreases the work load of healthcare provider. Shorter duration of hospital stay is also reported [21, 22]. The patients become more eligible for flap or grafting sooner [23, 24]. The costs are lower considering the number of debridement and the duration of hospital stay [25]. When VAC is used for eligible patients, the need for opening stoma is also reduced [26]. This has positive effects on the psychosocial condition of patients [20, 21, 27]. The inci-

dence for development of infections will be reduced as a confined environment is created with VAC. However, there are no relevant randomized studies in the literature.

VAC is supplementary in treatment of FG and the gold standard for its treatment is broad aggressive surgical wound debridement in combination with appropriate antibiotics. The treatment of FG is a process that requires multidisciplinary approach. The use of VAC creates granulation tissue earlier in the wound [28]. Therefore, the closure of the wounds of the patients occurs faster and can be healed easily with flap or skin graft operations. Appropriately secondary wound healing was provided in 77.8% of patients in the VAC group. However 57.9% of the patients in group 2 had secondary wound healing. Flap and graft necrosis was observed in group 2 while no complication was observed in the VAC group.

Limitations

Our limitations are the retrospective nature of the study and the relatively small number of patients. Prospective randomized controlled trials are needed with more patients.

CONCLUSION

Vacuum-Assisted Closure is a negative pressure treatment method based on the removal of liquid material from the wound by applying negative pressure to the wound surface intermittently or continuously. The number of debridement and hospital stay were lower in FG patients who were treated with applying VAC in our study. Also secondary wound healing was better and there was no loss of flap and skin grafts. We observed that using VAC is effective in diabetic patients with FG. In addition we observed an increase in patient comfort and the workload of the health care stuff is decreased.

Authors' Contribution

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

Conflict of interest

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

Financing

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

REFERENCES

1. Fournier JA. Gangrene foudroyante de la verge. Med Pract 1883;4:589-97.
2. Eke N. Fournier`s gangrene: a review of 1726 cases. Br J Surg 2000;87:718-28.
3. Thwaini A, Khan A, Malik A, Cherian J, Barua J, I Shergill I, et al. Fournier`s gangrene and its emergency management. Postgrad Med J 2006;82:516-9.
4. Czymek R, Schmidt A, Eckmann C, Bouchard R, Wulff B, Laubert T, et al. Fournier`s gangrene: vacuum assisted closure versus conventional dressing. Am J Surg 2009;187:168-76.
5. Morpurgo E. Galandiuk S. Fournier`s gangrene. Surg Clin N Am 2002;82:1213-24.
6. Yanar H. Taviloglu K. Ertekin C, Guloglu R, Zorba U, Cabioglu N, et al. Fournier`s gangrene: risk factors and strategies for management. Word J Surg 2006;30:1750-4.
7. Furr J, Watts T, Street R, Cross B, Slobodov G, Patel S. Contemporary trends in the inpatient management of Fournier`s gangrene: predictors of length of stay and mortality based on population-based sample. Urology 2016;102:79-84.
8. Angelis S, Apostolopoulos AP, Kosmas L, Balfousias T, Papanikolaou A. The use of vacuum closure-assisted device in the management of compound lower limb fractures with massive soft tissue damage. Cureus 2019;11:e5104.
9. Morykwas MJ, Simpson J, Punger K, Argenta A, Kremers L, Argenta J: Vacuum-assisted
closure: state of basic research and physiologic foundation. Plast Reconstr Surg 2006;117:121-6.
10. Oguz A, Gumus M, Turkoglu A, Bozdag Z, Ulger BV, Agacayak E, et al. Fournier's gangrene: a summary of 10 years of clinical experience. Int Surg 2015;5:934-41.
11. Heiner JD, Baldwin K, Laselle B. Fournier gangrene: rapid diagnosis with bedside ultrasonography. CJEM 2010;12:528-9.
12. Erdogan A, Aydogan I, Senol K, Uckan EM, Ersoz S, Tez M. Simple scoring system for prediction of mortality in Fournier `s gangrene. Eur J Trauma Emerg Surg 2016;42:513-8.
13. Korkut M, Icoz G, Dayangac M, Akgun E, Yeniay L, Erdogan O, et al. Outcome analysis in patients with Fournier`s gangrene: report of 45 cases. Dis Colon Rectum 2003;46:649-52.
14. Norton KS, Johnson LW, Perry T, Perry KH, Sehon JK, Zibari GB. Management of Fournier`s gangrene: an eleven year retrospective analysis of early recognition, diagnosis, and treatment. Am Surg 2002;68:709-13.

15. Canbaz H, Caglikulekci M, Altun U, Dirlik M, Turkmenoglu O, Tasdelen B, et al. Fournier`s gangrene : analysis of risk factors affecting the prognosis and cost of therapy in 18 cases. Ulus Travma Acil Cerrahi Derg 2010;16:71-6.
16. Yılmazlar T, Isık O, Ozturk E, Ozer A, Gulcu B, Ercan I. Fournier`s gangrene: Review of 120 patients and predictors of mortality. Ulus Travma Acil Cerrahi Derg 2014;20:333-7.
17. Mallikarjuna MN, Vijayakumar A, Patil VS, Shivswamy BS. Fournier`s gangrene: current practices. ISRN Surg 2012:2012:942437.
18. Smith GL, Bunker CB, Dinneen MD. Fournier`s gangrene. Br J Urol 1998;81:347-55.
19. Benjelloun EB, Souiki T, Yakla N, Ousadden A, Mazaz K, Louchi A, et al. Fournier`s gangrene: our experience with 50 patients and analysis of factors affecting mortality. World J Emerg Surg 2013;8:13.
20. Assenza M, Cozza V, Sacco E, Clementi I, Tarantino B, Passafiume F, et al. VAC treatment in Fournier`s gangrene: personal experience and literature review. Clin Ter 2011:162:e1-5.
21. Cuccia G, Mucciardi G, Morgia G, d'Alcontres FS, Gali A, Cotrufo S, et al. Vacuum-assisted closure for the treatment of Fournier`s gangrene. Urol Int 2009;82:426-31.
22. Durmish Y, Gervaz P, Bühler L, Bucher P, Zufferey G, Al-Mazrouei A, et al. Vacuum –assisted closure: its role in the treatment of complex abdominal and perineal wounds. J Chir 2007:144:209-13.
23. Ugur M, Oruc C, Yıldız I, Koca YS, Daban U. The role of co-administration of damage control surgery and vacuum-assisted closure in the treatment of perineal wounds. Turk J Surg 2018;34:229-30.
24. Lohsiriwat V. Persistent perineal sinus: incidence, pathogenesis, risk factors and management. Surg Today 2009;39:189-93.
25. Liu Z, Dumville JC, Hinchliffe RJ, Cullum N, Game F, Stubbs N, et al. Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. Cochrane Database Syst Rev 2018;10:CD010318.
26. Yucel M, Ozpek A, Basak F, Kilic A, Unal E, Yuksekdag S, et al. Fournier`s gangrene: a retrospective analysis of 25 patients. Ulus Travma Acil Cerrahi Derg 2017;23:400-4.
27. Wagner S, Greco F, Hoda MR, Kawan F, Heynemann H, Fornara P. Is intensive multimodality therapy the best treatment for Fournier gangrene? Evaluation of clinical outcome and survival rate of 41 patients. Surg Infect (Larchmt) 2011;12:379-83.
28. Chennamsetty A, Khourdaji I, Burks F, Killinger KA. Contemporary diagnosis and management of Fournier's gangrene. Ther Adv Urol 2015;7:203-15.

The European Research Journal 2021;7(2):209-217 Review

DOI: 10.18621/eurj.830973 *Pulmonary Diseases*

COVID-19 and hypercoagulability

Hasan Ölmez[1], Mustafa Tosun[1], Edhem Ünver[1], Mehmet Doğan[1], Nurten Arslan Işık[2]

[1]Department of Pulmonary Diseases, Erzincan Binali Yıldırım University School of Medicine, Erzincan, Turkey
[2]Department of Child Development, Erzincan Binali Yıldırım University Faculty of Health Sciences, Erzincan, Turkey

ABSTRACT

It has been observed that patients with COVID-19 infection may develop acute pulmonary embolism, acute myocardial infarction, limb thrombosis, and venous and/or arterial thrombosis, including central nervous system. Thrombosis formation in COVID-19 patients can be explained by the virchow triad. Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) can directly attack vascular endothelial cells, causing excessive activation of the immune system and cytokine storm, causing thrombosis. Increased prothrombotic factors such as antiphospholipid antibodies, elevated factor VIII, high fibrinogen, circulating prothrombotic microparticles, neutrophil extracellular traps have been reported in COVID-19 infection. It has been argued that complement-mediated endothelial damage, increase in pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8 and interferon-γ may be the cause of thrombosis. Autopsies of patients with COVID-19 revealed that the causes of death were pneumonia and pulmonary embolism. When monitoring COVID-19 patients, platelet, prothrombin time (PT) and activated partial thromboplastin time (aPTT), fibrinogen and D-dimer monitoring should be initiated every 1-2 days, especially in critically ill patients. High D-dimer levels are associated with high mortality; may indicate infection/sepsis, cytokine storm, and impending organ failure. Disseminated intravascular coagulation (DIC) may be seen in COVID-19 patients, but unlike DIC, fibrinogen is usually high. Clotting times and platelet counts are usually normal. Therefore, it is appropriate to use sepsis-induced coagulopathy (SIC) criteria in the follow-up of COVID-19 patients. Infected areas related to pulmonary embolism can be seen as radiological appearance. Some patients may have enlarged subsegmental pulmonary vessels. Treatment of the underlying disease is the most important treatment for all coagulopathies. Patients with venous thromboembolism, inpatient medical, surgical, and COVID-19 therapy should receive anticoagulant therapy unless there is a contraindication to anticoagulation (for example, active bleeding or severe bleeding within the previous 24 to 48 hours).

Keywords: COVID-19, hypercoagulability, severe acute respiratory syndrome

Coronavirus disease-19 (COVID-19) caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) is a potentially fatal disease. Many mechanisms can be involved in mortality. One of them is disseminated intravascular coagulation (DIC) caused by coagulopathy caused by SARS-CoV-2 [1-3]. This condition has been called thromboinflammation or COVID-19-associated coagulopathy by some experts [4, 5].

There are few studies on the state of hypercoagulability caused by COVID-19. Experience comes mostly from research on SARS, Middle East respira-

Received: ***November 26, 2020;*** *Accepted:* ***February 5, 2021;*** *Published Online:* ***February 6, 2021***

How to cite this article: *Ölmez H, Tosun M, Ünver E, Doğan M, Arslan Işık N. COVID-19 and hypercoagulability. Eur Res J 2021;7(2):209-217. DOI: 10.18621/eurj.830973*

Address for correspondence: *Nurten Arslan Işık, Assistant Professor, Erzincan Binali Yıldırım University Faculty of Health Sciences, Department of Child Development, Erzincan, Turkey. E-mail: nurtenarslanisik1@gmail.com, Mobile phone: +90 505 5273641*

e-ISSN: 2149-3189

tory syndrome (MERS), and the influenza virus. Studies have shown that severe COVID-19 patients are usually complicated with coagulopathy and most of the deaths have DIC [1]. It has been observed that patients with COVID-19 infection may develop venous and/or arterial thrombosis, including acute pulmonary embolism (PE), acute myocardial infarction, extremity thrombosis, and central nervous system [6].

PHYSIOPATHOLOGY

It has been suggested that the pathophysiology of akut PE is different from classical pulmonary thromboembolism and that thrombosis occurs locally in the lung vessels due to a local inflammatory process instead of the classical embolism from another part of the body [7]. Since the pathophysiology of thrombotic disease is different, it may be questioned whether the akut PE standard therapy (prophylactic or therapeutic) with low-molecular-weight heparin (LMWH), direct oral anticoagulants or vitamin K antagonist is sufficient. Thrombosis formation in COVID-19 patients can be explained by the virchow triad. SARS-CoV-2 protein, which causes viral pneumonia and inflammatory storm (cytokine storm) and DIC, infects human cells through angiotensin-converting enzyme 2 (ACE2). ACE2 is found in alveolar epithelial cells, arterial endothelial cells, small intestine epithelial cells, and immune tissues [8]. SARS-CoV-2 can activate the coagulation system by directly attacking vascular endothelial cells. SARS-CoV-2 can also activate the natural immune system after it enters the body. Overactivation of the immune system can cause cytokine storms, damage the microvascular system, activate the coagulation system while inhibiting fibrinolysis and anticoagulation systems. The RAAS pathway is activated by binding the virus to ACE2 and causing a decrease in enzyme expression. RAAS activation; With thrombocyte adhesion and aggregation, there is a theoretical risk of pulmonary embolism, pulmonary hypertension and fibrosis. It is known that the coagulation pathway can be activated by the contact system and the kallikrein/kinin system (KKS) [9]. Since KKS SARS-CoV-2 is dysregulated by the binding of type II pneumocytes to the ACE2 receptor, this may be a reasonable mechanism for the stated interaction between COVID-19 and pulmonary vessel thrombosis [10]. Prothrombotic factors such as circulating antiphospholipid antibodies and elevated factor VIII, high fibrinogen, circulating prothrombotic microparticles, neutrophil extracellular traps (NETs) have been reported in patients with severe COVID-19 [11, 12].

Antiphospholipid antibodies that can prolong activated partial thromboplastin time are common in viral infections. However, it is usually temporary and does not always mean that the risk of thrombosis increases [13, 14]. The induction of antiphospholipid syndrome (APS) by viral infection can be explained by a series of endothelial damage, platelet activation and thrombosis formation mediated by antiphospholipid antibodies. APS can present as catastrophic APS in many patients. Catastrophic APS and DIC are clinically similar and differential diagnosis can be difficult. APS manifests itself with more hypercoagulability tendency. Diagnosis depends mainly on the measurement of antiphospholipid antibodies.

Interleukin (IL)-6 is an important factor involved in the cytokine storm induced by SARS-CoV-2. IL-6 stimulates the liver to produce more thrombopoetin and fibrinogen [15]. Complement-mediated endothelial damage may also contribute to hypercoagulability [16]. Most cases of sepsis COVID-19 pneumonia meet the Sepsis Third International Consensus Criteria (sepsis-3) [17]. Besides endothelial damage with complement activation seen in sepsis, inflammatory and microthrombotic pathway activation predisposes to thrombosis and leads to DIC. The dysfunction of endothelial cells induced by infection results in excessive thrombin production and inhibition of fibrinolysis. This causes hypercoagulability in the infected patient, such as COVID-19 [18, 19]. Complement activation not only causes direct endothelial damage, but also involves leukocytes with the formation of C3a and C5a, which are responsible for the local release of pro-inflammatory cytokines such as interleukin IL-1, IL-6, IL-8 and interferon [20]. The resulting excessive host immune response lymphocytes, resident macrophages, monocytes and neutrophils cause strong pro-inflammatory response, causing severe collateral tissue damage, excessive vascular endothelial and alveolar epithelial cell damage. In addition, they cause microvascular thrombosis [21, 22]. In the late stages of acute respiratory distress syndrome (ARDS), the pro-

gression of endothelial damage with microvascular thrombosis may spread from the lung and affect the microvascular bed of the kidneys, brain, and other vital organs [23]. This progressive state may involve alveolar macrophage, complement activation lectin, the brain and other vital organs, and may contribute to multiple organ failure. This condition is called Endothelial Thromboinflammatory Syndrome. In addition, this excessive inflammatory response causes progressive worsening of ventilation / perfusion imbalances, loss of hypoxic vasoconstriction reflexes, and microvascular pulmonary thrombosis, in addition to the functional effects of ARDS pathogenesis [24]. In addition, hypoxia observed in severe cases of COVID-19 not only increases blood viscosity, but also stimulates thrombosis through a signaling pathway dependent on hypoxia-induced transcription factors (HIF) [25].

COVID-19 AUTOPSY CASES

Autopsy studies of patients with COVID-19 revealed that the common causes of death were pneumonia and PE [16, 26]. In another recently published autopsy study, vascular congestion and edema in the alveolar septum, mononuclear and lymphocyte infiltration, thrombus in small vessels and capillaries, vascular endothelial and intimal damage in the cardiovascular system, and microthrombus in the liver portal region have been demonstrated, which causes COVID-19 to thrombosis in many organs. show that it can cause [27, 28]. In 18 postmortem patients with COVID-19, all cases with deep vein thrombosis (DVT) were reported to have bilateral leg involvement and none of them were suspected before they died. These patients were older, obese male patients with diabetes mellitus and/or cardiovascular disease.

LABORATORY

While monitoring COVID-19 patients, platelet, prothrombin time (PT) and activated partial thromboplastin time (aPTT), Fibrinogen and D-dimer monitoring should be initiated every 1-2 days with diagnosis in critically ill patients. Table 1 and Table 2 show the laboratory parameters to be monitored in COVID-19 infection [29].

In a study, it was observed that acute extremity ischemia can develop in patients with COVID-19, especially when D-dimer levels are high [30]. High D-dimer levels at admission are associated with high mortality; may be a marker of infection/sepsis, cytokine storm and impending organ failure [31]. Therefore, hospital admission of patients with significantly higher D-dimer levels should be considered even in the absence of other signs of violence [32]. Schistocytes can be seen in peripheral smears of patients with COVID-19 infection. Increases in lactate dehydrogenase, ferritin, C-reactive protein, D-dimer and Interleukin seen in COVID-19 disease indicate that the disease is pro-inflammatory and prone to hypercoagulability [3]. Other diagnostic tests commonly performed in patients are prothrombin time and platelet count. Thrombocytopenia is generally considered an indicator of sepsis mortality. An increase in thrombocytopenia greater than five times has been associated with an increased risk of severe COVID-19 disease. In addition to the platelet count, PT and D-dimer levels, it may be useful to determine the serum fibrinogen level as recommended in the DIC guidelines of the International Society for Thrombosis and Hemostasis (ISTH). The significant increase in D-dimer, fibrin degradation products in patients in the state of ischemia supported the prediction that multiple microthrombosis occurs in the body. Experience with monitoring PT, D-dimer, platelet count, and fibrinogen levels for septic coagulopathy suggests that it can be helpful in determining the prognosis in patients with hospitalized COVID-19. If these parameters deteriorate, more aggressive critical care support may be required [33-35]. Coagulopathy in COVID-19 patients

Table 1. Laboratory values

Test	Result	Comment
Platelets	< 100.000/µL	Sepsis, high mortality
	< 150.000//µL	Severe illness
PT	> 3 sec increase	Intensive care patient
aPTT	> 5 sec increase	
Fibrinogen	< 150 mg/mn	High mortality
D-dimer	×4 increase	High risk patient

PT = prothrombin time, aPTT = activated partial thromboplastin time

Table 2. Evaluation of coagulopathy in COVID-19 infection

Respiratory Failure	Organ Failure	
COVID-19 Infection	pre-DIC	DIC
Fibrinogen, D-Dimer (partial increase)	D-Dimer, PT (severe increase)	PLT - decrease, PT - severe increase

DIC = disseminated intravascular coagulation, PT = prothrombin time

emerges on an average of 7 days. Decreased antithrombin-3 levels have been observed in patients, but this is very rare and routine monitoring is not recommended. Plasma tissue factor and plasminogen activator inhibitor-1 was found to be higher in patients with ARDS than in patients with no development [36]. The hypercoagulant status associated with COVID-19 meets the DIC criteria published by ISTH in 2009 (Table 3) [29, 33]. However, the most important clinical finding in COVID-19 is thrombosis, and the most important finding in acute decompensated DIC is bleeding. There are many laboratory findings similar to COVID-19 DIC. D-Dimer is significantly increased, mild thrombocytopenia may be seen. However, other coagulation parameters in COVID-19 are different from DIC. Unlike DIC in many COVID-19 patients, fibrinogen is usually elevated and clotting times and platelet counts are generally normal. PT and aPTT are normal or slightly prolonged in patients with COVID-19 infection, normal or increased platelet count, increased fibrinogen, increased D-Dimer values, Factor VIII activity increased, VWF antigen greatly increased, antithrombin and free protein S low protein C was found to be slightly increased. It suggests that the consumption of coagulation factors does not occur in COVID-19 [11]. In contrast, acutely decompensated DIC is associated with low fibrinogen due to consumption of coagulation factors. In one of the large series in which thromboembolic events were reported, none of the patients developed DIC [6].

Typically, bleeding is predominant in acute decompensated DIC. Thrombosis is predominant in chronic compensated DIC. Sometimes both situations can happen together. Therefore, the development of hypercoagulable in patients with COVID-19 is more similar to compensated DIC. However, in COVID-19, the platelet count and aPTT are usually normal. DIC definition of ISTH scoring system is based on laboratory findings and is designed for use only in patients with an underlying condition known to be associated with DIC [33]. A score of 5 or more indicates that DIC is possible. Despite this, DIC is diagnosed clinically. There is no gold standard or specific test in the diagnosis of DIC [33]. ISTH proposed a new category of sepsis-associated DIC, called sepsis-induced coagulopathy (SIC), which defines a stage earlier than DIC (Table 4) [29, 37]. Since the decrease in platelet count and PT prolongation are associated with increased

Table 3. ISTH DIC criteria

Variable	Value	Score
Thrombocyte × 109/L	> 100	0
	50-100	1
	< 50	2
D-Dimer (ng/mL)	< 400	0
	400-4000	2
	> 4000	3
Prolonged PT	< 3 sn	0
	3-6 sn	1
	> 6 sn	2
Fibrinogen g/L	> 1	0
	< 1	1

A score of > 5 suggests DIC. DIC = disseminated intravascular coagulation, ISTH = International Society for Thrombosis and Hemostasis, PT = prothrombin time

Table 4. Sepsis induced coagulopathy (SIC) criteria

Score	0	1	2
PT	< 1.2	> 1.3	> 1.4
Thrombocyte × 109/L	> 150	< 150	< 100
Total	0	1	> 2

Note:> 4 points makes SIC think. PT = prothrombin time

mortality, and hypofibrinogenemia is not common in sepsis, ISTH has previously confirmed the usefulness of this simple score, as it has developed SIC criteria to guide anticoagulant therapy [35]. In a study conducted by Tang *et al*. [38], it was shown that routine prophylactic use of heparin in patients with SIC score > 4 and D-Dimer > 3.0 mg/L decreased mortality.

RADIOLOGY

In patients with COVID-19 infection, atypical findings were observed along with typical findings such as peripheral ground glass, consolidation in thorax CT [39, 40]. Infected areas related to PE can be seen in thorax CT. In some patients, enlarged subsegmental pulmonary vessels can be seen [41, 42]. Dual energy CT imaging can be used to detect lung perfusion defects. Although PE has not been observed in many COVID-19 infections, striking perfusion abnormalities that have not been previously identified have been recorded [39].

In patients with COVID-19 pneumonia, increased perfusion in the areas of lung opacity and proximal lung areas and decreased perfusion in the peripheral lung areas were observed. This may be due to the relative insufficiency of physiological hypoxic pulmonary vasoconstriction and pulmonary vascular dilatation due to excessive activation of inflammation. Perfusion abnormalities suggest an intrapulmonary shunt towards regions where gas exchange is impaired with pulmonary vascular dilatation. As a result, ventilation-perfusion mismatch worsens and hypoxia develops.

TREATMENT

Treatment Indications

The most important treatment for all coagulopathies is the treatment of the underlying condition. Patients with VTE, inpatient medical, surgical, and COVID-19 therapy should receive anticoagulant therapy unless there is a contraindication to anticoagulation (active bleeding or severe bleeding within the previous 24 to 48 hours). All patients with COVID-19 should receive thromboprophylaxis, especially in the intensive care unit. Even in the absence of VTE, it would be appropriate to use moderate or therapeutic dose anticoagulation in severely ill patients. Some people without VTE should also receive prolonged thromboprophylaxis after discharge from the hospital. People with other risk factors such as immobilization, surgery, or trauma should use prophylactic anticoagulation after discharge. The risk of bleeding needs to be included in the decision-making process. In patients with COVID-19 who do not require hospitalization, thromboprophylaxis treatment may also be appropriate, especially for those with previous VTE or other thrombotic risk factors such as recent surgery, trauma or immobilization. It will be more correct for the clinician to make this decision. There is no study ad-

Table 5. Anticoagulant therapy in COVID-19 patients

1. High suspicion of acute thromboembolism- AMI, acute massive PE, DVT in extremity, arterial thrombosis- Thrombolytic therapy, anticoagulant should be given in therapeutic dose.
2. High suspicion of acute thromboembolism- AMI, acute massive PE, DVT in extremity, no arterial thrombosis- anticoagulant should be given at therapeutic dose.
3. Suspected acute thromboembolism can be low-anticoagulant therapy, patient-anticoagulant therapy continued or short-acting parenteral drugs can be switched.
4. Low suspicion of acute thromboembolism - patient not receiving anticoagulant treatment - being treated in hospital intensive care unit - anticoagulant (prophylactic, at therapeutic dose).
5. Low suspicion of acute thromboembolism - patient not receiving anticoagulant therapy - receiving treatment in hospital ward - prophylactic LMWH, Unfractionated heparin, fondaparinux.
6. Low suspicion of acute thromboembolism - patient not receiving anticoagulant treatment - not receiving hospital treatment - prophylactic anticoagulation should be given if the risky group.

AMI = acute myocardial infarction, DVT = deep venous thrombolism, LMWH = low molecular weight heparin, PE = pulmonary embolism

Table 6. Coagulopathy treatment in COVID-19 patients

1. Thrombosis prophylaxis in patients with 1st D-dimer < 1000 ng/ml a- CrCl > 30 ml/min, BMI < 40 kg/m^2: Enoxaparin 40 mg/day. BMI > 40 kg/m^2: Enoxaparin 40 mg 2×1 SC, BMI < 40 kg/m^2: Enoxaparin 40 mg/day SC b- CrCl < 30 ml/min: Standard heparin 5000 U SC 2×1 or 3×1 or Dose reduced low molecular weight heparin is recommended.
2. D-Dimer > 1000 ng/ml or patients with severe illness Enoxaparin: 0.5 mg/kg SC every 12 hours. a- CrCl < 30 ml/min: Standard heparin 5000 U SC 2×1 or 3×1 or dose reduced low molecular weight heparin recommended.
3. Patients with a previous history of atrial thrombosis or venous thrombosis (No change if taking more than 90 days, heparin in therapeutic dose is recommended if taking it for less than 90 days).

BMI = body mass index, CrCl = creatinine clearance, SC = subcutaneous

dressing thromboprophylaxis for patients in this category with COVID-19. Anticoagulant treatment in COVID-19 patients is summarized in Table 5 and Table 6 [43]. LMWH is the basis of treatment. However, heparin treatment should be avoided in cases where there are contraindications such as active bleeding, thrombocytopenia, HIT and heparin-induced allergy. In these cases, an alternative agent such as fondaparinux can be used.

Treatment Time

The duration of heparin prophylaxis should be decided based on the patient's thrombosis risk, mobilization, and returning of inflammation markers to normal levels. Individuals with documented VTE should receive anticoagulation therapy for at least three months. Among the post-discharge prophylaxis options, there are studies suggesting the use of 10 mg rivaroxaban daily for 31-39 days [4].

Treatment Success

In evaluating the effectiveness of heparin therapy, aPTT, ACT, AntiFXa, AT-3 and platelet levels should be monitored. A significantly better prognosis was observed with LMWH and anticoagulant therapy in COVID-19 patients [44]. In a retrospective study of 449 individuals with severe COVID-19, enoxaparin (40-60 mg once a day) was found to be associated with improved survival, especially in those with high D-Dimer [38]. In addition to its anticoagulant effect, it is thought that heparin binds inflammatory cytokines, inhibits neutrophil chemotaxis and leukocyte migration, neutralizes positively charged peptide C5a and sequesters acute phase proteins [2, 44, 45].

Treatment Failure

The prevalence of venous thromboembolism (VTE) is increasing, especially in critically ill individuals, despite prophylactic anticoagulation. The study by Klok *et al*. [6] showed that the use of LMWH prophylactic at low doses did not prevent thrombotic complications. In addition, it has been shown that the cumulative incidence of thrombotic complications in COVID-19 patients admitted to the intensive care unit is extremely high (> 30%) [6]. Despite the use of prophylactic anticoagulation, VTE, DVT and APE can be seen in one third of patients in the intensive care unit with COVID-19. In a study conducted, it was observed that DVT developed in 14% of 184 patients who received standard dose thromboprophylaxis in the intensive care unit due to COVID-19 infection [6]. Some experts have recommended more aggressive thromboprophylaxis dosage for the risk of VTE [43].

Plasminogen Activator (tPA)

Tissue plasminogen activator (tPA) is appropriate unless there is contraindication in cases of extremity-threatening DVT, massive APE, acute stroke and acute myocardial infarction.

Dipyridamole

Dipyridamole use may have anti-inflammatory,

antiaggregant and possible antiviral efficacy. However, there is no definitive recommendation for COVID-19 disease. Thrombosis prophylaxis should be administered to all COVID-19 patients and antiaggregant patients should be administered to those approved by the physician [36].

Mechanical Thrombosis Prophylaxis

In patients for whom pharmacological prophylaxis is contraindicated, mechanical thrombosis prophylaxis with intermittent pneumatic compression devices or compression stockings is recommended. Mechanical prophylaxis can be applied in addition to standard pharmacological prophylaxis in immobile patients.

Bleeding

Bleeding is less common in patients with COVID-19. However, it may occur especially in patients receiving anticoagulation or due to trauma. The bleeding approach is similar to people without COVID-19. Withdrawal of anticoagulant therapy may include specific treatments such as transfusions or factor replacement for thrombocytopenia or hypofibrinogenemia. Antifibrinolytic agents (tranexamic acid, epsilon aminocaproic acid) are generally not used in patients with DIC due to the concern that they may disrupt the balance against thrombosis. Fibrinogen is frequently increased in COVID-19. If there is no bleeding attributable to hypofibrinogenemia or dysfibrinogenemia (fibrinogen activity level < 150-200 mg/dL), fibrinogen supplementation is not required. Platelet suspension in a patient with major bleeding coagulopathy or DIC if the platelet count is <50×109/L; If PT and / or aPTT prolongation, INR > 1.8, fresh frozen plasma and fibrinogen concentrate or cryoprecipitate can be replaced if fibrinogen level is < 1.5 g/L. Protein complex concentrate is not recommended as recombinant FVIIa is unknown.

CONCLUSION

Coronavirus disease-19 (COVID-19) is a potentially fatal disease. SARS-COV2 can cause DIC. In addition, COVID-19 infection can also cause venous and / or arterial thrombosis, including APE, AMI, limb thrombosis, and central nervous system. When monitoring COVID-19 patients, platelet, PT and aPTT, fibrinogen and D-dimer monitoring should be initiated every 1-2 days, especially in critically ill patients. High D-Dimer levels are associated with high mortality; may be a marker of infection / sepsis, cytokine storm, and impending organ failure. DIC can be seen in COVID-19 patients. However, unlike DIC, fibrinogen is usually high. Clotting times and platelet counts are usually normal. Therefore, it is appropriate to use SIC criteria in the follow-up of COVID-19 patients. Treatment of the underlying disease is the most important treatment for all coagulopathies. A significantly better prognosis was observed in patients treated with LMWH anticoagulants. Bleeding is less common than clotting in patients with COVID-19. However, it may occur in patients receiving anticoagulation or due to trauma. The bleeding approach is similar to people without COVID-19.

Authors' Contribution

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

Conflict of interest

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

Financing

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

REFERENCES

1. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
3. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:844-7.

4. https://www.hematology.org/COVID-19/COVID-19-and-coagulopathy (Accessed on April 20, 2020).
5. Connors JM, Levy JH.. Thromboinflammation and the hypercoagulability of COVID−19. J Thromb Haemost 2020;18;1559-61.
6. Klok FA, Kruip MJHA, Van Der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thromb Res 2020;191:148-50.
7. Ciceri F, Beretta L, Scandroglio AM, Colombo S, Landoni G, Ruggeri A, et al. Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis. Crit Care Resusc 2020;22:95-7.
8. Krishna S, Eswaran N. Recent research progress and current understanding of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Asian J Biol 2020;10:9-21.
9. Schmaier AH. The plasma kallikrein-kinin system counterbalances the renin-angiotensin system. J Clin Invest 2002;109:1007-9.
10. Van de Veerdonk F, Netea MG, van Deuren M, van der Meer JW, de Mast Q, Bruggemann R, et al. Kinins and cytokines in COVID-19: a comprehensive pathophysiological approach. Preprints 2020;2020040023
11. Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, et al. Hypercoagulability of COVID−19 patients in intensive care unit. A report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemost 2020;18:1738-42.
12. Ranucci M, Ballotta A, Di Dedda U, Bayshnikova E, Dei Poli M, Resta M, et al. The procoagulant pattern of patients with COVID−19 acute respiratory distress syndrome. J Thromb Haemost 2020;18:1747-51.
13. https://www.esicm.org/wp-content/uploads/2020/04/863_author_proof.pdf (Accessed on April 25, 2020.
14. Bowles L, Platton S, Yartey N, Dave M, Lee K, Hart DP, et al. Lupus anticoagulant and abnormal coagulation tests in patients with Covid-19. N Engl J Med 2020;383:288-90.
15. Zhou Y, Fu B, Zheng X, Wang D, Zhao C, Qi Y, et al. Pathogenic T cells and inflammatory monocytes incite inflammatory stroms in severe COVID-19 patients. Nat Sci Rev 2020;6:998-1002.
16. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Transl Res 2020;220:1-3.
17. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801-10.
18. Levi M, van der Poll T. Coagulation and sepsis. Thromb Res 2017;149:38-44.
19. Schmitt FCF, Manolov V, Morgenstern J, Fleming T, Heitmeier S, Uhle F, et al. Acute fibrinolysis shutdown occurs early in septic shock and is associated with increased morbidity and mortality: results of an observational pilot study. Ann Intens Care 2019;9:19.
20. Monteleone G, Sarzi-Puttini PC, Ardizzone S. Preventing COVID-19-induced pneumonia with anticytokine therapy. Lancet Rheumatol 2020;2:e255-6.
21. Mastellos DC, Ricklin D, Lambris JD. Clinical promise of next-generation complement therapeutics. Nat Rev Drug Discov 2019;18:707-29.
22. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med 2017;377:562-72.
23. Tan CW, Low JGH, Wong WH, Chua YY, Goh SL, Ng HJ. Critically ill COVID−19 infected patients exhibit increased clot waveform analysis parameters consistent with hypercoagulability. Am J Hematol 2020;95:E156-8.
24. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. Covid-19 does not lead to a "typical" acute respiratory distress syndrome. Am J Respir Crit Care Med 2020;201:1299-300.
25. Gupta N, Zhao YY, Evans CE. The stimulation of thrombosis by hypoxia. Thromb Res 2019;181:77-83.
26. Begbie M, Notley C, Tinlin S, Sawyer L, Lillicrap D. The factor VIII acute phase response requires the participation of NFκB and C/EBP. Thromb Haemost 2000;84:216-22.
27. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 2020;323:1061-9.
28. Fox SE, Akmatbekov A, Harbert JL, Li G, Brown JQ, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. Lancet Respir Med 2020;8:681-6.
29. Memikoğlu O, Genç V. COVİD-19. E-Kitap, Ankara Üniversitesi Basımevi: Ankara, 2020.
30. Bellosta R, Luzzani, L, Natalini G, Pegorer MA, Attisani L, Cossu LG, et al. Acute limb ischemia in patients with COVID-19 pneumonia. J Vasc Surg 2020;72:1864-72.
31. Taylor FB, Toh CH, Hoots WK, Wada H, Levi M. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 2001;86:1327-30.
32. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID−19. J Thromb Haemost 2020;18:1023-6.
33. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. Br J Haematol 2009;145:24-33.
34. Di Nisio M, Baudo F, Cosmi B, D'Angelo A, De Gasperi, A, Malato A, et al. Diagnosis and treatment of disseminated intravascular coagulation: guidelines of the Italian Society for Haemostasis and Thrombosis (SISET). Thromb Res 2012;129:e177-84.
35. Iba T, Di Nisio M, Levy JH, Kitamura N, Thachil J. New criteria for sepsis-induced coagulopathy (SIC) following the revised sepsis definition: a retrospective analysis of a nationwide survey. BMJ Open 2017;7:e017046.
36. Turkey Ministry of Health, General Directorate of Public

Health, COVID-19 (SARS-CoV-2 Infection) Guide. April 12, 2020, pp. 64-8.
37. Iba T, Levy JH, Warkentin TE, Thachil J, van der Poll T, Levi M; Scientific and Standardization Committee on DIC, and the Scientific and Standardization Committee on Perioperative and Critical Care of the International Society on Thrombosis and Haemostasis. Diagnosis and management of sepsis−induced coagulopathy and disseminated intravascular coagulation. J Thromb Haemost 2019;17:1989-94.
38. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020;18:1094-9.
39. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV). Radiology 2020;295:202-7.
40. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. Radiology 2020;295:715-21.
41. Bai HX, Hsieh B, Xiong Z, Halsey K, Choi JW, Tran TML, et al. Performance of radiologists in differentiating COVID-19 from viral pneumonia on chest CT. Radiology 2020;296:E46-54.
42. Caruso D, Zerunian M, Polici M, Pucciarelli F, Polidori T, Rucci C, et al. Chest CT features of COVID-19 in Rome, Italy. Radiology 2020;296:E79-85.
43. Cuker A, Peyvandi F. Coronavirus disease 2019 (COVID-19): Hypercoagulability. UpToDate 2020. https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-hypercoagulability (Accessed on November 26, 2020).
44. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.
45. Poterucha TJ, Libby P, Goldhaber SZ. More than an anticoagulant: Do heparins have direct anti-inflammatory effects? Thromb Haemost 2017;117:437-44.