E-ISSN: 2602-3741

Year 2022
Volume 32
Issue 1

GENEL TIP DERGİSİ

The Journal of General Medicine

The Offical Journal of Selcuk University School of Medicine

EDITORIAL BOARD

Editorial Correspondence

Prof. Dr. İnci KARA
Selcuk University, School of Medicine
Department of Anesthesiology and Reanimation
Alaeddin Keykubat Campus Selçuklu/Konya 42075 TÜRKİYE

Phone: +90 (332) 24
Faks: +90 (332) 24

INSTRUCTIONS FOR AUTHORS

AIM AND SCOPE

The Journal will not consider manuscripts any that have been published elsewhere, or manuscripts that are being considered for another publication, or are in press. Studies previously announced in the congresses are accepted if this condition is stated. If any part of a manuscript by the same author(s) contains any information that was previously published, a reprint or a copy of the previous article should be submitted to the Editorial Office with an explanation by the authors A technical review is performed to confirm that all of the required documentation has been submitted and to conduct a preliminary evaluation of the manuscript and supplementary files to assess suitability for the Journal. The manuscript will be returned to the Author in the event of any deficiency. Genel Tıp Dergisi operates a blind review process. Contributions deemed suitable are then typically sent to a minimum of two independent expert reviewers in the field of study to assess the scientific quality of the paper. (You can see at the picture below).

The Editor/Editors are responsible for the final decision regarding acceptance or rejection of articles. The Editor's decision is final. If necessary, author(s) may be invited to submit a revised version of the manuscript. This invitation does not imply that the manuscript will be accepted for publication. Revised manuscripts must be sent to the Editorial Office within 4 (four) weeks, otherwise they will be considered as a new application. The corresponding author will be notified of the decision to accept or reject the manuscript for publication. Statements and suggestions published in manuscripts are the authors' responsibility and do not reflect the opinions of the Editor, Associate Editors and the Editorial Board members. The manuscript will not be returned to the authors whether the article is accepted or not. Copyright fee is not paid for the articles published in the journal. A copy of the journal will be sent to the corresponding author.

Language of the Journal

The official languages of the Journal are English. The manuscripts that are written in English, which makes the abstracts available to a broader audience.

Authorship Criteria

After accepted for publication, all the authors will be asked to sign "CoyrightTransfer Form" which states the following: " This work is not under active consideration for publication, has not been accepted for publication, nor has it been published, in full or in part (except in abstract form). I confirm that the study has been approved by the ethics committee. " All authors should agree to the conditions outlined in the form. Genel Tıp Dergisi has agreed to use the standards of the International Committee of Medical Journal Editors. The author(s) should meet the criteria for authorship according to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. It is available at www.icmje.org.

Ethical Responsibility

The protocol of clinical research articles must be approved by the Ethics Committee. In all studies conducted on humans, the "Material and Method" section was approved by the relevant committee or the Helsinki Declaration of Principles (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/). It should be stated in the text that all persons included in the study signed the am Informed Consent Form ". The articles submitted to the Genel Tıp Dergisi will be deemed to have been conducted in accordance with the Helsinki Declaration of Principles, and have received ethical and legal permissions and will not be held responsible. If the "Animal" item was used in the study, the authors stated that in the Material and Method section of the article, they protect the animal rights in their studies in accordance with the principles of Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) and that they have received approval from the ethics committees of their institutions. must specify.

In case reports, Informed Consent a should be obtained from patients regardless of the identity of the patient. If the article includes the institution (directly or indirectly) providing financial support for the commercial connection or work, the authors; the commercial product used, the drug, the company has no commercial relationship with, or if there is any relationship (consultant, other agreements, etc.), the editor must inform the presentation page. If Ethics Committee Approval is required in the article; the received document should be sent with the article.

The manuscript should be submitted to the Academic Plagiarism Prevention Program by the authors. It is the authors' responsibility to ensure that the article complies with the ethical rules. Policy of Screening for Plagiarism The manuscripts are scanned by the Journal using the iThenticate program for determination of plagiarism and non-ethical situations. Genel Tıp Dergisi will immediately reject manuscripts leading to plagiarism.

TYPES OF MANUSCRIPT

Manuscripts should be submitted online via https://dergipark.org.tr/tr/pub/geneltip

Original Articles should not exceed 3000 words and should be arranged under the headings of Abstract (not more than 250 words), Introduction, Materials and Methods, Results, Discussion, Conclusion and References. Case Reports should not exceed 1000 words and 10 references, and should be arranged as follows: Abstract, Introduction, Case Report, Discussion and References. It may be accompanied by only one figure or table. Letter to the Editor should not exceed 500 words. Short relevant comments on medical and scientific issues, particularly controversies, having no more than five references and one table or figure are encouraged. Where letters refer to an earlier published paper, authors will be offered right of reply. Reviews are not accepted unless written on the invitation of the Editorial Board.

PREPARATION OF MANUSCRIPTS

All articles submitted to the Journal must comply with the following instructions:

a) Submissions should be doubled-spaced and typed in Arial 10 points.
b) All pages should be numbered consecutively in the top righthand corner, beginning with the title page.
c) The title page should not include the names and institutions of the authors.
d) The manuscript should be presented in the following order: Title page, Abstract (English, Turkish), Keywords (English, Turkish), Introduction, Materials and Methods, Results, Discussion, Conclusion, Acknowledgements (if present), References, Figure Legends, Tables (each table, complete with title and foot-notes, on a separate page) and Appendices (if present) presented each on a separate page.

Title

The title should be short, easy to understand and must define the contents of the article.

Abstract

Abstract should be in both English and Turkish and should consist "Aim, Materials and Methods, Results and Conclusion". The purpose of the study, the setting for the study, the subjects, the treatment or intervention, principal outcomes measured, the type of statistical analysis and the outcome of the study should be stated in this section (up to 250 words). Abstract should not include reference. No abstract is required for the letters to the Editor.

Keywords

Not more than five keywords in order of importance for indexing purposes should be supplied below the abstract and should be selected from Index Medicus Medical Subject Headings (MeSH), available at www.nlm.nih.gov/meshhome.html.

Text

Authors should use subheadings to divide sections regarding the type of the manuscript as described above. Statistical methods used should be specified in the Materials and Methods section.

References

In the text, references should be cited using Arabic numerals in parenthesis in the order in which they appear. If cited only in tables or figure legends, they should be numbered according to the first identification of the table or figure in the text. Names of the journals should be abbreviated in the style used in Index Medicus. The names of all authors should be cited when there are six or fewer; when seven or more, the first three should be followed by et al. The issue and volume numbers of the referenced journal should be added.

References should be listed in the following form:

Journal article

Teke Z, Kabay B, Aytekin FO et al. Pyrrolidine dithiocarbamate prevents 60 minutes of warm mesenteric ischemia/reperfusion injury in rats. Am J Surg 2007;194(6):255-62.

Supplement

Solca M. Acute pain management: Unmet needs and new advances in pain management. Eur J Anaesthesiol 2002; 19(Suppl 25): 3-10.

Online article not yet published in an issue Butterly SJ, Pillans P, Horn B, Miles R, Sturtevant J. Off-label use of rituximab in a tertiary Queensland hospital. Intern Med J doi: 10.1111/j.1445-5994.2009.01988.x

Book

Sample 1: Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.
Sample 2: Sümbüloğlu K, Akdağ B. Regresyon Yöntemleri ve Korelasyon Analizi. Hatiboğlu Yayınevi: Ankara; 2007.

Chapter in a book Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93113.

Journal article on the Internet Abood S. Quality improvement initiative in nursing homes: The ANA acts in an advisory role. Am J Nurs [serial on the Internet] 2002 [cited 12 Aug 2002]; 102. Available from: www.nursingworld.org/AJN/2002/june/wawatch.htm Website Cancer-pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources [updated 16 May 2002; cited 9 Jul 2002]. Available from: www.cancer-pain.org

An organization as an author The Intensive Care Society of Australia and New Zealand. Mechanical ventilation strategy in ARDS: Guidelines. Int Care J Aust 1996;164:282-4.

Acknowledgements

The source of financial grants and the contribution of colleagues or institutions should be acknowledged.

Tables

Tables should be complementary, but not duplicate information contained in the text. Tables should be numbered consecutively in Arabic numbers, with a descriptive, self-explanatory title above the table. All abbreviations should be explained in a footnote. Footnotes should be designated by symbols in the following order: *,†, ‡, §, ¶.

Figures

All illustrations (including line drawings and photographs) are classified as figures. Figures must be added to the system as separate .jpg or .gif files (approximately 500x400 pixels, 8 cm in width and at least 300 dpi resolution). Figures should be numbered consecutively in Arabic numbers and should be cited in parenthesis in consecutive order in the text.

Figure Legends

Legends should be self-explanatory and positioned on a separate page. The legend should incorporate definitions of any symbols used and all abbreviations and units of measurements should be explained. A letter should be provided stating copyright authorization if figures have been reproduced from another source.

Measurements and Abbreviations

All measurements must be given in metric system (Système International d'Unités, SI). Example: mg/kg, µg/kg, mL, mL/kg, mL/kg/h, mL/kg/min, L/min, mmHg, etc. Statistics and measurements should always be given in numerals, except where the number begins a sentence. When a number does not refer to a unit of measurement, it is spelt out, except where the number is greater than nine. Abbreviations that are used should be defined in parenthesis where the full word is first mentioned. Some common abbreviations can be used, such as iv, im, po, and sc. Drugs should be referred to by their generic names, rather than brand names.

Editorial Correspondence

Prof. Dr. İnci KARA
Selcuk University, School of Medicine
Department of Anesthesiology and Reanimation
Alaeddin Keykubat Campus Selçuklu/Konya 42075 TÜRKİYE

Phone: +90 (332) 224 38 19
Faks: +90 (332) 221 21 84

CONTENTS

Received: 16 Jul 2021 | **Accepted:** 4 Nov 2021
DOI: 10.54005/geneltip.972458

ORIGINAL ARTICLE

Evaluation of Overall Survival Predictions In Inoperable Pancreas Ductal Adenocarcinoma

İnoperabl Pankreas Duktal Adenokarsinomunda Genel Sağ Kalım Öngörücülerinin Değerlendirilmesi

[1]Mustafa Erol, [1]Hasan Önner, [2]İlknur Küçükosmanoğlu

[1]Konya Şehir Hastanesi, Nükleer Tıp Birimi, Konya, Türkiye

[2]Konya Şehir Hastanesi, Tıbbi Patoloji Birimi, Konya, Türkiye

Correspondence

Hasan Önner, Konya Şehir Hastanesi, Nükleer Tıp Birimi, Konya, Türkiye Hastanesi, Nükleer Tıp Kliniği

E-Mail: hasanonner_1988@hotmail.com

How to cite ?

Erol M, Önner H, Küçükosmanoğlu İ. Evaluation of Overall Survival Predictions in Inoperable Pancreas Ductal Adenocarcinoma. Genel Tıp Derg. 2022;32(1):1-4.

ABSTRACT

Objective: In this study, we aimed to determine the independent predictive parameters of overall survival (OS) of patients with inoperable pancreatic ductal adenocarcinoma (PDAC) and to investigate whether these parameters can be used as potential biomarkers to shape precision medicine practices for PDAC patients.
Materials and Methods: The clinical and pathological data of patients who were diagnosed with inoperable pancreatic ductal adenocarcinoma between January 2016 and December 2019 and who underwent 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) in our department were retrospectively analyzed. Tumor diameter, maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were calculated from FDG PET/CT images. Univariate and multivariate Cox regression analyzes were performed to investigate the variable affecting overall survival. Overall survival data were analyzed using the Kaplan–Meier method, using the log-rank test.
Results: A total of 48 patients, 31 male and 17 female, with a mean age of 65.85 ± 1.64 were included in the study. In univariate Cox regression analyzes were performed to examine the factor affecting OS. Clinicopathological factors (tumor localization, tumor diameter, stage) and FDG PET/CT parameters (SUVmax, MTV and TLG) with a p-value of < 0.2 were compared to multivariate Cox regression analysis. TLG was found to be the only independent predictor of OS. In the Kaplan-Meier analysis, the median OS duration of the patients with a median value of TLG below 298.34 was 13.87 months, while the median OS duration was found to be 4.97 months in patients with a TLG value above this value.
Conclusion: In our study, TLG value, which is an FDG PET/CT parameter that reflects both the metabolic activity and the volume of the tumor, was found to be the only independent predictor of the OS of inoperable PDAC patients. TLG can be used as a potential biomarker for survival in patients with inoperable PDAC and may assist precision medicine applications.

Keywords: Pancreatic ductal adenocarcinoma; fluorodeoxyglucose; Positron emission tomography / computed tomography; total lesion glycolysis

ÖZ

Amaç: Bu çalışmada, inoperabl pankreas duktal adenokarsinom (PDAK) tanılı hastaların genel sağ kalımının (GSK) bağımsız öngörücü parametrelerini saptamayı ve bu parametrelerin PDAK hastaları için hassas tıp uygulamalarını şekillendirmede potansiyel biyobelirteç olarak kullanılıp kullanılamayacağını araştırmayı amaçladık.
Gereç ve Yöntem: Ocak 2016 - Aralık 2019 tarihleri arasında inoperabl pankreas duktal adenokarsinom tanısı alan ve bölümümüzde Flor-18 florodeoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografi (FDG PET/BT) tetkiki yapılan hastaların klinik ve patolojik verileri retrospektif olarak incelendi. FDG PET/BT görüntülerinden tümörün çapı, maksimum standardize tutulum değeri (SUDmaks), metabolik tümör volümü (MTV) ve toplam lezyon glikolizisi (TLG) hesaplandı. GSK üzerine etki eden değişkenlerin araştırılması için tek değişkenli ve çok değişkenli Cox regresyon analizleri yapıldı. GSK verileri Kaplan–Meier yöntemiyle, log-rank testi kullanılarak incelendi.
Bulgular: Çalışmaya ortalama yaşı 65.85 ± 1.64 olan 31'i erkek 17'si kadın toplam 48 hasta dahil edildi. GSK üzerine etki eden faktörleri incelemek için yapılan tek değişkenli Cox regresyon analizlerinde p değeri:< 0.2 olan klinikopatolojik faktörler (tümör lokalizasyonu, tümör çapı, evre) ve FDG PET/BT parametrelerinin (SUDmaks, MTV ve TLG) çok değişkenli Cox regresyon analizine dahil edilmesi sonucu TLG'nin, GSK'ın tek bağımsız öngürücüsü olduğu bulundu. Yapılan Kaplan-Meier analizinde, TLG'nin median değerinin 298.34'ün altında olan hastaların ortanca GSK süresi 13.87 ay iken, TLG değeri bu değerin üstünde olan hastalarda ortanca GSK süresi 4.97 ay olarak bulundu.
Sonuç: Çalışmamızda, tümörün hem metabolik aktivitesini hem de hacmini birlikte yansıtan, FDG PET/BT parametresi olan TLG değeri, inoperabl PDAK hastalarının GSK'nın tek bağımsız öngörücüsü olarak bulundu. TLG, inoperabl PDAK'lı hastalarda sağ kalım için potansiyel bir biyobelirteç olarak kullanılabilir ve hassas tıp uygulamalarına yardımcı olabilir.

Anahtar kelimeler: Pankreas duktal adenokarsinom; Florodeoksiglukoz; Pozitron emisyon tomografisi/bilgisayarlı tomografi; toplam lezyon glikolizi

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most prevalent exocrine malignancy of the pancreas with high mortality risk and is the 7th leading cause of cancer deaths worldwide (1) The five-year survival is reported to be 9% and this decreases to 2% in advanced stage PDAC (2). At the time of initial diagnosis, approximately 80% of the patients have locally spread or distant metastatic disease. The poor prognosis of PDAC may be related to the propensity for early metastatic spread (3). Surgery is the only curative treatment modality for PDAC (4). However, only 15-20% of patients are candidates for surgery (4). Effective imaging methods are needed to avoid unnecessary surgeries and to estimate the prognosis.

Fluorine-18-fluorodeoxyglucose positron emission tomography /computed tomography (FDG PET/CT) is a non-invasive imaging technique to evaluate the glucose metabolism of malignant cells (5). FDG PET/CT is used to diagnose and stage many malignancies, including pancreatic carcinoma. Prognostic dates achieved by F-18 FDG PET/CT in pancreas cancers have been reported in many studies (6-8). information obtained with FDG PET/CT in pancreatic cancer. However, most of these studies examined resected early-stage PDAC or both early and advanced-stage PDAC together indiscriminately.

In our study, we aimed to investigate the prognostic predictive values of clinicopathological factors (tumor localization, tumor diameter and stage), maximum standard uptake value (SUVmax), metabolic tumor volume (MTV) and total lesion glycolysis (TLG) of primary tumor obtained by FDG PET/CT, in patients with inoperable PDAC, and also independent predictive parameters for overall survival in patients with inoperable PDAC.

Materials-Methods

The clinical and pathological data of patients diagnosed as PDAC and followed up with FDG PET/CT in our department between January 2016 and December 2019 were investigated retrospectively. Resectable PDAC, intraductal papillary mucinous neoplasms, endocrine tumors, cystic neoplasms, pancreatic metastases, and duodenal, ampullary and biliary tract cancers were excluded from the study. According to these criteria, 48 patients were enrolled. The diagnosis of PDAC was confirmed histopathologically in all cases. The patients were staged according to the TNM classification of the International Union for Cancer Control (UICC) (9). Age, gender, lymph node metastasis status and overall survival of the patients were evaluated. Overall survival was recorded as the time passed from the date of FDG PET/CT to the date of death. The death dates of the patients were obtained from the hospital records.

Regular follow-ups that include physical examination, abdominal CT or ultrasonography and tumor markers were applied for all patients. The majority of patients were given gemcitabine-based chemotherapy, while some patients were given adjuvant palliative treatments.

Ethics Committee

The Approval with number 2021/023 from the medical faculty of KTO Karatay University was obtained for this study. Our studies are compatible with all procedures applied for studies with human participation, institutional and/or national research committee ethical standards and the 1964 Declaration of Helsinki and subsequent amendments or comparable ethical standards.

FDG PET/CT Imaging Protocol

Intravenous FDG (3.7 MBq/Kg) was given to patients for PET/CT imaging, after 6 hours of fasting. Blood glucose levels were lower than 200 mg/dl before the imaging in all patients. Sixty minutes after injection, PET/CT imaging was performed from the skull base to the upper thigh with Siemens 16 Truepoint PET/CT scanner (Siemens AG Medical Solutions, Erlangen, Germany). Images were evaluated in transaxial, coronal and sagittal plane sections with different colours and contrast slices. FDG PET/CT findings of the patients were interpreted together by two nuclear medicine specialists. SyngoTrueD VD20A software was used for image processing.

Calculation of FDG PET/CT Parameters

The region of interest was drawn from the FDG PET/CT images, including the regions showing pathological FDG uptake in the pancreas. The SUVmax and SUVmean were calculated from within the plotted area of interest. The MTV value, which shows the metabolic tumor volume in the selected area of interest, was calculated by an automatic software (SyngoTrueD VD20A) selecting the threshold of 42% of SUVmax in the area of interest recommended in the literature (10) for soft tissue tumors. The total lesion glycolysis (TLG) value was obtained by multiplying the MTV by the SUVmean values.

Statistical Analysis

Data were analyzed by SPSS 26.0 (SPSS Inc, Chicago, IL, USA). The normality of the distributions of the study variables was checked with the Kolmogorov-Smirnov test. Since all numerical variables did not show a normal distribution, their median values were used. Categorical variables were presented as n (%). Comparisons between groups were made using the Mann-Whitney-U or Kruskal-Wallis tests. Spearman's correlation test was used for the correlation of quantitative parameters. Univariate and multivariate regression analyzes were applied for the variables that affect overall survival. For overall survival, variables that were found to be at $p<0.2$ on univariate analysis were included in multivariate analysis. Overall survival data were analyzed by Kaplan–Meier method, using the log-rank test. A p-value of <0.05 was considered statistically significant.

Results

Forty-eight patients, (31 male and 17 female), with a mean age of 65.85 ± 1.64 years were enrolled in our study. Mean pancreatic tumor diameter: 38.50 mm, median SUVmax for pancreatic tumor: 10.30, median MTV value for pancreatic tumor 69.83, and median TLG value for pancreatic tumor: 298.34. The demographic and the clinical data of the patients are presented in Table 1.

Table 1. Patient Characteristics

	n (%)
Age	
≤65 years	23 (% 47.92)
>65 years	25 (% 52.08)
Gender	
Male	31 (% 64.58)
Female	17 (% 35.42)
Tumor localization	
Head	25 (% 52.08)
Corpus	23 (% 47.92)
Tail	0
Median tumor diameter (mm)	38.50
Stage	
Stage III	21 (% 43.75)
Stage IV	27 (% 56.25)
Median SUVmax	10.30
Median MTV	69.83
Median TLG	298.34

SUVmax, maximum standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis;

Table 2. Univariate and multivariate Cox regression analyzes for overall survival in patients with inoperable pancreatic ductal adenocarcinoma

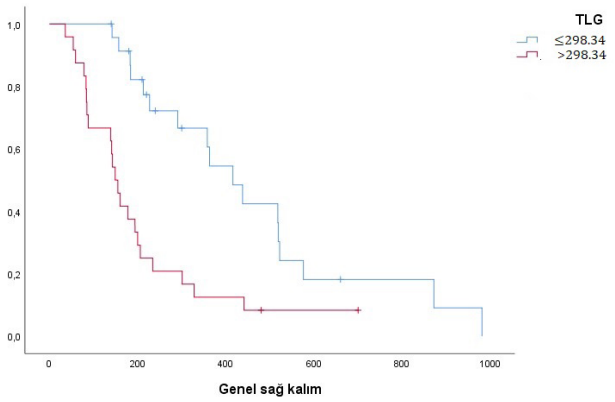
	Univariate analysis			Multivariate analysis		
	HR	**%95 CI**	**p**	**HR**	**%95 CI**	**p**
Age(≤65->65)		0.387-1.445				
Gender (Male-Female)		0.389-1.457				
Tumor localization (Head-Corpus)		0.930-3.352			0.756-3.419	
Tumor diameter (mm) (≤38.50->38.50)		0.565-1.077			0.294-1.737	
Stage (III-IV)		0.979-3.709			0.939-4.510	
SUVmax (≤10.30->10.30)		1.199-4.575			0.564-3.008	
MTV (≤69.83->69.83)		1.228-4.615			0.225-2.373	
TLG (≤298.34-298.34)		1.621-6.228			1.061-15.228	

CI, confidence interval; HR, hazard ratio; SUVmax, maximum standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis;

The tumor was located in the head of the pancreas in 25 patients (52.08%) and the corpus in 23 patients (47.92%). None of the patients has a tumor located in the tail of the pancreas in the study. Median MTV and TLG values of tumors located in the corpus of the pancreas were significantly higher than those located in the head part (p=0.06 and 0.013, respectively). No significant difference was found for SUVmax. Twenty-one (43.75%) and 27 (56.25%) of the patients were at stage III and stage IV respectively. No significant relation was found between FDG PET/CT parameters in stage groups of pancreas tumors. While significant moderate correlation was found between tumor diameter and MTV (r= 0.670, p: <0.001) and TLG (r= 0.668, p: <0.001) values, no significant correlation was found between tumor diameter and SUVmax values.

The median follow-up time was 6.93 months for the patients. Thirty-nine patients died during follow-up. Tumor localization, tumor diameter, stage, SUVmax, MTV and TLG were included in the multivariate analysis to investigate the factors that affect overall survival (Table 2). TLG was found to be the only independent predictive factor that affects overall survival [Hazard ratio (HR)= 4.019, 95% confidence interval (CI) 1.061-15.228, p= 0.041]. The median overall survival time was 13.87 months for patients with a median TLG value lower than 298.34 but was 4.97 months for those with higher values (p: <0.001). Overall survival curves of patients with TLG values higher and lower than 298.34 are shown in figure 1.

Figure 1. Overall survival curves of patients grouped by TLG values (≤298.34 - >298.34)



Discussion

Pancreatic ductal adenocarcinoma is an aggressive and lethal disease with a 5-year survival rate of only 2-9%. It has an increasing incidence trend all over the world and constitutes 1-2% of all cancers (2). Predicting prognosis in PDAC may aid to choose sensitive medicine practices. In our study, an FDG PET/CT parameter TLG, which shows both tumor volume and metabolism, was found as an independent predictor of overall survival in inoperable PDAC patients.

In patients with PDCA, a relationship between tumor size and overall survival was reported (11), however contrary publications have been published in the literature (12, 13). In our study, a significant and moderate correlation was found with tumor size and MTV and TLG values. In univariate regression analysis, Tumor diameter was found a significantly effective variable on overall survival, but on the contrary, it was not found as an independent predictive factor on overall survival in multivariate regression analysis. Stroma-dense desmoplastic reaction in the tumor, non-viable tumor cells due to the hypoxic environment around the tumor and intra-tumoral heterogeneity may be the factors that may cause tumor diameter has not a prognostic value.

SUVmax is a commonly used parameter in FDG PET/CT and shows the highest FDG uptake density in the area of interest but does not reflect the metabolic activity of the entire tumor. TLG was found a better prognostic predictor than SUVmax in many studies that involved both PDAC and different cancers (14, 15). In line with previous studies (6, 17), we found that SUVmax was not an independent predictive factor of overall survival in our study.

TLG, which defines the metabolic activity of the tumor and the tumor volume, may show total tumor burden excluding the non-neoplastic parts of the tumor (18, 19). Among the clinicopathological factors and FDG PET/CT parameters evaluated in our study, only TLG was the independent predictor of overall survival. Furthermore, we found that patients with a TLG value higher than 298.34 have approximately 9 months less survival than patients below this value.

The limitations of our study were its retrospective character, low patient number, and one-centre experience. In addition, TLG is affected by many factors such as partial volume effect, image resolution, reconstruction method, and the time elapsed between FDG injection and imaging. Therefore, prospective multicenter studies using standardized protocols on different FDG PET/CT scanners are needed to validate our results.

Conclusion

In our study, the TLG value obtained from FDG PET/CT, which shows both metabolic activity and volume of the tumor was found as an independent predictive parameter for the overall survival of patients in inoperable PDAC. TLG may be used as a potential biomarker in patients with inoperable PDAC and may aid to detect patients that need intense therapy.

References

1. Simoes PK, Olson SH, Saldia A, Kurtz RC. Epidemiology of pancreatic adenocarcinoma. Chin Clin Oncol 2017;6:24-24.

2. Siegel RL., Miller KD, Jemal A. Cancer statistics. CA: a cancer journal for clinicians 2016;66:7-30.

3. Addeo P, Velten M, Averous G, Faitot F, et al. Prognostic value of venous invasion in resected T3 pancreatic adenocarcinoma: depth of invasion matters. Surgery 2017;162:264-274.

4. Shaib Y, Davila J, Naumann C, El-Serag H. The impact of curative intent surgery on the survival of pancreatic cancer patients: a US Population-based study. ACG 2007;102:1377-1382.

5. Risum S, Høgdall C., Loft A, et al. Prediction of suboptimal primary cytoreduction in primary ovarian cancer with combined positron emission tomography/computed tomography—a prospective study. Gynecol Oncol 2008;108:265-270.

6. Nakata B, Nishimura S, Ishikawa T. Prognostic predictive value of 18F-fluorodeoxyglucose positron emission tomography for patients with pancreatic cancer. Int J Oncol 2001;19:53-58.

7. Maisey NR, Webb A, Flux GD, et al. FDG–PET in the prediction of survival of patients with cancer of the pancreas: a pilot study. Br J Cancer, 2000;83:287-293.

8. Zimny M, Fass J, Bares R, Cremerius U, et al. Fluorodeoxyglucose positron emission tomography and the prognosis of pancreatic carcinoma. Scand. J Gastroenterol 2000;35:883-888.

9. Brierley JD, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours. 7th ed. Geneva: John Wiley & Sons 2017;1025-1027

10. Lim JE, Chien MW Earle CC, et al. Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients. Ann Surg 2003;237:74-80.

11. Jamieson NB, Mohamed M, Oien KA, et al. The relationship between tumor inflammatory cell infiltrate and outcome in patients with pancreatic ductal adenocarcinoma. Ann Surg Oncol 2012;19:3581-3590.

12. Oshima M, Okano K, Muraki S, et al. Immunohistochemically detected expression of 3 major genes (CDKN2A/p16, TP53, and SMAD4/DPC4) strongly predicts survival in patients with resectable pancreatic cancer. Ann Surg 2013;258:336-346.

13. Önner H, Canaz F, Dinçer M, et al. Which of the fluorine-18 fluorodeoxyglucose positron emission tomography/computerized tomography parameters are better associated with prognostic factors in breast cancer?. Medicine 2019;98:22-28.

14. Kaida H, Toh U, Hayakawa M, et al. The relationship between 18F-FDG metabolic volumetric parameters and clinicopathological factors of breast cancer. Nucl Med Commun 2013;34:562-570.

15. Hatt M, Visvikis D, Albarghach NM, et al. Prognostic value of 18 F-FDG PET image-based parameters in oesophageal cancer and impact of tumour delineation methodology. Eur J Nucl Med Mol Imaging 2011;38:1191-1202.

16. Zhang H, Wroblewski K, Liao S, et al. Prognostic value of metabolic tumor burden from 18F-FDG PET in surgical patients with non–small-cell lung cancer. Acad Radiol 2013;20:32-40.

17. Erol M, Önner H, Taştekin G. Akciğer Kanserli Hastalarda F-18 FDG PET/BT Parametrelerinin Klinik Evre ile İlişkisi. Selcuk Med J 2021;37(1): 24-31.

18. Hatt M, Cheze-Le Rest C, Aboagye E, et al. Reproducibility of 18F-FDG and 3'-deoxy-3'-18F-fluorothymidine PET tumor volume measurements. J Nucl Med 2010;51:1368–76.

Received: 28 Jul 2021 | **Accepted:** 29 Oct 2021
DOI: 10.54005/geneltip.975767

ORIGINAL ARTICLE

Investigating Attitudes of Nurses Working in a State Hospital Towards Prevention of Pressure Ulcers

Bir Devlet Hastanesinde Çalişan Hemşirelerin Basinç Yaralarini Önlemeye Yönelik Tutumlarinin İncelenmesi

[1]Aziz Bulut, [2]Çiğdem Aksu, [3]Aliye Bulut, [3]Mehtap Aslan

[1]Gaziantep University, Faculty of Medicine, Dept. of General Surgery, Gaziantep / Turkey

[2]Gaziantep Islamic Science and Technology University, Faculty of Health Sciences, Dept. of Nursing, Gaziantep / Turkey

[3]Gaziantep Islamic Science and Technology University, Faculty of Medicine, Dept. of Public Health, Gaziantep / Turkey

[4]Bingol University, Faculty of Health Sciences, Dept. of Nursing, Bingol/ Turkey

Correspondence

Aziz Bulut, Gaziantep University, Faculty of Medicine, Dept. of General Surgery, Gaziantep / Turkey

E-Mail: drazizbulut@yahoo.com

How to cite ?

Bulut A, Aksu Ç, Bulut A, Aslan A. Investigating Attitudes of Nurses Working in a State Hospital Towards Prevention of Pressure Ulcers. Genel Tıp Derg. 2022;32(1):5-11.

ABSTRACT

Objective: This study was conducted in order to investigate the attitudes of nurses working in a state hospital towards prevention of pressure ulcers.
Materials and Methods: The population of the present study consisted of a total of 246 nurses, who were working in a public hospital located in a city center in Eastern Anatolia Region. The study, it was attempted to reach the whole population, and the data were collected from 241 nurses who voluntarily participated in the study. A "Questionnaire" with 31 questions, which was prepared by the researchers, was used to collect the data. The data on the questionnaire prepared by the support of literature were collected using Nurse Information Form with 18 questions to investigate attitudes of nurses towards prevention of pressure ulcers as well as Attitude Towards Pressure Ulcer Prevention Instrument consisting of 13 questions.
Results: The nurses with high school degree were determined to have higher attitudes towards the effect of pressure ulcers, towards the personal responsibility to prevent pressure ulcers, and towards the effectiveness of prevention of pressure ulcer. Attitudes of the nurses with high school degree towards personal sufficiency to prevent pressure ulcers were higher and the difference between the groups was significant ($p<0.05$).
Conclusion: It was observed that the variable of education level made a difference in the attitude towards preventing pressure sores. In addition, it was determined that nurses' attitudes towards preventing pressure ulcers were deficient.Within this context, each institution should determine pressure ulcer care protocols appropriate to standards and innovations, develop clinical practice guides, and ensure supervision of their convenience.

Keywords: Pressure Ulcer, Nurse, Prevention, Attitude, Attitude Scale.

ÖZ

Amaç: Bu araştırma, bir devlet hastanesinde çalışan hemşirelerin basınç yaralarını önlemeye yönelik tutumlarının incelenmesi amacıyla yapılmıştır.
Gereç ve Yöntem: Araştırmanın evrenini, Doğu Anadolu Bölgesindeki bir ilin merkezinde bulunan bir kamu hastanesinde çalışan toplam 246 hemşire oluşturmuştur. Araştırmada evrenin tamamına ulaşılmaya çalışılmış ve araştırmaya gönüllü olarak katılan 241 kişiden veri toplanmıştır. Verilerin toplanmasında araştırmacılar tarafından oluşturulan 31 soruluk "Anket Formu" kullanılmıştır. Literatürden destek alınarak oluşturulan anketteki veriler; hemşirelerin basınç ülserlerini önlemeye yönelik tutumlarını incelemek amacıyla 18 sorudan oluşan Hemşire Tanıtım Formu ve 13 sorudan oluşan Basınç Ülserlerini Önlemeye Yönelik Tutum Ölçeği kullanılarak toplanmıştır.
Bulgular: Lisans mezunu hemşirelerin basınç ülserlerinin etkisine yönelik, basınç ülserlerini önlemede kişisel sorumluluğa yönelik ve basınç ülserlerini önlemenin etkinliğine yönelik tutumlarının daha yüksek olduğu saptandı. Lise mezunlarının ise basınç ülserlerini önlemek için bireysel yeterliliğe yönelik tutumlarının daha yüksek olduğu ve gruplar arasındaki farkın anlamlı olduğu saptandı ($p<0,05$).
Sonuç: Basınç yaralarını önlemeye yönelik tutumda eğitim düzeyi değişkeninin fark oluşturduğu görülmüştür. Ayrıca hemşirelerin basınç ülserini önleme tutumlarının eksik olduğu belirlenmiştir. Bu bağlamda; her kurum standartlara ve yeniliklere uygun basınç ülseri bakım protokolleri belirlemeli, klinik uygulama rehberleri geliştirmeli ve uygunluğunun denetlemesini sağlamalıdır.

Anahtar Kelimeler: Basınç Ülseri, Hemşire, Önleme, Tutum, Tutum Ölçeği.

Introduction

Pressure ulcer is described as "localized injury to the skin and underlying soft tissue, usually over a bony prominence or related to medical or other devices" based on the translation from American National Pressure Ulcer Advisory Panel [NPUAP] by Wound, Ostomy and Continence Nurses Society (1,2). Pressure ulcer is an important health problem influencing patient and health care system and resulting in economic costs. Despite the increasing evidence and guidance regarding the prevention, preventive measurements are applied at the minimum level and pressure ulcer remain to be a serious problem at the

hospitals (3,4). Pressure ulcers usually cause pain and severe infections in patients, delay recovery, and prolong the length of hospital stay (5).

Pressure ulcers are the problems that have treatment taking a long time, disturb recovery programs, and cause high morbidity and mortality rates (6). Pressure ulcers may lead to development of complications such as depression, pain, and infection (7). The most critical complication of pressure ulcers is infections developing in elderly people whose diet and immune system are disturbed. Development of infection may increase the mortality by progressing to sepsis in these patient groups (8). Besides physical and psychological trauma pressure ulcers cause (9), they are a complication that can lead to delay in activities of daily living and an increase in health care expenses by prolonging their recovery process (10).

While the primary responsibility about the development of pressure ulcers was considered to belong to nurses in the past, today development of pressure ulcers is used as not only one of the quality indicators for nursing services, but also one of the quality indicators of healthcare service provided at the hospital. Therefore, care and responsibility of pressure ulcers are undertaken by all of the health care teams at the present time. Even though the responsibility for care and treatment of pressure ulcers are undertaken by all the team, nurses are the group who still needs to take mainly the responsibility for application of interventions to prevent pressure ulcers and for their care because they are the only group who provide an uninterrupted service of 24 hours to patients at the clinic (11). For this reason, nursing care includes the determination of patient groups at the risk of pressure ulcers as well as observation and evaluation of patients at risk in terms of pressure ulcers. Criteria making these observation and evaluation objective are the scales used to determine the risk of pressure ulcer. Starting from this, the aim of the present study is to investigate the attitudes of nurses working in a state hospital towards prevention of pressure ulcers.

Material and Method

Aim and Type of the Study

This study was conducted in quantitative design, descriptive and cross-sectional type.

Population and Sample Selection of the Study

The population of the present study consisted of a total of 246 nurses, who were working in a public hospital located in a city center in Eastern Anatolia Region. In the population and sample calculation for the research, in addition to reaching the volunteer participants, the "non-probabilistic random method" was used and the data were collected from 241 nurses who voluntarily participated in the study (Response rate: 98.0%).

Data Collection Tools

A "Questionnaire" with 31 questions, which was prepared by the researchers, was used to collect the data.

Questionnaire

The data on the questionnaire prepared by the support of literature were collected using Nurse Information Form with 18 questions to investigate attitudes of nurses towards prevention of pressure ulcers as well as Attitude Towards Pressure Ulcer Prevention Instrument (ATPUPI) consisting of 13 questions. The data were collected via face-to- face interview technique.

Nurse Information Form

Form consists of 18 questions including nurses' socio-demographic and descriptive information towards pressure ulcers.

Attitude Towards Pressure Ulcer Prevention Instrument

It was developed by Beeckman et al. in order to determine nurses' attitudes towards preventing pressure ulcers (12). It was found to be a valid and reliable scale. Cronbach's Alpha value of the scale's internal consistency reliability was determined as 0.79, and the Cronbach Alpha value for the sub-dimensions was found to be between 0.70-0.90.

The Turkish adaptation of the scale was made by Üstün (13), and the Cronbach Alpha value of the internal reliability of the scale, which was in the form of a 4-point Likert scale, was 0.714.

ATPUPI includes a total of 13 items in 5 subscales. Subscales of the instrument consist of 13 items in total; attitude towards personal sufficiency to prevent pressure ulcers (3 items), attitude towards the priority to prevent pressure ulcers (3 items), attitude towards the effect of pressure ulcers (3 items), attitude towards the personal responsibility to prevent pressure ulcers (2 items), and attitude towards the effectiveness of prevention of pressure ulcers (2 items). As the total mean scores of ATPUPI increase, attitude is expected to be positive. In this study, the alpha values of the sub-dimensions of the scale and the total score were found as Attitude towards personal sufficiency to prevent pressure ulcers 0.72, Attitude towards the priority to prevent pressure ulcers 0.77, Attitude towards the effect of pressure ulcers 0.71, Attitude towards the personal responsibility to prevent pressure ulcers 0.78, Attitude towards the effectiveness of the prevention of pressure ulcers 0.81, and Total alpha 0.75.

Data Assessment

Statistical Package for the Social Sciences-22 (SPSS-22) was used for the analysis, error controls and tables were made via the program. The Shapiro Wilk Test was used to determine whether the research data were

normally distributed. Research data were not normally distributed. Therefore, nonparametric tests were used in the analysis of the data. Descriptive data were indicated in number and percentage and $p < 0.05$ was accepted as the statistically significance level.

Ethical Consideration

The present study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by Bingöl University Ethics Committee (approval number: E.26634, date: 30.12.2019). With the principle of voluntarism, written and verbal information was provided, and the data was collected by filling out the forms by the participants, whose consent was obtained. The authors expressed no conflict of interest.

Results

Table 1. Findings About Socio-Demographic Characteristics of the Nurses (N=241)

Characteristics	Number	%
Age		
20-30 years of age	44	18.2
31-40 years of age	158	65.6
41-50 years of age	39	16.2
Gender		
Female	161	66.8
Male	80	33.2
Marital Status		
Married	150	62.2
Single	91	37.8
Educational Background		
High school	70	29.0
Bachelor	171	71.0
Tenure in the profession		
1-5 years	117	48.6
6-15 years	103	42.7
16 years and longer	21	8.7
Unit		
Surgical	130	53.9
Internal Medicine	111	46.1
Position		
Service Nurse	216	89.6
Intensive Care Nurse	25	10.4
The way of work		
Always day and always night	101	41.9
Night and day	140	58.1

Of the nurses participated in the study 66.8% were female and 62.2% were married. 71% of the nurses had bachelor's degree and 89.6% was service nurse (Table 1).

Table 2. Experiences of Nurses Regarding Pressure Ulcers (N=241)

	Number	%
Encountering pressure ulcer		
Never	91	37.8
Rarely	130	53.9
Frequently	20	8.3
Use of an instrument for risk assessment of pressure ulcer		
Yes	60	24.9
No	181	75.1
Dressing pressure ulcer		
None	127	52.7
Less than 10	89	36.9
Between 20-50	18	7.5
I don't remember the number	7	2.9
Receiving education on pressure ulcers		
Yes	89	36.9
No	152	63.1
Reflecting the education to nursing care		
Yes	79	32.8
No	148	61.4
Partially	14	5.8
Finding nursing practices towards prevention of pressure ulcers sufficient		
Sufficient	85	35.3
Partly sufficient	122	50.6
Insufficient	34	14.1

Of the nurses included in the study, 53.9% indicated that they rarely encounter pressure ulcers, 75.1% did not use any instrument for risk assessment of pressure ulcers, and 52.7% never dressed a pressure ulcer (Table 2).

Attitudes of the nurses, who participated in the study, towards personal sufficiency to prevent pressure ulcers, towards the priority to prevent pressure ulcers,

and towards the personal responsibility to prevent pressure ulcers were found to be higher than average. Attitudes of nurses towards the effect of pressure ulcers and towards the effectiveness of prevention of pressure ulcer were determined to be high (Table 3).

Table 3. Attitudes of the Nurses Towards prevention of Pressure Ulcer (N= 241)

				X	SS
Attitude towards personal sufficiency to prevent pressure ulcers (Competence)	3	10	7	6.72	1.28
Attitude towards the priority to prevent pressure ulcers (Priority)	5	10	7	6.84	0.80
Attitude towards the effect of pressure ulcers (Impact)	5	12	10		1.55
Attitude towards the personal responsibility to prevent pressure ulcers (Responsibility)	2	8	5	5.09	0.83
Attitude towards the effectiveness of prevention of pressure ulcer (Efficiency of prevention)	3	7	5	5.36	0.65
Total	26	42	34		2.53

As seen in Table 4; Although there was no significant difference in the total score and sub-dimension scores of the scale, it was observed that the mean rank/median values were higher in the variables of age, gender, education level, number of years of employment and unit of employment. It was determined that attitudes towards the effect of pressure ulcers, towards the effectiveness of prevention of pressure ulcer, and total mean scores were higher in nurses in the age range of 20-30 years than the other groups and the difference between the groups was not significant. Attitudes towards personal sufficiency to prevent pressure ulcers and towards the personal responsibility to prevent pressure ulcers were found to be higher in nurses at age range of 31-40 years. Results of the study revealed that attitudes towards personal sufficiency to prevent pressure ulcers, towards the effect of pressure ulcers, and towards the effectiveness of prevention of pressure ulcer, and total mean scores were higher in women compared to men. The nurses with bachelor's degree were found to have higher attitudes towards the effect of pressure ulcers, towards, towards the personal responsibility to prevent pressure ulcers, and towards the effectiveness of prevention of pressure ulcer. Nurses with a high school degree had higher attitude towards personal sufficiency to prevent pressure ulcers and the difference between the groups was significant ($p<0.05$). Nurses, who had a tenure of 16 years and longer in the profession, had higher attitudes towards personal sufficiency to prevent pressure ulcers and towards the priority to prevent pressure ulcers compared to the other groups. Those who had a tenure of 6-15 years in the profession, had higher attitudes towards the effect of pressure ulcers, towards the personal responsibility to prevent pressure ulcers, and towards the effectiveness of prevention of pressure ulcer. The nurses participating in the study and working in the surgical clinics were determined to have higher attitudes towards personal sufficiency to prevent pressure ulcers and the difference between the groups was significant ($p<0.05$). Nurses working in the internal medicine clinics, on the other hand, had higher attitudes towards the priority to prevent pressure ulcers, towards the effect of pressure ulcers, and towards the personal responsibility to prevent pressure ulcers. Attitudes of the nurses, working as a service nurse, towards personal sufficiency to prevent pressure ulcers were higher compared to the nurses working as intensive care nurse and the difference between the groups was significant ($p<0.05$). The nurses working at always day shift and always night shift had higher attitudes towards personal sufficiency to prevent pressure ulcers and higher total means scores and the difference between the groups was significant ($p<0.05$).

Discussion

Despite the developments and innovations in health care, pressure ulcers still remain as an important problem for patients and healthcare professionals (14,15). Today, although the determination of risk factors of pressure ulcers is made by nurses, interventions to prevent ulcers should be initiated in the early period. In the literature, it is emphasized that one of the reasons for the development of pressure sores is the lack of knowledge of nurses on this subject (16). In this study aiming to investigate the attitudes of nurses working in a state hospital towards prevention of pressure ulcers.

It is known that training programs on pressure ulcers and their prevention have a positive impact on knowledge of nurses, their prevention interventions, and attitudes (17, 18). It was stated that 63.1% of nurses did not receive education on pressure ulcer, 61.4% were not able to reflect the education to care, and 50.6% considered that nursing practices towards prevention of pressure ulcer were partly sufficient. In the study of Etafa (2019), it was determined that the majority of the nurses (66.7%) did not participate in any training on pressure sores (19), and in the study of Awali (2018), 74.6% of the nurses did not participate in the education about pressure sores (20). In the study conducted by Çelik et al. (2017) in our country, it was determined that 74.4% of the nurses received pressure ulcer training (21). When the literature is examined, it is emphasized that the practice and knowledge of nurses working in these units, especially in intensive care units, surgical and internal clinics, where the risk of pressure ulcer development is quite high due

Table 4. Comparison between Socio-demographic Characteristics of Nurses and Their Attitudes Towards Prevention of Pressure Ulcer (N= 241)

		Attitude towards personal sufficiency to prevent pressure ulcers		Attitude towards the priority to prevent pressure ulcers $\bar{X}$ ±SD		Attitude towards the effect of pressure ulcers $\bar{X}$ ±SD		Attitude towards the personal responsibility to prevent pressure ulcers $\bar{X}$ ±SD		Attitude towards the effectiveness of prevention of pressure ulcer $\bar{X}$ ±SD		Total $\bar{X}$ ±SD	
Age		**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**
	20-30	6.75 ± 1.31	122,02	6.89 ± 1.02	123,91	10.34 ± 1.60	135	5.05 ± 1.10	118,17	5.52 ± .73	134,98	34.55 ± 2.70	137,3
	31-40	6.77 ± 1.27	125,85	6.80 ± .70	118,35	9.91 ± 1.58	116,11	5.11 ± .78	122,66	5.34 ± .65	117,47	33.94 ± 2.51	118,44
	41-50	6.51 ± 1.34	100,21	6.95 ± .94	128,46	10.15 ± 1.33	125,03	5.05 ± .69	117,49	5.33 ± .53	119,53	34.00 ± 2.41	112,97
	KW	4.591		.911		2.828		.341		2.914		3.192	
	p	.101		.634		.243		.843		.233		.203	
Gender		**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**
	Female	6.84 ± 1.18	125,16	6.84 ± .77	122,38	10.06 ± 1.50	121,85	5.09 ± .77	120,49	5.37 ± .62	120,52	34.20 ± 2.35	123,99
	Male	6.50 ± 1.47	112,63	6.84 ± .88	118,22	9.98 ± 1.65	119,29	5.10 ± .95	122,03	5.36 ± .72	121,96	33.78 ± 2.86	114,98
	U	5.770.500		6.217.500		6.303.500		6.522.000		6.517.000		5.958.500	
	p	.172		.631		.783		.854		.862		.340	
Educational background		**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**
	High school	7.04 ± 1.35	138,01	6.84 ± .81	122,73	9.73 ± 1.50	108,26	5.03 ± .90	117,97	5.30 ± .73	113,67	33.94 ± 2.43	119,21
	Bachelor	6.60 ± 1.24	114,04	6.84 ± .81	120,29	10.15 ± 1.56	126,22	5.12 ± .80	122,24	5.40 ± .62	124	34.11 ± 2.58	121,73
	U	4.764.500		5.864.000		6.877.000		6.197.000		6.498.000		6.110.000	
	p	**.012**		.786		0.62		.622		.229		.797	
Duration of tenure in the profession		**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**
	1-5 years	6.78 ± 1.28	125,1	6.86 ± .85	124,35	10.00 ± 1.71	120,82	5.07 ± .93	120,88	5.37 ± .70	121,92	34.08 ± 2.77	124,68
	6-15 years	6.62 ± 1.23	115,97	6.80 ± .71	116,29	10.08 ± 1.36	121,96	5.17 ± .74	124,48	5.38 ± .61	120,1	34.04 ± 2.16	119
	16 years and longer	6.95 ± 1.60	122,83	6.95 ± 1.02	125,48	9.95 ± 1.56	117,31	4.86 ± .65	104,6	5.33 ± .58	120,26	34.05 ± 2.94	110,31
	KW	1.033		1.001		.083		1.856		.053		.920	
	p	.597		.606		.959		.395		.974		.631	
Unit		**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**
	Surgical	6.89±1.25	130,53	6.83±0.82	120,51	9.98±1.57	119,52	5.06±0.84	118,58	5.41±0.67	124,38	34.20±2.53	125,24
	Internal	6.53±1.30	109,84	6.84±0.78	121,57	10.08±1.52	122,73	5.11±0.81	123,83	5.31±0.61	117,05	33.89±2.52	116,04
	U	5.976.000		7.151.500		7.022.500		6.901.000		6.776.000		6.664.000	
	p	.017		.897		.714		.506		.348		.303	
Position		**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**
	Service Nurse	6.80 ± 1.27	124,67	6.85 ± .80	121,98	10.02 ± 1.53	120,47	5.07 ± .83	119,48	5.37 ± .65	120,8	34.12 ± 2.51	122,15
	Intensive Care Unit Nurse	6.08 ± 1.26	89,32	6.76 ± .83	112,52	10.08 ± 1.78	125,58	5.24 ± .83	134,16	5.32 ± .69	122,76	33.48 ± 2.69	111,1
	U	1.908.000		2.488.000		2.814.500		3.029.000		2.744.000		2.452.500	
	p	**.013**		.480		.722		.254		.878		.449	
The way of work		**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**	**$\bar{X}$ ± SD**	**Mean Rank**
	Always day and always night	6.94 ± 1.41	132,76	6.93 ± .91	126,68	10.16 ± 1.64	127,68	5.15 ± .90	123,77	5.34 ± .68	117,45	34.51 ± 2.68	132,06
	Night and day	6.57 ± 1.17	112,52	6.78 ± .72	116,9	9.94 ± 1.48	116,18	5.05 ± .78	119	5.39 ± .63	123,56	33.73 ± 2.37	113,02
	U	5.882.500		6.496.000		6.395.000		6.790.500		7.428.500		5.952.500	
	p	**.021**		.237		.194		.550		.439		**.035**	

to limitation of movement and many other factors, should be at a sufficient level (22,23).

When the relationship between socio-demographic characteristics of nurses and their attitudes towards prevention of pressure ulcer was examined; nurses in the age range of 20-30 years had higher attitudes towards the effect of pressure ulcers, towards the effectiveness of prevention of pressure ulcer and total mean scores compared to the other groups and the difference between the groups was insignificant. Attitudes towards personal sufficiency to prevent pressure ulcers and attitudes towards personal responsibility to prevent pressure ulcers were found to be higher in nurses in the age range of 31-40 years. The studies have revealed no correlation between age factor and attitude mean score (24,25).

The nurses with high school degree were determined to have higher attitudes towards the effect of pressure ulcers, towards the personal responsibility to prevent pressure ulcers, and towards the effectiveness of prevention of pressure ulcer. Attitudes of the nurses with high school degree towards personal sufficiency to prevent pressure ulcers were higher and the difference between the groups was significant ($p<0.05$). While there are studies in the literature reporting that educational status does not affect knowledge score of nurses significantly (21,26), there are also studies indicating that those with high level of education has significantly higher scores of knowledge (27,28).
The nurses, who had a tenure of 16 years and longer in the profession, had higher attitudes towards personal sufficiency to prevent pressure ulcers and towards the priority to prevent pressure ulcers than the other groups. Those, who had a tenure of 6-15 years in the profession, had higher attitudes towards the effect of pressure ulcers, towards the personal responsibility to prevent pressure ulcers, and towards the effectiveness of prevention of pressure ulcer. While studies revealed that duration of professional experience does not have a significant effect on knowledge scores of nurses about pressure ulcer prevention (18, 21,24,27,28), there is also study notifying that pressure ulcer prevention knowledge level of nurses having a longer duration of professional experience is significantly higher (27).

In the present study it was found that attitude of nurses, who participated in the study and were working in the surgical clinics, towards personal sufficiency to prevent pressure ulcers was higher and the difference between the groups was significant ($p<0.05$). Those working in the internal medicine clinics, on the other hand, had higher attitudes towards the priority to prevent pressure ulcers, towards the effect of pressure ulcers, and towards the personal responsibility to prevent pressure ulcers. Studies conducted at different units reported that experience of nurses to give care to the patient with pressure ulcer ranged between 11.5% and 90% (22,29). In the study conducted with nurses who worked in the surgical units at least for one year (29), it was determined that most of the nurses (90.7%) had experiences of providing care to patient with pressure ulcer.

Conclusion

Attitudes of the nurses, who participated in the study, towards personal sufficiency to prevent pressure ulcers, towards the priority to prevent pressure ulcers, and towards the personal responsibility to prevent pressure ulcers were found to be higher than average. In addition to, the nurses with high school degree were determined to have higher attitudes towards the effect of pressure ulcers, towards the personal responsibility to prevent pressure ulcers, and towards the effectiveness of prevention of pressure ulcer.

It is recommended to organize in-service training programs and symposiums introducing pressure ulcer and pressure ulcer risk diagnosis scales and presenting planning and practices for interventions to prevent pressure ulcers at certain intervals for nurses to enable them to provide care within specified qualifications.

References

1.National Pressure Ulcer Advisory Panel. NPUAP Pressure Injury Stages/ Categories 2016 (25.05.2020. Available from: http://www.npuap.org/ resources/educational-and-clinical resources/npuappressure-injury-stages/.

2.Wound Ostomy Incontinence Nurses Association. Pressure sore and its stages 2018 (27.05.2020. Available from: http://www.yoihd.org.tr/ images/cust_files/161118082243.pdf.).

3.Chaboyer W, Bucknall T, Webster J, McInnes E, Banks M, Wallis M, et al. Introducing A Care bundle To prevent pressure injury (INTACT) in at-risk patients: a protocol for a cluster randomised trial. Int J Nurs Stud 2015; 52(11):1659–68

4.Chaboyer W, Gillespie BM. Understanding nurses' views on a pressure ulcer prevention care bundle: a first step towards successful implementation. Journal of Clinical Nursing 2014; (23): 3415-3423.

5.Coyer F, Gardner A, Doubrovsky A, Cole R, Ryan FM, Allen C, Mc Namara G. Reducing pressure ınjuries ın critically ill patients by 66 using a patient skin ıntegrity care bundle (INSPIRE). American Association of Critical-Care Nurses 2015; 24(3):199-209.

6.Keller BP, Wile J, Vanramshorst B. Pressure ulcers in intensive care patients: a review of risks and prevention. Intensive Care Med. 2002; 28:1379-88.

7.Wolerton CL, Hobbs LA, Beeson T. Nosocomial pressure ulcer rates in critical care: perfomance improvement Project. J NursCareQual. 2005; 20:56-62.

8.Black JM. Moving toward consensus on deep tissue injury and pressure ulcer staging Adv Skin Wound Care. 2005; 18: 415-21.

9.Hampton S, Collins F. Reducing pressure ulcer incidence in a long-term setting. British Journal of Nursing 2005; 14(15): 6-12.

10.Varga MA, Holloway SL. The lived experience of the wound care nurse in caring for patients with pressure ulcers. Int Wound J. 2016;13(2):243–251. https://doi.org/10.1111/iwj.12279.

11.Uzun Ö, Tan M. A prospective, descriptive pressure ulcer risk factors and prevalence study at a university hospital in Turkey. Ostomy Wound Management. 2007;53(2): 44-56.

12.Beeckman D, Defloor T, Demarré L, Van Hecke A, Vanderwee K. Pressure ulcers: development and psychometric evaluation of the attitude towards pressure ulcer prevention instrument (APuP). Int J Nurs Stud. 2010;47(11):1432-41.

13.Üstün Y. Adapting the "Attitude Towards Pressure Ulcer Prevention Instrument" into Turkish and Studying its validity and reliability. Ege University Faculty of Health Sciences, Master Thesis, 2013.

14.Edsberg LE, Siyah JM, Goldberg M, McNichol L, Moore L, Sieggreen M. Revised National Pressure Ulcer Advisory Panel pressure injury staging system: revised pressure injury staging system. Journal of Wound, Ostomy, and Continence Nursing. 2016;43(6):585-597.

15.Shahin ESM, Dassen T, Halfens RJG. Incidence, prevention and treatment of pressure ulcers in intensive care patients: A longitudinal study. International Journal of Nursing Studies. 2019;46(4):413-421.

16.Jankowski MI, Nadzam MD. Identifying gaps,barriers, and solutions in implementing pressure ulcer prevention programs, The joint Commission. Journal on Quality and Patient Safety. 2011;37(6):154-160

17.Ebi WE, Menji ZA, Hunde BM. Nurses" knowledge and Perceived Barriers About Pressure Ulcer Prevention for Admitted Patients in Public Hospitals in Addis Ababa, Ethiopia. American Journal of Internal Medicine. 2017;5(1):1-6.

18.Hamdan AB, Javison S, Tamani J, Sashidharan S, Yahya OA, Hamoudi B. Oncology Nurses" Beliefs, Attitudes, Perceived Barriers towards Pressure Ulcer Prevention. Journal of Health Education Research and Development. 2018;6(4):6-14.

19.Etafa W, Argaw Z, Gemechu E, Melese B. Nurses" attitude and perceived barriers to pressure ulcer prevention. BMC Nursing. 2018;17(1):14-22

20.Awali ZM, Nagshabandi EA, Elgmail A. The Effect of Implementing Pressure Ulcer Prevention Educational Protocol on Nurses" Knowledge, Attitude and Practices. Nursing and Primary Care. 2018; 2(4):1-7.

21.Çelik S, Dirimeşe E, Taşdemir N, Aşık Ş, Demircan S, Eyican S. Pressure sore prevention and treatment knowledge of nurses. Medical Journal of Bakırköy. 2017;13(3):133-139.

22.Aslan A, Yavuz van Giersbergen M. Nurses' attitudes towards pressure ulcer prevention in Turkey. Journal of Tissue Viability 2016; 25: 66-73.

23.Abdel Rahman MS, Abdel Rahman RF, Al Assaf RM, Saleh MYN. Exploring Nurses' Knowledge and Perceived Barriers to Carry Out Pressure Ulcer Prevention and Treatment, Documentation, and Risk Assessment. American International Journal of Contemporary Research. 2014;4(4):112-119.

24.Kaddourah B, Shaheen A, Al-Tannir M. Knowledge and attitutes of health professionals towards pressure ulcers at a rehabilitation hospital. BMC Nursing. 2016; 15: 17-22.

25.Ünver S, Yıldız Fındık Ü, Kızılcık Özkan Z, Sürücü Ç. Attitudes of surgical nurses towards pressure ulcer prevention. Journal of Tissue Viability. 2017; 26: 277-281.

26.Aydoğan S, Çalışkan N. A descriptive study of Turkish intensive care nurses' pressure ulcer prevention knowledge, attitudes, and perceived barriers to care. Wound Management &Prevention. 2019;65(2):39–47.

27.Nuru N, Zewdu F, Amsalu S, Mehretie Y. Knowledge and practice of nurses towards prevention of pressure ulcer and associated factors in Gondar University Hospital, Northwest Ethiopia. BMC Nursing. 2015;14(34):1-8.

28.Yılmazer T, Tüzer H, Erciyas A. Knowledge and attitudes towards prevention of pressure ulcer:intensive care units sample in Turkey. Turkiye Klinikleri J Nurs Sci. 2019;11(2):140-147.

29.Tallier PC, Reineke PR, Asadoorian K, Choonoo JG, Campo M, Malmgreen-WallenC. Perioperative registered nurses knowledge, attitudes, behaviors, and barriers regarding pressure ulcer prevention in perioperative patients. Applied Nursing Research.2017; 36: 106-110.

Received: 29 Sep 2021 | **Accepted:** 21 Oct 2021
DOI: 10.54005/geneltip.999386

CLINICAL RESEARCH

The Efficacy of Preemptive Pregabalin Administration on Pre- and Postoperative Anxiety and Postoperative Analgesia in Arthroscopic Shoulder Surgery: A Prospective, Randomized Double-Blind, Placebo-Controlled Clinical Study

Artroskopik Omuz Cerrahisinde Preemptif Pregabalin Yönetiminin Postoperatif ve Postoperatif Anksiyete ve Postoperatif Analjezi Üzerine Etkinliği: Prospektif, Randomize, Çift Kör, Plasebo Kontrollü Bir Klinik Çalışma

[1]Faruk Çiçekci, [1]Mehmet Sargın, [2]Ahmet Yıldırım, [3]Muslu Kazım Körez, [1]Göksun Günaydin, [1]İnci Kara

[1]Department of Anesthesiology, Selcuk University, Medical Faculty, Konya, Turkey

[2]Department of Orthopedics and Traumatology, Selcuk University, Medical Faculty, Konya, Turkey

[3]Department of Biostatistics, Selcuk University, Medical Faculty, Konya, Turkey

Correspondence

Faruk Cicekci, Department of Anaesthesiology, Selcuk University, Medical Faculty Konya, Turkey

E-Mail: farukcicekci@yahoo.com

How to cite ?

Çiçekci F, Sargın M, Yıldırım A, Körez MK, Günaydın G, Kara İ. The Efficacy of Preemptive Pregabalin Administration on Pre- and Postoperative Anxiety and Postoperative Analgesia in Arthroscopic Shoulder Surgery: A Prospective, Randomized Double-Blind, Placebo-Controlled Clinical Study. Genel Tıp Derg. 2022;32(1):12-18.

ABSTRACT

Aim: Few studies have investigated pregabalin use as preemptive analgesia in the management of acute pain and anxiety following arthroscopic shoulder surgery. We hypothesized that the preemptive use of oral pregabalin might decrease pain and postoperative anxiety on arthroscopic shoulder surgery pain during the initial 48 hours.
Patients and methods: In this prospective, randomized, double-blind, placebo-controlled study, 65 eligible patients were randomly divided into two groups, the preemptive pregabalin 150 mg (group P) and the control group (group C). The primary outcomes were pain levels measured both rest and during active motion based on a visual analog scale (VAS). Secondary outcomes were the level of anxiety (STAI-S and STAI-T), patient satisfaction, and complications.
Results: Group P showed lower pain ($p < 0.001$), lower opioid consumption ($p < 0.001$), longer time to first requirement of analgesia ($p < 0.001$), and lower rescue analgesic dose ($p < 0.001$) than the control group at postoperative 48 h follow-up. Also, group P showed less preoperative and postoperative anxiety ($p < 0.001$) and greater patient satisfaction ($p < 0.001$) than group C. The rate of postoperative adverse effects was similar between the groups ($p > 0.05$).
Conclusion: The preemptive use of oral pregabalin received 150 mg daily for 2 days before surgery provided postoperative analgesia in both rest and active motion, and improved preoperative and postoperative anxiety levels and greater patient satisfaction in patients undergoing arthroscopic surgery.

Keywords: analgesia; anxiety; preemptive; pregabalin; orthopedic surgery

ÖZ

Arka plan: Artroskopik omuz cerrahisini takiben akut ağrı ve anksiyete tedavisinde pregabalinin preemptif analjezi olarak kullanımını araştıran az sayıda çalışma bulunmaktadır.
Amaç: Bu çalışmada, artroskopik omuz cerrahisinde oral pregabalinin preemptif kullanımının postoperatif ilk 48 saat boyunca pre-postoperatif anksiyeteyi ve postoperatif ağrıyı azaltabileceğini hipotezini kurduk.
Hastalar ve yöntemler: Bu prospektif, randomize, çift kör, plasebo kontrollü çalışmada, 65 uygun hasta rastgele iki gruba, preemptif pregabalin 150 mg (grup P) ve kontrol grubu (grup C) olarak ayrıldı. Birincil sonuçlar, görsel analog skalaya (VAS) dayalı olarak hem dinlenme hem de aktif hareket sırasında ölçülen ağrı seviyeleriydi. İkincil sonuçlar anksiyete düzeyi (STAI-S ve STAI-T), hasta memnuniyeti ve komplikasyonlardı.
Bulgular: Grup P, kontrol grubuna göre daha düşük ağrı ($p < 0.001$), daha az opioid tüketimi ($p < 0.001$), ilk analjezi ihtiyacına kadar daha uzun süre ($p < 0.001$) ve daha düşük kurtarma analjezik dozu ($p < 0.001$) gösterdi. Ayrıca grup P, grup C'ye göre daha az preoperatif ve postoperatif anksiyete ($p < 0.001$) ve daha fazla hasta memnuniyeti ($p < 0.001$) gösterdi. Postoperatif yan etkilerin oranı gruplar arasında benzerdi ($p > 0.05$).
Sonuç: Ameliyattan 2 gün önce günde 150 mg oral pregabalinin preemptif kullanımı, artroskopik cerrahi geçiren hastalarda hem istirahat hem de aktif harekette postoperatif analjezi sağladı ve preoperatif ve postoperatif anksiyete düzeylerini iyileştirdi ve hasta memnuniyetini artırdı.

Anahtar Kelimeler: analjezi; anksiyete; preemptif; pregabalin; ortopedik cerrahi

Introduction

Postoperative pain control after arthroscopic shoulder surgery optimizes postoperative rehabilitation, reduces anxiety, and can increase patient satisfaction and postoperative healing by providing amnesia and sedation (1). In these patients, intra-articular local anesthetic infiltration, regional nerve blocks, patient-controlled analgesia (PCA) with intravenous opioids, and oral nonsteroidal anti-inflammatory and gabapentinoid drugs are available for postoperative pain management (2,3).

Recently, gabapentinoids such as pregabalin have also been shown to have potential in the treatment of acute postoperative pain as part of multimodal analgesia due to their possible opioid consumption-reducing effects and prevention of post-surgical chronic pain (2). Pregabalin is an anticonvulsant drug that reduces calcium entry into the nerve terminals of the central nerve and also reduces levels of substance P, glutamate, and noradrenaline, all of which play a major role in creating a feeling of pain. It is well known that pregabalin reduces central sensitization and hyperalgesia after tissue injury by inhibiting calcium influx in voltage-gated calcium channels (3). These theoretical advantages have led to clinical trials confirming the analgesic effectiveness of oral pregabalin for postoperative pain management in various surgical procedures (4,5).

We hypothesized that the preemptive use of oral pregabalin received 75 mg of twice daily for 2 days before surgery might decrease total morphine consumption and extend the time to the first requirement for analgesia by reducing arthroscopic shoulder surgery pain during the initial 48 hours. The secondary objectives were to assess postoperative anxiety, patient satisfaction, and the adverse effects associated with pregabalin.

Materials and methods

Ethical statement

This prospective, randomized, double-blind, placebo-controlled, single-center study was conducted at Selcuk University, Medical school, Department of Anesthesiology and Reanimation between December 2019 and March 2021. This study was approved by the Clinical Research Ethics Committee of Selcuk University of School of Medicine (Ref No: 25.07.2019.2019/12) and registered on the Clinical Trials website (ClinicalTrials.gov Identifier: NCT: 04675671). Written informed consent was obtained from all participants.

Study design and population

Patients with American Society of Anesthesiologists physical status (ASA-PS) I-II, aged 18-65 years, who were scheduled for elective arthroscopic shoulder surgery (Bankart or rotator cuff repair) under general anesthesia were included in the study. Patients with major neurologic or psychiatric problems, cardiovascular, metabolic, respiratory, renal disease or coagulation abnormalities, body mass index (BMI) over 40 kg/m2, chronic alcohol and substance use, a history of upper gastrointestinal bleeding or perforation, using more than 5 mg/day of oral morphine or equivalent opioids (more than 1 month), and patients who were allergic to the drugs used in the study were excluded.

Study intervention and randomization

Two days before the scheduled surgery, all patients were randomly assigned to the pregabalin group (n=41) and the control group (n=41) by the first anesthesiologist according to a computerized randomization table (https://www.randomizer.org). All patients completed Spielberg's State-Trait Anxiety Inventory (STAI-T) and Spielberger's State Anxiety Scale (STAI-S) questionnaires on their own in the presence of an anesthesiologist before preoperative administration of pregabalin. The STAI-S test was completed again at the postoperative 24th hour. The hospital pharmacy prepared all medications in similar capsules, and all study drugs were administered orally with sips of water by a nurse who was not involved in other processes of this study. Patients in the pregabalin group received 75 mg of pregabalin twice daily for 2 days before surgery. The control group received a placebo capsule at the same point in time. The last doses were received one hour before induction of anesthesia. To ensure the double-blind design in this study, the randomization status of the participants were not be disclosed to the anesthesiologists collecting data, the orthopedic surgeon and the nurse giving the drugs

No other sedative premedication was given to the patients. Anesthesia was induced using propofol 2 mg.kg-1 and remifentanil 0.5-1 µg.kg-1, and tracheal intubation was facilitated with rocuronium 0.6 mg.kg-1. Anesthesia was maintained with a continuous infusion of remifentanil 0.05-0.2 µg.kg-1. min-1 and sevoflurane 2-2.5%. All surgeries were performed by an experienced orthopedic surgeon. At the end of the surgery, sevoflurane and remifentanil were stopped and residual neuromuscular paralysis was antagonized, and extubation was performed when the patient had sufficient respiration. Age, sex, BMI, the subtype of surgery, the time of surgery and anesthesia were recorded.

After the surgery was completed, all patients were transferred to the recovery room. Postoperative analgesia was standardized to morphine in patient-controlled analgesia (PCA; bolus 1 mg, lock-out 5 min, limit 25 mg/4 h). In patients with visual analog scale (VAS) values of less than 5, the PCA lock-out was extended to 10 min. Participants did not routinely receive non-steroidal anti-inflammatory drugs (NSAIDs). However, they were given dexketoprofen (Arveles, UFSA Ilaç, Istanbul Turkey) as a rescue analgesic during the first postoperative 48 hours in the event of VAS values of ≥3. Physical therapy was started 24 hours after surgery. Physical therapy sessions were conducted by the same physiotherapist. Twenty milligrams of IV metoclopramide was given only to patients with nausea and vomiting.

Data collection and outcome

The pre-postoperative pain was measured and evaluated using a VAS (0 = no pain to 10 = worst pain). This parameter was measured from the pre-postoperative pain on the first day until the second postoperative day (in the post-anesthesia care unit (PACU), 1, 3, 6, 12, 24, 36, and 48-hour intervals). VAS values were measured at 24 and 48 hours during both rest and active motion physical therapy because the shoulder is not moved within the first 24 hours. In addition, total morphine consumption, the time to the first requirement for analgesia, patient satisfaction

(Insufficient; 1, Satisfactory; 2, Good; 3, Excellent; 4) and the number of rescue analgesias required were recorded.

To measure anxiety levels, STAI-T and STAI-S questionnaires were used (6). Both STAI-T and STAI-S consist of 20 items with four-point Likert scales (Not at all, Somewhat, Moderately, Very much). The values obtained in each scale range between 20-80 points; 20-40 is defined as low-level anxiety, 41-60 as moderate anxiety, and 61-80 high-level anxiety. The Turkish form was validated by Le Compte and Öner (7) and a validity-reliability study was guided. The internal consistency and reliability of the Turkish form was between 0.94 and 0.96 for the STAI-S and between 0.83 and 0.87 for the STAI-T the Kuder-Richardson alpha reliability. In the present study, McDonald's w coefficient was 0.942 for the STAI-S and McDonald's w coefficient was 0.888 for STAI-T scale.

The adverse effects of pregabalin including nausea, sleepiness, headache, dizziness, and blurred vision were also evaluated during the postoperative 48-hour period.

Sample size

The primary outcome of the study was VAS scores at 48 postoperative hours. In Ahn et al.'s study (4), the mean VAS score at 48 hours was 4.5 ± 1.5 in the control group and 3 ± 1.7 in the pregabalin group. Accordingly, we determined that 37 patients would be required in each group to show this difference with a 5% significance level and power of 95% using the two-sided independent samples t-test. Allowing for a 10% drop-out rate during the study period, 41 patients were enrolled in each group. Power analysis was performed using the "pwr" package in R 3.6.0 (https://www.r-project.org).

Statistical analysis

All statistical analysis was performed using the R Version 3.6.0 software (www.r-project.org). The Shapiro-Wilk test and Q-Q plots were used to check the normality of the data, and Levene's test was used to evaluate the homogeneity of variances of the groups. The demographic and clinical characteristics of the participants are demostraded using descriptive statistics. Numerical variables are expressed as mean ± standard deviation or median (IQR, interquartile range: 25th percentiles – 75th percentiles), and categorical variables are described as counts (n) and percentages (%). The independent samples t-test, Chi-square test with Yates's continuity correction, and exact test with Monte Carlo simulation when expected counts in cells were greater than 20%, were used to compare the study groups according to the demographic and clinical characteristics. The Mann-Whitney U test was used to examine the difference of the groups according to VAS scores, both preoperative and postoperative. The exact test with Monte Carlo simulation, Fisher's exact test, and Chi-square test with Yates's continuity correction were used to determine the association between groups and adverse effects. The exact test with Monte Carlo simulation, the Mann-Whitney U test and the independent samples t-tests were used to examine the difference of the groups according to the delivery and demand of drugs on PCA, time of first analgesia, rescue analgesia, total morphine consumption, pre and post-operative STAI-S score, and preoperative STAI-T score. Moreover, the paired-samples t-test was used to compare preoperative STAI-S and postoperative STAI-S. A Wilcoxon test was conducted to determine whether there was a statistically significant difference between preoperative and postoperative STAI-S scores. All graphs are presented with mean ± standard deviation. A p-value of less than .05 was considered statistically significant.

Results

A total of 65 of 82 patients assigned for the study were included in this study. Seventeen patients from both groups (due to not meeting inclusion criteria, declining to participate, data loss, and admission to the intensive care unit) were excluded. The remaining eligible patients are presented in the Consolidated Reporting Standards (CONSORT) flowchart (Fig 1). The demographic and clinical characteristics of the patients are presented in Table 1. There were no significant differences between the groups including age, sex, BMI, ASA-PS, anesthesia, and surgical duration and surgery type ($p > 0.05$).

Preoperative and postoperative pain was evaluated using the VAS pain scale, shown in Figure 2. Although the postoperative VAS pain scores in the PACU at the 1st, 3rd, 6th, 12th, and 36th hours were statistically significantly lower in group P than in group C ($p < 0.001$, $p = 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.002$, and $p < 0.001$, respectively), there was no difference between the groups in terms of the preoperative measurement and postoperative measurement at 48 hours ($p = 0.118$ and $p = 0.306$, respectively). However, there was a difference between the groups' VAS pain scores with activity regarding the preoperative measurement and the postoperative 24th, 36th, and 48th hours ($p < 0.001$, $p < 0.001$, $p < 0.001$, and $p = 0.003$, respectively) (Fig 2).

The time to the first analgesia was significantly longer in group P than in group C (240 (180-308.75) vs. 97.5 (70-121.25) min; median (IQR); $p < 0.001$). Also, the rescue analgesic dose was significantly lower in group P than in group C (0 (0-1) vs. 2.5 (2-3); $p < 0.001$). The total morphine consumption was significantly lower in group P than in group C (12 (9.25-14) vs. 23 (14.25-30.75) mg; median (IQR); $p < 0.001$). Patient satisfaction was better in group P than in group C (3 (3-3.75) vs. 2 (2-3); $P < 0.001$) (Table 2).

The median preoperative STAI-T score in the pregabalin group was no difference between the groups (41 (37 – 47) vs. 44 (38 – 50); median (IQR); $p = 0.563$). There was no significant difference in the median preoperative STAI-S score assessments in between group P and C (46 (35.75 – 54) vs. 48 (42 – 54); median (IQR); $p = 0.176$). But, the median postoperative STAI-S score in group P was significantly lower than in group C (40 (34-45) vs. 46.5 (42.5-51.75); median (IQR); $p = 0.001$) (Table 3).

The group P showed significantly difference within the groups in terms of pre-postoperative STAI-S (p = 0.025) , but the group C showed no significantly difference within the groups in terms of pre postoperative STAI-S (p = 0.526) (Table 3).

In the postoperative period, the most common adverse effects were dizziness and headache, which were seen in both groups (p = 0.579 and p = 0.729, respectively). In this study, although other adverse effects such as pruritus, nausea, and vomiting were mostly reported among patients in group C, the difference was not statistically significant. Other adverse effects were sleepiness and blurred vision (Table 4)

Table 1. Demographic and clinical characteristics of the study groups

Parameters	Pregabalin (*n*=32)	Control (*n*=33)	
Age (years)	45.37 ± 13.54 (18 – 65)	45.93 ± 14.33 (18 – 65)	.875[a]
Gender (M/F)	24 (75.0) / 8 (25.0)	18 (54.5) / 15 (45.4)	.104[b]
BMI (kg/m^2)	26.87 ± 3.51	25.92 ± 3.17	.270[a]
ASA-PS (I/II)	19 (59.3) / 13 (40.6)	17 (51.5) / 16 (48.4)	.604[b]
Anesthesia time (min.)	95.67 ± 11.35 (80 – 120)	91.60 ± 9.34 (75 – 110)	.167[a]
Surgical time (min.)	73 ± 10.46 (54 – 100)	71.50 ± 9.02 (55 – 90)	.401[a]
Operation type (Bankard/RCR)	6 (18.7) / 26 (81.2)	8 (24.2) / 25 (75.7)	.794[b]

M/F; Male/Female, BMI; Body Mass Index, ASA-PS; American Society of Anesthesiologists physical status, RCR; Rotator Cuff Repair
Data were expressed as mean ± standard deviation (range: min – max), or counts (*n*) and percentages (%)
[a] Independent samples *t*-test
[b] χ^2 test with Yates continuity correction

Table 2. Postoperative Results

Parameters	Pregabalin (*n*=32)	Control (*n*=33)	
Time of analgesia for the first time (min.)	240 (180 – 308.75)	97.5 (70 – 121.25)	**< .001**[a]
Rescue analgesia dose	0 (0 –1)	2.5 (2 – 3)	**< .001**[a]
Total morphine consumption (ml)	12 (9.25 – 14)	23 (14.25 – 30.75)	**< .001**[a]
Patient Satisfaction	3 (3 – 3.75)	2 (2 – 3)	**< .001**[a]

Data were expressed as median (IQR: 25th percentile – 75th percentile)
Bold values indicated that statistically significant difference between groups.
a Mann-Whitney U test

Table 3. The pre-postoperative STAI-S and preoperative STAI-T score assessments in the groups.

Parameters	Pregabalin (*n*=32)	Control (*n*=33)	*p*-value[1]
Preoperative STAI-T	41 (37 – 47)	44 (38 – 50)	.563
Preoperative STAI-S	46 (35.75 – 54)	48 (42 – 54)	.176
Postoperative STAI-S	41 (34 – 45.25)	48 (45 – 52)	**.001**
***p*-value[2]**	**.025**	.526	

Spielberg's Trait Anxiety Inventory (STAI-T), Spielberger's State Anxiety Scale (STAI-S)
Data were expressed as median (IQR: 25th percentile – 75th percentile)
Bold values indicated that statistically significant difference between groups.
p-value[1] was calculated using Mann Whitney U test
p-value[2] was calculated using Wilcoxon test (Preoperative STAI-S vs. postoperative STAI-S)

Table 4. Adverse events

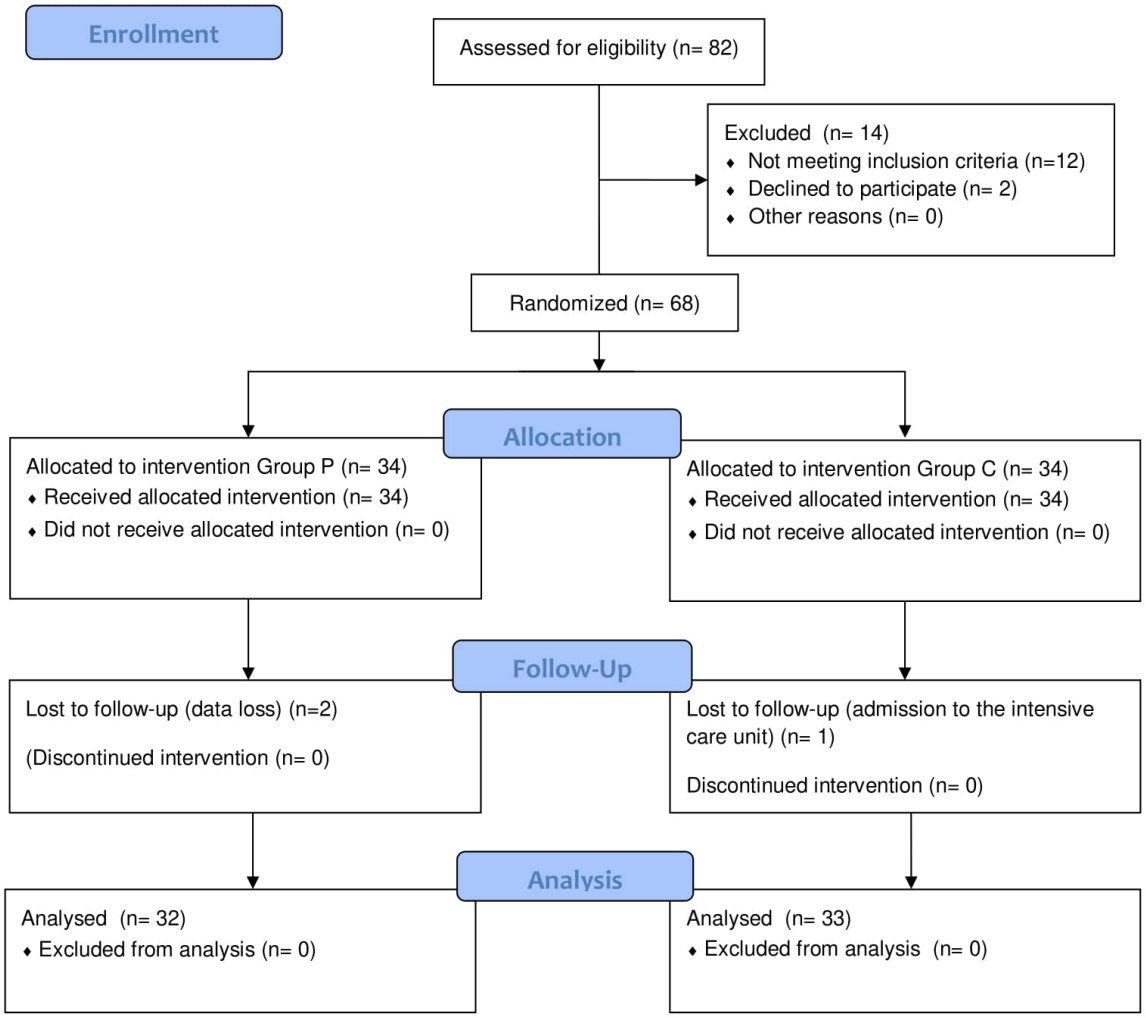
Events	Pregabalin (*n*=32)	Control (*n*=33)	*p*-value
Nausea	0 (0)	1(3.3)	.628[a]
Sleepiness	3 (9.3)	1 (3.3)	.612[b]
Headache	6 (18.7)	4 (13.3)	.729[c]
Dizziness	11 (34.3)	8 (26.7)	.579[c]
Blurred vision	3 (9.3)	1 (3.3)	.612[b]

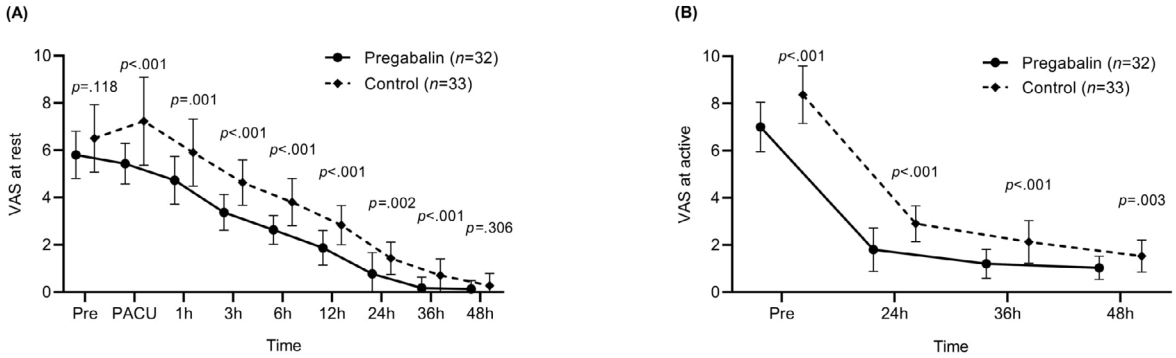
Data were described as numbers (*n*) and percentages (%)
[a] Exact test with Monte-carlo simulation
[b] Fisher exact test
[c] χ^2 test with Yates continuity correction

Discussion

This study was designed to evaluate the efficacy of preemptive pregabalin administration in adult patients undergoing arthroscopic shoulder surgery. Significant beneficial effects of using oral pregabalin received 150mg of daily for 2 days before surgery on n both rest and active motion pain intensity and anxiety were observed in the postoperative periods. In addition, receiving pregabalin preoperatively the time to first analgesia, the total morphine consumption, rescue analgesia and patient satisfaction also showed better results in the postoperative periods. Besides the beneficial effects mentioned above, pregabalin was not accompanied by an increase in adverse effects.

In addition to patient perceptions of discomfort, arthroscopic shoulder surgery is associated with severe post-operative pain that hinders healing and rehabilitation of the shoulder (8). The use of oral pregabalin for postoperative pain in orthopedics surgeries has led to clinical studies confirming its analgesic efficacy. In a study by Ahn et al., a preoperative dose of 150 mg pregabalin was benefecial in controlling pain intensity using a lower amount of opioids over 48 hours after arthroscopic shoulder surgery (4). Mishriky et al. shown that pregabalin was provided better postoperative analgesia compared with placebo at rest (5). Eskandar et al. demostrated that the VAS scores of the pregabalin group were significantly lower until postoperative 8 hours than in a control group when 300 mg was administered at 12 hours and 1 hour before surgery (9). The authors noted lower opioid consumption and higher satisfaction scores in the pregabalin group. But, the pregabalin group did not have a statistically significant increase in dizziness. In a similar study by Bang et al., the VAS scores up to the 12th hour postoperatively were significantly lower in the group that received 300 mg of pregabalin 2 hours before the preoperative compared with the placebo group. However, fentanyl consumption in postoperative 24th hour was similar. Although there





was no reduction in opioid use, the pregabalin group reported reduced respiratory distress, nausea, vomiting and urinary retention compared with the control group (10). There are also studies showing the effectiveness of preemptive pregabalin on postoperative pain in various laparoscopic abdominal operations (11-14). In our study, a dose of 150 mg of pregabalin daily for 2 days was used, similar to the literature, and pain scores at both rest and during activity were found to be lower in the pregabalin group compared with the control group for a long period, up to the postoperative 48th hour.

Although modern surgical techniques have developed and become safer, it is known that most patients with medium and large surgery experience preoperative anxiety (15). The effectiveness of pregabalin against general anxiety and its use as an adjuvant in the multimodal treatment of postoperative analgesia has led to recent research. Perioperative use of pregabalin suggests that it may be a attenuates preoperative anxiety, and reduces postoperative pain scores (16). There are many studies in the literature regarding STAI measurements of preoperative anxiety. Kindler et al. found that the mean preoperative STAI value was 39 (17). In the study of Kim et al., the mean STAI-S and STAI-T scores were 43.8 and 42.7, respectively (18). According to Domar et al., the average preoperative anxiety score was 45 on the STAI scale (19). In a recent study of urology patients by Demirkol et al., the authors demonstrated a preoperative mean STAI score of 39.16 ± 0.42 (20). In other studies in Turkey, mean preoperative STAI values ranged from 36 to 42.4 (21,22). In the present study, the mean preoperative STAI-S value was 46 and the postoperative STAI-S value was found as 40 in the group using preemptive pregabalin. The literature provides insufficient studies using pregabalin preoperatively for trait and state anxiety in patients undergoing a surgical procedure that produces pre- and postoperative pain and anxiety, such as arthroscopic shoulder surgery. In our study, the postoperative STAI-S score was significantly lower than in the control group. A total of 300 mg of pregabalin administration for 2 days preoperatively resulted in a significant decrease in anxiety levels.

STAI-S is the anxiety state that can change depending on the stress of a particular moment, whereas STAI-T reflects the personality tendency that affects the total anxiety of the person (23). For this reason, both STAI scales were used in our study, considering that the personality disposition of the patients may also affect their current anxiety.

Yucel et al. reported that the improved analgesia and anxiolysis attributable to pregabalin contributed to increased patient satisfaction (24).

In another study conducted by Myles et al. with 10811 patients, it was reported that moderate or severe pain was associated with low patient satisfaction (25). Dexter et al. reported that pain was associated with low patient satisfaction (26). Patient satisfaction levels in the pregabalin group in our study were found to be superior to the control group.

Pregabalin adverse effects are dose-dependent and usually temporary (27). We stated in our study that the main complications were nausea and dizziness. In addition, adverse effects such as headache, sleepiness, and blurred vision were seen. Previous study has been stated that pregabalin reduce nausea-vomiting (5). However, the incidence of these complications was similar between our groups and was consistent with another previous study (28).

This study has some advantages. This is a prospective randomized double-blind, plasebo-controlled clinical study, both pain levels and anxiety assessments were performed and evaluated regularly within the first 48 hours postoperatively. However, this study has some limitations. First, the study was part of a single-center self-answer questionnaire. Secondly, the sample size was small. Therefore, study results cannot be generalized to the general population. Thirdly, preoperative side effects were not followed up in patients receiving pregabalin. However, there were no preoperative adverse effects that were severe enough to cause exclusion from the study.Finally, the pregabalin dose was used preoperatively, it was not continued postoperatively.

Conclusion

In patients undergoing arthroscopic shoulder surgery, use of oral pregabalin received 150 mg of daily for 2 days before surgery reduced postoperative pain both at rest and with active movement. As a secondary result, it has been shown to improve anxiety and provide better patient satisfaction. Pregabalin may be a useful addition to a multimodal postoperative pain management strategy in selected patients.

Compliance with Ethics Guidelines

This study was approved by the Clinical Research Ethics Committee of Selcuk University of School of Medicine (Ref No: 25.07.2019.2019/12) and registered on the Clinical Trials website (ClinicalTrials.gov Identifier: NCT 04675671). All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Information Availability

The information sets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Disclosures

None

Informed Consent

Informed consent was obtained from all individual participants included in the article.

Funding

The authors received no financial support for the research and/or authorship of this article.

Conflict of interest

No author has a conflict of interest that relates to the content discussed in this article.

References

1.White PF. Pharmacologic and clinical aspects of preoperative medication. Anesth. Analgesia 1986;65:963-74.

2.Durkin B, Page C, Glass P. Pregabalin for the treatment of postsurgical pain. Expert Opin. Pharmacother. 2010;11:2751-8.

3.Guay DR. Pregabalin in neuropathic pain: a more "pharmaceutically elegant" gabapentin? Am J Geriatr Pharmacother 2005;3:274–87.

4.Ahn S, Byun SH, Park K, Ha JL, Kwon B, Kim JC. Analgesic efficacy of preemptive pregabalin administration in arthroscopic shoulder surgery: a randomized controlled trial. Can J Anesth/J Can Anesth 2016;63:283-89.

5.Mishriky B, Waldron, N, Habib A. Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis. Br. J. Anaesth. 2014;114:10-31

6.Spielberger CD, Auerbach SM, Wadsworth AP, Dunn TM, Taulbee ES. Emotional reactions to surgery. J Consult Clin Psychol 1973;40:33-8.

7.Öner N, Le Compte A. Durumluk-Sürekli kaygı envanteri elkitabı, 20. Basım İstanbul: Boğaziçi Üniversitesi Yayınları. State-Trait Anxiety Inventory Handbook, 20th Edition Istanbul: Boğaziçi University Press, 1985. p.3-5. (Turkish).

8.Ilfeld BM, Morey TE, Wright TW, Chidgey LK, Enneking FK. Continuous interscalene brachial plexus block for postoperative pain control at home: a randomized, double-blinded, placebo controlled study. Anesth Analg 2003; 96: 1089-95.

9.Eskandar AM, Ebeid AM. Effect of pregabalin on postoperative pain after shoulder arthroscopy. Egypt J Anaesth. 2013;29:363-7.

10.Bang SR, Yu SK, Kim TH. Can gabapentin help reduce postoperative pain in arthroscopic rotator cuff repair? A prospective, randomized, double-blind study. Arthroscopy. 2010;26:106-11.

11.Agarwal A, Gautam S ,Gupta D, Agarwal S, Singh PK, Singh U. Evaluation of a single preoperative dose of pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy. Br J Anaesth. 2008;101:700–704.

12.Esmat IM, Farag HM. Comparative study between paracetamol and two different doses of pregabalin on postoperative pain in laparoscopic cholecystectomy. Saudi J Anaesth. 2015;9:376–80.

13.Balaban F, Yagar S, Ozgok A, Koc M, Gullapoglu H. A randomized placebo-controlled study of pregabalin for postoperative pain intensity after laparoscopic cholecystectomy. J Clin Anesth. 2012;24:175–8.

14.Akhavanakbari G, Entezariasl M, Isazadehfar K, Mirzarahimi T. The effects of oral pregabalin on postoperative pain of lower limb orthopedic surgery: A double blind, placebo controlled trial. Perspect Clin Res. 2013;4:165- 68.

15.Caumo W, Schmidt AP, Bergmann J. Risk factors for preoperative anxiety in adults. Acta Anaesthesiol Scand 2001;45:298-307.

16.Shimony N, Amit U, Minz B, et al. Perioperative pregabalin for reducing pain, analgesic consumption, and anxiety and enhancing sleep quality in elective neurosurgical patients: a prospective, randomized, double-blind, and controlled clinical study. J Neurosurg 2016;125:1513-22.

17.Kindler CH, Harms C, Amsler F, Ihde-Scholl T, Scheidegger D. The visual analog scale allows effective measurement of preoperative anxiety and detection of patients' anesthetic concerns. Anesth Analg 2000;90:706-12.

18.Kim WS, Byeon GJ, Song BJ, Lee HJ. Availability of preoperative anxiety scale as a predictive factor for hemodynamic changes during induction of anesthesia. Korean J Anesthesiol 2010;58:328-33.

19.Domar AD, Everett LL, Keller MG. Preoperative anxiety: Is predictable entity? Anesth Analg 1989;69:763–70.

20.Demirkol MK, Tarhan F, Yazıcı O, Hamarat MB, Kafkaslı A. Evaluation of Preoperative Anxiety Level of Urological Surgery Patients and The Effects of Surgical Informing. South. Clin. Ist. Euras. 2019;30:337-342.

21.Demir A, Akyurt D, Ergün B, Haytural C, Yiğit T, Taşoğlu İ et al. Anxiety therapy in cardiac surgery patients. Turkish Journal of Thoracic and Cardiovascular Surgery. 2010;18:177-182. (Turkish)

22.Arlı SK. Evaluation of the Preoperative Anxiety With Apais and STAI-I Scales. Journal of Hacettepe University Faculty of Nursing. 2017;4:38-47. (Turkish)

23.Schwarzer R. Anxiety (Internet). 2020. Available from http:// www. macses.ucsf.edu/research/psychosocial/anxiety.php, Accessed May 26, 1997

24.Yücel A, Özturk E, Aydogan MS et al. Effects of 2 Different Doses of Pregabalin on Morphine Consumption and Pain After Abdominal Hysterectomy: A Randomized, Double-Blind Clinical Trial. Current Therapeutic Research. 2011;72:173-83.

25.Myles PS, Williams DL, Hendrata M, Anderson H, Weeks AM. Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10811 patients. Br J Anaesth 2000;84:6-10.

26.Dexter F, Aker J, Wright WA. Development of a measure of patient satisfaction with monitored anesthesia care: the Iowa Satisfaction with Anesthesia Scale Anesthesiology. 1997;87:865-73.

27.George RB McKeen DM Andreou P Habib AS A randomized placebo-controlled trial of two doses of pregabalin for postoperative analgesia in patients undergoing abdominal hysterectomy. Canadian Journal of Anaesthesia. 2014;61:551-7.

28.Gajraj NM. Pregabalin: its pharmacology and use in pain management. Anesth Analg 2007;105:1805-15.

Received: 1 Oct 2021 | **Accepted:** 14 Dec 2021
DOI: 10.54005/geneltip.1002843

ORIGINAL ARTICLE

The Effect of Gene Mutations on Disease Severity Scores in Pediatric Familial Mediterranean Fever Patients

Ailevi Akdeniz Ateşi Tanılı Çocuk Hastalarda Gen Mutasyonlarının Hastalık Ciddiyet Skorları Üzerine Etkisi

[1]Vildan Güngörer, [2]Alaaddin Yorulmaz, [1]Şükrü Arslan

[1]Department of Pediatric Rheumatology, Selçuk University Medical School, Konya, Turkey

[2]Department of Pediatrics, Selçuk University Medical School, Konya, Turkey

Correspondence

Vildan Güngörer, Department of Pediatric Rheumatology, Selçuk University School of Medicine, Konya, Turkey

E-Mail: vildan_61183@hotmail.com

How to cite ?

Güngörer V, Yorulmaz A, Arslan Ş. The Effect of Gene Mutations on Disease Severity Scores in Pediatric Familial Mediterranean Fever Patients. Genel Tıp Derg. 2022;32(1):19-26.

ABSTRACT

Objectives: Familial Mediterranean Fever (FMF) is a self-limiting autoinflammatory disease. In order to better understand the prognosis of diseases, disease severity scores are used. The aim of this study is to determine the effect of genetic mutations on disease severity scores in children with FMF.
Methods: Patients aged 0-18 years who were diagnosed with FMF according to Yalçınkaya-Özen diagnostic criteria and whose gene analysis was performed were evaluated retrospectively. Pras et al's scoring system, Mor et al's scoring system and International severity score of FMF (ISSF) scoring system were applied to all patients. Genotypes were compared according to disease severity scores.
Results: When the patients were divided into 4 groups as M694V homozygous, heterozygous, M694V/ other allele combined heterozygous and other mutations, according to the score of Pras et al., the frequency of mild disease tended to be less in the M694V homozygous group. When the patients divided as homozygous M694V, heterozygous M694V, heterozygous E148Q, heterozygous M694V/ M680I combined mutations, according to the score of Pras et al., mild disease was found to be less common in the homozygous M694V group. When patients were divided into homozygous and heterozygous M694V (combined with other allele or single) groups, the disease was more severe in the homozygous M694V group according to the three scoring systems. In the concordance analysis between scoring systems, while a good agreement was found between Mor et al.'s scoring system and ISSF, the agreement with Pras et al.'s scoring system was weak
Conclusions: Based on the scoring system described by Pras et al., the rate of severe disease was higher in patients with homozygous M694V allele, whereas the rate of mild disease was statistically significantly higher in the heterozygous group (combined with other allele or single) compared with homozygous group. From this, we can conclude that the M694V homozygous mutation causes more severe disease than the M694V heterozygous mutation, and even more severe disease than its combination with another pathogenic mutation, one of which is M694V.

Keywords: Familial Mediterranean Fever, genotype, disease severity scores, clinic, treatment

ÖZ

Amaç: Ailevi Akdeniz Ateşi (AAA) kendi kendini sınırlayan otoinflamatuar bir hastalıktır. Hastalıklarınprognozunu daha iyi anlamak için çeşitli klinik kriterlerin bir kombinasyonuna göre puanlanan hastalık şiddeti skorları kullanılır. Bu çalışmanın amacı, AAA'lı çocuklarda genetik mutasyonların hastalık şiddeti skorlarına etkisini belirlemektir.
Gereç ve Yöntemler: Yalçınkaya-Özen tanı kriterlerine göre AAA tanısı konan ve gen analizi yapılan 0-18 yaş arası hastalar retrospektif olarak değerlendirildi. Tüm hastalara Pras ve arkadaşlarının skorlama sistemi, Mor ve arkadaşlarının skorlama sistemi ve Uluslararası AAA şiddet skoru (ISSF) skorlama sistemi uygulandı. Hastalar genetik mutasyonlarına göre sınıflandırılarak hastalık şiddeti skorları karşılaştırıldı.
Bulgular: Hastalar M694V homozigot, heterozigot, M694V/diğer alel birleşikheterozigot ve diğer mutasyonlar olarak 4 gruba ayrıldığında Pras ve arkadaşlarının hastalık ağırlık skoruna göre M694V homozigot olanlarda hafif hastalık sıklığı daha az bulunduHastalar en sık bulunan homozigot M694V, heterozigot M694V, heterozigot E148Q ve birleşik heterozigot M694V/M680I mutasyonlar olarak 4 gruba ayrıldığında, Pras ve ark.'ın skorlama sistemine göre homozigot M694V grubunda hafif hastalık sıklığı daha az saptandı. Hastalar homozigot M694V grubu ve heterozigot M694V (diğer bir alelle birleşik ya da tek) grubu olarak ikiye ayrıldığında, üç skorlama sistemine göre homozigot M694V grubunda hastalık daha şiddetliydi. Skorlama sistemleri arasındaki uyum analizinde Mor ve ark. ve ISSF skorlama sistemleri arasında güçlü bir uyum saptanırken, Pras ve ark. skorlama sistemi ile diğer skorlar arası uyum zayıf bulundu.
Sonuçlar: According to the scoring system defined by Pras et al., patients with homozygous M694V allele had a higher rate of severe disease than all other groups. . Buradan M694V homozigot mutasyonun, M694V heterozigot mutasyondan daha şiddetli hastalık yaptığı ve hatta biri M694V olmak üzere diğer bir patojenik mutasyon ile kombinasyonundan da daha şiddetli hastalık yaptığı sonucuna varabiliriz.

Anahtar Kelimeler: Ailevi Akdeniz Ateşi, genotip, hastalık şiddet skorları, klinik, tedavi

Introduction

Familial Mediterranean Fever (FMF) is a self-limiting autoinflammatory disease characterized by inflammation of the serosal surfaces and recurrent episodes of fever along with abdominal pain, arthralgia, arthritis, serositis, and erysipelas-like rash, typically lasting 6–72 hours during attacks (1-3). Although it is seen all over the world, its incidence is higher in ethnic groups living in the Eastern Mediterranean geography, especially Turks, Arabs, Armenians and Jews, compared to other countries. Its prevalence in these geographies varies between 1 in 500- 1000 (1). The most serious complication of the disease is amyloidosis, which can cause long-term morbidity and mortality (4). The Mediterranean fever (MEFV) gene is an autosomal gene that follows the autosomal recessive mode of inheritance and is present on the short arm of the sixteenth chromosome (5). Although only five mutations were found in 85% of the patients, 385 mutations were detected according to the latest data from the Infevers website (6, 7). The most common mutations were M694V, M680I, M694I, and V726A mutations in exon 10, which are believed to be associated with disease severity.

The scoring systems described by Pras et al. (8) and Mor et al. (9) and the International Severity Score of Familial Mediterranean Fever (ISSF) (10) are the most commonly used scoring systems to determine disease severity in FMF. Thanks to these scoring systems, it is possible to classify FMF patients according to disease severity and to try to predict their prognosis. Various demographic, clinical and laboratory findings are used in scoring systems. The scoring systems used in FMF are shown in Table 1.

To date, there are a limited number of studies evaluating the relationship between disease severity scores and gene mutations. For this purpose, we aimed to examine the relationship between three different disease severity scores and gene mutations in patients followed up at our clinic.

Methods

Patients

Patients aged 0-18 years, who were diagnosed with FMF and underwent gene analysis between 2017-2020 in the Pediatric Rheumatology outpatient clinic of Selcuk University Faculty of Medicine, were included in the study.According to the diagnostic criteria by Yalçınkaya and Özen, the presence of at least two of the criteria among fever >38C° measured in the axillary area, abdominal pain, chest pain, arthritis, and a positive family history, lasting 6–72 hours in at least three attacks, were considered sufficient for the diagnosis (11). Patients whose genetic analysis was not performed and patients who did not comply with their follow-up and treatment were not included in the study.

Demographic, clinical, genetic, and laboratory characteristics of these patients were recorded retrospectively from their records and the computer information system. In light of this information, the patients' disease was scored according to the disease severity scoring system by Pras et al. and Mor et al. as well as the ISSF, and the disease severity was classified as mild, moderate, and severe. FMF disease severity scoring systems are summarized in Table 1.

Genetic Analysis of MEFV gene

DNA isolation was performed from the peripheral blood samples of the patients and 22 mutations (M694V, M694I, M680I, V722M, V726A, E148Q, R202Q, R761H, P369S, A744S, E230K, K695R, L110P, U148Q, F479L, R761U, M694 del, I692 del, T681I, A408G, T267I, and E167D) in the 2nd, 3rd, 5th and 10th exons of the MEFV gene were analyzed by fragment analysis. In cases where no mutations could be detected in these, the whole gene sequencing technique, which is an advanced genetic analysis technique, was used. Gene analysis was performed from the mother and father for the detection of combined heterozygous mutations..

The relationship between common genotypes and alleles and disease severity scores were investigated. Mutations were divided into four groups, as homozygous, heterozygous, heterozygous combined, and no mutation, for comparison and evaluated both in terms of disease severity scores.

In addition, patients were divided into four groups as homozygous M694V, heterozygous M694V, heterozygous M694V/other allele combined, and other mutations, and the groups were compared with each other in terms of disease severity scores. Homozygous M694V, heterozygous M694V, heterozygous E148Q, and heterozygous M694V/M680I combined mutations, which were the most common four genetic analysis results in our study, were similarly compared in terms of disease severity scores.

The study was approved by the local ethics committee on June 17, 2020 with the decision number 2020/258.

Statistical Analysis

IBM SPSS version 21 and SDATA version 15.1 were used for the statistical analyses. Descriptive statistics were described as mean±SD, minimum, and maximum. Frequency analysis was performed for categorical data. Chi-Square and Fisher's Exact tests were used to compare categorical variables. Categorical data, which were found to be correlated in the Chi-Square test, were subjected to Chi-Square Trend and Post hoc analyses. Numerical data were evaluated using the Mann-Whitney Utest. A value of $p<0.05$ was considered statistically significant.

Results

Demographic and Clinical Characteristics

Of the patients included in the study, 149 (49.1%) were female and 154 (50.8%) were male. The demographic and clinical characteristics of the patients are summarized in Table 2. The median age of the patients was 10 years (min-max: 10 months-18 years). The

median age at diagnosis was 6 years (min-max: 10 months-18 years). The median time from the onset of the complaints to the diagnosis was calculated as 2 years (min-max: 2 months-13 years). While the number of patients diagnosed under the age of 10 was 220 (72.6%), the number of patients diagnosed over the age of 10 was 83 (27.3%) (Table 2).

When the patients were evaluated in terms of clinical features, abdominal pain was seen in 290 patients (95.7%) and was the most common clinical feature. This was followed by fever in 283 patients (93.3%), joint pain in 164 patients (54.1%), fatigue in 80 patients (26.4%), chest pain in 64 patients (21.1%), and arthritis in 46 patients (15.2%) were followed. Detailed clinical examination is given in Table 2.The diagnosis of the patient with renal involvement was made by kidney biopsy.

Genetic Characteristics

While mutations were detected in 271 (89.4%) of the patients, no mutation was detected in 32 (10.6%) patients. Heterozygous mutations were detected in 136 (44.8%) patients, combined heterozygous mutations in 76 (25%) and homozygous mutations in 59 (19.4%) patients.

When the allele frequencies in the patients included in the study were examined, in total, mutations were detected in 359 alleles. The M694V allele was seen in 157 patients (43.7%) and was found to be the most common allele. The second and third most common alleles were M680I in 61 (16.9%) patients and V726A in 49 (13.6%) patients, respectively. Other common alleles included E148Q, R202Q.

When the mutations of the patients were examined, the most common mutation was M694V heterozygous mutation in 63 (23.2%) patients. This was followed by M694V homozygous mutation detected in 43 patients (15.8%). E148Q heterozygous mutation detected in 27 patients (9.96%) was the third most common genotype. M694V/M680I was detected in 25patients (8.85%), and it was determined as the 4th most common genotype. Other common genotypes were V726A heterozygous mutation, M680I heterozygous mutations. E148Q homozygous, V726A homozygous, and various combined heterozygous mutations were rare genotypes. The mutation frequencies of the patients in our study are shown in Table 3.

Association of Genotype with Disease Severity Scores

We observed that 47 patients belonged to the mild disease group, 198 patients belonged to the

Table 1: Disease Severity Scoring System in FMF

Pras et al. Disease Severity Scoring System			Mor et al. Disease Severity Scoring System	ISSF (International Severity Scoring System for Familial Mediterranean Fever)	
Parameter	Feature	Score	Criteria	Criteria	Score
Age of onset (year)	>31	0	1.≥1 site in a single attack (In at least 25% of the attacks)	1. Chronic sequela (including amyloidosis, growth retardation, anaemia, splenomegaly)	1
	21-31	1			
	11-20	2		2. Organ dysfunction (nephrotic range proteinuria, FMF related)	1
	6-10	3			
	<6	4			
Number of attacks per month	<1	1	2. ≥2 sites in the course of the disease	3. Organ failure (heart, renal, etc, FMF related)	1
	1-2	2			
	>2	3			
Arthritis	Acute	2	3. ≥2 mg/day colchicine to achieve remission	4. A. Frequency of attacks (average number of attacks between 1 and 2 per month)	1
	Persistent	3		B. Frequency of attacks (average number of attacks >2 per month)	2
Erysipelas-Like erythema		2	4. ≥2 pleuritic attacks during the course of the disease	5. Increased acute-phase reactants (any of C-reactive protein, serum amyloid A, erythrocyte sedimentation rate, fibrinogen) during the attack-free period, ≥2 weeks after the last attack (at least two times 1 months apart)	1
Amyloidosis		3	5. ≥2 Erysipelas-like erythema attacks during the courseof the disease	6. Involvement of more than two sites during an individual acute attack (pericarditis, pleuritis, peritonitis, synovitis, ELE, testis involvement, myalgia, and so on)	1
Colchicine Dosage (mg/day)	1	1	6. Age of onset<10 years	7. More than two different types of attack during the course of the disease (isolated fever, pericarditis, pleuritis, peritonitis, synovitis, ELE, testis involvement, myalgia, and so on)	1
	1,5	2			
	2	3			
	>2**	4		8. Duration of attacks (more than 72 h in at least three attacks in a year)	1
**2mg/day unresponsive 3–5 points were classified as mild disease, 6–9 points as moderate disease, and >10 as severe disease.			≥3 points was considered as severe disease, 2 points as moderate disease, and ≤1 points as mild disease.	9. Exertional leg pain (pain following prolonged standings and/or exercising, excluding other causes)	1
				Severe disease ≥6, intermediate disease 3–5, mild disease ≤2. *Criterion 4a/4b can give 0 or 1 or 2 points altogether according to the definition.	

Table 2: Clinical and Demographic Features of The Patients with Familial Mediterranean Fever

Variables	Median	Min-Max
Age (Year)	8	0.83-18
Age of Diagnosis (Year)	7	0.83-18
Time to Diagnosis	2	0.2-13
Attack Duration(Day)	3	0.25-10
Attack Frequency (Week)	4	1-72
Gender	**n=303**	**%**
Female	149	49.1
Male	154	50.8
Clinical Features	**n=303**	
Abdominal Pain	290	95.7
Continuous	262	86.5
Colic	28	9.2
Fever	283	93.4
37 C^0-38 C^0	29	9.6
≥38 C^0	254	83.8
Joint Pain	164	54.1
Fatique	80	26.4
Chest Pain	64	21.1
Arthritis	46	15.2
Ankle	29	9.6
Knee	15	5
Other Joints	8	2.6
Nausea-Vomiting	35	11.6
Constipation	27	8.9
Diarrhea	20	6.6
Headache	14	4.6
Myalgia	11	3.6
Unrest	11	3.6
Erysipelas-like rash	8	2.6

moderate disease group, and 58 patients belonged to the severe disease group according to the scoring system described by Pras et al. Further, we observed that 199 patients belonged to the mild disease group, 43 patients belonged to the moderate disease group, and 61 patients belonged to the severe disease group according to the scoring system described by Mor et al. Additionally, we observed that 176 patients belonged to the mild disease group, 106 patients belonged to the moderate disease group, and 21 patients belonged to the severe disease group according to the ISSF scoring system. Patients with homozygous, heterozygous, heterozygous combined, and no mutations were evaluated according to disease severity scores (Pras et al., Mor et al., and ISSF), and no difference was found between the genotypes in terms of disease severity according to all three scoring

Table 3: Mutation Frequency of Patients

Mutation	n (%)
M694V heterozygous	63 (23.2)
M694V homozygous	43 (15.8)
E148Q heterozygous	27 (9.96)
M694V-M680I compound heterozygous	25 (9.22)
V726A heterozygous	18 (6.64)
M680I heterozygous	14 (5.16)
M694V-V726A compound heterozygous	11 (4.05)
M680I-V726A compound heterozygous	10 (3.69)
R202Q heterozygous	8 (2.95)
M680I homozygous	7 (2.58)
M694V-E148Q compound heterozygous	5 (1.84)
R202Q homozygous	4 (1.47)
V726A-E148Q compound heterozygous	4 (1.47)
E148Q homozygous	3 (1.10)
M694V-R202Q compound heterozygous	3 (1.10)
M694V-M680I-R202Q compound heterozygous	2 (0.73)
V726A homozygous	2 (0.73)
V726A-R202Q compound heterozygous	2 (0.73)
M694V-U148Q compound heterozygous	2 (0.73)
M680I-E148Q compound heterozygous	2 (0.73)
Other*	16 (5.90)
Total	271 (100)

*Rare mutations, one each.(A744S heterozygous, E148Q-P369S compound hererozygous, R202Q-R761H

compound heterozygous, M680I-R202Q compound heterozygous, M694V-R761U compound heterozygous,

V722M heterozygous, R761U heterozygous, M694V-L110P compound heterozygous, M694I heterozygous,

P369S heterozygous, M694V-E230K compound heterozygous, E230K heterozygous, R202Q- A744S compound

heterozygous, V726A-M694I compound heterozygous, M694V-R202Q-E148Q compound heterozygous, M680I-

R761H compound heterozygous)

systems (p=0.571, p=0.630, and p=0.546, respectively). The evaluation of genotypes according to disease severity scores is shown in Table 4.

When patients were grouped as homozygous M694V, heterozygous M694V, heterozygous M694V/other allele and other mutations, a statistical difference was found between the groups in terms of disease severity scores according to Pras et al. (p=0.017). According to the score of Pras et al., the frequency of mild disease tended to be less in the M694V homozygous group. However, no statistically significant difference was found between the groups according to Mor et al. and ISSF (p= 0.608, 0.336, respectively) (Table 4).

When the patients with homozygous M694V, heterozygous M694V, heterozygous E148Q, and heterozygous M694V/M680I combined mutations, which were the most common mutations in our study, were compared in terms of disease severity scores according to the scoring system described by Pras et al., a significant difference was observed between

the groups, and mild disease was found to be less common in the homozygous M694V group (p=0.037). However, there was no difference between them in terms of disease severity accoring to the scoring system described by Mor et al. and the ISSF (Table 4).

When the group with heterozygous M694V and the groups with heterozygous M680I, heterozygous V726A, heterozygous E148Q, and heterozygous R202Q mutations, which were other common mutations, were compared, no difference was found between the mild-moderate and severe groups in terms of disease severity according to the three scoring systems (p=0.609, p=0.697, and p=0.519, respectively).

When the homozygous M694V group and the group with heterozygous M694V (combined with other allele or single) mutation were compared in terms of disease severity, a significant correlation was found indicating that the disease was more severe in the homozygous M694V group based on the three scoring systems (p=0.001, p=0.024, and p=0.050, respectively) (Table 5). When the direction of the correlation in the scores according to the scoring system described by Pras et al. was examined, it was observed that there were more patients with severe disease than those with mild disease in the group with homozygous mutations, and the heterozygous group tended to have more patients with severe disease than those with mild disease. With post hoc analysis, according to Pras et al.'s scoring system, those with mild disease were significantly higher in the heterozygous group compared to the homozygous group (z=2.5, X2=6.25, p= 0.04), while those with severe disease were significantly higher in the homozygous group than those with mild disease. (z=-2.5, X2= 6.25, p=0.04). In the scoring system described by Mor et al., the group with homozygous mutation had a tendency to have severe disease, whereas there was a tendency to have mild disease in the group with heterozygous mutation. In post hoc analysis, the p value was found to be 0.07 in both directions (z=-2.3, X2= 5.9, z=2.3, X2= 5.9, respectively). It was not statistically significant. According to the ISSF classification, mild disease was found to be more common in patients with heterozygous mutation but this was not statistically significant according to p<0.05.

When patients with and without the M694V allele were evaluated in terms of the disease severity scores according to the scoring systems described by Pras et al. and Mor et al. and the ISSF, no difference was found between the groups in terms of disease severity (p=0.453, p=0.657, and 0.336, respectively).

When we grouped and compared the disease severity scores of heterozygous mutations of the common alleles M694V, M680I, V726A, and E148Q as mild-moderate and severe, no difference was found between the groups according to all three disease severity scoring systems (p=0.766, p=0.939, and p=0.964, respectively).

In addition, when we classified the M680I and V726A mutations, which were the second and third most common mutations, into homozygous and heterozygous mutations and compared them based on mild-moderate and severe in terms of disease severity scores, no significant difference was found between the groups in terms of disease severity. When the patients with and without the M680I allele and the patients with and without the V726A allele were compared in terms of disease severity scores, no significant difference was found between the groups.

Similarly, in terms of E148Q and R202Q, which were other common mutations, no difference was found between the groups having homozygous and heterozygous mutations according to all three scoring systems when grouped based on the severity of the disease as mild-moderate and severe. There was no difference in disease severity between patients with and without the E148Q allele. When the presence and absence of the R202Q allele and disease severity scores were compared, no significant correlation was found.

Although there was no homozygous mutation among other mutations, including M694I, R761H, A744S, E130K, P369S, R761U, and V722M, when patients with heterozygous mutations and those without mutations were compared, no difference was found in terms of disease severity according to the three disease severity scoring systems. When the internal consistency of the scoring systems were evaluated with the SDATA statistical program Kappa analysis, a weak agreement was detected among Pras et al. SS and Mor et al. SS with kappa value of 0.357, agreement value of 80.12%, p<0.01. A weak agreement was found between Pras et al. SS and ISSF with a kappa value of 0.297, an agreement value of 81.85%, and p<0.01. However, a strong (good) agreement was found between the Mor et al. SS and ISSF, with a kappa value of 0.661, an agreeement value of 91.17%, and a p<0.01..

DISCUSSION

Due to the developments in the field of molecular genetics, we have been able to gain more knowledge regarding the FMF, which we assumed to have known about for a long time. In fact, genetic examination was added to the EURO Fever/PRINTO diagnostic criteria defined in 2019 for this disease, which was being diagnosed based on clinical criteria only, and the importance of genetic examination was revealed. Many mutations in the MEFV gene that cause FMF have been identified with recent studies on molecular genetics (12).

In the last 20 years, disease severity scores have been developed to determine the severity, prognosis and effective treatment of many diseases, including FMF. In FMF, the disease severity score, which was first developed by Pras et al.in 1997, was used for adult patients (8). In 2005, Mor et al. has been developed to a new scoring system to correct missing conditions such as lack of cause and effect relationship between severity markers and disease severity in Pras disease severity score. (9). Finally, in 2012, the international group of FMF experts developed the ISSF criteria. These criteria are suitable for use in children and adults in

Table 4: Evaluation of Genotypes According to Disease Severity Scores

		Heterozygous n:136 (%)	Homozygous n:59 (%)	Compound heterozygous n:76 (%)	No Mutation n:32 (%)	p
Pras et al. SS	Mild	25 (18.4)	3 (5.1)	12 (15.8)	7 (21.9)	
	Moderate	88 (64.7)	37 (62.7)	50 (65.8)	23 (71.9)	0.571
	Severe	23 (16.9)	19 (32.2)	14 (18.4)	2 (6.3)	
Mor et al. SS	Mild	94 (69.1)	30 (50.8)	50 (65.8)	25 (78.1)	
	Moderate	18 (13.2)	11 (18.6)	9 (11.8)	5 (15.6)	0.63
	Severe	24 (17.6)	18 (30.5)	17 (22.4)	2 (6.3)	
ISSF	Mild	82 (60.3)	26 (44.1)	47 (61.8)	21 (65.6)	
	Moderate	47 (34.6)	24 (40.7)	24 (31.6)	11 (34.4)	0.546
	Severe	7 (5.1)	9 (15.3)	5 (6.6)	0 (0)	
		M694V Heterozygous n: 63 (%)	M694V Homozygous n: 43 (%)	M694V/Other Compound heterozygous n: 52 (%)	Other Mutations n: 110 (%)	
Pras et al. SS	Mild	12 (19)	1 (2.3)	8 (16)	9 (8.1)	
	Moderate	42 (66.6)	27 (62.8)	35 (67.3)	68 (61.8)	0.017
	Severe	9 (14.2)	15 (34.9)	9 (17.3)	33 (30)	
Mor et al. SS	Mild	45 (71.9)	23 (53.5)	33 (63.4)	72 (65.5)	
	Moderate	9 (14.1)	8 (18.6)	7 (13.4)	14 (12.7)	0.608
	Severe	9 (14.1)	12 (27.9)	12(23.0)	24 (21.8)	
ISSF	Mild	40 (64.1)	20 (46.5)	31 (59.6)	62 (56.4)	
	Moderate	20 (31.3)	16 (37.2)	17 (32.6)	41 (37.3)	0.336
	Severe	3 (4.7)	7 (16.3)	4 (7.69)	7 (6.4)	
		M694V Heterozygous n:63 (%)	M694V Homozygous n:43 (%)	E148Q Heterozygous n:27 (%)	M694V/M680I Compound Heterozygous n:25 (%)	
Pras et al. SS	Mild	12 (19)	1 (2.3)	5 (18.5)	5 (20.0)	
	Moderate	42(66.6)	27 (62.8)	17 (63.0)	15 (60.0)	0.037
	Severe	9 (15.3)	15 (34.9)	5 (18.5)	5 (20.0)	
Mor et al. SS	Mild	45 (71.9)	23 (53.5)	18 (66.7)	15 (60.0)	
	Moderate	9 (14.1)	8 (18.6)	5 (18.5)	5 (20.0)	0.466
	Severe	9 (14.1)	12 (27.9)	4 (14.8)	5 (20.0)	
ISSF	Mild	40 (64.1)	20 (46.5)	17 (63.0)	14 (56.0)	
	Moderate	20 (31.3)	16 (37.2)	9 (33.3)	9 (36.0)	0.220
	Severe	3 (4.7)	7 (16.2)	1 (3.7)	2 (8.8)	

both clinical practice and drug trials (10).

Disease severity scores are now used in many diseases to evaluate disease severity more objectively. In previous studies, it was found that the disease severity scores showed more severe disease in the group carrying the homozygous M694V mutation (13-15). However, in a study from Turkey, it was observed that carrying the M694V mutation in one allele or two alleles did not change the severity of the disease (16). In another study, no difference was observed in terms of disease severity scores between common mutations (M694V, V726A, and M680I) and rare mutations (A744S, P369S, K695R, R761H, and F479L)

Table 5: Evaluation of M694V Homozygous and Heterozygous Mutations According to Patient Weight Scores

	M694V Homozygous n=43 (%)	M694V Heterozygous (combined with other allele or single) n=115 (%)	p
Pras et al. SS			
Mild	1 (2.3)	20 (17.3)	
Moderate	27 (62.7)	77 (66.9)	***0.004***
Severe	15 (34.8)	18 (15.6)	
Mor et al. SS			
Mild	23 (53.5)	79 (68.6)	
Moderate	8 (18.6)	14 (12.1)	***0.024***
Severe	18 (27.9)	22 (19.1)	
ISSF			
Mild	20 (46.5)	72 (62.6)	
Moderate	16 (37.2)	36 (31.3)	***0.050***
Severe	7 (16.2)	7 (6.0)	

(17). In a study that only aimed to evaluate the association of E148Q mutation with disease severity and evaluated homozygous M694V mutation with homozygous E148Q, heterozygous E148Q and heterozygous E148Q/Exon 10 combined mutations according to the scoring system described by Pras et al., it was observed that the disease had a more severe course in patients with homozygous M694V mutation (18). In the present study, according to the scoring system described by Pras et al., a correlation was found between homozygous M694V, heterozygous M694V, heterozygous M694V/other combined, and other genotypes, indicating that the rate of mild disease was lower in the M694V homozygous group. Similarly, a relationship was found in terms of disease severity in the comparison of the four most common genotypes: homozygous M694V, heterozygous M694V, heterozygous E148Q, and heterozygous M694V/M680I combined. In addition, when only homozygous M694V and heterozygous M694V groups were compared in pairs, the rate of severe disease tended to be higher in the homozygous group according to all three scoring systems. However, this was not statistically significant according to the scoring system described by Mor et al. and the ISSF. Based on the scoring system described by Pras et al., the rate of severe disease was higher in patients with homozygous M694V allele, whereas the rate of mild disease was statistically significantly higher in the heterozygous group compared with homozygous group. In light of all of these findings, we can say that the homozygous M694V mutation is associated with a more severe disease than other mutations that are common in the population. However, a sound comparison of homozygous M694V and other homozygous mutations could not be made as the incidence of homozygous mutation of other alleles (V726A, E148Q, and M680I) is very low in the population.

Although ISSF scoring was found to be the most appropriate scoring system for children in a recent study conducted in our country, we observed that other scoring systems are used more widely when the literature is examined. (18, 19, 20, 21). In our study, unlike other studies, 3 disease severity scores were used and in fact, the compatibility of these disease severity scores with each other was tried to be seen. According to our study, the results in the scoring system of Pras et al. were different from the scoring system of ISSF and Mor et al. As a matter of fact, in the concordance analysis between scoring systems, while a good agreement was found between Mor et al.'s scoring system and ISSF, the agreement with Pras et al.'s scoring system was weak.

Therefore, although patients with FMF were evaluated across a wide range in terms of genetic, and disease severity scores, the most important limitation of the study was the inability to perform statistical analysis due to the low number of patients for some genotypes.

We believe that further studies are warranted with large samples, multiple centers and even multiple ethnic groups for evaluating the relationship between clinical presentation and genotype and their relationship with disease severity scores in order to better understand FMF. Additionally, this will aid in the understanding of the effects of genetic mutations that have recently been added to the diagnostic criteria on clinical presentation and disease severity.

Acknowledgements: The authors thank Enago – https://www.enago.com.tr/ceviri/ for their assistance in manuscript translation and editing.

Funding: None

Conflict of Interest: The authors declare that there is no conflict of interest.

Author's Contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Vildan Güngörer, Alaaddin Yorulmaz and Şükrü Arslan. The first draft of the manuscript was written by Vildan Güngörer and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

1.Ozen S, Bilginer Y. A clinical guide to autoinflammatory diseases: familial Mediterranean fever and next-of-kin. Nat Rev Rheumatol. 2014; 10:135-47.

2.Yalçınkaya F, Group TFS. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. 2005.

3.Lidar M, Livneh A. Familial Mediterranean fever: clinical, molecular and management advancements. Neth J Med. 2007; 65: 318-24.

4.Cobankara V. Kiraz S. Ailesel akdeniz ateşi Hacettepe Tıp Dergisi Hacettepe Üniversitesi yayınları Ankara. 2000; 31: 310-9.

5.Tufan A, Lachmann HJ. Familial Mediterranean fever, from pathogenesis to treatment: a contemporary review. Turk J Med Sci. 2020;50: 1591-610.

6.Consortium FF. A candidate gene for familial Mediterranean fever. Nature genetics. 1997; 17: 25-31.

7.Schnappauf O, Chae JJ, Kastner DL, Aksentijevich I. The Pyrin Inflammasome in Health and Disease. Front Immunol. 2019; 10: 1745.

8.Pras E, Livneh A, Balow Jr JE, et al. Clinical differences between North African and Iraqi Jews with familial Mediterranean fever. American journal of medical genetics. 1998; 75: 216-9.

9.Mor A, Shinar Y, Zaks N, et al., editors. Evaluation of disease severity in familial Mediterranean fever. Seminars in arthritis and rheumatism; 2005: Elsevier.

10.Demirkaya E, Acikel C, Hashkes P, et al. Development and initial validation of international severity scoring system for familial Mediterranean fever (ISSF). Annals of the Rheumatic Diseases. 2016; 75: 1051-6.

11.Yalçınkaya F, Özen S, Özçakar ZB, et al. A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. Rheumatology. 2009; 48: 395-8.

12.Gattorno M, Hofer M, Federici S, et al. Classification criteria for autoinflammatory recurrent fevers. Annals of the rheumatic diseases. 2019;78: 1025-32.

13.Battal F, Silan F, Topaloğlu N, et al. The MEFV gene pathogenic variants and phenotype-genotype correlation in children with familial Mediterranean fever in the Çanakkale population. Balkan journal of medical genetics: BJMG. 2016; 19: 23.

14.Wilson M, Abou-Elalla AA, Zakaria MT,et al. Serum amyloid A Type 1 gene polymorphism in Egyptian children with familial Mediterranean fever. Pathobiology. 2016; 83: 295-300.

15.Yavuz S, Duru NS, Elevli M. Ailevi Akdeniz Ateşi Hastalarında Klinik, Laboratuvar Bulguları, Hastalık Ağırlık Skorları ve Gen Mutasyonları Arasındaki İlişki. Medical Bulletin of Haseki/Haseki Tip Bulteni. 2018; 56: 58-64..

16.Yalçınkaya F, Cakar N, Mısırlıoğlu M, et al. Genotype–phenotype correlation in a large group of Turkish patients with familial Mediterranean fever: evidence for mutation-independent amyloidosis. Rheumatology. 2000; 39: 67-72.

17.Soylemezoglu O, Kandur Y, Duzova A, et al. Familial Mediterranean fever with a single MEFV mutation: comparison of rare and common mutations in a Turkish paediatric cohort. Clinical and experimental rheumatology. 2015; 33: 152-5.

18.Aydın F, Çakar N, Özçakar ZB, et al. Clinical features and disease severity of Turkish FMF children carrying E148Q mutation. J Clin Lab Anal. 2019; 33: e22852.

19.Ayaz NA, Tanatar A, Karadag SG, et al. Comorbidities and phenotype-genotype correlation in children with familial Mediterranean fever. Rheumatol Int. 2021; 41: 113-20.

20.Guler T, Garip Y, Dortbas F, Dogan YP. Quality of life in Turkish patients with Familial Mediterranean Fever: Association with fatigue, psychological status, disease severity and other clinical parameters. The Egyptian Rheumatologist. 2018; 40: 117-21.

21.Ozcan G, Cayci S, Celikel Acar B et al. Is the performance of the international severity scoring system for familial mediterranean fever in children better than other scoring systems? International Journal of Clinical Practice, 2021, 75.11: e14678. doi: 10.1111/ijcp.14678. Epub 2021 Aug 18. PMID: 34328662.

Received: 8 Oct 2021 | **Accepted:** 22 Dec 2021
DOI: 10.54005/geneltip.1005969

ORIGINAL ARTICLE

Evaluation of the effectiveness of ultrasound-guided transversus abdominis plane block for chronic pain after lower abdominal surgery

Alt abdominal cerrahi sonrası gelişen kronik ağrı tedavisinde ultrason eşliğinde transversus abdominis plan bloğunun etkinliğinin değerlendirilmesi

[1]Ümit Akkemik, [2]Dostali Aliyev, [2]Güngör Enver Özgencil

[1]Department of Algology, Konya City Hospital, Konya, Turkey

[2]Department of Algology, Ankara University Faculty of Medicine, Ankara, Turkey

Correspondence

Ümit Akkemik, Department of Algology, Konya City Hospital, Konya, Turkey

E-Mail: umitak87@gmail.com

How to cite ?

Akkemik Ü, Aliyev D, Özgencil G. Evaluation of the effectiveness of ultrasound-guided transversus abdominis plane block for chronic pain after lower abdominal surgery. Genel Tıp Derg. 2022;32(1):27-31.

ABSTRACT

Aim: This study aimed to evaluate the effectiveness of ultrasound-guided transversus abdominis plane (TAP) block in patients diagnosed with chronic pain after undergoing lower abdominal surgery.
Methods: Patients who were admitted to the pain medicine clinic between January 1, 2016, and January 1, 2020, and underwent TAP block with the diagnosis of chronic pain after undergoing lower abdominal surgery were retrospectively analyzed. The visual analog scale (VAS) score was measured before the procedure and at the 1-month and 3-month follow-ups.
Results: The proportion of patients with a reduction in VAS scores of >50% after TAP block application was 50% at the 1-month follow-up and 72.5% at the 3-month follow-up. The changes in the VAS score was found to be statistically significant ($p < 0.05$).
Conclusion: Although ultrasound-guided TAP block seems to be an effective treatment method for chronic pain after lower abdominal surgery, further studies and clinical trials investigating different types of surgeries and including a larger number of patients are warranted.

Keywords: Chronic postoperative pain, abdominal wall, Pain Management, Nerve block

ÖZ

Amaç: Calışmamızda alt abdominal cerrahi sonrası gelişen kronik ağrı tanısı konulan hastalarda ultrason rehberliğinde transversus abdominis plan bloğunun etkinliğinin değerlendirilmesi amaçlanmıştır.
Metod: 1 Ocak 2016-1 Ocak 2020 tarihleri arasında ağrı polikliniğine başvuran ve alt abdominal cerrahi sonrası kronik ağrı tanısı ile TAP blok uygulanan hastalar geriye dönük
olarak incelendi. Hastaların işlem öncesi, işlem sonrası 1.ay ve 3. Ay Vizüel analog skala (VAS) değerleri karşılaştırıldı.
Bulgular: TAP blok uygulaması sonrası VAS skorlarında >%50 azalma olan hastaların oranı 1 aylık takipte %50 ve 3 aylık takipte %72,5 idi. VAS skorlarındaki değişiklikler istatistiksel olarak anlamlı bulundu ($p < 0.05$).
Sonuç: Ultrason rehberliğinde TAP blok alt abdominal cerrahi sonrası kronik ağrıda efektif bir tedavi yöntemi gibi görünmekle beraber, farklı ameliyat türlerinde ve daha fazla hastanın yer aldığı ileri çalışmalar ve klinik denemelerin yapılması gerekmektedir.

Anahtar Kelimeler: kronik postoperatif ağrı, abdominal duvar, ağrı tedavisi

Introduction

Abdominal surgery is one of the most frequently performed surgeries worldwide. Laparotomy and laparoscopic approaches are commonly used in this surgery (1). The most common reasons for visits to the hospital in patients with chronic pain syndrome after abdominal surgery are persistent pain in the abdomen, genital and perineal regions (2).While most abdominal surgeries are performed with excellent outcomes and minimal morbidity, a small proportion of patients experience postoperative discomfort and pain, thereby limiting their activity and productivity, increasing healthcare utilization, and reducing their quality of life due to their individual and social outcomes. Complete clinical recovery without complications is important for patients, and pain caused by surgical procedures remains an important clinical problem that severely affects postoperative rehabilitation.

Persistent postoperative pain is defined by the International Association for the Study of Pain as clinical discomfort lasting >3 months postoperatively without other causes of pain, such as chronic infection or pain from a chronic condition prior to surgery (3). The incidence of postoperative acute or chronic pain varies according to individuals and procedures. In a study that evaluated persistent pain lasting 12 months postoperatively, the incidence of moderate-to- severe postoperative pain in patients was 11.8%, the incidence of severe pain (numerical rating scale ≥6) was 2.2%, and

the incidence of neuropathic pain was 35.4%–57.1% (4).In the literature, the incidence rates reported in studies are classified according to the presence of preoperative pain or the severity of postoperative pain (Table 1).

Table 1. Incidence of Persistent Postsurgical Pain according to Surgical Procedure (3)

Cesarean section 15.4%
Cholecystectomy 3 to 56%
Hernia repair 5 to 35%
Hysterectomy 5 to 32%

Various mechanisms for the etiology of postoperative chronic pain have been proposed. The most widely accepted mechanism is the activation of high-threshold peripheral sensory neurons or neuropathic pain caused by inflammation or direct nerve injury at or near the surgical site. Neuroplastic changes in the peripheral and central nervous systems in response to acute postoperative pain have been suggested to play an important role in the development of postoperative chronic pain syndrome (5). Treatment protocols generally include oral or topical nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, and anticonvulsant drugs. However, interventional minimally invasive procedures (nerve block and neurolysis) and revision surgery may be required in patients in whom adequate pain reduction cannot be achieved with conventional drug therapy. Nerve blocks are considered among the treatment options for postoperative pain because of their reproducibility (6,7).

Anatomically, the spinal nerves from T7 to T11 run along the neurovascular plane that passes between the internal oblique and transverse abdominis in the anterior abdominal wall and is called the transversus abdominis plane (TAP). L1 (ilioinguinal and iliohypogastric) and T12 (subcostal nerve) also pass in the same plane (8). TAP block was first reported by Rafi et al., who described the traditional blind spot technique using Petit's lumbar triangle in 2001 (9). The increased prevalence of ultrasound guidance has enabled physicians performing TAP block to identify the appropriate tissue plane and perform the block with greater accuracy under direct visualization.

In this article, we discuss the effectiveness of TAP block applied using ultrasound guidance for patients diagnosed with chronic pain after undergoing lower abdominal surgery.

Methods

This study was performed with the approval of the Non Interventional Clinical Research Ethical Committee of the local ethics committee (reference number: i5-330-21). In this single-center study, the medical records of patients who applied to our clinic between January 1, 2016 and January 1, 2020 with the diagnosis of postoperative chronic pain and underwent TAP block were reviewed retrospectively. In this retrospective study, we reviewed the charts of 40 chronic abdominal pain patients treated TAP blocks after other forms of pain management had failed.

In our clinic, TAP block is performed with the lateral approach under the guidance of USG. After providing the necessary antiseptic conditions in the supine position, the linear probe is placed at the midpoint of the distance between the costal border and the iliac crest. The ideal image is obtained by moving the probe cephally or caudally. The needle is placed in the same plane with the ultrasound probe (in-plane technique) (10). As the needle tip passes through the muscle layers and fascias, a fascial click is experienced as in the blind technique, and the needle tip is advanced in a controlled manner under ultrasound guidance. After the second click is experienced (after passing the fascia of the internal oblique muscle), a 0.5–1 ml test dose is applied to determine the localization of the needle tip. Subsequently, the localization site is confirmed and aspirated at frequent intervals, and the injectable is administered into the neurofacial plane. In patients with obesity, it may not always be easy to distinguish the three muscle layers from each other because of the large amount of cutaneous–subcutaneous adipose tissue. In this case, it is important to keep in mind that the internal oblique muscle is considered as the thickest and the transversus abdominis muscle as the thinnest (11).

The study included patients in whom chronic abdominal wall pain persisted for at least 3 months after lower abdominal surgery, those who did not achieve benefits despite receiving medical treatment (NSAIDs, anticonvulsants, or antiepileptic drugs), those without organic pathologies (such as infection or hematoma) to explain the cause of pain, and those who underwent TAP block and were followed up for at least 3 months postoperatively. Patients who underwent tap block but were missing in their subsequent records were excluded from the study.

In our clinic, the pain levels of patients after TAP block are questioned once a month for 1-3 months, either by inviting them to the hospital or by calling them. Patients' data, including age, sex, body mass index (BMI), pain localization, and previous surgery, were recorded. Visual analog scale (VAS) score was recorded at the first admission as well as at the first and third months postoperatively, and the changes were compared using statistical analysis.

Statistical analysis

Statistical analysis was performed using SPSS 11.5 software for Windows. Descriptive statistics, including mean, standard deviation, median, and minimum-maximum values of numerical variables, were used. Statistical significance was accepted at a p-value of <0.05. frequency and percentage values were used for categorical variables. Variances in VAS score before

and after procedure was analyzed using Friedman's two-way test.

Results

TAP block was applied in a total of 56 patients upon their admission to the pain medicine department, according to the retrospective analysis. Sixteen of these patients were excluded because of the inaccessibility of their follow-up records. Of the 40 patients included in this study, 37,5% (15 patients) were female and 62,5% (25 patients) were male. The patients' mean age was 48.4 (20-78) years, mean height was 169.5 cm (minimum, 153 cm; maximum, 183 cm), mean weight was 74.8 kg (minimum, 52 kg; maximum, 105 kg), and mean BMI was 25.2 (minimum, 18.8; maximum, 43.7).

Table 2 shows the patients' data, including age, sex, height, BMI, and demographic characteristics. Information regarding the surgical procedures of the patients is shown in Table 3.

Table 2. Patients' Data Before Interventional Procedure

	mean±sd	min.-max.
Age (years)	49.4± 18.3	20-78
Height (cm)	169.5± 6.6	153-183
Weight (kg)	74.8± 11.8	52-105
Body Mass Index (BMI)	25.2±4.6	18.8-43.7

sd:standard deviation; min: minimum value;max: maximum value

Table 3. Surgical Indication of The Patients Before Interventional Procedure

Operation	Number of patients	Percent (%)
Appendectomy	3	7.5
Laparoscopic left hemicolectomy	4	10
Laparoscopic ectopic pregnancy termination	2	5
Laparoscopic ovarian cyst excision	3	7.5
Laparoscopic total hysterectomy	1	2.5
Total abdominal hysterectomy-bilateral	2	5
Right inguinal hernia repair	9	22.5
Left inguinal hernia repair	9	22.5
Cesarean section	3	7.5
Robotic prostatectomy	4	10
Total	40	100

Table 4. Pain Localization of The Patients

Pain localization	Number of patients	Percent (%)
Bilateral lower quadrant	3	7.5
Right lower quadrant	7	17.5
Right inguinal region	12	30
Left lower quadrant	7	17.5
Left inguinal region	11	27.5
Total	40	100

Table 5. VAS score change

N=40	mean±sd	p*
Before the procedure	6.9±0.8	
Post-procedure		
1 month	3.8±0.7	p=0.000
3 months	3.4±1.1	p=0.000

sd:standard deviation *p<0.05

Table 6. *Drug usage information of the patients before and after the procedure*

Total number of patients	Pre-procedure drug use information	Post-procedure drug use information (3th month after the procedure)
5	Gabapentin 800 mg p.o. (q8h)	Gabapentin 800 mg p.o. (q8h)
8	Gabapentin 800 mg p.o. (q8h)	Gabapentin 300 mg p.o. (q8h)
7	Gabapentin 800 mg p.o. (q8h)	-
10	Amitriptyline 25 mg p.o. (q.d.)	Amitriptyline 25 mg p.o. (q.d.)

p.o. per os, mg-milligram, q8h- every eight hours, q.d.- once a day.

Table 7. Opioid use information of patients before and after the procedure

Drug	Number of patients (n)	Persentage of total patients (%)
Number of patients using opioids before the procedure	21	52,5
Number of patients who did not use opioids before the procedure	19	47,5
Post-procedure opioid use (3th month after the procedure)		
Using	-	-
stop using	21	52,5

Table 8. NSAID use information of patients before and after the procedure

Drug	Number of patients (n)	Persentage of total patients (%)
Number of patients using NSAID before the procedure	32	80
Number of patients who did not use NSAID before the procedure	8	20
Post-procedure NSAID use (3th month after the procedure)		
Using	10	25
stop using	22	55

The pain localization of the patients was in the lower abdomen and was usually unilateral (Table 4). TAP block was applied bilaterally in 3 patients, on the right side in 19 patients, and on the left side in 18 patients under the ultrasound guidance.

A total of 8 mg of dexamethasone and 18 ml of 2% prilocaine mixture were injected into the patients who underwent unilateral TAP block. Patients who underwent bilateral TAP block were injected with a mixture of 8 mg of dexamethasone and 19 ml of 2% prilocaine on each side.

While the mean VAS score before the procedure was 6.9, the VAS scores 1 month and 3 months after the procedure were 3.8 and 3.4, respectively. The changes in the VAS score were found to be statistically significant ($p< 0.05$) (Table 5).

No complications (local anesthetic toxicity, liver, spleen, kidney laceration, and femoral nerve damage) were recorded in any of the patients. At the 3-month follow-up, it was determined that 5 of the 20 patients who used gabapentin 800 mg three times a day before the procedure continued the drug at the same dose, whereas 8 patients used gabapentin 300 mg three times a day and seven patients did not use the drug (Table 6). It was determined that 10 patients used the same dose of amitriptyline before and after the procedure. Since our study patients used opioid and non-steroidal anti-inflammatory drugs from different groups, these drugs could not be standardized by us (Table 7 and 8). None of the patients were using opioid drugs at the 3- month follow-up.

Discussion

In our study, the proportion of patients with a reduction in VAS score of >50% was 50% at 1- month follow-up and 72.5% at the 3-month follow-up. This study indicated that administering TAP block to patients with chronic pain after lower abdominal surgery without causing any complications or side effects.

Persistent postoperative pain is one of the most common complications of surgery and is a severe social problem. Chronic abdominal pain, which can persist for months after initial onset, can be particularly difficult to manage. Treatment options include anticonvulsants, antidepressants, topical medications such as lidocaine gel, multidisciplinary rehabilitation programs, complementary medicine, and opioids in the presence of severe pain. Depending on the location of pain in patients experiencing chronic pain resistant to medical therapy, a nerve block in the relevant innervation area may be feasible. A mixture of local anesthetics and glucocorticoids is commonly used. Nerve blocks can stop the transmission of pain signals, inhibit neuroinflammation, and promote the recovery of neural functions (12).

In the literature, TAP block is mostly focused on as an anesthetic method in abdominal surgeries. TAP block can be used in surgical procedures involving the lower abdominal region, such as cesarean section (13), hernia repair (14,15), appendectomy (16), and abdominal hysterectomy (17). In a meta-analysis of studies investigating postoperative pain management after cesarean section in which 524 patients in nine studies were evaluated, although the benefits of TAP block were not clearly proven in cases where it was applied after spinal anesthesia using opioids, it was emphasized that TAP block significantly contributed to postoperative pain control if applied after spinal anesthesia without intrathecal opioids (18). However, these studies show the efficacy of TAP block in postoperative acute pain.

Recent studies have shown that TAP block can be effective for the treatment of chronic abdominal wall pain. In a recently published study, TAP block was applied to 30 patients with chronic abdominal pain and improvement was reported in 79.5% of the patients (19). They reported that a significant decrease in the use of gabapentin was reported after the procedure compared to the pre-procedure and suggesting potential effectiveness in pain management.

TAP blocks have potential for both diagnostic and therapeutic use for chronic pain, particularly as they are related to chronic postoperative pain (20). For patients with chronic pain after abdominal surgery, it may be difficult to determine whether the pain is visceral or somatosensory. Pain relief following TAP block may help confirm the somatosensory origin of the symptoms (i.e., whether they are related to the superficial tissues or parietal peritoneum). Pain relief following TAP block is either due to a "hydrodissection" effect or the effect of a corticosteroid or local anesthetic agent. The duration of action of the agents selected for injection in our study was shorter than 3 months. Additional research is needed to assess this issue.

Although the complication rate after tap block is low, case reports about frightening complications such as local anesthetic toxicity, liver, spleen, kidney laceration, and femoral nerve damage are available in the literature (21,22). Performing the tap block under ultrasound guidance will reduce the complication rate. In our study, no complications were recorded.

Limitation

The main limitation of this study is the retrospective design and small number of patients. Since it is a retrospective study, the use of drugs by the patients could not be limited.

Conclusion

In our study, ultrasound guided TAP block was successfully applied in the management of chronic postoperative pain after lower abdominal surgery. Post-procedure pain levels of the patients decreased and their quality of life increased. The drug doses used decreased, and some patients did not need analgesic drugs after the procedure. Ultrasound-guided TAP block appears to be safe and effective, provided that the practicing experts have adequate training in the techniques to be employed. Effective management of chronic postoperative pain not only reduces the discomfort caused by pain but also improves patients' quality of life and physical activity.

Disclosures: There is no conflict of interest for all authors. Acknowledgements: None.

Funding: None.

References

1. Gupta A, Gandhi K, Viscusi ER. Persistent postsurgical pain after abdominal surgery. Tech Reg Anesth Pain Manage 2011;15(3):140–6.

2. Crombie IK, Davies HT, Macrae WA. Cut and thrust: antecedent surgery and trauma among patients attending a chronic pain clinic. Pain. 1998;76(1-2):167-171.

3. Macrae, W.A. and Davies, H.T.O. (1999) Chronic Postsurgical Pain. In: Crombie, I.K., Ed., Epidemiology of Pain, IASP Press, Deattle, 125-142

4. Richebé P, Capdevila X, Rivat C. Persistent Postsurgical Pain: Pathophysiology and Preventative Pharmacologic Considerations. Anesthesiology. 2018; 129:590–607

5. Tracey I. Imaging pain. Br J Anaesth. 2008;101(1):32-9.

6. Dîrzu DS, Boţ T, Ciuce C. Saphenous nerve block as a diagnosis tool for chronic postsurgical pain of the left medial calf. Clin Case Rep. 2018 4;6(2):454-455.

7. Piraccini E, Biondi G, Byrne H, Calli M, Bellantonio D, Musetti G et al. Ultrasound Guided Transversus Thoracic Plane block, Parasternal block and fascial planes hydrodissection for internal mammary post thoracotomy pain syndrome. Eur J Pain. 2018;22(9):1673-1677.

8. Webster K. The transversus abdominis plane (TAP) block: Abdominal plane regional anaesthesia. Update Anaesth2008;24:25-30.

9. Rafi AN. Abdominal field block: a new approach via the lumbar triangle. Anaesthesia. 2001;56(10):1024-6. doi: 10.1046/j.1365-2044.2001.02279-40.x.

10. Gürkan Y, Tekin M. Ultrasonografi Rehberliğinde Rejyonal Anestezi. Transversus Abdominis Plan Bloğu [in Turkish]. 2011; 145-51

11. Hadzic Periferik Sinir Blokları ve Ultrason Eşliğinde Rejyonal Anestezi İçin Anatomi. Edit. Admir Hadzic. 2. baskı. Çev.Edit. Ercan Kurt. Ultrason Eşliğinde Sık Kullanılan Trunkal ve Kutanöz Bloklar. [in Turkish]. 2013; 460-3.

12. Liu YM, Feng Y, Liu YQ, Lv Y, Xiong YC, Ma K, et al. Chinese Association for the Study of Pain:Expert consensus on chronic postsurgical pain. World J Clin Cases. 2021 26;9(9):2090-2099

13. Şahin Ö, Aksoy Y, Kaydu A, Gökçek E. Spinal anestezi uygulanan sezaryen operasyonlarında bilateral TAP bloğun analjezik tüketimine etkisi [in Turkish]. Ortadoğu Tıp Dergisi. 2018; 10(2): 149-153.

14. Theodoraki K, Papacharalampous P, Tsaroucha A, Vezakis A, Argyra E. The effect of transversus abdominis plane block on acute and chronic pain after inguinal hernia repair. A randomized controlled trial. Int J Surg. 2019;63:63-70. doi:10.1016/j.ijsu.2019.02.007.

15. Topal A, Sargın M, Kilicaslan A. The Effect of Transversus Abdominis Plane Block in Inguinal Hernioplasty on Chronic Pain. Eur J Gen Med. 2015;12(4), 291-297.

16. Reinoso-Barbero F, Población G, Builes LM, Castro LE, Lahoz AI. Successful ultrasound guidance for transversus abdominis plane blocks improves postoperative analgesia after open appendicectomy in children. Eur J Anaesthesiol. 2012;29(8):402-4.

17. Amr YM, Amin SM. Comparative study between effect of pre- versus post-incisional transversus abdominis plane block on acute and chronic post-abdominal hysterectomy pain. Anesth Essays Res. 2011;5(1):77-82.

18. Mishriky BM, George RB, Habib AS. Transversus abdominis plane block for analgesia after Cesarean delivery: a systematic review and meta-analysis. Can J Anaesth. 2012;59(8):766-78.

19. Abd-Elsayed A, Malyuk D. Efficacy of Transversus Abdominis Plane Steroid Injection for Treating Chronic Abdominal Pain. Pain Pract. 2018;18(1):48-52.

20. Macrae WA. Chronic post-surgical pain: 10 years on. Br J Anaesth. 2008;101(1):77–86.

21. Salaria ON, Kannan M, Kerner B, Goldman H. A Rare Complication of a TAP Block Performed after Caesarean Delivery. Case Rep Anesthesiol. 2017;2017:1072576.

22. Farooq M, Carey M. A case of liver trauma with a blunt regional anesthesia needle while performing transversus abdominis plane block. Reg Anesth Pain Med. 2008;33(3):274-275.

Received: 18 Oct 2021 | **Accepted:** 14 Jan 2022
DOI: 10.54005/geneltip.1011301

ORIGINAL ARTICLE

Evaluation of the COVID-19 pandemic process effect on the increase of Precocious Puberty and Premature Thelarche

Santral Puberte Prekoks ve Prematur Telarş Sıklığının Artmasında COVID-19 Pandemi Sürecinin Etkisinin Değerlendirilmesi

[1]Nesibe Akyürek

[1]Division of Pediatric Endocrinology and Diabetes, School of Medicine, Başkent University, Konya, Turkey

Correspondence

Nesibe Akyurek, Başkent University Department of Pediatric Endocrinology, Konya, Turkey. 42090 Konya-TURKEY

E-Mail: n_akyurek@yahoo.com.tr

How to cite ?

Akyürek N. Evaluation of the COVID-19 pandemic process effect on the increase of Precocious Puberty and Premature Thelarche. Genel Tip Derg. 2022;32(1):32-35.

ABSTRACT

Objective: To determinate COVID-19 pandemic process effect on the increase of Precocious Puberty and Premature Thelarche
Materials and Methods: Total 60 girls, younger than 8 years old, who complaint with breast development. Medical history and physical examination findings, bone age, free T4, TSH, FSH, LH, estradiol levels of patients were recorded in their first visits. According to LHRH test results patients were divided to subgroups such as PT and CPP. Differences in the use of technological tools were recorded before and during the pandemic
Results: Higher Body Mass Index (BMI) (P=0.033), bone age (P<0.001) basal LH (P<0.001), basal FSH (P<0.001), basal estradiol (P<0.001) in cases with central puberty precocious level was detected. There was no difference between the two groups in terms of age and weight. Compared to the pre-pandemic period, there was a significant increase in the use of technological tools (smartphone, computer, television) in both groups. In cases with PT, it was 2.54 ±0.65 hours/day before the pandemic and 6.22±1.25 hours/day during the pandemic (p<0.001), in cases with Spp it was 2.7 ±0.46 hours/day before the pandemic, 7.36±1.36 hours/day during the pandemic (p<0.001). The main reason for using technological tools was school lessons (4.6 ± 1.2 hours/day in cases with Pt, 5±1.2 hours/day in cases with Spp p =0.393).
Conclusion: In our study, it was observed that there was a significant increase in the use of technological devices and puberty symptoms started at a younger age in both groups after the pandemic. It was thought that environmental factors such as weight and increased use of electronic devices triggered the onset of puberty and the rate of progression.
Keywords: Precocious Puberty, Coronavirus, Pandemics

ÖZ

Amaç: Bu çalışmada amaç; COVID-19 pandemi sürecinin santralpuberte prekoks (SPP) ve prematur telarş (PT) sıklığının artış ve ilişkisini araştırmaktır.
Gereç ve Yöntem: Çocuk Endokrinoloji polikliniğine başvuran 60 kız hasta çalışmaya dahil edildi. Hastalarınilk başvuruanamnez ve fizik muayene bulguları, kemik yaşı, serbest T4, TSH, folikülstimüle edici hormon (FSH), lüteinize edici hormon (LH), estradiol (E2), düzeyleri kaydedildi. Gerekli olgularda yapılmış olan luteinize edici hormon releasing hormon (LH-RH) testi sonucuna göre PT ve SPP olarak ayrıldı.Pandemi öncesi ve sırasında teknolojik araçların kullanımındaki farklılıklar kayıt edildi.
Bulgular: Santral puberte prekokslu olgularda daha yüksek vücut kitle indeksi (VKİ)(P=0.034), kemik yaşı (p<0.001), bazal LH (P<0.001), bazal FSH(P<0.001), bazal estradiol (P<0.001) düzeyi tespit edildi. Yaş ve kilo bakımından her iki grup arasında farklılık yoktu. Her iki grupta da pandemi öncesine göre kıyaslandığındateknolojik araçların (akıllı telefon, bilgisayar, televizyon)kullanımında belirgin artış vardı. Prematur telarşı olan olgularda pandemi öncesinde 2,54 ±0,65 saat/gün pandemi sırasında 6,22±1,25 saat/ gün idi (p<0,001).SPP'li olgularda pandemi öncesinde 2,7 ±0,46 saat/gün pandemi sırasında 7,36±1,36 saat/gün idi (p<0,001). Teknolojik araçların kullanımının ana sebebi okul dersleri idi (PT olan olgularda 4,6 ± 1,2 saat/gün, SPP' li olgularda 5±1,2 saat/gün p=0,393).
Sonuç: Çalışmamızda her iki grubumuzda da pandemi sonrasında teknolojik alet kullanımında belirgin artış olduğu görüldü.Ayrıca santral puberte prekoks başlangıç yaşının erkene kaydığını saptandı.Kilo,elekronik aletlerin kullanımın artışı gibi çevresel faktörlerin ergenlik başlangıcını ve ilerleyiş hızını tetiklediğini düşünüldü.
Anahtar Sözcükler: Puberte Prekoks, Koronavirüs,Pandemik

Introduction

Puberty is the period in which reproductive functions and sexual maturity are acquired in the transition from childhood to adulthood (1). The first sign of puberty is often breast development in girls. Acceleration in somatic growth, development in internal and external genital organs, formation of secondary sex characteristics, and acquisition of reproductive capacity occur during this period (2). Breast development in girls at 8 years, pubic hair at 8.5 years, menarche at 9 years, and pubic hair growth at 9 years in boys is defined as precocious puberty.

Early puberty is examined in 3 groups as central,

peripheral precocious puberty, and benign variant puberty. Central precocious puberty occurs as a result of early maturation of the Hypothalomo-Pituitary-Gonadal (HPG) axis.

The mechanism of action of the neuroendocrine and genetic factors providing pubertal development is still not known. Previous epidemiological studies showed that stress, metabolic rate, bone maturation, and environmental factors are effective in pubertal development as well as ethnic and genetic factors. Nutrition, chronic diseases, frequent infections, migration, environmental pollution, insecticides, antiandrogens, and exposure to estrogen-like endocrine disruptors can be counted among the environmental factors that affect puberty (3). It was shown in most previous studies that the timing of puberty is affected largely by genetic factors, and it is considered that the timing of puberty is determined by genes at a rate of 50-80% (4).

Other signs of sexual maturation in premature Thelarche girls are growth spurt and isolated breast development without acceleration in bone age.

The Coronavirus Disease, named "COVID-19", which emerged in December 2019 in the city of Wuhan, China, was reported to the World Health Organization on December 31, 2019. The Coronavirus is considered to be the most important healthcare issue of the 21st Century because it has had serious effects on almost every age group. Based on the understanding that the Coronavirus is contagious, social isolation and quarantine measures increased gradually (5). Social isolation paved the way for the emergence of various psychological disorders in individuals (6). It is already known that children spend more time with digital media and technological tools than previous generations today (7). The fact that children have to spend most of their time at home causes them to spend more time with technological tools. The use of the internet, technology, and playing digital games rates increased in individuals who stayed at home for a long time with social isolation and quarantine measures (8). The purpose of the present study was to investigate the increase and relationship of the frequency of SPP and PT in the COVID-19 pandemic process.

Materials and Methods

The findings of the 60 female patients between the ages of 2 and 8 who applied to the Pediatric Endocrinology Clinic with the complaint of the onset of puberty findings were evaluated. The study was approved by Başkent University, Medical and Health Sciences Research Board (Project No: E-94603339-604.01.02-69825) and was supported by Başkent University Research Fund.

The study was conducted by examining the file records of the patients who applied between November 2020 and June 2021 retrospectively. The duration of the children's use of technological tools in the pre- and post-pandemic periods was recorded. Anthropometric measurements were made in the morning on an empty stomach and with shoes and top clothes of the child were on. Bodyweight was recorded as "kg" and height as "cm". Bodyweight and height Standard Deviation Score (SDS) values were calculated (9, 10). Body Mass Index (BMI) was calculated with the formula BMI=Body Weight (kg) / Height (m)2 (11). The pubertal staging was performed according to Marshall and Tanner Method (12). The levels of follicle-stimulating hormone, LH, and E2 were recorded. LH-RH stimulation test results were used to differentiate between central prepubertal precocious and PT. Bone age was evaluated according to the Greulich-Pyle Method (13). Pituitary Magnetic Resonance (MR) imaging data of the patients with central precocious puberty were used.

Precocious Puberty: Breast development that initiated before the age of 8 accompanied by one or more of the symptoms (menstruation, pubic hair, bone age more than 2SDS ahead of the calendar age), increased gonadotropin (LH, FSH), and/or sex steroid (estradiol in females) levels was defined as the LH-dominant response to the LH-RH test.

Premature Thelarche: It was defined as the development of the breast with pubic hair and axillary hair without acceleration in bone age or growth, and FSH dominant response in the LH-RH test.

Statistical Evaluation

The SPSS 25.0 program was used for statistical analyses. A descriptive analysis was made for the parameters in the study. The categorical variables were shown as frequency and percentage, and the continuous variables were expressed as mean ± standard deviation. Whether the data showed normal distribution or not was evaluated with the Kolmogorov-Smirnov Test. The T-Test was used for the group comparisons of the normally distributed continuous variables, the Mann-Whitney Test was used for group comparisons of the non-normally distributed variables, and the Pearson Correlation Test was used to calculate the correlation coefficients. Statistical significance level was taken as $p < 0.05$.

Results

The characteristics of the cases are presented in Table 1. PT was detected in 76.6% (n=46) and SPP in 23.4% (n=14) of the Study Group. In the pituitary MRI examination of the 14 cases that had early puberty, a Pineal cyst was detected in 1 patient, 1 had Rathke-cleft cyst, and microadenoma was detected in 1 patient. Two of the 23 patients who underwent the LH-RH test were diagnosed as SPP.

Elevated BMI (P=0.034), bone age (p<0.001), height SDS (p=0.050), basal LH (P<0.001), basal FSH(P<0.001),

and basal estradiol (P<0.001) levels were found in the study. No differences were detected between the two groups in terms of age and weight.

When compared to the pre-pandemic period, significant increases were detected in the use of technological tools (smartphones, computers, televisions) in both groups. In cases with premature Thelarche, it was 2.54 ±0.65 hours/day before the pandemic and 6.22±1.25 hours/day during the pandemic (p<0.000). In cases with SPP, it was 2.7 ± 0.46 hours/day before the pandemic and 7.36±1.36 hours/day during the pandemic (p<0.000). The main reason for using technological tools was school lessons (4.6 ± 1.2 hours/day in cases with PT, 5±1.2 hours/day in cases with SPP, p=0.393).

A positive correlation was detected between the use of electronic devices, bone age, and body weight in the study group (Table 2).

Table 1: General characteristics of the study group

		Puberty	p
Age	6.52±0.83		0.246
Weight (kg)			0.499
Weight SDS	1.54±1.15	1.57±0.85	0.531
Height (cm)	127±8.5	131±11	0.202
Height SDS	1.21±1.1	1.44±1.64	0.050
Body Mass Index (kg/m^2)	18.72±3.4	19.4±1.02	0.034
BMI-SDS	1.1±1.07	1.4±0.4	0.080
Bone age (years)	8.02±1.24	9.7±1.4	<0.001
LH. IU/L	0.07± 0.05	1.5±1.4	<0.001
FSH. IU/L	1.4±0.88	4.4±2.2	<0.001
Estradiol (pmol/L)	11.45±7.2	22.6±17.9	<0.001
Post-pandemic exposure to technological devices (hours)	6.22±1.25	7.36±1.36	<0.001
Pre-pandemic exposure to technological devices (hours)	2.54 ±0.65	2.72±0.46	0.286

SDS: Standard Deviation Score, FSH: Follicle -Stimulating Hormone, LH: Luteinizing Hormone

Table 2: The correlation between electronic device use, body weight, and bone age

	p	r
Body weight	0.053	0.254
Bone age	0.001	0.495

Discussion

Puberty is a process representing the neuroendocrine changes occurring in the transition from childhood to adulthood and the accompanying changes in somatic and sexual functions. Although the onset of puberty is already well known, the timing of puberty varies. Genetic and environmental factors also play roles in its timing (14).

True puberty occurs with the activation of the HPG axis. Early activation of the axis is called SPP (15). All of our cases that were diagnosed with precocious puberty were SPP.

Advanced bone age and acceleration in growth are observed in the development of early puberty (16). In the present study, bone age, BMI, and height SDS were found to be higher in patients with SPP, similar to the literature data (16, 17).

The COVID-19 outbreak was classified by the World Health Organization as an "international public health emergency" on January 30, 2020, and was then declared a "global epidemic (i.e. pandemic)" on March 11, 2020. After the increasing number of cases in the entire world, the first COVID-19 case was detected in Turkey on March 11, 2020 (8). Social isolation and quarantine measures increased gradually with the understanding that the Coronavirus is infectious (5). The COVID-19 pandemic will inevitably have socioeconomic and psychological effects.

Recent studies examining various effects of the pandemic have gained momentum. It was found that 30.9% of adults and children were at high risk for Post-Traumatic Stress Disorders during the pandemic process (17). Again, a survey study that examined the prevalence of behavioral problems in school-age children during quarantine in the pandemic showed that children had positive social behaviors (10.3%), distress (8.2%), behavioral problems (7.0%), peer problems (6.6%), Attention Deficit - Hyperactivity Disorder (6.3%), and emotional problems (18). It is already known that children spend more time with digital media and technological tools than previous generations today. The fact that children have to spend most of their time at home causes them to spend more time with digital tools. The rates of using the internet, technology, and playing digital games increased in individuals who stayed at home for a long time because of social isolation and quarantine measures. In a recent study, the duration of students playing digital games was examined, and it was found that this time increased at significant levels during the pandemic when compared to the pre-pandemic period, and students played digital games on the phone the most (8).

In the present study, significant increases were detected in the use of technological tools (smartphone, computer, television) when compared to the pre-pandemic period. It was also remarkable that the mean age of our cases that had SPP was low and the cases were idiopathic. Stress, metabolic rate, bone maturation, and environmental factors play major roles in pubertal development as well as ethnic and genetic factors. Weight gain in the pandemic period

and increased exposure to digital tools may pose a risk factor for precocious puberty and premature Thelarche. A positive correlation was found in the study between the use of electronic devices and bone age and body weight.

As a conclusion, it was found in the present study that children spent more time with digital tools during the pandemic period when compared to the pre-pandemic period, and puberty symptoms started at a younger age. We think that long periods of inactivity in front of the screen may cause weight gain and early puberty. Opportunities must be initiated for children to spend sufficient time in the open air and meet their physical movement needs. Families, children, and teachers must be made aware of this issue. Attention must be drawn to activities that can keep children away from the screen, and they must not be allowed to be alone with the screen for a long time.

The present study is one of the rare studies that examine the relations between the COVID-19 pandemic process and SPP and PT in Turkish children. For this reason, studies that will address this issue with more cases and additional findings are still needed.

References

1.Partsch CJ, Heger S, Sippell WG. Management and outcome of central precocious puberty. ClinEndocrinol 2002; 56: 129-48.

2.Wheeler MD.Physicalchanges of puberty. Endocrinol Metab Clin North Am 1991;20: 1-14.

3.Parent AS, Teilmann G, JuulA, et al. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. Endocr Rev. 2003;24:668-93.

4.Sharma JC. The genetic contribution to pubertal growth and development studied by longitudinal growth data on twins. Ann Hum Biol. 1983;10:163-71.

5.Üstün Ç, Özçiftçi S. COVID-19 Pandemisinin sosyal yaşam ve etik düzlem üzerineetkileri: Bir değerlendirme çalışması. Anadolu Kliniği Tıp Bilimleri Dergisi, 2020;25:142-53.

6.Caoa, W, Fanga, Z, Houc, G, et al. The psychological impact of the COVID-19 epidemic on college students in China. Psychiatry Research,2020; 287: 1-5.

7.Vanderloo LM, Carsley S, Aglipay M,et al. Applying Harm Reduction Principles to Address Screen Time in Young Children Amidst the COVID-19 Pandemic. J Dev Behav Pediatr. 2020;41:335-6.

8.Aktaş B, Daştan NB. Covid-19 pandemisinde üniversite öğrencilerindeki oyun bağımlılığı düzeyleri ve pandeminin dijital oyun oynama durumlarına etkisi. Bağımlılık Dergisi,2021; 22: 129-38.

9.Neyzi O, Gunoz H, Furman A, et al. Weight, height, head circumferenceand body massindex references for Turkish children. Cocuk Sağlığı ve Hastalıkları Dergisi 2008; 51:1-14.

10.Neyzi O, Furman A, Bundak R, et al. Growth references for Turkish children aged 6 to 18 years. Acta Paediatr 2006;95:1635-41.

11.Bundak R, Furman A, Gunoz H,et al.Body massindex references for Turkish children. Acta Paediatr 2006; 95:194-8.

12.Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in girls. Arch Dis Child 1969; 44:291-303.

13.Atay Z, Turan S, GuranT,et al. The prevalence and risk factors of premature the larche and pubarche in 4- to8-year-old girls. Acta Paediatr 2012;101:71-5.

14.Bundak R, Darendeliler F, Günöz H,et al. Puberty and Pubertal Growth in Healthy Turkish Girls: No evidence for secular trend. J Clin Res Ped Endo 2008; 1:8–14.

15.Neely EK, Crossen SS. Precocious puberty. Curr Opin Obstet Gynecol 2014; 26:332-8.

16.Çatlı G, Erdem P, Anık A, et al. Clinical and laboratory findings in the differential diagnosis of central precocious puberty and premature the larche. Turk Pediatri Ars2015; 50:20-6.

17.Davico C, Ghiggia A, Marcotulli D et al. Psychological Impact of the COVID-19 Pandemic on Adults and Their Children in Italy. Front Psychiatry. 2021 Mar 12; 12:572997

18.Liu Q, Zhou Y, Xie X, et al. The prevalence of behavioral problems among school-aged children in home quarantine during the COVID-19 pandemic in china. J Affect Disord. 2021 Jan 15;279:412-6.

Received: 26 Oct 2021 | **Accepted:** 16 Nov 2021
DOI: 10.54005/geneltip.1014726

ORIGINAL ARTICLE

The Evaluation of the Relation Between Nasal Polyp Etiopathogenesis and the Amount of Biofilm

Nazal Polip Etiopatogenezi ve Biofilm Miktarı Arasındaki İlişkinin Değerlendirilmesi

[1]Kazım Bozdemir, [2]Elif Ersoy Çallıoğlu, [3]Bülent Ulusoy, [4]Selami Candan, [1]Serkan Serifler, [4]Nurcan Ozyurt Koçakoğlu, [2]Yuce İslamoğlu

[1]Yıldırım Beyazıt University, Faculty of Medicine, Department of Otorhinolaryngology Ankara

[2]Ankara Bilkent City Hospital, Otorhinolaryngology Clinic, Ankara

[3]Selçuk University, Faculty of Medicine, Department of Otorhinolaryngology, Konya

[4]Gazi University, Faculty of Sciene, Department of Biology, Ankara

Correspondence

Kazım Bozdemir, Üniversiteler Mahallesi 1604. Cadde No: 9, 06800, Çankaya/ ANKARA

E-Mail: kazimbozdemir@gmail.com

How to cite ?

Bozdemir K, Ersoy-Çallıoğlu E, Ulusoy B, Candan S, Serifler S, Ozyurt-Koçakoğlu N, İslamoğlu Y. The Evaluation of the Relation Between Nasal Polyp Etiopathogenesis and the Amount of Biofilm. Genel Tıp Derg. 2022;32(1):36-38.

ABSTRACT

Objective: To evaluate the effect of biofilm layer on polyp formation in nasal polyposis by comparing the amount of biofilm layer on polyp tissue and the normal mucosa.
Materials and Methods: This study is a prospective study. 14 patients who underwent functional endoscopic sinus surgery (FESS) for nasal polyposis were evaluated. Patients were had no history of previous FESS. Tissue samples were obtained from lower turbinate (Group 1 n:14) and from nasal polyp (Group 2, n:14) of the same nasal cavity. Biofilm presence was identified using scanning electron microscopic (SEM) morphological findings. In biofilm positive samples, the presence of biofilm in less than 25% of the surface area was classified as (+), between 25-50% as (++) , and over 50% as (+++).
Results: In Group 2, with SEM imaging, (+++) biofilm presence was detected in 9 patients and (++) biofilm was detected in 5 patients. In Group 1, no biofilm was detected 8 patients, while; (+++), (++), and (+) biofilm presence was detected in 1, 2, and 3 patients respectively. Significant difference was found between group 1 and group 2 with respect to the amount of biofilm according to SEM (p =0.000).
Conclusion: In samples, statistically significant difference was found between polyp tissue and normal mucosa in terms of the amount of biofilm. However, further studies with larger patient series are required in order to reach a definitive conclusion on the effect of biofilm on pathogenesis of polyp.

Keywords: Biofilm; Nasal Polyp; Microscopy, Electron, Scanning

ÖZ

Amaç: Polip dokusu ve normal mukoza üzerindeki biyofilm tabakası miktarını karşılaştırarak nazal polipoziste biyofilm tabakasının polip oluşumuna etkisini değerlendirmek amaçlanmaktadır.
Materyal ve Metod: Bu çalışma, prospektif bir çalışma olup nazal polipozis nedeniyle fonksiyonel endoskopik sinüs cerrahisi (FESS) uygulanan 14 hasta değerlendirildi. Hastalar, daha önce endoskopik sinüs cerrahisi geçirmemiş hastalardan oluşmaktaydı. Doku örnekleri, aynı nazal kaviteden alt konkadan (Grup 1, n:14) ve nazal polip dokusundan (Grup 2, n:14) alındı. Biyofilm varlığı, Scanning elektron mikroskobu (SEM) morfolojik bulgular kullanılarak tanımlandı. Biyofilm pozitif örneklerde, görüntülenen yüzey alanının %25'inden az sahada biyofilm varlığı (+), %25-50 arası (++) ve %50'den fazla sahada biyofilm varlığı (+++) olarak sınıflandırıldı.
Bulgular: Grup 2'de SEM görüntülemede 9 hastada (+++) biyofilm mevcudiyeti saptanırken 5 hastada (++) biyofilm tespit edildi. Grup 1'de ise 8 hastada biyofilm saptanmazken 1 hastada (+++), 2 hastada (++) ve 3 hastada (+) biyofilm varlığı saptandı. SEM bulgularına göre biyofilm miktarı açısından grup 1 ve grup 2 arasında anlamlı fark bulundu (p=0.000).
Sonuç: Örneklerde, polip dokusu ile normal mukoza arasında biyofilm miktarı açısından istatistiksel olarak anlamlı fark bulundu. Bununla birlikte, biyofilmin polip patogenezine etkisi konusunda kesin bir sonuca varmak için daha geniş hasta serileri ile yapılacak çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Biyofilm; Nazal Polip; Scanning-Electron Mikroskopi

Introduction

Biofilm, is the structure produced by micororganisms which attach to a surface and form a polymeric gelatinous layer (1). Biofilm may develop in vivo or in vitro on inorganic surfaces and can protect microrganism from osmotic stress, phage remnants, toxic components and antibiotics. Cells with this structure are more resistant to antimicrobial agents than planktonic cells and have barriers preventing contact with antimicrobial agents or decreasing susceptibility to them (2). Nasal polyps are benign mucosal protrusions with multifactorial causes and characterized by mucosal inflammation and enlarge towards lumen in nasal cavity. They have a pedunculated, gelatinous structure with smooth surface. The etiology of nasal polyps are multifactorial and although various factors such as infection, allergy, immunological factors, metabolic and hereditary diseases and autonomic dysfunction has been reported, etiology is still controversial.

There are many studies in the literature establishing that there is biofilm layer on nasal polyp tissue, which

regresses with treatment (3-5). Although these studies indicate that biofilm layer influences nasal polyposis treatment, the role of biofilm in the etiopathogenesis of nasal polyps still remains to be elucidated.

Therefore the aim of the present study was to evaluate the effect of biofilm layer on the development of polyp in patients with nasal polyposis by comparing the amount of biofim on polyp tissue with that on adjacent normal mucosal tissue in the same nasal cavity and hence excluding other additional factors which may lead to biofilm formation.

Materials and Methods

The present study is a prospective study carried out with the approval of local ethics committee (13.11. 2019, No.111) and informed consent of patients.

Subjects

14 patients (4F,10M) who underwent endocopic sinus surgery between 2019-2020 for nasal polyposis were evaluated. Detailed history was elicited and physical examination and radiological investigation was carried out. All patients had history of nasal steroid agent and antibiotherapy use. None had undergone endoscopic sinus surgery previously. Tissue samples at the size of 3x3mm were obtained during operation from nasal polyp tissue (group 2,study group) and normal inferior turbinate (group 1, control grup) of the same nasal cavity. Patients with immune supression, fungal sinusitis, and ciliary disorders such as granulomatous disease and cystic fibrosis were excluded from the study.

In Group 1 and Group 2 patients, biofilm was identified by using SEM morphological findings. The presence and amount of biofilm was compared between two groups.

Scanning Electron Microscopic (SEM) evaluation

For scanning electron microscopy, tissue samples were fixed with 2.5% glutaraldehyde (pH 7.2, sodium phosphate buffer) after they were rinsed three times in sodium phosphate buffer, dehydrated with from 50 to 100% alcohol series. After the dehydration, the samples were dried with hexamethyldisilazane (HMDS). Finally, they were mounted on aluminium SEM stubs. The stubs were covered with gold by using a sputter coater (Polaron SC 502) and samples were examined and photographed with a JEOL JSM 6060 LV SEM to determine biofilm presence in 10 kV.

Biofilm presence was identified using SEM morphological findings such as 3-dimensional structure, variation in the dimension of microorganisms embedded in polyp matrix, and residue of multiple layers of tissue and microorganism. 3x3mm size samples from nasal cavity were examined. With this examination, the presence of biofilm was evaluated and in biofilm positive samples, similar to previous studies, (6,7) the presence of biofilm in less than 25% of surface area was classified as (+), between %25-50 as (++) and over %50 as (+++).

Statistical Evaluation

The statistical analysis of the data obtained was carried out with SPSS Statistics program. As categorical variables were used, descriptive statistics were expressed with frequancy and percentage and in two by two comparisons chi-square test was used. $p<0.05$ value was considered significant for all results.

Results

14 patients who have undergone endoscopic sinus surgery were evaluated in the present study. There were 4 female and 10 male patients. Mean age of the patients was 46,62 (34-66). In SEM examination; in Grup 2, biofilm presence was detected at the degree of (+++) (Figure 1a-d) in 9 patients and at the degree of (++) in 5 patients (Table 1). In Group 1, no biofilm was detected in 8 patients, (figure 2a-d), 1 patient had (+++), 2 patients had (++), and 3 patients had (+) biofilm presence (Table 1). Significant difference was found between Group 1 and Group 2 in terms of amount of biofilm detected with SEM ($p=0.000$) (Table 1).

Table 1: Biofilms levels detected in nasal polyps and inferior turbinates

	SEM grading of biofilm formation				
Tissue sample	**None**	**+**	**++**	**+++**	**P***
Polyp (n=14)	0	0	5	9	0,000
Turbinate (n=14)	8	3	2	1	

*p value shows the results of Chi square test

Figure 1. A- D: (+++) biofilm formation in nasal polyps on SEM;

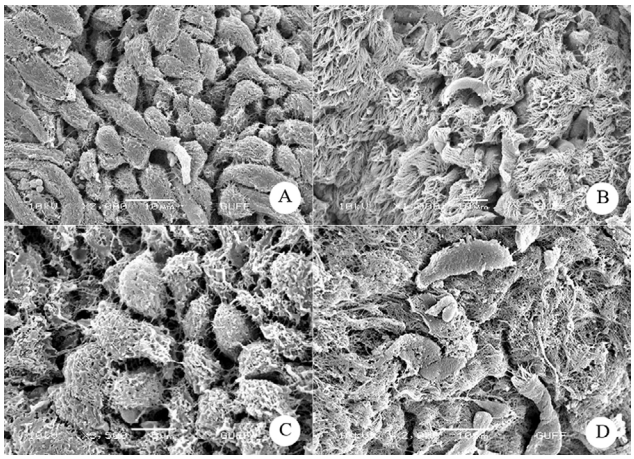
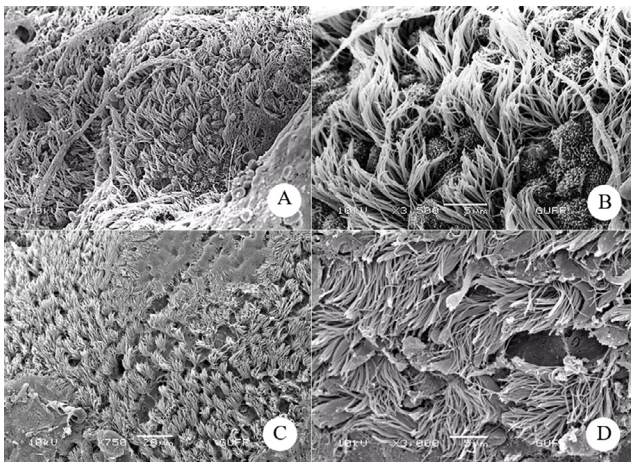


Figure 2. A-D: Absence of biofilm on SEM in the mucosa of the inferior turbinate.



Discussion

Biofilm may protect microorganisms from osteomic stress, phage residues, toxic compounds and antibiotics. They hence defend bacteria as well as leading to the enhancement of damage in host by producing endotoxins and other virulance factors. Many studies have demonstrated the presence of biofilm in at least %65 of human bacterial infections (8-11).

Biofilms can be detected in the majority of patients with chronic rhinosinusitis (12,13). Sanclement et al. (12) determined the presence of bi ofilm in 24 out of 30 affected individuals and in 0 out of 4 controls subjects. Galli et al. (13) have reported that there may be marked destruction of the ciliated epithelium in the biofilm development. The presence of biofilm on the mucosa of chronic rhinosinusitis patients can be a cause for the persistent tissue inflammation as well as antibiotic resistance and antimicrobial therapy failures (14). Recent research has revealed that the presence of the bacterial biofilms may predispose patients to worse outcomes after sinus surgery (15).

In addition, chronic sinusitis is most likely a manifestation of the interaction of several host and environmental factors with various microorganisms. Some studies have demonstrated that epigenetic influences could induce a disease's development (16).

The presence of biofilm on nasal polyp tissue was demonstrated in many studies (3-5) nevertheless, etiology of nasal polyposis and the role of biofilm tissue still remains to be elucidated. Zernotti et al. (3) determined the presence of biofilm in 9 of 12 patients who underwent operation for nasal polyposis and established that biofilms give rise to tissue hyperplasia by increasing nasal mucosa damage and the number of inflammatory cells. In many studies, it has been proposed that biofilm tissue may set the stage for development of nasal polyps (9-11).

Likewise, our findings also support the aforementioned suggestions as regards the association of biofilms with nasal polyps. In the present study, nasal polyp tissue and adjacent normal nasal mucosa tissue were obtained from the same nasal cavity for evaluation, which eliminated other factors which may lead to biofilm formation. This aspect of the study helped to support the role of biofilm in the etiopathogenesis of nasal polyposis from a different perspective compared to other studies on etiopathogenesis. In addition, in view of this association, it would be reasonable to state that we may be in need of modifications in the management strategies of nasal polyps.

Contrary to these studies, there are studies reporting that biofilm tissue has no effect on polyp etiology (17). Berezza et al. (17) reported that biofilms were be present in patients undergoing sinus surgery for chronic rhinosinusitis with nasal polyps and also in healthy controls.

Conclusion

According to our findings nasal polyps are associated with bacterial biofilm formations. However, the role of biofilms in the etiology of nasal polyps is unclear. Further studies with larger patient series rare required in order to reach a definitive conclusion on the impact of biofilm on the etiopathogenesis of polyp.

References

1.Leone S, Molinaro A, Alfieri F, et al. The biofilm matrix of Pseudomonas sp. OX1 grown on phenol is mainly constituted by alginate oligosaccharides. Carbohydr Res 2006;341: 2456 –61.

2.O'Toole G, Kaplan HB. Biofilm formation as microbial development. Annual Reviews in Microbiology, 2000; 49-79.

3.Zernotti ME, Angel Villegas N, Roques Revol M, Baena-Cagnani CE, Arce Miranda JE, Paredes ME. Evidence of bacterial biofilms in nasal polyposis. J Investig Allergol Clin Immunol 2010; 20: 380–5.

4.Mladina R, Poje G, Vukovi K, Risti M, Musi S. Biofilm in nasal polyps. Rhinology 2008; 46:302–7.

5.Korkmaz H, Ocal B, Tatar EC, et al. Biofilms in chronicrhinosinusitis with polyps: is eradicationpossible? Eur Arch Otorhinolaryngol 2014; 271:2695-702.

6.Tatar EÇ, Tatar I, Ocal B, et al. Prevalence of biofilms and their response to medical treatment in chronic rhinosinusitis without polyps. Otolaryngol Head Neck Surg 2012; 146:669-75.

7.Saylam G, Tatar EC, Tatar I, Ozdek A, Korkmaz H (2010). Association of adenoid surface biofilm formation and chronic otitis media with effusion. Arch Otolaryngol Head Neck Surg 2010; 136:550-5.

8.Vuong C, Kocianova S, Voyich JM, et al. (2010) A crucial role for exopolysaccharide modification in bacterial biofilm formation, immune evasion, and virulence. J Biol Chem 2010; 279:54881-6.

9.Tripathi A, Kern R, Conley DB, et al. Staphylococcal exotoxins and nasal polyposis: analysis of systemic and local responses. Am J Rhinol 2005; 19:327-33.

10.Seiberling KA, Conley DB, Tripathi A, et al. Superantigens and chronic rhinosinusitis: detection of staphylococcal exotoxin in nasal polyps. Laryngoscope 2005; 115: 1580-5.

11.Bernstein JM, Ballow M, Schliever PM, Rich G, Allen C, Dryja D. A superantigen hypothesis for the pathogenesis of chronic hyperplasic sinusitis with massive nasal polyposis. Am J Rhinol 2003;17: 321-6.

12.Sanclement JA, Webster P, Thomas J, Ramadan HH. Bacterial biofilms in surgical specimens of patients with chronic rhinosinusitis. Laryngoscope 2005; 115: 578-82.

13.Galli J, Calò L, Ardito F, et al. Damage to ciliated epithelium in chronic rhinosinusitis: what is the role of bacterial biofilms? Ann Otol Rhinol Laryngol 2008; 117:902-8.

14.Singh P, Mehta R, Agarwal S, Mishra P. Bacterial biofilm on the sinus mucosa of healthy subjects and patients with chronic rhinosinusitis (with or without nasal polyposis). J Laryngol Otol 2015; 129: 46–9.

15.Bendouah Z, Barbeau J, Hamad WA, Desrosiers M. Biofilm formation by Staphylococcus aureus and Pseudomonas aeruginosa is associated with an unfavorable evolution after surgery for chronic sinusitis and nasal polyposis. Otolaryngol Head Neck Surg 2006; 134:991-996.

16.Sanderson AR, Leid JG, Hunsaker D. Bacterial biofilms on thesinus mucosa of human subjects with chronic rhinosinusitis. Laryngoscope 2006; 116:1121-6.

17.Bezerra TF, Pádua FG, Ogawa AI, Gebrim EM, Saldiva PH, Voegels RL. Biofilm in chronic sinusitis with nasal polyps: pilot study. Braz J Otorhinolaryngol 2009; 75:788-93.

Received: 30 Nov 2021 | **Accepted:** 5 Jan 2022
DOI: 10.54005/geneltip.1022548

ORIGINAL ARTICLE

Our Experiences in Acute Arterial Embolism Treatment with Endovascular Techniques in Lower Extremity

Endovasküler Yöntemlerle Tedavi Ettiğimiz Akut Alt Ekstremite Emboli Deneyimlerimiz

[1]Mehmet Atay, [2]Onur Saydam

[1]Bahçelievler Devlet Hastanesi Kalp ve Damar Cerrahi Kliniği, İstanbul

[2]Tepecik Eğitim ve Araştırma Hastanesi, Kalp ve Damar Cerrahi Kliniği, Izmir

Correspondence

Mehmet Atay, Kocasinan Merkez, Karadeniz Cd. No:48, Bahçelievler Devlet Hastanesi Kalp ve Damar Cerrahi Birimi 34186 Bahçelievler/İstanbul

E-Mail: drataym@gmail.com

How to cite ?

Atay M, Saydam O. Our Experiences in Acute Arterial Embolism Treatment with Endovascular Techniques in Lower Extremity. Genel Tıp Derg. 2022;32(1):39-44.

ABSTRACT

Objectives: The study aims to retrospectively evaluate the 1-year results of endovascular treatment with rheolytic thrombectomy or catheter-directed thrombolytic infusion therapy in acute femoro-popliteal bypass graft occlusion.
Methods: The patients who had a history of femoro-popliteal by-pass operation and during their follow-up diagnosed with ipsilateral acute limb ischemia between 2016 and 2018 were included. The total of 13 patients were included and they were divided into two groups according to their treatment methods. (Rheolytic thrombectomy (RT): 8; catheter-directed thromolytic infusion (CDT): 5).
Results: There was no statistically significant difference between the two groups in terms of demographic data and Rutherford embolism classification. RT and CDT infusion primary patency values were 87.5% and 80% for 6 months, 75% and 60% for 12 months, respectively. Secondary patency values were found to be 100% in both groups for 6 months, and 87.5% and 80% for 12 months, respectively. There was no significant difference between the two groups in terms of primary and secondary patency.
Conclusion: Endovascular therapy can be preferred in the treatment of acute femoro-popliteal by-pass graft occlusion in selected patient groups due to its less invasiveness, early mobilization, and low mortality and morbidity rates compared to surgery.
Keywords: acute limb ischemia, catheter-directed thrombolytic therapy, rheolytic thrombectomy

ÖZ

Amaç: Çalışmada akut femoro-popliteal baypas greft oklüzyonunda reolitik trombektomi veya kateter aracılı trombolitik infüzyon tedavisi ile endovasküler tedavinin 1 yıllık sonuçlarını retrospektif olarak değerlendirmeyi amaçladık.
Yöntem: 2016-2018 yılları arasında daha önceden femoropopliteal baypas operasyonu geçiren ve takipleri sırasında ipsilateral akut ekstremite iskemisi tanısı alan 13 hasta çalışmaya dahil edildi. Hastalar tedavi yöntemlerine göre iki ayrı gruba ayrıldı. (Reolitik trombektomi (RT): 8; Kateter aracılı trombolitik infüzyonu (KAT): 5).
Bulgular: İki grup arasında demografik veriler ve Rutherford emboli sınıflaması açısından anlamlı fark yoktu. RT ve KAT infüzyon tedavi gruplarında primer patensi 6 ay için sırasıyla %87,5 ve %80, 12 ay için %75 ve %60 idi. Sekonder patensi her iki grupta 6 ay için %100, 12 ay için sırasıyla %87,5 ve %80 bulundu. Primer ve sekonder patensi açısından iki grup arasında anlamlı fark saptanmadı.
Sonuçlar: Akut femoropopliteal greft oklüzyonu tedavisinde cerrahiye göre daha az invaziv olması ve erken mobilizasyon, düşük mortalite ve morbidite oranları nedeniyle seçilmiş hasta grubunda endovasküler tedavi tercih edilebilir.
Anahtar Kelimeler: akut ekstremite iskemisi, kateter aracılı trombolitik, reolitik trombektomi

Introduction

Acute limb ischemia (ALI) is a clinical picture that threatens limb viability (1). ALI is characterized by sudden deterioration in limb perfusion which can develop on an embolic or thrombotic background is one of the important causes of morbidity and mortality (2,3).

Embolectomy surgery has survived without serious modifications since the development of the embolectomy catheter by Thomas Fogarty in 1963 and is still considered the gold standard treatment in ALI (4,5). However, with the developing technologies, less invasive endovascular methods have been begun to be used more frequently in ALI especially in patient with history of femoro-popliteal bypass (FPB) (2).

One of the most important reasons why alternative methods come to the fore in acute on chronic peripheral arterial disease patients is that conventional embolectomy cannot be performed selectively due to status of outflow arteries, especially in vessels below the knee, and as a result, complete revascularization cannot be achieved. Besides, the higher incidence of complications of surgical embolectomy in cases with accompanying chronic peripheral artery disease and the need for additional interventions for complete revascularization can be counted as another reason. (6).

Among the endovascular treatments, the most commonly used alternatives to embolectomy are percutaneous mechanical thrombectomy, rheolytic thrombectomy (RT), and catheter-directed thrombolytic (CDT) treatments (6). These treatment methods can be used individually or in combination with each other or with additional endovascular methods such as balloon angioplasty, stent implantation and/or atherectomy (7,8). Although endovascular methods have theoretical advantages, there are still debates regarding the safety and efficacy of the procedure in practice.

For this reason, in the present study, it is aimed to present the early results of patients with FPB history and were diagnosed ipsilateral acute lower extremity ischemia by imaging methods and were therefore treated with RT and/or CDT.

Materials and Methods

Thirteen patients with ALI due to acute FPB graft occlusion and underwent endovascular treatment with RT or CDT between 2016 and 2018 were included. The patients' clinical information, demographic data and past intervention histories were scanned retrospectively from files and electronic media.

The study protocol was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (Approval Date: 15/11/2021, No: 2021/494).

Patients older than 18 years of age with a history of FPB operation and had 4 or more symptoms or signs according to Rutherford classification as a result of acute FPB graft occlusion were included in the study. Patients with motor and sensory deficits and irreversible ischemia, patients with an estimated duration of intraluminal thrombus older than 14 days, patients with contraindications to antiplatelet therapy, anticoagulants or thrombolytic drugs, and patients with life-threatening contrast allergy were excluded from the study.

In addition to clinical evaluation, color Doppler ultrasonography (CDU) was initially performed for the patients. Computed tomography angiography (CTA) imaging was applied to patients whose CDU results were significant in terms of acute FPB graft occlusion. (Figure-1)

After the diagnosis of acute FPB graft occlusion, all patients were admitted to the intensive care unit (ICU). A loading dose of 5000 IU of unfractionated heparin was given and infusion was initiated to keep the activated partial thromboplastin time at twice the control level. Fluid resuscitation was also initiated with a dose of 100 ml/hour. Patients were followed up at 6-hour intervals with hemogram, coagulation factors, kidney, and liver markers.

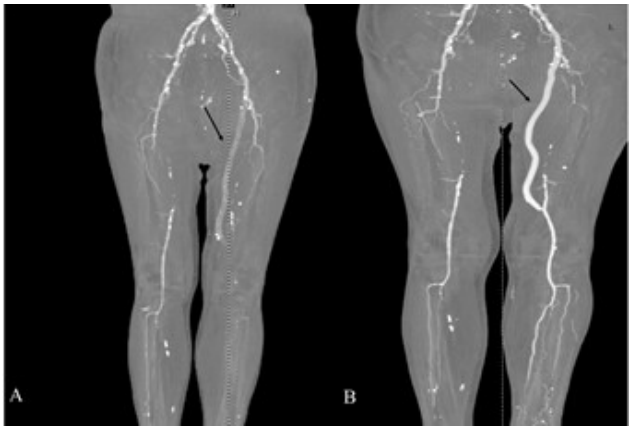
Emergency intervention was planned for the patients, and they were processed on the same day they were admitted to the hospital. All patients underwent endovascular treatment either with RT or CDT infusion.

The patients were placed in the supine position. All procedures were performed under hemodynamic monitoring and local anesthesia. Arterial intervention in the patients was planned as retrograde crossover from the contralateral leg.

After the sheath was introduced under the guidance of ultrasonography, the procedure was initiated with the control of activated coagulation time. The graft occlusion was passed using a 0.035 hydrophilic guidewire with a guidance of 5-Fr straight tip or angled guide catheter.

Thrombolytic infusion was performed as continuous infusion with valved Infusion Catheters (The Cragg-McNamara™ Micro Therapeutics Infusion Catheter, Medtronic, USA) or with "power pulse" mode of RT (AngioJet™, Boston Scientific, USA) according to operator preference and experience. (Figure-2)

Figure-1. 3D examination image in angiographic computed tomography. A: Pre-operative view of total occluded graft. B: endovascular procedure and 12th month graft appearance in the follow-up period



Under "power-pulse" mode device make direct thrombolytic infusion into the thrombus in order to make aspiration more efficient in patients who underwent RT. For this, it was prepared to be given during RT with 10 mg of tPA in 50 mL of physiological saline. During the procedure, arteriography was performed intermittently to localize the thrombus. The RT duration did not exceed 480 seconds to prevent hemolysis and other complications. In case of residual thrombus in the final angiogram, the procedure was not prolonged and selective thrombolytic infusion was administered for 24 hours against residual thrombus.

In patients who underwent CDT, alteplase (tPA, Actilyse, flacon 50mg, Boehringer Ingelheim Gmbh, Ingelheim am Rhein, Germany) was given as a bolus by diluting 10 mg in sheath exactly with isotonic (9). 10 minutes later thrombolysis, the catheter was inserted into the thrombus and tPA infusion of 1 mg/h was started. The laboratory's normal reference range of fibrinogen was 170-420 mg/dL. Below 170 mg/dL, the tPA dose decreased to 0.5 mg/h. Below 100 mg/dL, tPA infusion was stopped. Control arteriography was performed at the end of the first 24 hours. Patients with residual thrombus were given an additional 12 hours of thrombolytic infusion (Figure-3).

Figure-2. Patient treated with endovascular methods. A: pre-operative angiographic view, PTFE graft total occluded, B: The lesion was crossed with a wire, after the thrombolytic infusion, aspiration and thrombectomy with the help of a catheter, C: Presence of residual thrombus in post-catheter imaging, D: Balloon angioplasty into the graft, 1: proximal segment, 2: Distal segment

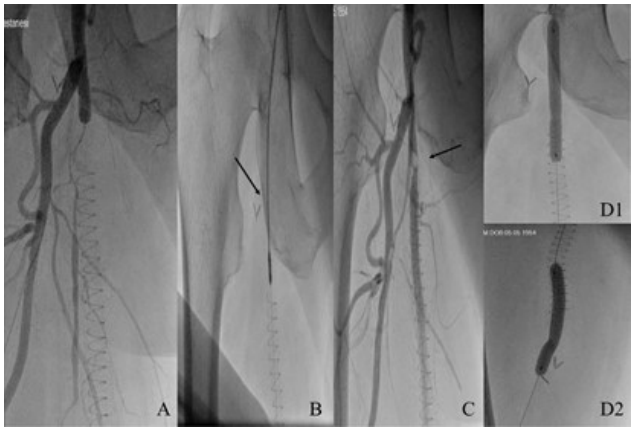
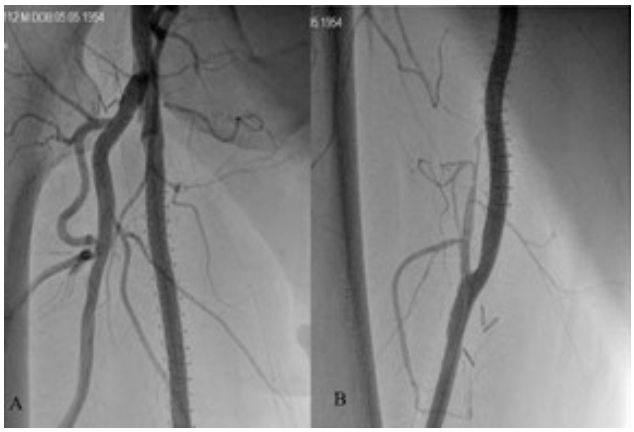


Figure-3. Control angiography after completion of 24-hour thrombolytic infusion, A: proximal segment, B: distal segment



At the end of the control arteriography after both procedures, in the presence of severe residual flow-limiting stenosis, balloon angioplasty was performed, and in cases where it was not sufficient, self-expandable nitinol stent implantation was performed.

Post-operative follow-up

Low molecular weight heparin was administered routinely for 5 days post-operatively in all patients. In addition, acetylsalicylic acid (ASA) 100 mg was started to be administered. Vitamin K antagonist was initiated in patients with atrial fibrillation. After discharge dual antiaggregant therapy (clopidogrel 75mg, ASA 100mg) was continued in patients who were not started on a vitamin K antagonist.

The patients' follow-ups at the 3rd, 6th and 12th months were recorded.

The primary endpoint of the study was the technical success of endovascular therapy, defined as complete or near-complete revascularization (classified as the completing the revascularization without any residual stenosis greater than 30 % or flow-limiting stenosis at the final angiography) of the occluded artery, and the patency rate of the target vessel at the end of 12 months (primary patency, PP).

Clinical success, defined as improvement of the Rutherford classification in one or more classes compared to the preprocedural Rutherford classification at the first month follow-up, was determined as mortality and unplanned amputation within the first 30 days and patency (secondary patency, SP) of the target vessel after the need for additional intervention within 12 months.

Statistical Analysis

The NCSS (Number Cruncher Statistical System, 2007, Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) as well as the Mann Whitney U test were used for the comparison of non-normally distributed parameters between the two groups. The Pearson Chi-Square test was used to compare qualitative data. Significance was evaluated at $p<0.001$ and $p<0.05$ levels.

Results

A total of 13 patients, 11 (84.6%) males and 2 (15.4%) females, who had a previous FPB and developed ALI during follow-up were included in the study. Of the 13 patients included in the study, 8 patients underwent RT, while 5 patients underwent CDT.

The mean age of the patients participating in the study was 64.5 (±7.4) years. There was no significant difference between the mean age of the patients who underwent RT or catheter-mediated thrombolysis ($p=0.87$). There was no significant difference between the groups in terms of demographic data or comorbidities. Demographic data and additional diseases of the patients included in the study are given in Table 1.

Table 1. Patients Demographics and Comorbidities

Age(y)	CDT (n=5) (38.5%)	RT (n=8) (61.5%)	P value
	64±8.7	64.8±7.1	0.87
Males	5 (100%)	6(75%)	0.49
Hypertension	4 (80%)	6(75%)	0.84
Hyperlipidemia	5(100%)	4(50%)	0.11
CAD	4(80%)	4(50%)	0.57
DM	4(80%)	2(25%)	0.10
COPD	2(40%)	5(62.5%)	0.59
AF	1(20%)	2(25%)	0.84
Current Smoker	5(100%)	6(75%)	0.49

CDT: catheter directed thrombolysis, RT; rheolytic thrombectomy, Y; year, CAD; coronary artery disease, DM; diabetes mellitus, COPD; chronic obstructive pulmonary disease, AF; atrial fibrillation

When the patients were evaluated according to Rutherford acute ischemia criteria at the time of admission to the emergency department, 4 patients

were classified as 2a (30.8%) and 9 patients as 2b (69.2%). There was no significant difference between the groups in terms of Rutherford criteria (p=0.57).

All patients included in the study had a history of unilateral FPB with an 8mm ring polytetrafluoroethylene (PTFE) graft. Seven patients had a history of right lower extremity bypass, while 6 patients had a history of left lower extremity FPB (p=0.72). The mean FPB age was 45.9±14.9 months. There was no significant difference between the groups in terms of FPB age (p=0.82).

The median time from the onset of ALI symptoms to the treatment of the patients was determined as 4 (min-max 2-8) hours. There was no significant difference between the groups in terms of time until the procedure (p=0.31).

An additional dose of thrombolytic infusion was administered to 4 patients who underwent RT because they had residual thrombi.

In addition to RT and CDT treatments, endovascular intervention was performed in 5 patients (38.5%) at the end of the procedure. Flat balloon angioplasty was performed on the proximal and distal anastomosis sites in four patients, while self-expandable stent implantation was performed on the distal anastomosis site in one patient. There was no significant difference between the two groups in terms of the need for additional intervention.

The technical success rate was determined as 92.3% (n=12). Surgical embolectomy as well as endarterectomy and patchplasty procedures were performed in the proximal and distal anastomosis regions in one patient whose thrombus could not be resolved despite the application of thrombolytic infusion for 24 hours after RT. There was no significant difference between the groups in terms of technical success (p=0.41).

The mean hospital stay was found to be 56.3±16.5 hours. There was no significant difference between the groups in terms of length of stay (p=0.06). In the subgroup analysis, patients admitted with Rutherford 2a (42±15.5) had a shorter hospital stay compared to those presenting with Rutherford 2b (62.7±13.1) (p=0.03).

Total PP at 6th and 12th months was 92.3% and 69.2%, respectively. When the patients who underwent RT and CDT were compared, the 6-month PP values were 87.5% and 80%, while the 12-month PP values were 75% and 60%. There was no statistically significant difference between the groups in this respect (p=0.58). Total SP at 6th and 12th months was 100% and 84.6%, respectively. When the patients who underwent RT and CDT were compared, 6-month SP values were 100% in both groups, while 12-month SP values were 87.5% in the RT group and 80% in the CDT group. There was no statistically significant difference between the groups (p=0.73). (Table 2)

Table 2. Kaplan-Meier's estimates of early and late outcome in overall series

	6 months	12 months	P value
Overall Primary Patency	92.3%	69.2%	
Primary Patency			
CDT	80%	60%	0.58
RT	87.5%	75%	
Overall Secondary Patency	100%	84.6%	
Secondary Patency			
CDT	100%	80%	0.73
RT	100%	87.5%	

CDT: catheter directed thrombolysis, RT; rheolytic thrombectomy

Although no major hemorrhagic complication was encountered in any patient, localized hematoma and ecchymosis were observed at the vascular sheath insertion site, which did not require interruption of the thrombolytic infusion. No additional surgical intervention was performed for this condition, and ecchymosis and hematoma conditions of the patients regressed in the follow-ups.

Hematuria was observed in 5 (62.5%) patients who underwent RT. And it was regressed with fluid resuscitation. Bradycardia and acute renal failure were not observed in any patient. An unplanned amputation was performed in a patient who underwent RT. This patient came in with Rutherford 2b. After the procedure, distal metatarsal amputation was planned. However, below-knee amputation was performed due to defects in wound healing after amputation.

No mortality was observed during the study.

Discussion

In the current study we found that endovascular procedures in acute lower extremity graft occlusions can be performed with high success rates and comparable primary patency rates regardless of the type of endovascular procedure performed.

There are also studies on patients with acute on chronic limb ischemia and treated with endovascular manner showing 85-97% technical success rates (10, 11). One of the reasons for the high technical success achieved in the current study can be the short latency duration for the intervention. Early intervention can lead to early initiation of thrombolytic therapy which may increase the chances of success (6). There are also studies which showed lower technical success rates as 38-70% (12, 13). The low success rate in these studies may be explained by the length of time to initiate the operation and the smaller PTFE grafts diameter.

Thrombolytic infusion, can be given directly through venous and arterial routes via catheters, or it can be given into the lesion through RT catheter. In a study by Lian et al, primary patency was 60% for 6 months and 76.67 for 12 months in patients treated with CDT method. Again in the same study, it was stated that

CDT method can be used safely and effectively in primary treatment, especially for small vessels in acute arterial thromboembolism (14). However, Vakhitov et al followed the patients they included in their study for an average of 126.3 months. In the long-term follow-up, the CDT method was reported as insufficient and it was reported that additional methods may be needed to provide adequate distal perfusion (15).

Although the symptoms regressed in 9 patients who underwent the procedure, balloon angioplasty was applied to the stenosis in the proximal and distal FPB graft in 4 patients with additional lesions, and post-procedure stent was applied in 1 patient. There was no statistically significant difference between the two groups in terms of the need for additional intervention.

Braitwaithe et al. reported that they treated 50% of the patients within 4 hours with bolus dose tPA in the treatment of acute ischemia (16). Gürsoy et al. administered a bolus dose of tPA on the lesion in a patient who underwent surgical embolectomy 6 times within 2 days and developed distal embolism again, and reported that this method was applicable in a selected patient group (17). In our experience, bolus administration of high-dose tPA into the lesion will accelerate thrombolysis and patients with acute leg ischemia will be treated more easily and quickly compared to surgery. The catheter can be embedded in the thrombus in order to provide full benefit to the patients and to make the thrombolytic infusion at the maximum concentration, especially during the continuation of the treatment. In addition to early and accurate diagnosis in the treatment of acute embolic diseases, the chosen treatment method is also determinative on mortality and morbidity (2, 7).

Symptom onset and processing times were similar in both groups, and there was no statistically significant difference between them. Considering the treated patients, the best results were seen in patients who applied and were processed in the first 6 hours after symptom onset (18). In case of perfusion, especially after a long ischemia period, compartment syndrome and related hypoesthesia of the foot and paresis of the finger may develop due to the development of reperfusion damage. In addition, acidosis, acute renal injury (ARI), pulmonary insufficiency, extremity loss and possible death may develop (7, 19). No patients in the study group developed compartment syndrome, ARI, or acidosis.

Although we did not observe these complications in our patients. Those complications can be observed after endovascular procedures especially after RT. In the study by Odeh et al, including a total of 243 patients, the need for embolectomy and the incidence of compartment syndrome were lower in the group supported by RT. It was also reported that less bleeding, shortened lysis time, and a decrease in hospitalization time were detected (20). In another study on venous system thrombi, it was reported that catheter-mediated thrombolytic and rheolytic thrombectomy may increase hemolysis and cause ARI (21).

Although the success of endovascular thrombolysis techniques is shown to be higher in native vessels in some studies, higher technical success rates are observed in femoropopliteal bypass grafts compared to native vessels, similar to our study (15, 22).

There is no clear evidence in the literature in favor of thrombolysis or surgery (23). Looking into the literature, 30-day amputation rates are around 10-30% when new treatment methods are included and thrombolysis is recommended, if it isbe performed without delay in native artery ischemia that occurred in less than 14 days (9). It is thought that endovascular intervention reduces the complication rate because it allows rapid diagnosis and treatment in patients.

Small sample size and the retrospective design are the major limitations of the study.

Conclusion

Endovascular therapy can be preferred in the treatment of selected patient groups due to its less invasiveness compared to surgery, early mobilization, and low mortality and morbidity rates. Although it is not possible to make a choice between surgical or endovascular methods, we believe that detailed studies are needed to make a decision on this issue.

References

1.Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg 2007;45(Suppl S):S5–67.

2.Hage AN, McDevitt JL, Chick JFB, et al. Acute Limb Ischemia Therapies: When and How to Treat Endovascularly. Semin Intervent Radiol. 2018;35(5):453-460. doi: 10.1055/s-0038-1676321.

3.Atay M, Gürsoy M, Bakuy V, ve ark. Akut üst ekstremite arteryel embolileri: 2 yıllık klinik deneyimimiz. Bakırköy Tıp Dergisi 2016;12(4):202-206.

4.T.J. Fogarty, J.J. Cranley, R.J. Krause, et al. A method for extraction of arterial emboli and thrombi Surg Gynecol Obstet, 116 (1963), pp. 241-244.

5.Umemoto T, Hirasawa K, Matsuda Y, et al. A novel fully percutaneous thrombectomy technique with balloon occlusion guiding catheter and over-the-wire Fogarty catheter for acute limb ischemia. Journal Of The American College Of Cardiology 2017;70(18): Suppl B, pp:8149

6.Olinic DM, Stanek A, Tătaru DA, et al. Acute Limb Ischemia: An Update on Diagnosis and Management. J Clin Med. 2019;8(8):1215. Published 2019 Aug 14. doi:10.3390/jcm8081215

7.McNally MM, Univers J. Acute Limb Ischemia. Surg Clin North Am. 2018 Oct;98(5):1081-1096. doi: 10.1016/j.suc.2018.05.002. PMID: 30243449.

8.Bayır A, Ak A. Acil olgularda trombolitik tedavi. Genel Tıp Derg 2003; 13: 81-88.

9.Working Party on Thrombolysis in the Management of Limb Ischemia. Thrombolysis in the management of lower limb peripheral arterial occlusion--a consensus document. J Vasc Interv Radiol. 2003;14(9 Pt 2):S337-49. doi: 10.1016/s1051-0443(07)61244-5. PMID: 14514841.

10.Poursina O, Elizondo-Adamchik H, Montero-Baker M, et al. Safety and efficacy of an endovascular-first approach to acute limb ischemia. J Vasc Surg. 2021 May;73(5):1741-1749. doi: 10.1016/j.jvs.2020.10,002. Epub 2020 Oct 15. PMID: 33068768.

11.Koraen L, Kuoppala M, Acosta S, et al. Thrombolysis for lower extremity bypass graft occlusion. Journal Of Vascular Surgery

2011;54(5): 1339-1444

12.Vesely TM, Idso MC, Audrain J, et al. Thrombolysis versus Surgical Thrombectomy for the Treatment of Dialysis Graft Thrombosis: Pilot Study Com - paring Costs. Journal of Vascular and Interventional Radiology 1996;7(4):507-512

13.Yılmaz G, Sincer İ, Erdal E. Catheter-directed intra-arterial thrombolysis for lower extremity arterial occlusions. ol J Cardiol 2019; 22: 54-9. DOI: 10.14744/ Anatol J Cardiol 2019. 63296

14.Lian WS, Das SK, Hu XX, et al. Efficacy of intra-arterial catheter-directed thrombolysis for popliteal and infrapopliteal acute limb ischemia. J Vasc Surg 2020;71(1):141-148

15.Vakhitov D, Suominen V, Korhonen J, et al. Independent factors predicting early lower limb intra-arterial thrombolysis failure. Ann Vasc Surg 2014; 28: 164-9.

16.Braithwaite BD, Buckenham TM, Galland RB, et al. Prospective randomized trial of high-dose bolus versus low-dose tissue plasminogen activator infusion in the management of acute limb ischemia. Thrombolysis Study Group. Br J Surg. 1997 May;84(5):646-50. PMID: 9171752.

17.Gürsoy M, Bakuy V, Atay M, et al. Hybrid approach in patients with recurrent brachial artery embolism. Ulus Travma Acil Cerr Derg 2014;20(1):56-58

18.Saraç A, Akan H, Demirağ MK, ve ark. Akut Atardamar Tıkanıklıklarında Lokal Trombolitik Tedavi. J. Exp. Clin. Med. 2004; 21(2):78-83

19.Yetkin U, Gürbüz A. Akut Arter Tıkanmalarına Genel Bakış. Van Tıp Dergisi 2002;9(1)

20.Odeh K, Ullah R, Hashim H, et al. Comparative Study on Catheter-Directed Thrombolysis – Continuous Tissue Plasminogen Activator Versus Angiojet Catheter Power Pulse Spray Rheolytic Thrombectomy Outcome Study: Single-Center Experience. Journal of the American College of Cardiology. 2017;69(11):2016. doi:10.1016/s0735-1097(17)35405-0

21.Shen Y, Wang X, Jin S, et al. Increased risk of acute kidney injury with percutaneous mechanical thrombectomy using AngioJet compared with catheter-directed thrombolysis. Journal of Vascular Surgery: Venous and Lymphatic Disorders 2019;7(1):29-37

22.Plate G, Oredsson S, Lanke J. When is thrombolysis for acute lower limb ischemia worthwhile? Eur J Vasc Endovasc Surg 2009; 37: 206-12

23.Darwood R, Berridge DC, Kessel DO, et al. Surgery versus thrombolysis for initial management of acute limb ischemia. Cochrane Database Syst Rev. 2018 ;10;8(8):CD002784

Received: 21 Nov 2021 | **Accepted:** 21 Jan 2022
DOI: 10.54005/geneltip.1026585

ORIGINAL ARTICLE

Retrospective Analysis of Childhood Poisonings

Çocukluk Çağı Zehirlenmelerinin Geriye Dönük Olarak İncelenmesi

[1]Emine Beyaz, [2]Sonay Gökçeoğlu

[1]Muş Alparslan Üniversitesi, Sağlık Bilimleri Fakültesi, Hemşirelik Bölümü, Muş/ Türkiye

[2]Şanlıurfa İl Sağlık Müdürlüğü, Şanlıurfa/ Türkiye

Correspondence

Emine Beyaz, Muş Alparslan Üniversitesi, Sağlık Bilimleri Fakültesi, Hemşirelik Bölümü, Muş/ Türkiye

E-Mail: emine.egokceoglu@gmail.com

How to cite ?

Beyaz E, Gökçeoğlu S. Retrospective Analysis of Childhood Poisonings. Genel Tıp Derg. 2022;32(1):45-48.

Note:

The study was presented as an oral presentation at the 1st International Congress of Innovative Approaches in Nursing in Erzurum on June 20-22, 2019.

ABSTRACT

Objective: The aim is to determine the extent of the types of poisoning and the factors influencing them.

Materials and Methods: The study was carried out between January and July of 2019. Hospital records of 107 cases who had presented to the pediatric emergency department for poisoning were retrospectively reviewed. In the analysis, descriptive statistics and the chi-square tests from univariate analyses were used. The SPSS 20.0 package program was used to analyze the data.
Results: 49.5% of the cases were girls, and 5.6% were villagers. 51.4% of poisonings occurred in spring, 68.2% were oral, drugs (%51.4) were the most common poisoning agents. Poisoning of the drugs were observed 17.4% less frequently in the age group 6-12 years than in other age groups, 60.3% less frequently in those who lived in the city center than in those who lived in the district, and 75.3% less frequently in those who took the drug orally than by other means ($p<0.05$). Poisoning occurred in 33.6% between 12:00-17:59. When analyzed by age group, poisonings are most common in the age group 0-5 years with 62.6%. Symptoms developed after poisoning in 72.0% of cases. In cases of poisoning, supportive treatment was the most commonly applied method, with 79.4%. There was no mortality due to poisoning in any of the cases.
Conclusions: Drug poisoning was detected in the majority of the cases. The risk of drug poisoning was lower in children living in rural areas and the age group 6-12 years.

Keywords: Child, pediatric nursing, poisoning, prevention

ÖZ

Amaç: Zehirlenme tiplerinin düzeyini ve etkileyen faktörleri belirlemek amaçlanmıştır.
Gereç ve Yöntem: Araştırma Ocak ile Temmuz 2019 ayları arasında yapılmıştır. Çocuk acil servise zehirlenme nedeniyle başvuran 107 olgunun hastane kayıtları geriye dönük olarak incelenmiştir. Analizde tanımlayıcı istatistikler ve tek değişkenli analizlerden Ki-Kare testi kullanılmıştır. Veriler SPSS 20.0 paket programı kullanılarak analiz edilmiştir.
Bulgular: Olguların %49.5'i kız cinsiyet, %5.6'sı köy ikametlidir. Zehirlenmelerin %51.4'ü ilkbaharda, 68.2'si oral yolla, %51.4'ü ilaçlarla gerçekleşmiştir. İlaçlar ile zehirlenme 6-12 yaş grubunda %17.4 ile diğer yaş gruplarından daha az; merkezde yaşayanlarda %60.3 ile ilçede ikamet edenlerden, etkeni oral yolla alanlarda %75.3 ile diğer yollarla alanlardan daha fazla görülmüştür ($p<0.05$). Zehirlenmeler %33.6 ile en fazla 12.00-17.59 saatleri arasında gerçekleşmiştir. Yaş gruplarına göre incelendiğinde %62.6 ile en fazla 0-5 yaş grubu zehirlenmelerle karşılaşılmaktadır. Olguların %72.0'ında zehirlenme sonrası semptom gelişmiştir. Zehirlenmelerde %79.4 ile en fazla destekleyici tedaviye başvurulmuştur. Zehirlenme sonucu hiçbir olguda ölüm yaşanmamıştır.
Sonuçlar: Olguların çoğunluğunda ilaçlar ile zehirlenme görülmüştür. Kırsalda yaşayan ve 6-12 yaş grubunda olan çocuklarda ilaçla zehirlenme riski daha düşüktür.

Anahtar kelimeler: Çocuk, çocuk hemşireliği, zehirlenme, önleme

Introduction

Poisoning endanger public health that requires rapid diagnosis and treatment and can lead to death. They frequently occur in childhood (1,2). High sensitivity at a young age and incomplete neuromotor development make poisoning important in children (3-5).

Poisoning cases also account for a significant proportion of emergency department admissions. According to the American Poison Control Center, more than two million children contact pediatric emergency services each year due to poisoning (6). Drug intoxication is the most common cause of poisoning. While the negative effects of drugs in adults are due to the use of drugs for suicidal purposes, they are due to accidents in the age group 1-5 years (7-9). Caustic/corrosive substance poisoning, particularly with cleaning products, is also frequent in children under five years of age (10). The most common causes of accidental poisoning are that the chemicals and medicines in the house are easily accessible to children, that there are too many medicines in the house, that some medicines are marketed in flashy colors and styles, that the people taking care of the child are not adequately trained, that chemical products used in agriculture are applied without adequate knowledge and that stoves and water heaters are used carelessly (11).

In cases of poisoning, early diagnosis is important to maintain a good general condition and prevent death.

Therefore, a differential diagnosis of poisoning should be established when unexplained signs and symptoms are present in one-year-old infants (12). When taking the medical history in poisonings, the toxic agent kind, amount, method, and time of administration, pre-existing disease status, poisoning symptoms, treatment modalities, and the cause of poisoning (accident, suicide) should be emphasized (13). Although children presenting with poisoning are usually asymptomatic, life-threatening findings can rarely be observed (14). In poisonings, the fundamental approach is to avoid or minimize the toxic substance's absorption, alter its metabolism, accelerate its excretion, administer systemic antidotes, and provide symptomatic treatment (15).

The causes, forms, and agents of poisoning may be influenced by age, gender, sociocultural characteristics, months, and seasons (16). This study aimed to determine the extent of the types of poisoning and the factors influencing them.

Method

Research design

The study has a descriptive design. It was conducted at State Hospital between January and July 2019. The study examined 107 children aged 0-18 years who were admitted to the hospital with a diagnosis of poisoning (excluding suicides) between January and July 2019. Due to missing data in the file records, 43 cases could not be included in the study. A structured information form was used to acquire data from hospital records.

Data collection

The information form examined age, gender, place of residence, the season of admission to the hospital, time of exposure (from 00:00 at night, divided into 6-hour periods), time of complaints, time of admission to hospital, type of toxic substance intake, agent of poisoning, presence of symptoms of poisoning, methods of treatment.

Study variables

The dependent variable of the study is the type of poisoning in the cases. Independent variables are age, gender, place of residence, the season of admission to the hospital, time of the poisoning, and route of ingestion of toxic substances.

Statistical analysis

Descriptive statistics (number, percentage) and the chi-square test from univariate analyses were used in the study. The SPSS 20.0 package program was used to analyze the data.

Ethical approval and cost

The Ethics Committee of University (issue 28/03/2019-E.7185) and the relevant hospital (issue 20/06/2019-5220) gave written approval for the study. The ethical principles of "Confidentiality and Protection of Confidentiality" and "Respect for Autonomy" were met. The researcher bore all costs of the study.

Results

62.6% of the cases were in the age group 0-5 years, 49.5% were girls, and 50.5% were boys. 72.9% of patients lived in the city center, 27.1% lived in villages and districts. 51.4% of poisonings were observed in the spring season. Autumn data could not be assessed in the study because they were not contained in patient records. Poisoning occurred in 33.6% between 12:00-17:59. It was found that the time elapsed between exposure to the agent (the time of poisoning) and the onset of symptoms was (0- min). Admission to the hospital was made within an average of 100.4 minutes after poisoning. At the earliest, the admission to the hospital was made after 5 minutes at the earliest and 1440 minutes at the latest. 68.2% of cases were exposed to toxic substances orally, 30.8% by inhalation, 0.9% by the skin and mucous membranes.

48.6% of poisonings were non-pharmacological; pharmacological agents caused 51.4%. Poisoning of drugs are observed 17.4% less frequently in the 6-12-year-old age group than in the other age groups, 60.3% in those living in the city center and more frequently in those living in the district, 75.3% in those taking the agent orally than in those receiving it by other means ($p<0.05$) (Table 1).

The most common three agents in the distribution of drug poisonings are analgesics-antipyretics with 32.7%, cardiac drugs with 18.2%, and antibiotics with 10.9% (Table 2).

Table 2. Distribution of drug poisoning

Drugs	*N*	*%*
Analgesic-antipyretic	*18*	*32.7*
Antiepileptic	*4*	*7.3*
Cardiovascular	*10*	*18.2*
Psychiatric drugs	*5*	*9.1*
Respiratory system drugs	*1*	*1.8*
Antihypertensives	*1*	*1.8*
Iron preparations	*3*	*5.5*
Oral antidiabetics	*2*	*3.6*
Multiple drug poisoning	*1*	*1.8*
Antibiotics	*6*	*10.9*
Antiemetic	*2*	*3.6*
GIS drugs	*3*	*5.5*
Vitamin	*3*	*5.5*
Hormone	*4*	*7.3*

*Some people have been poisoned with more than one drug.

Among the non-pharmacological forms, poisoning by CO and caustic-corrosive substances was observed most frequently (Table 3).

Table 3. Distribution of non-pharmacological poisonings by agents

	N	%
Caustic-corrosive	10	19.2
CO poisoning	33	63.5
Scorpion sting	1	1.9
Pesticide	6	11.5
Food	2	3.8
Total	52	100

Symptoms were observed in 65.5% of drug poisonings. In nonpharmacological poisonings, the degree of symptom development is 78.8%. GIS findings (nausea, vomiting, abdominal pain) were the most common, with 43.9% cases. This is followed by general symptoms (weakness, fatigue, etc.) with 43.0%, CNS findings (alteration of consciousness, impaired concentration, drowsiness) with 30.8%, the respiratory system with 16.8% (respiratory distress, dyspnea), skin with 14.0%, and oral findings with 6.5%. In cases of poisoning, more than one method of treatment was preferred at the same time. Supportive treatment was used most frequently with 79.4%. Gastric lavage was performed in 38.3% of cases, the activated charcoal in 27.1%, nasal oxygen in 25.2%, antidote in 5.6%, and vomiting in 0.9%. There was no mortality due to poisoning in any of the cases.

Discussion

The study was conducted in a semi-rural city where socioeconomic and educational levels have improved in recent years. The majority of the studied poisoning cases are children under five years of age living in the city center of Mus.

This study observed drug poisoning more frequently (51.4%) than non-pharmacological poisoning (48.6%). Studies have supported this finding. Araz et al. (2016) attributed 62.0% of poisoning to pharmacological factors and Ozkaya et al. (1996) 62.5% (11,12).

The study examined several factors that influenced the type of poisoning. The groups under five years of age were the most affected by poisoning, and drug poisoning was found to be less frequent in the age group 6-12 years than in other age groups ($p<0.05$). Similar to this study, in a study conducted in Spain, the most common cases were encountered under the age of five. It was found that 67.0% of the 2.157 poisoning cases followed up were children under four years of age (17). This study hypothesized that the positive situation in the 6-to 12-year-old age group was due to several reasons. The first is that the psychological fluctuations in adolescence have not completely started in this age range, which can also be called the intermediate period. This is because the onset of puberty increases the incidence of poisoning from drug-induced suicide attempts in children over 12 years of age. Other reasons include better neuromotor development in children at 6-12 years of age and a reduction in time spent at home with school (18,19). Children who spend time at home, especially children under five, have a great risk of finding drugs and chemicals in an accessible place. Children are most often poisoned by drugs that are easily accessible and used by themselves (20). In fact, this study found that children were most often poisoned with analgesic-antipyretic medications. The fact that these drugs, which doctors often prescribe, can be purchased without a prescription means that they are found in abundance in households and are considered innocent more than necessary (11). On the other hand, the carelessness of families and leaving their children alone leads to poisoning by cleaning products (2,4,11). In this study, caustic-corrosive substances were identified as one of the two most common causes of nonpharmacological poisoning

Table 1. Distribution of sociodemographic characteristics by type of poisoning

	Poisoning Type						
	Drug Poisoning		**Non-pharmacological Poisoning**				
Characteristics	**N**	**%***	**N**	**%***	**%****	**X²**	**P**
Age							
0-5 years	44	65.7	23	34.3	62.6		
6-12 years* **	4	17.4	19	82.6	21.5		
13-18 years	7	41.2.	10	58.8	15.9	16.82	**<0.001**
Gender							
Girl	30	56.6	23	43.4	49.5		
Boy	25	46.3	29	53.7	50.5	0.76	0.383
Place of residence							
Town	8	27.6	21	72.4	27.1		
City center	47	60.3	31	39.7	72.9	7.77	**<0.001**
Admission season							
Spring	33	60.0	22	40.0	51.4		
Summer	10	43.5	13	56.5	21.5		
Winter	12	41.4	17	58.6	27.1	3.37	0.185
Way of getting toxic substance							
Oral	55	75.3	18	24.7	68.2		
Respiratory and Cutaneous mucous-membranes	0	0.0	34	100.0	31.8	49.73	**<0.001**
Poisoning time							
00:00-05:59	5	33.3	10	66.7	14.0		
06:00-11:59	17	47.2	19	52.8	33.6		
12:00-17:59	14	56.0	11	44.0	23.4		
18:00-23:59	19	61.3	12	38.7	29.0	3.63	0.303

*Row percentage, **Column percentage, ***Differential group

(1). The other factor is CO poisoning, which is assumed to be associated with the families' low socioeconomic status and the negative environmental-warming conditions (21,22).

The way the active substance is taken during poisoning also influences the type of poisoning. In the study, drug poisonings were mostly caused by oral ingestion of the agent ($p<0.05$). The literature also supports the finding (23-25). The fact that medicines commonly used at home are mostly taken orally, especially children under five years of age trying to recognize objects by mouth, explains this situation (4,11).

In this study, the number of poisoning cases was found to be higher in children living in the city center than in children living in rural areas ($p<0.05$). In the case of suspected poisoning, easier access to health care facilities for downtown residents may have increased the number of admissions to the hospital. However, because working parents are more common than those who live in rural areas, it is assumed that children are more alone, and the factor of the caregiver is the most important (5).

Limitations

The study has some limitations. Patient information was obtained through the hospital's record registration system. Because the study was retrospective, patient data were analyzed from medical records as much as possible, and it was not possible to examine the sociodemographic and sociocultural characteristics of the families. Only a part of the cases admitted to the hospital could be recorded. When symptoms developed in symptomatic cases, they could not be distinguished from the data in the files.

Conclusions

In the study, drug-induced poisonings are high. Aside from the fact that analgesic/antipyretic/anti-inflammatory medications and CNS medications are common in poisonings, and attempts to raise awareness of this issue among children and their parents, additional safety measures on issues such as the use, storage, and access to these medications in children should be added to the agenda. Poisonings with these drugs are especially important because of the high mortality and need for intensive care. Therefore, it is believed that preventing the over-the-counter supply of such medications and making the drug boxes in a way that children cannot easily open them can reduce the number of drug poisonings.

Financial support

No financial support was received for the study.

Conflict of interest

There is no conflict of interest among the authors.

References

1.Akgul F, Er A, Celebi Celik F, et al. Retrospective analysis of childhood poisoning. J Pediatr Emerg Intensive Care Med 2016;3:91-6

2.Güven Baysal S, Yıldız FM. Evaluation of epidemiological and demographic features of childhood poisoning cases. Aegean J Med Sci 2018;1:37-42.

3.Binay C, Sahin GT, Bicer S, et al. Evaluation of acute poisonings in pediatric emergency department in 2006. JAEM 2010;9:31-40.

4.Gülez P, Agın H, Apa H, et al. Evaluation of drug poisoning in children. Journal of Dr Behcet Uz Children s Hospital 2011;1:105-9

5.Akıcı N, Bayoglu D, Gürbüz T, et al. Investigation of poisoning in children aged six years and younger and children older than six years. Marmara Pharm J 2013;17:35-41.

6.Mowry JB, Spyker DA, Brooks DE, McMillan N, Schauben JL. 2014 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 32nd Annual Report. Clin Toxicol (Phila) 2015;53:962-1147.

7.Yılmaz HL, Derme T, Yıldızdas D, Alhan E. Evaluation of childhood poisonings in Cukurova region. Nobel Medicus 2009;5:35-44.

8.Yıldıztepe E, Aksay NH, Demir O, et al. Analysis of the year 2007 data of Dokuz Eylül University drug and poison information center, Turkey. Turkiye Klinikleri J Med Sci 2010;30:1622-30.

9.Sahin S, Carman KB, Dinleyici EC. Acute poisoning in children; data of a pediatric emergency unit. Iran J Pediatr 2011;2:479-84.

10.McKenzie LB, Ahir N, Stolz U, Nelson NG. Household cleaning product-related injuries treated in US emergency departments in 1990-2006. Pediatrics 2010;126:509-16.

11.Araz C, Toklucu MO, Güven S, et al. Retrospective analysis of childhood poisoning in Umraniye. Haydarpasa Numune Med J 2016;56.

12.Ozkaya B, Kansoy S, Aksit S, Akın M, Sarıoglu B. Childhood poisonings. J SSK Tepecik Hosp Turkey 1996;6:194-200.

13.Sarvan S, Efe E, Isler A. Evaluation of acute intoxication in children seen in emergency services. JCP 2020;18:470-83.

14.Shannon M. Ingestion of toxic substances by children. N Engl J Med 2000;342:186-91.

15.Oztoprak U, Energin MV. Evaluation of patients admitted to the pediatric emergency department with intoxication. J Contemp Med 2020;10:585-90.

16.Sümer V, Güler E, Karanfil R, et al. Evaluation of the poisoning cases who applied to the pediatrics emergency unit. Turk Arch Ped 2011;46:234-40.

17.Mintegi S, Fernandez A, Alustiza J, et al. Emergency visits for childhood poisoning: a 2-year prospective multicenter survey in Spain. Pediatr Emerg Care 2006;22:334-8.

18.Kendirci Peltek HN, Colakoglu Yaglı E, Hızlı S, et al. Evaluation of intoxication cases who referred to pediatric emergency room in our hospital. Turkish J Pediatr Dis 2011;5:29-35.

19.Polat S, Ozyazıcıoglu N, Tüfekci FG, Yazar F. The investigation of 0-18-year age group cases applying to the pediatric emergency department. Journal of Atatürk University School of Nursing 2005;8:55-62.

20.Ozdemir R, Bayrakci B, Teksam O, Yalcın B, Kale G. Thirty-three-year experience on childhood poisoning. Turk J Pediatr 2012;54:251-9.

21.Bicer S, Sezer S, Cetindag F, et al. Evaluation of acute intoxications in pediatric emergency clinic in 2005. Marmara Med J 2007;20:12-20.

22.Güzel IS, Kibar AE, Vidinlisan S. Evaluation of demographic characteristics in intoxication cases who admitted to emergency room in pediatric unit. Journal of General Medicine 2011;21:101-7.

23.Bükülmez A, Tahta EG, Sen AT, Alpay F. Evaluation of patients with intoxication admitted to the pediatric emergency service. Kocatepe Medical Journal 2013;14:11-6.

24.Kelebek F, Satar S, Kozacı N, et al. Emergency medicine admissions of pediatric intoxicated cases. Eurasian J Emerg Med 2014;13:67-70.

25.Aygin D, Acıl H. The study of the intoxiation cases of the patients (0-18 years) admitting to pediatric emergency unit. Med Bull Sisli Etfal Hosp 2014;48:27-33.

Received: 30 Nov 2021 | **Accepted:** 13 Dec 2021
DOI: 10.54005/geneltip.1026753

ORIGINAL ARTICLE

Evaluation of English 'Pediatric Basic Life Support' and 'Pediatric Cardiopulmonary Resuscitation' Videos in YouTube

YouTube Kaynaklı İngilizce 'Pediatrik Temel Yaşam Desteği' ve 'Pediatrik Kalp Masajı' Videolarının Değerlendirilmesi

[1]Osman Mücahit Tosun, [2]Bülent Hanedan, [1]Hasan Nabi Ündar, [1]Serdal Bozdoğan, [2]Bedia Mine Hanedan, [2]Mustafa Atçı

[1]Konya Numune Hastanesi. Ferhuniye Mah. Hastane Cd. No:22, 42060 Selçuklu/KONYA

[2]Konya Şehir Hastanesi. Anesteziyoloji ve Reanimasyon Kliniği. Akabe Mah. Adana Çevre Yolu Cad. No:135 42020 Karatay / KONYA.

Correspondence

Osman Mücahit Tosun, Konya Numune Hastanesi. Ferhuniye Mah. Hastane Cd. No:22, 42060 Selçuklu/KONYA

E-Mail: osman.mucahid@gmail.com

How to cite ?

Tosun OM, Hanedan B, Tutar HN, Bozdoğan S, Hanedan BM, Atçı M. Evaluation of English 'Pediatric Basic Life Support' and 'Pediatric Cardiopulmonary Resuscitation' Videos in YouTube. Genel Tıp Derg. 2022;32(1):49-54.

ABSTRACT

Aim: Pediatric Basic Life Support is the initiation of cardiopulmonary resuscitation (CPR) until advanced life support is available. The American Heart Association (AHA) 2015 guideline recommends the people to perform CPR.
YouTube is a video sharing site where internet users can learn about many topics, including health. Everyone can upload videos easily. Therefore, there is no control mechanism for the accuracy and up-to-dateness of the videos. Thus, there is a risk of spreading incorrect or inaccurate information. After the pediatric CPR and BLS guidelines were updated in 2015, we aimed to evaluate the quality and content of the videos published in English on YouTube.
Materials and Methods: The YouTube website was searched on 15th June, 2020, using the terms "pediatric cardiac massage" and "pediatric BLS". A total of 200 videos were evaluated by three anesthetists in terms of instructional, content, up-to dateness and resource.
Results: 33 videos included in the study were evaluated according to Azer SA criteria. 14 videos were found to be useful and 19 of them as misleading. The average total viewing times and daily viewing counts of useful videos were found to be higher. When evaluated in terms of content, similar results were obtained in both groups.
Conclusion: This research shows that viewers value videos more being educational than content. For this reason, we think that while editing videos, Azer criteria should be taken into account as an objective criterion and their content should be prepared according to current guidelines.

Keywords: basic cardiac life support, cardiopulmonary resuscitation, CPR

ÖZ

Amaç: Pediyatrik Temel Yaşam Desteği (TYD), ileri yaşam desteği sağlanana kadar kardiyopulmoner resüsitasyonun (CPR) başlatılmasıdır. Amerikan Kalp Derneği (AHA)'nın 2015 kılavuzu, normal halkın kalp masajı yapmasını teşvik etmektedir.
YouTube, herkesin video yükleyebildiği veya izleyebildiği; videoların doğruluk ve güncelliği konusunda kontrol mekanizması olmayan, sağlık dahil pek çok konuda bilgi edinilebilen bir sitedir. Pediyatrik CPR ve TYD kılavuzunun 2015 yılında güncellenmesi sonucu, yeni bilgiler ışığında çalışma yapılması ihtiyacı doğmuştur. Bu sebeple, AHA 2015 pediyatrik CPR ve BLS kılavuzu sonrası İngilizce olarak yayınlanan YouTube videolarının kalite ve içeriğini değerlendirmeyi amaçladık.
Materyal ve Metod: YouTube internet sitesine 15 Haziran 2020'de "pediatric basic life support" ve "pediatric cardiac massage" yazılarak, toplam 200 video incelendi. Videolar, eğiticilik, içerik, güncellik ve kaynak açısından iki anestezist tarafından değerlendirildi.
Bulgular: Çalışmaya dahil edilen 33 video Azer SA kriterlerine göre değerlendirilerek; 14'ü eğitici olmak bakımından faydalı, 19'u ise yanıltıcı olarak bulundu. Faydalı videoların, yanıltıcı olan videolara göre; ortalama toplam izlenme süreleri, günlük izlenme sayıları daha yüksek tespit edildi. İçerik açısından değerlendirildiğinde her iki grupta da benzer sonuçlar elde edildi.
Sonuç: Bu durum izleyicilerin içerikten ziyade videoların eğitici olmasına daha fazla değer verdiğini göstermektedir. Bu sebeple videolar düzenlenirken hem objektif kriter olarak Azer kriterlerinin göz önünde olması, hem de içeriklerinin güncel kılavuzlara göre hazırlanması gerektiğini düşünmekteyiz.

Anahtar kelimeler: temel kalp yaşam desteği, kardiyopulmoner resüsitasyon, CPR

Introduction

YouTube is a social networking site that has become extremely popular in recent years. Both medical professionals and the ordinary people can access information on medical issues on Youtube. Anyone registered on YouTube can upload videos to the platform. Uploaded videos do not undergo any quality control procedure(1). Despite the ease of access to information, severe legal, moral, personal and professional problems occur due to misinformation on Youtube caused by lack of control mechanisms(2, 3). Not only medical students and other healthcare students, but also the lay public use the Internet to obtain health-related information. Studies conducted in the USA have shown that 4.5% of all internet searches are related to health(4).

Cardiac arrest is a serious medical emergency and immediate intervention can greatly increase the victim's chance of survival. Pediatric Basic Life Support (BLS) is a systemic approach including evaluation of patients, contacting emergency medical services, and initiation of cardiopulmonary resuscitation (CPR) in pediatric patients until advanced life support is provided(5, 6). Initiation of CPR as soon as possible increases the chance of survival by 2-3 times(7). A study conducted in the US reported that it is common for the American public to train themselves in CPR by watching videos online (8).

There are limited studies investigating the validity of YouTube videos on CPR and BLS. The majority of existing studies focus on adult CPR videos(9-11). A previous study was conducted on pediatric CPR and BLS based on the 2010 guideline(12). However, these guidelines are updated every five years by a team of experts after reviewing clinical and experimental data and new literature evidence. The aim of the present research is to examine whether English YouTube videos on pediatric CPR and BLS prepared according to the 2015 AHA guideline are consistent with the new guidelines, provide accurate information, and whether they are educationally useful or misleading.

Materials and Methods

"Pediatric basic life support" and "pediatric cardiac massage" keywords were searched on YouTube (https://www.youtube.com; YouTube, LLC, San Bruno; CA; USA) on June 15, 2020. Videos uploaded after the 2015 AHA guideline was published were examined by two independent anesthesiologists. In case of a difference of opinion, a third anesthetist was consulted to reach a consensus.

Top 100 videos listed on the first 5 pages for each keyword were included in the evaluation(Figure 1). The reason why only the first five pages was included in the research was that later pages mostly contain unrelated videos and previous studies have shown that viewers most often watch videos on the first couple of page(9, 13).

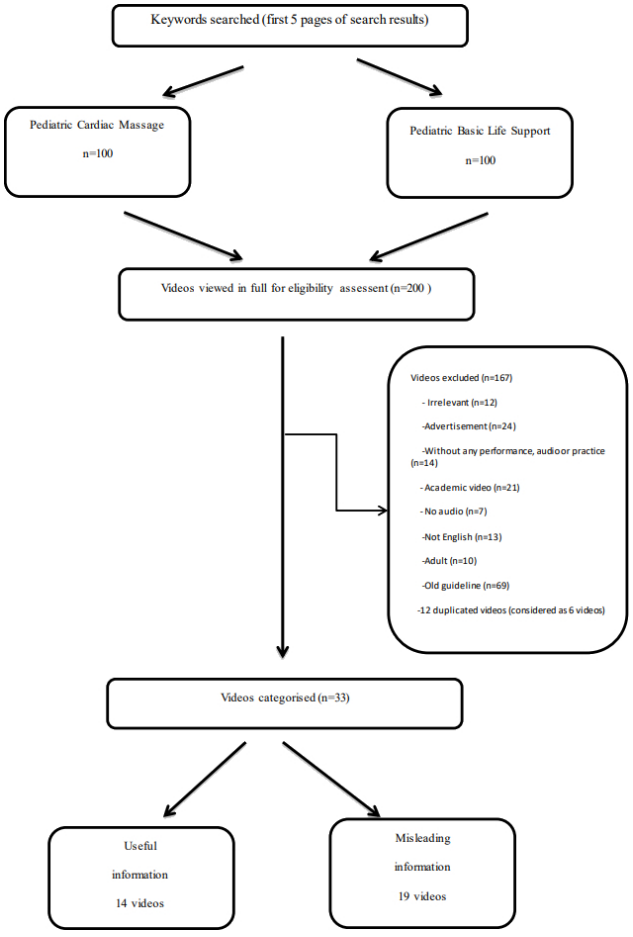
Exclusion criteria

- Uploaded before 2015,
- Irrelevant,
- Containing advertisements,
- Without any performance, sound or practical application,
- Uploaded for academic purposes,
- Videos in a language other than English,
- Adult BLS or CPR videos,
- Repeated videos.

Assessment of videos

Assessment of the videos in terms of educational characteristics was performed by a modified methodology following the criteria published by Azer SA. As shown in Table 1, five major and six minor criteria were determined to evaluate the accuracy of the content, the clarity of the message, the presence of expert opinions on the subject, informativeness of the video, and technical design. Two points were given for each of the major criteria and one point was given for each of the minor criteria. With the condition that all the major criteria must be met, videos with a total score of 13 or more points were categorized as useful. These criteria have been successfully used in many previous studies (1, 14, 15).

Figure 1. Consort Diagram of the YouTube videos in the study.



Collection of Data

Total views, time since upload, daily views, video length (seconds), likes/dislikes received, and uploader characteristics were recorded for each evaluated video. The popularity of videos was assessed using the video power index.

VPI = Popularity x rating / 100
Popularity = number of likes x 100 / (like + dislike)
Rating = number of views / day

Table1. Assesing tools of the videos global quality score according to modified Azer criteria

Major criteria
1.Providing scientifically correct information about TYD and CPR.
2.Clear images
3.Idendification of the upload source
4.Clear explanation of the issue
5.Clear sound and no background noise
Minor criteria
1.The video covers the topic identified in the title.
2.Designed at the level of undergraduate medical science students.
3.The time to download is reasonable.
4.Information about the video uploader is up-to-date.
5.The educational objectives are stated.
6.Demonstrating the CPR or BLS procedure on a human instead of illustration.

Uploader Characteristics

The videos were divided into four categories according to their uploaders: Personal uploads (1), private education companies and foundations (2), hospitals (3), and national health services and universities (4). (Table 4)

Table 4. UK Total points of videos

	UK Total Point	
Characteristic	**R value**	**P value**
Total view	**0.377**	**0.031**
Video length, second	0.257	0.149
Duration on YouTube (month)	0.159	0.378
Views per day	**0.388**	**0.026**
Video Power Index (VPI)	**0.366**	**0.036**
Comprehensiveness score	**0.384**	**0.027**

Evaluation of Up-to-dateness and Accuracy in Terms of Video Content

All videos were evaluated by two independent anesthetists for information accuracy, up-to-dateness, and content (using a 10-point measure including the CPR stages) according to the 2015 AHA guidelines (Table 2). In case of a difference of opinion, a third anesthetist was consulted to reach a consensus.

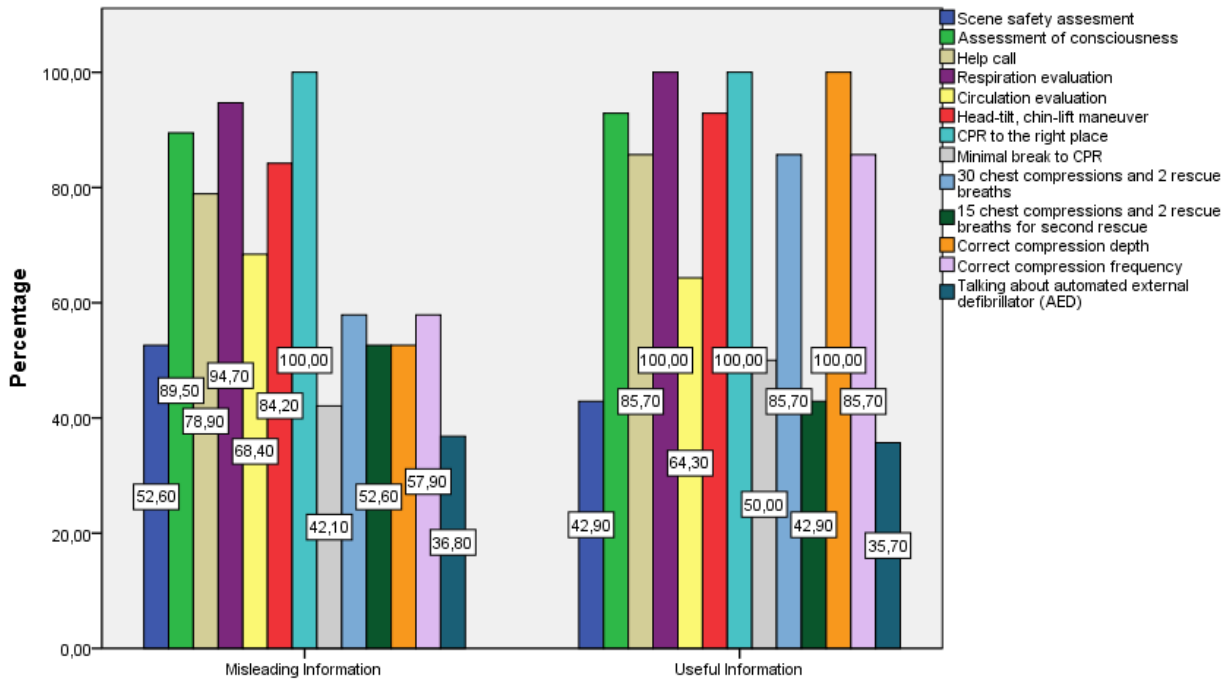
Table 2. Assesment of the videos according to content and up-to dateness

Evaluation of the Information Accuracy of the Videos	
Accurate Information: Includes all phases related to CPR; up-to-date, accurate and learning-helpful videos.	
Misinformation: Contains misleading information about CPR (eg, insufficient compression depth and frequency	
Relevance:	
	Current videos: Prepared according to the 2015 AHA guidelines
	Older videos: Prepared according to pre-2015 AHA guidelines
Evaluation of the content (1p Each)	
Consciousness assessment	
Respiratuary evaluation	
Circulation assesment	
Head tilt, chin lift maneuver	
Calling for help	
CPR to correct area	
Adequate compression depth	
Correct number of compressions	
30:2 for a single person, 15:2 more than one person	
Mention of AED	

Table 5. General features of videos

	All videos (n=33)	**Useful Information (n=14)**	**Misleading Information (n=19)**	**p**
Total view	15685(1021-71362)	38307(9068-76646)	3456(228-28991)	**0.038**
Video length, second	307(182-567)	307(206-576)	218(146-567)	0.308
Duration on YouTube (month)	18.00(12.00-34.00)	16.00(13.00-40.00)	18.00(8.00-34.00)	0.715
Views per day	13.17(2.84-99.19)	53.69(8.31-121.04)	6.40(.78-30.26)	**0.035**
Video Power Index (VPI)	10000(1000-47289)	38758(8200-56680)	2800(200-14800)	**0.023**
GQS score	3±1	4(4-4)	3(2-4)	**0.026**
Reliability score	3.55±1.12	4.00(4.00-5.00)	3.00(2.00-4,00)	**0.028**
Comprehensiveness score	70.40±18.15	76.92(61.54-84,62)	61.54(53.85-92.31)	0.108
UK total point	11.24±3.09	14.00(13.00-15.00)	9.00(8.00-11.00)	**<0.001**

Figure 2. Criteria used of evaluation of the video contents



Tablo 3. Sources of uploads among CPR and BLS education videos

	Source of uploads			
		Private instution	Hospital	Individuals
All videos	10 (100%)	9 (100%)	7 (100%)	7 (100%)
	1a (10%)	5a, b (55,6%)	6b (85,7%)	2a, b (28,6%)
	9a (90%)	4a, b (44,4%)	1b (14,3%)	5a, b (71,4%)
p value	**0,013**			

Statistical Analysis

IBM-Statistical Package for Social Sciences (IBM-SPSS Inc.,Chicago, IL, USA) 22.0 program was used for data analysis. 'Shapiro–Wilk test' was used to check whether the data were normally distributed. Continuous variables were expressed as mean and standard deviation or median (interquartile range) depending on whether the variables were normally distributed or not, and categorical variables were expressed as numbers and percentages. Continuous variables were analyzed with the 'independent samples t-test' for normally distributed variables. 'Mann-Whitney U test' was used for analyzing non-normally distributed continuous variables. Pearson and Spearman correlation analysis was used to investigate the relationship between total video score and basic video features. Inter-rater agreement was calculated with the Cohen's Kappa score. $p < 0.05$ was accepted as statistically significant in all analyses.

Results

The keywords "pediatric cardiac massage" and "pediatric basic life support" were used on Youtube to search for videos and the first five pages of listed results were included in the evaluation. Accordingly, a total of 200 videos were included in the research, 100 videos for each keyword. 167 videos were excluded from the research based on the exclusion criteria. Of these, 12 were irrelevant, 24 contained advertisements, 21 did not contain any sound or performance, 21 were academic videos, 12 were not in English, 10 contained information on adult CPR or BLS, 55 were prepared according to the outdated guideline, and 12 videos were duplicates. As a result, 33 videos were included in the evaluation. Of these, 14 were categorized as useful and 19 were categorized as misleading.

The average number of views for the videos included in the present research was 15.685 (1.021-71.362). Average video length was 307 seconds (182-567). On average, the videos were uploaded on YouTube for 18 months (12-34). Average daily views was 13.17 (2.84-99.19). According to these statistics, the mean VPI was found to be 10.000 (1.000-47.289), the mean Global quality score was 3±1, and the mean reliability score was 3.55±1.12. The videos with useful information were compared to the videos that were categorized as misleading. Accordingly, total watch time [38.307 (9.068-76.646)-3.456 (228-28.991)], daily views [53.69 (8.31-121.04)-6.40 (78-30.26)], video power index [38.758 (8.200-56.680)-2.800 (200-14.800)], global quality scores [4 (4-4)-3 (2-4)], accuracy score [4.00

(4.00-5.00)])-3 (2.00-4.00)] and UK total score [14.00 (13.00-15.00)-9.0 (8.0-11.0)] were significantly higher in useful videos compared to misleading videos ($p < 0.05$). However, there is no significant difference found between the groups in terms of video length and time after videos were uploaded to YouTube ($p>0.05$). (Table 5)

Video contents were evaluated in terms of mentioning key topics including environment safety, evaluation of consciousness, calling for help, respiratory evaluation, evaluation of circulation, performing the head-back-chin-up maneuver, performing CPR on the right location, minimum interruption to CPR, 30:2 ratio for single rescuer and 15:2 ratio for double rescuer, correct compression depth and frequency, and use of automatic external defibrillator (AED). No statistically significant difference was found between the groups in terms of these topics (Figure 2).

Inter-rater agreement for total scores for Pediatric CPR and Pediatric basic life support videos was evaluated with the Cohen's kappa statistic. Cohen's kappa value was 0.756, indicating a strong inter-rater agreement (95% CI: 0.531–0.981). Videos categorized as educationally useful and misleading were compared according to uploader characteristics. It was found that useful videos were mostly uploaded by hospitals, while misleading videos were mostly uploaded by universities or Local Health Institutions. A statistically significant difference was found between useful and misleading videos in terms of uploader characteristics ($p = 0.013$) (Table 3).

A significant correlation was found between total video score and total views, daily views, video power index and comprehensiveness score ($r=0.377$, $p=0.031$; $r=0.388$, $p=0.026$; $r=0.366$, $p=0.036$; respectively). No significant correlation was found between total video score and video length and time passed after video was uploaded to YouTube. ($r=0.257$, $p=0.149$; $r=0.159$, $p=0.378$; respectively) (Table 4).

Discussion

In the present research, English videos on 'pediatric CPR' and 'Basic Life Support' uploaded on YouTube were evaluated in terms of whether they complied with new guidelines, provided correct and accurate information, and whether they were educationally useful or misleading. Based on the evaluations, it was found that only 16.5% of the videos were suitable to be included in the study. Despite the keyword search, 83.5% of the videos were excluded from the study. Exclusion rate was previously found as between 80% and 94% in various studies(9, 11, 16, 17). The fact that the majority of the search results were excluded from the study indicates that most videos are uploaded with tags unrelated to the video content. Furthermore, some videos are uploaded solely for advertisement purposes. In addition, videos prepared according to outdated guidelines are still available on YouTube. This may limit the access of viewers to up-to-date information on pediatric CPR and BLS on YouTube, and increase the likelihood that irrelevant and/or misleading videos are accessed.

In a previous study, Beydilli et al. found that 33.3% of the videos pediatric CPR and BLS were useful. In this study, compliance with current guidelines was taken as the criterion of usefulness. In another study, Azer SA et al. examined videos on cardiovascular and respiratory examination and reported that 28% of the videos were educationally useful(17). Azer SA et al. conducted another study on nervous system examination, and reported that 47% of the videos were useful (20). In the present research, 42% (14) of the videos were found useful. However, when all 300 videos listed on the top five pages were evaluated, it was found that only 7% of the videos were useful. This result suggests that the educational level of the evaluated videos on YouTube is insufficient.

The biggest problem with open platforms such as YouTube is that account authentication cannot be performed and people can anonymously upload videos on virtually any subject. In the present research, it was found that 21% of the videos on pediatric CPR and BLS were uploaded by individuals. In the study of Beydilli et al., this rate was 34%. In another study, Murugiah et al. reported that half of the videos examined were uploaded by unauthenticated individuals. Although information can be disseminated quickly through YouTube, the absence of control mechanisms for uploading videos allows anyone to upload videos on any subject, including medical issues. Platform likes YouTube have initially been used for entertainment purposes, but now they have gained traction as learning platforms as well. Therefore, allowing people to easily upload videos to these platforms without any control can increase the risk of rapid dissemination of erroneous information.

While educationally useful videos were mostly uploaded by hospitals, unhelpful or misleading videos were mostly uploaded by universities, national health institutions, and individuals. In their study, Azer SA et al. also reported similar findings(1). This clearly demonstrates that health professionals should take more initiative in disseminating useful information.

Total views, daily views, video power index, reliability scores and global quality scores of the videos categorized as useful according to Azer SA criteria were higher compared to misleading videos. This result demonstrates that useful videos attract more attention from viewers. In terms of content, it was determined that basic CPR steps such as environment safety, evaluation of consciousness, evaluation of respiration and circulation, calling for help, head-back-chin-up maneuver, and performing CPR on the right location were mentioned almost equally in both groups. This shows that viewers value educational quality more than content. Current information, such

as compression depth and correct CPR frequency, is mentioned more commonly in useful videos, albeit not sufficiently. Automated external defibrillator was mentioned in the 2015 AHA guidelines. In the videos evaluated in both groups, automated external defibrillator was mentioned in only 35% of the videos. In the study of Elicabuk et al., AED was mentioned in 14% of the videos evaluated. Minimal interruption to CPR was mentioned in only 50% of the videos and this ratio was low. When the groups were compared in terms of all content parameters, there was no statistically significant difference between the groups. In light of the above-mentioned results, it can be the concluded that the AHA current guideline is ignored on most of the videos on YouTube. Furthermore, content alone is not a healthy criterion for video quality and usefulness. Therefore, we recommend that Azer criteria should be taken into account when creating videos for YouTube and video content should be prepared in accordance with the current guidelines.

There are certain limitations of this study. The most important limiting factor was that the study was evaluated according to previous guideline rather than the current October, 2020 AHA guideline. Videos uploaded to portals other than YouTube were not evaluated and non-English videos were not included the study. Another limitation was that the scores for "reliability, GQS, and UK usefulness" were calculated subjectively.

Conclusion

Based on the results of the present research, it can be concluded that it is quite difficult to access videos directly related to CPR on YouTube. Furthermore, most videos related to CPR were prepared according to outdated guidelines. Useful videos received more likes and views, but no significant difference was found between the videos in terms of content. These factors limit the use of YouTube for pediatric CPR training and informational purposes. Correct and high-quality CPR significantly increase the chance of survival. Therefore, we recommend that YouTube videos on pediatric CPR should be prepared in accordance with current guidelines, UK usefulness criteria should be taken into account to increase views and likes, and a YouTube Health section should be created for easy access to videos directly related to pediatric CPR.

Financial support:

No financial support was used in the study.

Conflict of interest:

There is no conflict of interest between the authors.

References

1.Azer SA. Understanding pharmacokinetics: are YouTube videos a useful learning resource? European review for medical and pharmacological sciences. 2014;18(13):1957-67.

2.Sutherland S, Jalali A. Social media as an open-learning resource in medical education: current perspectives. Advances in medical education and practice. 2017;8:369-75.

3.Pearson D, Bond MC, Kegg J, Pillow T, Hopson L, Cooney R, et al. Evaluation of Social Media Use by Emergency Medicine Residents and Faculty. West J Emerg Med. 2015;16(5):715-20.

4.Eysenbach G, Köhler C. Health-related searches on the Internet. Jama. 2004;291(24):2946.

5.Basnet B, Bhandari R, Moore M. Initial resuscitation for Australasian Triage Scale 2 patients in a Nepalese emergency department. Emergency medicine Australasia : EMA. 2012;24(4):430-4.

6.Lee DH, Kim CW, Kim SE, Lee SJ. Use of step stool during resuscitation improved the quality of chest compression in simulated resuscitation. Emergency medicine Australasia : EMA. 2012;24(4):369-73.

7.Sekimoto M, Noguchi Y, Rahman M, Hira K, Fukui M, Enzan K, et al. Estimating the effect of bystander-initiated cardiopulmonary resuscitation in Japan. Resuscitation. 2001;50(2):153-60.

8.Liu KY, Haukoos JS, Sasson C. Availability and quality of cardiopulmonary resuscitation information for Spanish-speaking population on the Internet. Resuscitation. 2014;85(1):131-7.

9.Murugiah K, Vallakati A, Rajput K, Sood A, Challa NR. YouTube as a source of information on cardiopulmonary resuscitation. Resuscitation. 2011;82(3):332-4.

10.Tutar MS, Emre E, Hanedan B, Hanedan B. Evaluation of YouTube-based 'Basic Life Support'and 'Cardiopulmonary Resuscitation'Videos in Turkish. DÜSTAD Dünya Sağlık ve Tabiat Bilimleri Dergisi.2021(1):68-87.

11.Yaylaci S, Serinken M, Eken C, Karcioglu O, Yilmaz A, Elicabuk H, et al. Are YouTube videos accurate and reliable on basic life support and cardiopulmonary resuscitation? Emergency medicine Australasia : EMA. 2014;26(5):474-7.

12.Beydilli H, Serinken M, Eken C, Elicabuk H, Dal O, Acar E, et al. The validity of YouTube videos on pediatric BLS and CPR. Telemedicine and e-Health. 2016;22(2):165-9.

13.Azer SA, AlGrain HA, AlKhelaif RA, AlEshaiwi SM. Evaluation of the Educational Value of YouTube Videos About Physical Examination of the Cardiovascular and Respiratory Systems. Journal of medical Internet research. 2013;15(11):e241.

14.Azer SA. Can "YouTube" help students in learning surface anatomy? Surgical and Radiologic Anatomy. 2012;34(5):465-8.

15.Azer SA, AlEshaiwi SM, AlGrain HA, AlKhelaif RA. Nervous system examination on YouTube. BMC Medical Education. 2012;12(1):126.

16.Elicabuk H, Yaylacı S, Yilmaz A, Hatipoglu C, Kaya FG, Serinken M. The Reliability of Turkish "Basic Life Support" and "Cardiac Massage" Videos Uploaded to Websites. Eurasian J Med. 2016;48(1):15-9.

17.Şaşmaz MI, Akça AH. Reliability of trauma management videos on YouTube and their compliance with ATLS(®) (9th edition) guideline. European journal of trauma and emergency surgery : official publication of the European Trauma Society. 2018;44(5):753-7.

Received: 24 Nov 2021 | **Accepted:** 9 Feb 2022
DOI: 10.54005/geneltip.1028077

ORIGINAL ARTICLE

Retrospective evaluation of newborn cases who were followed up with the diagnosis of hypernatremic dehydration

Hipernatremik dehidratasyon tanısı ile takip edilen yenidoğan olgularımızın retrospektif değerlendirilmesi

[1]Esma Keleş Alp

[1]Dr. Ali Kemal Belviranlı Kadın Doğum ve Çocuk Hastalıkları Hastanesi, Çocuk Sağlığı ve Hastalıkları Kliniği, Konya

Correspondence

Esma Keleş Alp, Dr. Ali Kemal Belviranlı Kadın Doğum ve Çocuk Hastalıkları Hastanesi, Çocuk Sağlığı ve Hastalıkları Kliniği, Konya

E-Mail: esmaalp@hotmail.com

How to cite ?

Keleş-Alp E. Retrospective evaluation of newborn cases who were followed up with the diagnosis of hypernatremic dehydration. Genel Tıp Derg. 2022;32(1):55-60.

ABSTRACT

Aim: The aim of our study is to evaluate the demographic characteristics and epidemiological risk factors of neonatal hypernatremic dehydration and to discuss the precautions applied in our clinic in order to reduce the number of dehydration cases in the light of the literature.
Materials and Methods: Newborns who were hospitalized in our neonatal intensive care unit with the diagnosis of HD, whose serum sodium level was >147 mmol/L and born at >37 weeks were evaluated retrospectively. Babies with illnesses that would adversely affect nutritional status were excluded from the study.
Results: Mean gestational week of 54 cases included in the study was 39.19±1.07.22. The mean birth weight was 3244.06±458.46 gr. while the mean weight of hospitalization was 2880.28±514.54 gr. The percent of weight loss was found to be 8.51±3.14%. The mean age of hospitalization was 3.7±2.05 days and the mean duration of hospitalization day was 2.26±1.42 days. On admission, 11 (20.4%) patients had fever, 6 (11.1%) patients had jaundice, 3 (5.6%) patients had discomfort, 30 (55.5%) patients had more than one complaint and dehydration was detected in 4 (7.4%) patients during control admission of pediatric outpatient clinic. On physical examination, 46 (85.2%) patients had mild dehydration, 7 (13%) had moderate dehydration, and 1 (1.9%) patient had severe dehydration. The mean serum sodium value of the patients was 150.44±3.62 mmol/L, mean serum urea value was 45.5±18.13 mg/dl, and mean serum creatinine value was 0.79±0.34 mg/dl at the time of admission. The etiologies of dehydration were breast milk insufficiency in 37 (68.5%) cases, inability to breastfeed effectively due to nipple problems in 2 (3.7%) cases, and errors in breastfeeding technique in 15 (27.7%) cases. A positive correlation was found between the degree of dehydration and percent of weight loss and the serum sodium value ($p<0.001$).
Conclusion: In our study, it was found that the most common cause of hypernatremic dehydration was breast milk insufficiency. Considering other reasons, giving breastfeeding education to mothers before discharge from the hospital seems to be important in preventing hypernatremic dehydration.

Keywords: Newborn, weight loss, hypernatremia, dehydration, breast milk, education.

ÖZ

Amaç: Çalışmanın amacı neonatal HD olgularının demografik özelliklerini ve epidemiyolojik risk faktörlerini ortaya koyarak, dehidratasyon olgularının sayısını azaltmak amacıyla kliniğimizde uygulanan önlemleri literatür eşliğinde tartışmaktır.
Yöntem ve Gereçler: Yenidoğan servisimize hipernatremik dehidratasyon tanısı ile yatırılmış ve serum sodyum değeri 147 mmol/L ve üzeri olan, 37 hafta ve sonrası doğan bebekler retrospektif olarak değerlendirildi. Beslenmeyi olumsuz etkileyecek hastalığı olan bebekler çalışma dışı bırakıldı.
Bulgular: Çalışmaya alınan 54 olgunun ortalama doğum haftası 39,19±1,07 idi. Doğum ağırlıkları ortalama 3244,06±458,46 gr. iken, yatış ağırlıkları ortalama 2880,28±514,54 gr. idi. Yüzde ağırlık kaybı ise %8,51±3,14 olarak bulundu. Hastalar ortalama 3,7±2,05 günlükken yatmış ve hastanede 2,26±1,42 gün kalmışlardı. Başvuru şikayeti 11 (%20,4) hastada sadece ateş, 6 (%11,1) hastada sadece sarılık, 3 (%5,6) hastada sadece huzursuzluk, 30 (%55.5) hastada ise birden fazla başvuru şikayeti varken, 4 (%7,4) hastanın rutin kontrolünde dehidratasyon saptandı. Fizik muayenede 46 (%85,2) hastada hafif düzeyde, 7 (%13) hastada orta düzeyde, 1 (%1,9) hastada ise ağır düzeyde dehidratasyon bulguları vardı. Hastaların başvuru anındaki ortalama serum sodyum değeri 150,44±3,62 mmol/L, serum üre değeri 45,5±18,13 mg/dl, serum kreatinin değeri 0,79±0,34 mg/dl idi. 37 (%68,5) vakada anne sütü yetersizliği, 2 (%3,7) vakada meme başı sorunları nedeniyle etkin emzirememe, 15(%27,7) vakada ise emzirme tekniğindeki yanlışlıklar nedeniyle dehidratasyon gelişmişti. Dehidratasyon derecesi ve yüzde ağırlık kaybı ile serum sodyum değeri arasında pozitif korelasyon ($p<0.001$) saptandı.
Sonuç: Çalışmamızda hipernatremik dehidratasyona en sık anne sütü yetersizliğinin yol açtığı bulunmuştur. Diğer nedenler de göz önüne alınarak annelere hastaneden taburculuk öncesi emzirme eğitiminin verilmesi hipernatremik dehidratasyonu önlemede önemli görünmektedir.

Anahtar kelimeler: Yenidoğan, kilo kaybı, hipernatremi, dehidrasyon, anne sütü, eğitim.

Introduction

There is no doubt that breastfeeding is the safest and best way to feed babies (1). Breastfeeding provides social, psychological, economic, developmental and environmental benefits not only to the baby but also to the mother, family and society (2). It is accepted all over the world that breastfeeding has positive effects on

growth, development and neurological development in addition to decreasing the frequency of acute and chronic infections, immunological, inflammatory, allergic, endocrine and cancer diseases on children (2-4). Inadequate secretion of breast milk or inability to suckle causes hypernatremic dehydration (HD), especially in the first week of life (5,6). In recent years the worldwide increase in breastfeeding has led to a decrease in the incidence of HD in infants (2,7,8). Different results have been reported regarding the incidence of HD in neonates (6). In the study of Moritz et al., the incidence of hypernatremia associated with insufficient secretion of breast milk in a 5-year period was reported as 1.9%, while Ünal et al. reported the prevalence of hypernatremia as 4.1% among 169 term babies in their study which as conducted between 2002 and 2005 years (9,10). In a study of Oddie et al. in a region with 32015 live births, it was reported that eight (0.88%) of 907 cases admitted to the hospital within the first month had HD (11). The most important cause of HD is considered to be insufficient breast milk intake (12-16). The problem that causes HD is fluid deficiency in the body and the accumulation of sodium in the body to provide sufficient volume in the circulation (2). The high sodium content in breast milk at the beginning also contributes to HD. The amount of sodium in breast milk decreases with the increase of lactation and milk secretion (17). In some cases, the reason is that the baby cannot grasp the nipple and empty the milk due to nipple problems or incorrect breastfeeding techniques, despite the fact that breast milk is sufficient. During first days, the amount of breast milk is low, the mother's knowledge and skills in the breastfeeding methods are insufficient, cesarean delivery, low number of breastfeeding episodes, breastfeeding incompatibility between mother and baby, low education level of the mother, mistakes in breastfeeding technique and nipple problems are the main causes of breastfeeding insufficiency (18-21). Also, the two most common reasons for readmission to neonatal services in recent years, when early discharge practices are widely applied; are hyperbilirubinemia and dehydration (22, 23).

Hypernatremia is defined as a serum sodium value above 146 mEq/L for newborns (24,25). The serum sodium ≥150 mEq/L in neonates is a potentially life-threatening condition (26). Hypernatremic dehydration can progress with complications such as acute renal failure, disseminated intravascular coagulation, convulsions, peripheral artery thrombosis, cavernous vein thrombosis, intracranial bleeding and death in the neonatal period. Its treatment also carries serious risks such as brain edema and convulsions (27-29). Despite such important complications, detection of the problem by both mother and doctor is delayed due to the active and strong sucking reflex of hypernatremic infants during physical examination (5,30). Particularly, early discharge, not being called for early control, cesarean delivery and high sodium level in breast milk have been reported as risk factors (11,31).

The aim of our study is to evaluate the causes and related factors of HD accompanied by literature and to determine the early measures to be taken to prevent HD in our hospital and other health institutions.

Materials and Methods

The file records of newborns born 37 weeks and older who were hospitalized in our neonatal service due to HD between June 2016 and June 2020, and whose serum sodium levels 147 mEq/L and above (24,25), were retrospectively reviewed. Babies with sepsis, hypothyroidism, Down syndrome, cleft palate-lip, metabolic disease, congenital anomalies and babies born before 37 weeks were excluded from the study. A total of 54 cases were included in the study. The patient's delivery type, gender, education level of the mother, the number of children in the family, etiological factors (factors causing insufficient breast milk intake; breast milk insufficiency, nipple problems, wrong breastfeeding technique), the season in which baby was diagnosed, how many days old baby was hospitalized, diet (formula, breast milk or mix), complaints at admission (fever, jaundice, decreased sucking, restlessness, hypoactivity, decreased urine output, decreased stool), degree of dehydration, percent of birth weight loss, whether acute kidney failure has developed, duration of hospital stay were noted from file records. Acute renal failure was defined as the presence of any of the following; serum creatinine value ≥ 0.3 mg/dl (≥26.5 µmol/l) within 48 hours; or an increase of 1.5 times or more in serum creatinine compared to baseline, known or predicted to have developed within the last 7 days; or urine volume < 0.5 ml/kg/h in the last 6 hours (32).

Statistical analysis

Data were analyzed using with SPSS 16.0 computer program. Data were expressed as a percentage or as median (data range) or mean±SD depending on whether the distribution was homogeneous. Chi-square and Student's T tests were used for comparisons. Bivariate logistic regression, Pearson and Spearman correlation tests were used for correlation analysis. P values <0.05 were considered statistically significant.

Results

The mean gestational week of 54 cases included in the study was 39.19±1.07 (Table 1). Of the cases, 22 (40.7%) were female and 32 (59.3%) were male. While the mean birth weight was 3244.06±458.46 g and the mean hospitalization weight was 2880.28±514.54 g. The mean weight loss was 8.51±3.14 percent. The delivery method was spontaneous vaginal delivery in 27 (50%) patients and cesarean section in 27 (50%) patients. 34 (63%) cases were first children, 9 cases (16.7%) born in spring, 18 (33.3%) born in summer, 19 (35.2%) born in autumn, and 8 (14%) born in winter. The cases were hospitalized at a mean age of 3.7±2.05 days and stayed in the hospital for 2.26±1.42 days.

The complaints at admission were only fever in 11 (20.4%) patients, only jaundice in 6 (11.1%) patients, only restlessness in 3 (5.6%) patients, and fever, jaundice, and vomiting in 30 (55.5%) patients. It was determined that more than one of the complaints of decrease, restlessness, decrease in movements, decrease in the amount of urine, decrease in the amount of feces were present. In addition, HD was detected in 4 (7.4%) patients during routine control. On physical examination, signs of mild dehydration were found in 46 (85.2%) patients, moderate in 7 (13%) patients, and severe in 1 (1.9%) patient. In the laboratory examinations of the patients at the time of admission, the mean serum sodium value was 150.44±3.62 mmol/L. The mean serum urea and creatinine values were 45.5±18.13 mg/dl, and 0.79±0.34 mg/dl, respectivelly (Table 2). In addition, while there was no acute renal failure in 43 (79.6%) cases, acute renal failure developed in 11 (20.4%) patients. Dehydration was caused by insufficient breast milk in 37 (68.5%) cases, inability to breastfeed effectively due to nipple problems in 2 (3.7%) cases, and due to mistakes in breastfeeding technique dehydration in 15 (27.7%) cases.

Mean maternal age was 25.93±5.32 years and 18 (33.3%) mothers were primary school graduated, 15 (27.8%) mothers were secondary school graduated, 12 (22.2%) mothers were high school graduated, 8 (14.8%) mothers had a university level education, and 1 (1.9%) mother could only read and write (Table 3). In addition, 43 (79.6%) patients were fed only with breast milk, 7 (13%) with both breast milk and formula, and 4 (7.4%) with only formula.

Table 1: Demographic and laboratory data of study population.

Variable	N:50 (mean±SD)	Percentage (%)
Gestational week (week)	39.19±1.07	
Birth weight (grams)	3244.06±458.46	
Gender		
Girl	22	40.7
Boy	32	59.3
Weight of hospital admission (grams)	2880.28±54.54	
Weight loss		8.51±3.14
Type of birth		
Vaginal	27	50
Cesarean section	27	50
Order of birth		
First child	34	63
Second child	12	22
Third and over	8	15
Season of birth		
Spring	9	16.7
Summer	18	33.3
Autumn	19	35.2
Winter	8	14.8
Age at time of hospitalization (day)	3.7±2.05	
Hospitalization time (day)	2.26±1.42	

Correlation analyzes showed that there was a positive correlation between serum sodium value and degree of dehydration ($p<0.001$, $r=0.567$) and percent of weight loss ($p<0.001$, $r=0.609$) (Table 4).

Table 2: Laboratory data of the study group at the time of hospitalization.

Variable	Mean±SD
Serum sodium level (mmol/L)	150.44±3.62
Serum urea level (mg/dl)	45.5±18.3
Serum creatinine level (mg/dl)	0.79±0.34

Table 3: Distribution of demographic data of the mothers in the study group.

Variable	N:54 (Mean±SD)	
Age of mother (year)	25.93±5.32	
Education level		
Only read and write	1	1.9
Primary school	18	33.3
Secondary school	15	27.8
High school	12	22.2
University	8	4.8
Nutritional status of babies		
Breast milk	43	796
Breast milk and formula	7	13
Formula	4	74

Table 4: Correlation analysis of factors that may be associated with serum sodium level.

Variable	R value	P value*
Degree of dehydration	0.567	<0.001
Percentage of loss of birth weight	0.609	<0.001
Education level of mother	0.789	0.267
Nutritional status	0.901	0.348
Age of mother	0.861	0.437
Hospitalization time	0.683	0.079

*Analysis of Pearson correlation.

Discussion

The neonatal period is the most sensitive period of life in terms of fluid and electrolyte balance. Breast milk is undoubtedly the most ideal food for the baby. In recent years, the importance given to breast milk in the nutrition of newborns has been increasing (2). The American Academy of Pediatrics recommends that

almost every baby should be breastfed after birth (33). If breast milk is insufficient and the mother does not realize it, frequency of hypernatremia may increase.

Studies have reported that most of the cases were fed with breast milk only (21,34-36). In our study, most of the cases were tried to be fed with only breast milk, but dehydration developed because it was insufficient. The mean age of the mothers was lower in line with other studies. However, we did not find a correlation between maternal age and serum sodium value. This can indicate that the level of consciousness of young mothers has also increased.

Hypernatremic dehydration is more common in the first babies of parents, and in the study of Livingstone et al., the frequency was found to be 17% in babies of primiparous mothers (27). In our study, 34 (63%) of the cases were the first babies of their mothers. Similarly, in the study of Ünal et al. (n=169), it was reported that 74.6% of the cases with HD were the first babies of their mothers (10). In the study of Çakır et al., the first baby rate was found to be 76.4% (35). The fact is that mothers who have their first babies do not have breastfeeding experience and cannot determine the severity of the disease in their babies. This situation appears as an important factor in the development of this problem. However, in our study, we did not find a correlation between being the first baby and serum sodium level. This can show that mothers have become more conscious about baby feeding, even if it is their first baby, through pregnant education. In addition, in most studies, the male sex ratio of HD cases was found to be higher than females (21,3-36). In our study, the rate of male cases was also higher. However, the reason for this difference is unclear.

In studies, the education level of the mothers of babies with HD was found to be low. (21,34,37). However, in only one of the studies, no correlation was found between the degree of dehydration of the patient and the education level of the mother (37). The mothers of our cases had mostly primary and secondary education. In our study, no significant relationship was found between maternal education and the degree of dehydration.

There are studies supporting that HD is more common in warm seasons (34). However, there are also studies reporting that the season is not a risk factor (38). The majority of our cases were also hospitalized during the seasons when the air temperature was high. We did not find a relationship between serum sodium and seasons. We suggest that high ambient temperature will increase the body's fluid requirement and adversely affect dehydration.

In a review of many studies, it was shown that cesarean delivery is a risk factor for HD (26). The results of many studies are in the same direction as the results of the reviews (39,40). In addition, there are studies reporting that there is no difference in HD between normal birth and cesarean section (41). On the other hand, there are also publications reporting that HD patients are more often born vaginally (10,34-37). In our cases, the rate of normal and cesarean delivery was equal. On the other hand, the rate of cesarean section was low as %28 in our hospital during the year 2021. It is known that late onset of lactation and insufficient nutrition of the baby in cesarean delivery play a role in the development of hypernatremia (42). On the other hand, the fact that the rate of babies with HD who were born normally is higher than expected in some studies can be explained by the earlier discharge of mothers with normal delivery and the fact that breastfeeding practices are discharged before they are fully developed during training. In addition, this result can be explained by the fact that the insufficiency of breast milk in babies of cesarean mothers who stayed longer in the hospital was noticed earlier by healthcare professionals and additional fluid support was started early.

It has been reported that the problem usually occurs within the first 10 days of life and the duration of admission to the hospital for infants varies between 3 and 21 days. (5,11,21,43,44). In our study, the mean age at admission was 3.7±2.05 days (2-14 days) lower than the studies conducted in previous years. This decrease is a positive and pleasing finding showing that mothers' awareness of dehydration increased compared to previous years and they brought their babies to the hospital earlier. We did not find a relationship between the number of days the patient was hospitalized and the serum sodium value. We interpreted this as the reason why most of our patients were hospitalized in the first 5 days with a sodium value below 160 mEq/l.

Average length of stay in hospital has been reported to be between 1.9 and 2.6 days (21,35). Our results are consistent with these values. As the urea, creatinine, sodium levels and the degree of dehydration increase, the length of stay in the hospital also increases. However, we did not find a correlation between these values and the length of stay in our study. This result can be explained by the small number of our cases and the sodium levels being less than 160 mEq/in most of the patients.

It has been reported that parents of babies with HD are generally unaware of their baby's problem and dehydration detected during routine examination or when they apply to the hospital for another reason (45-4). In our cases, complaints were only fever in 11 (20.4%) patients, only jaundice in 6 (11.1%) patients, satiety due to insufficient breast milk and crying a lot due to this reason in 3 (5.6%) patients, whereas in 30 (11.1%) patients, the complaints were fever, jaundice, decrease in sucking, restlessness, decrease in movements, decrease in urine amount and decrease in stool amount. 4 (7.4%) patients were detected in the routine control. Similar to our results, in other studies conducted in Turkey, it was found that the most common accompanying findings were jaundice and fever, and they were the primary reasons for admission (21,35,37,38,49). However, Çakır et al. and

Unal et al. reported that the most common complaint of admission was decrease in sucking (10,36).

Pathological weight loss is usually detected on physical examination. In studies, average weight loss is reported to be between 11.5-17.1% (18,30,36,44). In our study, we found the mean weight loss was 8.51±3.14 percent, significantly lower than previous studies. This reflects the benefit of training on baby care and nutrition for pregnant and new mothers. We found a positive correlation between weight loss and serum sodium elevation. On physical examination, 46 (85.2%) patients had mild dehydration, 7 (13%) patients had moderate dehydration, and 1 (1.9%) patient had severe dehydration. In addition, we found a significant relationship between serum sodium value and the degree of dehydration ($p<0.001$). These rates show that mothers are now more conscious than before and that they apply to the hospital when the baby's dehydration is at a milder level. Of course, the contribution of facilitating access to hospitals and pediatricians cannot be denied.

In studies, the serum sodium value is reported to be between 146-207 mmol/L (21,34,37,50,51). In our study, sodium values ranged between 147-162 mmol/L. The fact that the highest limit in our patients was lower than in previous studies indicates an increase in family awareness. There was prerenal acute renal failure in 79.6% of our cases. Previous studies reported this rate as 66.7%-68.6% (10,39). The reason for dehydration was insufficient breast milk in 37 (68.5%) cases, inability to breastfeed effectively due to nipple problems in 2 (3.7%) cases, and mistakes in breastfeeding technique in 15 (27.7%) cases. Similarly, in the study of Bülbül et al., breast milk insufficiency was found in 78% of the cases, incorrect breastfeeding method in 18%, and nipple problems in 4%. These results show that mothers should be aware of breast milk insufficiency from the pregnancy period, we should teach them correct breastfeeding techniques, and we should solve the nipple problems before birth.

The most common complication detected during treatment in patients with HD is convulsion (19,47,52). This usually develops during rapid rehydration with hypotonic fluids (15,19). No seizure was observed in any of our patients during the treatment. This result can be explained both by the fact that the hospitalization sodium values of our patients are not very high (the highest sodium value is 162 mmol/L) and by giving appropriate fluid therapy.

In conclusion, hypernatremic dehydration can be prevented by educating mothers about breast milk insufficiency and proper breastfeeding techniques starting from the pregnancy period and calling them for frequent check-ups until breast milk becomes sufficient in the first 10 days and they are sure that the baby is adequately fed. Being the first baby and being born in the warmer months are risk factors. Babies with these features should be monitored more closely. It is pleasing that the awareness of mothers has increased and babies have started to be diagnosed earlier with the pregnant trainings and breastfeeding trainings that have been carried out in our country in recent years. Also, these trainings should be further expanded.

Financial Support: This research received no specific grant from any funding.

Conflicts of Interest: None.

Ethical standard: This is a retrospective study. The authors assert that all procedures contributing to this study comply with the ethical standarts of the Turkish Council of Medical Research and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by T.C. Sağlık Bakanlığı, Konya İl Sağlık Müdürlüğü on 04.03.2021 with the number of E-86737044-806.01.03.

References

1.American Academy of Pediatrics, Breastfeeding and the use of human milk. Work Group on Breastfeeding. Pediatrics 1997;100:1035-9.

2.Cağlar MK, Altugan FS, Ozer I. Exclusively Breastfeeding and hypernatremic dehydration. Iranian J Publ Health 2005;34.1-11.

3.Scariati PD, Grummer-Strawn LM, Fein SB. A longitudinal analysis of infant morbidity and the extent of breastfeeding in the United States. Pediatrics 1997;99:E5.

4.Reynolds A. Breastfeeding and brain development. Pediatr Clin North Am 2001;48:159- 71.

5.Laing I, Wong C. Hypernatraemia in the first few days: is the incidence rising? Arch Dis Child Fetal Neonatal Ed 2002;87:158-62.

6.Neiffert MR . Prevention of breastfeeding tragedies. Pediatr Clin North Am 2001;48:273- 97.

7.Smith RG. Severe hypernatremic dehydration in a newborn infant. Pediatr Child Health 1998;3:413-5.

8.Kapkan JA, Siegler RW, Schmunk GA. Fatal hypernatremic dehydration in exclusively breastfed newborn infants due to maternal lactation failure. Am J Forensic Med Pathol 1998;19:19-22

9.Moritz ML, Manole MD, Bogen DL, Ayus JC. Breastfeeding-associated hypernatremia: are we missing the diagnosis? Pediatrics 2005;116:e343-e347.

10.Unal S, Arhan E, Kara N, Uncu N, Aliefendioglu D. Breast feeding associated hypernatremia: Retrospective analysis of 169 term newborns. Pediatr İnt 2008;50:29-34

11.Oddie S, Richmond S, Coulthard M. Hypernatremic dehydration and breast feeding. Arch Dis Childhood 2001;85:318-20.

12.Neville M, Morton J. Physiology and endocrine changes underlying human lactogenesis II. J Nutrition 2001;131:3005-8.

13.Berk E, İçağasıoğlu D, Büyükkayhan D, Güllтekin A, Cevit O. Hypernatremic dehydration in insuicient breastfed newborns. Erciyes Med J 2010;32:5-8.

14.Özdemir OMA, Alkılıç L, Yıldırım N, Adalı F, Yener Oztürk S. Analysis of Newborn Infants with Hypernatremic Dehydration. Türkiye Klinikleri J Pediatr 2010;19:298-302.

15.Mutlu M, Bahat E, Aslan Y. Hypernatremia in newborns. Türkiye Klinikleri J Pediatr 2008;17:130-4.

16.Macdonald PD. Postnatal weight monitoring should be routine. Arch Dis Child 2007;92:374-5.

17.Modi N. Avoiding hypernatraemic dehydration in healthy term infants. Arch Dis Child 2007;92:474-5.

18.Vatansever Ü, Duran R, Acunas B. Hypernatremic dehydration in exclusively breast-fed infants. J Trakya Uni Fac Med 2007;24:190-3.

19.Molteni KH. Initial management of hypernatremic dehydration in the breast fed infant. Clin Pediatr 1994;33:731-40.

20.Anand SK, Robinson RG, Lieberman E. Neonatal hypernatremia associated with elevated sodium concentration of breast milk. J Pediatr 1980;96:66-8.

21.Bülbül A, Can E, Uslu S, Nuhoglu A. Hypernatremic dehydratation in term infants. Turk Arch Ped 2009;44:84-8.

22.Lain SJ, Roberts CL, Bowen JR, Nassar N. Early discharge of infants and risk of readmission for jaundice. Pediatrics 2015;135:314-21.

23.Hall RT, Simon S, Smith MT. Readmission of breast-fed infants in the first 2 weeks of life. J Perinatol 2000;20:432-7.

24.Burritt MF, Slockbower JM, Forsman RW, Offord KP, Bergstralh EJ, Smithson WA. Pediatric reference intervals for 19 biologic variables in healthy children. Mayo Clin Proc 1990;65:329-36.

25.Lo SF. Laboratory Testing in Infants and Children. In: Behrman RE, Kliegman RM, Jenson HB. Nelson Textbook of Pediatrics, eds. New York: Elsevier, 2016:3460-3464.

26.Lavagno C, Camozzi P, Renzi S et al., Breastfeeding-Associated Hypernatremia A Systematic Review of the Literature. J Hum Lac 2016;32:67-74

27.Livingstone VH, Willis CE, Abdel-Wareth LO, Thiessen P, Lockitch G. Neonatal hypernatremic dehydration associated with breast-feeding malnutrition: a retrospective survey. CMAJ 2000;162:647-52.

28.Musapaşaoğlu H, Agildere AM, Teksam M, Tarcan A, Gurakan B. Hypernatraemic dehydration in a neonate: brain MRI findings. Br J Radiol 2008;81:57-60

29.Yıldızdaş HY, Satar M, Tutak E, Narl N, Buyukcelik M, Olu F. May the best friend be an enemy of not recognized early:hypernatremic dehydration due to breastfeeding. Pediatr Emerg Care 2005;21:445-8.

30.Ergenekon E, Unal S, Gücüyener K, et al., Hypernatremic dehydration in the newborn period and long-term follow up. Pediatr Int 2007;49:19-23.

31.Atasay B, Günlemez A, Ünal S, Arsan S. Hypernatremic dehydration in a breast fed neonate. J Ankara Üni Fac Med 2003;56:39-44.

32.The Kidney Disease Improving Global Outcomes (KDIGO) Working Group. Definition and classification of acute kidney injury. Kidney Int Suppl 2012;2:19-36.

33.Gartner LM, Morton J, Lawrence RA, et al. American Academy of Pediatrics Section on Breastfeeding. Breastfeeding and the use of human milk. Pediatrics 2005;115:496-506.

34.Akgün A, Katar S, Taşkesen M, Obek MN. Yenidoğan döneminde önemli bir sorun: hipernatremik dehidratasyon. Göztepe Med J 2010;25:126-31.

35.Güzoğlu N, Kızılelma A, Sarı FN, Uras N, Dilmen U. The Evaluation of Neonatal Cases with Hypernatremic Dehydration. Turkish J Ped 2013;3:124-7.

36.Çakır EP, Aliefendioğlu D, Tufan E, Altug U, Kırlı E. Hypernatremic dehydration: an unrare problem in newborns. Turkish J Ped 2010;4:89-93.

37.Tayman C, Tonbul A, Aydemir S, Kosus A, Tatllı MM. Clinical findings and treatment recommendations of hypernatremic dehydration due to breast milk. Dicle Med J 2010;37:254-62.

38.Uras N, Karadağ A, Doğan G, Tonbul A, Tatlı MM. Moderate hypernatremic dehydration in newborn infants: retrospective evaluation of 64 cases. J Matern Fetal Neonatal Med 2007;20:449-52.

39.Manganaro R, Mami C, Marrone T, Marseglia M, Gemelli M. Incidence of dehydration and hypernatremia in exclusively breast-fed infants. J Pediatr 2001;139:673-5.

40.Gül A, Takçı Ş, Albayrak SE, Sonmego E. Hypernatremic Dehydration in Term and Late Preterm Infants: Retrospective Analysis. The Journal of Gynecology-Obstetrics and Neonatology 2017;4:52-5.

41.Basiratnia MN, Pishva N, Dehghani A. Prevalence of Breastfeeding–associated Hypernatremia among Hospitalized Hyperbilirubinemic Neonates. Iran J Neon 2014;5:12-6.

42.Vestermark V, Hogdall CK, Birch M, Plenov G, Toftager-Larsen G. Influence of the mode of delivery on initiation of breast-feeding. Eur J Obstet Gynecol Reprod Biol 1991;38:33-8.

43.Harding D, Moxham J, Cairns P. Weighing alone will not prevent hypernatremic dehydration. Arch Dis Child Fetal Neonatal Ed 2003;88:349.

44.Kul M, Gürsel O, Kesik V, Duranoglu L, Sarıcı SU, Alpay F. Analysis of neonatal cases with hypernatremic dehydration. Gülhane Med J 2006;48:162-5.

45.Chilton LA. Prevention and management of hypernatremic dehydration in breast-fed infants. West J Med 1995;163:74-6.

46.Clarke TA, Markarian M, Griswold W, Mendoza S. Hypernatremic dehydration resulting from inadequate breast-feeding. Pediatrics 1979;63:931-2.

47.Roddey OF, Martin ES, Swetenburg RL. Critical weight loss and malnutrition in breastfed infants. Am J Dis Child 1981;135:597-9.

48.Rhuston AR, Lambert GP, Katcher AL, Frangakis D. Dehydration in breast-fed infants. JAMA 1982;248:646.

49.Ergin H, Şahin Ö, Özmert D, Ozdemir MA, Kucuktascı K, Hatipoglu C. Hypernatremic Dehydration in Breastfed Infants Hypernatremic Dehydration in Breastfed Infants. J Current Ped 2013;11:51-6.

50.Cooper WO, Atherton HD, Kahana M, Kotagal UR. Increased incidence of severe breastfeeding malnutrition and hypernatremia in a metropolian area. Pediatrics 1995;96:957-60.

51.Bolat F, Oflaz BM, Güven AS, et al. What Is the Safe Approach for Neonatal Hypernatremic Dehydration? A Retrospective Study From a Neonatal Intensive Care Unit. Pediatr Emerg Care 2013;29:808-13.

52.Sarıcı SÜ, Alpay F, Serdar MA, Yesilkaya E, Gokcay E. Neonatal hypernatremic dehydration resulting from inadequate breast-feeding and high sodium content of breastmilk: a case report. Türkiye Klinikleri J Pediatr 2001;10:45-8.

Received: 30 Nov 2021 | **Accepted:** 5 Jan 2022
DOI: 10.54005/geneltip.1029623

ORIGINAL ARTICLE

Assessment of subclinical atherosclerosis with carotid intima-media thickness in patients with scleroderma

Sklerodermalı hastalarda karotis intima-media kalınlığı ile subklinik aterosklerozun değerlendirilmesi

[1]Sina Aliielkhchi, [1]Demet Menekse Gerede Uludağ, [1]Kerim Esenboğa, [2]Murat Turgay, [1]Mustafa Kılıçkap

[1]Department of Cardiology, Ankara University School of Medicine, Ankara, Turkey

[2]Department of Rheumatology, Ankara University School of Medicine, Ankara, Turkey

Correspondence

Kerim Esenboğa, Department of Cardiology, Ankara University School of Medicine, Cebeci, Ankara, Turkey, 06590.

E-Mail: kerimesenboga@yahoo.com

How to cite ?

Aliielkhchi S, Gerede-Uludağ DM, Esenboğa K, Turgay M, Kılıçkap M. Assessment of subclinical atherosclerosis with carotid intima-media thickness in patients with scleroderma. Genel Tıp Derg. 2022;32(1):61-67.

ABSTRACT

Aim: Inflammation has an important role in the development of atherosclerosis. The risk of atherosclerosis and its complications is higher for patients with diseases such as systemic lupus erythematosus and rheumatoid arthritis in whom inflammatory activity is higher than for healthy individuals. However, several studies have shown conflicting results in patients with scleroderma. In this study, carotid intima-media thickness (CIMT) was compared in patients with scleroderma and a control group.
Methods: Thirty patients diagnosed with scleroderma (mean age 51.3 ± 11.8 years) and 30 healthy volunteers were included in the study. The groups were similar regarding age, gender, and risk factors for atherosclerosis.
Results: There was no statistically significant difference between the groups in terms of age, gender, lipid level, hypertension, and diabetes mellitus prevalence (p>0.05). The mean CIMT (scleroderma group: 0.070±0.011, control group: 0.048±0.008, p<0.001) and the maximum CIMT (scleroderma group: 0.076±0.013, control group: 0.054±0.009, p<0.001) were statistically significantly higher in the patients with scleroderma. There was a statistically significant correlation between the mean CIMT and hsCRP (r=0.48, p<0.001); and the mean CIMT and the erythrocyte sedimentation rate (r=0.50, p=0.007) in the scleroderma group. The maximum CIMT and the mean CIMT were significantly higher in patients with diffuse type scleroderma compared to the patients with localized scleroderma (p values 0.001 and 0.011, respectively).
Conclusion: Our results show that CIMT is higher in patients with scleroderma compared to the control group, and this is associated with increased inflammatory activity.

Keywords: atherosclerosis; carotid intima-media thickness; inflammation; scleroderma

ÖZ

Amaç: Enflamasyon ateroskleroz gelişiminde önemli bir role sahiptir. Enflamatuvar aktivitenin yüksek olduğu sistemik lupus eritematozus ve romatoid artrit gibi hastalıkları olan hastalarda ateroskleroz ve ateroskleroza bağlı gelişebilecek komplikasyon riski sağlıklı bireylere göre daha yüksektir. Bununla birlikte, birkaç çalışma sklerodermalı hastalarda çelişkili sonuçlar göstermiştir. Bu çalışmada karotis intima-media kalınlığı (KİMK) kullanılarak sklerodermalı hastalar ve kontrol grubu karşılaştırıldı.
Yöntemler: Çalışmaya skleroderma tanısı konan 30 hasta (ortalama yaş 51.3 ± 11.8 yıl) ve 30 sağlıklı gönüllü dahil edildi. Gruplar yaş, cinsiyet ve ateroskleroz için risk faktörleri açısından benzerdi.
Bulgular: Gruplar arasında yaş, cinsiyet, lipid düzeyi, hipertansiyon ve diabetes mellitus prevalansı açısından istatistiksel olarak anlamlı fark yoktu (p>0.05). Ortalama KİMK (skleroderma grubu: 0.070±0.011, kontrol grubu: 0.048±0.008, p<0.001) ve maksimum KİMK sklerodermalı hastalarda (skleroderma grubu: 0.076±0.013, kontrol grubu: 0.054±0.009, p<0.001) istatistiksel olarak anlamlı derecede yüksekti. Ayrıca ortalama KİMK ile hsCRP arasında (r=0.48, p<0.001) ve ortalama KİMK ile eritrosit sedimantasyon hızı arasında (r=0.50, p=0.007) skleroderma grubunda istatistiksel olarak anlamlı fark izlendi. Diffüz tip sklerodermalı hastalarda maksimum KİMK ve ortalama KİMK, lokalize sklerodermalı hastalara göre anlamlı olarak daha yüksekti (sırasıyla p değerleri 0.001 ve 0.011).
Sonuç: Sonuçlarımız, kontrol grubuna göre sklerodermalı hastalarda KİMK'nin daha yüksek olduğunu ve bunun artmış enflamatuar aktivite ile ilişkili olabileceğini göstermektedir.

Anahtar kelimeler: ateroskleroz; enflamasyon; karotis intima-medya kalınlığı; skleroderma

Introduction

Atherosclerosis is a process that develops in the intima layer of large and intermediate arteries. The most obvious event is endothelial dysfunction and low-grade inflammatory activity in the pathophysiological process. Today, atherosclerotic disease is accepted as a low-grade inflammatory event (1). Revealing the association between high sensitive C-reactive protein (hsCRP), which has recently gradually gained importance as an indicator of inflammatory activity, suggests that inflammatory activity has a role in determining the progression and complications of atherosclerosis in addition to its initiation (2). Flow-mediated vasodilation (FMD) and carotid intima-media thickness (CIMT) in the brachial artery are two non-invasive tests used for subclinical atherosclerosis, vascular structure and function (3,4). CIMT can be

used to diagnose structural change in the vessel wall early. CIMT increase is correlated with cardiovascular risk factors (5,6) and is an independent predictor of cardiovascular and cerebrovascular events (7,8).

Connective tissue diseases are diseases characterized by more inflammatory activity than that observed in atherosclerosis. Cardiovascular risk is higher and cannot be explained with conventional risk factors in systemic lupus erythematosus (SLE), a prototype of these diseases (9). In addition, CIMT, a non-invasive method for detecting atherosclerosis, is higher in these patients. Immunological and inflammatory changes are claimed to have a role in these changes (9). Similarly, study results have suggested that subclinical atherosclerosis is seen significantly more in patients with rheumatoid arthritis (RA) (10). However, data have also shown increased histological inflammation and decreased atherosclerosis in patients with rheumatoid arthritis compared to a control group (11). The conflicting results may result from the unique properties of each rheumatologic disease.

Data about scleroderma are limited. Data have shown that CIMT increases with age and disease duration (12). In addition, the flow-dependent vasodilation ability of the brachial artery decreases as an indicator of endothelial dysfunction, and CIMT increases as an indicator of subclinical atherosclerosis in patients with scleroderma (13). However, data suggesting that angiographically-visible coronary artery disease is not different from a control group were also obtained (14). Since low-grade inflammation plays a role in the pathogenesis of atherosclerosis, subclinical atherosclerosis is seen more in the scleroderma group in which immune/inflammatory activity is more prominent. However, there is less information about this issue and conflicts compared to other rheumatologic diseases. Subclinical, early atherosclerosis has been investigated in patients with scleroderma in many groups. Conflicting results were reported in the studies that used CIMT as an indicator of early atherosclerosis. Although some researchers did not find significant changes in CIMT and intraluminal diameter (15-17), others found significant increases in CIMT in patients with scleroderma (13,18).

Therefore, we aimed to evaluate whether CIMT, an indicator of subclinical atherosclerosis that can be evaluated non-invasively, is high or not in patients with scleroderma compared to controls matched for risk factors.

Methods

Patient selection

Patients who were being followed up with a diagnosis of scleroderma at the Rheumatology Clinic of our hospital were included in the study. Patients who did not agree to participate or who had a history of coronary artery disease, cerebrovascular disease, peripheral artery disease, or aortic aneurysm (which are regarded as coronary artery disease equivalent), history of infection within the recent one year, chronic renal failure, or collagen tissue disease except scleroderma were excluded. The control group was matched with the study group regarding age, gender, and coronary artery risk profile to minimize the potential conflicting effect. A total of 60 individuals (30 patients and 30 controls) who met the inclusion criteria and provided informed consent were enrolled in the study. The study protocol was approved by our institute's ethics committee.

Laboratory analysis

Biochemistry tests, fasting plasma glucose, blood urea nitrogen (BUN), creatinine, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglyceride, sedimentation rate, C-reactive protein (CRP), and rheumatoid factor (RF) were analyzed. High sensitive CRP and RF were tested with the immunonephelometric method (Dade Behring BN II System, Germany).

Of immunological tests, anti-nuclear antibody (ANA) was the evaluated with the indirect immunofluorescent method, and anticentromer antibody and anti Scl-70 were evaluated with the immunoblot method. These tests were not performed in the control group.

Carotid artery intima-media thickness measurement
B-Mode ultrasonography examinations were conducted with a 13 MHz linear array transducer using Vivid 7 ultrasonography device (Vivid 7, GE Medical Systems Inc., Chicago, USA). All ultrasonography examinations were performed in the right coronary artery by the same operator. Images were recorded in a digital environment and interpreted off-line.

The patient's head in the supine position was taken to mild extension from the neck, and the transducer was placed transverse on the midline of the cervical region. The transducer was mildly shifted to right and left, and the carotid arteries were visualized from the transverse section. The transducer was rotated in the longitudinal section, and the carotid bulbus was localized. Images were obtained from the segment approximately 1 cm before the bulbus level, and the bulbus and internal carotid artery in the longitudinal plane. The lumen-intima and media-adventitia interfaces of the posterior wall of the carotid artery were made visible using the magnification-zooming functions of the device. At least 3 measurements were performed from the posterior wall in each segment, and the mean value was found. The maximum CIMT and the mean CIMT were used for statistical analysis.

Statistical analysis

SPSS 11.5 (Statistical Package for Social Sciences-SPSS, Inc., Chicago, Illinois) for Windows was used to analyze the data. Normally distributed parameters were expressed as mean ± standard deviation (SD) and compared using Student's t test for independent

groups. Parameters not normally distributed were expressed as the median (interquartile range: IQR) in addition to the mean ± standard deviation (SD) and compared with the Mann-Whitney U test. The correlation between the CIMT and inflammatory markers in the scleroderma group was evaluated with the Spearman correlation. A p level of <0.05 was accepted as statistically significant.

Results

A total of 60 patients (30 scleroderma patients and 30 controls) were included in the study. The baseline clinical characteristics of the patients are shown in Table 1. The mean age was 51.3 ± 11.7 years in the patient group and 49.3 ±10.5 years in the control group; no significant difference was found between the groups (p=0.51). No difference was detected between the groups regarding age, diabetes mellitus, hypertension, smoking, total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels (Table 1).

Table 1. Comparison of baseline characteristics of the control and patient groups. Values are the mean ± standard deviation or n (%).

	Scleroderma (n=30)	Control (n=30)	P value
Age	51.3 ± 11.7	49.3 ±10.5	0.51
Gender			
Female n (%)	29 (96.7)	29 (96.7)	1.00
Male n (%)	1 (3.3)	1 (3.3)	
Diabetes mellitus n (%)	1 (3.3)	1 (3.3)	1.00
Hypertension n (%)	5 (16.7)	5 (16.7)	1.00
Smoking n (%)	5 (16.7)	5 (16.7)	1,00
Total cholesterol (mg/dl)	189.1 ± 56.4	186.1 ± 39.8	0.81
LDL cholesterol (mg/dl)	113.5 ± 45.7	109.9 ± 33.0	0.73
HDL cholesterol (mg/dl)	48.3 ± 7.9	50.1 ± 10.6	0.48
Triglyceride (mg/dl)	135.2 ± 57.8	134.8 ± 61.6	0.98

The maximum and mean CIMT measurements were statistically significantly higher in the patients with scleroderma compared to the controls, as shown in Table 2 and Fig. 1 and 2.

Table 2. Carotid intima-media thickness of the scleroderma and control groups

	Scleroderma (n=30)	Control (n=30)	p value
Maximum CIMT (cm)	0.076 ± 0.013	0.054 ± 0.009	< 0.001
Mean CIMT (cm)	0.070 ± 0.011	0.048 ± 0.008	< 0.001

The rheumatologic and inflammatory markers in the patients with scleroderma are summarized in Table 3. A positive moderate correlation was observed between the inflammatory markers, hsCRP and sedimentation, and mean CIMT (r=0.48, p<0.001 for hsCRP; r=0.50, p=0.007 for sedimentation). Anticentromer antibody was negative in all patients, and antiScl was positive in all patients except two so they were not included in the statistical evaluation.

Diffuse type scleroderma was detected in 20 patients and localized scleroderma in 10 patients. The maximum and mean CIMT values were higher in the diffuse group as the result of assessments made for these subgroups (Table 4, Fig. 3 and 4). In addition, duration of disease was significantly longer in patients with diffuse type compared to patients with localized type [mean (SD): 13.00 (4.14) years; median (IQR) 12.50 (6.50) years in diffuse type; mean (SD): 8,50 (6.19) years; median (IQR) 7.50 (8.75) years in localized, p=0.024]. Similarly, triglyceride levels were also higher in patients with diffuse type [mean (SD): 154.00 (58.34) mg/dl; median (IQR) 140.00 (60.00) mg/dl in diffuse type; mean (SD): 97.80 (35.25) mg/dl; median (IQR) 89.50 (57.50) mg/dl in localized, p=0.011]. No significant difference was found between the two groups regarding the other conventional risk factors for atherosclerosis and inflammatory markers.

Table 3. Rheumatologic and inflammatory markers (n=30 in the scleroderma group)

	Mean ± SD	Median	IQR
hsCRP (mg/L)	4.9 ± 5.4	0.97	1.63
Sedimentation (mm/h)	23.2 ± 18.24	19.00	17.00
ANA	2.2 ± 0.76	2.0	1.0
RF (IU/ml)	12.6 ± 8.33	10.1	2.5

SD: Standard deviation; IQR: interquartile range; hsCRP: high sensitive C-reactive protein; ANA: antinuclear antibody; RF: rheumatoid factor

Table 4. CIMT values in diffuse and localized scleroderma

	Diffuse type		Localized type		p
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Maximum CIMT	0.082 ± 0.011	0.080 (0.020)	0.066 ± 0.008	0.070 (0.010)	0.001
Mean CIMT	0.074 ± 0.010	0.073 (0.017)	0.062 ± 0.009	0.065 (0.015)	0.011

IQR: Interquartile range; CIMT: carotid intima media thickness; SD: standard deviation

Discussion

Atherosclerosis is a multifactorial and multistage disease. There is chronic inflammation in all stages of the disease, which continues until the plaque ruptures (19). CAD risk increases in inflammatory diseases such as RA and SLE. CAD is responsible for mortality in patients with RA. Cerebrovascular diseases are the

second most common factor responsible for mortality in patients with RA (20). Subclinical atherosclerosis risk was high in RA independently from conventional risk factors (10). In a 2006 study conducted with 57 Indian patients with RA who did not have CAD, conventional risk factors and CAD risk equivalents, CIMT measured from bifurcation of the common carotid artery was significantly higher in patients compared to controls, and it was concluded that subclinical atherosclerosis was more frequent in these patients (10).

Cardiovascular morbidity and mortality are higher in SLE, an inflammatory disease, compared to controls. A study showed that atherosclerosis risk is high in patients with SLE (21). Cardiovascular event prevalence was between 6% and 10% and yearly incidence was 1.5% in prospective cohort studies (22,23). Another case-control study showed that MI risk was high in patients with SLE (24). CIMT was high in patients with SLE who had cardiovascular findings compared to the ones who did not have cardiovascular risk factors and the control group. Inflammation is considered to have a role in atherosclerosis development in patients with SLE. Elevated CRP was associated with atheroma plaque and high CIMT in a cohort composed of 214 patients with SLE (25). C3 elevation was associated with the size of atheroma plaque and coronary artery calcification and was evaluated as an indicator showing that inflammation increases CVD risk in patients with SLE (26).

Similarly, macrovascular disease and subclinical atherosclerosis risk are suggested to be high in patients with scleroderma in whom inflammatory activity is high. A meta-analysis was published on this subject recently. The meta-analysis included 14 CIMT and 7 FMD studies. This analysis showed that the patients with scleroderma had increased atherosclerosis compared to healthy controls (27).

Figure 1. Maximum carotid intima-media thickness in the patients with scleroderma and control groups.

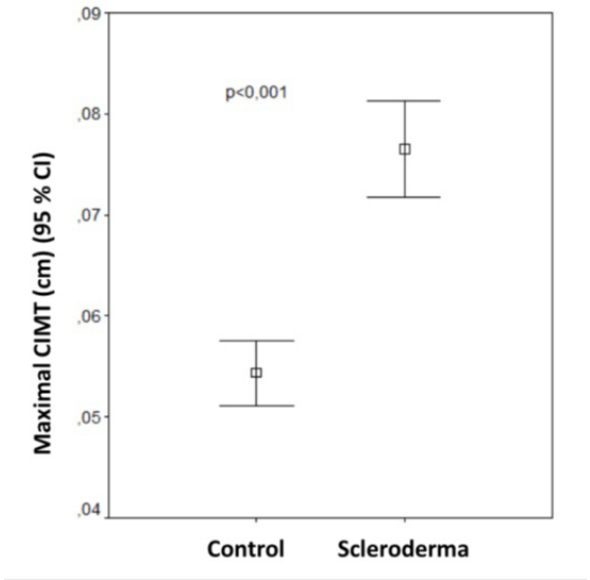


Figure 2. Mean carotid intima-media thickness in the patients with scleroderma and control groups.

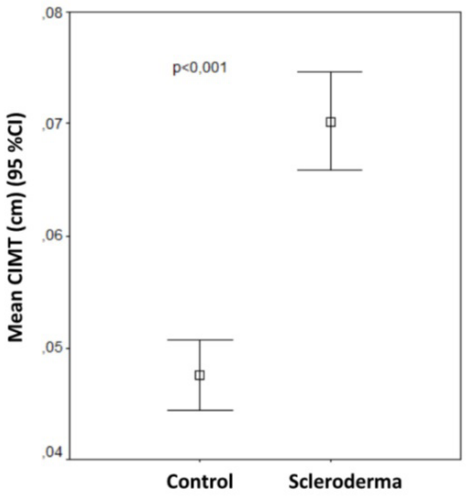


Figure 3. Maximum carotid intima media thickness (CIMT) in diffuse and localized scleroderma.

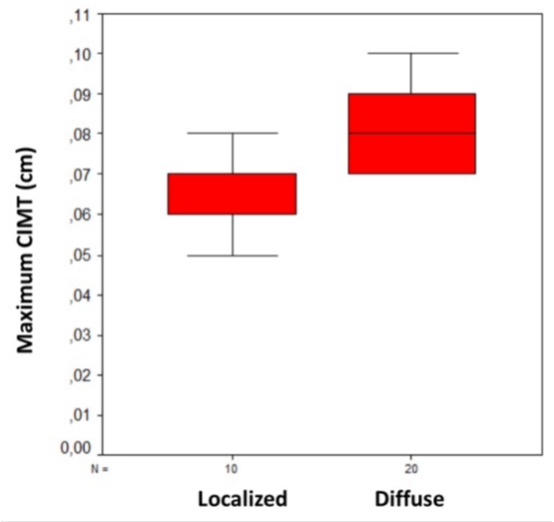
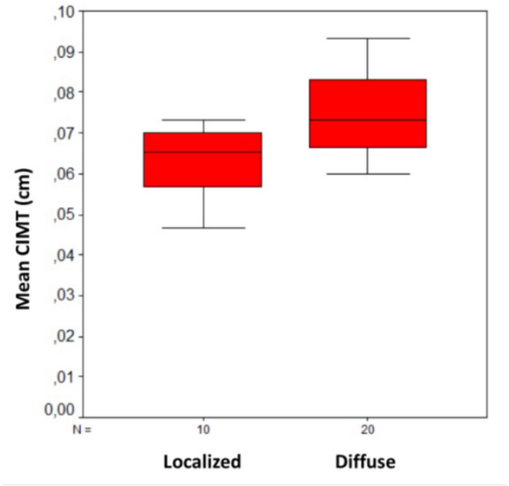


Figure 4. Mean carotid intima media thickness (CIMT) in diffuse and localized scleroderma



However, data on this issue are conflicting. In a study about macrovascular disease in 172 patients with scleroderma with suspicion of CAD, the presence of CAD was evaluated with coronary angiography, and CAD prevalence was reported as less high compared to the general population (14). However, coronary angiography is not sufficient for showing atherosclerosis, because coronary angiography is a diagnostic method that evaluates only coronary artery lumen through administering a contrast medium. Mild plaques, particularly ones that expand outward not inward (positive remodeling), may easily be overlooked on coronary angiography. In addition, reference segments that we evaluate (assume) as normal on coronary angiography may also have atherosclerotic plaques as atherosclerosis shows diffuse involvement. Thus, coronary artery disease prevalence does not provide accurate information when evaluated with coronary angiography.

In a 2007 study conducted in Italy based on the data that macrovascular disease risk is high in patients with scleroderma, 35 patients with scleroderma and 20 controls were evaluated. Endothelial functions and presence of subclinical atherosclerosis were evaluated by measuring FMD and CIMT in the brachial artery. Conventional CAD risk factors were also considered. FMD was impaired and a significant increase was detected in CIMT in the patients with scleroderma, but an association was not detected between impaired CIMT and FMD and conventional risk factors (13). These findings may suggest that early atherosclerosis development occurs more frequently in patients with scleroderma. Although the prevalence of conventional risk factors of atherosclerosis is high in patients with scleroderma, it is not clear how it affects macrovascular disease development or whether accelerates it or not. An association was not detected between conventional risk factors and macrovascular disease in that study. It was hypothesized that the factors such as inflammation, cytokines, and increased lipid oxidation could play a role in the pathogenesis of subclinical atherosclerosis. In addition, an association was not detected between subclinical atherosclerosis and duration, clinical course and laboratory features of scleroderma disease (13).

In a study, high prevalence of intermittent claudication was associated with peripheral arterial disease in patients with scleroderma; however, cardiovascular and cerebrovascular events were detected not to be higher than general population (28). In contrast, impaired FMD and increased CIMT are accepted as significant markers of atherosclerotic disease. In addition, increased FMD and CIMT are used as a strong predictor of cardiovascular disease and cerebrovascular events (29).

Lekakis et al. detected that FMD was impaired and CIMT increased in 12 patients who had primary or scleroderma-related Raynaud phenomenon (30). Szucs et al. observed that FMD was impaired; however, CIMT did not increase in 29 patients with scleroderma (12).

Macedo et al. found a slight increase in the intima-medial thickness of the common carotid artery in patients with scleroderma, but there was no statistical significance compared to the control group (17). However Schiopu et al. showed patients with scleroderma had a higher prevalence of carotid plaque and elevated serum proteins than matched controls (31).

Although data show that subclinical atherosclerosis risk is high in patients with scleroderma, researchers have proposed that these patients should be supported by new studies due to the presence of conflicting results and since data were obtained from a limited number of studies (27,32). Atherosclerosis is a chronic inflammatory disease. Data suggest that early atherosclerosis may develop in some autoimmune rheumatic diseases. The role of classical and non-classical risk factors is also known in these diseases. Scleroderma is characterized by vasculopathy, and microvascular involvement is common. Macrovascular involvement was also reported in some studies. Distal artery disease in fingers is a classical factor in patients with scleroderma. Although conflicting results were reported for CIMT measurement in these patients, data are also available reporting that the prevalence of coronary artery and cerebrovascular disease is not high (14,33).

The presence of non-classical risk factors such as lipoprotein (a), oxidized LDL, and inflammation is also real in addition to the classical risk factors. Moreover, increased vascular injury-related markers such as antibody against oxidized LDL and soluble vascular adhesion molecules are associated with vascular injury in these patients.

The aim of our study was to evaluate the presence of subclinical atherosclerosis in patients with scleroderma through measuring CIMT due to conflicting and complex results. CIMT was compared in patients with scleroderma and a control group. Thirty patients diagnosed with scleroderma and 30 healthy controls were included in the study. Groups were similar regarding age, gender, and risk factors for atherosclerosis. Mean and maximum CIMT values were significantly high in the patients with scleroderma. In addition, a statistically significant relationship was found between mean CIMT and hsCRP and between mean CIMT and the erythrocyte sedimentation rate. This correlation was not shown in previous studies. In our study, subclinical atherosclerosis was more prominent in patients with scleroderma compared to the control group. This may have resulted from the increased inflammatory activity in the patients with scleroderma. In the assessment performed for the subtypes of scleroderma, CIMT was significantly higher in the diffuse type compared to the localized type. Although no difference was detected between the diffuse

and limited groups regarding inflammatory markers, duration of disease was longer and triglyceride was higher in the diffuse type; no difference was detected in the other risk factors for atherosclerosis. These findings suggest that inflammation plays a role in the CIMT increase in patients with scleroderma; however, the difference between diffuse and localized types suggest that long-term disease activity plays a role instead of the grade of inflammation. An important limitation is the small number of patients in the subgroups. The possible difference in levels of inflammatory markers between the subgroups could not be shown. Although the major risk factors for atherosclerosis were similar, finding different triglyceride levels could be due to a phenomenon developing in the small number of cases.

Data about early atherosclerosis are conflicting in patients with scleroderma. This conflict may be explained by multiple factors such as methodological differences, comorbidities, and different ratios of diffuse and localized diseases.

Limitations

Our study is a single center and cross-sectional study and included small patient and control groups. The patient numbers in scleroderma subgroups are not sufficient.

Conclusion

CIMT measurements were statistically significantly higher in the patients with scleroderma compared to the control group. This suggests that subclinical atherosclerosis prevalence increased in the patients with scleroderma. Subclinical atherosclerosis in the patients with scleroderma was associated with increased inflammatory activity in these patients. In addition, CIMT was greater in the diffuse type compared to the localized type.

Supporting these findings with further studies and evaluating whether it has a prognostic value would provide important knowledge about the pathophysiology of rheumatic diseases and atherosclerosis.

Conflicts of interest

The authors declare that there is no conflict of interest.

Financial support

The authors declare that this study has received no financial support.

Ethics approval

The study protocol was approved by the Research Ethics Committee of Ankara University Medical Faculty. Approval number: 128-3583 and date: 21st April 2008.

References

1.Mallika V, Goswami B, Rajappa M. Atherosclerosis pathophysiology and the role of novel risk factors: a clinicobiochemical perspective. Angiology 2007;58:513-22.

2.Ridker PM, Cannon CP, Morrow D, et al. C-Reactive protein levels and outcomes after statin therapy. N Engl J Med 2005; 352: 20–8.

3.Fathi R, Marwick TH. Noninvasive tests of vascular function and structure: why and how to perform them. Am Heart J 2001;141:694–703.

4.Corretti MC, Anderson TJ, Benjamin EJ, et al. International Brachial Artery Reactivity Task Force. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol 2002; 39: 257–65.

5.Chambless LE, Heiss G, Folsom AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. Am J Epidemiol 1997;146:483–94.

6.Davis PH, Dawson JD, Riley WA, Lauer RM. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age. The Muscatine Study. Circulation 2001;104:2815–9.

7.Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb 1991;11:1245–9.

8.O'Leary DH, Polak JF, Kronmal RA, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med 1999; 340:14–22.

9.Soubrier M, Mathieu S, Dubost JJ. Atheroma and systemic lupus erythematosus. Joint Bone Spine 2007; 74:566-70.

10.Grover S, Sinha RP, Singh U, et al. Subclinical atherosclerosis in rheumatoid arthritis in India. J Rheumatol 2006; 33:244-7.

11.Aubry MC, Maradit-Kremers H, Reinalda MS, et al. Differences in atherosclerotic coronary heart disease between subjects with and without rheumatoid arthritis. J Rheumatol 2007; 34:937-42.

12.Szucs G, Tímár O, Szekanecz Z, et al. Endothelial dysfunction precedes atherosclerosis in systemic sclerosis--relevance for prevention of vascular complications. Rheumatology (Oxford) 2007; 46:759-62.

13.Bartoli F, Blagojevic J, Bacci M, et al. Flow-mediated vasodilation and carotid intima-media thickness in systemic sclerosis. Ann N Y Acad Sci 2007;1108:283-90.

14.Akram MR, Handler CE, Williams M, et al. Angiographically proven coronary artery disease in scleroderma. Rheumatology (Oxford) 2006; 45:1395-8.

15.Cheng KS, Tiwari A, Boutin A, et al. Carotid and femoral arterial wall mechanics in scleroderma. Rheumatology 2003; 42:1299–305.

16.Stafford L, Englert H, Gover J, Bertouch J. Distribution of macrovascular disease in scleroderma. Ann Rheum Dis 1998; 57:476–9.

17.Macedo R, Andretta M, Albers C, et al. Evaluation of carotid artery intima-media complex thickness as a marker of vascular damage secondary to accelerated atherogenesis in progressive systemic sclerosis Rev Col Bras Cir 2012;39:10-5.

18.Bartoli F, Angotti C, Fatini C, et al. Angiotensin-converting enzyme I/D polymorphism and macrovascular disease in systemic sclerosis. Rheumatology 2007; 46:772–5.

19.Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002;105:1135–43.

20.Sattar N, McInnes IB. Vascular comorbidity in rheumatoid arthritis: potential mechanisms and solutions. Curr Opin Rheumatol 2005;17:286-92.

21.Urowitz MB, Bookman AA, Koehler BE, et al. The bimodal mortality pattern of systemic lupus erythematosus. Am J Med 1976; 60:221-5.

22.Bruce IN, Urowitz MB, Gladman DD, Ibanez D, Steiner G. Risk factors for coronary heart disease in women with systemic lupus erythematosus: the Toronto Risk Factor Study. Arthritis Rheum 2003; 48:3159-67.

23.Manzi S, Meilahn EN, Rairie JE, et al. Age-specific incidence

rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. Am J Epidemiol 1997;145: 408-15.

24.Fischer LM, Schlienger RG, Matter C, Jick H, Meier CR. Effect of rheumatoid arthritis or systemic lupus erythematosus on the risk of first-time acute myocardial infarction. Am J Cardiol 2004;93:198e200.

25.Selzer F, Sutton-Tyrrell K, Fitzgerald SG, et al. Comparison of risk factors for vascular disease in the carotid artery and aorta in women with systemic lupus erythematosus. Arthritis Rheum 2004;50:151-9.

26.Maksimowicz-McKinnon K, Magder LS, Petri M. Predictors of carotid atherosclerosis in systemic lupus erythematosus. J Rheumatol 2006;33:2458-63.

27.Au K, Singh MK, Bodukam V, et al. Atherosclerosis in Systemic Sclerosis- A Systematic Review and Meta Analysis. Arthritis Rheum 2011;63: 2078–90.

28.Veale DJ, Collidge TA, Belch JJF. Increased prevalence of symptomatic macrovascular disease in systemic sclerosis. Ann Rheum Dis 1995;54: 853–5.

29.de Groot E, Hovingh GK, Wiegman A, et al. Measurement of Arterial Wall Thickness as a Surrogate Marker for Atherosclerosis. Circulation 2004;109 [Suppl I]:III-33-8.

30.Lekakis J, Mavrikakis M, Papamichael C, et al. Short-term estrogen administration improves abnormal endothelial function in women with systemic sclerosis and Raynaud's phenomenon. Am. Heart J 1998; 136: 905–12.

31.Schiopu E, Au KM, McMahon MA, et al. Prevalence of subclinical atherosclerosis is increased in systemic sclerosis and is associated with serum proteins: a cross-sectional, controlled study of carotid ultrasound. Rheumatology (Oxford) 2014; 53:704-13.

32.Tsifetaki N, Georgiadis AN, Alamanos Y, et al. Subclinical atherosclerosis in scleroderma patients. Scand J Rheumatol 2010;39:326-9.

33.Youssef P, Englert H, Bertouch J. Large vessel occlusive disease associated with CREST Syndrome and scleroderma. Ann Rheum Dis 1993;52:464–6.

Received: 1 Dec 2021 | **Accepted:** 25 Jan 2022
DOI: 10.54005/geneltip.1031265

ORIGINAL ARTICLE

Evaluation of Dermatology Consultations Requested From The Pediatric Clinic

Pediatri Kliniğinden İstenen Dermatoloji Konsültasyonlarının Değerlendirilmesi

[1]Cahit Yavuz [2]Cüneyt Uğur

[1]Department of Dermatology, Konya City Hospital, Konya, Turkey

[2]Department of Pediatrics, University of Health Sciences Turkey, Konya City Health Application and Research Center, Konya, Turkey.

Correspondence

Cahit Yavuz, Akabe Mah. 42020, Karatay, KONYA.

E-Mail: yavuzcahit@yahoo.com

How to cite ?

Yavuz C, Uğur C. Evaluation of Dermatology Consultations Requested From The Pediatric Clinic. Genel Tip Derg. 2022;32(1):68-71.

ABSTRACT

Objective: The aim of this study was to evaluate the clinical, demographic, and diagnostic characteristics of pediatric patients consulted to the dermatology department.
Methods: Patients who were consulted to the dermatology department from pediatric clinic of Konya City Hospital between January 2021 and August 2021 were scanned retrospectively. The demographic data of the patients, the pediatric department requesting consultation, their complaints at admission, the reasons for asking for consultation, and the diagnoses they received as a result of the consultation were recorded.
Results: A total of 296 patients, 150 (50.7%) females and 146 (49.3%) males were evaluated. Median age of patients was 5.5 (1.5-10.5) years. The outpatient clinic was seen to have made the most requests for consultation. The most frequent complaints on presentation were redness of the skin in 168 (56.8%) cases and itching in 36 (12.2%). The five most common diagnoses made as a result of the consultation were unspecified dermatitis in 47 (15.9%) cases, scabies in 34 (11.5%), insect bite in 17 (5.7%), atopic dermatitis in 13 (4.4%), and seborrheic dermatitis in 13 (4.4%). When the diagnoses were examined according to the age groups, unspecified dermatitis was usually seen in the 0-2, 6-11, and 12-18 years age groups and insect bite was more common in the 3-5 years age group.
Conclusion: The establishment of effectively functioning consultation mechanisms not only facilitates a correct diagnosis for the patient and appropriate treatment, but also can shorten the length of hospital stay for patients and can reduce economic costs.

Keywords: Pediatrics, Dermatology, Consultation, Diagnoses

ÖZ

Amaç: Bu çalışmanın amacı dermatoloji bölümüne konsülte edilen çocuk hastaların klinik, demografik ve tanısal özelliklerini değerlendirmektir.
Materyal-Metod: Ocak 2021 ile Ağustos 2021 tarihleri arasında pediatri kliniğinden istenen dermatoloji konsültasyonları retrospektif olarak değerlendirilmiştir. Hastaların demografik verileri, konsültasyon istenme sebepleri, konsültasyon sonucu verilen tanılar kayıt edilmiştir.
Bulgular: 150'si (50.7%) kadın ve 146'sı (49.3%) erkek olmak üzere 296 hasta değerlendirilmiştir. Hastaların ortanca yaşı 5.5 (1.5-10.5) yıl idi Ayaktan hasta polikliniği en çok konsültasyon istenen çocuk kliniği bölümü olarak görülmüştür. En sık konsültasyon istenme sebebi 168 (%56.8) hastada kızarıklık ve 36 (%12.2) hastada kaşıntı olarak bulunmuştur. Konsültasyon sonrası en sık verilen 5 tanı 47 (%15.9) hastada tanımlanmamış dermatit, 34 (%11.5) hastada skabiyez, 17 (%5.7) hastada haşere ısırığı, 13 (%4.4) hastada atopik dermatit ve 13 (%4.4) hastada seboreik dermatit olarak bulunmuştur. Yaş grupları arasındaki tanılara bakıldığında tanımlanmamış dermatit 0-2, 6-11 ve 12-18 yaş grubunda daha sık görülürken haşere ısırığı 3-5 yaş grubunda daha sık olduğu görülmüştür.
Sonuç: Etkin işleyen konsültasyon mekanizmalarının kurulması, hastaya doğru tanı konulması ve uygun tedaviyi sağlamanın yanı sıra, hastaların hastanede kalış sürelerini kısaltabilir ve ekonomik maliyetleri azaltabilir.

Anahtar kelimeler: Pediatri, Dermatoloji, Konsültasyon, Tanı

Introduction

Although the majority of the dermatology department patient group are outpatients, the importance of consultations from other clinics are becoming more important. Consultations are important for the diagnosis, treatment and follow up of patients (1). There may be dermatological problems in patients seen in the pediatric emergency department, the pediatric outpatient clinic and the pediatric wards of inpatients. Just as for every branch, there is a demand for opinions and help on the subject of problems related to the branch of dermatology. Although dermatological problems may be associated with a primary dermatological disease, they may also be seen in the form of skin findings of accompanying systemic diseases.

That primary dermatoses can be seen in the pediatric age group and that skin findings occur in many inflammatory, infective, and systemic diseases increase the importance of dermatology consultations. The assistance of dermatology consultations provides the advantages of correct diagnosis and effective treatment and a shorter length of stay in hospital for the patient. Dermatology consultations of patients encountered on the pediatric clinics are important in the training of healthcare personnel, especially in tertiary level training hospitals (2).

The majority of pediatricians who are first consulted about diseases that involve the skin and can be seen in the pediatric age group are specialists. It has been determined that a third (9%-32%) of pediatric consultations are generally with the dermatology department (3, 4). Pediatric dermatology is special and important for both branches. The aim of this study was to evaluate the clinical, demographic, and diagnostic characteristics of pediatric patients consulted to the dermatology department.

Materials and Methods

The study was conducted in accordance with the principles of the Helsinki Declaration. Approval for the study was granted by the Local Ethics Committee (Konya City Hospital, TUEK Commission, decision no:799, dated:2021).

Patients who were consulted to the dermatology department from Konya City Hospital pediatric emergency department, pediatric outpatient clinics and pediatric inpatient service between January 2021 and August 2021 were scanned retrospectively. All the patients were evaluated by a pediatrician and a dermatologist. The demographic data of the patients, the pediatric department requesting consultation, their complaints at admission, the reasons for asking for consultation, and the diagnoses they received as a result of the consultation were recorded.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) Windows software (ver. 22; IBM SPSS, Chicago, USA) was used for all statistical analyses. Descriptive statistical methods were used in the analysis of the data. Normality tests including Kolmogorov-Smirnov and Shapiro-Wilk tests, was used to determine the distribution of data. Normally distributed data were expressed as mean ± standard deviation, and not normally distributed data were expressed as median (25th-75th percentile). Categorical variables were specified as number (n) and percentage (%).

Results

A total of 296 patients, 150 (50.7%) females and 146 (49.3%) males, with a median age of 5.5 (1.5-10.5) years and an age range of 1 day -18 years were evaluated. The outpatient clinic was reported to have made the most requests for consultation, followed by the emergency department and the inpatient wards (Table 1).

Table 1. Distribution of patients according to demographic and clinical characteristics

		n (%)
Sex	Female	150 (50.7)
	Male	146 (49.3)
Age-years	0-2	89 (30.1)
	3-5	56 (18.9)
	6-11	87 (29.4)
	12-18	64 (21.6)
Pediatric division	Emergency	30 (10.1)
Clinic	Outpatient	239 (80.7)
Clinic	Inpatient	27 (9.1)

Table 2. Distribution of patients according to their complaints

Complaints	n (%)	Complaints	n (%)
Rash	168 (56.8)	Acne	5 (1.7)
Pruritus	36 (12.2)	Darkness of skin	4 (1.4)
Hair loss	16 (5.4)	Mass	4 (1.4)
Swelling	11 (3.7)	Light spot	3 (1.0)
Diaper dermatitis	8 (2.7)	Ulcers	2 (0.7)
Red spot	8 (2.7)	Bruise	2 (0.7)
Brown spot	7 (2.4)	White spot on nail	2 (0.7)
Oral ulcers	7 (2.4)	Whitening of skin	1 (0.3)
White spots	6 (2.0)	Redness on tongue	1 (0.3)
Dryness	5 (1.7)		

The most frequent complaints on presentation were redness of the skin in 168 (56.8%) cases and itching in 36 (12.2%) (Table 2). The five most common diagnoses made as a result of the consultation were unspecified dermatitis in 47 (15.9%) cases, scabies in 34 (11.5%), insect bite in 17 (5.7%), atopic dermatitis in 13 (4.4%), and seborrheic dermatitis in 13 (4.4%) (Table 3). The patients were grouped in age ranges of infancy: 0-2 years, pre-school: 3-5 years, school-age: 6-11 years, and adolescents: 12-18 years. When the diagnoses were examined according to the age groups, unspecified dermatitis was usually more in the 0-2, 6-11, and 12-18 years age groups and insect bite was more common in the 3-5 years age group (Table 4).

Table 3. Distribution of most frequently seen 22 dermatological disorders,

Inflammatory Dermatitis	Infections	Various
	Viral	
	Warts 8(2,7)	Hemangiomas 8 (2,7)
Dermatitis 47 (15,9)	Molloscum contagiosum 5 (1,7)	Acne vulgaris 6 (2,0)
Atopic dermatitis 13 (4,4)	Herpes simplex virüs 4 (1,4)	Alopecia areata 6 (2,0)
Seborrheic dermatitis 13 (4,4)	*Bacterial*	Oral apthtae 6 (2,0)
Pruritus 9 (3,0)	Pyoderma 6 (2,0)	Vitiligo 6 (2,0)
Diaper dermatitis 8 (2,7)	Impetigo 4 (1,4)	Melanocytik nevi 5 (1,7)
Psoriasis 6 (2,0)	*Fungal*	Callus 4 (1,4)
Pityriasis rosea 5 (1,7)	Tinea capitis 9 (3,0)	Others 67 (22,7) (two or less patients)
	Parasitic	
	Scabies 34 (11,5)	
	Insect bite 17 (5,7)	
Parameters were expressed as n (%)		

Discussion

In this single-centre, retrospective study without a control group, 296 patients referred to the dermatology outpatient clinic by various pediatric clinics between January 2021 and August 2021. The majority of the patients were outpatients. The most common reason for consultation was redness in the skin and as a result of the consultations, most of diagnoses were unspecified dermatitis and scabies.

Just as there may be pathologies related to the skin on presentation at hospital, they may also develop during the follow-up of hospitalization. In addition to the findings of primary dermatological diseases, findings may also present in the form of skin involvement of accompanying diseases (3). Problems related to exposed areas of skin are noticed early but if lesions in areas covered by clothes are not reported by the patient and a thorough physical examination is not made, they can be easily overlooked. Therefore, a detailed physical examination is of great importance in the determination of dermatological problems, especially in pediatric patients (1).

The aim of dermatology consultations is to identify skin pathologies and reveal systemic problems that may be related. In a study by Adisen et al. (5) the majority of dermatology consultations were reported to from the internal diseases department, and both pediatric and adult emergency departments. Consultations requested from pediatric clinics were reported to constitute 21.2% of all dermatology consultations. Similar to other studies, the majority of the dermatology consultations for the pediatric patient group in this study were found to be requested from pediatric outpatient clinics (3, 6 7).

In this study, there was no difference between the genders. The patients for whom consultation was requested were usually infants or school-age children. Previous studies reported that more consultations were requested in infancy (3, 6).

Penate et al. (4) stated that the most common

Table 4. Distribution of most frequently seen 10 dermatological disorders according to age groups

0-2 years		3-5 years		6-11 years		12-18 years	
n = 89		n = 56		n = 87		n = 64	
Dermatitis	20 (22.5)	Insect bite	8 (14.3)	Dermatitis	12 (13.8)	Dermatitis	10 (15.6)
Scabies	11 (12.4)	Dermatitis	5 (8.9)	Scabies	12 (13.8)	Scabies	8 (12.5)
Atopic dermatitis	7 (7.9)	Tinea capitis	5 (8.9)	Warts	5 (5.7)	Acne vulgaris	4 (6.3)
Seborrheic dermatitis	6 (6.7)	Atopic dermatitis	4 (7.1)	Alopecia areata	4 (4.6)	Oral aphtae	3 (4.7)
Insect bite	6 (6.7)	Hemangiomas	3 (5.4)	Pityriasis rosea	4 (4.6)	Alopecia areata	2 (3.1)
Diaper dermatitis	5 (5.6)	M. contagiosum	3 (5.4)	Tinea capitis	4 (4.6)	Callus	2 (3.1)
Hemangiomas	5 (5.6)	Pruritus	3 (5.4)	Insect bite	3 (3.4)	Epidermal cyst	2 (3.1)
Pruritus	3 (3.4)	Seborrheic dermatitis	3 (5.4)	Xerosis cutis	3 (3.4)	Contact dermatitis	2 (3.1)
Impetigo	2 (2.2)	Scabies	3 (5.4)	Pruritus	3 (3.4)	Psoriasis vulgaris	2 (3.1)
Pyoderma	2 (2.2)	Oral aphtae	2 (3.6)	Tinea corporis	3 (3.4)	Seborrheic dermatitis	2 (3.1)
Others	22 (24.8)	Others	17 (30.2)	Others	34 (39.3)	Others	27 (42.3)
Parameters were expressed as n (%)							

diagnoses as a result of pediatric dermatology consultation were inflammatory dermatitis such as atopic dermatitis and seborrheic dermatitis, followed by infections, primarily viral infections. Similarly in this study, the leading diagnosis was inflammatory dermatitis followed by infections, primarily scabies. Inflammatory dermatitis was determined in 81 (27.4%) of the 296 patients. Inflammatory dermatitis is a finding which can usually be seen in a young age group because of skin sensitivity, and is important as it can be accompanying other comorbid infections.

In a study conducted by Daye et al. (9) it was reported that the majority of pediatric dermatology consultations resulted in a diagnosis of eczema and dermatitis, similar to this study. In patients diagnosed with eczema and dermatitis, this is important as it may be an initial finding of atopic dermatitis, allergic contact dermatitis and other dermatological diseases which can subsequently develop. It is therefore important that this group of patients are followed up as outpatients in the dermatology outpatient clinic.

Unlike other studies, scabies, which has been frequently met in our region in recent years, was the second most common reason for consultation. A diagnosis of scabies was made in 34 (11.5%) patients in this study. Different studies have shown different results related to scabies encountered in pediatric dermatology consultations. Srinivas et al reported a diagnosis of scabies in 22 (4.5%) of 486 patients while Afsar et al diagnosed scabies in 1 (0.2%) of 539 patients (3, 7).

In two separate studies by McMahon et al and Afsar et al, the pediatric department making the most requests for consultation was the pediatric inpatient wards followed by the pediatric hematology department (6, 7). In this study, the most requests for consultation were from the pediatric outpatient clinics.

In a study by Cruz-Manzano et al. (8) drug reaction was at the rate of 11.5% in 1427 pediatric consultations, and in this study drug reaction was determined in 1 patient. It was reported that drug reactions occur more in pediatric oncology group patients (8).

When the results of ths study were examined overall, the third most frequent diagnosis after inflammatory dermatitis and infections was found to be hemangioma from vascular anomalies. McMahon et al. (6) reported that vascular anomalies were the second most common reason for hospitalisation. Similar to the study by Afsar et al. (7), the low rate of vascular anomalies seen in consultations in the current study could be due to this group of patients usually being followed up in the dermatology outpatients clinic.

Diagnoses seen at lower rates as a result of consultations were acne vulgaris, alopecia areata, recurrent oral aphthae, and vitiligo. As expected, acne vulgaris was determined most in the adolescent period of 12-18 years, at the rate of 2%, which was similar to the findings of Daye et al (9).

Limitations of this study could be stated as that it was retrospective and conducted in a single centre. The fact that the study was conducted in a tertiary level hospital also makes it difficult to generalize the results. Another limitation was that there was no information about the dermatological treatments applied to the patients and the outcomes.

Conclusion

Dermatological diseases often occur in childhood. The establishment of effectvely functioning consultation mechanisms not only facilitates a correct diagnosis for the patient and appropriate treatment, but also can shorten the length of hospitalization for pediatric patients and can cost-effective. In this process, we think that the cooperation of the relevant branches and training between the branches will be beneficial. Nevertheless, there is a need for further, prospective, controlled studies of larger number of patients to be able to achieve them and similar benefits.

Conflict of interest: Authors declare no conflict of interest

Funding information: None

References

1.Penate Y, Guillermo N, Melwani P, et al. Dermatologists in hospital wards: an 8-year study of dermatology consultations. Dermatology 2009;219(3):225-231.

2.Moon AT, Castelo-Soccio L, Yan AC. Emergency department utilization of pediatric dermatology consultations. J Am Acad Dermatol 2016;74:1173-1177.

3.Srinivas SM, Hiremagalore R, Venkataramaiah LD, et al. Pediatric dermatology inpatient consultations: a retrospective study. Indian J Pediatr 2015;82(6):541-544.

4.Peñate Y, Borrego L, Hernández N, et al. Pediatric dermatology consultations: a retrospective analysis of inpatient consultations referred to the dermatology service. Pediatr Dermatol 2012;29(1):115-118.

5.Adisen E, Ünal S, Gürer MA. Dermatology Consultations. Turkderm-Archieves of The Turkish Dermatology and Venerology 2006;40(4):126-129.

6.McMahon P, Goddard D, Frieden IJ. Pediatric dermatology inpatient consultations: a retrospective study of 427 cases. J Am Acad Dermatol 2013;68(6):926-931.

7.Afsar FS. Analysis of pediatric dermatology inpatient consultations in a pediatric teaching hospital. Arch Argent Pediatr 2017;115(6):377-384.

8.Cruz-Manzano M, Brau-Javier CN, Valentin-Nogueras S, Figueroa-Guzmán LD. Pediatric Inpatient and Emergency Dermatology Consultations: A 5-Year Retrospective Analysis P R Health Sci J 2018;37:105-109.

9.Daye M, Temiz SA, Durduran Y, Balevi S, Dursun R, Ataseven A, Ozer I. Analysis of Consultation Cases Referred from Pediatrics Department to Dermatology Outpatient Clinic: Retrospective Study. Clin Exp Health Sci 2019; 9: 300-303.

Received: 1 Dec 2021 | **Accepted:** 29 Dec 2021
DOI: 10.54005/geneltip.1030254

ORIGINAL ARTICLE

Lumbar Posterior Transpedicular Screw Fixation and Fusion Applications; What We Do Peroperatively with 117 Spinal Instability Cases

Lomber Posterior Transpediküler Vida ile Fiksasyon ve Füzyon Uygulamaları; 117 Spinal İnstabilite Olgusunda Peroperatif Olarak Neler Yapıyoruz?

[1]Güray Bulut, [2]Murat Hamit Aytar, [3]Mustafa Güdük

[1]Medipol University, Nisa Hospital, Department of Neurosurgery, Istanbul.

[2]Acibadem Mehmet Ali Aydınlar University, Vocational School of Health, Department of First and Emergency Aid, Istanbul.

[3]Acibadem Mehmet Ali Aydınlar University, School of Medicine, Department of Neurosurgery, Istanbul.

Correspondence

Murat Hamit Aytar, Acıbadem Kozyatağı Hastanesi, Nöroşirürji Kliniği, Begonya Sk, No:12, Kozyatağı, Istanbul, Türkiye

E-mail: hamit.aytar@acibadem.edu.tr

How to cite ?

Bulut G, Aytar MH, Güdük M. Lumbar Posterior Transpedicular Screw Fixation and Fusion Applications; What We Do Peroperatively with 117 Spinal Instability Cases. Genel Tıp Derg. 2022;32(1):72-76.

ABSTRACT

Objective: In this study, we aimed to share our surgical principles and surgical outcomes in cases of fixation and fusion with lumbar posterior transpedicular screw-rod systems in our clinic.
Methods: 117 patients who underwent posterolateral fusion surgery with lumbar posterior transpedicular screw-rod system between 2014 and 2017 were evaluated retrospectively. Dynamic lumbar radiographs, computed tomography and magnetic resonance imaging were performed in all cases before the operation. All patients were operated with microsurgical principles and internal fixation and posterolateral fusion were performed with posterior interpedicular screw-rod systems. Stabilization systems were evaluated with lumbar X-ray and/or computed tomography on the first postoperative day. In the 1st and 3rd months, lumbar X-rays were repeated.
Results: All these patients, in whom lumbar spinal instability was detected clinically and radiologically, had lower back and/or leg pain and different levels of neurological deficits. Of the cases, 23 were male and 94 were female. The mean age was 53.4 years. According to the Meyerding classification, there were grade I and II spondylolisthesis in 69, and 8 cases respectively, spinal stenosis in 28 cases, burst fracture in 1 case, compression fracture in 3 cases, disc herniation in 11 cases. The mean follow-up period was 28.6 months.
Conclusions: Meticulous case selection, careful preoperative planning and adherence to spinal microsurgery principles will increase the success rate in lumbar posterior internal fixation and posterolateral fusion surgeries.

Keywords: Lumbar spine, Instrumentation, posterolateral fusion, microsurgery

ÖZ

Amaç: Bu çalışmada kliniğimizde lomber posterior transpediküler vida-rod sistemleri ile fiksasyon ve füzyon vakalarında cerrahi prensiplerimizi ve cerrahi sonuçlarımızı paylaşmayı amaçladık.
Gereç ve Yöntem: 2014-2017 yılları arasında lomber posterior transpediküler vida-rod sistemi ile posterolateral füzyon cerrahisi uygulanan 117 hasta retrospektif olarak değerlendirildi. Operasyon öncesi tüm olgulara dinamik lomber radyografiler, bilgisayarlı tomografi ve manyetik rezonans görüntüleme yapıldı. Tüm hastalar mikrocerrahi prensipler ile opera edildiler ve posterior interpediküler vida-rod sistemleri ile internal fiksasyon ve posterolateral füzyon uygulandı. Postoperatif birinci gün lomber grafi ve/veya bilgisayarlı tomografi ile stabilizasyon sistemleri değerlendirildi. Postoperatif 1. ve 3. aylarda lomber grafiler tekrarlandı.
Bulgular: Lomber spinal instabilitenin klinik ve radyolojik olarak tespit edildiği tüm bu hastalarda bel ve/veya bacak ağrısı ve farklı düzeylerde nörolojik defisitler vardı. Vakaların 23'ü erkek, 94'ü kadındı. Ortalama yaş 53.4 idi. Meyerding sınıflamasına göre sırasıyla 69 ve 8 olguda grade I ve II spondilolistezis, 28 olguda spinal stenoz, 1 olguda patlama kırığı, 3 olguda kompresyon kırığı, 11 olguda disk hernisi mevcuttu. Ortalama takip süresi 28.6 ay idi.
Sonuç: Lomber posterior internal fiksasyon ve posterolateral füzyon ameliyatlarında titiz vaka seçimi, ameliyat öncesi dikkatli planlama ve spinal mikrocerrahi prensiplerine bağlılık başarı oranını artıracaktır.

Anahtar Kelimeler: Lomber omurga, enstrumantasyon, posterolateral füzyon, mikrocerrahi

Introduction

Lumbar stabilization of patients with spinal instability by posterior transpedicular screw fixation and posterolateral fusion is a common procedure, often used to provide stability to the unstable spine, to prevent injury to the neurological structures, to reduce the misalignment and deformity, to increase the likelihood of fusion, and to reduce long-term pain. But the indications are not standardized still [1,2]. Radiological diagnosis should not be considered as the sole criterion for surgery; pain and neurological findings decreasing the quality of life are also important parameters [3].

The success of fusion procedures with spinal instrumentation has increased with the development of instrumentation techniques, use of high-resolution radiological examinations, better understanding of bone healing, improvements in pre- and postoperative care, aggressive rehabilitation programs, and improvement

of surgical skills and experience of surgeons [4-7].

The successful implementation of transpedicular screw-rod systems depends on a thorough knowledge of pedicle anatomy, biomechanical properties of the instrumentation, proper patient selection, pre-operative planning and adequacy of operating room equipment.

In this study, we presented our series and experience.

Materials and Methods

117 patients with lumbar spondylolisthesis who had lumbar stabilization and posterolateral fusion with posterior transpedicular screw-rod systems between 2014-2017 were reviewed retrospectively.

Their clinical charts, radiological studies, operative notes and follow-up results were studied. Patients' age, sex, neurological examination findings, number of segments with transpedicular screw fixation, complications, and clinical outcomes were noted. Prolo follow-up criteria was used for assessment of clinical outcome.

All cases had anteroposterior, lateral, and hyperflexion-hyperextension lumbar radiographies, lumbar computed tomography (LCT), lumbar magnetic resonance imaging (LMRI) studies pre-operatively (Figure 1). Additionally, bone scintigraphy was performed in patients who had multiple lesions in the vertebrae by radiological imaging, and bone densitometry was done for patients with suspected osteoporosis.

Pedicle diameters and corpus depths were measured, and transpedicular screw projections were marked for the planned levels on LCT pre-operatively.

All patients were given prophylactic antibiotics 1 dose pre-operatively and 2 doses postoperatively. Surgical gel pillows were placed bilaterally to support and patients were given neutral prone position. Skin was brushed with antiseptic solutions for 5 minutes. In order to see the lumbar lordosis and the position of the vertebrae in the prone position, the images were taken with C-arm fluoroscopy, and compared with the pre-operative radiographs. After the pedicle projections were determined, the facet joint surfaces were decorticated. Using a pedicle drill, a nest was opened in the vertebra corpus by applying gentle pressure in a controlled manner, which would be appropriate to the screw size determined from the lateral of the facet joint. Each hole was checked with a round tip probe. Transpedicular screws were placed in these slots according to pre-operative calculations under guidence of C-arm fluoroscopy (Figure 2). The tip of each screw was placed reaching anterior to the 2/3 of the corpus length. Transpedicular screws were fixed with rigid rods modelled according to the lumbar curve, one transverse connection was used for segment stabilizations of 3 and above. Transverse binders were not used in 2-segments stabilization. No effort was made for reduction.

In all cases, microsurgical principles were applied according to the pathology. In cases who underwent discectomy, intervertebral space was supported with posterior lumbar interbody fusion (PLIF) and transforaminal lumbar interbody fusion (TLIF). After facet and transverse process decortication, autogenous bone grafts were placed, and screws were fixed. Spongostan was placed on the dura in laminectomy levels. Patients were transfused 1 unit of erythrocyte suspension.

The patients were mobilized with a lumbar corset supported by steel bars on the same day postoperatively. On postoperative day 1, direct radiological radiographs were taken (Figure 3). In necessary cases LCT was done. The cases used lumbar corset for 3 months. Our clinical results were controlled by Prolo's follow-up scale.

Results

There was a total of 117 cases. Ninety-four (80.3%) of them were female and 23 (19.7%) were male (f/m=4.1) (Table 1). The mean age was 53.4±9.7 (range=19-75) years and 83 cases were 50 years or older (Table 2).

Table 1. Distribution of patients according to sex, age and indications

	Number of patients	%
Male	23	19.66
Female	94	80.34
10-29 years	2	1.71
30-49 years	32	27.35
50 years and older	83	70.94
Meyerding Grade 1	69	58.97
(Listhesis after LDH surgery)	(5)	
Meyerding Grade 2	8	6.84
Spinal stenosis	25	21.37
Lumbar disc herniation	9	7.69
Vertebrae fracture	4	3.42

Table 2: Physical examination results of the patients before surgery

	Number of patients	%
Motor deficits	55	47.01
Reflex alterations	75	64.10
Sensorial alterations	71	60.68
Laseque test positivity	109	93.16
Femoral strain test positivity	15	12.82
Neurogenic claudication	35	29.91

All cases had lower back and/or leg pain at admission and various neurological deficits. Laseque test positivity rate was especially high (93.16%) (Table 3).

Table 3: Distribution of the number of patients with transpedicular screws applied segment

	Number of patients	%
2 segments	13	11.11
3 segments	67	57.26
4 segments	29	24.79
5 segments	8	6.84

There were 69 Meyerding grade I, 8 Meyerding grade II spondylolisthesis cases. Spondylolistehezis was at L3-4 level in 9 cases, L4-5 level in 36 cases, L5-S1 level in 30 cases. Two of the cases had spondylolisthesis at 2 levels. Spinal stenosis was seen in 25 cases (1 case single level, 15 cases 2 levels, 8 cases 3 levels, 1 case 4 levels). Disc herniation was present in 9 cases (2 cases at 1 level, 2 cases at 2 levels, 5 cases at 3 levels) 1 case burst fracture, 3 cases compression fracture (Table 4). The median follow-up period was 28 (range=3-48) months.

Table 4: Complications

	Number of patients	%
Dura injury	2	1.7
Subcutaneous CSF collection	4	3.4
Superficial cutaneous infection	1	0.85
Screw breakage	4	3.4
Re-operation	5	4.27

Thirteen cases had 2-segment, 67 cases had 3-segment, 29 cases had 4-segment and 8 cases had 5-segment transpedicular screw-rod stabilization (Table 5).

Table 5: Clinical outcomes according to Prolo follow-up criteria

	Number of patients	%
Excellent	35	29,91
Good	77	65,81
Medium	4	3,42
Poor	1	0,85

In 2 cases with intraoperative dural damage, dura was repaired primarily. There were no cases of postoperative cerebrospinal fluid (CSF) fistula. However, postoperative CSF collection was observed in 4 cases in which peroperative macroscopic dural damage was not observed. Serial skin aspirations under USG uidance were performed for these cases, and no additional surgical procedure was needed for them. Superficial skin infection developed in 1 patient and treated with appropriate antibiotherapy. No instrument infection was observed. In one postoperative case, the screw was replaced by re-operation, due to misplacement of screw out of the L5 pedicle which was causing radicular symptoms. In 4 cases, screw breakage was seen unilaterally (L5 in 3 cases, S1 in 1) and replaced with new ones by re-operation (Table 6).

Postoperatively, 112 (95.7%) of 117 patients who had various degrees of back and/or leg pain at addmission had no leg pain. Of these, 41 (35.04%) were found to have moderate intermittent lower back pain, which did not prevent them from performing normal daily activities and working. There was 1 patient who had 4-segment stabilization from L3 to S1 with worsened complaints. Medical treatment and physical therapy were applied. But his complaints did not fade. Complaints were thought to be due to rigid stabilization. The transpedicular screw rod system was removed. The patient's complaints decreased. Our results according to Prolo follow-up scale was; excellent in 35 (29.91%) cases, good in 77 (65.81%) cases, medium in 4 (3.42%) cases and poor in 1 (0.85%) case.

Discussion

The first fixation procedure was performed by Hadra in the thoracolumbar spine by using wires in 1889 [8]. The first spinal fusion was performed in 1911 by two different surgeons named Albee and Hibbs. Albee used autologous tibia graft, separated the spinous processes and placed the tibial graft in between them. Hibbs, on the other hand, placed overhanging spinous layers on the laminae [9,10].

Transpedicular screw-rod systems have been found to provide much better segmental fixation compared to other posterior instrumentation systems such as laminar hook-rod or segmental wire-rod [11,12]. However, in cases where the posterolateral fusion is the only intervention, especially in cases with discectomy, the unbalanced distribution of the load on the vertebral column can increase the pressure on the transpedicular screw-rod systems. The findings of some authors support the view that adding interbody fusion gives superior mechanical strength to the vertebral structure. Three-column stabilization provides protection to neighboring mobile normal segments and prevents mechanical pain syndromes [13-15]. In our cases, we performed pre-operative surgical planning considering the stabilization of three columns. We did laminectomy only in the stenotic levels, and discectomy if there was an indication. In cases that we performed discectomy, we applied appropriate support (TLIF, PLIF) materials to the disc space. In addition, the screws were fixed with rigid rods which were given form in a manner that was appropriate to the pre-operative lumbar vertebral alignment. No reduction was applied to any patient unless required. Thus, we observed that postoperative lower back pain was decreased by maintaining the stability of the anterior, middle and posterior colons. This decreased postoperative analgesic use, and allowed earlier mobilization. In addition, we observed that reducing the load on the transpedicular screw rod system reduced the complications of screw-rod systems.

Lehman et al. reported 32 cases with posterior lumbar fusion which were followed for more than 30 years. They found that instability developed above

the fusion segment in about half of the cases and stenosis developed in about one third. However, these adjacent segment degenerations did not correlate with clinical symptoms [16]. Forty-nine cases who underwent posterior lumbar fusion and posterior interbody fusion were followed for five years. It was emphasized that the apparent adjacent segment degeneration was correlated with the clinic and that the development of pseudoarthrosis was a protective factor for adjacent segment degeneration [17]. Although our patients had early follow-up results, no pseudoarthrosis and adjacent segment changes were observed in our cases.

Thanks to instrumental fusion operations, cases can be mobilized in the early period and their return to daily living activities is faster. Patients with short segment stabilization had less pain both in late postoperative and early postoperative follow-up periods. In patients who underwent multisegment stabilization, the postoperative operative pain was more severe. In the late postoperative period, the patients had more pain symptoms due to waist inactivity.

Recently, non-instrumentation decompression has been preferred especially in patients with spinal stenosis. However, the appropriate treatment modality for lumbar spinal stenosis with spondylolisthesis is instrumentation and fusion in addition to decompression [18-20]. Providing the stability of the back and middle columns in particular; ligamentum flavum, facet joints and surgical interventions performed on the discs may impair the mechanical stability of the spine. Furthermore, pedicle systems have important advantages especially in elderly and osteoporotic patients. The best fixation in the osteoporotic vertebra is obtained from the pedicle, lumbar lordosis is preserved or restored, and fusion rates are increased by increasing rotational stability. The patients in our group were generally 50 years of age or older and constituted 71 percent of all patients. Many studies have similar approaches. For example, Fischgrund et al. Compared the rates of instrumentation and instrumentation-free fusion in cases with spinal stenosis and spondylolisthesis and reported that instrumentation increased fusion [21].

Posterior transpedicular screw-rod application have its own advantages and disadvantages compared to other stabilization systems (hook and wire) applied to the lumbar region. Pedicle screws are more effective and advantageous than other instrumentation systems in fixing the spine rigidly. They can be used in laminectomy performed vertebrae. The instrumentation level can be kept shorter and they are appropriate for the instrumentation of the sacrum. Screw-rod systems can additionally provide normal spinal curvature [11,13,14,22-24].

During pedicle screw application; complications such as screw malposition, spinal cord injury, retroperitoneal organ injury, infection, screw breakage and screw stripping, lack of appropriate instrumentation, prolonged operation time, excessive blood loss can be observed [25-30]. The most important complication of pedicle screw application is the incorrect placement of the screw. Radix, dura, cauda equina or spinal cord injury may occur in this case. In order to minimize or eliminate this risk, pre-operative planning should be performed very well and rigorous surgery should be performed. Measurements of each spine to be applied to the transpedicular screw should be calculated on pre-operative LCT and / or LMRI. The screw delivery angles should be determined and ensure that sufficient material is in stock. Surgical technique, experience, use of scopy and anatomical correlation in posterior transpedicular screw applications minimize the possible complications.

Postoperative late complications can be due to the structural features of the instruments used They can be used in laminectomy performed vertebrae and the patient's changing biomechanics. Implant fractures are quite common in that period. They can be used in laminectomy performed vertebrae, These are usually caused by metal fatigue. Again, loosening of implants with screw or hook-rod connection loosening or connection errors due to production may be seen [28,31]. Especially the spinal dura under L5 and below is much thinner. Although there is no mechanical injury, we think it causes CSF leakage and collection. We recommend that the L5 and six dura materin should be controlled with the valsalva maneuver during the operation and if there is any CSF leak, it should be repaired. In addition, we think that it is useful to place the hemovak drainage for drainage away from this area. In Table 6, it is seen that our complications are low in comparison with the series in the literature. In pre-operative preparation, we think that calculating screw lengths, pedicle diameters and screw insertion angles on LCT and LMRI reduce possible transpedicular screw complications. We think that especially pre-operative preparation is very important in surgical success.

The results of posterolateral transpedicular screw-rod application in the literature are variable. In the lumbar spinal stenosis decompression surgery, good and excellent results were reported at 80%. However, in most studies, early and mid-term results are good and in long-term follow-up, the results deteriorate over time and restenosis may develop [31,32]. Turner et al. studied long-term results and reported good and excellent results of in 64% of cases. In the same study, it was reported that good and perfect result rate increased to 85% in the presence of degenerative spondylolisthesis [7,31]. In our study, our good and excellent results are at 95%. This rate is quite high with our study with a mean follow-up of 28.6 months. This success depends on careful and appropriate surgical application, microsurgical application and surgical experience, careful patient selection, good and careful pre-operative preparation. However long-term results should be studied with prospective randomized studies.

Conclusions

Posterior transpedicular fixation and posterolateral fusion applications improve the quality of life. Patients can return to their daily lives and jobs faster. Patient selection is very important. We recommend that pre-operative preparation be performed as carefully as possible. We believe that it will facilitate the operation and minimize the complications related to transpedicular screw systems. We also recommend that all procedures except transpedicular screw rod applications should be performed by microsurgical technique.

Funding

No funding was received for this research.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Institutional Review Board of Istanbul Medipol University 16.4.2020/292) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

References

1.Japanase Orthopaedic Association. Assesement of surgical treatment for low back pain. Journal of the Japanese Orthopaedic Association, 1984; 58: 1183-1187.

2.Vaccaro AR, Garfin SR. Degenerative lumbar spondylolisthesis with spinal stenosis: A prospective study comparing decompression and decompression with intertransverse processes arthrodesis. A critical analysis spine, 1997; 22: 368-369.

3.Zileli M, Özer F: Spinal cord and spinal surgery, Volume 1, third edition, İzmir: İnter Tıp, 2014:701-712.

4.Dickman AC, Fessler GR, Macmillan M. Transpedicular screw-rod fixation of the lumbar spine: Operative technique and outcome in 104 cases. J Neurosurg 1992; 77: 860-870.

5.Issack PS, Cunningham ME, Pumberger M, Hughes AP, Cammisa FP Jr. Degenerative lumbar spinal stenosis: Evaluation and management. Review article. J Am AcadOrthop Surg 20: 527-535, 2012.

6.Miao J, Wang S, Park WM, Xia Q, Fang X, Torriani MP, et al. Segmental spinal canal volume in patients with degenerative spondylolisthesis. Spine J 13: 706–712, 2013.

7.Wang G, Karki SB, Xu S, Hu Z, Chen J, Zhou Z, et al. Quantitative MRI and X-ray analysis of disc degeneration and paraspinal muscle changes in degenerative spondylolisthesis. J Back MusculoskeletRehabil 28: 277–285, 2015.

8.Hadra BE. Wiring the spinous processes in Pott's disease. Trans Am Orthop Assoc 4. 1891; 206-210.

9.Albee FH. Transplantation of a portion of the tibia into the spine for Pott's disease. JAMA 1911; 57: 885-886.

10.Hibbs RA. An operation for progressive spinal deformities. NY Med J 1911; 93: 1013-1016.

11.Abumi K, Panjabi MM, Duranceau J. Biomechanical evaluation of spinal fixation devices Part III. Stability provided by six spinal fixation devices and interbody bone graft. Spine 1989; 14: 1249-1255.

12.Rosa La G, Conti A, Cacciola F, Cardali S, La Torri D, Gambadauro NM et al. Pedicle screw fixation for isthmic spondylolisthesis: does posterior lumbar interbody fusion improve outcome over posterolateral fusion? J Neurosurg(Spine 2) 2003; 99: 143-150.

13.Krag MH, Fredrickson BE, Yuan HA. Biornechanics of the transpedicle spinal fusion. The Lumbar Spine Philadelphia 1990; 916- 940.

14.Krag MH. Biomechanics of thorocolumbar spinal fixation A Rewiew. Spine 16(Supply 3) 1991; 84-99.

15.Ruetten S, Komp M, Merk H, Godolias G. Surgical treatment for lumbar lateral recess stenosis with the full-endoscopic interlaminar approach versus conventional microsurgical technique: A prospective, randomized, controlled study. Clinical article. J Neurosurg Spine 10: 476-485, 2009.

16.Lehman TR, Spratt KF. Long-term follow -up of lower lumbar fusion patients. Spine 1987; 12: 97-104.

17.Rahm MD, Hall BB. Adjacent-segment degeneration after lumbar fusion with instrumentation: a retrospective study.J Spinal Disord 1996; 9: 392-400.

18.Herno A, Airaksinen O, Saari T, Luukkonen M. Lumbar spinal stenosis: A matched-pair study of operated and non-operated patients. Br J Neurosurg 10: 461-465, 1996.

19.Malmivaara A, Slätis P, Heliövaara M, Sainio P, Kinnunen H, Kankare J, et all. Surgical or nonoperative treatment for lumbar spinal stenosis? A randomized controlled trial. Spine 32: 1-8, 2007.

20.Yücetaş C, Üçler N, Özdemir N. Lumbar Stenosis and Listhesis: Time of Stabilization. TürkNöroşirDerg 28(2):238-243, 2018.

21.Fischgrund JS, Mackay M, Herkowitz HN, Brower R, Montgomery DM, Kurz LT. Degenerative lumbar spondylolisthesis with spinal stenosis: a prospective, randomized study comparing decompressive laminectomy and arthrodesis with and with-out spinal instrumentation. Spine 1997, 22(24):2807-2812.

22.Ashman RB, Galpin RD, Corin JD, Johnston CE. Biomechanical analysis of pedicle screw instrumentation systems in a corpectomy model. Spine 1989; 14: 1398-1405.

23.Gurr KR, McAfee PC. Cotrel-Dobousset instrumentation in adults. A preliminary report. Spine 1988; 13: 510-520.

24.Yogonondan N, Larson SJ, Pintar F, Maiman DJ, Reinartz J, Sances A Jr. Biomechanics of lumbar pedicle screw plate fixation in trauma. Neurosurg 1990; 27: 873- 881.

25.Gaines RW Jr. The use of pedicle-screw internal fixation for the operative treatment of spinal disorders. J Bone Joint Surg (Am) 2000; 82: 1458-1476.

26.Güven O, Esemenli T, Yalçın S. Transpedicular fixation in the treatment of various spinal disorders. Acta ChirBelg 1993; 93: 188-192.

27.Halvorson TL, Kelley LA, Thomas KA, Whitecloud TS 3rd, Cook SD. Effects of bone mineral density on pedicle screw fixation. Spine 1994; 19: 2415-2420.

28.Postacchini F, Cinotti G. Bone regrowth after surgical decompression for lumbar spinal stenosis. J Bone Joint Surg Br 1992; 74-B(6):862-869.

29.West JL III, Ogilvie JW, Bradford DS. Complications of the variable screw plate pedicle screw fixation. Spine 1991; 16: 576-579.

30.Whitecloud TS III, Butler JC, Cohen JL, Candelora PD. Complications with the variable spinal plating system. Spine 1989; 14: 472-476.

31.Turner JA, Ersek M, Herron L, Deyo R. Surgery for lumbar spinal stenosis. Attempted meta-analysis of the literature. Spine 1992; 17(1): 1-8.

32.Truumees E, Fischgrund J, Herkowitz H. Management of spinal stenosis adjacent to a previously treated segment. Semin Spine Surg 1999; 11: 282-291.

Received: 3 Dec 2022 | **Accepted:** 25 Jan 2022
DOI: 10.54005/geneltip.1032165

ORIGINAL ARTICLE

Predictive Value of Monocyte to High-Density Lipoprotein Cholesterol Ratio (MHR) in Schizophrenia Patients with Stable Coronary Artery Disease

Stabil Koroner Arter Hastalığı Olan Şizofreni Hastalarında Monosit/Yüksek Yoğunluklu Lipoprotein (MHR) Oranının Öngördürücülüğü

[1]Mustafa Candemir [2]Alparslan Cansız

[1]Gazi University, Faculty of Medicine, Department of Cardiology, Ankara, Turkey

[2]Selçuk University, Faculty of Medicine, Department of Psychiatry, Konya, Turkey

Correspondence

Alparslan CANSIZ, Selçuk University, Faculty of Medicine, Department of Psychiatry, Konya, Turkey

E-Mail: alpcan2861@gmail.com

How to cite ?

Candemir M, Cansız A. Predictive Value of Monocyte to High-Density Lipoprotein Cholesterol Ratio (MHR) in Schizophrenia Patients with Stable Coronary Artery Disease. Genel Tıp Derg. 2022;32(1):77-83.

ABSTRACT

Aim: We aimed to investigate whether the monocyte/high-density lipoprotein ratio (MHR) has a potential value in the diagnosis of schizophrenia and in predicting the presence of comorbid coronary artery disease (SPCAD).
Material and Method: A total of 281 participants were enrolled in this cross-sectional study. Of the participants, 85 (Group 1) were diagnosed with schizophrenia and stable coronary artery disease, and 92 (Group 2) were diagnosed with only schizophrenia. 104 (Group 3) participants in the control group had no disease.
Results: MHR was highest in group 1 and higher in group 2 than in group 3. Group 1 was 18.91 (13.38-23.60) group 2: 13.68 (11.11-16.66) and group 3: 12.50 (9.13-15.68), respectively; p<0.001 for both). Conversely, HDL was the lowest in group 1, while it was lower in group 2 than in group 3 (38.52 ± 9.45 vs. 42.76 ± 9.12 vs. 47.00 ± 11.87, respectively p<0.05 for both). The cutoff value of MHR for SPCAD was 12.77, with a sensitivity of 79% and a specificity of 43%. This value for SP was 10.73, with a sensitivity of 79% and a specificity of 50%.
Conclusion: High MHR which indicates an enhanced inflammation and oxidative stress was found a significant and independent marker in SP and SPCAD.

Keywords: Coronary artery disease, inflammation, monocyte to high-density lipoprotein ratio, oxidative stress, schizophrenia

ÖZ

Amaç: Bu çalışmada şizofreni ve stabil koroner arter hastalığı olan şizofreni hastalarında (SKAH-Ş) monosit/yüksek yoğunluklu lipoprotein oranının (MHO) tanıda öngördürücü değerinin olup olmadığını araştırmayı amaçladık.
Gereç ve yöntem: Bu kesitsel çalışmaya toplam 281 katılımcı alındı. Katılımcıların 85'ine şizofreni ve stabil koroner arter hastalığı (Grup 1), 92'sine ise sadece şizofreni (Grup 2) tanısı konuldu. Kontrol grubundaki 104 katılımcının (Grup 3) ise hiçbir hastalığı yoktu.
Bulgular: MHO grup 1'de en yüksek iken grup 2'de grup 3'e göre daha yüksekti (grup 1: 18.91 (13.38-23.60); grup 2: 13.68 (11.11-16.66); grup 3: 12.50 (9.13-15.68); her iki karşılaştırma için p <0.001). Buna zıt olarak, HDL grup 1'de en düşük iken grup 2'de grup 3'e göre daha düşüktü (grup 1: 38.52 ± 9.45; grup 2: 42.76 ± 9.12; grup 3: 47.00 ± 11.87; her iki karşılaştırma için p <0.05). MHO' nun kesme puanı stabil koroner arter hastalığı olan şizofreni hastalarında 12.77 ve üzeri alındığında duyarlılık %79, özgüllük ise %43 bulundu. Sadece şizofreni hastalarında ise kesme değeri 10.73 ve üzeri alındığında duyarlılık % 79, özgüllük ise % 50 bulundu.
Sonuç: Artmış inflamasyon ve oksidatif stresi gösteren yüksek MHO, şizofreni ve stabil koroner arter hastalığı olan şizofreni hastalarında önemli ve bağımsız bir belirteç olarak bulundu.

Anahtar kelimeler: Koroner arter hastalığı, inflamasyon, monosit/yüksek yoğunluklu lipoprotein oranı, oksidatif stres, şizofreni

Introduction

Schizophrenia is a serious mental disorder that manifests itself with disturbances in thought, perception and behavior, and causes severe morbidity and mortality. It is known that its lifetime prevalence is approximately 1% (1). The first hypotheses proposed in schizophrenia, which has a multi-factorial etiology, pointed to neurotransmitter imbalance. In recent genetic studies, genetic regions associated with oxidative stress and inflammation stand out (2). Studies on blood cells, cytokines, inflammatory proteins, and tissue levels reveal the role of the immune system and inflammation in schizophrenia (3-5). Studies on oxidative stress show that there is a decreased antioxidant capacity in addition to increased oxidant activity in schizophrenia (6). It has been reported that both pro-inflammatory markers and oxidative stress are increased independent of antipsychotic treatment (6, 7).

Studies reveal that oxidative stress and inflammation may be effective not only in the etiology but also in the development of co-morbid conditions observed in the disease. It has been shown that the frequency of cardiovascular diseases increases 1.20 to 1.81 times and mortality increases 2 to 3 times in patients with schizophrenia (3, 6). Genetic factors, insulin resistance, impaired hypothalamic-hypopituitary-adrenal axis, increased oxidative stress and inflammatory response are thought to facilitate the development of cardiovascular diseases in patients with schizophrenia by forming a common ground (8-10).

Inflammation and oxidative stress are known to play an important role in the development and progression of atherosclerosis (11). Macrophages and monocytes are the most important cells that mediate the secretion of pro-inflammatory and pro-oxidant cytokines at inflammation site (12). These cells were determined to provide the release of inflammatory cytokines and tissue remodeling in the pathophysiology of coronary artery disease (13). Conversely, high-density lipoprotein cholesterol (HDL-C) prevents the formation of atherosclerosis by creating a defense mechanism in endothelial cells with its antioxidant effect (14, 15). This result has been supported by many studies (16). In addition, HDL-C inhibits monocyte activation and the proliferation and differentiation of monocyte progenitor cells (17). The ratio of these two parameters (monocyte/HDL-C ratio (MHR)) has been identified as a new marker, as high monocyte count and low HDL-C play a role in diseases with inflammatory and oxidative stress in the pathophysiology. This ratio is a relatively simple and inexpensive indicator of systemic inflammation obtained from the total blood count. In addition, this marker has predictive and prognostic importance in cardiovascular diseases such as coronary artery disease (18, 19). In the study of Kızıltunç et al., it was found that MHR was associated with the severity of coronary artery disease in 760 patients who underwent coronary angiography under elective conditions (20). In a recent study, 74 schizophrenic patients were compared with healthy controls for MHR. In that study, MHR was higher in the patient group than in healthy individuals (21).

MHR, which is a practical and inexpensive instrument, can be used to detect early systemic inflammatory events such as cardiovascular disease in patients with schizophrenia. However, there is no study investigating MHR in schizophrenia patients with coronary artery disease in the literature (SPCAD). For this reason, our study has two aims; i- to determine the diagnostic value of MHR in patients with schizophrenia, ii- The capacity of MHR to predict the presence of coronary artery disease in patients with schizophrenia.

Material and Method

All subjects were retrospectively reviewed admitted to a tertiary hospital with schizophrenia between January 2009 and February 2020. The demographic and clinical data of the patients were obtained from their electronic medical records. Patients admitted with a diagnosis of schizophrenia for at least 6 months were included. In addition, the diagnosis of schizophrenia was confirmed by at least 2 psychiatrists. The diagnosis of the patients was made according to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (22). All patients were between 18-65 years old. Patients with an active infection during the blood draw, acute coronary syndrome, history of acute or chronic liver or kidney disease, autoimmune disease, cancer, hematological disorders, severe valvular disease, rheumatic disease or using antihyperlipidemic drugs were planned to be excluded from the study. Among the patients diagnosed with schizophrenia, patients with stable angina pectoris were selected. After all, it was determined that 91 patients with schizophrenia were diagnosed with stable angina pectoris. Six of these patients had missing file information. Thus, 85 schizophrenia patients with coronary disease were included in the study as Group 1. The diagnosis of stable angina pectoris was made in accordance with the criteria specified in the guidelines. All patients with stable angina pectoris underwent coronary angiography. Coronary angiographies of the patients were performed after the blood results were evaluated in the study. Group 2 (n=92) included patients with schizophrenia who were age-matched to the first group and did not have any cardiac diagnosis. In order to increase the accuracy of the analyzes, the control group was also included in the study (group 3, n=104). This group was selected as age-matched to the previous groups among the individuals who were not found to have any pathology when they were admitted to the cardiology outpatient clinic with any cardiac complaints. The demographic and clinical data of the patients were obtained from their electronic medical records.

An approval (approval no. 2020/483) of the Local Ethics Committee of Selçuk University was obtained for the research.

Laboratory Analysis

Routine blood tests obtained in the last three months in the psychiatry and cardiology clinics to which the participants applied were included in the analysis. Basic hematologic parameters, such as monocyte count were measured with an auto analyzer. Serum total cholesterol, triglyceride, and HDL-C concentrations were analyzed by using an automated chemistry analyzer. Serum low-density lipoprotein cholesterol (LDL-C) values were estimated by the formula of Friedewald or directly measured if triglyceride > 400 mg/dL. MHR ratio was calculated by division of monocyte count by HDL-C.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 23.0 (SPSS Inc, Chicago, IL, USA). The

Kolmogorov-Smirnov method was used to test the distribution pattern. Data were presented as mean and standard deviation, median and interquartile range, or proportions. The Chi-square test was used to compare the proportions of the different groups. One-way analysis of variance or Kruskal-Wallis tests were used to compare continuous variables among different groups according to the distribution pattern of the variable. When an overall significance was observed in a normally distributed variable, the post hoc Tukey's test was performed. When an overall significance was observed in an abnormally distributed variable, pairwise differences were evaluated using the Mann-Whitney U test and the Bonferroni correction was applied to adjust for multiple comparisons. Stepwise multivariate logistic regression analysis was done to examine the association between the functional significance of the lesions and other variables. Variables with P < 0.25 in univariate logistic regression were included in a multivariate logistic regression model. In the logistic regression model, MHR level was assumed to be a binary variable according to the cutoff point detected in the receiver operating characteristic (ROC) curve analysis. A difference with a p-value <0.05 was considered statistically significant.

Results

A total of 281 participants were enrolled in the study. Of the participants, 85 (Group 1; mean age 37.06 ± 11.27, 22 females and 63 males) were diagnosed with schizophrenia and stable coronary artery disease and 92 (Group 2; mean age 37.36 ± 10.50, 35 females and 57 males) were diagnosed only schizophrenia. 104 (Group 3; mean age 35.40 ± 11.01, 49 females and 55 males) participants in the control group had no disease. Demographic characteristics were similar across all groups. There were no significant differences between groups with respect to the serum biochemical parameters of glucose, creatinine, hemoglobin, platelets, lymphocyte, ALT, AST, total cholesterol, triglycerides, LDL-C (Table 1).

Monocytes count (700.00 (575.00-800.00) vs. 600.00 (500.00-700.00) vs. 500.00 (400.00-675.00) vs, p < 0.001) and MHR (18.91 (13.38-23.60) vs.13.68 (11.11-16.66) vs. 12.50 (9.13-15.68), p<0.001) were significantly higher in group 1 than the other group 3, while HDL-C (38.52 ± 9.45 vs. 42.76 ± 9.12 vs. 47.00 ± 11.87, p<0.001) was lower. The cutoff value of MHR for schizophrenia was 10.73, with a sensitivity of 79% and a specificity of 50%,

Table 1. Baseline characteristics and laboratory findings of the study participants.

	Group 1 (n=85)	Group 2 (n=92)	Group 3 (Control) (n=104)	*p*
Age, mean (SD), years	37.06 ± 11.27	37.36 ± 10.50	35.40 ± 11.01	0.40
Sex (Male), n (%)	63 (74.1)	57 (62.0)	55 (52.9)	0.10
Hypertension, n (%)	51 (60)	64 (69.6)	61 (58.7)	0.24
Diabetes mellitus, n (%)	32 (37.6)	28 (30.4)	27 (26)	0.22
Smoke, n (%)	26 (31)	31 (34)	36 (35)	0.83
Dyslipidemia, n (%)	43 (50.6)	43 (46.7)	36 (34.6)	0.16
EF, %	60.00 (52.00-65.00)	62.00 (55.00-65.00)	65.00 (61.00-67.00)	0.15
Glucose, mg/dl	98.00 (91.00-147.50)	102.00 (93.00-129.00)	101.00 (91.00-125.00)	0.26
BUN, mg/dl	17.59 ± 6.06	16.34 ± 4.94	15.75 ± 6.63	0.12
Creatine, mg/dl	0.88 (0.80-1.10)	0.82 (0.72-0.98)	0.82 (0.70-0.97)	0.07
WBC count, (× 10^3/ml)	8.80 (7.20-10.25)*	7.55 (6.60-9.10)	7.45 (6.30-8.70)	0.01
Hemoglobin, gr/dl	13.74 ± 1.76	13.53 ± 2.09	13.29 ± 1.68	0.26
RDW, %	14.00 ±1.72	13.00 ± 1.32	13.85 ± 1.81	0.31
PLT, (× 10^3/ml)	241.00 (193.50-277.00)	235.00 (186.25-286.00)	235.00 (194.25-286.00)	0.34
Neutrophil count	5300.00 (4500.00-6750.00)*	4600.00 (3700.00-5450.00)	4450.00 (3500.00-5500.00)	<0.001
Lymphocyte count	2257.06 ± 907.08	2275.76 ± 930.81	2373.26 ± 775.76	0.90
Monocyte count	700.00 (575.00-800.00)*	600.00 (500.00-700.00)*	500.00 (400.00-675.00)*	<0.001
AST u/l	22.00 (16.00-29.00)	21.00 (17.00-27.00)	20.00 (17.00-25.25)	0.22
ALT u/l	21.50 (15.00-31.00)	20.00 (14.75-30.25)	19.00 (14.00-27.00)	0.07
Triglyceride mg/dl	148.24 ± 73.75	160.88 ± 82.83	148.67 ± 85.52	0.49
Total cholesterol, mg/dl	185.82 ± 44.74	185.36 ± 56.71	197.03 ± 44.89	0.17
LDL, mg/dl	116.03 ± 41.40	113.16 ± 45.72	122.93 ± 38.16	0.24
HDL, mg/dl	38.52 ± 9.45*	42.76 ± 9.12*	47.00 ± 11.87*	<0.001
MHR	18.91 (13.38-23.60)*	13.68 (11.11-16.66)*	12.50 (9.13-15.68)*	<0.001

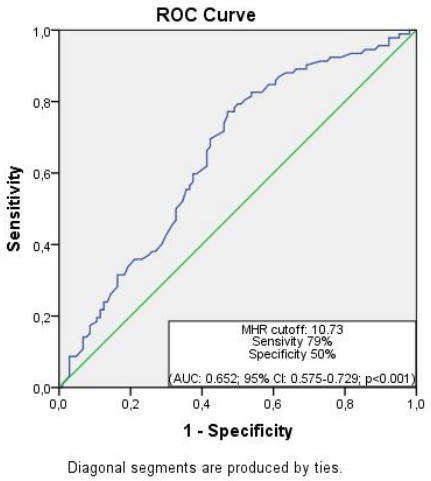
Results are expressed as mean ± SD or median (IQR) or frequency (%)

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: Blood Urea Nitrogen, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, MHR: monocyte to high-density lipoprotein cholesterol ratio, PLT: platelets, RDW: Red cell distribution width, WBC: white blood cells. * denotes statistically significant cells after Tukey or Games-Howell adjustment.

(AUC: 0.652; 95% confidence interval (CI): 0.575-0.729; p<0.001) on ROC curve analysis (Figure 1). Multivariate logistic regression analysis including hypertension, dyslipidemia, glucose, ALT, total cholesterol, LDL-C, MHR demonstrated that MHR was the only independent predictor of schizophrenia (OR: 1.438, CI: 1.268-1.631, P<0.001) (Table 2).

The cutoff value of MHR for schizophrenia and stable coronary artery disease was 12.77, with a sensitivity of 79% and a specificity of 43% (area under the curve (AUC): 0.695, 95% confidence interval (CI):0.616-0.775; p<0.001) on ROC curve analysis (Figure 2). Three models were generated by multivariate logistic regression analysis to predict SPCAD. MHR was found to be the best independent predictor in all models (OR: 1.471, CI: 1.283-1.688, P<0.001) (Table 3).

Figure 1. Receiver operating characteristic (ROC) curve analysis of MHR in schizophrenia patients.



AUC: area under the curve; CI: confidence interval; MHR: monocyte to high-density lipoprotein cholesterol ratio.

Table 2. Multivariate logistic regression analysis showing independent predictors in schizophrenia patients.

	Univariate		**Multivariate**	
	OR (95 % CI)	***p***	**OR (95 % CI)**	***p***
Sex (Male)	1.396 (0.789-2.470)	0.252	-	-
Hypertension	1.611 (0.892-2.910)	0.114	1.138 (0.509-2.546)	0.753
Dyslipidemia	1.658 (0.932-2.947)	0.085	1.761 (0.807-3.845)	0.155
Glucose	1.004 (0.998-1.010)	0.159	1.005 (0.998-1.013)	0.166
ALT	1.019 (0.994-1.045)	0.132	1.018 (0.985 -1.051)	0.292
Total cholesterol	0.995 (0.990-1.001)	0.111	1.014 (0.996-1.033)	0.129
LDL	0.994 (0.988-1.001)	0.106	0.980 (0.959-1.001)	0.063
MHR	1.422 (1.264-1.600)	**<0.001**	1.438 (1.268-1.631)	**<0.001**

OR: Odds Ratio, CI: Confidence Interval ALT: alanine aminotransferase LDL: low-density lipoprotein cholesterol, MHR: monocyte to high density: lipoprotein cholesterol ratio, Bold values denote statistical significance at the p < 0.05 level.

Table 3. Multivariate logistic regression analysis showing independent predictors in schizophrenia patients with coronary artery disease.

Model	**OR (95 % CI)**		**Univariate**		**Multivariate**	
			p	**OR (95 % CI)**	***p***	
1	A	Sex (Male)	1.758 (0.925-3.343)	0.085	0.728 (0.270-1.962)	0.531
		Hypertension	0.656 (0.353-1.221)	0.184	0.444 (0.163 -1.206)	0.111
		Creatine	1.102 (0.620-1.957)	0.741	-	-
		WBC	1.000 (1.000-1.000)	0.641	-	-
		Neutrophil	1.000 (1.000-1.002)	**0.002**	1.000 (1.000-1.001)	**0.009**
		MHR	1.448 (1.278-1.641)	**<0.001**	1.471 (1.283-1.688)	**<0.001**
2	A +	Monocyte	-	**-**	1.002 (1.000-1.003)	**0.014**
3	A +	HDL	-	**-**	0.953 (0.920-0.989)	**0.010**

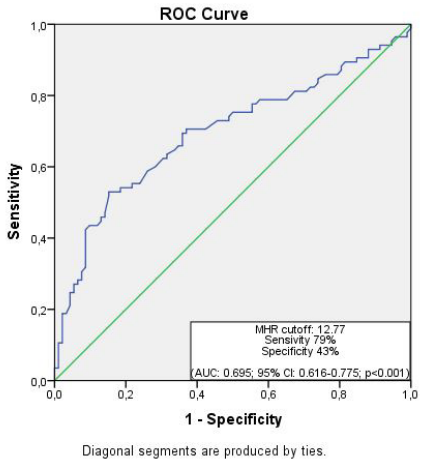
Model 1 includes sex, hypertension, creatine, WBC, neutrophil, and MHR.

Model 2 includes sex, hypertension, creatine, WBC, neutrophil, and monocyte.

Model 3 includes sex, hypertension, creatine, WBC, neutrophil, and HDL.

OR: Odds Ratio, CI: Confidence Interval WBC: white blood cells. MHR: monocyte to high density: lipoprotein cholesterol ratio, HDL: high-density lipoprotein. Bold values denote statistical significance at the p < 0.05 level.

Figure 2. Receiver operating characteristic (ROC) curve analysis of MHR in schizophrenia patients with coronary artery disease.



AUC: area under the curve; CI: confidence interval; MHR: monocyte to high-density lipoprotein cholesterol ratio.

Discussion

In our study, MHR was found higher in SPCAD compared to schizophrenia patients without coronary artery disease and the control group. In addition, increased MHR was found to have a diagnostic value both for schizophrenia and for predicting the presence of coronary artery disease in schizophrenia patients.

Genetic studies reveal the prominent role of inflammatory parameters in schizophrenia. Among the single nucleotide polymorphisms detected in schizophrenia, it has been shown that the strongest relationship with the disease is in the genes responsible for the complement system (C4) (23). Studies show that the C4 complement protein enables the synapses to be pruned by microglia and that the C4A protein is expressed more in schizophrenia patients than in controls. It is thought that neuron-microglia interaction through the complement system plays a role in the pathogenesis of schizophrenia. In addition to many parameters in the detection of systemic inflammation, whole blood and biochemistry measurements offer practical and effective methods. In a recent meta-analysis evaluating the studies investigating neutrophil-lymphocyte ratio (NLR), which is shown as one of these, it has been shown that NLR increases both in the first episode and in chronic schizophrenia patients (3). It has also been reported that there is a linear relationship between increased NLR and increased disease severity. Studies evaluating monocytes in patients with schizophrenia state that the number of monocytes increases in both follow-up and first-episode patients (24, 25). It is stated that the increase in monocytes in patients with schizophrenia is a peripheral indicator of microglia activation in the brain (24). Our findings show that MHR increases similarly to NLR in patients with schizophrenia compared to controls, and monocyte activation can also be mentioned in patients in our sample.

It is known that lipid metabolism is impaired in patients with schizophrenia. In a meta-analysis including 19 studies, it was revealed that first-episode psychosis patients who did not use any medication had a decrease in total cholesterol and HDL-C levels and an increase in triglyceride levels (26). Based on this, low HDL-C levels in schizophrenia patients are considered to be associated with both the etiology of schizophrenia and increased cardiovascular comorbidity (27). Consistently with the literature, in our study, HDL-C levels were lower in schizophrenia patients with coronary artery disease compared to both the control group and schizophrenia patients without cardiovascular disease. Although the cross-sectional design of our study does not allow interpreting the causal relationship, it can be stated that lipid metabolism should be closely monitored in patients with schizophrenia. In addition, ROC analysis shows that MHR can be used as a new biomarker in patients with schizophrenia.

Inflammation and oxidative stress are well-known mechanisms during the development and progression of atherosclerosis (13). It has been stated that the number of monocytes, one of the basic cells of the human immune system, is an independent predictive marker in atherosclerotic plaque formation and plaque progression (28). Since the sensitivity of monocytes to chemokines increases in hypercholesterolemic patients, it has been expressed that these cells play a more prominent role in the atherosclerotic process (29). HDL-C, which reduces the effects of the hypercholesterolemic environment, has anti-inflammatory and anti-oxidant properties and is known as a negative acute phase reactant, has an important role in preventing the formation of atherosclerosis (29-32). HDL-C inhibits active monocytes (33) and inhibits the endothelial expression of adhesion molecules, preventing monocyte passage from the artery endothelium (34). In addition, HDL-C has determined shown to play an important role in protection against atherosclerosis, unlike monocytes (35) and HDL-C is an important marker for the prognosis of cardiovascular diseases (36). Kızıltunç et al. (20) found they MHR was associated with the severity and extent of coronary artery disease. MHR has also been proven to be an independent marker that predicts in-hospital mortality and 5-year major adverse cardiovascular events (MACE) in patients with ST-segment elevation myocardial infarction (32). Based on all these study results, it can be considered that MHR is a valuable marker in atherosclerotic heart diseases and deserves to be investigated in other cardiovascular conditions.

Cardiovascular diseases are the leading cause of early death in patients with schizophrenia. It has been reported that the life expectancy in schizophrenia patients decreases by 15-20 years compared to the normal population due to cardiovascular diseases (37). In addition, it is known that patients with schizophrenia go to examinations less for their physical

health and talk less about their complaints (38). Therefore, early diagnosis of cardiovascular diseases and other metabolic disturbances is very important in schizophrenia patients. Few biomarker studies have been conducted to define cardiovascular disease risk in patients with schizophrenia (39). Our research reveals that increased MHR has high power in predicting stable coronary artery disease in patients with schizophrenia. This information suggests that systemic inflammation is an important mediator of the development of cardiovascular disease in patients with schizophrenia, as well as known environmental risk factors. As a marker of systemic inflammation and oxidative stress, MHR could provide information on the common origins of schizophrenia and cardiovascular disease.

Our study has some limitations. First is the relatively small sample size and its retrospective design. Second, since our study was in a cross-sectional design, it does not provide information about which disease started first. Third, antipsychotic drugs have some effects on cardiac functions and we could not test whether the drugs taken by the patients had an effect on MHR. Fourth, it is not documented that patients who were determined to have no coronary artery disease from their history and records have normal coronaries. Fifth, only those with a diagnosis of coronary artery disease were not included in the analysis. Another limitation is that although the exclusion criteria were applied to the control group, the control group may not reflect and the characteristics of the general population due to the design of the study. Finally, other inflammatory markers such as CRP and oxidative stress markers have not been evaluated.

Conclusion

Our study is the first to investigate MHR in patients with schizophrenia and reveal its relationship with coronary artery disease. We found that MHR, which can be easily obtained from complete blood count and biochemistry measurement, was higher in patients with schizophrenia. In addition, our study has added a new observation to the literature that a higher MHR level may have a diagnostic value for coronary artery disease, especially in patients with schizophrenia. However, our findings should be confirmed with large-scale prospective studies.

Acknowledgments

Declaration of Conflicting Interests
The Authors declare that there is no conflict of interest.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

References

1.McCutcheon RA, Reis Marques T, Howes OD. Schizophrenia-An Overview. JAMA psychiatry. 2019:1-10.

2.Liu J, Li M, Luo XJ, Su B. Systems-level analysis of risk genes reveals the modular nature of schizophrenia. Schizophrenia research. 2018;201:261-9.

3.Trépanier MO, Hopperton KE, Mizrahi R, Mechawar N, Bazinet RP. Postmortem evidence of cerebral inflammation in schizophrenia: a systematic review. Molecular psychiatry. 2016;21(8):1009-26.

4.Gallego JA, Blanco EA, Husain-Krautter S, Madeline Fagen E, Moreno-Merino P, Del Ojo-Jiménez JA, et al. Cytokines in cerebrospinal fluid of patients with schizophrenia spectrum disorders: New data and an updated meta-analysis. Schizophrenia research. 2018;202:64-71.

5.Karageorgiou V, Milas GP, Michopoulos I. Neutrophil-to-lymphocyte ratio in schizophrenia: A systematic review and meta-analysis. Schizophrenia research. 2019;206:4-12.

6.Flatow J, Buckley P, Miller BJ. Meta-analysis of oxidative stress in schizophrenia. Biological psychiatry. 2013;74(6):400-9.

7.Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biological psychiatry. 2011;70(7):663-71.

8.Guest PC. Insulin Resistance in Schizophrenia. Advances in experimental medicine and biology. 2019;1134:1-16.

9.Leonard BE, Schwarz M, Myint AM. The metabolic syndrome in schizophrenia: is inflammation a contributing cause? Journal of psychopharmacology (Oxford, England). 2012;26(5 Suppl):33-41.

10.Karanikas E, Antoniadis D, Garyfallos GD. The role of cortisol in first episode of psychosis: a systematic review. Current psychiatry reports. 2014;16(11):503.

11.Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. The New England journal of medicine. 2005;352(16):1685-95.

12.Ancuta P, Wang J, Gabuzda D. CD16+ monocytes produce IL-6, CCL2, and matrix metalloproteinase-9 upon interaction with CX3CL1-expressing endothelial cells. Journal of leukocyte biology. 2006;80(5):1156-64.

13.Hansson GK. Inflammatory mechanisms in atherosclerosis. Journal of thrombosis and haemostasis : JTH. 2009;7 Suppl 1:328-31.

14.Kuvin JT, Rämet ME, Patel AR, Pandian NG, Mendelsohn ME, Karas RH. A novel mechanism for the beneficial vascular effects of high-density lipoprotein cholesterol: enhanced vasorelaxation and increased endothelial nitric oxide synthase expression. American heart journal. 2002;144(1):165-72.

15.Kuvin JT, Patel AR, Sidhu M, Rand WM, Sliney KA, Pandian NG, et al. Relation between high-density lipoprotein cholesterol and peripheral vasomotor function. The American journal of cardiology. 2003;92(3):275-9.

16.Soria-Florido MT, Schröder H, Grau M, Fitó M, Lassale C. High density lipoprotein functionality and cardiovascular events and mortality: A systematic review and meta-analysis. Atherosclerosis. 2020;302:36-42.

17.Wang P, Wang Y, Ma W, Li H, Chen H. High-density lipoprotein cholesterol and intracoronary thrombosis burden. Coronary artery disease. 2013;24(1):1-5.

18.Karataş MB, Çanga Y, Özcan KS, İpek G, Güngör B, Onuk T, et al. Monocyte to high-density lipoprotein ratio as a new prognostic marker in patients with STEMI undergoing primary percutaneous coronary intervention. The American journal of emergency medicine. 2016;34(2):240-4.

19.Wu TT, Zheng YY, Chen Y, Yu ZX, Ma YT, Xie X. Monocyte to high-density lipoprotein cholesterol ratio as long-term prognostic marker in patients with coronary artery disease undergoing percutaneous coronary intervention. Lipids in health and disease. 2019;18(1):180.

20.KIZILTUNÇ E, Alsancak Y, Sezenöz B, Özkan S, Sivri S, Alsancak AD, et al. Relationship between monocyte/high-density lipoprotein cholesterol ratio and angiographic severity and extent of coronary artery disease. Koşuyolu Heart Journal. 2017;20(1):30-5.

21.Sahpolat M, Ayar D, Ari M, Karaman MA. Elevated Monocyte to High-density Lipoprotein Ratios as an Inflammation Markers for Schizophrenia Patients. Clinical psychopharmacology and neuroscience : the official scientific journal of the Korean College of Neuropsychopharmacology. 2021;19(1):112-6.

22.Association AP. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR): American Psychiatric Association; 2000.

23.Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, et al. Schizophrenia risk from complex variation of complement component 4. Nature. 2016;530(7589):177-83.

24.Mazza MG, Capellazzi M, Lucchi S, Tagliabue I, Rossetti A, Clerici M. Monocyte count in schizophrenia and related disorders: a systematic review and meta-analysis. Acta neuropsychiatrica. 2020;32(5):229-36.

25.Weber NS, Gressitt KL, Cowan DN, Niebuhr DW, Yolken RH, Severance EG. Monocyte activation detected prior to a diagnosis of schizophrenia in the US Military New Onset Psychosis Project (MNOPP). Schizophrenia research. 2018;197:465-9.

26.Misiak B, Stańczykiewicz B, Łaczmański Ł, Frydecka D. Lipid profile disturbances in antipsychotic-naive patients with first-episode non-affective psychosis: A systematic review and meta-analysis. Schizophrenia research. 2017;190:18-27.

27.Douglas J, Nasrallah HA. Low high-density lipoprotein and psychopathology: A review. Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists. 2019;31(3):209-13.

28.Johnsen SH, Fosse E, Joakimsen O, Mathiesen EB, Stensland-Bugge E, Njølstad I, et al. Monocyte count is a predictor of novel plaque formation: a 7-year follow-up study of 2610 persons without carotid plaque at baseline the Tromsø Study. Stroke. 2005;36(4):715-9.

29.Bath PM, Gladwin AM, Martin JF. Human monocyte characteristics are altered in hypercholesterolaemia. Atherosclerosis. 1991;90(2-3):175-81.

30.Murphy AJ, Chin-Dusting JP, Sviridov D, Woollard KJ. The anti inflammatory effects of high density lipoproteins. Current medicinal chemistry. 2009;16(6):667-75.

31.Murphy AJ, Woollard KJ. High-density lipoprotein: a potent inhibitor of inflammation. Clinical and experimental pharmacology & physiology. 2010;37(7):710-8.

32.Açıkgöz SK, Açıkgöz E, Şensoy B, Topal S, Aydoğdu S. Monocyte to high-density lipoprotein cholesterol ratio is predictive of in-hospital and five-year mortality in ST-segment elevation myocardial infarction. Cardiology journal. 2016;23(5):505-12.

33.Yvan-Charvet L, Pagler T, Gautier EL, Avagyan S, Siry RL, Han S, et al. ATP-binding cassette transporters and HDL suppress hematopoietic stem cell proliferation. Science (New York, NY). 2010;328(5986):1689-93.

34.Cockerill GW, Rye KA, Gamble JR, Vadas MA, Barter PJ. High-density lipoproteins inhibit cytokine-induced expression of endothelial cell adhesion molecules. Arteriosclerosis, thrombosis, and vascular biology. 1995;15(11):1987-94.

35.Barter P. The role of HDL-cholesterol in preventing atherosclerotic disease. European Heart Journal Supplements. 2005;7(suppl_F):F4-F8.

36.Roberts CK, Ng C, Hama S, Eliseo AJ, Barnard RJ. Effect of a short-term diet and exercise intervention on inflammatory/anti-inflammatory properties of HDL in overweight/obese men with cardiovascular risk factors. Journal of applied physiology (Bethesda, Md : 1985). 2006;101(6):1727-32.

37.Ringen PA, Engh JA, Birkenaes AB, Dieset I, Andreassen OA. Increased mortality in schizophrenia due to cardiovascular disease - a non-systematic review of epidemiology, possible causes, and interventions. Frontiers in psychiatry. 2014;5:137.

38.von Hausswolff-Juhlin Y, Bjartveit M, Lindström E, Jones P. Schizophrenia and physical health problems. Acta psychiatrica Scandinavica Supplementum. 2009(438):15-21.

39.Onen S, Taymur I. Evidence for the atherogenic index of plasma as a potential biomarker for cardiovascular disease in schizophrenia. Journal of psychopharmacology (Oxford, England). 2021;35(9):1120-6.

Received: 6 Aug 2021 | **Accepted:** 21 Nov 2021
DOI: 10.54005/geneltip.979748

ORIGINAL ARTICLE

Association between Platelet to Lymphocyte ratio and Intraventricular hemorrhage in extremely immature infants

İleri derecede immatür bebeklerde Trombosit Lenfosit oranı ile İntraventriküler kanama arasındaki ilişki

[1]Musa Silahlı

[1]Başkent Üniversitesi Tıp Fakültesi, Konya Uygulama ve Araştırma Merkezi, Çocuk sağlığı ve Hastalıkları Anabilim Dalı, Yeni Doğan Bilim Dalı, Konya

Correspondence

Musa Silahlı, Hoca cihan Mah. Saray Cad. No:1 Selçuklu Konya Posta kodu:42090

E-Mail: msilahli@gmail.com

How to cite ?

Silahlı M. Association between Platelet to Lymphocyte ratio and Intraventricular hemorrhage in extremely immature infants. Genel Tıp Derg. 2022;32(1):84-88.

ABSTRACT

Aim: Intraventricular hemorrhage (IVH) is a serious complication of premature births, especially in newborns with very low birth weight. It's important to be able to predict IVH. In this study, the relationship between thrombocyte lymphocyte ratio (TLR) and intraventricular hemorrhage in premature infants born under 28 weeks was examined.
Materials and Methods: In the last 5 years, the medical records of infants with less than 28 weeks of gestational age (n=78) born in our hospital have been retrospectively examined. Obtained parameters from the whole blood count, especially the relationship between TLR and IVH were examined.
Results: White blood cell and lymphocyte counts were significantly higher in severe IVH (grade 3-4), while TLR was found to be significantly lower (16048±5265 & 11972±10915, p=0.043; 10705±4537 & 6329±8101, p=0.007; 36.9±22.7 & 56.7±37.9 p=0.012, respectively). When the white blood cell, lymphocyte count, and TLR's diagnostic performance in predicting severe IVH were evaluated by ROC curve analyses, it was observed that the strongest performance belonged to the TLR (Area under the curve, AUC for WBC: 0.644; ALS: 0.687; TLR: 0,691, respectively). TLR can estimate severe IVH with 94% sensitivity and 43% specificity at a cut-off value below 55.84.
Conclusion: TLR can be used as a valuable marker for predicting IVH in extremely premature infants.

Keywords: Intraventricular hemorrhage; platelet lymphocyte ratio; premature infants.

ÖZ

Amaç: İntraventriküler hemoraji (IVH), özellikle çok düşük doğum ağırlıklı yeni doğanlarda prematüre doğumların ciddi bir komplikasyonudur. IVH'yi tahmin edebilmek oldukça önemlidir. Bu çalışmada 28 hafta altında doğan prematüre bebeklerde doğumda bakılan trombosit lenfosit oranı (TLO) ve intraventriküler hemoraji (IVH) arasındaki ilişki incelenmek istenmiştir.
Gereç ve yöntem: Son 5 yılda hastanemizde yatan 28 hafta altı prematüre bebeklerin (n=78) dosyaları geriye dönük incelendi. Doğum sonrası bakılan tam kan verilerinden elde edilen parametreler ve özellikle TLO ve IVH arsındaki ilişki incelendi.
Bulgular: Beyaz küre ve lenfosit sayıları ciddi IVH'de (grade 3-4) anlamlı yüksek bulunurken, TLO anlamlı düşük bulunmuştur (sırasıyla 16048±5265 & 11972±10915, p=0,043; 10705±4537 & 6329±8101, p=0,007; 36,9±22,7 & 56,7±37,9 p=0,012). Beyaz küre, lenfosit sayısı ve TLO'nun ciddi IVH'i öngörmede tanısal performansları ROC eğrisi analizleri ile değerlendirildiğinde en güçlü performansın TLO'ya ait olduğu gözlemlendi (sırasıyla eğri altında kalan alan WBC: 0,644; ALS: 0.678; TLO:0,691). TLO kesme değeri 55,84 altındaki değerlerde %94 sensitivite ve %43 spesifite ile ağır IVH'i tahmin ettirebilir.
Sonuç: TLO ileri derecede immature bebeklerde ciddi IVH'iöngörmede değerli bir belirteç olarak kullanılabilir.

Anahtar kelimeler: Intraventriküler kanama; Trombosit lenfosit oranı; prematüre

Introduction

Intraventricular hemorrhage (IVH) is one of the most important complications of this high-risk group, causing mortality and long-term sequelae in severely immature infants. In studying the etiology of IVH, it is known to be multifactorial (1) and related to both prenatal and postnatal factors (2). The occurrence of IVH may be due to many environmental and medical risk factors. These include assisted reproductive techniques (IVF), non-administration of antenatal steroids, antenatal maternal bleeding, maternal medical risk factors, chorioamnionitis, external birth, prematurity/low birth weight, low APGAR scores, male gender, early sepsis, hypoxemia, hypercapnia, hypocapnia, pneumothorax, pulmonary hemorrhage, respiratory distress syndrome (RDS), and treatment with vasopressors (3-6). TLR is an indicator of the balance between inflammation and thrombosis. Inflammatory conditions in the body lead to increased production of megakaryocytes and associated thrombocytosis. Furthermore, it is recognised that increased platelet counts and

decreased lymphocyte counts are associated with both aggregation and inflammation and are therefore risk indicators for inflammation (7-10). Lymphopenia is common in childhood and the neonatal period and can be included among the etiologic factors under the main headings such as infections, genetic causes, iatrogenic causes, and systemic diseases. A lymphocyte count of less than 2500 /mm3 in the neonatal period is generally considered lymphopenia (18).

Whole blood indices related to platelets, which are indicators of inflammation in the neonatal period, have been evaluated in relation to neonatal and especially preterm morbidities. There are studies suggesting that there is an association between platelet-related markers including platelet mass index, mean platelet volume and IVH (11).
Here, TLR was calculated in whole blood samples collected at the first hospitalization of preterm infants younger than 28 weeks, and the relationship between IVH was to be investigated.

Materials and Methods

This single-centre, retrospective study was conducted at Başkent University, Konya Application and Research Centre, Konya, Turkey. This study was approved by the Ethics Committee of Başkent University (project number: KA19/70). The medical records of 78 preterm low birth weight infants treated in the neonatal intensive care unit of our hospital during the last 5 years were retrospectively reviewed. Preterm infants with a gestational age of less than 28 weeks and a birth weight of less than 1200 g were included in the study.

Clinical data and demographic information, including week of gestation, sex, weight; prenatal steroid administration, respiratory distress syndrome (RDS), oxygen consumption days; bronchopulmonary dysplasia (BPD), maximum oxygen demand in the first three days of life, intraventricular hemorrhage; hemodynamically significant patent ductus arteriosus, complete blood count on admission, parenteral nutrition days, necrotizing enterocolitis (NEC); The incidence of sepsis and ROP and length of hospital stay were obtained from the medical records of the admitted infants. Patients admitted to the neonatal intensive care unit later than the third day of life, infants with genetic anomalies and other severe congenital malformations were excluded from the study. Infants included in the study underwent cranial usg by postnatal day 7 (usually postnatal day 3) and were classified into grades 1-4 according to the Papilla classification (12). Grade 1: bleeding from germinal matrix, Grade II: intraventricular hemorrhage, Grade III: intraventricular hemorrhage and dilatation, Grade IV: intraventricular and intraparenchymal hemorrhage. Of the 78 cases, 7 cases were not included in the study due to lack of data on early exitus and IVH. A total of 71 cases were divided into 2 groups, one group with severe IVH (grade 3-4, n=17) and the other group with mild IVH or no IVH (grade 1-2 or no IVH, n=54). TLR and neutrophil-to-lymphocyte ratio (NLR) were calculated from complete blood count data on day 1.

Descriptive statistics of scale variables are presented as mean ± standard deviation (SD) or median (range), as appropriate. Demographic and clinical continuous variables were compared using 2 independent T tests for normally distributed values and the Mann-Whitney U test for nonnormally distributed values. Parameters that did not conform to the normal distribution were transformed to the normal distribution using the two-step approach defined by Garry Templeton (13). Z-scores for kurtosis and skewness and Kolmogorov-Smirnov statistics were used to determine whether continuous variables were normally distributed. Categorical variables were compared using the Fisher'sExact test. ROC (Reciever operating charactheristic) curves and area under the curve were evaluated to assess the diagnostic performance of complete blood count values and indices for IVH. Optimal cut-off values were calculated by the Youden method using the web-based interactive system developed by Goeksulluk Göksulluk et al (17). The statistical significance level was set as $p < 0.05$ for all tests. SPSS (Chicago, Illinois, USA) version 26 was used for all data analyses.

Results

Data were collected from a total of 78 cases under 28 weeks. The mean gestational week and birth weight were 26.1 ± 1.2 weeks and 844 ± 206 grams, respectively. 52% of the cases were female and 48% were male. When examined for IVH, the data of 7 cases could not be obtained due to death or other reasons. There were 17 cases in the group with severe IVH and 54 cases in the other group. There were no significant differences between the groups in terms of gestational week, birth weight, sex, mode of delivery, administration of surfactant and antenatal steroids (Table 1). On evaluation of intubation status, it was found that intubation rate was higher in the group with severe IVH, however this was not statistically significant (47% & 33%). However, it was found that the intubation time was significantly longer in the severe IVH group than in the mild IVH group (5(0-21) & 1.5 (0-51), p=0.031). This statistical difference was considered an effect rather than a cause. There was no difference between groups in duration of nasal Cpap use, total time of oxygen exposure, maximum oxygen demand in the first 3 days, and total length of hospital stay. The mortality rate was slightly higher in the severe IVH group (47% & 25%), although there was no statistically significant difference between the groups. There was no difference in neonatal early and late morbidities between groups in terms of ROP requiring laser treatment, advanced stage NEC and BPD at any stage, while hemodynamically significant PDA was about three times more common in the severe IVH group (62.5% & 26.9%.) p=0,016) (Table 1). When complete blood count parameters were examined on the first day of admission, no difference was observed between the groups in terms of absolute neutrophil count (ANC), hemoglobin levels, neutrophil to lymphocyte ratio (NLR) and platelet count. While

white blood cell count (16048±5265 & 11972±10915, p=0.043) and absolute lymphocyte count (ALC) (10705±4537 & 6329±8101, p=0.007) were significantly higher in the severe IVH group, TLR was significantly lower in the severe IVH group (36.9±22.7 & 56.7±37.9; p=0.012) (Table 2). The diagnostic performance of whole blood parameters WBC, ALC and TLR in predicting severe IVH was evaluated by ROC curve analysis. When the diagnostic performance of white blood cell, lymphocyte count and TLR in predicting severe IVH was evaluated by ROC curve analyzes, the strongest performance was observed for TLR (area under the curve AUC: WBC: 0.644 (95% CI: 0.520-0.768) ; ALS: 0.687(95% CI: 0.563-0.811); TLR: 0.691(95% CI: 0.562-0.820)) (Table 3). According to the analysis of ROC, values below the cut-off value of 55.84 for TLR were considered predictive of severe IVH with a sensitivity of 94% and a specificity of 43% (Figure 1).

Figure 1: ROC curve showing the diagnostic performance of TLR values in predicting severe IVH

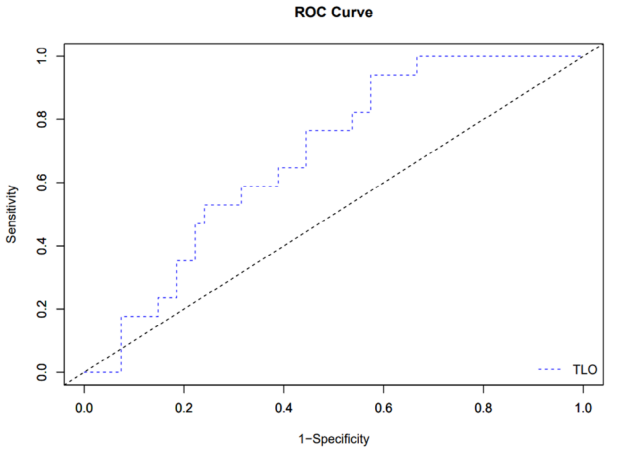


Figure caption: Area under the curve AUC: 0.691 (CI 95 %: 0.562-0.82) Optimal cut-off value: 55.84; sensitivity: %94, specificity: %43.

Discussion

While IVH is primarily responsible for the increase in mortality in extremely low birth weight preterm infants, it is associated with neurological deficits that can affect lifelong social life in surviving cases. This study shows a moderate correlation between TLR, calculated from first admission blood, and severe IVH (grade 3-4) in low birth weight infants. Because it helps predict which infants are more likely to have severe IVH, it will help clinicians provide these patients with better hemodynamic balance that can influence IVH, control fluctuations in cerebral perfusion pressure, and take additional measures to maintain optimal blood gas parameters.

In a recent study investigating the risk factors for IVH, 495 preterm infants less than 29 weeks of age were studied, and it was found that the rate of IVH at any stage was 24.4%, while the rate of severe IVH was reported to be 9.7% (14). In our study, the rate of severe IVH was 23.9% (17/71) in our group of patients. We think that this high rate is related to inadequate perinatal care and high number of outpatient admissions in our unit. While the mean gestational week and birth weight of the severe IVH group were similar to our study, it was observed that the antenatal steroid rates in our study group were quite low (41% & 66%) compared to this study. This study mainly investigated the risk factors related to the association between IVH and PDA treatment. They showed that medical treatment of PDA with indomethacin in the early phase significantly reduced severe IVH, although the association with whole blood indices was not studied. Similarly, in our hospital, we start medical management of hemodynamically significant PDA by echocardiographic examination of preterm infants between the postnatal 48-72 hours before the appearance of clinical findings. In our study group, hemodynamically significant PDA was observed about 3 times more frequently in the group with severe IVH than in the group without IVH. This and, as evidenced by our study, the association between hemodynamically significant PDA and IVH is related to fluctuations in cerebral perfusion pressure and a phenomenon called steal phenomenon. At patient admission, cases with a TLR value below the cut-off value are considered to be at high risk of IVH, and approaches may be brought to the fore by earlier evaluation of echocardiography or prophylactic PDA closure treatments. There are also significant associations between prenatal steroids and hemodynamically significant PDA. Better postnatal lung development, lower surfactant requirements, less or shorter intubation, better oxygenation, better blood gas levels, and less hemodynamically significant PDA are observed in patients given prenatal steroids. The cumulative result of these data can be interpreted as better hemodynamics. When studies examining the relationship between TLR and intracranial hemorrhage were reviewed in the literature, it was found that high TLR levels were associated with worsening Glasgow Coma Scale scores and neurological impairment in a study conducted in adult patients. The authors explained the underlying scientific fact by proposing that secondary brain damage after cerebral hemorrhage is associated with inflammation (15). The need for numerous external interventions (central line, intubation, and surfactant applications) for preterm infants to be open to infection and survive leaves this fragile population alone with inflammation and cytokines. The difference between our study and this study is that the TLR of our patients was lower in the group with severe IVH. This could be related to the different bone marrow responses of preterm infants to inflammation, or to the predominance of lymphocytes in the complete blood count in the first 4 years of childhood, or to the higher likelihood of low platelet levels in preterm infants compared with adults. Also, in a study examining neonatal outcomes in preterm infants with maternal TLR, it was found that mothers with high prenatal maternal TLR levels had a higher rate of delivery of infants less than 1500 g and a higher rate of intracranial hemorrhage in preterm infants. Although the prenatal blood results of the mothers of our babies were not included in our

Table 1: Baseline characteristics of the groups

	Grade 3-4 IVH	No IVH or Grade 1-2	P value
GW; Mean. ±SD	25,94± 1,144	26,44± 1,144	,118
BW; Mean. ±SD	838,24 ±160	884,72 ±198	,384
Sex; male, n (%)	9(52,9)	25(46,3)	,782
Delivery mode; C/S, n (%)	13(76,5)	44(81,5)	,730
Antenatal steroid use; n (%)	7(41,2)	22(40,7)	1
Surfactant application; n (%)	15(88,2)	51(94,4)	,587
Intubation rate, n (%)	8(47,1)	18(33,3)	,389
Intubation duration; median (min-max)	5(0-21)	1,5(0-51)	**,031**
Max Fio2 requirement first 3 DOL, median (min-max)	40(23-90)	35(25-100)	,131
O2 duration median (min-max)	21(4-153)	43,5(2-286)	,427
Cpap duration, median (min-max)	10(0-40)	14(0-59)	,331
Exitus n (%)	8 (47,1)	14 (25,9)	,134
Hospital stay length (min-max)	56(4-153	63,5 (1-190)	,582
HsPda, n (%)	10(62,5)	14(26,9)	**,016**
Culture proven sepsis, n (%)	8(47,1)	26 (48,1)	1
Laser requiring ROP n (%)	5 (41,7)	8(19,5)	,140
BPD any stage; n (%)	8 (80)	36(87)	,612
Advanced stage NEC; n (%)	4(23,5)	11(20,4)	,745

Abbreviations: IVH: Intraventricular hemorrhage; **GW**: gestational week; **BW**: Birth weight; **Cpap**: Continuous positive airway pressure; **HsPDA**: Hemodynamically significant patent ductus arteriosus; **ROP**: Retinopathy of prematurity; **BPD**: Broncopulmonary dysplasia; **NEC**: Necrotizing enterocolitis

Table 2: IVH and complete blood count parameters on first admission

	Grade 3-4 IVH	No IVH or Grade 1-2	P value
Transformed WBC; Mean ± SD	16048± 5265	11972± 10915	**,043**
Hgb Mean ± SD	15,8±2,5	16,7±2,4	,162
Transformed ANC Mean ±SD	3652±4904	4072±5411	,777
Transformed ALC Mean ±SD	10705±4537	6329±8101	**,007**
Transformed NLR Mean ±SD	0,69±1,1	0,90±1,4	,583
Transformed TLR Mean ±SD	36,9±22,7	56,7±37,9	**,012**
Transformed PLT Mean ±SD	212490±53417	230915±51058	,205

Abbreviations: **IVH**: Intraventricular hemorrhage; **WBC**: White blood cell; **ALC:** Absolute lymphocyte count; **TLR:** Thrombocyte lymphocyte ratio; **ANC**: Absolute neutrophil count; **NLR**: Neutrophil to lymphocyte ratio; SD: Standard deviation

Table 3: ROC (Receiver operating Curve) analysis results showing the diagnostic performance of WBC, ALS and TLR variables in predicting Grade 3-4 IVH

Area Under the Curve						
Test Result Variable(s)	Area	Std. Error a	Asymptotic Sig.b	Asymptotic 95% Confidence Interval		
				Lower Bound	Upper Bound	
N_dist_WBC	0,644	0,063	0,076	0,52	0,768	
N_dist_ALS	0,687	0,063	0,021	0,563	0,811	
N_dist_TLO	0,691	0,066	0,019	0,562	0,82	

Abbreviations: **WBC:** White Blood Cell; **ALC:** Absolute lymphocyte count; **TLR:** Thrombocyte lymphocyte ratio.

data set, maternal inflammation (chorioamnionitis) may have caused changes in the postnatal blood count and TLR may be a postnatal reflection of the prenatal events. In the intrauterine period, mother and child are one unit, prenatal situations cause transient and permanent changes in many infants. Affecting the fetus is considered as a part of the systemic inflammatory response syndrome. Maternal diabetes, chorioamnionitis and premature rupture of membranes can be given as examples. Looking at the studies on antenatal events and neonatal outcomes in the literature, conditions such as maternal chorioamnionitis are known to be responsible for preterm birth and neonatal sepsis in the short postnatal period and bronchopulmonary dysplasia, periventricular locomalacia and cerebral palsy in the long term (19).

In their study investigating the correlation between maternal whole blood parameters and neonatal whole blood parameters, Akgün et al. evaluated the results of 783 pregnant women who had no maternal risk factors and they showed that there was a negative correlation between maternal TLR, delivery week and birth weight (20). Although the relationship between maternal whole blood data and infant whole blood data was not evaluated in this study, the correlation between maternal TLR and birth weights and birth weeks suggests that an inflammatory process induces labor and causes preterm birth and low birth weights. We also did not analyze maternal whole blood data in our study, but we found a weak positive correlation between birth week and birth weights and TLR. The association between antenatal steroid use and TLR was not statistically examined because studies were generally not included more studies or as exclusion criteria because of concerns that antenatal steroid use might have an impact on whole blood indices. However, in our data set, we found no statistical difference between the first day TLR of babies whose mothers received a full dose of antenatal steroid and those whose mothers did not. The lack of this difference could be related to the intrauterine environment, stress, and active maternal steroidogenesis causing preterm birth of very immature babies in our study group. Studies in which maternal steroid hormone levels are also measured and maternal adrenocortical hormone biosynthesis can be assessed are needed to evaluate this relationship.

The relationship between other whole blood indices such as MPV, plateletcrit (thrombocrit), platelet mass index, PDW and morbidity in preterm infants less than 32 weeks was studied (16). It was found that the thrombocyte parameters can be a significant indicator for the assessment of IVH stage. We did not measure plateletcrit in our study, but we found no similar significant difference between severe and mild IVH in terms of platelet count, one of the platelet parameters studied.

Considering the important aspects and limitations of the study: first, we could not find any study that investigated the association between TLR and severe intracranial hemorrhage in extremely premature infants. We think that this aspect is important. The limitations are the inability to perform logistic regression modeling to determine risk factors and the inability to understand whether TLR is an independent risk factor because it is a retrospective study with a small sample size and only 17 cases of severe IVH.
Consequently, TLR values measured on the first day of patient admission are a useful and cost-effective indicator that can be used to predict severe IVH in extremely preterm infants less than 28 weeks. If clinicians can predict severe IVH, they should also be more careful not to expose highly fragile immature babies to additional risks that may affect intracranial hemorrhage, such as hemodynamic instability, uncontrolled carbon dioxide fluctuations in blood gas. To understand whether TLR is an independent risk factor for predicting severe IVH in extremely immature infants, well-designed, prospective, randomized, large-scale, multicenter, guideline-based studies are needed in which hemodynamic monitoring and respiratory management are regulated with strict protocols, especially in the first 3 days of life which IVH is frequently observed.

References

1.Ballabh P. Intraventricular hemorrhage in premature infants: mechanism of disease. Pediatr Res. 2010;67:1-8.

2.Duppré P, Sauer H, Giannopoulou EZ, et al. Cellular and humoral coagulation profiles and occurrence of IVH in VLBW and ELWB infants. Early Hum Dev. 2015;91:695-700.

3.McCrea HJ, Ment LR. The diagnosis, management, and postnatal prevention of intraventricular hemorrhage in the preterm neonate. Clin Perinatol 2008; 35:777–92.

4.Salonvaara M, Riikonen P, Kekomaki R, et al. Effects of gestational age and prenatal and perinatal events on the coagulation status in premature infants. Arch Dis Child Fetal Neonatal Ed 2003;88: F319–23.

5.Linder N, Haskin O, Levit O, et al. Risk factors for intraventricular hemorrhage in very low birth weight premature infants: a retrospective case-control study. Pediatrics 2003;111: e590.

6.Poralla C, Traut C, Hertfelder HJ, et al. The coagulation system of extremely preterm infants: influence of perinatal risk factors on coagulation. J Perinatol 2012; 32:869–73

7.Wang Z, Peng S, Wang A, et al. Platelet lymphocyte ratio acts as an independent predictor of prognosis in patients with renal cell carcinoma. Clin Chim Acta. 2018; 480:166- 172.

8.Chen H, Xue H, Liu W, et al. Meta-analysis of Platelet Lymphocyte Ratio as A Prognostic Factor for Non-small Cell Lung Cancer. Zhongguo Fei Ai Za Zhi. 2019; 22: 289-298.

9.Shen Y, Huang X, Zhang W. Platelet-to-lymphocyte ratio as a prognostic predictor of mortality for sepsis: interaction effect with disease severity-a retrospective study. BMJ Open. 2019 25;9(1):e022896.

10.Djordjevic D, Rondovic G, Surbatovic M, et al. Neutrophil-to-Lymphocyte Ratio, Monocyte-to Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, and Mean Platelet Volume-to-Platelet Count Ratio as Biomarkers in Critically Ill and Injured Patients: Which Ratio to Choose to Predict Outcome and Nature of Bacteremia? Mediators Inflamm. 2018; 15;2018:3758068.

11.Korkmaz L, Bastug O, Ozdemir A, et al. Can platelet mass index be a parameter to predict intraventricular hemorrhage in very-birth -weight newborns? Am J Perinatol. 2018; 36:1188– 97.

12.Papille LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1500 gm. J Pediatr. 1978; 92:529–34.

13.Templeton, G. F.. A Two-Step Approach for Transforming Continuous Variables to Normal: Implications and Recommendations for IS Research. Communications of the Association for Information Systems. 2011; 28, pp-pp. https://doi.org/10.17705/1CAIS.02804

14.Khanafer-Larocque I, Soraisham A, Stritzke A, et al. Intraventricular Hemorrhage: Risk Factors and Association With Patent Ductus Arteriosus Treatment in Extremely Preterm Neonates. Front Pediatr. 2019; 7:408.

15.Zhang W, Shen Y. Platelet-to-Lymphocyte Ratio as a New Predictive Index of Neurological Outcomes in Patients with Acute Intracranial Hemorrhage: A Retrospective Study. Med Sci Monit. 2018; 24:4413-4420.

16.Go, H., Ohto, H., Nollet, K. E., et al. Using platelet parameters to anticipate morbidity and mortality among preterm neonates: a retrospective study. Frontiers in pediatrics, 2020, 8: 90

17.Goksuluk D, Korkmaz S, Zararsiz G, Karaagaoglu AE. easyROC: An Interactive Web-tool for ROC Curve Analysis Using R Language Environment. The R Journal, 2016; 8:213-230.

18.Buckley RH. Primarycombinedantibody and celulerimmundeficiencies. In: Behrman RE, Kliegman RM, Jenson HB, editors. Nelson textbook of pediatrics. 19 thedition. Philadelphia: WB saunders; 2012. P.731-40.

19.Kim CJ, Romero R, Chaemsaithong P, Chaiyasit N, Yoon BH, Kim YM. Acutechorioamnionitis and funisitis: definition, pathologicfeatures, and clinicalsignificance. Am J ObstetGynecol. 2015 Oct;213(4 Suppl):S29-52. doi: 10.1016/j.ajog.2015.08.040. PMID: 26428501; PMCID: PMC4774647.

20.Akgun, N., Namli Kalem, M., Yuce, E., et al. Correlations of maternalneutrophiltolymphocyteratio (NLR) and platelettolymphocyteratio (TLR) withbirthweight. TheJournal of Maternal-Fetal&NeonatalMedicine, 2017; 30(17): 2086-2091.

Received: 30 Dec 2021 | **Accepted:** 9 Feb 2022
DOI: 10.54005/geneltip.1051135

ORIGINAL ARTICLE

Quantitative analysis of thyroid gland blood supply in children and adolescents

Çocuklarda ve ergenlerde tiroid bezi kanlanmasının kantitatif analizi

[1]Emine Uysal, [1]Mehmet Öztürk, [2]Zuhal Bayramoğlu, [1]Hakan Cebeci

[1]Selçuk University Faculty of Medicine, Department of Radiology, Konya, Türkiye
[2]Istanbul Faculty of Medicine, Department of Radiology, İstanbul, Türkiye

Correspondence

Emine Uysal, Selcuk University Faculty of Medicine, Department of Radiology, Alaeddin Keykubat Yerleşkesi, Akademi Mah. Yeni Istanbul Street. No:369, 42030, Konya, Turkey

E-Mail: druysalemine@gmail.com

How to cite ?

Uysal E, Öztürk M, Bayramoğlu Z, Cebeci H. Quantitative analysis of thyroid gland blood supply in children and adolescents. Genel Tıp Derg. 2022;32(1):89-94.

ABSTRACT

Aim: This study aims to determine the reference vascularization index (VI) values for the thyroid gland in healthy children and adolescents using Super microvascular imaging (SMI). It was also investigated that the correlation between thyroid vascularity and thyroid lobe volumes, age, sex, weight, height, and body mass index (BMI).
Materials and Methods: One hundred and twenty-four children and adolescents without a thyroid gland and systemic disease, and medical history affecting the thyroid gland were included in the study. Participants with abnormal thyroid function tests were excluded from the study. Age, gender, height, and weight were recorded before ultrasonography and SMI examinations. After the grayscale ultrasonography, VI values for each participant were obtained using SMI. The association between the VI and thyroid lobe volumes, age, sex, weight, height, and BMI values were analyzed.
Results: Median values of the age, height, weight, and BMI of 124 participants were 10 (6-12) years, 130 (120-152) cm, 30.5 (21-47) kg, 17.55 (15.37-21.14) kg/m2, respectively. Median (IQR) values of the left and right thyroid lobe volumes were 1.4 (0.9-2.07) mL and 1.9 (1.2-3.07) mL, respectively, and the mean VI value was 5.31±1.84%. There was no significant association of VI values with the thyroid lobe volume. Also, there was no relation between the mean VI values and the auxological parameters.
Conclusion: This study defines the VI values of thyroid glands in healthy adolescents and children. It also demonstrated no correlation between VI values of the thyroid gland and thyroid lobe volume, sex, age, weight, height, and BMI.

Key Words: adolescents, children, superb microvascular imaging, thyroid gland, ultrasonography, vascularization index

ÖZ

Amaç: Bu çalışma sağlıklı çocuk ve ergenlerde Süper mikrovasküler görüntüleme (SMG) kullanılarak tiroid bezi için referans vaskülarizasyon indeksi (Vİ) değerlerini belirlemeyi amaçlamaktadır. Ayrıca tiroid vaskülaritesi ile tiroid lob hacimleri, yaş, cinsiyet, ağırlık, boy ve vücut kitle indeksi (VKİ) arasındaki korelasyon da araştırıldı.
Gereç ve yöntem: Tiroid bezi hastalığı, sistemik hastalığı olmayan ve tiroid bezini etkileyen bir tıbbi geçmişi olmayan 124 çocuk ve ergen çalışmaya dahil edildi. Tiroid fonksiyon testleri anormal olanlar çalışma dışında bırakıldı. Katılımcıların yaşı, cinsiyeti, boyu ve kilosu ultrasonografi ve SMG tetkikleri öncesinde kaydedildi. Gri skala ultrasonografik incelemeden sonra, SMG kullanılarak her bir katılımcı için Vİ değerleri elde edildi. Vİ ile tiroid lob hacimleri, yaş, cinsiyet, ağırlık, boy ve VKİ değerleri arasındaki ilişki analiz edildi.
Bulgular: Yüz yirmi dört katılımcının yaş, boy, kilo ve VKİ ortanca değerleri sırasıyla 10 (6-12) yıl, 130 (120-152) cm, 30.5 (21-47) kg, 17.55 (15.37-21.14) kg/m2 idi. Sol ve sağ tiroid lob hacimlerinin medyan (IQR) değerleri sırasıyla 1.4 (0.9-2.07) mL ve 1.9 (1.2-3.07) mL ve ortalama Vİ değeri % 5.31 ± 1.84 idi. Sol ve sağ tiroid lob hacimleri ile Vİ değerleri arasında anlamlı bir ilişki yoktu. Aynı zamanda, ortalama Vİ değerleri ile oksolojik parametreler arasında bir ilişki saptanmadı.
Sonuç: Bu çalışma, sağlıklı ergen ve çocuklarda tiroid bezlerinin normal Vİ değerlerini tanımlamaktadır. Tiroid bezinin Vİ değerleri ile tiroid lob hacimleri, cinsiyet, yaş, ağırlık, boy ve VKİ arasında herhangi bir ilişki tespit edilmedi.

Anahtar Kelimeler: ergenler, çocuklar, superb mikrovasküler görüntüleme, tiroid bezi, ultrasonografi, vaskülarizasyon indeksi

Introduction

Ultrasonography (US) has been proven to be a valuable imaging method in diagnosing diffuse and focal lesions of the thyroid gland (1). The examinations of thyroid gland volume and echogenicity of thyroid parenchyma are essential in the initial evaluation and subsequent follow-up of thyroid diseases (2). Grayscale and Doppler US imaging are the basic imaging modalities used in functional and morphologic evaluations of thyroid disorders (3, 4). Hypoechogenicity and heterogeneity of the thyroid parenchyma in grayscale US images are the most important indicators of parenchymal diseases. However, to date, those features have been general findings for these diseases and are not helpful in the differential diagnosis. Detection of increased thyroid vascularity on the Doppler US examination is very significant for thyroid

diseases (5). Thyroid parenchymal blood supply has been shown to increase, especially in Graves' disease and early stages of Hashimoto's thyroiditis.

Superb microvascular imaging (SMI) is an ultrasonographic imaging method that could successfully distinguish low-speed current signals from tissue motion artifacts. This feature may also display low-speed currents and small vessels, even in high resolution and in detail (6). For the motion suppression, alterations in the locations of structures are extracted out frame by frame, and only the color imaging sections are left. Compared with conventional Doppler techniques, it uses a higher frame rate, and the most prominent advantage of SMI is that it has accomplished imaging very fine vascular structures (7). SMI has two modes, color, and monochrome.

Color-coded Doppler signals accompany the grayscale US images simultaneously in color SMI mode; in comparison, monochrome mode enhances the visibility of low-current vessels by suppressing background signals. Utilizing the vascularization index (VI) parameter, SMI allows quantitative data analysis. VI is a ratio of colored pixels to the total of the gray and colored pixels within the area of interest, which is calculated by the automated application. Its unit is expressed as a number between 0 and 100 (8, 9).

Several studies have evaluated the difference in thyroid vascularity between children with thyroid parenchymal diseases such as Hashimoto thyroiditis and Graves' disease and the control group using SMI (8, 9, 10). Surprisingly, until now, there has been only one study in literature, determining normative vascularity values of thyroid parenchyma in healthy children (11). The purpose of our study is to determine reference VI values of the thyroid gland using SMI in healthy children and adolescents. We also intended to investigate the correlation between thyroid vascularity and thyroid lobe volumes, age, sex, weight, height, and body mass index (BMI).

Materials and Methods

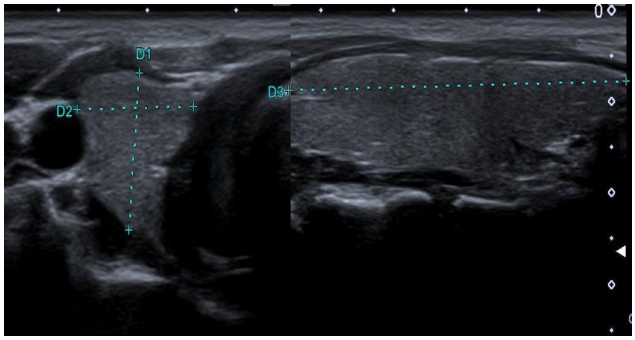
Study design and patients

The local ethics committee approved this prospective study (Document Date and Number: 04/07/2018-2018/274), and written informed parental consent was obtained before US examinations. One hundred twenty-four children and adolescents (62 boys and 62 girls) aged 3-17 years were evaluated from January 2019 to May 2019. The participants without a known thyroid gland and systemic disease and medical history affecting the thyroid gland were included. The exclusion criteria were abnormal ultrasonography findings of the thyroid gland and previous diagnosis with a thyroid disorder (e.g., neoplastic, infectious, autoimmune, or inflammatory). Participants with abnormal thyroid function tests were excluded from the study. Children under three years old were not included in the study since they would not stand still during the examination. Age, gender, height, and weight of the children and adolescents were noted before the US and SMI examinations. BMI was calculated using BMI = weight (kg)/height (m)2. The study participants were arranged into three subgroups primarily by age as 3 to 6 years (preschool, n = 36), 7 to 12 years (school age, n = 61), and 13 to 17 years (adolescent, n = 27). Besides, the subjects were subsequently divided into two subgroups: those over ten years old (adolescents) and those under ten years old (children). Quantitative thyroid vascularity values for each group were obtained using VI. The association of vascularity amount in the thyroid gland with thyroid lobe volumes, age, sex, weight, height, and BMI values were analyzed.

US and SMI technique

All US and SMI examinations were performed using an Aplio 500 US system (Toshiba Medical Systems, Tokyo, Japan) equipped with an 11–15-MHz linear array transducer. Examinations were carried out by a radiologist with two years of SMI experience. Subjects were examined in the supine position with the neck in mild hyperextension. Thyroid parenchyma with homogeneous echotexture without cystic or solid nodular lesions was defined as normal. Patients with heterogeneity, cystic or solid lesions of the thyroid parenchyma were not included in the study. The volume of each thyroid lobe was calculated in cubic millimeters (milliliter) using the formula "0.52 x width x length x height" **(Figure 1).**

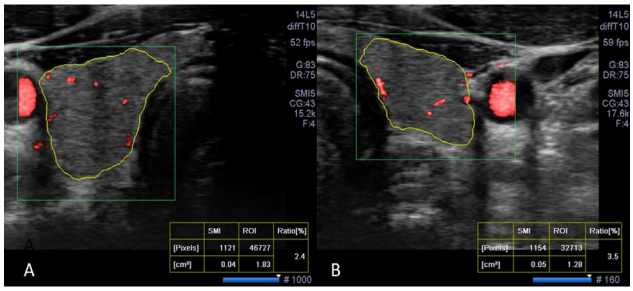
Figure 1. Measurement of right thyroid lobe volume from images obtained in the transverse and sagittal plane.



After this, the SMI software was activated. SMI investigation used a frame rate greater than 50-Hz; the pulse repetition frequency set was 220 to 234 Hz. We used Color SMI mode and set the color gain to 30 to 40 decibels to suppress background artifacts. The participants were also asked not to swallow and to remain motionless during the examination. Durmaz et al. (9) reported no difference in the mean VI values of the thyroid gland between the axial and longitudinal plan measurements. That would mean that instead of making many measurements to achieve the average vascularity value of the thyroid gland, the mean VI value acquired in any plan could be used with accuracy. Therefore, in our study, we obtained thyroid

gland VI measurements in the transverse plane. SMI analyses were carried out from the middle zone of the left and right lobes in the horizontal section. In color mode, regions of interest (ROI) in both thyroid lobes were manually outlined from the lobe boundaries, including the entire lobe. For quantitative evaluation, VI described as the ratio of colored pixels to a total of the gray and colored pixels was calculated automatically by the device **(Figure 2).** The mean thyroid gland VI value was calculated from the VI values obtained from the right and left thyroid lobes ([right thyroid lobe VI+left thyroid lobe VI]/2).

Figure 2 A, B. Color SMI of the thyroid gland. To evaluate thyroid gland vascularity, VI values were measured by manually drawing the bilateral thyroid lobe contours on the transverse sections.



Statistical analysis

All data were recorded in Microsoft Office Excel and processed for statistical analysis using SPSS, version 21.0 (IBM Corp.). The distribution of the data was assessed with the Kolmogorov-Smirnov test. Descriptive statistics of the data were expressed as mean±standard deviation (SD) [minimum, maximum], or median with interquartile range (IQR). Differences in auxological parameters and thyroid lobe volume parameters among the age and gender groups were tested using the Kruskal-Wallis test or Mann-Whitney U test. The Student's t-test or ANOVA test was used to compare the mean vascularity indices among the age and gender groups. Correlation analysis of the auxological, thyroid lobe volume, and VI parameters were performed using Spearman's correlation test. Variables with p values less than 0.05 were considered statistically significant at the 95% confidence interval.

Results

Descriptive statistics of auxological parameters (age, height, weight, and BMI), left and right thyroid lobe volumes, and VI values of the participants, are given in Table 1. The median (IQR) values of the age, height, weight, and BMI in 124 children were 10 (6-12) years, 130 (120-152) cm, 30.5 (21-47) kg, 17.55 (15.37-21.14) kg/m2, respectively. Median (IQR) values of the left and right thyroid lobe volumes were 1.4 (0.9-2.07) mL and 1.9 (1.2-3.07) mL, respectively, and the mean VI value was 5.31±1.84%.

The comparison of the median age, height, weight, BMI values of the participants, median left and right thyroid lobe volumes, and mean VI parameters among three age groups are given in **Table 2**. The median age, height, and weight values were significantly different between the three age groups and showed a remarkable increase with age (p=0.001). The median BMI values in groups 2 and 3 were significantly higher compared to group 1 (p=0.001). However, there was no significant difference in median BMI values between groups 2 and 3. The median values of the right and left thyroid lobe volumes significantly differed between the three age groups and also increased with age (p=0.001). In contrast, no considerable differences existed in terms of the thyroid gland mean VI values among these groups (p=0.39).

The comparison of the median age, height, weight, BMI values of the participants, median left and right thyroid lobe volumes, and mean VI parameters among the two age groups are presented in **Table 3**. The medians for age, height, weight, BMI, and the left and right thyroid lobe volumes were significantly higher in group 2 compared to group 1 (p=0.001). Besides, the mean VI values of the thyroid gland did not significantly differ between groups 1 and 2 (p=0.53).

The comparison of the median age, height, weight, weight, BMI values of the participants, median left and right thyroid lobe volumes, and mean VI parameters among gender groups are given in **Table 4**. The medians for age, height, weight parameters, and the left and right thyroid lobe volumes were significantly higher in males compared to females (p=0.001). There were no significant differences in the median BMI of the participants (p=0.27) and mean VI (p=0.74) of the thyroid gland among gender groups.

Table 1. Descriptive statistics of auxological parameters, thyroid lobe volumes and average vascularity index in 124 children.

	Minimum	Maksimum	Mean	Std. Dev.	Median	Interquartile range
Age (years)	3	17	9.55	3.75	10	6-12
Height (cm)	85	180	134	22	130	120-152
Weight (kg)	13	85	35.64	17.98	30.5	21-47
BMI (kg/m^2)	10.5	30.5	18.61	4.42	17.55	15.37-21.14
Right lobe volume (mL)	0.4	9	2.35	1.42	1.9	1.2-3.07
Left Lobe volume (mL)	0.1	4.6	1.6	0.94	1.4	0.9-2.07
Average VI (%)	0.65	10.75	5.31	1.84	5.4	4.16-6.67

Table 2. Comparison of mean±std. Dev/median (IQR) values of auxological parameters, thyroid lobe volumes, and average vascularity index among three age groups by the ANOVA test* / Kruskal Wallis or Mann-Whitney U‡ test.

	Age group 1 (3-6 years) (n:36)	**Age group 2** (7-12 years) (n:61)	**Age group 3** (13-17 years) (n:27)	**p**
Age (years)	5 (4-6)	10 (9-11)	15 (13-15)	**0.001**
Height (cm)	110 (91-117)	135 (129-148)	162 (153-167)	**0.001**
Weight (kg)	18 (16-21)	33 (25.25-47.5)	50 (40-60)	**0.001**
BMI (kg/m^2)	15.85 (14.32-17.35)	18.36 (15.37-22)	18.55 (17.12-25.76)	**Group 1 vs 2: 0.001** Group 2 vs 3: 0.14
Right lobe volume (mL)	1.1 (0.82-1.37)	2.3 (1.6-2.85)	4 (3-5)	**0.001**
Left Lobe volume (mL)	0.8 (0.6-0.9)	1.5 (1.1-2)	2.4 (1.9-3.5)	**0.001**
Average VI (%)	5.47±1.34	5.4±2.15	4.89±1.62	0.39*

Table 3. Comparison of mean±std. Dev/median (IQR) values of auxological parameters, thyroid lobe volumes, and average vascularity index among two age groups by the t-test* / Mann-Whitney U test.

	Age group 1 (3-10years) (n:72)	**Age group 2** (11-17 years) (n:52)	**p**
Age (years)	7 (5-9)	13 (12-15)	**0.001**
Height (cm)	120 (110-130)	155 (145-164)	**0.001**
Weight (kg)	21.5 (18-27.5)	48 (40-60.75)	**0.001**
BMI (kg/m^2)	15.9 (14.58-18.29)	19.29 (17.3-24.91)	**0.001**
Right lobe volume (mL)	1.5 (1.02-1.97)	3.6 (2.42-4.1)	**0.001**
Left Lobe volume (mL)	0.95 (0.7-1.37)	2.1(1.7-2.8)	**0.001**
Average VI (%)	5.4 ±1.61	5.18±2.12	0.53*

Table 4. Comparison of mean±std. Dev/median (IQR) values of auxological parameters, thyroid lobe volumes, and average vascularity index among two age groups by the t-test* / Mann-Whitney U test.

	Gender Groups		p
	Male (n:62)	Female (n:62)	
Age (years)	11 (8.75-13)	8 (5-11)	**0.001**
Height (cm)	145 (120-157)	126 (110-144)	**0.001**
Weight (kg)	36 (24.75-53.25)	25 (19.75-40)	**0.003**
BMI (kg/m^2)	17.76 (15.55-22.29)	17.35 (15.27-19.64)	0.27
Right lobe volume (mL)	2.35 (1.5-3.7)	1.8 (1.1-2.75)	**0.006**
Left Lobe volume (mL)	1.65 (1-2.45)	1.1 (0.8-1.8)	**0.001**
Average VI (%)	5.36 ± 1.99	5.25 ± 1.69	0.74*

Table 5. Correlation analysis of auxological parameters with thyroid lobe volumes and average vascularity index by Spearman's correlation analysis

Compared variables	**r**	**p**
Age vs mean thyroid volume	**0.84**	**0.001**
Right lobe volume vs right lobe VI	0.09	0.87
Left lobe volume vs left lobe VI	0.02	0.98
Average VI vs age	-0.01	0.85
Average VI vs height	-0.11	0.2
Average VI vs weight	-0.14	0.12
Average VI vs BMI	-0.09	0.32

Table 5 presents the results of the correlation analysis. The age of the participants was significantly and strongly correlated with the left and right thyroid lobe volumes (p=0.001, r=0.84). There was no relationship between the left and right thyroid lobe volumes and thyroid gland VI values. There were also no significant associations of the mean VI parameters with the auxological parameters.

Discussion

A significant portion of children may be affected by thyroid gland diseases such as goiter, hyperthyroidism, hypothyroidism, nodular diseases, and autoimmune thyroiditis (12). Whereas goiter and nodular diseases have rarely been observed in childhood, autoimmune thyroiditis is the most common thyroid gland disease in children and adolescents (13, 14). A multidisciplinary approach based on physical examination, blood tests, and radiological imaging techniques have been used to diagnose thyroid gland diseases (15). Although the grayscale US is the primary imaging method for investigating thyroid pathologies, US findings of the thyroid parenchyma are not sufficient to make a definitive diagnosis (16). The most frequent sonographic finding in diffuse thyroid parenchymal diseases is generally parenchymal heterogeneity and, it is non-specific and may be seen in many diseases affecting the thyroid gland.

Nevertheless, it has been reported that the investigation of thyroid parenchymal vascularity using Doppler US is beneficial in diagnosing thyroid parenchymal diseases. The diagnostic performance of color and power Doppler sonography and the influence of resistivity index detected by color Doppler US in the assessment of thyroid parenchyma have been studied in many trials (17, 18, 19). Moreover, some studies have declared that color Doppler techniques have substantial restrictions in evaluating vascularity (6, 20, 21). SMI remarkably reduces motion artifacts and allows the low-speed blood flow to be displayed in the capillaries (6, 19). Conventional Doppler techniques have also been shown to have less sensitivity for detecting abnormal vascularity in thyroid parenchymal diseases than SMI (8, 9, 10).

In a study thyroid gland VI value was reported as 4.59% for the right lobe and 4.23% for the left lobe in healthy children (11). Adaletli et al. reported the mean VI value of the thyroid gland in 40 healthy children as 7.3% in their study involving children with thyroid dyshormogenesis and the control group (22). A previous study of pediatric patients with Hashimoto thyroiditis, evaluating the diagnostic role of SMI and grayscale and Doppler US in thyroid pathologies, reported an average VI value of the thyroid gland as 7.95% in 33 healthy controls (8). In another study investigating the success of the VI acquired using SMI in diagnosing Hashimoto thyroiditis by Durmaz et al. (9), the thyroid gland VI value was stated to be 4.74% in healthy children. In the present study, too, the thyroid gland mean VI value was determined as 5.31±1.84% in 124 healthy children and adolescents. These different results in the literature may be due to differences in the number and age average of the study population, and differences occurred secondary to the measurement of the device and its user.

Previously, numerous researches conducted in children and adolescents have attempted to evaluate various organs in the head and neck region with SMI and aimed to reveal the normative VI values of these organs (23, 24). Caliskan et al. 's study (23) determined normative vascularity values of the parotid gland in healthy adolescents and children using SMI, reported no correlation between vascularity values and gender, age, or BMI. In another trial evaluating the palatine tonsil vascularity by using SMI, it was demonstrated that tonsillar vascularity significantly decreased in the transition from school age to adolescence and was affected by BMI changes. The authors have suggested that tonsil vascularity does not differ by gender (24). Our study results revealed the left and right thyroid lobe volumes to be smaller in girls than in boys. There was, in contrast, no significant difference between girls and boys in the thyroid gland mean VI value (5.25±1.69% in girls vs. 5.36±1.99% in boys). No significant correlation was also elicited in the current study between the thyroid gland VI values and thyroid lobe volumes, weight, height, and BMI. Considering that there may be changes in thyroid gland functions in different age groups and the transition from childhood to adolescence, we measured the mean values of VI separately for five different age groups. The vascularization index of the thyroid gland did not significantly differ, in our study, between preschool, school, and adolescent age groups. Likewise, the thyroid gland mean VI value was similar in participants under and over ten years. We could not find any relationship between thyroid gland vascularity value and age. Öztürk et al. (11), similar to our study, did not detect a correlation between thyroid gland vascularity with gender and age in children, but differently, they found a negative correlation with BMI.

SMI provides high-resolution imaging of vessels without using any contrast agents (24). It has been utilized to evaluate synovial inflammation in rheumatoid arthritis and characterize hepatic lesions and breast masses (26, 27, 28, 29). Furthermore, it is also used to evaluate thyroid nodules' preoperative evaluation (30). In current studies using SMI in the pediatric age group, VI values have been found to be significantly higher in patients with Hashimoto thyroiditis and Graves' disease than in healthy subjects (8, 9, 10). In one study evaluating thyroid vascularity in the patients with Hashimoto thyroiditis and the control group, conventional doppler findings did not differ significantly between the patients in the early stage of thyroiditis and the control group. At the same time, the VI values obtained using SMI were significantly higher in those in the early stage of thyroiditis compared to the control group (8). This finding suggested that SMI is useful to diagnose also patients with thyroiditis who are in the

early stages of the disease. The normative VI values of the thyroid gland found in our study for children and adolescents may be beneficial in diagnosing thyroid parenchymal diseases.

The present study has some limitations. Firstly, the study cohort included a limited number of participants. It would be useful to perform large-scale studies in children and adolescents to correctly determine the thyroid gland's normative vascularity values. Secondly, since the study was prospective, VI measurement was performed from the localization with the best blood supply during the examination. The third limitation was that children under three years old were not included in the study. Finally, since VI measurements were made by a single radiologist, the interobserver agreement could not be evaluated.

In conclusion, our study defines the normative VI values of thyroid glands in healthy adolescents and children. Remarkably, no correlation between the thyroid gland VI values and thyroid lobe volumes, sex, age, weight, height, and BMI were demonstrated. These data may be helpful for the design of further studies regarding thyroid parenchyma diseases. In addition, it would be beneficial to use SMI, which is a valuable imaging method in addition to grayscale US, and to compare the obtained VI values with normative values in the diagnosis of thyroid gland diseases in children.

References

1.Kim SJ, Kim EK, Park CS, et al. Ultrasound guided fine-needle aspiration biopsy in nonpalpable thyroid nodules: is it useful in infracentimetric nodules? Yonsei Med J 2003;44:635–40.

2.Taş F, Bulut S, Eğilmez H, et al. Normal thyroid volume by ultrasonography in healthy children. Ann Trop Paediatr 2002;22:375–9.

3.Wu CC, Torng JK. Duplex Doppler ultrasonography for the functional evaluation of diffuse thyroid diseases. J Med Ultrasound 2009;17:183–6.

4.Erdogan MF, Anil C, Cesur M, Baskal N, Erdogan G. Color flow Doppler sonography for the etiologic diagnosis of hyperthyroidism. Thyroid 2007;17:223–8.

5.dos Santos TARR, Pina ROG, Souza MTP, Chammas MC. Graves' disease thyroid color-flow Doppler ultrasonography assessment: review article. Health 2014;6: 1487.

6.Jiro H. Seeing the unseen new techniques in vascular imaging Superb Microvascular Imaging. Toshiba Med Rev 2014.

7.Zhan J, Diao XH, Jin JM, Chen L, Chen Y. Superb Microvascular Imaging—a new vascular detecting ultrasonographic technique for avascular breast masses: a preliminary study. Eur J Radiol 2016;85:915–21.

8.Bayramoglu Z, Kandemirli SG, Caliskan E, et al. Assessment of paediatric Hashimoto's thyroiditis using superb microvascular imaging. Clin Radiol 2018;73:1059.e9–15.

9.Durmaz MS, Akyürek N, Kara T, et al. Quantitative assessment of thyroid gland vascularization with vascularization index using color superb microvascular imaging in pediatric patients with hashimoto thyroiditis. Ultrasound quarterly 2019;35:281-9.

10.Bayramoglu Z, Kandemirli SG, Akyol Sarı ZN, et al. Superb Microvascular Imaging in the Evaluation of Pediatric Graves Disease and Hashimoto Thyroiditis. J Ultrasound Med 2019;9999:1–9

11.Ozturk M, Durmaz MS, Ateş F, et al. Assessment of thyroid gland vascularity with superb microvascular imaging in healthy children and its relationship with potential factors. J Pediatr Endocrinol Metab 2020;33:1139-45.

12.Rallison ML, Dobyns BM, Meikle AW, et al. Natural history of thyroid abnormalities: prevalence, incidence, and regression of thyroid diseases in adolescents and young adults. Am J Med 1991;91:363–70.

13.Brown RS. Autoimmune thyroiditis in childhood. J Clin Res Pediatr Endocrinol 2013;1:45–9.

14.Brix TH, Hegedüs L. Twin studies as a model for exploring the etiology of autoimmune thyroid disease. Clin Endocrinol (Oxf) 2012;76:457–64.

15.Corrias A, Mussa A, Baronio F, et al. Diagnostic features of thyroid nodules in pediatrics. Arch Pediatr Adolesc Med 2010;164:714–9.

16.Moon HJ, Sung JM, Kim EK, et al. Diagnostic performance of grayscale US and elastography in solid thyroid nodules. Radiology 2012;262:1002–13.

17.Banaka I, Thomas D, Kaltsas G. Value of the left inferior thyroid artery peak systolic velocity in diagnosing autoimmune thyroid disease. J Ultrasound Med 2013;32:1969-78.

18.Acar T, Ozbek SS, Erdogan M, Özgen AG, Demirel SO. US findings in euthyroid patients with positive antithyroid autoantibody tests compared to normal and hypothyroid cases. Diagn Interv Radiol 2013;19:265-70.

19.Sarikaya B, Demirbilek H, Akata D, Kandemir N. The role of the resistive index in Hashimoto's thyroiditis: a sonographic pilot study in children. Clinics (Sao Paulo, Brazil) 2012;67:1253-7.

20.Machado P, Forsberg F. Initial experience with a novel microvascular flow imaging technique. Toshiba Med Rev 2014.

21.Arslan S, Karahan AY, Oncu F, et al. Diagnostic performance of superb microvascular imaging and other sonographic modalities in the assessment of lateral epicondylosis. J Ultrasound Med 2018;37:585–93

22.Adaletli I, Bayramoglu Z, Caliskan E, et al. Multi-parametric Ultrasound Evaluation of Pediatric Thyroid Dyshormonogenesis. Ultrasound Med Biol 2019;45:1644-53.

23.Caliskan E, Ozturk M, Bayramoglu Z, Comert RG, Adaletli I. Evaluation of parotid glands in healthy children and adolescents using shear wave elastography and superb microvascular imaging. La radiologia medica 2018;123:710-8.

24.Caliskan E, Ozturk M, Bayramoglu Z, Adaletli I. Superb Microvascular Imaging of Palatine Tonsils in Healthy Children: A Preliminary Study. Ultrasound Q. 2018;34:71-6.

25.Goddi A, Fanizza M, Bortolotto C. Vector flow imaging techniques: an innovative ultrasonographic technique for the study of blood flow. J Clin Ultrasound 2017;45:582-8.

26.Orlandi D, Gitto S, Perugin Bernardi S, et al. Advanced power Doppler technique increases synovial vascularity detection in patients with rheumatoid arthritis. Ultrasound Med Biol 2017;43:1880–87.

27.Yokota K, Tsuzuki Wada T, Akiyama Y, Mimura T. Detection of synovial inflammation in rheumatic diseases using Superb Microvascular Imaging: comparison with conventional power Doppler imaging. Mod Rheumatol 2018;28:327–33.

28.Park AY, Seo BK, Woo OH, et al. The utility of ultrasound Superb Microvascular Imaging for evaluation of breast tumour vascularity: comparison with colour and power Doppler imaging regarding diagnostic performance. Clin Radiol 2018;73:304–11.

29.Lee DH, Lee JY, Han JK. Superb Microvascular Imaging technology for ultrasound examinations: initial experiences for hepatic tumors. Eur J Radiol 2016;85:2090–5.

30.Kong J, Li JC, Wang HY, et al. Role of superb microvascular imaging in the preoperative evaluation of thyroid nodules: comparison with power Doppler flow imaging. J Ultrasound Med 2017;36:1329-37

Received: 16 Dec 2021 | **Accepted:** 21 Jan 2022
DOI: 10.54005/geneltip.1037269

ORIGINAL ARTICLE

Mode of Presentation and Associated Autoimmune Diseases in Children with Autoimmune Hepatitis

Otoimmün Hepatit Tanılı Çocuklarda Başvuru Şekli ve Eşlik Eden Otoimmün Hastalik Varlığı

[1]Nelgin Gerenli, Coşkun Çeltik

[1]Sağlık Bilimleri Üniversitesi Ümraniye Eğitim Ve Araştırma Hastanesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Gastroenteroloji Bilim Dalı

Correspondence

Nelgin Gerenli, Sağlık Bilimleri Üniversitesi Ümraniye Eğitim Ve Araştırma Hastanesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Gastroenteroloji Bilim Dalı

E-Mail: nelgingerenli@gmail.com

How to cite ?

Gerenli M, Çeltik C. Autoimmune Diseases in Children with Autoimmune Hepatitis. Genel Tıp Derg. 2022;32(1):95-101.

ABSTRACT

Aim: Autoimmune hepatiti (AIH) is an inflammatory disease of the liver with variable clinical presentations. 20-40% of the patients with AIH had another associated autoimmune or autoinflammatory disease. This study aimed to assess mode of presentation, biochemical features and outcomes in children with AIH, as well as to evaluate the frequency of concomitant autoimmune diseases (CAIDs).
Materials and Methods: 17 children, aged 6 to 18 years were enrolled. The mode of presentation and accompanying autoimmune diseases were recorded. Biochemical parameters as well as immunoglobulin G levels were evaluated either at time of submission and thereafter.
Results: Fourteen patients had type-1AIH (10 females, 4 males), and three (2 males, 1 female) had type-2AIH. The mode of presentation was acute in 53% and incidental enzyme elevation in 47% of them. There was an associated autoimmune or auto-inflammatory disease in 35% of the patients, 12% had vitiligo, 6% had celiac disease, 6% had juvenile idiopathic arthritis, 6% had Familial Mediterranean Fever, and one patient had both type-1diabetes mellitus and Hashimoto thyroiditis (HT). The subjects with CAIDs were females (6 patients) with insidious type of presentation. Autoimmune diseases were observed in 24% of the parents (3 had HT, 2 had vitiligo).
Conclusion: AIH is a rare but important cause of chronic liver disease in children. Frequent association with autoimmune diseases should be kept in mind as the clinical expression of the associated disease can be extremely variable therefore diagnosis and treatment delay may occur.

Key words: Autoimmune hepatitis, child, extrahepatic autoimmune diseases

ÖZ

Giriş ve Amaç: Otoimmün hepatit (OİH)çocukluk çağında nadir görülen karaciğerin inflamatuar hastalığıdır. Klinik prezantasyon çok değişkendir. OİH olan hastaların yaklaşık %20-40'nda eşlik eden otoimmün hastalıklar gözlenebilir. Bu çalışmamızda OİH tanısı almış çocukların başvuru şekli, biyokimyasal parametreleri, eşlik eden otoimmün veya otoinflamatuar hastalık varlığının araştırılması amaçlanmıştır.
Gereç ve Yöntem: Yaşları 6 ila 18 arasında değişen, OİH tanısı almış 17 değerlendirildi. Başvuru şekli, laboratuvar bulguları, eşlik eden otoimmün veya otoinflamatuar hastalıklar, anne-babada otoimmün hastalık varlığı kayıt edildi. Biyokimyasal parametreler başvuru şekline ve eşlik eden otoimmün hastalık varlığına göre kıyaslandı.
Bulgular: OİH olan çocukların on dördü (10 kız, 4 erkek) tip1 OİH, üçü (1 kız, 2 erkek) ise tip-2OİH tanısı almıştı. Hastaların %53 akut hepatit, % 47 ise insidental karaciğer enzim yüksekliği nedeniyle başvurmuştu. OİH olan çocukların %35'inde eşlik eden bir veya birden fazla otoimmün veya otoinflamatuar hastalık gözlendi. En sık vitiligo (%12), ikinci sıklıkta ise Çölyak hastalığı (% 6) juvenil idiopatik artrit (%6), Ailevi Akdeniz ateşi %6 oranında gözlendi. Tip-1 OİH nedeniyle takip edilen bir hastada hem tip 1 diabetes mellitus hem de Hashimoto tiroiditi (HT) vardı. Eşlik eden otoimmün hastalığı olan çocukların hepsinin cinsiyeti kız ve insidental olarak enzim yüksekliği nedeniyle başvurmuş olanlardı. Hasta ebeveynlerinin % 24 de otiommün hastalık (üç kişide HT, iki kişide vitiligo) vardı.
Sonuç: Çocuklarda OİH, kronik karaciğer hastalığının nadir fakat önemli nedenleri arasındadır. OİH ile birlikte diğer otoimmün ve otoinflamatuar hastalıkların da eşlik edebileceği, erken tanının tedavinin gecikmemesi açısından önemli olduğu unutulmamalıdır.

Anahtar kelimeler: Otoimmün hepatit, çocuk, karaciğer dışı otoimmün hastalıklar vaskülarizasyon indeksi

Introduction

Autoimmune hepatitis (AIH) is a chronic, immune-mediated disease of the liver, characterized by elevated IgG levels and presence of specific autoantibodies. The inflammatory destruction of the liver tissue may consequently lead to cirrhosis and hepatic failure, making AIH the one of the leading causes of end-stage liver disease (1). The worldwide prevalence of AIH among patients with liver disease is between 11% and 20% (2). Due to its insidious presentation, the prevalence in the pediatric population is unknown however increasing incidence of the disease in children was reported (3,4). AIH is more frequent in female patients, with a female: male ratio of 3:1 (1,4). There are two types of AIH; type 1 (AIH-1),

defined by the presence of smooth muscle antibodies (SMA) and/or antinuclear antibodies (ANA), and type 2 (AIH-2), characterized by the presence of anti-liver/kidney microsome type 1 antibodies (LKM-1) (4). The SMA, ANA, and anti-LKM-1 are the serological markers of autoimmune hepatitis, and antibodies to mitochondria (AMA) are the serological hallmarks of primary biliary cirrhosis (PBC), however these serological features are not diagnostic, and other associated manifestations are necessary to establish the correct diagnosis (5). The clinical presentations of the disease are variable, from asymptomatic elevated levels of the liver enzymes to fulminant liver failure (1,2,3) Although acute hepatitis is the most frequent presentation in the pediatric age group, AIH usually has fluctuant course, partially explaining the delay between the first symptoms or signs and the diagnosis of the disease (6). Interestingly, in 20-40% of the adult patients, another concomitant autoimmune disease (CAID) such as thyroiditis, celiac disease, type 1 diabetes mellitus (DM type1), vitiligo, ulcerative colitis and mixed connective diseases were observed, either presented before, at the onset of the disease or later during the follow-up (1,5). However pediatric studies reported that CAIDs (excluding inflammatory bowel diseases) have been less frequently observed (7,8,9)

This study aimed to assess the mode of presentation, biochemical features and outcomes in children with AIH, as well as to evaluate the frequency of concomitant autoimmune disease in children with AIH.

Patients and Methods

This retrospective study consisted of 17 children, 6-18 years of age, with a definite diagnosis of AIH who were admitted to the Pediatric Hepatology Clinics between August 2014 and October 2021. The demographic and clinical features of the patients, and their laboratory, treatment and clinical outcomes were reviewed. The diagnosis of AIH was confirmed based on the scoring system of the International Autoimmune Hepatitis Group (10,11).

The presenting symptoms, physical evaluation, accompanying autoimmune disease and family history of associated diseases were recorded from the medical records. Routine laboratory tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), total immunoglobulin G (IgG), total bilirubin and conjugated bilirubin, albumin, alpha fetoprotein (AFP), prothrombin time (PT), international normalized ratio (INR) and viral serologic tests for hepatitis A, B, C, Epstein–Barr virus, Cytomegalovirus, Parvovirus and Human Immunodeficiency Virus) were also recorded. Ultrasonographic evaluation of the liver parenchyma in case of chronicity was performed, and doppler ultrasound was used to exclude portal hypertension. Anti-smooth muscle antibodies (SMA), antimitochondrial antibodies (AMA), liver-kidney microsomal antibodies-1 (LKM-1), and antinuclear antibodies (ANA) were used as the serologic markers for autoimmune hepatitis (11). These antibodies, even not diagnostic, are useful for the classification of the disease (12). Serum ANA, SMA, AMA, and LKM-1 antibodies were studied by immunoblot assay and levels beyond 1/40 titer were considered "positive". Patients whose autoantibody levels were negative or ANA or SMA was positive were considered to have type 1 AIH and patients whose LKM autoantibody levels were positive were considered to have type 2 AIH. Levels of the immunoglobulin G(IgG) were screened either at the presentation and thereafter as elevated serum IgG has been reported to be the best diagnostic predictor for AIH (3,12).

All patients underwent a liver biopsy. Three of them had fulminant disease so the biopsy was performed during corticosteroid treatment after normalization of the coagulation parameters. Histopathological evidence of necro-inflammatory hepatocellular injury, portal mononuclear cell infiltration with plasma cells, parenchymal collapse was essential for the diagnosis of AIH. Inflammatory activity and fibrosis degree were evaluated using Ishak's histological activity index (13,14). Magnetic resonance cholangiopancreatography (MRCP) was performed to all patient with definite AIH diagnosis to exclude associated small bile duct pathologies (15). After AIH diagnosis was confirmed and treatment was started the patients were evaluated every two weeks in the first 2-3 months of treatment and every 3 months thereafter in uncomplicated cases (15). Remission induction and maintenance treatment, response, relapse, and drug side effects were collected from the patient charts.

Association of the AIH with other autoimmune and autoinflammatory disorders as well as autoimmunity in first degree relatives were recorded.

Methylprednisolone 2 mg/kg/day was started as a primary therapy for all patients. Azathioprine was added after 3-4 weeks of steroid treatment (15). All patients were tested genetically for Thiopurine methyltransferase (TPMT) mutations, to detect a TPMT deficiency. Azathioprine was switched to mycophenolate mofetil (MMF) in patients with side effects (3,15). Clinical and laboratory remission (aminotransferases, autoantibodies, and gamma globulin within normal limits) with negative autoantibodies (ANA, ASMA, anti-LKM-1) for at least 24 months was accepted as complete response to treatment (15, 16). The reactivation of the disease was considered when laboratory manifestations such as elevated aminotransferase levels, increased gamma globulin fractions, or the reappearance of autoantibodies were detected (15).

The study was approved by the local Institutional Ethical Board.

The results were analyzed by the Statistical Package for the Social Sciences (SPSS) version 22 for Windows (SPSS Inc.; Chicago, IL, USA). Shapiro Wilks test was

used to determine the distribution of the variables. The results were expressed as mean and standard deviation (SD) for normally distributed variables, while median and interquartile range for non-normally distributed variables. Independent samples t-test was used for comparison of normally distributed variables and Mann-Whitney U test was used for comparison of non-normally distributed variables. Related-samples Friedman's test was used for three groups of related variables and if difference was found pairwise comparison was applied to compare among groups. The comparison of two related groups was made with Paired-samples T-test for normally distributed, and Wilcoxon signed ranks test for non-normally distributed variables. Chi-square test was used for categorical variables. P values of less than 0.05 were accepted as significant.

Results

Seventeen children (11 females, 6 males), with a mean age of 11,57 (± 3,58) years, diagnosed with AIH were enrolled. The mode of presentation was acute hepatitis in 53% (29% with acute hepatitis, 24% with signs of fulminant hepatic failure) and incidental enzyme elevation in 47% of them. Fourteen patients (10 females, 4 males) had AIH-1 and three (2 males, 1 female) had AIH-2. There was an associated autoimmune or auto-inflammatory disease in six (35%) patients. All subjects with associated autoimmune disease were females (6 patients), two patients (12%) had vitiligo, one (6%) had celiac disease, one (6%) patient had juvenile idiopathic arthritis (JIA), one (6%) had Familial Mediterranean Fever (FMF), and one patient had both type 1diabetes mellitus (DM) and Hashimoto thyroiditis (HT). None of our patients had concomitant inflammatory bowel disease (IBD). Autoimmune diseases were observed in 24% of the parents of the children with AIH (three had HT, two had vitiligo).

At the diagnosis, mean weight standard deviation score (SDS) of the study group was 0.24 ± 0.85, mean height SDS was -0.49 ± 1.08, and mean body mass index SDS was 0.55 ± 0.93.

In the entire study group, hematologic parameters showed mild anemia in nine (53%) and moderate thrombocytopenia in two (12%) patients. Mean hemoglobin was 12.09±1.41 gr/dl, white blood cell count was 6932±1733/mm3, platelet count was 222.866 ± 56.553/mm3, median erythrocyte sedimentation rate was 23 mm/h. The median level of ALT at diagnosis was 558 (280-893) IU/L and AST was 382 (170-1134) IU/L.

The levels of ALT, GGT, total and conjugated bilirubin, INR were significantly higher in patients with acute or fulminant presentation compared to ones with incidental mode of presentation. Albumin was lower in patients with acute presentation. Total IgG, hemoglobin and platelet counts were not different (Table-1).

The comparison of anthropometric and biochemical parameters showed no difference among patients with isolated AIH and those with one or more associated autoimmune disease except a mild significance for INR (Table-2).

Elevated levels of all biochemical parameters decreased thereafter with appropriate treatment (Table-3).

Autoimmune profile of the children with AIH was as follows: ASM antibodies were positive in 58%of the patients, ANA in 82%, anti-LKM-1 in 18%, AMA in 12%, while p-ANCA positivity was observed in 35% of the cases (Table-4). The patients with strong ANA positivity were further evaluated regarding the differential diagnosis of Systemic Lupus Erythematosus (SLE). All liver biopsies were compatible with AIH. None of the patients had increased GGT and ALP levels. MRCP was performed to all patients, revealing no small or large bile duct involvement. Also, none of our patients had associated primary sclerosing cholangitis to be considered as overlap syndrome.

Methylprednisolone was the primary treatment protocol. No TPMT deficiency was detected consequently AZA was started to all patients, however two children were intolerant to it, accordingly they were switched to MMF.

The complete response to therapy had been achieved in all the patients except for one with AIH type2 who was non-adherent to treatment. He had two serious relapses presented as acute hepatitis, however he rejected to use medications regularly, therefore his enzyme levels as well as total IgG levels remained elevated. The reactivation of the disease was observed in 41% (7 children) of the patients, who were successfully treated with steroid dosage increment. None of the children was suitable for treatment discontinuation. There was no difference in term of response to treatment and rates of relapse between patients with incidental or acute presentation as well as between children with or without associated autoimmune or autoinflammatory disease.

Discussion

The present study revealed that children with AIH more frequently had concomitant autoimmune or autoinflammatory diseases than previously reported (6,7). The increased incidence of the IBD in children with AIH and PBS is well known, however AIH and other autoimmune disorder association was described less frequently (7,8). AIH may be associated with autoimmune disorders like thyroiditis, IBD, hemolytic anemia, vitiligo, celiac disease, insulin-dependent diabetes, Behçet's disease, idiopathic thrombocytopenia, and Addison disease, which were shown to exist in approximately 20% of the children (5,9,15). The exact frequency with exclusion of the IBD is not reported in children however studies from adult series showed that 10-20% of the patients with AIH had

concomitant autoimmune disease (CAID) (6,7,17). Previous studies reported that CAIDs tend to cluster in female patients with AIH-1 (17,18), accordingly in the current trial, all the children with CAIDs were females. Similarly recent trials from the Netherlands demonstrated that significantly more women with AIH had associated AID than men with AIH (19) which might be explained by hormonal variations, since both androgens and estrogens appear to inhibit and enhance immune activity (18). Past studies showed that the most common AIDs associated with type 1 AIH are autoimmune thyroiditis, type 1 diabetes and UC (7,18), whereas in the present study vitiligo was observed more frequently, fallowed by HT, type 1DM, Celiac disease, and FMF. Interestingly vitiligo was observed more frequently in patient with type 2 AIH (20), however in the present study one patient had type 1 and the other had type 2 AIH. Gregorio et al. published a 20-year follow-up work of pediatric AIH patients at King's College Hospital and reported that 20% of the patients had CAIDs, which included thyroiditis, vitiligo, type 1 diabetes and IBD (7). They also reported almost a similar frequency of CAIDs between children with type 1 AIH and type 2 AIH (7). Interestingly in a study from Argentina, children with AIH had lower frequencies of CAIDs compared to adults with AIH (13% vs 39%) (21). The authors suggested that the age increases the incidence of the development of CAIDs (21). However, the present study showed that in a pediatric population frequency as high as in adult series could be observed. Along with, children may present with syndromes associated with AIH (2,4). Therefore, children may also have AIH as a component of autoimmune polyendocrinopathy syndromes (APECEDs) (15). We had a one child with type 1 AIH, HT and type 1DM. Although she did not fulfil the criteria for APECED, she might develop the other associated diseases later in life (2,4). The diagnosis of the CAID is particularly important as prompt treatment should be initiated without delay (15).

Of note the frequency of autoimmunity was also increased in the first-degree relatives of the subjects with AIH (5,17,18). Gregorio et al reported a frequency as high as 40% in the relatives of the children with AIH (7). Although none of the first-degree relatives in our case series had AIH, 24% of the parents had autoimmune disorders.

In the current trial 81% of the patients had AIH type 1, whereas type 2 AIH was observed only in three patients, two of them boys. The previous studies both in children and adults reported that type 1AIH is more prevalent than type 2 (5,6). According to the previous pediatric studies, the female predominance was noted (8,9). Female to male ratio in children vary in different countries from almost equal in United States to 4:1 in South America and UK (8,9,15,19). The onset was usually uncharacteristic with chronic presentation predominating in adults, whereas pediatric reports as also in our study, showed that acute presentation is more prevalent (5, 9,15). Correspondingly in a trial from Argentina the acute viral hepatitis–like presentation was observed in 54% of adult AIH patients, which was significantly lower than the frequency observed in the children with AIH (54% vs. 70%) (**21**). Our patients with insidious mode of presentation were found to be more likely to have lower serum ALT compared to symptomatic patients (p 0.001). As expected, levels of total bilirubin and INR were increased in patients with acute onset. These results were like that reported by Feld et al. (22), who also noted that asymptomatic patients were older, however in the present study there was no age differences between acutely or insidiously presented subjects. Interestingly there were no differences among laboratory parameters

Table-1: Demographic, anthropometric, and biochemical parameters according to mode of presentation in children with AIH

	Incidental	Acute/Fulminant hepatitis	P
Age (mean ± SD) (years)	11.1 ± 3.50	12.0 ±3.81	0.432[a]
Sex (male/female) (n)	3/5	2/7	
Weight SDS	0.007 ± 0.71	0.508 ± 0.97	0.233[a]
Height SDS	-0.26 ± 0.95	-0.74 ± 1.24	0.650[a]
BMI SDS	0.26 ± 0.70	0.88 ± 1.09	0.261[a]
ALT (median (IQR)) (IU/L)	344.5 (165-464)	895.0 (638-1317)	0.001[b]
Total bilirubin (median (IQR) (mg/dl)	1.00 (0.64-1.51)	6.55 (1.93-8.42)	0.001[b]
Conjugated bilirubin (median (IQR) (mg/dl)	0.34 (0.13-0.75)	4.50 (0.64-6.84)	0.001[b]
GGT (median (IQR) (IU/L)	56.0 (23.7-117)	120.0 (56-124)	0.038[b]
Albumin (median (IQR) (g/dl)	4.20 (4.1-4.37)	3.30 (3.12-4.27)	0.037[b]
INR (median (IQR)	1.20 (1.1-1.38)	1.60 (1.21-1.85)	0.011[b]
IgG (median (IQR) (mg/dl)	2168 (1942-2514)	2607 (2165-5867)	0.080[b]
Platelet (mean ± SD) (/mm3)	246.250 ± 49.169	196.142 ± 55.496	0.191[a]
Hemoglobin (mean ± SD) (g/dl)	12.3 ± 1.02	11.8 ± 1.81	0.650[a]
Legend: SD, standard deviation; IQR: interquartile range; ALT, alanine aminotransferase, □-glutamyl transferase; IgG, immunoglobulin G; BMI: body mass index;			
INR, international normalized ratio			
* a: Independent samples T test (mean ±SD); b: Mann-Whitney U test (median (1st quartile-3rd quartile))			

Table-2: Demographic, anthropometric, and biochemical parameters according to the presence of associated autoimmune diseases in children with AIH

	No associated auto-immune disease	Associated autoimmune disease	P
Age (mean ± SD) (years)	11.6 ± 3.39	11.3 ± 4.35	0,651[a]
Sex (male/female) (n)	5/6	0/6	
Weight SDS	0.37 ± 0.91	-0.02 ± 0.73	0.269 [a]
Height SDS	-0.69 ± 1.14	-0.07 ± 0.90	0.687 [a]
BMI SDS	0.81 ± 0.82	0.03 ± 0.99	0.132 [a]
ALT (median (IQR)) (IU/L)	672 (386-891)	456 (230-1526)	0.763 [b]
Total bilirubin (median (IQR)) (mg/dl)	1.63 (0.96-5.91)	1.20 (0.72-8.25)	0.615 [b]
Conjugated bilirubin (median (IQR) (mg/dl)	0.70 (0.34-3.24)	0.80 (0.11-6.57)	0.580 [b]
GGT (median (IQR) (IU/L)	87.9 (49-120)	109 (27-138)	0.651 [b]
Albumin (median (IQR) (g/dl)	4.20 (3.35-4.40)	3.90 (3.25-4.15)	0.362 [b]
INR (median (IQR)	1.41 (1.19-1.74)	1.20 (1.09-1.30)	0.049 [b]
IgG (median (IQR) (mg/dl)	2433 (263-5822)	2197 (2062-2524)	0.447 [b]
Platelet (mean ±SD) (/mm3)	214.900 ± 55.322	238.800 ± 61.900	0.191 [a]
Hemoglobin (mean ±SD) (g/dl)	12.1 ± 1.64	11.9 ± 0.95	0.650 [a]
Legend: SD, standard deviation; IQR: interquartile range; ALT, alanine aminotransferase; GGT, □-glutamyl transferase; IgG, immunoglobulin G;			
INR, international normalized ratio			
* a: Independent samples T test (mean ±SD); b: Mann Whitney U test (median (1st quartile-3rd quartile))			

Table-3: Biochemical parameters at onset of the disease, 3 and 6 months after treatment in patients with AIH.

Parameter	At onset	3rd month	6th month	P*
ALT (median(IQR)) (IU/L)	558 (280-893)	51 (29-81)	24 18-43)	0.000 [a]
AST (median(IQR)) (IU/L)	382 (170-1134)	53 (46-63)	26 (20-32.5)	0.000 [a]
ALP (median(IQR)) (IU/L)	165 (98-261)	123 (76-157)	80 (74-129)	0.003 [a]
GGT (median(IQR)) (IU/L)	109 (37-120)	34 (17-64)	23 (13.5-33.5)	0.000 [a]
Total bilirubin (median(IQR)) (mg/dl)	1.62 (1.89-6.3)	0.58 (0.42-1.06)	0.45 (0.40-0.69)	0.000 [a]
Conjugated bilirubin (median(IQR)) (mg/dl)	0.80 (0.24-4.1)	0.33 (0.21-0.56)	0.22 (0.20-0.36)	0.000 [a]
Total IgG (median(IQR)) (mg/dl)	2285 (2129-3226)	1680 (1250-1888)	1260 (1030-1482)	0.000 [a]
Albumin (median(IQR)) (mg/dl)	4.10 (3.25-4.40)	4.30 (4.24-4.74)	-	0.002 [b]
PT (median(IQR)) (s)	15.5 (14-18.8)	13.8 (13.3-15.5)	-	0.009 [b]
INR (median(IQR))	1.3 (1.17-2.26)	1.15 (1.09-1.36)	-	0.001 [b]
Legend: IQR, interquartile range; ALT, alanine aminotransferase; AST, aspartate aminotransferase;				
GGT, □-glutamyl transferase; IgG, immunoglobulin G; INR, international normalized ratio; PT, prothrombin time				
* a: Related-samples Friedman's test ; b: Wilcoxon signed ranks test.				

Table-4: Autoantibody profile in children with AIH

Autoantibody	Type-1 AIH	Type-2 AIH
ANA	9	1
SMA	11	0
LKM-1	0	3
AMA	0	2
p-ANCA	4	2
ANA+SMA	7	0
LKM-1 +AMA	0	2
Legend: ANA, antinuclear antibodies; SMA, Anti-smooth muscle antibodies;		
LKM-1, liver-kidney microsomal antibodies-1, AMA, antimitochondrial antibodies;		
p-ANCA, Perinuclear antineutrophil cytoplasmic antibodies.		

in settings of concomitant autoimmune diseases. IgG is usually raised at presentation in both types (3,7,22). as well as in the present study where independently of mode of presentation or association of other autoimmune or auto-inflammatory disease, the total IgG levels were elevated in all the patients. Yassin et al (23) reported elevated IgG levels at least 1.5 times and above in all the children with AIH. However, some pediatric studies showed IgG levels increment in only 60-85 % of the patients (6,24). Pando et al revealed that children with either acute or non-acute onset of the disease had significantly higher levels of total IgG at presentation compared to adults (21). The detection of several autoantibodies is still the hallmark of the diagnosis (1,15). Autoimmune profile of our patients was consistent with diagnosed type, however two children with type 2 AIH and positive anti- LKM 1 antibody had also AMA positivity. Although AMAs remain the serological hallmark for PBC diagnosis, in 3.6% to 34% of the patients with AIH, especially in type-2, AMA presence was reported (11, 25). Nevertheless, most researchers agree that the presence of AMA in AIH does not identify a subgroup of patients requiring different therapeutic options or leads to development of PBC (11). In addition, a long-term Canadian trial has shown that in patients with classical AIH who were AMA-positive over a follow-up of up to 27 years did not develop PBC (26).

In all patients with suspected AIH, including those with acute presentation with normal coagulation parameters, a liver biopsy should be performed, not only for diagnosis but also for the evaluation of disease severity (8,15). The present study showed that even in the acutely presented subjects liver biopsy could be safely done after normalization of the coagulation parameters.

Treatment improves the prognosis and reduces the formation of fibrosis and progression to cirrhosis in patients with AIH (9,11). Children with AIH usually well respond to immunosuppressive treatment with corticosteroids combined with immunomodulators. (15, 27). Standard maintenance therapy for all forms of AIH is the combination of low doses of prednisone and azathioprine (9,15), however in case of intolerance to AZA, MMF or cyclosporine usage is recommended (28). In the present case series Azathioprine was discontinued in two patients; in the first, because of severe skin eruptions and second child had persistent pancytopenia. In these cases, MMF was introduced. The expected frequency of remission with treatment is around 80% (6, 15, 28). This was observed also in the current case series, where complete response to treatment was achieved in 94% of the children. Only one patient had treatment failure (6%), because of non-adherence. Interestingly a study comparing pediatric and adult subjects with AIH showed that despite the higher doses of immunosuppressives in children, the treatment response was poorer compared to adults, suggesting that pediatric and adult AIH are different clinical entities with genetic associations (21). Rodriguez et al. also observed lower frequencies of treatment response (78.3%) with frequent relapses in children and adolescent with AIH (16). Teufel et al. (17) compared the rates of relapses of AIH in patients with and without CAIDs and found no significant differences in the number of relapses between the groups. However, in a multicenter study from Netherlands, CAIDs were shown to be independent risk factor for early relapse in AIH patients after withdrawal of immunosuppression (19).

Unlike in adults, the criteria for discontinuation of the treatment for children with AIH has not been clarified. Adult guidelines recommend withdrawal of therapy for patients who achieved a complete response after two years of treatment, and in absence of histological cirrhosis, yet it's not clear if remission also includes the disappearance of the autoantibodies (5,29). Pediatric hepatology committee suggests treating children for at least 2 to 3 years and withdrawal of treatment if transaminase and IgG levels have been normal with negative autoantibodies for at least one year (15). According to this protocol, successful complete withdrawal of treatment however is possible only in 20% of patients with AIH-1, but not possible in AIH-2, with relapse in 45% of the children (8,15). Here with, none of the presents study subjects fulfilled criteria for ceasing therapy.

The present trail had few limitations. First, this report includes a relatively small number of patients, accordingly a large population from multicentric date are needed in order to review the association of AIH with other autoimmune or autoinflammatory diseases in children. On the other hand, the data were retrospectively collected, so a prospective, well-structured study would give more precise results featuring AIH and CAIDs in children.

Conclusion: AIH is a rare but important cause of chronic liver disease in children. AIH must always be included in the differential diagnosis of elevated liver enzymes in children, as early treatment avoids progression to cirrhosis. Frequent association with autoimmune or autoinflammatory diseases also should be kept in mind as the clinical expression of the concomitant disease can be extremely variable therefore diagnosis and treatment delay may occur (18, 30). Accordingly pediatric hepatologist should be aware of this association and prompt follow up should be designed for children with multiple CAIDs.

References

1.European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. J Hepatol. 2015;63:971-1004.

2.Mieli-Vergani G, Vergani D, Czaja AJ, et al. Autoimmune hepatitis. Nat Rev Dis Primers. 2018;12:18017.

3.Werner M, Prytz H, Ohlsson B, et al. Epidemiology and the initial presentation of autoimmune hepatitis in Sweden: a nationwide study. Scand J Gastroenterol. 2008;43:1232–40.

4.Sokollik C, McLin VA, Vergani D, Terziroli Beretta-Piccoli B, Mieli-Vergani G. Juvenile autoimmune hepatitis: A comprehensive review. J Autoimmun. 2018;95:69-76.

5.Mack CL, Adams D, Assis DN, et al. Diagnosis and Management of Autoimmune Hepatitis in Adults and Children: 2019 Practice Guidance and Guidelines From the American Association for the Study of Liver Diseases. Hepatology. 2020;72:671-722.

6.Mieli-Vergani G, Vergani D. Autoimmune hepatitis in children: what is different from adult AIH? Semin Liver Dis. 2009;29:297-306.

7.Gregorio GV, Portmann B, Reid F, et al. Autoimmune hepatitis in childhood: a 20 years experience. Hepatology. 1997;25:541-7.

8.Gregorio GV, Portmann B, Karani J, et al. Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood: a 16-year prospective study. Hepatology. 2001;33:544-53

9.Floreani A, Liberal R, Vergani D, Mieli-Vergani G. Autoimmune hepatitis: Contrasts and comparisons in children and adults - a comprehensive review. J Autoimmun. 2013;46:7-16.

10.Volk M, Reau N. Diagnosis and Management of Autoimmune Hepatitis in Adults and Children: A Patient-Friendly Summary of the 2019 AASLD Guidelines. Clin Liver Dis (Hoboken). 2021;17:85-9.

11.Gatselis NK, Zachou K, Koukoulis GK, Dalekos GN. Autoimmune hepatitis, one disease with many faces: etiopathogenetic, clinico-laboratory and histological characteristics. World J Gastroenterol. 2015;21:60-83.

12.Zachou K, Rigopoulou E, Dalekos GN. Autoantibodies and autoantigens in autoimmune hepatitis: important tools in clinical practice and to study pathogenesis of the disease. J Autoimmune Dis. 2004;1:2.

13.Nakaji M, Hayashi Y, Ninomiya T, et al. Histological grading and staging in chronic hepatitis: its practical correlation. Pathol Int. 2002;52:683-90.

14.Ishak K, Baptista A, Bianchi L et al. Histological grading and staging of chronic hepatitis. J. Hepatol. 1995; 22: 696–9.

15.Mieli-Vergani G, Vergani D, Baumann U, et al. Diagnosis and Management of Pediatric Autoimmune Liver Disease: ESPGHAN Hepatology Committee Position Statement. J Pediatr Gastroenterol Nutr. 2018;66:345-360.

16.Rodrigues AT, Liu PM, Fagundes ED, et al. Clinical Characteristics and Prognosis in Children and Adolescents With Autoimmune Hepatitis and Overlap Syndrome. J Pediatr Gastroenterol Nutr. 2016;63:76-81.

17.Teufel A, Weinmann A, Kahaly GJ, et al. Concurrent autoimmune diseases in patients with autoimmune hepatitis. J Clin Gastroenterol. 2010;44:208-13.

18.Wong GW, Heneghan MA. Association of Extrahepatic Manifestations with Autoimmune Hepatitis. Dig Dis. 2015;33:25-35.

19.Van Gerven NM, Verwer BJ, Witte BI, et al. Dutch Autoimmune hepatitis STUDY group: Epidemiology and clinical characteristics of autoimmune hepatitis in the Netherlands. Scand J Gastroenterol 2014;49:1245–1254.

20.Clemente MG, De Virgiliis S. Autoantigen characterization in liver/kidney microsome positive hepatitis. Dig Liver Dis. 2000;32:39-45.

21.Pando M, Larriba J, Fernandez GC, et al. Pediatric and adult forms of type I autoimmune hepatitis in Argentina: evidence for differential genetic predisposition. Hepatology. 1999;30:1374-80.

22.Feld JJ, Dinh H, Arenovich T, et al. Autoimmune hepatitis: effect of symptoms and cirrhosis on natural history and outcome. Hepatology. 2005;42:53-62.

23.Yassin S, De Lacy R, Pillay K, Goddard E. Characteristics and Outcomes of Autoimmune Hepatitis from a Tertiary Paediatric Centre, Cape Town, South Africa. J Trop Pediatr. 2020;66:448-457.

24.Fallatah HI, Akbar HO, Qari YA. Autoimmune hepatitis: Single-center experience of clinical presentation, response to treatment and prognosis in Saudi Arabia. Saudi J Gastroenterol. 2010;16:95-9.

25.Farid E, Isa HM, Al Nasef M, Mohamed R, Jamsheer H. Childhood Autoimmune Hepatitis in Bahrain: a Tertiary Center Experience. Iran J Immunol. 2015;12:141-8.

26.O'Brien C, Joshi S, Feld JJ, Guindi M, Dienes HP, Heathcote EJ. Long-term follow-up of antimitochondrial antibody-positive autoimmune hepatitis. Hepatology. 2008;48:550-6.

27.Low AS, Tan M, Garcia A, Aw M, Quak SH. Childhood autoimmune hepatitis in a paediatric unit of a tertiary care hospital. Singapore Med J. 2014;55:648-51.

28.Sucher E, Sucher R, Gradistanac T, et al. Autoimmune Hepatitis-Immunologically Triggered Liver Pathogenesis-Diagnostic and Therapeutic Strategies. J Immunol Res. 2019;2019:9437043.

29.Harrison L, Gleeson D. Stopping immunosuppressive treatment in autoimmune hepatitis (AIH): Is it justified (and in whom and when)? Liver Int. 2019;39:610-620.

30.Guo L, Zhou L, Zhang N, Deng B, Wang B. Extrahepatic Autoimmune Diseases in Patients with Autoimmune Liver Diseases: A Phenomenon Neglected by Gastroenterologists. Gastroenterol Res Pract. 2017;2017:2376231.

Received: 12 Nov 2021 | **Accepted:** 22 Dec 2021
DOI: 10.54005/geneltip.1022644

CLINICAL RESEARCH

Is in-hospital mortality associated with neurological outcomes in patients with endovascular aortic repair? Results from a single centre

Endovasküler aort onarımı yapılan hastalarda nörolojik sonuçlar ile hastane mortalitesi arasındaki ilişki

[1]Levent Altınay, [1]Elif Coşkun Sungur, [2]İlker İnce

[1]Zonguldak Bülent Ecevit University, Faculty of Medicine, Department of Cardiovascular Surgery, Zonguldak, Turkey.

[2]Health Sciences University, Dışkapı Yılıdırım Beyazıt Education and Research Hospital, Department of Cardiovascular Surgery, Ankara, Turkey.

Correspondence

Levent Altınay, Health Sciences University, Dışkapı Yılıdırım Beyazıt Education and Research Hospital, Department of Cardiovascular Surgery, Ziraat Mah. Şehit Ömer Halisdemir Cad. No: 20 Dışkapı/ANKARA.

E-Mail: laltinay@gmail.com

How to cite ?

Altınay M, Coşkun-Songur E, İnce İ. Is in-hospital mortality associated with neurological outcomes in patients with endovascular aortic repair? Results from a single centre. Genel Tıp Derg. 2022;32(1):102-107.

ABSTRACT

Aim: Herein, we aimed to present our results of thoracic and abdominal endovascular aortic repair (EVAR/TEVAR) procedures for thoracoabdominal aortic pathologies and the relation between the post-procedural neurological adverse events and in-hospital mortality.
Material and Method: Patients who underwent EVAR/TEVAR procedures between November 2016 and May 2021 were included in this retrospective study. Patients with a history of any cerebrovascular event before the intervention were excluded. Patients were divided into two groups according to the occurrence of any early neurological complications in the postoperative period in hospital.
Results: A total of 47 patients were included in this retrospective study. Group 1 included 37 (78.7%) patients who had no neurological complications in the early postoperative period. Group 2 included 10 (21.3%) patients who had a postoperative neurological complication. The intensive care unit (ICU) stay time was significantly longer in Group 2 compared with Group 1 (1.7 ± 2.0 days in Group 1 vs 6.2 ± 5.1 days in Group 2, p = 0.021). The overall mortality rate was 19.1% (9 of 47 patients). The mortality rate of Group 2 was significantly higher than Group 1 (2 of 37 [5.4%] patients in Group 1 vs 7 of 10 [70%] patients in Group 2, p = 0.001). The American Society of Anesthesiologists (ASA) physical classification score was significantly higher in Group 2 than Group 1 (3.5 ± 0.6 in Group 1 vs 4.1 ± 0.3 in Group 2, p = 0.016). The most common early postoperative neurological complication was a lack of recovery of consciousness in the postoperative period (no postoperative consciousness).
Conclusion: The occurrence of any postoperative neurological adverse event is associated with in-hospital mortality following TEVAR/EVAR procedures.

Keywords: EVAR, TEVAR, neurological deficit, in-hospital mortality

ÖZ

Amaç: Torakoabdominal aort patolojilerinde EVAR/TEVAR sonuçlarımızı ve post-prosedural nörolojik olaylar ile hastane mortalitesi arasındaki ilişkiyi sunmak.
Gereç ve yöntem: Kasım 2016 – Mayıs 2021 arasında EVAR/TEVAR işlemi uygulanmış hastalar bu retrospektif çalışmaya alındı. İşlem öncesi herhangi bir nörolojik olay öyküsü olan hastalar çalışmaya alınmadı. Post-prosedural erken nörolojik komplikasyonların oluşuna göre hastalar iki gruba ayrıldı.
Bulgular: Toplam 60 hasta değerlendirildi. Grup 1 nörolojik komplikasyon olmayan 37 (%78.7) hasta, Grup 2 post-prosedural nörolojik komplikasyon olan 10 (%21.3) hastadan oluştu. Yoğunbakımda kalış süresi Grup 2'de anlamlı derecede uzundu (1.7 ± 2.0 gün Group 1 vs 6.2 ± 5.1 gün Group 2, p=0.021). genel mortalite oranı %19.1 (47 hastada 9) idi. Grup 2 mortalite oranı anlamlı derecede yüksekti (37 hastada 2 (%5.4) Group 1'de vs 10 hastada 7 (%70) Group 2'de, p=0.001). Amerikan Anesteziyolojistler Birliği fiziksel sınıflama skoru Grup 2'de anlamlı derecede yüksekti (3.5 ± 0.6 Group 1 vs 4.1 ± 0.3 Group 2, p=0.016). En sık erken postprosedural nörolojik komplikasyon bilinç olmamasıydı.
Sonuç: Erken postprosedural nörolojik komplikasyon oluşması, TEVAR ve EVAR prosedürlerinin hastane mortalitesini artmasına katkı yapmaktadır.

Anahtar kelimeler: EVAR, TEVAR, nörolojik komplikasyon, hastane mortalitesi

Introduction

In recent years, thoracic and abdominal endovascular aortic repair (EVAR/TEVAR) procedures have become common techniques for thoracoabdominal aortic pathologies such as aortic dissections and aneurysms. The main goal is to exclude the aortic lesion (i.e. aneurysm or false lumen after aortic dissection) from circulation by implanting a fabric-covered stent across the lesion. EVAR/TEVAR techniques are strongly recommended as the preferred treatment approach in certain patient groups with thoracic and abdominal aortic pathologies (1–3).

Neurological complications such as paraplegia and stroke rates after TEVAR procedures have been reported to be between 0.8% and 1.9% and between 2.1% and 3.5%, respectively (4). Transfer status, emergency intervention, preoperative white blood cell count (WBC), preoperative serum creatinine and

left subclavian artery (LSA) coverage have been reported as variables associated with an elevated risk of postoperative stroke after TEVAR (5).

The mortality rate after TEVAR has been reported to be between 3% and 9.5% (6,7). The 1-year all-cause mortality after TEVAR has been reported to be between 10% and 18% (8,9) and between 4% and 12% after EVAR (10,11). Age, emergency case, preoperative WBC, preoperative serum creatinine level, concurrent aortic arch debranching procedures and chronic obstructive pulmonary disease (COPD) are independent risk factors for mortality (5,6).

Messe et al. (12) reported ischaemic neurological complications in 85 (38%) of 224 patients with descending/thoracoabdominal aortic pathologies who underwent open surgery repair procedures. They also found significantly higher mortality rates in patients with neurological complications than in patients without neurological complications ($p < 0.001$).

Herein, we aimed to present our results of endovascular repair of descending thoracic aortic aneurysm (DTAA), abdominal aortic aneurysm (AAA) and thoracoabdominal aortic aneurysm (TAA) pathologies and the relation between the neurological outcomes and in-hospital mortality rates in these patients.

Material and Method

Patients who underwent EVAR/TEVAR procedures between November 2016 and May 2021 were included in this retrospective study. Patients with a history of any cerebrovascular event before the intervention were excluded. Patient data were collected from hospital records. Patients were divided into two groups according to the occurrence of any early neurological complications in the postoperative period in hospital. Mortality rates were calculated for both groups. Local ethical committee approval was obtained for the study.

The surgical procedure

All operations were performed under local anaesthesia in the angiography laboratory except concomitant peripheral arterial bypass or visceral artery bypass surgery, which were performed under general anaesthesia. The patient's heart rate and rhythm were monitored with electrocardiography and their blood pressure was monitored with invasive blood pressure monitoring. A 5000 IU bolus of intravenous heparin was administered at the beginning of all procedures and activated clotting time was monitored and maintained at over 150 seconds. All interventions were performed through femoral artery access. After proper disinfection and coverage of surgical sites, both femoral arteries were exposed with the open surgical technique if bifurcated stent graft implantation was planned. For cases in which only tubular graft implantation was planned, only one femoral artery was exposed and percutaneous access was achieved on the other side. In TEVAR, generally one-sided open surgical access and one-sided percutaneous access were achieved. In EVAR, bilateral accesses were achieved with the open surgical technique. In TEVAR, a 0.035-inch, 300-cm guidewire (Shunmei polytetrafluoroethylene [PTFE]-coated guidewire, Shunmei Medical, Shenzhen, PRC) was introduced into the femoral artery through a 6F/7F introducer sheath. Then, a 6F pigtail catheter (Dxterity 6F diagnostic catheter, Medtronic, Santa Rosa, CA, USA) was loaded over the guidewire and placed in a proper position in the thoracic aorta to get angiographic images of the descending aorta. The main body of the aortic stent graft (Valiant Captivia, Medtronic) was introduced through a 24F introducer sheath (Sentrant, 24F 28 cm, Medtronic) in the contralateral femoral artery, which was exposed with open surgical technique. The thoracic aortic stent graft was deployed according to the measurements of the angiography images taken previously in the procedure. The pigtail catheter was pulled back and replaced in the thoracic aorta through the stent graft and control angiography images were obtained to check for any signs of endoleak. If a type 1 endoleak was observed, then an extension graft (aortic cuff) was placed and balloon dilatation of the grafts was performed. The procedure was complete if no signs of endoleak were seen. The femoral artery was repaired with 6/0 or 7/0 propylene primary sutures. An open surgical bypass with an 8 mm synthetic PTFE graft was performed from the left common carotid artery (LCCA) to the LSA if coverage of the ostium of the LSA was planned at the beginning of the procedure.

In EVAR procedures, both femoral artery accesses were achieved with open surgery. Angiographic images were obtained as described above. The main body of the abdominal aortic stent graft (Endurant II, Medtronic) was placed just below the renal artery orifice to avoid renal artery occlusion through either left or right femoral artery access. Then, the contralateral limb of the graft was introduced through contralateral femoral artery access and placed in the contralateral limb of the stent graft with enough overlapping length. Large size introducer sheaths (24F Sentrant, Medtronic) were used in both femoral arterial access sites. Balloon angioplasty was performed with a balloon catheter (Reliant, Medtronic) in the proximal and overlapping sections of the graft to stabilise the graft in the aorta and to minimise the risk of endoleak (type I and III). Control angiography images were obtained to check for any signs of endoleak (especially types I and III). Finally, sheaths in the femoral arteries were removed and femoral arteries were repaired with 6/0 or 7/0 propylene sutures if there was no sign of endoleak.

All cases were completed with technical success. The patients were taken into the intensive care unit (ICU) for postoperative follow-up. A total of 3000 ml of intravenous crystalloid fluid infusion over a period of 24 hours, 100 mg acetylsalicylic acid (ASA) and 150 mg clopidogrel were administered orally to all patients in

the ICU if applicable. The patients were transferred to the ward on the second postoperative day. They were discharged on the third postoperative day if no problems had occurred during the follow-up. They received a prescription for 100 mg ASA and 75 mg clopidogrel once-a-day orally.

Statistical analysis

SPSS v13 software was used for statistical analysis. The qualitative data are expressed as a percentage (%) and the quantitative data are expressed as mean ± standard deviation (SD). The distribution of the data was tested for normality with the Kolmogorov–Smirnov test. The significance of the continuous data was tested with Student's t-test if distributed normally and the Mann–Whitney U test if distributed non-normally. Categorical variables were compared with the chi-square test. A p value < 0.05 was considered to indicate statistical significance.

Results

A total of 60 patients who underwent EVAR/TEVAR procedures were evaluated. Forty-seven patients were included according to the inclusion criteria. Group 1 included 37 (78.7%) patients who had no neurological complications in the early postoperative period. Group 2 included 10 (21.3%) patients who had a postoperative neurological complication. The preoperative characteristics of the patients are presented in Table 1.

The number of EVAR cases was 30 (63.8%), the number of TEVAR cases was 11 (23.4%) and the number of combined EVAR and TEVAR cases was 6 (12.8%). There was no significant difference in the number of aortic interventions between the groups (p = 0.104). The ICU stay time was significantly longer in Group 2 than in Group 1 (1.7 ± 2.0 days in Group 1 vs 6.2 ± 5.1 days in Group 2, p = 0.021). The in-hospital stay time was longer in Group 2 but it was not statistically significant (p = 0.160). Open surgery was not needed in the study patients. The overall mortality rate was 19.1% (9 of 47 patients). The mortality rate of the Group 2 was significantly higher than Group 1 (2 of 37 [5.4%] patients in Group 1 vs 7 of 10 [70%] patients in Group 2, p = 0.001).

The mean transverse aorta diameter was 6.2 ± 0.6 cm (range 5.5–7.8 cm) in Group 1 and 6.8 ± 1.3 cm (range 5.5–9.9 cm) in Group 2 (p = 0.151). The distribution of mean transverse aortic diameters according to aortic pathologies is presented in Table 2. One patient had an arterio-venous fistula between the abdominal aorta and the inferior vena cava; the transverse diameter of the abdominal aorta was 8.5 cm in this patient.

Table 1. Preoperative data

	Group 1 (n=37)	Group 2 (n=10)	P value
Age mean ± SD	72.7 ± 11.8	74.8 ± 8.9	0.604
Male n(%)	30 (81)	7 (70)	0.461
EF mean ± SD	48.6 ± 9.5	48.3 ± 12	0.935
Triglyceride mg/dl mean ± SD	153.7 ± 72.7	158.4 ± 88.2	0.862
LDL mg/dl mean ± SD	118.2 ± 51.6	125.0 ± 70.9	0.734
Preoperative creatinine mg/dl mean ± SD	1.2 ± 0.9	1.5 ± 0.8	0.262
Preoperative white blood cell count mean ± SD	11.4 ± 7.7	8.8 ± 2.4	0.360
Preoperative arrhythmia n(%)			0.182
None	27 (72.9)	5 (50)	
AF	9 (24.3)	4 (40)	
AV block	1 (2.7)	0	
Pacemaker	0	1 (10)	
Peripheral artery disease n(%)	6 (16.2)	0	0.078
Preoperative malignancy n(%)	5 (13.5)	1 (10)	0.762
Preoperative COPD n(%)	17 (45.9)	6 (60)	0.429
Tobacco product consumption n(%)	26 (70.2)	7 (70)	0.987
Diabetes mellitus n(%)	14 (37.8)	5 (50)	0.490

SD: Standard deviation; EF: Ejection fraction (%); LDL: Low density lipoprotein; AF: Atrial fibrillation; AV block: Atrioventricular block; COPD: Chronic obstructive pulmonary disease;

Table 2. Aortic pathology and aorta diameters

	Group 1 (n=37)		Group 2 (n=10)	
	N (%)	Mean ± SD (cm)	N (%)	Mean ± SD (cm)
Abdominal aorta aneurysm	20 (54.0)	6.3 ± 0.7	2 (20)	7.3 ± 0.5
Thoracic aorta aneurysm	5 (13.5)	6.0 ± 0.4	1 (10)	6.9
Type 3 dissection	1 (2.7)	6.1	2 (20)	5.9 ± 0.6
Abdominal aorta + iliac artery aneurysm	5 (13.5)	6.1 ± 0.6	2 (20)	6.7 ± 1.2
Ruptured abdominal aorta aneurysm	1 (2.7)	6.6	0	
Ruptured thoracic aorta aneurysm	0		1 (10)	6.7
Thoracic + abdominal aorta aneurysm	2 (5.4)	5.8 ± 0.4	2 (29)	7.7 ± 3.1
Ruptured thoracic + abdominal aorta aneurysm	2 (5.4)	6.7 ± 1.2	0	
Type 3 dissection + abdominal aorta aneurysm	1 (2.7)	6.3	0	

SD: Standard deviation

Table 3. Postoperative data

		Group 1 (n=37)	Group 2 (n=10)	P value
Emergency surgery n(%)		15 (40.5)	7 (70)	0.095
ASA risk score mean ± SD		3.5 ± 0.6	4.1 ± 0.3	0.016
ES transfusion units mean ± SD		1.2 ± 2.4	1.1 ± 1.6	0.939
ICU stay time days mean ± SD		1.7 ± 2.0	6.2 ± 5.1	0.021
In-hospital stay time days mean ± SD		7.0 ± 4.0	10.1 ± 6.1	0.160
Transvers aorta diameters (cm) mean ± SD		6.2 ± 0.6	6.8 ± 1.3	0.151
Aortic pathology n(%)				0.197
	AAA	19 (51.4)	2 (20)	
	TAA	5 (13.5)	1 (10)	
	Type 3 dissection	1 (2.7)	2 (20)	
	AAA + CIAA	5 (13.5)	2 (20)	
	Ruptured AAA	1 (2.7)	0	
	Dual AAA	1 (2.7)	0	
	Ruptured TAA	0	1 (10)	
	TAA + AAA	2 (5.4)	2 (20)	
	Ruptured TAA + AAA	2 (5.4)	0	
	Type 3 dissection + AAA	1 (2.7)	0	
Aortic intervention n(%)				0.104
	EVAR	26 (70.3)	4 (40)	
	TEVAR	6 (16.2)	5 (50)	
	TEVAR + EVAR	5 (13.5)	1 (10)	
Aortic graft diameter (mm) mean ± SD		33.1 ± 5.7	33.8 ± 7.0	0.764
Aortic graft length (mm) mean ± SD		143.3 ± 48.9	147.9 ± 44.4	0.990
Femoro-femoral bypass n(%)		6 (16.2)	1 (10)	0.189
Type of endoleak n(%)				0.869
	None	28 (75.7)	7 (70)	
	Type 1	3 (8.1)	1 (10)	
	Type 2	1 (2.7)	0	
	Type 3	3 (8.1)	1 (10)	
	Type 1 + type 3	1 (2.7)	1 (10)	
	Type 1 + type 2	1 (2.7)	0	
Embolization types				0.551
	None	24 (64.9)	6 (60)	
	Arterial coil	5 (13.5)	3 (30)	
	Balloon angioplasty	4 (10.8)	1 (10)	
	Iliac artery occluder	1 (2.7)	0	
	Coil + balloon angioplasty	3 (8.1)	0	
Access site complications n(%)		7 (18.9)	2 (20)	0.930
Mortality n(%)		2 (5.4)	7 (70)	0.001

ASA: American Society of Anesthesiologists; ES: Erythrocyte suspension; SD: Standard deviation; ICU: Intensive care unit; AAA: Abdominal aortic aneurysm; TAA: Thoracic aortic aneurysm; CIAA: Common iliac artery aneurysm; EVAR: Endovascular aneurysm repair; TEVAR: Thoracic endovascular aneurysm repair.

The American Society of Anesthesiologists (ASA) physical classification score was significantly higher in Group 2 compared with Group 1 (3.5 ± 0.6 in Group 1 vs 4.1 ± 0.3 in Group 2, p = 0.016). Left carotid-subclavian artery bypass was performed in one patient after the TEVAR procedure in Group 2. Femoro-femoral bypass was performed in six (16.2%) patients in Group 1 and one patient (10%) in Group 2 (p = 0.189). Aorta-superior mesenteric artery bypass was performed in one patient who had an AAA in Group 2. Arterial coil embolisation and/or balloon angioplasty were performed according to the type of endoleak. The postoperative data are presented in Table 3. The most common early postoperative neurological complication was the lack of recovery of consciousness during the postoperative period (no postoperative consciousness). The distribution of the postoperative neurological complications is presented in Table 4.

Table 4. Type of neurological complications

	N (%)
Cognitive dysfunction	2 (4.3)
Acute cerebral ischemia	2 (4.3)
Seizures	1 (2.1)
No postoperative consciousness	5 (10.6)

Discussion

According to the results of this study, it is possible to say that early postoperative neurological complications after EVAR and/or TEVAR procedures are strongly related to in-hospital mortality.

Periprocedural ischaemic events after EVAR/TEVAR procedures are related to dislodged multiple emboli by manipulation of catheters, guidewires, large-calibre delivery sheaths, and devices in the diseased aortic wall (13,14). The main blood supply of the spinal cord comes from the vertebral, segmental and hypogastric arteries. The anterior spinal artery is formed by the branches that come off each vertebral artery before they join together to form the basilar artery. The two posterior spinal arteries are formed by the branches of the posterior cerebellar artery (PICA) or by the branches of pre-atlantal vertebral arteries. These three arteries are fed by additional arteries throughout their course at each spinal cord level through the intervertebral foramen; these vessels are called segmental arteries. These segmental arteries branch into anterior and posterior radicular arteries and spinal medullary arteries which feed anterior and posterior spinal arteries.

Extensive coverage of the aorta by endografts (15,16), perioperative hypotension (17), covering the LSA orifice (13,18), shorter native aorta segment proximal to the celiac artery (19), previous or concomitant TEVAR and EVAR (15,20) are associated with post-procedural spinal cord ischaemia and neurological complications. We performed left carotid-subclavian artery bypass in one patient with thoracic aortic pathology because the orifice of the LSA was covered by the aortic stent graft. We avoided covering a thoracic aorta segment longer than 20 cm in a single session to prevent spinal cord ischaemia and possible neurological complications.

The incidence of pelvic ischaemic complications after open infrarenal aortic surgery is about 2% but the associated mortality rate is over 40% (21,22). The ischaemic complication rate after EVAR is between 3% and 10% (23). Interruption of hypogastric arterial circulation and limb occlusion contribute to the mechanism of post-EVAR pelvic ischaemia (24). Maldonado et al. reported that colonic and spinal cord ischaemia after EVAR is associated with high post-procedural morbidity and mortality (25).

Xue et al. (26) compared the results of patients with and without spinal cord ischaemia after TEVAR and reported that post-TEVAR ICU stay and in-hospital stay times are significantly longer in patients with spinal cord ischaemia. In our study, the mean ICU stay time was significantly longer in patients who had post-procedural neurological complications (p = 0.021). The mean in-hospital stay time was also longer in these patients but it was not statistically significant (p = 0.160).

The ASA risk score is used to evaluate the patient's status, predict perioperative risk and improve patient outcomes (27). It ranges from a healthy patient (ASA I) to a brain-dead patient (ASA VI). The ASA score was significantly higher in Group 2 patients in this study. Moreover, patients of Group 2 were admitted with a more haemodynamically unstable preoperative status. We think that these factors had an additive effect on postoperative neurological adverse events and raised the in-hospital mortality rates in this group as a result.

Limitations of the study

The study was retrospective and was conducted in a single centre. The patient number was low because endovascular treatment is expensive and most of the emergent patients could not reach a health centre on time in our region. Patients with aortic disease commonly had a peripheral arterial disease such as carotid artery disease and it was difficult to find patients without preoperative cerebral ischaemic events to include in the study group.

Conclusion

The occurrence of any postoperative neurological adverse event is associated with in-hospital mortality following TEVAR and EVAR procedures. Additional studies with more patients should be conducted on this subject.

Acknowledgements: None.

ETHICAL DECLARATIONS

Ethics Committee Approval: It was approved by the Ethics Committee of the Zonguldak Bülent Ecevit University.

Informed Consent: The study was conducted retrospectively so no written informed consent was needed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

References

1.Upchurch GR, Escobar GA, Azizzadeh A, et al. Society for Vascular Surgery clinical practice guidelines of thoracic endovascular aortic repair for descending thoracic aortic aneurysms. J Vasc Surg. 2021;73:55S-83S.
2.Usta S. Our endovascular therapy application for descending aortic pathology. Turkish J Thorac Cardiovasc Surg. 2012;243–8.

3.Demirtas S. Single center experience in endovascular aortic repair: review of technical and clinical aspects. Dicle Med J / Dicle Tip Derg. 2014;41:564–73.

4.Ben-Shlomo Y, Spears M, Boustred C, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol. 2014;63:636–46.

5.Hu FY, Fang ZB, Leshnower BG, et al. Contemporary evaluation of mortality and stroke risk after thoracic endovascular aortic repair. J Vasc Surg. 2017;66:718-727.e5.

6.Chung J, Corriere MA, Veeraswamy RK, et al. Risk factors for late mortality after endovascular repair of the thoracic aorta. J Vasc Surg. 2010;52:549–55.

7.Scali ST, Chang CK, Feezor RJ, et al. Preoperative prediction of mortality within 1 year after elective thoracic endovascular aortic aneurysm repair. J Vasc Surg. 2012;56:1266–73.

8.Goodney PP, Travis L, Lucas FL, et al. Survival after open versus endovascular thoracic aortic aneurysm repair in an observational study of the Medicare population. Circulation. 2011;124:2661–9.

9.Fairman RM, Criado F, Farber M, et al. Pivotal results of the Medtronic Vascular Talent Thoracic Stent Graft System: the VALOR trial. J Vasc Surg. 2008;48:546–54.

10.Malas MB, Freischlag JA. Interpretation of the results of OVER in the context of EVAR trial, DREAM, and the EUROSTAR registry. Semin Vasc Surg. 2010;23:165–9.

11.Quinney BE, Parmar GM, Nagre SB, et al. Long-term single institution comparison of endovascular aneurysm repair and open aortic aneurysm repair. J Vasc Surg. 2011;54:1592–7; discussion 1597-8.

12.Messé SR, Bavaria JE, Mullen M, et al. Neurologic Outcomes from High Risk Descending Thoracic and Thoracoabdominal Aortic Operations in the Era of Endovascular Repair. Neurocrit Care. 2008;9:344–51.

13.Buth J, Harris PL, Hobo R, et al. Neurologic complications associated with endovascular repair of thoracic aortic pathology: Incidence and risk factors. A study from the European Collaborators on Stent/Graft Techniques for Aortic Aneurysm Repair (EUROSTAR) Registry. J Vasc Surg. 2007;46:1103-1111.e2.

14.Morales JP, Taylor PR, Bell RE, et al. Neurological Complications Following Endoluminal Repair of Thoracic Aortic Disease. Cardiovasc Intervent Radiol. 2007;30:833–9.

15.Gravereaux EC, Faries PL, Burks JA, et al. Risk of spinal cord ischemia after endograft repair of thoracic aortic aneurysms. J Vasc Surg. 2001;34:997–1003.

16.Drinkwater SL, Goebells A, Haydar A, et al. The Incidence of Spinal Cord Ischaemia Following Thoracic and Thoracoabdominal Aortic Endovascular Intervention. Eur J Vasc Endovasc Surg. 2010;40:729–35.

17.Chiesa R, Melissano G, Marrocco-Trischitta MM, et al. Spinal cord ischemia after elective stent-graft repair of the thoracic aorta. J Vasc Surg. 2005;42:11–7.

18.Matsumura JS, Rizvi AZ. Left subclavian artery revascularization: Society for Vascular Surgery® Practice Guidelines. J Vasc Surg. 2010;52:65S-70S.

19.Feezor RJ, Martin TD, Hess PJ, et al. Extent of Aortic Coverage and Incidence of Spinal Cord Ischemia After Thoracic Endovascular Aneurysm Repair. Ann Thorac Surg. 2008;86:1809–14.

20.Kawaharada N, Morishita K, Kurimoto Y, et al. Spinal cord ischemia after elective endovascular stent-graft repair of the thoracic aorta□. Eur J Cardio-Thoracic Surg. 2007;31:998–1003.

21.Brewster DC, Franklin DP, Cambria RP, et al. Intestinal ischemia complicating abdominal aortic surgery. Surgery. 1991;109:447–54.

22.Järvinen O, Laurikka J, Salenius J-P, et al. Mesenteric Infarction after Aortoiliac Surgery on the Basis of 1752 Operations from the National Vascular Registry. World J Surg. 1999;23:243–7.

23.Becquemin J-P, Kelley L, Zubilewicz T, et al. Outcomes of secondary interventions after abdominal aortic aneurysm endovascular repair. J Vasc Surg. 2004;39:298–305.

24.Carroccio A, Faries PL, Morrissey NJ, et al. Predicting iliac limb occlusions after bifurcated aortic stent grafting: anatomic and device-related causes. J Vasc Surg. 2002;36:679–84.

25.Maldonado TS, Rockman CB, Riles E, et al. Ischemic complications after endovascular abdominal aortic aneurysm repair. J Vasc Surg. 2004;40:703–10.

26.Xue L, Luo S, Ding H, et al. Risk of spinal cord ischemia after thoracic endovascular aortic repair. J Thorac Dis. 2018;10:6088–96.

27.Daabiss M. American Society of Anaesthesiologists physical status classification. Indian J Anaesth. 2011;55:111–5.