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Publication status of pharmacology specialty theses in scientific journals in Turkey

Türkiye'de farmakoloji alanında yapılan uzmanlık tezlerinin bilimsel dergilerde yayınlanma durumları

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Ethics Committee Approval: The study was approved by Kahramanmaraş Sütçü İmam University Faculty of Medicine Ethical Committee of Clinical Trials (2020/10-03). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma Kahramanmaraş Sütçü İmam Üniversitesi Tıp Fakültesi, Klinik Araştırmalar Etik Kurulu (2020/10-03) tarafından onaylandı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

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Abstract

Aim: The publication of theses is the main indicator in revealing the scientific efficiency of a country. To the best of our knowledge, the publication status of pharmacology specialty theses has not been reported before. The aim of this study is to evaluate the publication status of medical pharmacology theses published by the departments of medical pharmacology of medical faculties in our country between 2006 and 2016 in scientific journals.

Methods: A total of 108 pharmacology residency theses published between 2006 and 2016 and registered into the system from all Medical Pharmacology departments of all medical faculties in our country, as accessed from in Higher Education Council National Thesis Center's Internet database (https://tez.yok.gov.tr/ulusaltezmerkezi/), were included in this observational study. These theses were analyzed and evaluated in terms of the year they were written in, the institution in which they were prepared, the academic title of the thesis advisor, research type, its publication status in scientific journals, publication features, author's gender and other features of the author of the thesis.

Results: As a result of the research conducted, it was found that 61 (56.5%) of the 108 pharmacology specialty theses written between 2006-2016 had been published in the
scientific journals. Forty-seven (77.0%) of these publications were published in a medical journal with Science Citation Index (SCI) / Science Citation Index-Expanded (SCI-E) indexes, 9 (14.8%) in other international indexes, 3 (4.9%) in TUBITAK ULAKBIM TR index and 2 (3.3%) in national refereed journals.

Conclusion: The rate of publication of the residency theses written after the completion of medical pharmacology residency training and publication as articles in the journals within the scope of SCI / SCI-E was quite high.

Keywords: Pharmacology, Specialty Theses, Publication, Turkey

Öz

Amaç: Tezlerin yayınlanması, bir ülkenin bilimsel etkinliğini ortaya çıkarmanın temel göstergesidir. Bildiğimiz kadarıyla farmakoloji uzmanlık tezlerinin yayınlanma durumu daha önce bildirilmemiştir. Bu çalışmada, ülkemizdeki tıp fakültelerinin tıbbi farmakoloji anabilim dalları tarafından 2006-2016 yılları arasında yayınlanan tıbbi farmakoloji tıpta uzmanlık tezlerinin bilimsel dergilerde yayına dönüştürülme durumunun değerlendirilmesi amaçlanmıştır.

Yöntemler: Gözlemsel olan bu çalışmaya Mayıs 2020 tarihinde Yüksek Öğretim Kurulu Başkanlığı Ulusal Tez Merkezi internet veri tabanında (https://tez.yok.gov.tr/UlusalTezMerkezi/) yer alan, ülkemizdeki tüm tıp fakültelerinin tıbbi farmakoloji anabilim dalı birimlerinden sisteme girilmiş 2006-2016 yılları arasında yayınlanmış 108 adet farmakoloji uzmanlık tezi dahil edilmiştir. Bu tezler yapıldıkları yıl, yapıldıkları kurum, tez danışmanın akademik ünvanı, tezin hangi araştırma türü olduğu, yayınlanma durumu, yayına ait özellikler, yazar cinsiyeti ve tez yazarlarına ait diğer özellikler açısından incelenip değerlendirilmiştir.

Bulgular: Çalışmamızda yapılan araştırmalar sonucunda 2006-2016 yılları arasında yapılmış 108 adet farmakoloji uzmanlık tezinin 61'i (%56,5) yayınlanmıştır. Bu yayınların 47'si (%77,0) Science Citation Index (SCI) / Science Citation Index-Expanded (SCI-E), 9'u (%14,8) uluslararası diğer indekslerde, 3'ü (%4,9) TUBİTAK ULAKBİM TR dizin, 2'si (%3,3) ulusal hakemli dergilerde yayınlanmıştı.

Sonuç: Bu çalışmada, Türkiye'de tıbbi farmakoloji uzmanlık eğitimi tamamlandıktan sonra yazılan uzmanlık tezlerinin yayına dönüşme oranı ve SCI/SCI-E kapsamındaki dergilerde makale olarak yayınlanma oranı oldukça yüksek bulunmuştur.

Anahtar kelimeler: Farmakoloji, Uzmanlık tezi, Yayın, Türkiye

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Introduction

Pharmacology is the science that investigates the sources of drugs, their chemical and physical properties, the body's intake, their mode of action and the methods of making them available to the patient. Research in pharmacology is carried out mainly for the treatment, diagnosis, prophylaxis of diseases and other medical purposes. In parallel with this purpose, the main task of the medical pharmacology resident is to participate in the educational activities determined by the department within the framework of a certain program, and to ensure that he / she learns the basic subjects of medical pharmacology, acquires the basic knowledge and skills necessary for conducting experimental research, and conducts and evaluates practical applications s/he has learned.

In our country, those who receive medical pharmacology residency education in medical faculties are obliged to conduct a thesis study, and authoring a thesis constitutes an important part of the specialty education. By getting the students to author a thesis, it is aimed to provide residency students with many skills such as forming a hypothesis, data collection, analysis, interpretation of results and authoring articles [1]. In terms of academic advancement and making significant contributions to science, it is important to turn the theses into publications. It is a very challenging process for medical residency students to have their theses published, and in the researches conducted in many departments, it has been determined that the rates of medical residency theses being turned into publications are quite low [2-5]. According to our literature review, no studies evaluating the publishing status of medical pharmacology residency theses written in our country were found.

In this study, we aimed to evaluate and reveal the publication status of the medical pharmacology theses published by the departments of medical pharmacology of medical faculties in our country between 2006 and 2016 in scientific journals.

Materials and methods

In this descriptive study, the screening model was used to evaluate the publication status of medical pharmacology residency theses in scientific journals. All steps of the study were carried out according to the basic principles of Helsinki declaration. The study was approved by Kahramanmaraş Sütçü İmam University Faculty of Medicine Ethics Committee of Clinical Trials (2020/10-03).

A total of 108 pharmacology residency theses published between 2006-2016 and registered into the system from all Medical Pharmacology departments of all medical faculties in our country, as accessed from in Higher Education Council National Thesis Center's Internet database (https://tez.yok.gov.tr/ulusaltezmerkezi/) in May 2020, were included in this study. Considering that the period for the thesis to be turned into a publication might be prolonged, specialty theses published between 2017-2020 were not included. In addition, theses with multiple entries in the subject section were examined one by one, and specialty theses that did not belong to the medical pharmacology department were excluded from the study.

Whether the thesis has been turned into a publication or not was determined by searching the author, the name and surname of the thesis advisor, and the title of the thesis in both Turkish and English over Google academic (https://scholar.google.com/), PubMed Central (PMC) (https://www.ncbi.nlm.nih.gov/pmc/), and PubMed (https://pubmed.ncbi.nlm.nih.gov/), and by comparing the title and summary of the thesis with the title, subject and abstract of the thesis. The publications determined to have been adapted from a thesis by considering the full text, abstract or author names and title were taken into consideration. It was revealed in which one(s) of the databases of Science Citation Index (SCI), Science Citation Index-Expanded (SCI-E), other international fields (PubMed, Medline, Scopus, Index Copernicus etc.), and TUBITAK ULAKBIM TR index the journals where the theses were published were included by examining the websites of these databases and journals. Whether the physicians who wrote the theses were working as a medical pharmacologist or in another field and the institutions that they are currently working in was determined by running Internet search. The gender of the author of the thesis, the faculty of medicine where the thesis was prepared, the institution where the author is currently working, the status of the author continuing his/her professional life in the department of medical pharmacology, the sequence of the author's name in the publication, the academic title of the thesis advisor when the thesis was registered in the system, whether the thesis was a clinical or animal experiment, the national or international directory where the thesis was published, and the period that lasted until the thesis was published were evaluated.

Statistical analysis

The data were analyzed using SPSS 15.0 software package. Numerical data were presented as mean and standard deviation (SD), and categorical variables were given as numbers and percentages. Chi-square test was used in the analysis of categorical data. The value of $P<0.05$ was considered statistically significant.

Results

A total of 108 medical pharmacology theses which were published in the National Thesis Center database between 2006 and 2016 were included in the study.

Fifty (46.3%) of the thesis authors were male and 58 (53.7%) were female. Of the thesis advisors, 74 (68.5%) were professors, 28 (25.9%) were associate professors, 6 (5.6%) were assistant professors.

It was determined that 61 (56.5%) of the specialty theses written in the field of medical pharmacology between 2006 and 2016 were published in a scientific journal, and 47 (43.5%) were not. Forty-seven (77.0%) of these publications were published in SCI / SCI-E, 9 (14.8%) in other international indexes, 3 (4.9%) in TUBITAK ULAKBIM TR index and 2 (3.3%) in national refereed journals.

The study type of 108 theses was evaluated. Prospective clinical studies were carried out in 10 (9.3%) of the theses, retrospective and survey studies in 7 (6.5%), cell culture studies in 8 (7.4%), and animal experimental studies in 83 (76.9%). Six (60.0%) prospective clinical studies, 4 (57.1%) retrospective and survey studies, 3 (37.5%) cell culture studies, 48 (57.8%) animal

experimental studies were published as shown in Table 1. Six (9.8%) of 61 published theses were prospective clinical studies, 4 (6.6%) were retrospective and survey studies, 3 (4.9%) were cell culture studies, and 48 (78.7%) were animal experimental studies (p<0.001).

The mean publication period of the 61 published theses was 3.20 (2.34) (0-11) years. 4 (6.6%) of the theses were published in a scientific journal in the same year of the thesis publication date, 14 (23.0%) of them 1 year later, 11 (18.0%) of them 2 years later, 10 (16.4%) of them 3 years later, 4 (3.7%) of them 4 years later, 7 (11.5%) of them 5 years later, 3 (4.9%) of them 6 years later, 6 (9.8%) of them 7 years later, 1 (1.6%) of them 8 years later, and 1(1.8%) of them 11 years later than the thesis publication date. The mean number of authors of the publications was 4.92 (2.19) (1-11) individuals. Two (3.3%) publications had 1 author, 5 (8.2%) had 2 authors, 11 (18.0%) had 3 authors, 8 (13.1%) had 4 authors, 13 (21.3%) had 5 authors, 10 (16.4%) had 6 authors, 7 (11.5%) had 7 authors, 1 (1.6%) had 8 authors, 1 (1.6%) had 9 authors, 1 (1.6%) had 10 authors, and 2 (3.3%) had 11 authors. The owners of the theses were the first name in 52 (85.2%) of the publications, the second name in 3 (4.9%), the third in 5 (8.2%) and the seventh and last name in 1 (1.6%) of the publications. When 61 published theses in a scientific journals were examined, it was determined that 31 (50.8%) of the owners of the theses were female [23 (74.2%) of these were published in SCI / SCI-E, 4 (12.9%) in other international indexes, 2 (6.5%) in TUBITAK ULAKBIM TR index, 2 (6.5%) in national refereed journals] and the owners of 30 (49.2%) theses were male [24 (80.0%) of these were published in SCI / SCI-E, 5 (16.7%) in international indexes, 1 (3.3%) in TUBITAK ULAKBIM TR index]. There was no significant difference between the rate of publication of the theses written by females and males (Table 1; *P*=0.493).

When the institutions where the 108 thesis holders are currently working were examined, it was seen that 38 (35.2%) of the 108 individuals were working as faculty members in the medical pharmacology departments of the medical faculties of different universities, 16 (14.8%) were working as faculty members in the pharmacology departments of medical faculties in the same university, 1 (0.9%) was working as a teaching assistant in the same university, 19 (17.6%) were working as faculty members in the pharmacology departments of medical faculties in different universities, 2 (1.9%) were working as faculty members in the pharmacology departments of medical faculties in foreign universities, 49 (45.4%) were working as specialist doctors in various institutions, 17 (15.7%) were working as specialist doctors in private institutions, and 3 (2.8%) as specialist doctors in different clinical branches, 1 (0.9%) was working as a faculty member in different clinical branches in foreign universities. Twenty (52.6%) of the 38 individuals working as faculty members in the medical pharmacology departments of the medical faculties of various universities were male and 18 (47.4%) were female. It was determined that the theses of 33 (86.8%) of the 38 authors working as faculty members in medical pharmacology departments of medical faculties of various universities were published in a scientific journal (21 of them were published in SCI / SCI-E, 7 of them in other international indexes, 3 of them in TUBITAK ULAKBIM TR index, and 2 of them in national refereed journals), and that the theses of 5 (14.2%) were not published. The theses of 21 (42.9%) of 49 authors working as specialists in various hospitals were published in a scientific journal (20 in SCI / SCI-E, 1 in other international indexes) and the theses of 28 (57.1%) authors were not published. The theses of 3 (100.0%) of the 3 people working as specialists in different clinical branches were not published in a scientific journal (Table 1).

Table 1: Publication and knowledge pattern of pharmacology specialty thesis holders

	Published n (%)	Not-Published n (%)	*P*-value
Gender of author			
Male	30 (60.0)	20 (40.0)	0.493
Female	31 (53.4)	27 (46.6)	
Current institution of author			
Faculty members in the same university	13 (81.3)	3 (18.8)	<0.001
Faculty members in different universities	18 (94.7)	1 (5.3)	
Specialist doctors in various institutions	21 (42.9)	28 (57.1)	
Specialist doctors in private institutions	7 (41.2)	10 (58.8)	
Specialist doctors in different clinical branches	0 (0.0)	3 (100)	
Teaching assistant	0 (0.0)	1 (100)	
Faculty members in different clinical branches in foreign universities	0 (0.0)	1 (100)	
Faculty members in the pharmacology departments in foreign universities	2 (100)	0 (0.0)	
Study type			
Cell culture studies	3 (37.5)	5 (62.5)	0.733
Animal experimental studies	48 (57.8)	35 (42.2)	
Prospective clinical studies	6 (60.0)	4 (40.0)	
Retrospective and survey studies	4 (57.1)	3 (42.9)	

Discussion

This study is a descriptive study evaluating the publication of medical pharmacology theses published in our country in scientific journals. In our study, the rate of publication of medical pharmacology theses conducted between 2006 and 2016 in scientific journals was found to be 56.5%, and the rate of unpublished theses was determined as 43.5%.

In this study, it was aimed to evaluate the publication status of medical pharmacology theses in scientific journals and to present current results. Similar to some studies that have been carried out so far, an 11-year period was evaluated in our study [3,4]. Scherer et al. [6] reported that 5 years is required for the studies to be turned into publications. Considering this, thesis studies carried out after 2016 were not included in our study. Kalcıoğlu et al. [7] stated that the time between the delivery of the publication and being published in some SCI journals can take up to 3.5 years. In a study evaluating the rate of publication of the otolaryngology (ENT) specialty theses written between 2007 and 2012 in scientific journals, the mean time for the publication of the otolaryngology (ENT) specialty theses was 3.15 years [8]. In our study, the mean time for publication was 3.20 (2.34) (0-11) years.

In our study, 61 (56.5%) of the 108 medical pharmacology specialty theses written between 2006 and 2016 were published in scientific journals. Forty-seven (77.0%) of these publications were published in SCI / SCI-E, 9 (14.8%) in other international indexes, 3 (4.9%) in TUBITAK ULAKBIM TR index and 2 (3.3%) in national refereed journals. This shows that the rates determined in our study are much higher than the rates reported from different branches in our country [3, 8]. There are many studies investigating the rate of specialty theses written in various branches being turned into publications in our country, and the rates determined in these studies range from 6.5% to 57.3% [2-5,8-11]. In a study conducted in 2019, Seringeç [12] reported that 47 (57.3%) of the 87 physiology

specialty theses were published in scientific journals, 15 of which (18.3%) were published in journals within the scope of SCI and 17 (20.7%) of which were published in SCI-E journals. In a study conducted in 2018 [9] in which the rate of publication in scientific journals of urology theses written between 2008-2011 was investigated, the rate was 49.7%, and 32.7% of these publications were published in SCI-E journals, 10.4% in international journals, 6.5% in other international index journals and 6.5% of them in national index journals. Çetinet al. [8] reported that the publication rate of ENT specialty theses was 35.6%, the rate of publication in national journals was 14.1% and the rate of publication in international journals was 21.4%. In a study, the publication rate of the theses written in the field of Emergency Medicine between 1998 and 2013 [10] was reported as 27.1%, and in a different study conducted in 2016 [3], the rate of publication of theses prepared in the field of neurosurgery between 2004 and 2013 in SCI / SCI-E indexed journals was 18.0%. As a result of the studies, investigating the publication rates of specialty theses and doctoral dissertations prepared on Medical Microbiology, Clinical Microbiology and Infectious Diseases between 1997-2007 in international journals, it was reported that 10.7% of Microbiology and Clinical Microbiology specialty theses and 10.2% of specialty theses on Infectious Diseases and Clinical Microbiology were turned into publications [4]. In a study conducted in the field of public health between 1978 and 2010 [11], 295 specialty theses were analyzed and the rate of publication in international journals was 13.6%. In their study in 2016, Üçer et al. [5] reported that the rate of publication in scientific journals of the theses written as a result of family medicine specialty training was 11.5%, and 0.8% of them were published in SCI journals, 3.1% in SCI-E journals and 7.6% in national journals. In a study conducted between 1981-2008 [13], it was shown that the publication rate of 140 Family Medicine specialty theses was 9.4%. In a study conducted between 1980-2005 [2], it was reported that the rate of 22,625 medical specialty theses being turned into publications in SCI-E indexed journals was 6.2%.

Study types of pharmacology specialty theses in the department of medical pharmacology were evaluated. Sixty-one (56.5%) of 108 theses were published. The rate of publication of animal experimental studies was higher (78.7%) than other study types (Prospective clinical studies (9.8%), retrospective and survey studies (6.6%), cell culture studies (4.9%)). In a study published in 2019 [12], the high rate of studies with animal experiments determined (73.2%) shows that the results are in parallel with our study. Çetin et al. [8] reported that the publication rate of studies with animal experiments was higher (%37.7) than other types of studies.

When the institutions where the 108 thesis owners are currently working were evaluated, 38 (35.2%) of them were working as faculty members in the pharmacology departments of medical faculties in different universities, 49 (45.4%) were working as specialist doctors in various institutions, 17 (15.7%) as specialist doctors in private institutions, 3 (2.8%) as specialist doctors in different clinical branches and 1 (0.9%) was working as a faculty member in different clinical branches in foreign universities. In a study, it was reported that the rate of faculty members in different universities was higher than the other groups [12]. The publication rate of those who were working as faculty members in the pharmacology departments of the medical faculties of various universities was 33 (86.8%), whereas the publication rate of those who were working as specialist doctors in various institutions was 21 (42.9%). In parallel with our study, Seringeç [12] reported that the publication rate of those who were working as faculty members in the physiology departments of the medical faculties of various universities was 73.7%. Twenty-one out of 33 faculty members were published in SCI / SCI-E, 7 in other international indexes, 3 in TUBITAK ULAKBIM TR index, and 2 in national refereed journals. In accordance with our study, Yuksel et al. [9] reported that the rate of publication of theses in SCI-E journals was higher (32.7%) than the other indexed journals.

Limitations

The main limitation of our study is that the change of the title of the thesis during the conversion to the article may have caused the misevaluation. Secondly, there may be data errors of the theses, entered into the database incorrectly. The other limitation is that the change of the female authors' surname may have caused the missing evaluation.

Conclusions

It was determined in our study that the rate of the specialty theses written in the Medical Pharmacology department of the medical faculties in Turkey as an article and the rate of these articles to be published in SCI/SCI-E indexed journals were quite high.

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Research article
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Evaluation of 39 pediatric cases who underwent open and laparoscopic splenectomy: A retrospective cohort study

Çocuklarda açık ve laparoskopik splenektomi yapılan olguların 39 olgu eşliğinde değerlendirilmesi: Retrospektif kohort çalışma

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Abstract

Aim: In children, aside from trauma-related splenic injury and splenic cysts, splenectomy is frequently performed in hematological diseases due to splenomegaly and thrombocytopenia. The most preferred method in children in the past years was open splenectomy. Today, laparoscopic splenectomy has become a preferred method by pediatric surgeons due to increasing laparoscopic surgical experience. The aim of this study is to present the results of the case series who underwent laparoscopic and open splenectomy in our clinic.

Methods: All patients who underwent laparoscopic and open splenectomy between 2008-2019 in our clinic were included in the study. Four ports were used in the laparoscopic splenectomy procedure and port locations differed according to patient age and spleen size. The completely liberated spleen was taken into the specimen removal bag and removed after morcellation. Open surgical method was preferred in cases where the long axis of the spleen was 200 mm or higher. Demographic data, splenectomy indications, surgical techniques and postoperative follow-up data were evaluated retrospectively.

Results: Splenectomy was performed laparoscopically in 24 of 39 patients (16 male, 23 female) and with the open method in 15 patients. Surgical indications included hereditary spherocytosis (n=15), idiopathic thrombocytopenic purpura (n=6), beta-thalassemia (n=3) in laparoscopically operated patients and hereditary spherocytosis (n=8), idiopathic thrombocytopenic purpura (n=4) and beta-thalassemia (n=3) in patients operated with the open method. Simultaneous cholecystectomy was performed in 11 cases due to cholelithiasis. The duration of the surgery was significantly longer [132 (47) and 90 (21) min., respectively $P<0.001$], and time until oral feeding [2.3 (0.8) and 3.9 (1.1) days, respectively $P<0.001$] as well as the length of hospitalization were significantly shorter in laparoscopic surgery compared to open surgery [3.80 (1.3) vs. 5.5 (1.2) days, respectively $P<0.001$].

Conclusion: Laparoscopic splenectomy is a safe method that should be preferred primarily in experienced centers for earlier feeding, shorter hospitalization times and better cosmetic results.

Keywords: Children, Open splenectomy, Laparoscopic splenectomy

Öz

Amaç: Çocuklarda splenektomi sıklıkla travmaya bağlı dalak hasarı, dalak kistleri dışında, splenomegali ve trombositopeni nedeni ile hematolojik hastalıklarda yapılmaktadır. Çocuklarda geçmiş yıllarda daha çok tercih edilen yöntem açık splenektomiydi. Günümüzde laparoskopik cerrahi deneyimlerinin artması sonucunda laparoskopik splenektomi çocuk cerrahları tarafından da tercih edilen bir yöntem haline gelmiştir. Bu çalışmanın amacı kliniğimizde laparoskopik ve açık cerrahi yöntemle dalak cerrahisi yapılan olgu serisinin sonuçlarını sunmaktır.

Yöntemler: Kliniğimizde 2008-2019 yılları arasında laparoskopik ve açık yöntemle splenektomi yapılan tüm olgular çalışmaya dahil edildi. Laparoskopik splenektomi işleminde 4 port kullanıldı, port yerleşimleri hasta yaşı ve dalak boyutuna göre farklılıklar gösterdi. Tamamen serbestleştirilen dalak spesimen çıkarma torbası içine alınarak parçalanarak çıkartıldı. Dalak uzun aksının 200 mm ve üzerinde olduğu olgularda açık cerrahi yöntem tercih edildi. Olguların demografik verileri, splenektomi endikasyonları, ameliyat teknikleri ve ameliyat sonrası takip verileri retrospektif olarak değerlendirildi.

Bulgular: Çalışmaya alınan 39 hastanın (16 erkek, 23 kadın) 24'ine laparoskopik, 15'ine açık yöntemle splenektomi yapıldı. Ameliyat endikasyonları; laparoskopik splenektomi yapılan olgularda herediter sferositoz (n=15), idiopatik trombositopenik purpura (n=6), Beta-talasemi (n=3), açık cerrahi splenektomi yapılan olgularda ise herediter sferositoz (n=8), idiopatik trombositopenik purpura (n=4), Beta-talasemi (n=3) idi. Kolelithiazis nedeniyle 11 olguya eşzamanlı kolesistektomi yapıldı. Laparoskopik cerrahide ameliyat süresi açık cerrahiye göre anlamlı derecede daha uzundu [sırasıyla 132 (47)'e karşılık 90 (21) dk, $P<0,001$]. Laparoskopik cerrahide oral beslenmeye kadar geçen süre açık cerrahiye göre anlamlı derecede daha kısaydı [sırasıyla 2,3 (0,8)'e karşılık 3,9 (1,1) gün, $P<0,001$]. Ayrıca, hastanede yatış süresi laparoskopik cerrahide açık cerrahiye göre anlamlı olarak daha kısaydı [sırasıyla 3,8 (1,3)'e karşılık 5,5 (1,2) gün, $P<0,001$].

Sonuç: Laproskopik splenektomi; oral beslenmeye geçiş sürelerinin daha kısa, hastanede yatma sürelerinin ve kozmetik sonuçlarının daha iyi olması nedeniyle deneyimli merkezlerde öncelikli olarak tercih edilmesi gereken güvenli bir yöntemdir.

Anahtar kelimeler: Çocuk, Açık splenektomi, Laparoskopik splenektomi

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Introduction

In children, splenectomy is performed in traumatic rupture, splenic cysts, hematological diseases such as hereditary spherocytosis, idiopathic thrombocytopenic purpura, thalassemia, sickle cell disease and autoimmune hemolytic anemia, and rarely, in tumors [1,2]. Traditionally, until the 1990s, splenectomy was performed with the open method in children and adults. Laparoscopic splenectomy is a technically challenging and demanding procedure, especially in children. With pediatric surgeons' increasing experience in laparoscopic surgery in the recent years, laparoscopic splenectomy became an effective and safe surgical technique [3].

The aim of this study is to present the results of the case series of laparoscopic and open splenectomy procedures performed in our clinic.

Materials and methods

Ethical approval for this study (Ethics Committee Ataturk University- file no: B.30.2.ATA.0.01.00/152) was granted by the Ethics Committee of Ataturk University, Erzurum, Turkey on 26 March 2019. The study involved 39 patients who underwent open or laparoscopic splenectomy surgery in our clinic between 2008 and 2019. Demographic data of the cases, indications for splenectomy, surgical techniques, complications, duration of surgery, time until postoperative oral feeding and hospitalization times were recorded. The patients were divided into two groups as those who underwent laparoscopic and open surgery. These two groups were compared in terms of complications, duration of surgery, time until postoperative oral feeding, and length of hospital stay.

Statistical analysis

Statistical analysis was performed with SPSS Statistics version 20.0 (IBM, Armonk, NY, USA). Normal distribution of data was assessed with the Kolmogorov–Smirnov test or histogram. Descriptive statistics included the mean with standard deviation or percentages depending on the characteristics of the data. Continuous variables were expressed as mean and standard deviation (SD). The groups were compared using the t-test for normally-distributed independent variables, and the Mann–Whitney U test for non-normally distributed data. Nominal variables were compared using the Chi-square test. A *P*-value of less than 0.05 was considered statistically significant.

Results

Splenectomy was performed laparoscopically in 24 of the 39 patients (16 males, 23 females) and with the open method in 15 cases. There were no statistically significant differences between the laparascopic and open surgeries in terms of gender (male:11 / female:13 and male:5 / female:10, respectively, P=0.440) and age [10.5 (3.4) and 10.3 (2.9), respectively, P=0.839]. Surgical indications included hereditary spherocytosis (n=15), idiopathic thrombocytopenic purpura (n 6), Beta-thalassemia (n=3) in laparoscopically operated patients and hereditary spherocytosis (n=8), idiopathic thrombocytopenic purpura (n=4) and Beta-thalassemia (n=3) in patients operated with the open method (Table 1).

Surgical method

In patients undergoing laparoscopic splenectomy, 4 ports were used, and port locations differed according to patient age and spleen size. In ultrasonographic measurements, the mean long axial length of spleen was 141.00 (32.05) mm, the longest being 210 mm. In 2 of the patients who underwent laparoscopic splenectomy, the peripheral veins were sealed with Ligasure cautery without ligation of the splenic artery and vein. In the others, splenic artery and vein were isolated, ligated with the hem-o-lok clips (Figure 1), after which the spleen was dissected from surrounding tissue. The completely liberated spleen was taken into the specimen removal bag and removed after morcellation.

The open surgical method was performed in cases when total splenectomy was planned, in patients with spleens longer than 150mm during the former period when laparoscopic surgical experience was insufficient, and in those with spleens longer than 200 mm. In the open surgical method, the spleen was removed by entering the abdomen through a left subcostal incision, and after ligation of the splenic artery and vein.

Cholecystectomy was performed in 11 cases with concomitant cholelithiasis, 4 of which were performed in addition to laparoscopic splenectomy, and 7 of which accompanied open surgery.

Perioperative findings

All patients were included in the routine vaccination program (Streptococcus Pneumoniae, Haemophilus Influenzae, and Neisseria Meningitidis) one month before the operation. In a patient who underwent splenectomy with open surgical method because of a large-sized spleen (210 mm), blood transfusion was required due to peroperative bleeding. None of the other patients had any peroperative complications. Accessory spleen was observed and removed in two cases. The duration of the surgery was significantly longer [132 (47) and 90 (21) min., respectively P<0.001], and time until oral feeding [2.3 (0.8) and 3.9 (1.1) days, respectively P<0.001] as well as the length of hospitalization were significantly shorter in laparoscopic surgery (Table 1). During the postoperative period, 11 patients with platelet values between 747-1490 ($10^3/\mu L$) were administered anticoagulant therapy due to thrombocytosis and none developed venous thrombosis. Transfusion rate was low in patients with hereditary spherocytosis and Beta thalassemia during postoperative follow-up. Thrombocytopenia continued in one of the patients with ITP and the other patients were cured. No complications were detected in the patients during the 1 year follow-up period.

Table 1: Demographic data and perioperative findings

	Laparoscopic (n=24)	Open method (n=15)	*P*-value
Gender (M/F)	11/13	5/10	0.440*
Age [mean. (SD)] (years)	10.5 (3.5)	10.3 (2.9)	0.839**
Surgical indications			
Hereditary spherocytosis (n)	15	8	0.787*
Idiopathic thrombocytopenic purpura (n)	6	4	
Beta-thalassemia (n)	3	3	
Spleen size	141 (32)	158 (38)	0.184**
Duration of surgery (minutes)	132 (47)	90 (21)	<0.001**
Time until oral feeding (days)	2.3 (0.8)	3.9 (1.1)	<0.001**
Duration of hospitalization (days)	3.8 (1.3)	5.5 (1.2)	<0.001**
Follow-up duration (years)	3.4 (2.1)	6.0 (0.9)	<0.001**

All values are presented as mean (SD: Standard Deviation) or n, M: Male, F: Female, * Chi-Square test, ** Mann-Whitney U test

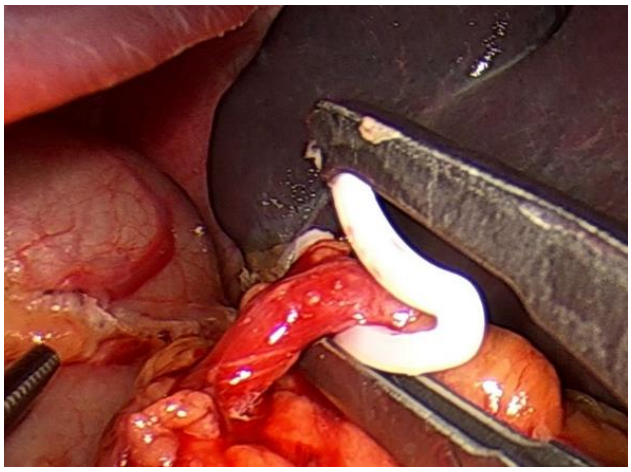

Figure 1: Clipping of splenic artery with hem-o-lok clips

Discussion

The major key findings of this study were the shortened duration of hospitalization and time until oral feeding with laparoscopic surgery.

In children, splenectomy is performed due to traumatic rupture, splenic cysts, hematological diseases such as hereditary spherocytosis, idiopathic thrombocytopenic purpura, sickle cell disease and autoimmune hemolytic anemia, and rarely, tumors [1,2,4-6]. With the increase in laparoscopic experience of pediatric surgeons in the recent years, laparoscopic surgery has been used more frequently in all pediatric surgery fields. Laparoscopic splenectomy is a safe and effective procedure with shorter hospital stay and lower complication rates in children who require splenectomy for hematological disorders and other reasons [3]. During open and laparoscopic splenectomy, hemorrhage control can be highly challenging, especially in large spleens [7,8]. For hemorrhage control during laparoscopic splenectomy, we first clipped the splenic artery, then the splenic vein [8]. Since the diameter of the splenic vascular structures is small in young children, hemorrhage control can be safely achieved by directly sealing the hilar vascular branches with the vein sealing device without the need for dissection of the splenic artery and vein. In 2 patients who underwent laparoscopic splenectomy (5 and 6 years old), we ligated the peripheral small vessels by using vessel sealing devices without using any clips. In a patient with a large spleen who underwent open total splenectomy, peroperative transfusion was required due to bleeding. None of the laparoscopically operated cases had uncontrolled bleeding, required transfusion or transition to open surgery due to bleeding.

Laparoscopic splenectomy and cholecystectomy are convenient and safe methods in concomitant pathologies of the spleen and gallbladder [9,10]. Since 11 of our cases also had cholelithiasis, cholecystectomy was performed simultaneously, among which four were performed laparoscopically, and seven, in addition to open surgical procedure.

The mean operative times for laparoscopic splenectomy were reported as 97 minutes by Targorona et al. [11], 120 minutes by Deng et al. [12], 80 minutes by Ates et al. [3], and 133 minutes by Ultria et al. [10]. In our study, the mean operative duration was 132 minutes for laparoscopic surgery, and 90 minutes for open surgery, which were both consistent with the literature. The duration of laparoscopic surgery is longer, especially during the former period when laparoscopic experience is less, in cases where the spleen is over 150 mm in size and in those with concomitant cholecystectomies. The mean duration of operation was significantly shorter in open surgery. Removal of the spleen by morcellation after placement in the specimen removal bag is one of the principal factors which prolongs the process.

Early postoperative oral intake, and short hospitalization time are among the most preferred reasons for laparoscopic surgery. The mean duration of hospitalization was reported as 4 days by Targorona et al. [11], and 5 days by Deng et al. [12]. In our series, mean time until oral feeding in patients who underwent laparoscopic and open splenectomy were 2.32 and 3.93 days, respectively, and mean hospital stay, 3.80 days and 5.53 days, respectively. The duration until oral feeding and hospital stay were significantly shorter in laparoscopic surgery.

Those with large spleens are particularly at risk in terms of laparoscopic surgical technique and venous thrombosis. Thrombocytosis and portal venous thrombosis are important problems in the post-operative period in patients undergoing splenectomy [13]. Venous thrombosis in children is rarer than adults, but since the risk factors are not clear, platelet values should be closely monitored after the surgery. The increase in the number of platelets after splenectomy can be used as a marker for venous thrombosis [14,15]. Portal venous Doppler should be performed to exclude portal venous thrombosis in patients with severe or unexplained abdominal pain, fever and vomiting after splenectomy. Doppler ultrasonography can be performed routinely for control purposes in asymptomatic patients as well, especially in those with large spleens [13]. In our study, intravenous hydration and anticoagulation treatment was administered to 11 patients who developed postoperative thrombocytosis. Venous thrombosis did not develop in any of the patients, who were all followed up with Doppler ultrasonography.

Limitations

The main limitations of this study are its retrospective nature and small sample size. Less biased results can be obtained with prospective studies. However, our study is important because it compares open and laparoscopic surgical methods in terms of duration of surgery, complications, transition to oral feeding, and hospital stay. Although we have stated that a large spleen constitutes a major difficulty in laparoscopic surgery, especially at the beginning of the learning curve, the fact that we have not performed a thorough analysis on the subject and limited number of patients are among the major limitations of this study. The reason we could not analyze the effect of spleen size is because we preferred open surgery, especially when our laparoscopic experience was not sufficient, in patients with spleens of ≥150 mm in size at the beginning, and ≥200 mm in size later in the learning curve.

Conclusions

The complication rate is exceptionally low in laparoscopic splenectomy in children. Laparoscopic splenectomy, a minimally invasive approach with increased surgical experience, is far superior to open surgical procedure in terms of faster postoperative recovery, earlier feeding, shorter hospital stays, better cosmetic results, and perioperative and

postoperative advantages. Therefore, we think that the laparoscopic method will be accepted by surgeons with sufficient experience as a standard method in cases requiring splenectomy.

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Comparison of effectiveness between polyethylene glycol 4000 and lactulose in the treatment of pediatric functional constipation

Çocuklarda fonksiyonel konstipasyon tedavisinde polietilen glikol 4000 ve laktuloz etkinliklerinin karşılaştırılması

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Abstract

Aim: Functional constipation is a common illness in children that requires close follow-up and long-term treatment. This study aims to compare the effectiveness of lactulose and PEG 4000 in the treatment of pediatric functional constipation.

Methods: One hundred and twenty-three patients included in this cross-sectional study were all diagnosed with functional constipation according to Rome IV criteria. The ages of the patients, who were all referred to the pediatric gastroenterology outpatient clinic between November 2017 and May 2018, ranged between 8 months and 4 years. Patients with accompanying organic diseases were excluded from the study. Children treated with Lactulose were included in the LAC group and those treated with PEG 4000 were included in the PEG group. The number of bowel movements, Bristol Stool Form Scale (BSFS), pain during bowel movements, formation of anal fissures and fecal impaction at diagnosis and during follow-up were noted from the patient files. A comparison was then made in 1st and 3rd months between the diagnostic findings and follow-up of patients in both groups.

Results: There were no age or gender-based differences between the two groups. Sixty-two (50%) patients received lactulose and the remaining 61 patients (50%) received PEG 4000 as treatment. At the end of the third month, patients had improved significantly more in the PEG group in terms of number of daily bowel movements, the presence of pain during bowel movement and median BSFS score (P<0.001).

Conclusion: While lactulose and PEG 4000 are both effective in the treatment of functional constipation in children, PEG 4000 is a more effective and successful treatment option compared to lactulose without increased side effects.

Keywords: Child, Polyethylene glycol 4000, Lactulose, Constipation

Öz

Amaç: Fonksiyonel konstipasyon çocukluk çağında sık görülen ve yakın takip gerektiren bir hastalıktır. Tedavide PEG 4000 tedavisinin daha etkili olduğu düşünülmektedir. Bu çalışmada fonksiyonel konstipasyonu olan çocuklarda PEG 4000 ve laktuloz tedavilerinin etkinliklerini karşılaştırmayı amaçladık.

Yöntemler: Çalışma Roma 4 kriterlerine göre fonksiyonel konstipasyon teşhisi konulan çocukları içermektedir. Bu çalışma karşılaştırmalı ve kesitsel bir çalışmadır. Çocuk Gastroenteroloji polikliniğine Kasım 2017 ve Mayıs 2018 tarihleri arasında başvuran 123 hasta dahil edilmiştir. Eşlik eden organik hastalığı saptanan hastalar çalışma dışı bırakılmıştır. Laktuloz tedavisi verilen çocuklar LAC grup, PEG 4000 tedavisi verilen çocuklar PEG grup olarak tanımlandı. Hastaların tanı ve takipte bağırsak hareketlerinin sayısı, Bristol Stool Score Form Ölçeği (BSFS), bağırsak hareketleri sırasında ağrı, anal fissür oluşumu ve fekal inkontinans kaydedildi. Daha sonra sırasıyla LAC grup ve PEG grup hastaların takibi arasında 1. ve 3. aylarda karşılaştırma yapılmıştır.

Bulgular: Çalışmaya 123 hasta alındı. 62 hastaya (%50) laktuloz ve geri kalan 61 hastaya (%50) tedavi olarak PEG 4000 verildi. Yaş ve cinsiyet açısından iki grup açısından fark saptanmadı. Üçüncü ayın sonunda, PEG grup çocuklarda iyileşme, günlük bağırsak hareketlerinin sayısı, bağırsak hareketi sırasında ağrı varlığı ve medyan BSFS skoru açısından laktuloz tedavisi gören hastalardan anlamlı olarak farklılık saptandı (P<0,001).

Sonuç: Hem laktuloz hem de PEG 4000, çocuklarda fonksiyonel konstipasyonun tedavisinde etkili olsa da, PEG 4000 tedavisi yan etkileri arttırmayan, laktuloza kıyasla daha etkili ve başarılı bir tedavi seçeneğidir.

Anahtar kelimeler: Çocuk, Polietilenglikol 4000, Laktuloz, Konstipasyon

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Introduction

Constipation is a common digestive problem, which accounts for 3-5 % of all admissions to pediatric service and 25% of pediatric gastroenterological disorders [1]. In children, constipation can be defined as a decrease in the frequency of bowel movements, hard stool, and pain during bowel movement. While 95% of the patients do not have an organic cause, metabolic or endocrine disorders, anorectal anomalies or Hirschsprung's disease may cause constipation in the rest of the cases [2,3]. Functional constipation (FC) is the most common cause of childhood constipation. The diagnosis of functional constipation is made according to the ROME IV criteria [4].

Constipation influences the emotional well-being, appetite, and life quality of the affected children. Traditional therapies for constipation include bowel retraining, fiber-rich diet, more water intake, physical exercise and the use of various laxatives and stool softeners.

Lactulose, a semisynthetic disaccharide, is an osmotic laxative used in the treatment of constipation. Although the treatment outcome is usually favorable, drug compliance and treatment success are negatively affected due to gastrointestinal side effects and drug intolerance [5].

Polyethylene glycol 4000 (PEG 4000) is a non-toxic, water-soluble, high-molecular polymer which is not absorbed in the gastrointestinal tract after oral administration. PEG 4000 acts as an osmotic agent that increases the water content of the stool. Several clinical trials have indicated that PEG 4000 is effective in treating constipation in adults and children [6,7].

The objective of this study is to determine the effectiveness of the frequently used osmotic laxatives and PEG 4000 in the treatment of functional constipation in children and to compare their advantages.

Materials and methods

Patients

This study included a total of 123 patients aged between 8 months and 4 years, who were referred to the pediatric gastroenterology outpatient clinic of Gaziosmanpaşa Taksim Training and Research Hospital between November 2017 and May 2018. Information about patients were obtained from patient files. All had functional constipation per Rome IV criteria. Displaying at least two of the following problems defines functional constipation: Two bowel movements or fewer per week for at least 2 months, painful bowel movement, hard stool, large and lumpy stool, and the presence of fecal mass in rectum. The patients who had previous gastrointestinal surgery, an underlying endocrine disease (hypothyroidism, diabetes mellitus), cerebrospinal disease, cerebral palsy, food allergy, celiac disease, pediatric psychiatric disorders, oncological diseases as well as those who had constipation due to other primary diseases were excluded from the study. Informed consent forms were obtained from the parents of all patients at the beginning of the study.

Study design

Patients were started on lactulose (1 g/kg/day, 2 doses) or PEG 4000 (0.5 g/kg/day, 2 doses) for treatment. The patients were assigned to either treatment group based on their outpatient clinic application number, where those with odd numbers received lactulose (LAC group) and those with even numbers were given PEG 4000 (PEG group). The patients and the parents were called for controls during the second week, and in the 1st and 3rd months of treatment. In the second week of the treatment, the participants received an interview about compliance concerning their treatment as well as an examination for underlying organic diseases. During each of these controls, the number of bowel movements, stool type based on the Bristol Stool Form Scale (ASFS), pain during bowel movements, the formation of anal fissures and fecal impaction were analyzed and subsequently noted in the patient files.

The diagnostic and follow-up findings of patients who were on Lactulose and PEG 4000 treatment were compared.

Statistical analysis

The normality of numerical variables was analyzed with the Kolmogorov Smirnov test. Pearson's chi-square test was carried out to compare the differences between categorical variables. Independent Samples t-test and Mann Whitney U test were deployed for normally and non-normally distributed independent variables, respectively. Descriptive statistics were presented as median (interquartile range, IQR). Friedman Test was used for more than two dependent variables. The differences between the measurements were compared with the Wilcoxon test and evaluated with Bonferroni correction (P=0.05/3=0.017). In statistical analyses, Jamovi Project (2017, Version 0.8, www.jamovi.org) was used, and the level of statistical significance (P-value) was set at 0.05. The required sample size was calculated as 96 patients, as determined by the statistical program, considering 30% difference between the groups. The sample size was calculated with StatsDirect software version 2.7.9 (StatsDirect Ltd., England, UK).

Results

A total of 123 patients with a mean age of 27.5 (12) months were included in the study. There were 62 females (50%). Sixty-two patients (50%) received lactulose and the remaining 61 (50 %) received PEG 4000 as treatment. There were no age and gender-based differences between the groups. In the LAC group, the duration of complaints prior to treatment and the presence of anal fissures were significantly lower (P=0.002, P<0.001, respectively) (Table 1).

The analysis of patients' response to treatment suggests that both treatment groups posted significant improvement in the number of daily bowel movements and the BSFS score at the end of the 3rd month in comparison to baseline values (P<0.001, P<0.001 and P<0.001, P<0.001, respectively) (Table 2).

The comparison of the number of bowel movements, pain during bowel movements, the BSFS score, and soiling at baseline and in the 1st and 3rd months for both treatment groups are presented in Table 3. The differences in terms of median BSFS score (P=0.002) and frequency of soiling (P=0.003) were statistically significant. The BSFS score at baseline was significantly higher in LAC group (median 2; range: 1-2) than the PEG group (median 1; range: 1-2), while PEG group treatment was found to have a higher frequency of soiling at baseline (45.9 %) compared to the LAC group (20.97 %).

At the end of the first month, both the median number of daily bowel movements and median BSFS score in PEG 4000 group (median 4; range 3-4) was significantly higher than that in the LAC group (median 3; range3-4) (P=0.033, P=0.042, respectively). On the other hand, there were no significant differences between the groups in terms of pain during bowel movement and soiling at the end of the first month (P=0.156 and P=0.473, respectively) (Table 3). PEG group displayed significantly better results in number of daily bowel movements, presence of pain during bowel movement and median BSFS score as opposed to patients who received lactulose treatment at the end of the 3rd month (P<0.001, P=0.001, P<0.001, respectively) (Table 3).

Table 1: Comparison of the groups in term of general characteristics at baseline

	Groups		
	LAC group	PEG group	*P*-value
n (%)	62	61	
Age mean (standard deviation)	26.53 (12.54)	29.23(11.98)	0.225*
Gender			
Male	32(51.61 %)	29(47.54 %)	0.652**
Female	30(48.39 %)	32(52.46 %)	
Anal Fissure			
Absent	46(74.19 %)	26(42.62 %)	<0.001**
Present	16(25.81 %)	35(57.38 %)	
Mean duration of the complaint (months)	6(4-8)	8(5-12)	0.002***

LAC: lactulose, PEG: Polyethylene glycol, * Independent samples t test, ** Chi-Square test, *** Mann Whitney U test

Table 2: Comparison of number of daily bowel movements and the Bristol Stool Form Scale score at baseline and at the end of 1st and 3rd months in treatment groups

Treatment method	Variables	Baseline	1st month	3rd month	*P*-value*
LAC group	Number of daily bowel movements	2(2-2)	3(3-4)	4(3-4)	<0.001
	Bristol Stool Form Scale Score	2(1-2)	3(2-3)	3(3-3)	<0.001
PEG group	Number of daily bowel movements	2(1-3)	4(3-4)	5(5-6)	<0.001
	Bristol Stool Form Scale Score	1(1-2)	3(3-3)	4(3-4)	<0.001

LAC: lactulose, PEG: Polyethylene glycol, * Friedman test

Table 3: The comparison of groups in terms of the number of daily bowel movements, BSFS score, presence of soiling, and presence of pain during bowel movement at baseline and at the 1st and 3rdmonths

		Groups n (%) or median (IQR)		
		LAC group	PEG group	*P*-value
Time Baseline	Number of daily bowel movements	2 (2-2)	2 (1-3)	0.907*
	Pain during bowel movement (n, %)			
	Absent	8 (12.9 %)	5 (8.2 %)	0.396**
	Present	54 (87.1 %)	56 (91.8 %)	
	BSFS score	2 (1-2)	1 (1-2)	0.002*
	Soiling (n, %)			
	Absent	49 (79.03 %)	33 (54.1 %)	0.003**
	Present	13 (20.97 %)	28 (45.9 %)	
1st month	Number of daily bowel movements	3 (3-4)	4 (3-4)	0.042*
	Pain during bowel movement (n, %)			
	Absent	16 (25.81 %)	23 (37.7 %)	0.156**
	Present	46 (74.19 %)	38 (62.3 %)	
	BSFS score	3 (2-3)	3 (3-3)	0.033*
	Soiling (n, %)			
	Absent	62 (100 %)	61 (100 %)	n/a
	Present	0 (0 %)	0 (0 %)	
3rd month	Number of daily bowel movements	4 (3-4)	5 (5-6)	<0.001*
	Pain during bowel movement (n, %)			
	Absent	43 (69.35 %)	57 (93.44 %)	0.001**
	Present	19 (30.65 %)	4 (6.56 %)	
	BSFS score	3 (3-3)	4 (3-4)	<0.001*
	Soiling (n, %)			
	Absent	62 (100 %)	61 (100 %)	n/a
	Present	0 (0 %)	0 (0 %)	

LAC: lactulose, PEG: Polyethylene glycol, BSFS: Bristol Stool Form Scale, * Mann Whitney U test, ** Chi-Square test, n/a: not applicable

Discussion

The pathophysiology of FC is yet to be fully understood. It is likely to be multifactorial. In the United States, 99% of pediatric gastroenterologists were aware of the Rome criteria for FC. However, only 45% of them were using these criteria in clinical practice [7,8]. In this study, Rome IV criteria were used. A recent multicenter study including 465 infants in Italy reported that 11.6%, 13.7%, and 10.7% of the infants fulfilled Rome III criteria for FC at 3, 6, and 12 months following birth.

One of the most important causes of constipation in children is stool withholding due to painful and difficult bowel movement [8]. The presence of fecal mass in the rectum can also lead to fecal incontinence and hospital visits because of involuntary bowel evacuation. Lactulose and PEG 4000 are among the laxative treatment alternatives in patients with constipation [9]. Lactulose is not digested in the intestines, and through osmotic effects, it softens the feces, facilitates gas formation via intestinal bacteria, reduces stool pH and increases intestinal peristalsis. Therefore, bloating, indigestion and gas problems are highly likely during the treatment [10]. Lactulose is frequently prescribed for children in pediatric clinics, but its effectiveness is lower than that of liquid paraffin and PEG 4000, and hence, it often requires additional treatment [11,12].

Similarly, PEG, a polymer of linear structure, is an osmotic laxative that holds water through hydrogen bonds. PEG is minimally (1%) metabolized and absorbed in the intestines [13]. PEGs are named by their molecular weights such as PEG 3350 and PEG 4000 with molecular weights of 3350 and 4000 g/mol, respectively. Iso-osmotic PEGs rather than hypo-osmotic types are more popular since they do not cause electrolyte imbalance [14]. Both lactulose and PEG 4000 treatments need to be used with care to avoid electrolyte imbalance and fluid loss and provide parents with necessary and adequate information. In a study conducted by Dupond et al. [15], PEG group had no change in the levels of serum electrolytes, total protein, folate, vitamins A and D, and iron for 3 months contrary to the LAC group.

In this study, fecal impaction rates increased in both PEG and LAC groups as their BSFS score decreased. This finding supports the pathophysiology of constipation. In other words, as the stiffness of the stool increases, the child withholds the stool in the rectum due to painful bowel movement, which results in fecal impaction [16,17]. In this study, there was no significant difference between the treatment groups in terms of either soiling or pain during bowel movement at the end of the first month. This rate is likely to be lower in families who practice psychological and supportive treatments. On the other hand, differences between the treatment methods were statistically significant in terms of the number of bowel movements, pain during bowel movement and median BSFS score at the end of the third month: The median number of weekly bowel movements in PEG group was significantly higher. We considered that this might be linked with the better softening of the stool in PEG 4000 treatment. Voskuijl et al. [18] reported that PEG group had better stool consistency and less fecal impaction than LAC group. In a study of pediatric patients with functional constipation, Poddar et al. [19] found that both PEG and lactulose were equally effective. However, they added that a significantly higher number of children in LAC group had to be switched over to PEG treatment due to a lack of effectiveness in the LAC group. Chen et al. [20] found that PEG was more effective than other laxatives including lactulose. Candy et al. [21] reported a significant increase in the number of weekly bowel movements in PEG-treated children in comparison to lactulose-treated children, indicating a higher efficacy for

PEG. Loening-Baucke [22] reported a higher success rate when PEG was used compared to other laxatives. Gremse et al. [23] found a significantly higher level of success in PEG treatment compared to lactulose. Jarzębicka et al. [24] noted a significantly higher number of bowel movements per week in the patients using PEG in comparison to lactulose.

In a meta-analysis, Candy and Belsey [25] stated that PEG was either more or equally efficient in constipated children, and they did not find any evidence indicating lower effectiveness of PEG in comparison to other laxatives. They also found more side effects in lactulose-users. Bae et al. [26] reported that constipated pediatric patients using PEG 4000 had benefited from additional fluid intake, which was related to bowel movements and stool consistency. Wang et al. [27] also reported that PEG 4000 was safe and more effective than lactulose for the treatment of constipation in children. Treepongkaruna et al. [28] found that PEG 4000 had higher effectiveness than lactulose for the treatment of chronic constipation in young children and it was well tolerated. It has been stated in Cochrane reviews 2018 as well as in ESGHAN- NASGHAN 2014 guideline that PEG is more effective and superior in the treatment of FC in children [29,30].

In this study, both lactulose and PEG 4000 treatment were found to be effective in FC in accordance with the literature information. PEG 4000 treatment was more effective and superior than lactulose treatment without increased side effects.

PEG 4000 should be used as the first option for FC treatment in children. In cases where PEG 4000 is not feasible, lactulose treatment may serve as a suitable alternative.

Limitations

A double-blind placebo-controlled study would yield more objective results in terms of demonstrating drug efficacy. PEG and LAC group are not homogeneously distributed in clinical findings. However, PEG treatment appears more effective, although the symptoms of constipation are more severe. Furthermore, the education level of the family and the child behavior in withholding stool are both significant. Another limitation of the study is the omission of taking sociocultural level of the patients' family into account.

Conclusions

PEG 4000 is more effective than lactulose with fewer side effects in the treatment of functional constipation in children. We think that it may be preferable in cases where lactulose therapy is ineffective. Family education on diet and toilette training also plays a significant role in the treatment, along with medical therapy.

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Does the overhang of tibial component in fixed bearing medial unicondylar knee arthroplasty affect 1-year results?

Sabit tip medial unikondiler diz artroplastisinde tibial komponentin kemik yüzeyden taşması 1 yıllık sonuçları etkiler mi?

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Abstract

Aim: Unicondylar knee arthroplasty (UKA) is an effective treatment for single-compartment knee arthrosis. The compatibility of the size of the components with the bone is one of the factors determining patient satisfaction. With this study we aimed to investigate the effect of size concordance of the tibial component and bone in fixed bearing UKA on functional scores and pain.

Methods: Demographic data, preoperative and postoperative 1-year visual analog pain scale (VAS) and Oxford Knee Scores (OKS) were collected from 43 patients operated by a single surgeon with a fixed bearing UKA implant (Zimmer UKA, Warsaw USA) for this prospective cohort study. Patients were then grouped according to radiological compliance of the tibial component to the bone as perfect match or overhang, and the groups were compared in terms of pain and functional scores.

Results: Among 43 patients included in the study, 9 (20.9%) were males and 34 (79.1%) were females. The mean age of the patients was 62.1 (8.1) years. The median VAS and OKS scores of the patients before surgery were 6 (3-8) and 26 (21-30), respectively. Postoperatively, VAS score decreased to 1 (0-2), while OKS increased to 44 (37-48) (P<0.001 for both). There were only 3 patients with underhang. Twenty-two (52.1%) patients had perfect match and 18 (41.9%) had an overhang from the bone surface. There was no patient with an overhang greater than 3mm. The VAS and OKS scores at post-operative 1-year of 18 patients with overhang and 22 patients without bone overhang were similar (P=0.674 and P=0.873, respectively).

Conclusion: The overhang of the tibial component in fixed bearing unicondylar knee arthroplasty is common, however, this does not affect functional results in 1-year follow-up. Nevertheless, the sizing of the component should be checked by adequate means.

Keywords: Unicondylar, Knee, Arthroplasty, Function, Implant size

Öz

Amaç: Unikondiler diz artroplastisi (UDA) tek kompartman artrozunda etkinliği kanıtlanmış bir tedavidir. Kemik ile implant bileşenlerinin uyumu hasta memnuniyetini etkileyen faktörlerden biridir. Bu çalışma ile kemik ve tibial bileşen uyumunun ağrı ve fonksiyon skorları üzerindeki etkisini incelemeyi amaçladık.

Yöntemler: Bu prospektif kohort çalışmasında tek cerrah tarafından opere edilmiş 43 sabit tip UDA (Zimmer UKA, Warsaw, ABD) hastasının demografik verileri, cerrahi öncesi ve cerrahi sonrası birinci yıldaki vizüel analog ağrı skalası (VAS) ve Oxford Knee Score (OKS) sonuçları incelenmiştir. Hastalar radyolojik olarak kemik yüzey ile implantın uyumuna göre mükemmel uyum ve taşma olarak gruplanmıştır. Ardından grupların ağrı ve fonksiyon skorları karşılaştırılmıştır.

Bulgular: İncelenen 43 hastanın 9'u (%20,9) erkek ve 34'ü (%79,1) kadındır. Ortalama yaş 62,1 (8,1) yıldı. Cerrahi öncesi VAS ve OKS ortanca değerleri sırasıyla 6 (3-8) ve 26 (21-30) idi. Cerrahi sonrasında VAS 1'e (0-2) düşerken OKS 44'e (37-48) yükselmiştir (her ikisi için P<0,001). Sadece 3 hastada implant kemikten daha küçüktü. 22 (%52,1) hastada kemik ile protez arasında tam uyum mevcuttu. 18 (%41,9) hastada ise kemik yüzeyden taşma izlenmiştir, ancak bu hastalardan hiçbirinde fark 3 mm'den fazla değildir. Mükemmel uyum ve taşma grubunun cerrahiden sonraki birinci yıl VAS ve OKS sonuçları karşılaştırıldığında anlamlı bir fark olmadığı görülmüştür (sırasıyla P=0,674 ve P=0,873).

Sonuç: Sabit tip unikondiler diz artroplastisinde taşma sık görülürken bunun cerrahi sonrası birinci yıl ağrı ve fonksiyonel sonuçlar üzerinde bir etkisi yoktur. Yine de implant seçimi yapılırken taşmanın önüne geçmek için gerekli önlemler alınmalıdır.

Anahtar kelimeler: Unikondiler, Diz, Artroplasti, Fonksiyon, İmplant büyüklüğü

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Ethics Committee Approval: This study was approved by the Ethics Committee of Ankara University, Faculty of Medicine (7/13/2020-I6-390-20). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
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Introduction

Unicondylar knee arthroplasty (UKA) is an effective and successful treatment method that has been used for a long time in isolated single-compartment knee arthrosis [1,2]. For a successful and long-lasting UKA, the quality of the surgical procedure is as important as the patient selection. The amount of correction of the underlying varus, the arrangement and placement of the components used are very important [3,4]. In particular, the compatibility of the size of the components with the bone is one of the factors that determine patient satisfaction [5].

Joint pain, which does not dissolve after surgery, is often the most prominent complaint regarding prosthesis. Especially incompatibility and overhang of the components with bone surface may lead to permanent pain [6]. Although similar studies in total knee arthroplasty have shown a detrimental effect on patient satisfaction and functional outcomes of implant overhang, there are not enough studies investigating this situation in unicondylar knee arthroplasty [7,8]. In unicondylar knee arthroplasty, where there is more fear of tibial component collapse than total knee arthroplasty, there is a tendency among surgeons to choose a larger sized implant.

With this study, we aimed to investigate the size concordance of the tibial component and bone in fixed bearing unicondylar knee arthroplasties and evaluate the effect of the underhang or overhang if present on functional scores.

Materials and methods

This study complies with Helsinki Declaration and has the approval of the Ethics Committee of Ankara University Faculty of Medicine (13/7/2020- I6-390-20). All patients who underwent medial fixed bearing unicondylar knee arthroplasty in our department in 2018 and who were followed up for at least one year were included in the study. Surgical indications for unicondylar knee arthroplasty were gonarthrosis in only one compartment of the knee with bone-to-bone contact, an intact anterior cruciate ligament and knee varus less than 15°.

From a total of 47 patients who received UKA, 1 patient was excluded due to lateral compartment UKA, 2 patients were excluded for being lost to follow-up before the 1-year control and 1 patient was excluded because she did not have the appropriate x-rays.

All patients were operated by a single surgeon who had at least 5 years of UKA experience and performed more than 50 unicondylar knee arthroplasties. After exsanguination and application of tourniquet, a 7-10 cm skin incision was made. Arthrotomy was achieved by the midvastus approach. Cemented fixed bearing unicondylar knee implants were used in all patients (Zimmer High Flex Unicompartmental, Warsaw USA). Femoral side was prepared with the help of the intramedullary guide, then a tibia cut was made with the extramedullary guide as recommended by the manufacturer. With the measuring apparatus provided in the surgical set, the size of the tibial components was decided. Also, the insert thickness appropriate for the medial collateral ligament tension was selected by using tension guide with trials. After the trial, the original implants were fixed with cement and the incisions were closed (Figure 1).

Figure 1: X-rays showing the antero-posterior and lateral knee views of a patient with UKA.

Demographic data (age, gender, BMI), size of the implant used, pain visual analog scale (VAS) values before and at the 1-year follow-up were obtained from the patient files. Functional results were evaluated with the Turkish Oxford Knee Score (OKS) of the patients obtained before the surgery and at the first-year follow-up [9]. The radiological evaluation was made by an experienced orthopedic surgeon (MK) other than the one who performed the surgeries. The long leg and knee AP and side radiographs were used. The amount of varus correction in coronal plane and the conformity between the bone and tibial component were explored in both the coronal and sagittal plan. Any underhang or overhang were measured in mm with PACS. Patients were grouped according to radiological compliance of the tibial component to the bone as perfect match, underhang or overhang.

Statistical analysis

Kruskal–Wallis test was used to compare continuous values and Chi-square statistical test was used to compare categorical data for each of the groups. Statistical significance level was set at *P*-value <0.05.

Results

Among 43 patients included in the study, 9 (20.9%) were male and 34 (79.1%) were female. The mean age of the patients was 62.1(8.1) years. The mean body mass index was 30.4(4.2) $kg.m^{-2}$. While the average varus alignment in the operated leg before surgery was 9.3°(4.3°), it decreased to 2.8°(1.9°) postoperatively. Preoperatively, the median VAS and OKS scores of the patients were 6 (3-8) and 26 (21-30), respectively. After surgery, VAS score decreased to 1 (0-2), while OKS increased to 44 (37-48). The improvement of both VAS and OKS were statistically significant ($P<0.001$ for both).

The postoperative x-rays of the patients revealed that only 3 patients had underhang in the sagittal plane. Therefore, the underhang group was not included in the evaluation of functional results and VAS scores. In 22 patients, bone and implant were perfectly matched in both the coronal and sagittal planes. In 18 (41.9%) of the patients, the tibial component was observed to overhang from the bone surface. While 6 patients had mismatch in the sagittal plane (overflowing from the posterior of the tibia), the remaining 12 patients had medial overhang. In both plans, no patient had an overhang greater than 3mm.

The change of VAS and OKS scores of 18 patients with overhang and 22 patients without bone overhang were similar ($P=0.674$ and $P=0.873$ respectively) (Table 1).

Table 1: Table showing the age, gender, pain and functional scores of the perfect implant-bone match group and overhang group

		Perfect match	Overhang	*P*-value
n		22	18	
Age		61.9	62.1	0.999
Gender	Male	5	3	0.898
	Female	17	15	
VAS	Preoperative	6 (3-7)	5 (3-8)	0.674
	Postoperative*	1 (0-2)	1 (0-2)	
OKS	Preoperative	26 (21-29)	27 (22-30)	0.873
	Postoperative*	43 (37-48)	44 (37-48)	

VAS: Visual Analog Scale, OKS: Oxford Knee Score, * Postoperative 1-year

Discussion

The results of our fixed bearing unicondylar knee arthroplasty series show that there is no significant relationship between the presence of overhang and functional results. Only 51.2% of patients had perfect fit. However, it should be remembered that none of the patients with incompatibility had an overhang of more than 3 mm.

The current literature shows that the perfect fit of the proximal tibia and the tibial component is lower than predicted [10,11]. Chau et al. [12] reported that the one-to-one fit was only seen in 3% of 149 Oxford unicondylar knee arthroplasties they examined. Similar results can be seen with the total knee cases in the literature [8,13]. Although the exact compliance rate reported in our series is 51.2%, the percentage of overhang is still noteworthy. Almost half of the cases have an implant protruding from the surface of the bone in one of the two plans. Still, this overhang was less than 3 mm in every case.

Anatomical studies indicate that perfect bone-implant match is exceedingly challenging to achieve because the implant sizes increase by 2 mm increments and the antero-posterior and medio-lateral lengths are constant [10]. Also, the rotation of the tibial bone cut can lead to direct size mismatch [6,14]. Although techniques such as robotic surgery or patient specific instrumentation have been introduced by the industry to correct rotational and alignment problems, there is still no definitive solution to such issues [15–17]. Another important factor is the difference in bone morphology and sizes in men and women. It is known that compliance decreases, especially as the tibia becomes smaller [12]. Although gender-specific implants are currently available, their efficacy is also controversial [18]. It should be taken into consideration that we had more female patients than males and they tend to have implants smaller in size.

Manufacturers and various authors suggest that small placement of the tibial component is associated with early aseptic loosening of the implant, particularly in unicondylar knee arthroplasty, so underhang should be avoided [19,20]. In the proximal tibia, the cortex is stronger and the implant subsidence and the risk of periprosthetic fracture are lower when the implant makes direct contact with the cortex [15]. Gudena et al. state that overhanging up to 2mm is acceptable in Oxford knee implants [21].

Unfortunately, we do not know our long-term results, for which studies with longer follow-up periods should be conducted.

The overhang of the tibial component from the bone is an important problem leading to patient dissatisfaction, especially by causing soft tissue irritation. An in vitro cadaver study has shown that overhang over 2 mm creates a significant amount of tension in MCL [21]. There is only one study in UKA that compares functional results with tibial overhang by Chau et al. [12]. They examined the relationship of the tibia with the component in the Oxford model knee prosthesis in the coronal plane and showed that 70% of patients had less than 3mm overhang, which did not affect the functional results. Only 9% of the patients had more than 3mm of overhang with complaints. Similarly, there are large series in total knee arthroplasty literature showing that the oversized tibial component does not affect functional results [22–24]. Akin to those, our study emphasized that overhang does not affect functional results in patients.

It should not be forgotten that the surgical technique is not the only factor determining functional results and patient satisfaction. Other factors such as alignment and soft tissue balance are as important as the choice of component size [25,26]. For example, in a national database review where revised UKAs were examined, it was stated that technical defects related to alignment, bone cut or cementing constituted more than half of the revision indications but there was only a 9% error regarding the implant size [11].

Limitations

It is clear that our study has some limitations. First, 4.6% of the patients were lost to follow-up. Although this ratio is small, their inclusion in the study would have increased its power. In addition, standard postoperative radiographs were used as the measurement method. It is known that computed tomography is a more successful method especially in evaluating rotation and measuring small overhangs, however, it is unethical to use CT only for study purposes due to the high ionizing radiation. The most critical point of the study that needs improving is the lack of long-term follow-up.

Conclusion

The overhang of the tibial component seems a common occurrence in fixed bearing unicondylar knee arthroplasty, but this does not affect functional results in 1-year follow-up. Nevertheless, the sizing of the component should be checked by adequate means like preoperative templating, intraoperative x-rays or use of fluoroscopy.

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Does social isolation cause secondary injury in general surgery patients?

Sosyal izolasyon, genel cerrahi hastalarında ikincil hasara neden olur mu?

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Abstract

Aim: Social isolation during the pandemic has been reported to cause secondary injury to some patient groups. The fear of secondary injury causes patients and health workers to ignore rules of social isolation. Here we aimed to evaluate secondary injury among general surgery patients during the pandemic.

Methods: In this retrospective cross-sectional study, 279 patients, consulted from emergency departments to general surgery departments at Başkent University Ankara and Konya Research Centers, were analyzed. The patients were divided into two groups according to admission periods (Group 1: March 01 - May 01, 2019; n=163, Group 2: March 01 - May 01, 2020; n=116).

Results: The mean age of Group 2 (50.4 (19.3)) was less than Group 1 (55.4 (20.4)). Gender (P=0.28), malignancy (P=0.53), comorbidity (P=0.27) distributions were similar. There was no significant difference in terms of admission complaints (P=0.88) and complaint durations (P=0.068). Acute cholecystitis rate was significantly higher in Group 2 (P=0.005), and the rate of non-specific patients was significantly higher in Group 1 (P=0.003). Hospitalization (P=0.46), type of treatment (P=0.3), surgical procedure (P=0.27), length of stay (P=0.66) and mortality rate (P=0.5) were similar.

Conclusion: Our results showed no secondary injury to general surgery patients due to the pandemic. During this period, social isolation did not decrease the hospital admission of critically ill patients.

Keywords: Pandemics, Mortality, COVID-19

Öz

Amaç: Pandemi dönemlerinde uygulanan sosyal izolasyonun bazı hasta gruplarında ikincil hasara neden olduğunu gösteren yayınlar mevcuttur. İkincil hasar gelişebileceği korkusu ile hastalar ve hekimler tarafından sosyal izolasyon kurallarına aykırı tavırlar gösterilebilmektedir. Çalışmadaki amacımız; COVID-19 pandemisi sırasında Türkiye'de uygulanan sosyal izolasyonun, genel cerrahi hastalarında meydana getirdiği ikincil hasarları değerlendirmekti.

Yöntemler: Başkent Üniversitesi Ankara ve Konya Uygulama ve Araştırma Merkezleri erişkin acil servisinden genel cerrahi bölümüne konsülte edilen 279 hasta retrospektif olarak incelendi. Hastalar başvuru dönemine göre iki grupa ayrıldı (Grup 1: 01 Mart - 01 Mayıs 2019; n=163, Grup 2: 01 Mart - 01 Mayıs 2020; n=116). Hastaların demografik karakteristikleri, klinik bilgileri ve tedavi özellikleri hastane otomasyon sistemi aracılığı ile kayıt edilerek her iki grup karşılaştırıldı.

Bulgular: Grup 2'nin yaş ortalaması (50,4 (19,3)), grup 1 (55,4 (20,4))'e göre daha düşüktü ve bu düşüş istatistiksel olarak anlamlıydı (P=0,038). Grupların cinsiyet (P=0,28), malignite (P=0,53), komorbidite (P=0,27) dağılımları benzerdi. Gruplar arasında başvuru şikayetleri (P=0,88) ve şikayet süreleri (P=0,068) açısından anlamlı fark saptanmadı. Grupların tanıları karşılaştırıldığında Grup 2'de akut kolesistit oranı anlamlı olarak daha yüksek tespit edildi (P=0,005). Ayrıca non-spesifik hasta oranı grup 1'de anlamlı olarak daha fazla idi (P=0,003). Gruplar arasında hospitalizasyon (P=0,46), tedavi şekli (P=0,3), yapılan cerrahi prosedür (P=0,27), yatış süresi (P=0,66) ve mortalite oranı (P=0,5) açısından istatistiksel olarak anlamlı bir fark saptanmadı.

Sonuç: Yaptığımız araştırma sonuçlarına göre merkezimize başvuran hastalarda sosyal izolasyona bağlı gelişen ikincil hasarlanma ile karşılaşmadık. Bu dönemde hastaların sosyal izolasyonda olmaları ciddi klinik problemleri var iken hastaneye başvurularını azaltmamış sadece gereksiz acil başvurusu sayısını azaltmıştır.

Anahtar kelimeler: Pandemi, Mortalite, COVID-19

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Introduction

COVID-19 has spread all around the world within a brief time after its emergence and was declared a pandemic by the World Health Organization (WHO) on 12 March 2020 [1,2]. A number of measures concerning public health, economic, and sociocultural fields have been taken in countries affected by the disease. Social isolation forms the basis of those measures [3]. It is the most effective method that slows the spread of the disease. Several studies have shown that social isolation process leads to secondary injury in some patient groups [4,5]. No study has yet investigated the impact of social isolation from the viewpoint of general surgery. The present study aimed to examine social isolation's effects concerning general surgery by comparing patients consulted with the general surgery department by the emergency department at our center during the pandemic with patients consulted within the preceding period.

Materials and methods

Our study was approved by Başkent University Medicine and Health Sciences Research Committee (Date 02/06/2020, No KA20/212). It enrolled a total of 279 patients who were consulted by the Adult Emergency Department with the General Surgery Department at Başkent University Ankara and Konya Practice and Research Centers. Since the symptoms and diagnoses of patients presenting to the Emergency Department may show seasonal variations, the data from the spring of 2019 were chosen to be compared with the data from the pandemic. The patients were divided into two groups according to their date of presentation (Group 1: 01 March - 01 May 2019; Group 2: 01 March - 01 May 2020). A cross-sectional study was conducted by retrospectively reviewing the patients' data regarding their demographic features, comorbidities, admission complaints, duration of symptoms, diagnoses, consultation results, treatment modalities, applied treatments, length of hospital stay, and mortality rates from the hospital automation system. To perform a more accurate statistical analysis, the patients' admission complaints were grouped under 5 main titles (Table 1). Their diagnoses were encoded by ICD-10 diagnostic codes and grouped accordingly (Table 2) [6]. Patients who remained undiagnosed after the assessment were recorded as having a "non-specific diagnosis". Surgical procedures were grouped according to the interventional procedures list issued by R.T. Ministry of Health [7]. Again, to perform an accurate statistical analysis, the surgical procedures were grouped under certain titles (Table 3). The patients who were consulted with another department after a physical examination and diagnostic tests were separately grouped.

Statistical analysis

The statistical analysis of the study data was conducted using SPSS version 25.0 statistical software. The normality of data distribution was tested using the Kolmogorov-Smirnov test and the Shapiro-Wilk test. Data without normal distribution were expressed as mean and compared using the Mann Whitney-U test. Categorical data were compared using Chi-square or Fisher's exact test. A *P*-value of less than 0.05 was considered statistically significant for all statistical analyses.

Table 1: Distribution of the patient complaints

Complaint	Group 1 n (%)	Group 2 n (%)
Abdominal pain (with or without nausea and vomiting)	148 (90.8)	109 (94)
Inguinal pain	5 (3.1)	2 (1.7)
Anal pain	3 (1.8)	1 (0.9)
Bloody emesis, bloody stool	3 (1.8)	2 (1.7)
Traffic accident, fight related injuries	4 (2.5)	2 (1.7)

Table 2: Patient diagnoses and ICD-10 diagnostic codes

ICD-10 CODE	Diagnosis	Group 1 n (%)	Group 2 n (%)	*P*-value
	Non-specific	41 (25.2)	12 (10.3)	0.003
K35	Acute appendicitis	29 (17.8)	27 (23.3)	NS*
K81	Cholecystitis	22 (13.5)	32 (27.6)	0.005
K56	Paralytic ileus and intestinal obstruction without hernia	20 (12.3)	11 (9.5)	NS*
K52	Other non-infective gastroenteritis and colitis	13 (8)	11 (9.5)	NS*
K57.3	Diverticular disease of large intestine without perforation or abscess	7 (4.3)	5 (4.3)	NS*
K40-K46	Hernia	8 (4.9)	3 (3.6)	NS*
N83	Non-inflammatory disorders of ovary, fallopian tube and broad ligament	5 (3.1)	1 (0.9)	NS*
K85	Acute pancreatitis	4 (2.5)	2 (1.7)	NS*
K60	Fissure and fistula of anal and rectal regions	1 (0.6)	0 (0)	NS*
K61	Abscess of anal and rectal regions	2 (1.2)	1 (0.9)	NS*
K64	Hemorrhoids and perianal venous thrombosis	2 (1.2)	1 (0.9)	NS*
C51-C58	Malignant neoplasms of female genital organs	2 (1.2)	1 (0.9)	NS*
C15-C26	Malignant neoplasms of digestive organs	2 (1.2)	3 (2.6)	NS*
K92.2	Gastrointestinal hemorrhage, unspecified	1 (0.6)	3 (2.6)	NS*
K55.0	Acute vascular disorders of intestine	1 (0.6)	0 (0)	NS*
S36	Injury of intra-abdominal organs	1 (0.6)	1 (0.9)	NS*
K27.1	Peptic ulcer, site unspecified, acute with perforation	0 (0)	1 (0.9)	NS*
K63.1	Perforation of intestine (non-traumatic)	0 (0)	1 (0.9)	NS*

NS* not significant

Table 3: Distribution of the surgical procedures performed in the patients

Surgical procedure	Group 1 n (%)	Group 2 n (%)
No surgery (medical treatment), n (%)	122 (74.8)	77 (66.4)
Appendectomy (open and laparoscopic), n (%)	24 (14.7)	27 (23.3)
Resection of small intestine, Colectomy, n (%)	7 (4.3)	2 (1.7)
Cholecystectomy (open and laparoscopic), n (%)	4 (2.5)	5 (4.3)
Abscess drainage, n (%)	3 (1.8)	1 (0.9)
Hernia repair (inguinal, umbilical, incisional), n (%)	3 (1.8)	2 (1.7)
Exploratory laparotomy, n (%)	0 (0)	1 (0.9)
Repair for perforated peptic ulcer disease, n (%)	0 (0)	1 (0.9)

Results

In our study, 163 patients in Group 1 and 116 patients in Group 2 were consulted with the department of general surgery. Table 4 summarizes various characteristics of the patients in both study groups. Accordingly, the mean age of the patients in Group 2 was significantly lower than that of patients in Group 1 (50.4(19.3) vs 55.4(20.4), P=0.038). Both groups of patients had statistically comparable distributions of gender (P=0.28), symptom duration (P=0.068), malignancy (P=0.53), and comorbidities (P=0.27).

The most common admission complaint in both groups was abdominal pain, which showed no statistically significant difference between the two groups (P=0.88). An analysis of the diagnoses showed that there was a significant difference between both groups concerning the "non-specific "and "cholecystitis" diagnoses. The rate of non-specific diagnoses was 25.2% (n=41) in Group 1 while it dropped to 10.3% (n=12) in Group 2 (P=0.003). The rate of acute cholecystitis was 13.5% (n=22) in Group 1 while it rose to 27.6% (n=32) in Group 2 (P=0.005). The results of the consultations showed no significant differences between both groups in terms of hospital admission, discharge, consultation with another department, and treatment refusal (P=0.46). Both groups had statistically similar proportions of patients treated medically or surgically (P=0.3). The distribution of surgical procedures was similar in both groups (P=0.27). No significant difference was found between the two groups with regards to the duration of hospital stay (P=0.66). The mortality

rate of Group 1 was 2.5% (n=4) while it dropped to 1.7% (n=2) in Group 2, but the difference was insignificant (*P*=0.5) (Table 4).

Table 4: The patients' demographic and clinical characteristics

	Group 1 (n:163)	Group 2 (n=116)	*P*-value
Age, year, mean (SD)	55.4 (20.4)	50.4 (19.3)	0.038
Gender			0.28
Male, n (%)	78 (47.9)	63 (54.3)	
Female, n (%)	85 (52.1)	53 (45.7)	
Duration of symptom, day, mean (min-max)	1 (0-60)	2 (1-20)	0.068
Malignancy, n (%)	32 (19.6)	19 (16.4)	
Comorbidity, n (%)	84 (51.5)	52 (44.8)	
Results			0.46
Hospitalize	87 (54.3)	73 (62.9)	
Discharge	54 (33.1)	31 (26.7)	
Consultation to the other departments	3 (1.8)	2 (1.7)	
Refusal of Treatment	19 (11.7)	10 (8.6)	
Type of treatment			0.3
Surgical treatment	103 (63.2)	65 (56)	
Medical treatment	41 (25.2)	39 (33.6)	
Length of stay, day, mean (min-max)	3 (1-46)	3 (1-19)	NS*
Death	4 (2.5)	2 (1.7)	NS*

NS* not significant

Discussion

During the COVID-19 pandemic, taking certain measures has become obligatory in the field of public health as in many other fields. In the current literature, it is recommended for patients to avoid hospital presentation and for surgeons to postpone elective surgical procedures [8,9]. Taking the recommended measures has brought about the possibility of delayed diagnosis and treatment, potentially increasing mortality, and morbidity rates [4,5].

It is well-known that COVID-19's mortality rises in advanced age. Therefore, studies have stressed that aged individuals should take extra care to socially isolate themselves [10]. In our study, the mean age of the patients significantly dropped in Group 2 (50.4(19.3)) compared to Group 1 (55.4(20.4)). We believe that the aged population taking greater care for social isolation caused this difference.

A study that was reported by Kılınç et al. [11] in 2009 examined gender and age distribution of patients presenting to the emergency department. It revealed that, among individuals aged 65 years or older, women more commonly presented to the emergency department. Although our study did not find any significant differences concerning gender between the study groups, Group 2 contained more men than Group 1. This may stem from a lower mean age in Group 2 than Group 1.

As is known, COVID-19 has a more severe course in patients with immunosuppression or comorbidities such as hypertension, and the mortality rate rises as high as 8% in such groups [12]. Despite the differences being statistically non-significant, Group 2 had a 3.2% lower malignancy rate and a 6.7% lower comorbidity rate than Group 1. This finding may be a sign that patients with malignancy or comorbidities have adapted to social isolation.

In our country, patients can easily access emergency departments of tertiary health centers. Therefore, patients generally prefer to present to emergency departments rather than visiting their family physicians or outpatient clinics. According to several studies, about 10-12% of patients presenting to emergency departments with abdominal pain do not receive any diagnosis [13,14]. In our study, the corresponding rate was 25.2% in Group 1 and 10.3% in Group 2, with both numbers being above the other countries' average numbers. A comparison of Group 1 and Group 2, on the other hand, reveals a drop as much as 14.9% in Group 2, which was statistically significant. In our opinion, this drop originates from a reduced number of unnecessary presentations to the emergency department due to social isolation during the pandemic.

Acute cholecystitis constitutes a considerable percentage of general surgical emergencies, and its definitive treatment is cholecysteectomy. However, some uncomplicated acute cholecystitis cases may be treated with antibiotics as a bridge to cholecystectomy [15]. In our study, the number of patients who were diagnosed with acute cholecystitis significantly increased in Group 2 compared with those in Group 1. However, no significant difference was found between the cholecystectomy rates of both groups. Many studies to date have recommended postponing elective surgeries during the pandemic [8,9]. We also opted to postpone surgery and administered first-line medical treatment in patients with uncomplicated acute cholecystitis.

Overcrowding in emergency departments may cause a sense of dissatisfaction in some patients, making them refuse treatment at their own will [16]. From a standpoint of general surgery, fear of undergoing a surgical procedure may be another reason for patients to leave the emergency department. According to our findings, there was a 1.4% non-significant drop in the number of patients refusing treatment in Group 2. We believe that this drop resulted from the relief of the emergency department's overcrowding and the preference of medical therapy during the pandemic.

Limitations

Small study size and collection of study data from two centers from the same region may be considered as the limitations of our study. The study may be extended by collecting data from a larger number of patients from different geographical regions. Additionally, a study enrolling outpatients may achieve more statistically significant results.

Conclusion

In our study, our results showed no secondary injury to general surgery patients due to the pandemic. During this period, social isolation did not decrease the hospital admission of critically ill patients. However, the pandemic decreased the unnecessary admissions to emergency clinic. We also showed that with precautions, urgent surgical cases can be successfully managed during the pandemic.

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Theory of mind deficits in bipolar disorder in remission

Remisyon dönemi bipolar bozuklukta zihin kuramı işlev bozukluğu

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Ethics Committee Approval: This study was granted approval by the Uludağ University, Clinical Research Ethics Committee (date: 5/13/2014 number: 2014-10/14). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma, Uludağ Üniversitesi Etik Kurulu tarafından (tarih: 13.05.2014, no: 2014–10/14) onaylanmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

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Abstract

Aims: Theory of Mind (ToM), a concept used to describe an individual's social cognitive abilities that play roles in social interaction, may have a significant role in explaining the clinical variables and social problems of affective disorders. This study aims to determine whether ToM functions are impaired in Bipolar Disorder (BD) compared to healthy controls as well as investigate the association between clinical variables of ToM deficit and social competence.

Methods: A total of 50 patients diagnosed with BD who were in remission and 50 healthy control subjects were included in this cross-sectional study. Demographic data and medical history of participants were assessed, and Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Eyes test, Hinting Task, Social Adaptation and Self-Evaluation Scale (SASS), Wechsler Adult Intelligence Scale-Revised (WAIS-R) tests were administered.

Results: There were no significant differences with regards to age, gender and BDI scores between patient and control groups. Hinting test (P=0.001), Eyes test (P=0.001), SASS (P=0.007) and WAIS-R (P=0.001) scores were higher in the control group. There was a significant correlation between Hinting Test and WAIS-R (r=0.430, P=0.001), and between Eyes Test and age (r.-0.590, P=0.001), duration of bipolar disorder (r=-0.554, P=0.001), number of manic attacks (r=0.590, P=0.001) and WAIS-R (r=0.343, P=0.050). Logistic regression analysis showed that compared to the patient group, control group was related to Eyes test by 1.2-fold for each point increase in Eyes test (P=0.001) and 1.3-fold for each point increase in Hinting test (P=0.003).

Conclusion: ToM deficit was an essential factor that separated BD patients in remission from healthy individuals. ToM deficit may play a role in the essential pathology or affect the presence, or even onset, of BD.

Keywords: Bipolar disorder, Remission phase, Theory of mind, Social cognition

Öz

Amaç: Zihin kuramı (ZK) bireyin sosyal etkileşimde rol oynayan sosyal bilişsel yeteneklerini tanımlamak için kullanılan bir kavramdır ve duygu durum bozukluklularının kliniğinde ve sosyal problemlerini açıklamakta önemli bir rolü olabilir. Bu çalışmanın amacı, remisyon döneminde olan bipolar bozukluk (BB) hastalarında sağlıklı kontrollere göre zihin kuramı yetilerinde bozukluk olup olmadığı ve ZK kusurunun cinsiyet, eğitim düzeyi, hastalık süresi, atak sayısı, hastaneye yatış öyküsü, öz kıyım girişimi öyküsü gibi klinik değişkenler ve sosyal uyum ile ilişkisini araştırmaktır.

Yöntemler: Çalışma kesitsel dizaynda tasarlanmış ve remisyon döneminde olan 50 BB hastası ve 50 sağlıklı katılımcıdan oluşan kontrol grubu dahil edilmiştir. Demografik bilgiler ve hastalık öyküsü alınmış, Beck Depresyon Envanteri (BDE), Beck Anksiyete Envanteri (BAE), İma Testi, Gözler Testi, Sosyal Uyum ve Kendini Değerlendirme Ölçeği (SUKDÖ), Muhakeme Becerisi (MB) testleri uygulanmıştır.

Bulgular: Gruplar arasında yaş, cinsiyet ve BDE puanları arasında anlamlı fark yoktu. İma testi (P=0,001), Gözler Testi (P=0,001), SUKDÖ (P=0,007) ve MB (P=0,001) puanları kontrol grubunda anlamlı olarak yüksek idi. İma testi ve MB arasında anlamlı pozitif korelasyon vardı (r=0,430, P=0,001). Göz Testi ile yaş (r=-0,555, P=0,001), hastalık süresi (r=-0,554, P=0,001), manik atak sayısı (r=-0,590, P=0,001) ve MB (r=0,343, P=0,050) arasında korelasyon saptandı. Lojistik regresyon analizi ile kontrol grubunun hasta grubu ile kıyaslandığında Gözler testinde her puan artışı ile 1,2 kat (P=0,001), İma testinin her puan artışı 1.3 kat (P=0,003) ilişkili olduğu gözlendi.

Sonuç: ZK kusurunun, diğer özellikleri ne olursa olsun BB düzelme döneminde olan bireyi sağlıklılardan ayıran önemli bir etmen olduğu saptanmıştır. ZK kusurunun BB'nin temel patolojisinde yer aldığı ve patolojinin varlığını etkilediği düşünülmüştür.

Anahtar kelimeler: Bipolar bozukluk, Remisyon fazı, Zihin Kuramı, Sosyal kognisyon

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Introduction

Bipolar mood disorder is a chronic disease characterized by periodical and recurrent course of depressive, manic, or mixed episodes as well as subthreshold symptomatic or asymptomatic periods, leading to loss of social and occupational function [1].

Theory of Mind (ToM) is a concept used to describe an individual's social cognitive abilities that play a role in social interaction. ToM, otherwise known as "mental theory" or "mentalization capacity", is the individual's ability to perceive that other people have a different mind from their own as well as the individual's comprehension of mental states including intentions, beliefs, and desires [2].

Some studies have divided the ToM into socio-cognitive and socio-perceptive paradigms [3,4]. Socio-cognitive Theory of mind is defined as the person's capability to deduce the underlying mental state of other people based on their behaviors. The second paradigm, socio-perceptive ToM, is the person's capacity to perceive the mental state of other people based on directly observable information. The Eyes Task is the most common tool for measuring this function [5].

ToM deficit in BD has been shown in studies and imaging methods. However, the correlation between its clinical features and ToM has not been comprehensively investigated. Most studies on ToM deficit have been conducted on patients diagnosed with autism and schizophrenia. Studies on patients with affective disorders are limited.

This study respectively examines the relationship between ToM deficit and clinical symptoms, social coherence, and cognitive functions in BD patients in remission.

Materials and methods

The study group consisted of patients who were admitted to the Department of Mental Health and Diseases outpatient clinic of the university hospital, diagnosed with "Bipolar Affective disorder" according to the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV), in remission period, and met the study's inclusion criteria. The control group consisted of volunteers who met inclusion criteria, had no psychopathology based on psychiatric examination, no history of psychiatric disorders and were not undergoing any medical treatment.

- Patient group inclusion criteria: 18-65 years of age, BD diagnosis according to DSM-IV, in remission period (Young Mania Rating Scale ≤4), no Axis I pathology other than BD
- Control group inclusion criteria: 18-65 years of age, no presence or history of psychiatric illness or severe physical/neurologic disease, informed written consent obtained before study participation
- Exclusion criteria: Individuals with a condition preventing the administration of tests (illiteracy), organic brain pathology, history of substance or alcohol abuse/addiction, benzodiazepine use, and mental retardation were excluded from the study.

Both groups underwent a psychiatric evaluation. Appropriate tests were administered on the same day by a psychiatrist and a clinical psychologist.

Administered forms and tests

All study participants completed a sociographic data form developed for the study within a face-to-face interview session with the study conductor, along with Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Hinting Task, Eyes test, Social Adaptation and Self-Evaluation Scale (SASS), Wechsler Adult Intelligence Scale-Revised (WAIS-R) tests.

Beck Depression Inventory: This depression scale consists of 21 questions with each response scored from 0-3. Total score intervals are as follows: 1-10 normal, 11-16 moderate affective disorder, 17-20 clinical depression, 21-30 moderate depression, 31-40 moderate-to-severe depression, and 41-63 severe depression. The Turkish validity and reliability study was conducted by Hisli [6].

Beck Anxiety Inventory: Beck et al. developed the scale in 1988 [7]. Turkish validity and reliability was conducted by Ulusoy et al. [8]. The self-assessment scale evaluates the person's frequency of anxiety symptoms and consists of 20 questions, each scored between 0-3. The items assess how bothered the individual is by the symptoms during the past week. A high score represents elevated levels of anxiety.

Hinting Task: One of the advanced ToM tests, the Hinting Task was developed by Corcoran et al. [9]. The test consists of ten brief passages demonstrating the interaction between two characters. Each passage ends with one of the characters distinctly hinting at something. The test administrator asks the subject what they believe the character was implying. An appropriate initial response grants two points, and the test continues to the next passage. If the subject does not respond the first time correctly, the story continues, and a more obvious hint is given. If the subject responds correctly at the second hint, one point is given. If no correct response is given for the passage, zero points are given. Total scores range from 0-20 [9]. The test's Turkish adaptation was initially conducted by Bora et al. [10] and later by Taş et al. [11].

Eyes Task: The Eyes Task assesses the person's ability to form inferences based on the photographs of people's eyes only. The test also comprises functions such as facial perception and identifying emotions—the Turkish adaptation for adults, along with the test's validity and reliability study were conducted by Yildirim et al. [12]. The test consists of 36 questions with four options for each photograph of a person's eyes. Results are assessed according to the number of correct responses.

Social Adaptation and Self-Evaluation Scale: This scale was developed by Bosc et al. [13] to determine "social functioning" in depression patients for use in clinical research. The 21-item self-assessment, in which the only one of the first two items is answered according to occupational status, for a total of 20 responses, is scored between 0-3. Three main factors were identified according to the results of the factor analysis of SASS. Factor 1 represents 32% of the total variance, Factor 2, 8%, and Factor 3, 5%. Therefore, factor 1 alone has the power to represent the whole scale with all its items.

Wechsler Adult Intelligence Scale-Revised (WAIS-R): Developed by Wechsler [14], this scale is used to measure the person's vocabulary as well as usage of words and self-expression, sensitivity to new information, long-term memory, and when necessary, regrouping, and semantic memory [15].

Ethics: The study received ethics approval by the Uludag University Clinical Research Ethics Committee (date: 5/13/2014 number: 2014-10/14), and informed consent was obtained from all participants.

Statistical analysis

Statistical analysis of the data was carried out on the SPSS 25.0 statistical package program. Conformity of the variables to normal distribution was evaluated with analytical methods (Kolmogorov–Smirnov / Shapiro–Wilks tests). Descriptive findings were expressed as distribution of number and percentage, median, and interquartile range (IQR) values. Dependent variables were assessed as continuous variables. In the analysis of the correlation between dependent and independent variables, Student's t-test and Mann-Whitney U test were used to assess independent variables with two categories. Pearson Chi-square test, Fisher's exact Chi-square test, and Fisher-Freeman-Halton tests were used to evaluate categorical data. Pearson's correlation analysis was applied in measurement-type variables. Logistic regression analysis was used for the retrospective elimination between control and patient groups using ToM tests. The *P*-value <0.05 was considered the level of significance of all analyses and correlations.

Results

A total of 100 volunteers between 18-65 years of age were included in the study, with 50 patients and 50 controls. The patient group consisted of 30 females and 20 males, while the control group consisted of 33 females and 17 males. There were no significant differences between the groups with regards to gender (*P*=0.679), educational status (*P*=0.474), and marital status (*P*=0.512). The patient group included 11 (22%) patients with a history of suicidal attempt and 31 (62%) with previous hospitalizations.

Median and IQR of Age, BDI, BAI, Hinting Task, Eyes Task, SASS, and WAIS-R tests for both groups are presented in Table 1. There were no significant differences between age, gender and BDI scores between patient and control groups. Hinting test (*P*=0.001), Eyes test (*P*=0.001), SASS (*P*=0.007) and WAIS-R (*P*=0.001) scores were higher in the control group.

Correlation of clinical variables with ToM tests inpatient group is presented in Table 2. There was a significant correlation between Hinting Test and WAIS-R (r=0.430, *P*=0.01). Also there were significant correlations between Eyes Test and age (r=-0.555, *P*=0.001), duration of bipolar disorder (r=-0.544, *P*=0.01), number of manic attacks (r=-0.590, *P*=0.01) and WAIS-R (r=0.343, *P*=0.05). When age was controlled, negative correlation between Eyes Test and Number of Manic Attacks increased to r=-0.650. On the other hand, when age was controlled, negative correlation between Eyes Test and Duration of Bipolar Disorder decreased to r=-0.252, which was insignificant (*P*=0.081).

Logistic regression analysis with clinical variables and ToM tests between control and patient groups are presented in Table 3. The logistic regression model was statistically significant in both steps. In Step 2, compared to the patient group, control group was related to Eyes test by 1.2-fold for each point increase in Eyes test (*P*=0.001) and 1.3-fold for each point increase in Hinting test (*P*=0.003).

Table 1: Comprasion of sociodemografic variables

		Patients Median (IQR)	Control Median (IQR)	Statistics	*P*-value
Age		39.0 (32.0-50)	38.0 (34.0-39.0)	Z:0.842	0.400
Gender	Male	60.0% (n:30)	66.0% (n:33)	χ^2:0.386	0.339
	Female	40.0% (n:20)	34.0% (n:17)		
BDI		5.0 (1.0-9.3)	5.5 (1.8-10.0)	Z:0.118	0.906
BAI		6.5 (3.0-14.0)	5.0 (2.0-10.0)	Z:2.019	0.044
Hinting Test		15.0 (12.8-17.0)	18.0 (16.8-18.3)	Z:4.524	0.001
Eyes Test		20.0 (15.7-23.0)	24.0 (22.0-27.0)	Z:4.826	0.001
SASS		39.5 (34.0-46.3)	44.0 (40.0-47.0)	Z:2.707	0.007
WAIS-R		22.5 (17.0-25.3)	28 (24.8-31.0)	Z:5.063	0.001

BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; SASS: Social Adaptation and Self-Evaluation Scale; WAIS-R: Wechsler Adult Intelligence Scale-Revised.

Table 2: Correlation analysis of clinical variables with ToM tests in patient group

	Hinting Test r	Eyes Test r
Age	-0.140	-0.555**
Age at Bipolar disorder onset	0.095	-0.092
Duration of disorder	-0.134	-0.544**
Number of hospitalization	0.072	-0.270*
Number of manic attacks	-0.001	-0.590**
Number of depressive attacks	0.184	-0.127
BDI	0.075	-0.049
BAI	0.133	-0.026
SASS	0.267	-0.243
WAIS-R	0.430**	0.343*

BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; SASS: Social Adaptation and Self-Evaluation Scale; WAIS-R: Wechsler Adult Intelligence Scale-Revised, r: Pearson correlation coefficient; * *P*<0.05; ** *P*<0.01

Table 3: Logistic regression analysis with clinical variables and ToM tests between control and patient groups

		χ^2	R^2	*b* (SE)	*P*-value	OR
Step 1	Model	38.027	0.422		0.001	
	Eyes Test			0.181 (0.057)	0.001	1.198
	Hinting Test			0.272 (0.104)	0.009	1.313
	SASS			0.057 (0.044)	0.199	1.058
	Constant			-10.744 (2.478)	0.001	
Step 2	Model	36.318	0.406		0.001	
	Eyes Test			0.188 (0.056)	0.001	1.207
	Hinting Test			0.304 (0.102)	0.003	1.355
	Constant			-9.021 (1.962)	0.001	

Variables entered on Step 1: Age, WAIS-R, Eyes Test, Hinting Test and Social Adaptation and Self-Evaluation Scale (SASS), OR: Odds ratio

Discussion

In this study, the Eyes Task and Hinting Tasks were administered in patient and control groups to evaluate the socio-perceptive and socio-cognitive paradigms of ToM deficit, respectively.

According to total scores of both Eyes and Hinting Tasks, the patients in remission had significantly impaired mental comprehension compared to healthy controls, suggesting decreased socio-cognitive and socio-perceptive function. These findings are consistent with a study by Bora et al. [16], in which healthy controls had a higher level of function in comprehending mental states compared to euthymic BD patients. The results of our study suggest that BD patients face difficulties in daily and working life in interpreting facial and body language of others and in rapid decision-making due to socio-perceptive and socio-cognitive deficits. This seems to be associated with decreased functions, even when patients are in remission.

Similarly, Bora et al. [16] found no association between age of onset and ToM deficit. Our study also found that the Eyes Task score decreased with an increase in several previous manic episodes, accounting for decreased socio-perception. These findings, together with data from other studies, are indicative that neuronal loss in the brain is associated with many previous episodes rather than early-onset [17-19].

Upon screening the literature, we did not encounter any study which reported an association between age and socio-perceptive paradigm of ToM in BD patients. Although the small patient sample of our cross-sectional study included many

confounding factors such as intelligence, our study was the first to show that socio-perceptive deficit increased with age.

Some studies show that the WAIS-R intelligence test also measures reasoning [20-23]. Evaluation of our subjects' WAIS-R test results revealed that BD patients in remission had significantly impaired reasoning compared to healthy controls. This finding is consistent with the study by Wolkenstein et al. [24], indicating that the patient group had more reduced performance in the integration of conceptual information (reasoning) regarding other people, compared to the control group.

Frequent symptoms of anxiety in patients with chronic illness [25-26] has led to the questioning of the association between levels of anxiety and ToM. Therefore, anxiety levels of both groups were evaluated using BAI to find that it was significantly higher in the patient group. Correlation between BAI scores and Hinting and Eyes Task was evaluated, and no significant correlation was determined between anxiety levels and ToM deficit in BD patients in remission. This also led us to believe that ToM deficit may occur regardless of anxiety levels in BD patients in remission.

It is known that individuals acquire ToM ability required to adapt to their social environment and use this ability to solve problems encountered in their daily lives [27,28]. Therefore, patients with ToM deficit face difficulties in daily adaptation and socialization [29]. In this study, SASS was used to measure the social functionality of patients and healthy controls to reveal a significant difference between the groups. This finding is consistent with the literature [30].

WAIS-R test results were correlated with both the Hinting Task and Eyes Task tests. This connotes that reasoning ability is also associated with ToM. The deficit in reasoning causes difficulty in integration of conceptual information. It was inferred that both perceptual and cognitive impairments in these individuals occur as a result of this difficulty. Furthermore, evaluation of patients and healthy controls revealed that there was a correlation between the Hinting Task and Eyes Task, suggesting that socio-perceptive and socio-cognitive paradigms of ToM may be interrelated.

Limitations

The sample was few, making it challenging to generalize. Since patients were undergoing medical treatment during the study period, the association between clinical evaluation scales and cognitive functions could not be ruled out.

Conclusion

It was determined that the ToM deficit occurs independently from variables such as gender, social functionality level, anxiety levels, and history of depressive episodes. Socio-perceptive ToM function was inversely related to age and number of manic episodes. Reasoning ability positively impacted both socio-perceptive and socio-cognitive paradigms of ToM. ToM deficit also seems to be an essential factor distinguishing BD patients from healthy individuals. This is possible evidence that ToM deficit plays a role in the essential pathology or affects the presence, or even onset, of BD.

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Factors influencing malnutrition risk in hospitalized pediatric patients and the application of STRONGkids scoring

Hastanede yatan pediatrik hastalarda yetersiz beslenme riskini etkileyen faktörler ve STRONGkids skorlaması uygulaması

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Abstract

Aim: A significant factor affecting the response to treatment in children is malnutrition. To reduce its risk and morbidity, necessary precautions should be taken on the first day of hospitalization. It is highly essential to obtain clues that assist with the early detection of malnutrition at the time of hospitalization. In this study, we aimed to show the risk factors, body measurements and the importance of a scoring system in its early detection and evaluation. To this end, we examined the accuracy of the STRONGkids score, which is a simple, useful, and practical scoring system, in detecting the risk of malnutrition.

Methods: Children between 0-18 years of age without any chronic diseases who were hospitalized due to acute infection were included in this retrospective cohort study. Those with chronic illnesses were left out of scope of our research. The duration and frequency of hospitalization, maternal age, number of births, birth weight, duration of breastfeeding and its continuation, transition period of supplemental nutrition intake, respective weights measured at the time of hospitalization and discharge were evaluated. By using Gomez and Waterlow, malnutrition degree and STRONGkids score were calculated and the risk of malnutrition was determined.

Results: Among all, 61% of the children included in the study were males. While the mean age was 34.67 (39.95) months, 84.62% of the children's age was less than or equal to 60 months and 15.38% were aged over 60 months. Based on the STRONGkids scores, 55.77%, 31.41% and 12.82% of the included cases were low, moderate, and high-risk in terms of malnutrition, respectively. The length of hospitalization, breastfeeding duration and maternal age were related with middle arm circumference.

Conclusion: Malnutrition risk should be evaluated together with various risk factors rather than one. The definition and classification of malnutrition vary based on the method used. Middle arm circumference can be used together with STRONGKIDS score in estimating the duration of hospitalization and the level of malnutrition.

Keywords: Child, Malnutrition, STRONGkids, Gomez, Waterlow

Öz

Amaç: Çocuklarda tedaviye yanıtı etkileyen önemli bir faktör malnutrisyondur. Hastaneye yatışın ilk gününde malnutrisyon açısından gerekli önlemlerin alınması malnutrisyonu önleyecek ve morbiditeyi azaltacaktır. Bu amaçla hastane yatışında malnutrisyonun erken saptanmasını sağlayacak ip uçlarına ihtiyaç vardır. Bu çalışmada malnutrisyonu erken tesbit etmede ve değerlendirmede göz önünde bulundurulması gereken risk faktörlerini, vücut ölçümlerini ve skorlama sisteminin önemini göstermeyi amaçladık. Bu amaçla da basit, kullanışlı ve pratik bir skorlama olan STRONGkids skoru tercih edilerek malnutrisyonu gösterme başarısı araştırılmıştır.

Yöntemler: Bu çalışma retrospektif bir kohort çalışmasıdır. Bu çalışmanın denekleri 0-18 yaşları arasında herhangi bir kronik hastalığı olmayan çocuklar iken, altta yatan kronik hastalıkları olan hastalar araştırmamızın dışında bırakılmıştır. Akut enfeksiyon nedeniyle hastaneye yatırılan pediyatrik hastalar çalışmaya alındı. Hastanede yatış süresi ve sıklığı, anne yaşı, doğum sayısı, doğum kilosu, emzirme süresi ve emzirmenin devamı, ek besin alımının geçiş süresi, hastaneye yatış ve taburculuk sırasında ölçülen ilgili ağırlıklar değerlendirildi. Gomez ve Waterlow kullanılarak yetersiz beslenme derecesi ve STRONGkids skoru kullanılarak yetersiz beslenme riski belirlenmiştir.

Bulgular: Çalışmaya dahil edilen çocukların %61'i erkek, %39'u kadındı. Yaş ortalaması 34,67 (39,95) aydı. Çocukların %84,62'si 60 aydan küçük ve %15,38'i 60 ayın üzerindedir. Hastaların STRONGkids değerlendirmesi olguların %55,77'si için düşük, %31,41'i için ılımlı ve %12,82 yüksek risk grubu olarak değerlendirildi. Orta kol çevresi ile hastanede yatış süresi, emzirme süresi ve anne yaşı ilişkili bulunmuştur.

Sonuç: Malnutrisyon riski, tek bir risk yerine çok yönlü risk faktörleri ile birlikte değerlendirilmelidir. Malnutrisyon tanımı ve sınıflandırılması kullanılan yönteme göre değişmektedir. Orta kol çevresi, hastaneye yatış süresini ve yetersiz beslenme düzeyini tahmin etmede STRONGkids skoru ile birlikte kullanılabilir.

Anahtar kelimeler: Çocuk, Malnutrisyon, STRONGkids, Gomez, Waterlow

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Introduction

Malnutrition is a change in the balanced body composition due to a lack of nutrition [1]. Protein-energy malnutrition (PEM) remains a major health problem in less developed countries. Nearly, 60% of pediatric mortality under the age of five is due to malnutrition [2]. Deaths due to diarrhea and lower respiratory tract infections, which are responsible for pediatric deaths in developing and underdeveloped countries, may occur twice as more frequent in case of malnutrition. Clinical findings vary depending on the duration and severity of the nutritional deficiency, quality of nutrition as well as factors unique to the patient (i.e., age, underlying chronic disease, acute infections, etc.). Heavily malnourished patients can be easily noticed during hospitalization and clinical examinations. On the other hand, it may take a longer time to diagnose moderately or mildly malnourished patients. In this case, the nutrition plan of each patient should be adjusted by the doctor, energy needs should be determined, anthropometric measurements and biochemical parameters should be analyzed [3,4]. The degree of malnutrition is determined by Gomez and Waterlow's classifications in children with protein-energy malnutrition [5,6]. In developed countries, PEM emerges due to hospital stay and insufficient nourishment following underlying chronic diseases and surgical procedures [7,8]. In underdeveloped countries, on the other hand, PEM develops due to errors in nutritional content or inadequate and low-quality malnutrition as well as frequently recurring infections [9]. Although the rate of malnutrition is lower in studies conducted at separate times and in different regions of Turkey, malnutrition remains significant for both healthy and hospitalized children.

The European Society of Clinical Nutrition and Metabolism recommends a nutritional screening guide for adult patients; however, this guideline is not intended for pediatric patients [10]. Clinical scales that determine the nutritional risk of adult patients have been available for many years [11]. Similar clinical scales have been developed for hospitalized children and tested in small cohort groups [12,13]. One of these scales in determining the risk of malnutrition is STRONGkids [5,15]. The STRONGkids score includes 4 parameters: Subjective clinical evaluation, nutritional status, presence of underlying high-risk diseases, nutritional intake, and loss assessment (diarrhea, vomiting, inadequate weight gain or loss). Therefore, we aimed to determine the rate and degree of malnutrition among patients aged between 0-18 years at the pediatric clinic of our hospital via Gomez and Waterlow classifications and evaluate the use and importance of the STRONGkids score in determining the risk of malnutrition.

Materials and methods

Study population

This study was approved by the Ethical Committee of Taksim Education and Research Hospital on 22.05.2019 (no: 73). Pediatric patients aged between 0-18 years who were admitted to the hospital due to acute infections such as pneumonia were included in the study. Patients with underlying chronic diseases, oncological patients, patients with immunodeficiency, congenital heart disease or chronic diarrhea were excluded. Patients who underwent surgery within a month, as well as those with frequent hospitalizations were also left out of the study population.

Definition of malnutrition

Height, weight and other measurements of the patients during hospitalization were measured and recorded by a physician from the pediatric clinic. Anthro and anthroplus programs were deployed for evaluating the results [16,17]. For acute malnutrition (AM), Weight-for-Height –(WFH) score or Body Mass Index (BMI) for age Z scores were analyzed. For Z scores ≥-3 and <-2, moderate malnutrition was considered and for Z scores below -3, severe malnutrition was denoted. For Z scores ≥-2, malnutrition was ruled out [10]. For chronic malnutrition (CM), height-for-age (HFA) Z scores of ≥-3 and <-2 were deemed moderate malnutrition and scores <-3 as severe malnutrition while scores ≥ 2 showed lack of CM per WHO classification [18]. Middle arm circumference, subscapular and triceps skinfold thickness were also measured with a caliper instrument in pediatric patients under 60 months. The duration and number of hospitalizations, maternal age, number of births, birth weight, breastfeeding status, breastfeeding duration, transition period of supplemental nutrition intake, admission weight and discharge weight were also assessed. The degree of malnutrition was determined with Gomez and Waterlow, and the risk of malnutrition was determined by STRONGkids scoring.

STRONGkids nutritional risk screening tool

Physicians assessed the risk of malnutrition with the STRONGkids survey conducted after direct examination of the patients [14]. STRONGkids is a malnutrition risk assessment tool comprising 4 distinct parameters: A subjective clinical evaluation (1 pt), a high-risk disease (2 pts), nutritional intake (1 pt) and weight loss or poor weight gain (1 pt). Patients who scored 0 in STRONGkids survey were categorized as “low-risk” as opposed to those considered “medium-risk” with a score ranging between 1 and 3 and “high-risk” with a score between 4-5.

Statistical analysis

Categorical variables were summarized in numbers and percentages. The normality assumption of the numerical variables was checked with the Kolmogorov Smirnov test. Mann Whitney U test was used in the comparison of two independent groups characterized by non-normally distributed numerical variables. Kruskall Wallis H test was used in comparisons of more than two independent groups of non-normally distributed numerical variables. Differences between the groups were evaluated by the Dwass-Steel-Critchlow-Fligner test. Pearson Chi-Square was used in 2x2 tables whereas Fisher's Exact Test was used in RxC tables. Z scores were calculated with the help of WHO Child Growth Standards SPSS Syntax File (https://www.who.int/childgrowth/software/en). Statistical analyses were carried out with the Jamovi project (2019, Jamovi (Version 0.9.5.12) [Computer Software] (Retrieved from https://www.jamovi.org) and statistical significance was set at *P*-value <0.05.

Results

Patient demographics and basic clinical features

One hundred fifty-six children were included in the study, for which the minimum number of patients was determined as 140 for statistical significance purposes. While 61% of these children were male and 39% were female, their mean age was 34.67 (39.95) months. 84.62% of the children were aged 60 months or younger and 15.38% were older than 60 months. The mean ages of the children who were younger and older than 60 months was 20.51(16.94) months and 112.58 (40.44) months, respectively. The STRONGkids evaluation of the children suggested that 55.77%, 31.41% and 12.82% were in the low, medium, and high-risk categories, respectively, in terms of malnutrition (Table 1).

The mean duration and number of hospitalizations, age of mothers, number of births, birth weights of patients, duration of breastfeeding, time until switching to supplementary nutrition, weight at time of hospitalization and hospital discharge weights of patients, height, arm circumference, skin thickness of triceps, subscapular skin thickness and BMI values are all presented in Table 2.

The relationship between STRONGkids score and malnutrition parameters

No significant differences were detected between the nutritional status, malnutrition status by height, BMI by age, nutritional status by arm circumference, arm circumference SDS by age, triceps skin thickness SDS by age and BMI SDS by age with regards to STRONGkids evaluations (P>0.05 for each) (Table 3).

Acute-chronic malnutrition and chronic malnutrition were observed in 24.6% and 21.9% of patients with low STRONGkids score according to Waterlow classification, respectively. In patients with high STRONGkids scores, the prevalence of acute-chronic malnutrition and chronic malnutrition were 37.5% and 18.75%, respectively.

Table 1: Distribution of gender, age and STRONGkids analyses of the children

		n (%)	Mean (SD)	Median [Min-Max]
Age (month)		156 (100)	34.67 (39.95)	18 [1-192]
	≤60	132 (84.62)	20.51 (16.94)	14 [1-60]
	>60	24 (15.38)	112.58 (40.44)	96 [66-192]
		n (%)		
STRONGkids	Low risk	87 (55.77)		
	Medium risk	49 (31.41)		
	High risk	20 (12.82)		
Gender	Boys	95 (61)		
	Girls	61 (39)		

SD: Standard deviation

Table 2: Demographic and anthropometric characteristics of the children

		Mean (SD)	Median [Min-Max]
Length of Hospitalization (month)		5.61 (3.12)	5 [1-19]
Frequency of Hospitalization		1.62 (1.18)	1 [1-11]
Mother's Age (years)		29.67 (6.42)	30 [17-47]
Number of Births		2.61 (1.42)	2 [1-8]
Birth Weight (gram)		2956 (656)	3007.5 [260-4460]
Breastfeeding Status n (%)	Yes n (%)	59 (37.82)	
	No n (%)	97 (62.18)	
Duration of Breastfeeding (month)		14.73 (9.07)	17 [0.25-36]
Weaning time (month)		5.68 (2.24)	6 [0-12]
Admission Weight (kg)		13.49 (9.53)	11 [2.75-68]
Discharge Weight (kg)		13.73 (9.59)	11.28 [3-68]
Height (cm)		88.66 (24.47)	84.5 [47-166]
Arm Circumference (cm)		15.14 (2.82)	15 [6-30]
Skin Thickness of Triceps (cm)		11.9 (4.64)	10.75 [4-35]
Subscapular Skin Thickness (cm)		7.73 (2.47)	7 [3-19]
BMI (kg/m²)		15.64 (2.4)	15.33 [9.98-24.7]

BMI: body mass index, SD: standard deviation, Descriptive statistics provided as count (%)

Table 3: Comparison of nutritional status, according to STRONGkids evaluations

		STRONGkids			P-value
		Low	Medium	High	
Weight by height %	Acute-chronic malnutrition n (%)	18 (24.6)	7 (17.07)	6(37.5)	0.831
Weight by age %	Chronic malnutrition n (%)	16 (21.9)	9 (21.95)	3(18.75)	
	Normal n (%)	34 (46.6)	22(53.6)	6 (37.5)	
Waterlow classification	Acute malnutrition n (%)	5 (6.85)	3 (7.32)	1(6.25)	
Weight by height	Stunted n (%)	5 (7.25)	5 (14.71)	0 (0)	0.601
	Stunted and Obese n (%)	0 (0)	1 (2.94)	0 (0)	
Height by age	Normal (n (%))	50 (72.46)	24 (70.6)	12 (85.7)	
Waterlow classification	Obese n (%)	1 (1.45)	1 (2.9)	0 (0)	
	Weak n (%)	12 (17.4)	3 (8.8)	2 (14.3)	
	Weak and Short	1 (1.45)	0 (0)	0 (0)	
BMI by age	Overweight n (%)	10 (13.7)	2 (4.9)	1 (6.25)	0.581
	Very weak n (%)	5 (6.85)	2 (4.9)	1 (6.25)	
	Morbid obese n (%)	1 (1.37)	1 (2.4)	0 (0)	
	Normal n (%)	46 (63.01)	30(73.2)	13 (81.25)	
	Obese n (%)	0 (0)	2 (4.9)	0 (0)	
	Weak n (%)	11 (15.1)	4 (9.76)	1 (6.25)	
Arm circumference nutrition status by age	Heavy malnutrition n (%)	3 (3.45)	2 (4.08)	0 (0)	0.926
	Normal n (%)	77 (88.5)	45 (91.8)	19 (95)	
	Malnourishment n (%)	7 (8.05)	2 (4.08)	1 (5)	
Arm circumference SDS by age (SDS)	<(-1) - ≥ (-2) n (%)	8 (12.5)	7 (18.42)	2 (15.38)	0.882
	≤ (-2) n (%)	6 (9.38)	2 (5.26)	1 (7.69)	
	≥ (-1) n (%)	50 (78.13)	29(76.3)	10 (76.9)	
Triceps skin thickness by age (SDS)	< (-1) - ≥ (-2) n (%)	2 (3.45)	1 (2.7)	3 (23.08)	0.061
	≤ (-2) n (%)	1 (1.72)	0 (0)	0 (0)	
	≥ (-1) SDs n (%)	55 (94.83)	36 (97.3)	10 (76.92)	
BMI SDS by age	< (-1) - ≥ (-2) n (%)	14 (19.18)	9 (21.95)	5 (31.25)	0.712
	≤ (-2) n (%)	16 (21.92)	6 (14.63)	2 (12.5)	
	≥ (-1) n (%)	43 (58.9)	26(63.4)	9 (56.25)	

BMI: body mass index, SDS: standard deviation score

A significant relationship was detected between the mean length of hospital stay and middle arm circumference (P=0.015). Accordingly, the median length of stay in children with normal nutritional status was substantially shorter than those with severe malnutrition and malnutrition (Table 4). There were no significant differences between nutritional status, malnutrition status by height, BMI by age, arm circumference by age, triceps skin thickness by age, and median length of stay according to BMI assessments (P>0.05 for each).

The mean maternal age of the children and arm circumference by age differed significantly with regards to nutritional status (P=0.026, P=0.041, respectively). Accordingly, the mean age of the mothers of the children with normal arm circumferences by age was significantly higher than that of the malnourished children by age. The median duration of breastfeeding was significantly higher in children with normal nutritional status by arm circumference (P=0.003). The median duration of breastfeeding was similar with respect to nutritional status, malnutrition status by height, BMI by age, arm circumference by age, triceps skin thickness by age, and BMI by age (P>0.05 for each) (Table 4).

Table 4 shows no significant differences between the median values of the nutritional status, malnutrition status by height, BMI by age, nutritional status by arm circumference for age, arm circumference by age, triceps skin thickness by age, and transition to supplemental food by BMI assessments by age (P>0.05 for each) of the children included in the study.

No significant differences were found between the gender and age ratios of children in this study Likewise, in terms of STRONGkids evaluations, the medians of body weight, admission body weight, height, BMI, weight difference from admission-hospital discharge, duration and number of hospitalizations, maternal age, number of births, birth weight, duration of breastfeeding and duration of transition to supplementary nutrition were similar (P>0.05 for each) (Table 5).

Table 4: Comparison of hospitalization length based on nutritional status of the children

		Hospitalization Length (days)	*P*-value	Mother Age (years)	*P*-value	Breastfeeding Duration (month)	*P*-value	Weaning Time (month)	*P*-value
Weight by height %	Acute-chronic Malnutrition	6 [4-8]	0.147	27.29 (6.56)	0.282	10.5 [4.5–20]	0.915	6 [4.5-6]	0.309
Weight by age %	Chronic malnutrition	5 [4-8.5]		30.04 (6.03)		18 [3–24]		6 [4-6]	
Waterlow classification	Normal	4 [3-6]		28.73(5.3)		16 [8–18]		6 [6-6]	
	Acute malnutrition	5.5 [4-7.5]		28 (6.89)		10.5 [5.17–21]		6 [5-7.5]	
Weight by height	Stunted	7.5 [5-14]	0.055	30.5 (6.96)	0.297	18 [3–24]	0.334	6 [5-6]	0.083
Height by age z score	Stunted and Obese	3 [3-3]		36		[-]		0 [0-0]	
Waterlow Classification	Normal	5 [4-6]		28.73 (5.35)		17.5 [9–18]		6 [5-6]	
	Obese	5 [4-6]		29 (1.41)		8 [7–9]		7.5 [6-9]	
	Weak	6 [5-8]		27.41 (7.76)		5 [5–6]		6 [5-6]	
	Weak and Stunted	7 [7-7]		23		2 [2h2]		0 [0-0]	
BMI by age	Overweight	4 [3-5]	0.063	28.54 (4.12)	0.770	17 [10-18]	0.564	6 [5-6]	0.319
	Very weak	5.5 [3-9]		29.38 (9.87)		6 [6-6]		6 [1-6]	
	Morbid obese	3.5 [3-4]		33(4.24)		7 [7-7]		3 [0-6]	
	Normal	5 [4-7]		28.62 (5.67)		18 [8-20]		6 [5-6]	
	Obese	9 [6-12]		25 (4.24)		9 [9-9]		7.2 [5.5-9]	
	Weak	6 [5-8]		28.44 (6.88)		5 [2-24]		6 [5-6]	
Nutritional status by arm circumference	Heavy malnutrition	8 [6-13]	0.015*	30.2 (6.57)	0.026	2 [2-2]	0.003	6 [5-6]	0.095
	Normal	5 [3-7]		30.03 (6.39)		18 [9-24]		6 [5-6]	
	Malnourishment	7.5 [4-11]		24.4 (4.9)		3 [1-5]		5 [4-5]	
Arm circumference	< (-1) - ≥ (-2)	5 [4-7]	0.157	25.59 (5.27)	0.041	9 [2-16]	0.153	6 [4-6]	0.165
SDS by age	≤ (-2)	8 [5-8]		28.78 (5.97)		5 [3-22]		6 [5-6]	
	≥ (-1)	5 [3-7]		29.61 (5.88)		18 [9-19]		6 [5-6]	
Triceps skin thickness	< (-1) - ≥ (-2)	4 [3-8]	0.219	28 (3.03)	0.332	13.5 [5-22]	0.368	6 [5-6]	0.889
SDS by age	≤ (-2)	13 [13-13]		22		2 [2-2]		6 [6-6]	
	≥ (-1)	5 [4-7]		29.08 (6.03)		16.5 [8-19]		6 [5-6]	
BMI	< (-1) - ≥ (-2)	5.5 [4-8.5]	0.103	26.43 (4.89)	0.073	18 [6.5-23]	0.269	6 [5-6]	0.128
SDS by age	≤ (-2)	6 [5-8]		28.75 (7.79)		5 [2.5-15]		6 [4-6]	
	≥ (-1)	5 [4-7]		29.41 (5.47)		16 [8-18]		6 [5-6]	

* *P*<0.05, Kruskal-Wallis H test applied, Descriptive statistics provided in medians (inter-percentile ranges). BMI: Body mass index, SDS: Standard deviation score

Table 5: STRONGkids analysis of the children

	STRONGkids			*P*-value
	Low	Medium	High	
Gender, count (%)				
Male	50 (57.47)	35 (71.43)	10 (50)	0.157
Female	37 (42.53)	14 (28.57)	10 (50)	
Age (month), mean. (SD)	33.25 (39.92)	37.1 (43.17)	34.9(32.78)	0.652
Age, count (%)				
00-05 months	16 (18.39)	3 (6.12)	2 (10)	0.831
06-11 months	16 (18.39)	11 (22.45)	4 (20)	
12-23 months	17 (19.54)	11 (22.45)	3 (15)	
24-35 months	10 (11.49)	7 (14.29)	2 (10)	
36-47 months	5 (5.75)	4 (8.16)	3 (15)	
48-59 months	5 (5.75)	5 (10.2)	1 (5)	
60 months	5 (5.75)	1 (2.04)	1 (5)	
≥60 months	13 (14.94)	7 (14.29)	4 (20)	
Age (month), mean. (SD)				
>60 months	13 (14.94)	7 (14.29)	4 (20)	0.825
≤60 months	74 (85.06)	42 (85.71)	16 (80)	
Admission weight (kg)	10.6 [7-15.7]	12 [9.4-14.5]	11.58 [7.6-16.83]	0.449
Discharge weight (kg)	10.8 [7.23-15.7]	12 [9.6-14.2]	11.9 [7.65-16.93]	0.488
Height (cm)	82 [68.5-101]	87 [75-99]	85.5 [74.5-106]	0.361
Body mass index	15.56 [14.05-17.28]	15.59 [14.42-16.53]	14.94 [14.1-15.84]	0.571
Admission-Discharge weight difference (kg)	0.2 [0-0.4]	0.01 [-0.05-0.4]	0.16 [0-0.45]	0.181
Hospitalization duration (days)	5 [3-7]	5 [3-6]	5.5 [4-8]	0.624
Number of hospitalizations	1 [1-2]	1 [1-2]	1 [1-1]	0.364
Mother age (years)	30 [24-33]	29 [25-34]	31.5 [27.5-35.5]	0.571
Birth number	2 [1-4]	2 [2-3]	3 [2-4]	0.241
Birth weight (gram)	3070 [2750-3400]	3000 [2750-3250]	3000 [2850-3300]	0.907
Breast feeding duration	12 [6-18]	18 [9-24]	13 [6-22]	0.379
Weaning time	6 [5-6]	6 [5-6]	6 [6-6]	0.474

SD: Standard deviation, In descriptive statistics, categorical variables denoted with counts (%) and numerical variables with mean (standard deviation) and medians [inter-percentile range]

Discussion

Malnutrition remains an important health problem in hospitalized children in developing countries. Studies have been carried out for many years to determine the risk factors. PYMS and STAMP scores include anthropometric measurements, while STRONGkids classification also includes subjective criteria. Although there are similar steps in the scoring of these three methods in children, there are significant differences in the assessment [19]. While PYMS and STAMP include anthropometric measurements and may seem more successful in detecting malnutrition patients, STRONGkids is a more practical and useful method for determining malnutrition risk. Malnutrition rates ranging from 31.8% to 56.6% among hospitalized pediatric patients have been previously reported in Turkey [20]. These rates turn out to be much higher than reports from Germany, France, UK, and the US with results varying from 6% to14% [21]. In a similar study conducted in Turkey, 1513 hospitalized pediatric patients were screened with regard to malnutrition. 11.2% of the subjects had acute and 16.6% of the children had chronic malnutrition [22]. In our study, the chronic malnutrition rate was approximately 21% while the acute malnutrition rate was detected around 6.5%. A demographics and health survey conducted in 2018 on 2568 children below 5 years of age assessed the height and weight measurements of 1951 subjects and determined that less than 2% of them were malnourished whereas severely malnourished subjects accounted for less than 1% of the survey population [23].

In our study, the malnutrition rate was 21.9% in low-risk patients and 37.5% in high-risk patients according to STRONGkids, and these findings are consistent with studies and data from across the country. In the study by Joosten and Hulst, eight pediatric malnutrition screening tools were identified, and eight validation studies were incorporated. The authors defined only two tools (STRONGkids and PYMS) as the most practical and reliable [24]. In this meta-analysis, the most reliable scoring in terms of assessing children's nutritional risk and condition was noted as PYMS. Another study confirming malnutrition

screening tools for inpatients containing a meta-analysis was carried out by Huysentruyt et al [25]. In this study, four malnutrition screening tools (PYMS, STRONGkids, STAMP and PNRS) and 15 validation studies were reviewed. Authors of the study had difficulty in comparing the results while evaluating them since these studies were heterogeneous in nature. Therefore, they were not able to state the superiority of a single screening tool over other malnutrition screening methods. In another meta-analysis conducted by Teixeira and Viana, 5 malnutrition screening methods (PYMS, STRONGkids, STAMP, PNST and SGNA) were compared. In that study, authors displayed that STRONGkids and STAMP methods had the best clinical performance. On the other hand, STRONGkids scoring alone was not statistically sufficient to highlight the risk of malnutrition in our study. However, middle arm circumference as a simple additional measurement method was beneficial in assessing the malnutrition risk.

In studies conducted by Moeeni et al. [26] STRONGkids is described as a reliable and effective scoring method for showing the malnutrition risk. In our study, there was no significant relationship between malnutrition status of the three risk groups that were determined according to the STRONGkids score. However, the difference in acute-chronic malnutrition rates is remarkable in patients with low and high-risk scores.

The duration of hospitalization correlates with the middle arm circumference in indicating the malnutrition status of hospitalized children. In other words, the middle arm circumference of the hospitalized patients was lower as expected. The undisputed benefit of breastfeeding also draws attention to our study. As breastfeeding duration increased, malnutrition was observed less frequently. Middle arm circumference was higher in children who were breastfed. Similarly, the risk and rate of malnutrition were also lower. In another study conducted in Turkey, no significant relationship was found between malnutrition rate and age, sex, maternal age, number of maternal births and duration of breast milk intake [27]. In our study, the maternal age of the severely malnourished patients based on middle arm circumference was found to be high. Furthermore, patients with severe malnutrition based on BMI had longer periods of hospital stay. Similarly, in a study conducted with 157 children in Australia, it was observed that the length of hospital stay was longer in patients with malnutrition [28].

Limitations

To prevent any effect on malnutrition measurements and risk factors, patients with chronic diseases were not included in this study. However, a comparison group consisting of patients with chronic diseases could be drawn. Thus, the number of patients with high STRONGkids score could possibly be higher. The sociocultural level of families is also effective in the development of malnutrition. This variable is estimated by looking at factors such as the number of maternal births, breastfeeding duration, and birth weight. However, families could then be grouped as low, medium, and high groups based on the sociocultural level and subsequently, an intergroup comparison of STRONGkids score could also be made.

Conclusion

We believe that the use of more than one method rather than a single method or tool in determining malnutrition and malnutrition risk will provide more accurate and predictable results. STRONGkids scoring is a practical and useful method, and when evaluated together with malnutrition measurements, it provides promising concrete data for early detection of malnutrition and necessary precautions. Middle arm circumference is also a supplementary and practical measurement method for estimating malnutrition and length of hospital stay.

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Pregnancy outcomes in patients with MTHFR gene polymorphism: A case series

MTHFR gen polimorfizmi olan hastalarda gebelik sonuçları: Vaka serisi

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Abstract

Aim: Based on the literature, MTHFR polymorphism is common among the general population and is controversial in terms of treatment, as it is poorly associated with pregnancy complications. In this study, we aimed to investigate the relationship between treatment and pregnancy outcomes in patients with MTHFR polymorphism.

Methods: The data of 48 patients who were diagnosed with MTHFR C677T and A1298C polymorphism between June 2012 and April 2020 and followed up during their pregnancy were reviewed retrospectively. Demographic and clinical features of patients, pregnancy history, diagnosis, and perinatal complications were examined. Pre- and post-treatment clinical features of the patients were compared.

Results: Comparison of pre- and post-treatment pregnancy data of the patients revealed that live birth rates were significantly higher (pre-treatment: 9.4% post-treatment: 68.7%, *P*=0.001) and abortion rates were significantly lower after treatment (pre-treatment: 81.2%, post-treatment: 32.1%, *P*=0.001). Pregnancy complications were observed in 9 (18.3%) patients. It was observed that among patients with MTHFR gene mutation, live birth rates increased by 24.12-fold and by 3.76-fold for each year of decrease in the age of conception following treatment.

Conclusion: In pregnant women with MTHFR polymorphism, methionine-poor diet and medical treatment had a positive effect on pregnancy outcomes. It was also observed that among those with MTHFR gene polymorphism, young patients with MTHFR A1298C heterozygotes had the best treatment results.

Keywords: MTHFR C677T, MTHFR A1298C, Treatment, In-vitro fertilization, Abortion, Complication

Öz

Amaç: Literatürde MTHFR polimorfizminin genel popülasyonda sık görüldüğü, gebelik komplikasyonları ile zayıf ilişkili olduğu için tedavi konusunda tartışmalı olarak görülmektedir. Bu çalışmada MTHFR polimorfizmi olan hastalara tedavi ile gebelik sonuçlarının ilişkisinin araştırılması amaçlanmıştır

Yöntemler: Haziran 2012-Nisan 2020 tarihleri arasında *MTHFR C677T* ve *A1298C* polimorfizmi tanısı olan, gebeliği boyunca takip edilen ve tedavi uygulanan 48 hastanın verileri geriye dönük olarak taranmıştır. Hastaların demografik ve klinik özellikleri; demografik özellikleri, gebelik öyküsü, tanı perinatal komplikasyonlar incelenmiştir. Hastaların tedavi öncesi ve sonrası verileri karşılaştırılmıştır.

Bulgular: Hastaların uygulanan tedavi öncesi ve sonrası gebelik verileri karşılaştırıldığında canlı doğum oranlarını tedavi sonrasında anlamlı yüksek olduğu(tedavi öncesi: %9,4, sonrası: %68,7, *P*=0,001), abort oranlarının ise tedavi sonrasında anlamlı düşük olduğu gözlenmiştir(tedavi öncesi: %81,2, sonrası: %32,1, *P*=0,001). Hastaların toplam 9'unda (%18,3) gebelik komplikasyonu gözlenmiştir. *MTHFR* gen mutasyonu olan hastalardan tedavi sonrasında *MTHFR A1298C* heterozigot olanların 24,12 kat, gebe kalma yaşında her bir azalma için 3,76 kat gebeliğin canlı doğum ile sonuçlandığı gözlenmiştir.

Sonuç: MTHFR polimorfizmi olan gebelerde metiyoninden fakir diyet ve medikal tedavinin gebelik sonuçlarına olumlu etki ettiği kanaatine varılmıştır. Aynı zamanda MTHFR gen polimofizmleri içinden MTHFR A1298C heterozigot olan genç hastaların en iyi tedavi sonuçlarına sahip olduğu gözlenmiştir.

Anahtar kelimeler: MTHFR C677T, MTHFR A1298C, Tedavi, İn-vitro fertilizasyon, Abortus, Komplikasyon

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Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of Alanya Alaaddin Keykubat University, Faculty of Medicine (Date: 05/06/2020, No: 19-23). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
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Introduction

Methylenetetrahydrofolate reductase (*MTHFR*) is one of the enzymes involved in the amino acid metabolism and catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a substrate for homocysteine remethylation to methionine [1]. The *MTHFR C677T* and *A1298C* single-nucleotide polymorphisms of the *MTHFR* gene is common in the general population and their prevalence varies among populations [2]. These common mutations of the *MTHFR* result in a thermolabile variant of the enzyme with reduced activity in elevated temperatures, leading to increased homocysteine levels [3].

The increase in the homocysteine levels may cause impairment in the vascular smooth muscle cells and endothelium, disrupting the coagulation cascade and promoting thrombosis [4]. In addition, it induces a rapid autooxidation process, producing free radicals. Hyperhomocysteinemia becomes evident in the presence of reduced *MTHFR* enzyme activity, or folate, vitamin B6 and B12 deficiencies [5]. Folate deficiency causes cell cycle arrest in the S phase and an uracil misincorporation into deoxyribonucleic acid (DNA), leading to DNA double-strand breaks [6].

Recent studies have demonstrated that the *MTHFR C677T* and *A1298C* polymorphisms are common in women with recurrent pregnancy loss and the *MTHFR* gene structure has effects on fetal growth [7]. Also, folic acid supplementation before and during pregnancy with methionine-restricted diet has been shown to be beneficial to prevent pregnancy complications [8-10].

In the literature, there is a limited number of studies showing an association between the *MTHFR* gene polymorphism and pregnancy complications and its treatment is still controversial [11-12]. In the present study, we aimed to investigate the possible relationship between *MTHFR* gene polymorphism and pregnancy outcomes.

Materials and methods

This study was conducted at a private Obstetrics and Gynecology clinic between June 2012 and April 2018. A written informed consent was obtained from each patient. The study protocol was approved by the Clinical Research Ethics Committee of Alanya Alaaddin Keykubat University, Faculty of Medicine (Date: 05/06/2020-No. 19-23), and it was conducted in accordance with the principles of the Declaration of Helsinki.

Study design and study population

In this single-center, retrospective case series study, medical data of pregnant women were reviewed and those who were diagnosed with *MTHFR C677T* and *A1298C* polymorphism were included. The *MTHFR* gene polymorphism analyses were performed for myriad reasons (miscarriages, preeclampsia, birth defects, family history etc.) using the real-time polymerase chain reaction (PCR) method. Patients with antithrombin III, protein C, or protein S deficiency and factor V Leiden, prothrombin *20210A* mutations, autoimmune disorders or severe systemic diseases which could affect the study results were excluded from the study. Finally, a total of 48 patients with *MTHFR C677T* and *A1298C* polymorphism were included in the study.

All patients underwent a thorough examination and treatment before planning the next pregnancy. After diagnosis for MTHFR mutations, at least three months before the next pregnancy, methionine-restricted diet was initiated with folic acid supplementation at a dose of 5 mg twice a week for patients with *MTHFR* gene polymorphisms. Once the pregnancy was confirmed, treatment was modified as methionine-restricted diet, folic acid (5 mg twice a week), enoxaparin sodium 40 mg/day, vitamin B1, B2, B6, B9, and B12 throughout pregnancy and acetylsalicylic acid 100 mg/day until the 36th weeks of pregnancy. Pre-treatment and post-treatment clinical features of the patients were compared.

Demographic and clinical characteristics of the patients including age, parity and gravida, history of pregnancy, laboratory test results, gestational age, birth weight, perinatal complications such as preeclampsia, fetal growth restriction (FGR), premature rupture of membranes (PROM), placental abruption, and stillbirth were noted.

Statistical Analysis

Statistical analysis was performed using the SPSS for Windows version 21.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in median (min-max) or number and frequency, where applicable. Conformity of the variables to normal distribution was assessed visually (histogram and possibility graphs) and with analytical methods using the Kolmogorov–Smirnov/Shapiro–Wilks tests. For paired nominal data, the McNemar test was used for the comparison of the groups. Logistic regression analysis was carried out by the retrospective elimination method to the groups with stillbirth using genetic and clinical data. A *P*-value of <0.05 was considered statistically significant.

Results

The median age of the patients was 32.5 (range 23 to 41) years. A total of 54.2% of the patients were treated with *in vitro* fertilization (IVF). The most common *MTHFR* gene mutations were heterozygous *MTHFR C677T* in 62.2% (n=30) and heterozygous *MTHFR* A1298C in %47.9 (n=23). Demographic and clinical characteristics of the patients are presented in Table 1.

Table 1: Baseline demographic and clinical characteristics of patients

		Median(min-max) (n=48)
Age, years		32.5 (23-41)
Duration of marriage		9.5 (3-14)
Spontaneous pregnancy		45.8% (n=22)
IVF pregnancy		54.2% (n=26)
Follow-up, months		16.0% (8-32)
MTHFR C677T	Homozygous	31.1% (n=15)
	Heterozygous	62.2% (n=30)
MTHFR A1298C	Homozygous	2.1% (n=1)
	Heterozygous	47.9% (n=23)

Data are given in number and percentage or median (min-max), unless otherwise stated. IVF: in vitro fertilization, MTHFR: methylenetetrahydrofolate reductase

The number of parity and live births was significantly higher (*P*=0.001) and abortion rates were significantly lower after the treatment compared to pre-treatment rates (*P*=0.001). A comparison of pre- and post-treatment values are summarized in Table 2.

Nine (18.3%) patients had pregnancy complications. After the treatment, the rates of preeclampsia and FGR were both 8.4%. Post-treatment pregnancy complications are shown in Table 3.

The logistic regression analysis was used to predict risk factors for live birth in patients with *MTHFR* gene mutation. The analysis results were statistically significant (χ^2: 12.151, P=0.011) which explained 42.6% of all cases. The likelihood of live birth increased by 24.12 folds after treatment in patients with heterozygous *MTHFR A1298C* gene polymorphism. In addition, each decline in the maternal age resulted in a 3.76-fold increase in live births after treatment in these patients. In the present study, the highest and lowest maternal age were 41 and 23 years, respectively. The logistic regression analysis results are summarized in Table 4.

Table 2: Pre- and post-treatment values

(n=48)	Before treatment		After treatment		*P*-value*
	% (n)	Median (min-max)	% (n)	Median (min-max)	
Gravida	85.4 (44)	2.00 (0-9)	97.9 (47)	2.00 (0-4)	0.410
Parity	18.8 (9)	0.00 (0-1)	70.8 (34)	1.0 (0-2)	0.001
Abortion	81.2 (39)	2.00 (0-8)	32.1 (17)	1.0 (0-2)	0.001
Live birth	9.4 (5)	0.00 (0-1)	68.7 (33)	0.0 (0-2)	0.001

Data are given in number and percentage or median (min-max), unless otherwise stated. McNemar test was used for statistical analysis.

Table 3: Pregnancy complications after the treatment

Variable	% (n)
Preeclampsia	8.4 (4)
FGR	8.4 (4)
PROM	4.2 (2)
Oligohydramnios	4.2 (2)
Intrauterine death	2.1 (1)

Data are given in number and percentage, unless otherwise stated. FGR: fetal growth restriction, PROM: premature rupture of membranes

Table 4: Logistic regression analysis results for the factors predicting live birth

Variable*	χ^2	R^2	*P*-value	OR	95%CI
	12.151	0.426	0.011		
MTHFR A1298C (heterozygous)			0.019	24.12	2.30-105.3
Age (annual decrease)			0.021	3.76	1.21-8.40

* Only included variables are shown. OR: odds ratio, CI: confidence interval, MTHFR: methylenetetrahydrofolate reductase

Discussion

In this study, 48 patients diagnosed with *MTHFR C677T* and *A1298C* polymorphism were evaluated and the most common *MTHFR* gene mutations were heterozygous *MTHFR C677T* and heterozygous *MTHFR A1298C* mutations. The live birth rates were significantly higher and abortion rates were significantly lower after treatment. Pregnancy complications were observed in nine patients. The likelihood of live birth increased by 24.12-fold after treatment in patients with heterozygous *MTHFR A1298C* gene polymorphism. In addition, each decline in the maternal age resulted in a 3.76-fold increase in live births after treatment in these patients. In this study, the highest maternal age was 41 years and the lowest maternal age was 23 years.

In a study, Turgal et al. [10] employed a similar treatment protocol before and after pregnancy in 617 patients with *MTHFR* gene polymorphism. The authors classified the patients according to subtypes of *MTHFR* gene polymorphism and compared them with a control group without *MTHFR* gene polymorphism. They found no statistically significant difference in the gestational weeks at birth among the groups. However, similar to this study, the abortion rates significantly decreased in patients with *MTHFR* gene polymorphism from 40% at baseline to 10.8% at the end of treatment, indicating nearly four-fold decrease. In addition, increased severity of *MTHFR* gene polymorphism was associated with increased abortion and perinatal mortality rates and decreased term delivery rates. In another recent study including 121 patients, the effect of low-molecular-weight heparin (LMWH) on obstetric outcomes of recurrent miscarriage patients complicated with *MTHFR* gene polymorphism was investigated. The patients were divided into two groups as those receiving only folic acid and iron and those receiving folic acid, iron, and prophylactic doses of enoxaparin sodium. The live birth rate was higher in patients receiving enoxaparin sodium. Similarly, Brenner et al. [13] examined the efficacy and safety of enoxaparin sodium at a dose of 40 to 80 mg/day and enoxaparin resulted in live birth in 46 (75%) of 61 patients.

In the current study, pregnancy complications were observed in nine patients. In the study of Turgal et al. [10], the most common pregnancy complications included FGR, oligohydramnios, PROM, preeclampsia, and placental abruption. However, the rate of these complications was lower than previous pregnancies and there was no significant difference in the complication rate between the patients with and without *MTHFR* gene polymorphism. In another study, no significant differences were observed in the rates of stillbirth, preterm delivery, chorioamnionitis, preeclampsia, and FGR between the patients receiving and not receiving enoxaparin sodium during pregnancy [14]. Of note, some authors concluded that it was not necessary to add LMWH to the routine treatment regimen to prevent pregnancy complications [15]. In a meta-analysis including 3,559 cases with unexplained recurrent pregnancy loss and 5,097 healthy controls, *MTHFR C677T* gene polymorphism, but not *MTHFRA1298C* gene polymorphism, was found to be associated with preeclampsia [16]. In a study conducted in Denmark with 91,661 pregnant women, the *MTHFR C677T* gene polymorphism increased the risk of preeclampsia by 1.27-fold; however, there was no significant increase in the rate of other pregnancy complications [17].

Review of the literature reveals that the most favorable results for predicting live birth can be obtained in the presence of heterozygous *MTHFR A1298C* gene polymorphism (odds ratio: 3.76 per year). Turgal et al. [10] found significant differences in the perinatal complications between the previous pregnancies of the patients in the homozygous polymorphism, heterozygous polymorphism, and healthy control groups. The patients with *MTHFR C677T* gene polymorphism had a significantly higher abortion rate than those with *MTHFR A129C* gene polymorphism (56.9% *vs.* 44.8%, respectively; P=0.039). In another study including 439 pregnant women, the correlation between the *MTHFR C677T* gene polymorphism and IVF outcomes was investigated [18]. The presence of heterozygous *MTHFR C677T* gene polymorphism was associated with an improved embryo quality and increased likelihood of pregnancy than homozygous genotypes. Similarly, Ahangari et al. [19] evaluated the possible association between the *MTHFR C677T*, *A1298C*, *F2G20210A*, and *F5G1691A* genetic variants in Iranian women with recurrent miscarriage and found that the *MTHFR C677Tm* and *A129C* gene polymorphisms increased the recurrent pregnancy loss risk by 5.5 fold and 3.3 fold, respectively. In another case-control study conducted in India, recurrent early pregnancy loss was evaluated among 106 patients with the history of three or more recurrent early pregnancy loss and 140 healthy fertile controls with successful pregnancy outcomes [20]. The homozygous and heterozygous *MTHFR C677T* gene polymorphisms were associated with 6.30-fold and 1.96-fold

increased risks of idiopathic recurrent early pregnancy loss. Although the link between the *MTHFR* gene polymorphism and age in predicting live birth has not been clearly understood yet, some authors have proposed that advanced age is associated with reduced live birth rates [21]. In particular, age is of utmost importance in pregnancies in which IVF is used. The live birth rate has been reported as 43.7% in pregnancies in which IVF is used in the first cycle before 30 years of age; however, this rate tends to decrease to 10.7% in women aged 40 to 44 years [22].

Limitations

There are some limitations to our study. The single-center and retrospective design of the study with a relatively small sample size are the main limitations. Despite this limitation, the findings of this study are important because MTHFR polymorphisms are potential risk factors for negative pregnancy outcomes, and our findings contribute to the literature, which is controversial in terms of treatment.

Conclusion

These study results suggest that methionine-restricted diet, folic acid (5 mg twice a week), enoxaparin sodium 40 mg/day, acetylsalicylic acid 100 mg/day, vitamin B1, B2, B6, B9, and B12 throughout pregnancy exert positive effects on pregnancy outcomes in patients with *MTHFR* gene polymorphisms. In addition, the most satisfactory results can be achieved in younger patients with *MTHFR A1298C* heterozygous polymorphism. However, further large-scale, prospective studies are needed to establish a definite conclusion.

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Extraction and biological evaluation of external membrane vesicles of Brucella abortus as a candidate for brucellosis vaccine

Bruselloz aşısı için aday olarak Brucella abortus'un dış zar veziküllerinin ekstraksiyonu ve biyolojik değerlendirmesi

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Etik Kurul Onayı: Bu makale, insan katılımcılarla yapılan bir çalışma değildir. Hayvanlar üzerinde deney yoktur. Bu makalede, insan katılımcıları veya yazar tarafından gerçekleştirilen hayvanlar üzerinde yapılan hiçbir çalışma yoktur. Katılımcıların tanımlayıcı bilgisi yoktur.

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Abstract

Aim: Brucellosis is an endemic zoonotic disease affecting animal and human health. In the last several decades, much research has been performed to develop safer Brucella vaccines to control the disease. Outer membrane vesicles (OMVs) have been considered as immunogenic structures for a subunit vaccine to prevent human brucellosis. The aim of this study was to evaluate the external membrane vesicles of Brucella abortus as a candidate for brucellosis vaccine.

Methods: In this study *Brucella abortus*, S99 strain was used. Extraction of OMV after mass cultivation of Brucella abortus was performed by Ultracentrifugation and Sodium Dosoxycotinate. The SDS-PAGE method was used to observe the protein pattern and electron microscopy, to evaluate the physicochemical properties. The amount of LOS in OMV was also measured by LAL test. After determination of the protein concentration, mice were injected at a specific concentration and blood samples were obtained to evaluate the antibody. Finally, after serum isolation, the antibody production was measured by the ELISA method.

Results: The amount of protein present in OMV was 0.1 mg/ml. The size of OMV was 55 to 150 nm, and in the SDS-PAGE assessment, the protein range was >25 kDa. The LOS value in the LAL test was reported within the authorized range. Significant increase in IgG levels was observed after the first injection (P=0.001) compared to the control group, and in subsequent boosters as well. The highest response rate was observed in the second booster.

Conclusion: OMV maintains its spatial shape during extraction and has the potential to induce the production of a high degree of specific antibodies against Brucella abortus. For this reason, it can be considered as a candidate vaccine after examining clinical phases.

Keywords: External mucous vesicles, Brucella abortus S99, Brucellosis vaccine

Öz

Amaç: Bruselloz, hayvan ve insan sağlığını etkileyen endemik bir zoonotik hastalıktır. Son birkaç on yılda, hastalığı kontrol etmek için daha güvenli Brucella aşıları geliştirmek için çok araştırma yapılmıştır. Dış zar vezikülleri (OMV'ler), insan brusellozunu önlemek için bir alt birim aşı için immünojenik yapılar olarak düşünülmüştür. Bu çalışmanın amacı Brusella abortus'un dış zar veziküllerini bruselloz aşısı için aday olarak değerlendirmektir.

Yöntemler: Bu çalışmada Brucella abortus, S99 suşu kullanıldı. Brucella abortusun kitle kültivasyonundan sonra OMV ekstraksiyonu, Ultracentrifugation ve Sodium Dosoxycotinate tarafından gerçekleştirildi. SDS-PAGE yöntemi, fizikokimyasal özellikleri değerlendirmek için protein paternini ve elektron mikroskopisini gözlemlemek için kullanıldı. OMV'deki LOS miktarı da LAL testi ile ölçüldü. Protein konsantrasyonunun belirlenmesinden sonra farelere belirli bir konsantrasyonda enjekte edildi ve antikoru değerlendirmek için kan örnekleri alındı. Son olarak serum izolasyonundan sonra antikor üretimi ELISA yöntemi ile ölçüldü.

Bulgular: OMV'de mevcut protein miktarı 0,1 mg/ml idi. OMV'nin boyutu 55 ila 150 nm idi ve SDS-PAGE değerlendirmesinde protein aralığı >25 kDa idi. LAL testindeki LOS değeri yetkili aralıkta rapor edildi. İlk enjeksiyondan sonra IgG düzeylerinde (P=0,001) kontrol grubuna kıyasla ve daha sonraki güçlendiricilerde anlamlı artış gözlendi. En yüksek tepki oranı ikinci güçlendiricide gözlenmiştir.

Sonuç: OMV ekstraksiyon sırasında uzamsal şeklini korumaktadır ve Brucella düşüklerine karşı yüksek derecede spesifik antikorların üretimini indükleme potansiyeline sahiptir. Bu nedenle klinik fazları inceledikten sonra aday bir aşı olarak düşünülebilir.

Anahtar kelimeler: Dış mukoza vezikülleri, Brucella abortus S99, Bruselloz aşısı

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Introduction

Brucellosis is a zoonosis affecting approximately 500,000 people annually around the world. The disease remains endemic in many regions of the world including Latin America, Middle East, Africa, Asia, and the Mediterranean basin [1]. Research focused on the development of an ideal Brucella vaccine to prevent brucellosis in animals and humans has been performed since the beginning of twentieth century [2]. Currently, no licensed human or canine anti-brucellosis vaccines are available. In bovines, the most successful vaccine (S19) is only used in calves. Over the years, a wide variety of killed vaccines have been developed for protection against brucellosis. They have had limited acceptance and success. None have approached the protection levels afforded by live attenuated vaccines.[3]. Several antigenic fractions extracted from *Brucella* have been tested as a vaccine candidate, in association with a variety of adjuvants. Some of them included cell envelopes [4] and outer membrane proteins [5]. Vaccination is probably the most economic measure for control of brucellosis in endemic areas. Many countries have developed control measures for the eradication of the disease in livestock animal. These programs minimized the economic losses due to the abortion, infertility, and weak offspring and decreased milk production [6]. Presently, the vaccination programs are based on control of brucellosis mainly due to *B. melitensis* and *B. abortus* [7]. The use of the live-attenuated vaccines against brucellosis represents a risk due to its potential ability to revert to virulence, cause abortion in pregnant animals, and the fact that it is shed in milk. Live strains could infect people coming into contact with the vaccine for example, farmers, abattoir workers, and veterinarians. Smooth live attenuated vaccines suffer shortcomings such as residual virulence and serodiagnostic interference. Inactivated vaccines, in general, confer relatively low levels of protection. Recent developments to improve brucellosis vaccines include generation of knockout mutants by targeting genes involved in metabolism, virulence, and the lipopolysaccharide synthesis pathway, as well as generation of DNA vaccines, mucosal vaccines, and live vectored vaccines, which have all produced varying degrees of success. An ideal vaccine for use either in humans or in animals should meet the following criteria: It should be effective, avirulent and induce long-lasting protection [8]. Subunit vaccines, like recombinant proteins, are promising vaccine candidates because they are less biohazardous, well defined, avirulent, noninfectious, and nonviable [9]. The aim of this study was to evaluate the immunological properties of external membrane vesicles extracted from Brucella abortus in the animal model BALB/C.

Materials and methods

Bacterial strain

Brucella abortus strain 19 (S19) was obtained from the bacterial collection center. The culture was revived by inoculating on potato infusion agar (PIA) slant and incubating at 37°C for 72 hours, and subsequently plating on PIA plates to obtain a single colony.

Bulk massage

In order to achieve the proper cell mass for purification of OMV, a high volume of culture of bacteria should be prepared. At first, the bacterium was cultured in Brucella Agar, then the colonies were washed with buffer phosphate, transferred to Brucella broth medium and placed in a shaker incubator for 2 hours. Then the bacteria were transferred to fresh culture medium and kept at 37 °C for 24 hours. The microbial suspension was weighed in Brucella agar containing booths, thus a dephasic environment was provided for optimal growth of microorganisms, and again placed at 37 °C for one day and finally, the cell biomass was collected.

Extraction of OMV

Extraction of external membrane vesicles was performed on the basis of ultrasound diffusion and using solutions containing dezocyticulate and sucrose gradient. The Brucella passive cell body was centrifuged for about an hour at 6000 rpm at 4 °C. After washing twice with phosphate buffered saline (PBS pH=7.2), a solid mass of the cell was suspended in chloride buffer and homogenized for 30 minutes, after which the wet weight was determined. The suspension was centrifuged again at 6500 rpm for an hour at 4 °C. Cell suspension at 7.5 times of wet weight was suspended with a 0.1-m^3 buffer of triazole and 10 ml of ethylene diaminete tracycloacetic acid (EDTA). Then suspension was homogenized with a volume of 20/1 ratio, a 0.1 M Tris buffer solution containing 10mM EDTA and sodium deoxycholylate 100g/L and shaken vigorously. After 10 minutes, the cell mass was treated with sodium deoxycholate and separated by ultrasound diffusion for 1 hour at 16500 rpm at 4 °C. Then, cell pellet was centrifuged for 2 hours at 42,000 rpm at 4 °C and the suspension was obtained from a precipitate in a 0.1 molar buffer containing 10 mm EDTA and 5 g /L sodium, and shaken vigorously. After 10 minutes, the cell mass was treated with sodium deoxycholate and separated by ultrasound diffusion for 1 hour at 16500 rpm at 4 °C. Then, cell pellet was centrifuged for 2 hours at 42,000 rpm at 4 °C and the suspension was obtained from a precipitate in a 0.1 molar buffer containing 10 mm EDTA and 5 g/l sodium deoxycholate. For 2 hours, the clock was at 16500rpm and 4 °C. Then OMV was deposited in 15 ml of distilled water containing 3% soluble sucrose, passed through 0.2 micron filters to collect in sterile glass vials.

Electron microscopy

Membrane vesicles were ultrasonically treated to disperse the vesicles followed by attaching to Formvar/carbon-coated nickel grids. Grids were washed with a 0.01 M PBS supplement, 0.1% gelatin (PBG), and 0.5% BSA. The vesicles on the grids were fixed with 1% glutaraldehyde in PBS at 4°C for 60 minutes and negatively stained with 1% potassium phosphotungstate pH 7.5. The grids were examined using a Zeiss EM10C transmission electron microscopy operated at 80 KV.

Nanodrop

The standard concentration of the proteins of the extracted vesicles was measured using a nanodrape. The basis of this device is spectrophotometry.

Endotoxin determination

The biological activity of the endotoxin was measured using the QCL-1000® chromogenic Limulus amebocyte lysate (LAL) endpoint assay (Lonza, Walkersville, MD, USA). To this

end, 0.1 mL of LAL with 0.1 mL of the sample was incubated for 88 minutes at 38°C. Then, by adding 0.5 mL of the substrate, the mixture was incubated again for 3 minutes. Finally, after adding 0.1 mL glacial acetic acid solution, the reaction stopped. Optical density (OD) of the reaction mixture was determined by a spectrophotometer at 405 nm and the amount of Endotoxin in the sample was calculated using the standard curve.

LAL test

For the measuring the LPS in the sample, a Thermo Scientific Pierce LAL Chromogenic Endotoxin Quantitation Kit was used according to the manufacturer's protocol.

Pyrogenic test

The extracted external vesicle was tested on four healthy albino New Zealand rabbits. At the beginning of the study, the animal weight was limited between 1.8 and 3.8 kg. Three rabbits were used for testing and one for control. The OMV was injected into rabbit peripheral ear veins at a dose proportional to the rabbit weight. The animals' rectal temperature was measured using a digital thermometer. If the rabbit did not show a temperature rise of 0.6ºC or greater or the sum of the three single temperature increases did not exceed 1.4◦C, the test material was considered to have no toxicity.

Mice immunization

5 to 6-week-old female rats were used and randomly divided into two groups of ten each. One group received OMV at a concentration of 50 µg and the other group (control group) received PBS.

Evaluation of the level of total (IgG) antibody against OMV in immunized mice by ELISA

After blood sampling and serum collection, the level of antibody against the protein was evaluated by ELISA. Protein was prepared in PBS buffer at a concentration of 5 µg/100 µl. The mouse serum used was prepared in dilutions of 1: 250-1: 500-1: 1000 and 1: 2000. The mouse IgG concentration of 1.6000 was used and the samples were then read at 405nm wavelength.

Statistical analysis

Data were analyzed using Graphpad software, with which graph was depicted (San Diego, California USA). In addition, Analysis of variance and Tukey post-hoc test were used for comparing the means of groups and two by two comparisons were performed with SPSS version 20 (SPSS Inc. Chicago, IL, USA).

Results

Concentration study using Nanodrop

Nanodrop was used to estimate the concentration and quality of membrane vesicles extracted. Physicochemical analysis of vesicles extracted from Brucella abortus S99 revealed that the total protein content of membrane vesicles by nanodrop device was 1.42 mg/ml, which is acceptable.

Electrophoresis of membrane vesicles by SDS-PAGE

Electrophoretic Motion Analysis of Proteins in the Extracted Vesicles of Brucella abortus are shown in figure 1. According to the markers, the protein bands are in the 25 kDa region.

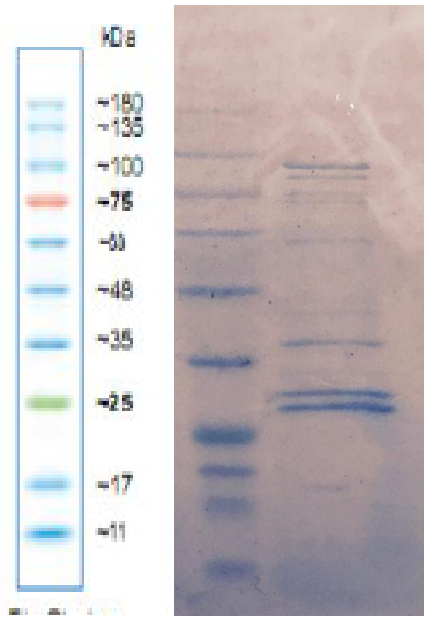

Figure 1: Protein pattern of outer membrane vesicles by SDS_PAGE method

Electron microscopy

The stability of the natural form of membrane vesicles at different stages of the purification process was investigated by electron microscopy. The spatial properties of the extracted membrane vesicles in negative contrast staining with the EM 900 electron microscope are shown below. As can be seen in the Figure 2, the extracted vesicle is about 50-50 nm and retains its spatial properties at various stages of extraction and purification.

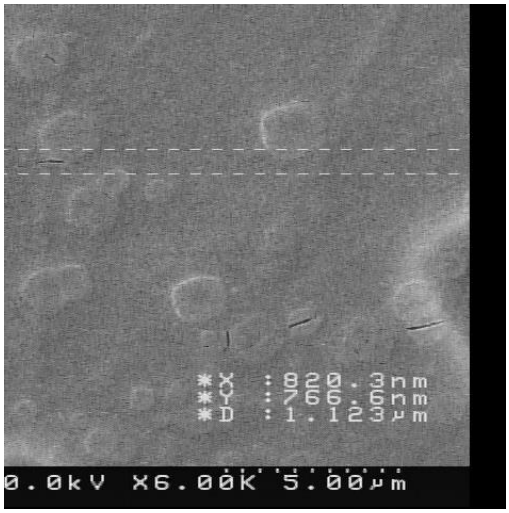

Figure 2: Electron micrograph of outer membrane vesicles

Determination of endotoxin levels in membrane vesicles by chromogenic Limulus amebocyte Lysate (LAL)

Results in this semi-quantitative test showed that the extracted vesicles were allowed to be used in the animal model within the safe limit (less than IU300).

Pyrogenic test

After the test, no significant increase in temperature was observed in rabbits, indicating a lack of pyrogenicity.

Evaluation of total IgG responses against OMV by ELISA

Results showed a significant increase in IgG antibody titers at all three doses compared to the control group (Figure 3). The highest response was seen on day 42 (the second injection booster) which showed a significant increase compared to the first injection and booster injection (P=0.001).

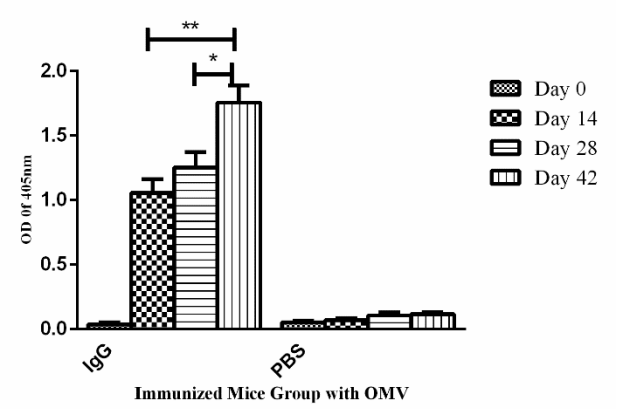

Figure 3: IgG antibody titer level against OMV Brucella on days 14, 28 and 42 after injection

Discussion

Control of zoonotic diseases in human populations has relied heavily on the control of animal disease. Over the last century, human brucellosis has been controlled by vaccination and culling within cattle, goat, and sheep herds. Despite past and current efforts to eradicate brucellosis, many human cases are reported annually worldwide [10].

Brucella can enter the host cell, especially macrophages, during its pathogenic process and grow and proliferate within these cells. In vaccination against Brucella infections in the animal model, attenuated live strains are usually injected [11]. The vaccine also has some disadvantages, such as abortion in pregnant animals and the possibility of bacterial secretion in vaccinated animal milk. The animal brucellosis vaccine is not an effective and safe vaccine against Brucella virulent strains. Therefore, extensive studies are currently underway to understand the protective mechanism against Brucella and the development of effective human Brucella vaccines [12]. Today, the control of brucellosis is based on the three principles of killing infected livestock, pasteurizing dairy products and vaccination. Human brucellosis vaccines, which are based on complete inactivation of the bacterium or live strains, are associated with two basic problems: First, they sometimes lead to disease, and second, to hypersensitivity reactions.

In recent years, immunogenicity with various antigens of Brucella species has been investigated in monovalent, conjugated, or recombinant forms. The key to designing a vaccine against this bacterium is to pay attention to the way of bacterial life [13].

The Brucella survival cycle in the body is intracellular, so only cellular immune responses are able to remove this bacterium from the body. In other words, the ability of macrophages to kill intracellular bacteria is mediated by the induction of this ability with the release of cytokines such as INF-γ. Therefore, it is important to select the antigen and the type of antigen-presenting cell unique to the body to stimulate the desired responses to eliminate this bacterium.

Protective immunity against brucellosis has been studied extensively in mouse models. From a clinical point of view, the most important strategy used to enhance the immunogenicity of compounds is the binding of a polysaccharide to a suitable protein vector, resulting in non-T lymphocyte-dependent antigen [14].

LPS has been selected as a potent protective antigen in all Brucella strains to induce non-T lymphocyte-dependent, T-dependent, and lymphocyte-induced responses by conjugating with a protein carrier and forming a hapten-carrier complex. The type of T lymphocyte response is very important. Stimulation of Th1 responses results in the secretion of cytokines such as INF-γ and stimulation of Th2 responses associated with antibody production. Although the presence of these antibodies may play a role in bacterial restriction, the importance of cellular response and cytokine production, including interferon-gamma, has priority in killing bacteria and clearing the body [15].

The outer membrane vesicles can be considered as a new vaccine candidate, due to the presence of various compounds including outer membrane proteins, lipopolysaccharide, peptidoglycan, and the recently discovered DNA and RNA in the OMV structure. It carries several bacterial native antigenic compounds and has therefore been considered for vaccine development. The remarkable properties of membrane antigens and their exposure to OMV have led to the physicochemical stability of its structure and therefore the protective and genomic properties of OMV have been confirmed by many bacteria [16]. In 2014, Acevedo et al., in a review of bacterial outer membrane vesicles and vaccine applications, demonstrated that OMVs were more applicable than previously understood and remain an important technology for the development of laboratory vaccines [17]. The LAL test showed the LPS level within the limit; although this macromolecule is a toxic compound, its small amount acts as a strong adjuvant. A previous study showed that discrepancy in the protein's bands could be used as protein effective biomarker for tuberculosis diagnosis. [18].

Limitations

Further research of the Molecular pathobiology and immunological properties would lead to the development of better and safer vaccines.

Conclusions

The results indicate that these structures may be suitable candidates for vaccination and be considered as a new generation of vaccines against Brucella infections, although further studies in this field are needed to evaluate antibody subclasses and responses.

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Demographic and clinical characteristics of children who were hospitalized and followed due to seizures

Nöbet nedeni ile yatırılan ve takip edilen çocuk hastaların demografik ve klinik özellikleri

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Abstract

Aim: Seizure is the most common neurological disorder of childhood. The causes of seizures in childhood, especially febrile convulsions (FC), is still not fully elucidated. In addition, diagnosis, follow-up and treatment are still controversial. In this study, we aimed to investigate the clinical/demographic features, laboratory results, electroencephalography and neuroimaging findings of children who were hospitalized and followed due to seizures.

Methods: This retrospective cohort study included 737 patients who were hospitalized and followed up due to seizures in the pediatric neurology department. Clinical features and laboratory results of the patients were evaluated.

Results: Among all, 53.1% of the patients who had febrile convulsions were males, 46.9% were females, and the mean age was 20.68 (5) months. The most important risk factors in febrile convulsion were positive family history (38.4%) and iron deficiency (42.9%). The most common source of infection was viral upper respiratory tract infections. While cerebrospinal fluid evaluations were normal in patients with ordinary febrile convulsions, that of 30 patients with complex febrile convulsions were coherent with meningitis. 437 patients were hospitalized with the diagnosis of epilepsy, among which 54.3% were males, and 45.7% were females. The mean age was 65.8 (54.8) months. Generalized tonic-clonic seizures were most common, while idiopathic epilepsy was the most frequently observed type. The most common risk factors in epilepsy patients were positive family history (26.2%), febrile convulsion (26.8%), and cerebral palsy (8.2%).

Conclusion: In this study, febrile convulsion and idiopathic epilepsy were the most determined causes of pediatric convulsion. Kinship marriage and positive family history are both the most important risk factors in febrile convulsions and epilepsy. Children with focal FC should be followed closely due to increased risk of epilepsy.

Keywords: Febrile convulsion, Seizure, Epilepsy

Öz

Amaç: Nöbet, çocukluk çağının en sık görülen nörolojik bozukluğudur. Çocukluk çağında nöbetlerin, özellikle febril konvülsiyonların nedenleri hala tam olarak aydınlatılamamıştır. Ayrıca tanı, takip ve tedavi halen tartışmalıdır. Bu çalışmada, nöbet nedeniyle hastaneye yatırılan ve takip edilen çocukların klinik özellikleri, laboratuvar sonuçları, elektroensefalografi ve beyin görüntüleme bulguları, tedavi yöntemleri ve demografik özelliklerinin araştırılması amaçlandı.

Yöntemler: Bu retrospektif kohort çalışmaya pediatrik nöroloji servisinde nöbet nedeniyle yatırılarak takip edilen 737 hasta dahil edilmiştir. Hastaların klinik özellikleri ve laboratuvar sonuçları retrospektif olarak değerlendirildi.

Bulgular: Hastaların 245'i febril konvülziyon, 437'si epilepsiydi. Febril konvülziyon geçiren hastaların %53,1'i erkek, %46,9'u kız, ortalama yaşları 20,6(5)aydı. Febril konvülziyon hastalarında en önemli risk faktörleri pozitif aile öyküsü(%38,4) ve demir eksikliği(%42,9) olarak belirlendi. En sık saptanan enfeksiyon kaynağı viral üst solunum yolu enfeksiyonlarıydı. Basit febril konvülziyon geçiren hastalarda beyin omurilik sıvısı değerlendirmeleri normalken, komplike febril konvülziyon geçiren 30 hastada menenjit ile uyumluydu. Epilepsi tanısı ile 437 hasta yatırılmıştı. Epilepsi hastalarının %54,3'ü erkek %45,7'si kadındı ve yaş ortalaması 65,8 (54,8) aydı. En sık jeneralize tonik klonik nöbetler görülmüştü ve en sık epilepsi tipi idiyopatik epilepsiydi. Epilepsi hastalarında en sık risk faktörleri pozitif aile öyküsü (%26,2), febril konvülziyon geçirme (%26,8) ve serebral palsiydi (%8,2).

Sonuç: Bu çalışmada çocukluk çağı nöbetlerinde en sık saptanan etiyolojik nedenler febril konvülziyon ve idiyopatik epilepsidir. Akraba evlilikleri ve pozitif aile öyküsü hem febril konvülziyonlarda, hem de epilepsi de en önemli risk faktörleridir. Fokal febril konvülziyon geçiren hastaların epilepsi gelişimi açısından yakın takibe alınmalıdır.

Anahtar kelimeler: Febril konvülsiyon, Nöbet, Epilepsi

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Introduction

A seizure is characterized by sudden, abnormal, and hypersynchronous discharge of cortical gray matter or brain stem neurons, sudden and temporary loss of consciousness, involuntary abnormal motor activity, sensory behavior, and autonomic dysfunction. The most common seizure type in childhood is febrile convulsion (FC), with an incidence of 2-5% [1,2]. Febrile convulsions are seizures that occur with fever, with no defined cause such as a central nervous system (CNS) infection, electrolyte imbalance, or poisoning in children older than 1 month of age who have not had a prior afebrile seizure. It is divided into two types as simple FC and complex FC, and occurs mostly around 18 months [3].

Epilepsy is sudden, iterative, and characteristically not triggered by an identifiable event. It is the most common neurological disease in childhood-adolescence. Epilepsy is most commonly seen in infancy. Its incidence decreases dramatically after the first year of life, and this decline continues throughout childhood [4]. In new clinical practice, epilepsy is defined by the presence of one of the following three conditions [5]:

1) At least two non-triggered (spontaneous) or reflex seizures with an interval of twenty-four hours

2) At least one non-triggered or reflex seizure and the risk of seizure recurrence within 10 years being similar to the risk in patients who had at least two untriggered seizures (at least 60%)

3) Presence of one of the epileptic syndromes

In our study, we aimed to investigate the seizure types, risk factors, and socio demographic characteristics of patients who were hospitalized and followed up due to seizures between January 2006-December 2010 at the Pediatric Health and Diseases Ward of our hospital.

Materials and methods

This retrospective cohort study includes 737 patients who were admitted to the pediatric neurology service of the Pediatric Health and Diseases Ward at Cumhuriyet University Medical Faculty Hospital between January 2006 and December 2010. Approval was obtained from the Ethics Committee of Cumhuriyet University Medical Faculty for the study (Approval date/number: 2010-06/09). Patients who were hospitalized and followed up due to seizures have been identified with scanned files from the hospital archive.

The patient's gender, age, parental consanguinity, family history of FC and epilepsy, gestational age, birth history, birth weight, additional diseases, seizure types, first seizure age, seizure frequency, treatment, neurological examination, EEG, imaging (computed tomography scan of the brain-CT or magnetic resonance imaging-MRI) and laboratory (complete blood count and routine biochemical tests, complete urinalysis, new-born screening results, cerebrospinal fluid results) results were compiled retrospectively from patient files.

Statistical analysis

TThe data in our study was uploaded to SPSS (version: 14.0) program. Chi-Square and Fisher's Exact Tests were used for determination of significance. Data were presented as numbers, mean and standard deviation, as necessary. $P<0.05$ was considered statistically significant.

Results

Among 737 patents included in the study, 245 patients had FC, 437 patients, epilepsy, and 55 (30 meningitis, 17 hypocalcemia, 5 hyponatremia, 3 hypoglycemia) patients had symptomatic seizures.

Among FC patients, 130 (53.1%) were males and 115 (46.9%) were females, with an overall mean age of 20.68 (5) months. The number of patients with complex and simple FC were 130 (53.1%) and 115 (46.9%), respectively. Consanguinity was detected between the parents of 54 patients (22%), 42 (17.1%) of which were 1st degree and 12 (4.9%) of which were 2nd degree kinship marriages. Ninety-four (38.4%) patients had a history of FC in their family. Family history (69/94) was significantly higher in the complex FC group than in the simple FC group (25/94) ($P=0.01$). Ninety-six (39.2%) patients had their first seizures before the age of one year, 111 (45.3%), between the ages of one and three years, and 38 (15.5%), between the ages of three and five years. The most frequent seizure type, generalized tonic-clonic seizures, were observed in 201 patients, followed by atonic seizures in 29 (11.8%), generalized tonic seizures in 9 (3.7%), clonic seizures in 4 (1.4%) and focal seizures in 2 (0.8%). Seventeen (6.9%) children were hospitalized with febrile status epilepticus (SE), among which ten (58.8%) were male, and 7 (41.2%) were female. Twelve had no seizure history while 5 had recurring FC.

Upper respiratory tract infections (URTIs) were the most common source of infection in 60% (147) of the patients (Table 1). The majority were considered viral upper respiratory tract infections based on examination and laboratory findings. One hundred and five (42.9%) patients had iron deficiency anemia.

Table 1: Fever causes of febrile convulsion patients

Fever causes	n	%
URTIs (viral/bacterial)	98/49	40/20
Pneumonia	28	11.4
EBV	3	1.2
UTI	23	9.4
AGE	25	10.2
Vaccine	6	2.4
STIs	4	1.6
Varicella	5	2.0
Sepsis	4	1.6
Total	245	100.0

URTIs: Upper respiratory tract infections, UTI: Urinary tract infection, EBV: Epstein Barr virus, AGE: Acute Gastroenteritis, STIs: Soft tissue infections

EEG was performed to 160 (65.3%) patients. EEG results were abnormal in 17% of those with complex FC and 4.3% of those with simple FC, the difference between which was significant ($P=0.02$). Prophylactic anti-epileptic medication was started in 138 (53.7%) cases. An afebrile seizure occurred during the follow-up of 14 FC patients (5.7%), all of which were diagnosed with epilepsy. All these patients had complex FC, the EEGs of all but one patient showed epileptic activity and 9 had focal seizures.

Computerized Brain Tomography (CBT), transfontanelle ultrasound and Magnetic Resonance Imaging (MRI) were performed to 49 (20%), 10 (4%) and 4 (1.6%) patients, respectively. All those who underwent imaging had febrile SE and complex FC. Benign external hydrocephalus, asymmetry in the lateral ventricles, arachnoid cyst, and

nonspecific nodular signal change were detected in 3 (1.2%), 2 (0.8%), 1 (0.4%) and 1 (0.4%) patients, respectively.

Among epilepsy patients, 251(54.3%) were male, and 211 (45.7%) were female, with an overall mean age of 65.8 (54.8) months. Forty (8.7%) patients were preterm, 416 (90%) were term and 6 (1.3%) were post-term. Seventy-four (16%) patients had a history of hypoxia during birth. Consanguinity was detected between the parents of 120 patients (25%), 106 (22.9%) of which were 1st degree and 14 (3%) of which were 2nd degree kinship marriages. One hundred and twenty-one (26.2%) patients had a history of seizures of their family, 100 (82.7%) of which had a history of FC, and 21 (17.3%), a history of epilepsy. In addition, 124 (26.8%) of epilepsy patients had a history of FC.

The seizure types of the patients are presented in Table 2. One hundred and forty-five (31.4%) patients were hospitalized with Status Epilepticus, among which no seizure histories were determined in 18 (12.4%). While 354 (76.6%) were using single anti-epileptic agents, 74 (16%) patients were taking 2 agents, and 34 (7.4%) were taking three or more.

Table 2: Seizure types of epilepsy patients

Seizure types	n	%
Partial		
Simple	15	3.4
Secondary Generalize	15	3.4
Complex	15	3.4
Generalized	12	2.7
Absence		
Tonic-clonic	269	61.6
Myoclonic	19	4.3
Tonic	13	3.0
Atonic	62	14.2
Lennox Gastaut Sydrome	3	0.7
Ohtahara Syndrome	1	0.2
Infantile Spasm	13	3.0
Total	437	100.0

One hundred and forty-nine (34%) epilepsy patients were considered to have idiopathic epilepsy. Neurological examinations of these patients were normal, and there were no concomitant diseases. The most common neurological disease was cerebral palsy (8.2%). Other commonly detected conditions included growth retardation in 36 (7.8%) patients, mental motor retardation in 29 (6.3%) patients, head trauma in 26 (5.6%), previous CNS (Central Nervous System) infection in 17 (3.9%), hydrocephalus in 7 (1.5%), undefined metabolic diseases in 7 (1.5%), Dyke Davidoff Masson Syndrome in 4 (0.4%), neurodegenerative diseases in 4, Rett Syndrome in 3 (0.6%), Glutaric Aciduria Type 1 in 3 (0.6%), Tuberous sclerosis in 2 (0.4%), kernicterus sequela in 2 (0.4%), and an intracranial mass in 1 (0.2%) patient. Cranial MRI was performed in 360 (77.9%) patients (Table 3).

Table 3: Cranial MRI findings of epilepsy patients

MRI findings	n	%
Normal	173	48
Ischemic gliotic lesion	40	11.1
Periventricular leukomalacia	38	10.5
Encephalomalasia	32	8.8
Atrophy	32	8.8
Nonspecific signal changes	14	3.8
Corpus callosum hypoplasia / agenesis	10/3	3.6
Hydrocephalus	7	1.9
Hypomyelination	4	1.1
Cerebrovascular disorders	4	1.1
Nodules/hamartoma compatible with tuberous sclerosis	2	0.55
Brain tumor	1	0.27

Discussion

Febrile convulsions are the most common pediatric seizures. Studies have reported that FC is more common in males compared to females. The male/female ratio has been reported as 1.46-1.8:1 in numerous studies [6-8]. In our study, the male/female ratio was 1.13:1, which was compatible with the literature. The first seizure is usually seen between 16 and 22 months [8-10]. In our study, the mean age of the first seizure was 20 months.

Although its etiology is still unknown, family history of FC, a disease of multifactorial-polygenic inheritance, was reported as 14.3-34% in first-degree relatives in numerous studies [6,8,11,12]. In our study, 38.4% of the patients had positive family history of FC, which supports familial predisposition.

The history of epilepsy in the families of patients ranges between 6.6-14% in previous studies [6,8,11,13]. In our study, the rate was 8.4%, coherent with the literature.

Especially in patients younger than one year of age, FC may be the only symptom of a central nervous system infection. The American Academy of Pediatrics suggests lumbar puncture for infants under 12 months of age presenting with simple FC, if not vaccinated against Haemophilus influenzae type B or Streptococcus pneumoniae or in case of antibiotic usage before the seizure [14]. However, in children with simple convulsions and normal neurological examinations, it is more preferred to use a follow-up approach without LP [8,15]. In our study, LP was performed to 79 patients with complex and simple FCs, and to 41 patients under 1 year of age. Central nervous system diseases were detected in 30 patients with complicated FC, and in none of the patients in the simple FC group. Based on our study, it may be suggested that stable patients with simple FC who had normal neurological examination findings can be followed without LP.

In febrile convulsions, the most common reason for fever is virus-induced URTIs [10]. Viral factors differ according to countries. Human herpesvirus (HHV-6) in the United States and Influenza A in Asian countries are the most frequently reported viral factors in FC [16,17]. In our country, according to a multicenter study by Carman et al. [18], at least one respiratory virus was detected in 82.8% of patients who had FC. In our study, active isolation studies have not been performed, but the most common reason for fever was viral URTIs based on physical examination and laboratory findings of the patients.

It is thought that low serum iron may lower the seizure threshold and lead to increased seizure occurrence in children with fever. In many studies, serum iron levels were low in patients with FC [8,19-21]. Iron deficiency anemia was detected in 105 (42.9%) of our patients in this study.

Anti-epileptic treatment is effective in preventing FC recurrence; however, the side effects may outweigh the benefits [3]. In particular, in simple FC, prophylactic long-term anti-epileptic usage is not recommended [22,23]. In our patient group, 132 patients (complex FC / simple FC 119/13) were treated with prophylactic phenobarbital treatment, and 12 patients (complex FC / simple FC 11/1) received intermittent rectal diazepam. The vast majority of patients undergoing treatment were complex FC patients. Although prophylactic long-term treatment is not recommended, the socio-economic level of the families, compliance with the treatment, and the geographical conditions of the region were effective in starting the treatment. In our study, the number of patients who started treatment was high, as

the socioeconomic level was low in the study area, and especially during winter, geographical access was frequently restricted.

Pediatric epilepsy is most commonly seen in nursing infants. Epilepsy decreases dramatically after the first year of life, and this decline continues throughout childhood [5]. As in FC, it is more common in males [24,25]. In our study, the male/female ratio was 1.18:1. The mean age of patients was 65.8 (54.8) months and 38.8% of the patients were under 2 years of age.

Many studies have shown that genetic factors make up about 40% of epilepsy etiopathogenesis [26]. Considering this information, idiopathic epilepsy has been reclassified as genetic epilepsy [27]. In the inheritance of epilepsy, consanguinity of parents and family history are of importance. In a case study in our country, the rate of kinship among parents of epilepsy patients was 16.2% [28]. In our study, the rate of consanguineous marriage was 25.9%.

In diverse studies, the rates of a family history of epilepsy were reported as 9.7% [29], 45.7% [30], and 63.3% [25], and 26.2% of patients were determined to have positive family history of seizures. About 17.3% of these patients had a history of epilepsy in their families and 82.7%, a history of FC. These differences can be explained with ethnic origin, inter-regional socioeconomic, and cultural factors.

Apart from genetic factors in children, prenatal and perinatal risk factors may be important in epilepsy and other neurological diseases. Perinatal asphyxia, preterm birth and brain damage are important risk factors for epilepsy, and under these conditions, the risk of occurrence epilepsy was reported as 18% [31]. In this study, 40 (8.7%) of epilepsy patients were born prematurely, and 74 (16%) of them had a history of perinatal asphyxia. Similarly, in a study conducted in our country, the rate of perinatal asphyxia was 13.3% [32]. We think that high rates of preterm delivery and perinatal asphyxia in our study is related to socioeconomic and geographical features of our region. Cerebral palsy (8.2%) was the most common risk factor for epilepsy in our study.

Head trauma is a known risk factor for epilepsy [33]. Especially in cases where post-traumatic consciousness changes occur, the occurrence risk of epilepsy increases. In a study conducted in our country, the rate of a history of head trauma in children with epilepsy was 12% [32]. In our study, a history of head injury was detected in 26 (5.6%) patients.

FC is considered a risk factor for epilepsy [32-35]. The risk of epilepsy after febrile convulsions is particularly high in complicated FC, developing in the form of focal seizures. Other risk factors include neuromotor growth retardation and a family history of epilepsy [35,36] The ratio of FC in patients who were followed-up with the diagnosis of epilepsy was between 12.4-36.3% [32,37,38]. In our study, epilepsy occurred during follow-up of 14 (5.7%) patients who had complex FC. Similarly, 124 (26.8%) epilepsy patients had a history of FC. As is seen, the history of FC in epilepsy patients is quite high compared to the rates of epilepsy detected in patients followed with FC diagnosis. This may be due to the short follow-up periods of FC patients, just as in our study.

Limitations

The main limitations of our study are its retrospective design and data being obtained from patient files. However, the first evaluation and all controls were made by pediatric neurologists. In addition, patient data were recorded on standard forms by pediatric neurologists. These factors reduced the limitation of the study due to its retrospective nature.

Conclusion

In our study, febrile convulsion and idiopathic epilepsy were the most determined causes of seizure etiology. Preterm birth, perinatal asphyxia, kinship marriage and positive family history are both the most important risk factors in febrile convulsions and epilepsy. These risk factors are preventable to a certain extent with more specific educational programs. Patients with complex FC who had focal seizures need to be monitored for a long-time for epilepsy occurrence. Furthermore, we suggest that patients with simple FC who are in good general condition can be monitored without LP. Iron deficiency should be investigated in patients with FC and treated, as necessary. Further, prospective, multicenter and long-term studies are needed to confirm our results.

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Our arteriovenous fistula experiences with grafts in hemodialysis patients

Hemodiyaliz hastalarında greft ile arteriyovenöz fistül tecrübelerimiz

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Ethics Committee Approval: This study has been approved by Adıyaman University Non-Interventional Clinical Research Ethics Committee with the session number dated 1/14/2020 and 2020/1-4. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma Adıyaman Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu tarafından 14.01.2020 ve 2020/1-4 tarihli oturum numarası ile onaylanmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

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Abstract

Aim: In patients whose life is dependent on hemodialysis, the most suitable vascular access routes are arteriovenous fistulas made with native vessels. However, in patients whose natural vessels are depleted, or not suitable, arteriovenous fistulas can be opened with artificial grafts. Our aim is to examine arteriovenous fistulas opened with synthetic grafts in hemodialysis patients who do not have native vascular access in the upper extremity and share our results.

Methods: Patients who underwent opening of an arteriovenous fistula with a synthetic graft to the upper extremities in Adıyaman University Faculty of Medicine, Cardiovascular Surgery Clinic between December 2012 and December 2018 were examined in this retrospective cohort study. They were screened for age, gender, end-stage renal failure etiology, complications in vascular access site, postoperative follow-up, and duration of use. Primary and secondary patency rates were determined.

Results: It was determined that synthetic grafts were used in 33 (15 males, 18 females) out of 436 arteriovenous fistulas (AVF) opened to 372 patients. The mean age was 59.2 (17) years. Left radiocephalic (RC) straight graft fistula was opened in 2 patients, left brachiocephalic (BC) straight graft fistula was opened in 12, left BC distal loop AVF in 13, right BC distal loop AVF in 1, left brachioaxillary (BA) distal loop AVF in 3 and right BA distal loop was used to open an AVF in 2 patients. Primary cumulative patency rates were as follows: 72% in the 3rd month, 65% in the 6th month, 42.24% in the 12th month. The secondary patency rates were 33.9% in the 60th month, 12% in the 60th month, 96.96% in the 12th and 24th months, 90.28% in the 36th and 48th months, 59.12% in the 60th month and 43.11% in the 72nd month.

Conclusion: In chronic renal failure patients who do not have a natural vascular access routes or whose natural routes have been exhausted, AVFs that are opened to the upper extremities with a synthetic graft are suitable vascular access routes for long-term dialysis.

Keywords: Chronic kidney failure, Hemodialysis, Synthetic graft, Arteriovenous fistula

Öz

Amaç: Yaşamı hemodiyalize bağımlı hastalarda, en uygun vasküler erişim yolu nativ damarlar ile yapılan arteriyovenöz fistüllerdir. Ancak doğal damarları tükenen veya uygun olmayan hastalarda, yapay greftler ile arteriyovenöz fistüller açılabilir**.** Amacımız üst ekstremitede vasküler erişim yolu olmayan hemodiyaliz hastalarında sentetik greft ile açılan arteriyovenöz fistülleri incelemek ve literatür eşliğinde sonuçlarımızı paylaşmaktır.

Yöntemler: Çalışma retrospektif kohort çalışması olarak tasarlandı. Aralık 2012-Aralık 2018 tarihleri arasında Adıyaman Üniversitesi Tıp Fakültesi Kalp ve Damar Cerrahisi Kliniği'nde üst ekstremitelere sentetik greft ile arteriyovenöz fistül açılan hastalar incelendi. Hastalar yaş, cinsiyet, son dönem böbrek yetmezliği etiyolojisi, komplikasyonlar vasküler erişim bölgesi, postoperatif takip ve kullanım süresi açısından tarandı. Birincil ve ikincil açıklık oranları belirlendi.

Bulgular: Toplamda 372 hastaya açılan 436 arteriyovenöz fistülden 33 (15 erkek, 18 kadın) hastaya sentetik greft ile arteriyovenöz fistül (AVF) açıldığı tespit edildi. Yaş ortalaması 59.2 (17) İdi. Hastaların 2'sinde sol radiyosefalik (RC) düz, 12'sinde sol brakiosefalik (BC) düz greft AVF, 13'ünde sol BC distal loop AVF, 1'inde sağ BC distal loop AVF, 3'ünde sol brakioaksiller (BA) distal loop AVF ve 2'sinde sağ BA distal loop ile AVF açıldığı görüldü. Primer kümülatif açıklık oranları; 3. ayda %72, 6. ayda %65, 12. ay %42,24. ayda %33, 60. ayda %12 iken sekonder açıklık oranları 12 ve 24. aylarda %96,96, 36 ve 48.aylarda %90,28, 60. ayda %59,12 ve 72 ayda %43,11 idi.

Sonuç: Nativ vasküler erişim yolu olmayan veya tükenen kronik böbrek yetmezliğindeki hastalarda, üst ekstremitelere sentetik greft ile açılan AVF'ler, uzun süre kullanılabilen diyaliz erişim yolu sağlayan, uygun bir vasküler erişim yoludur.

Anahtar kelimeler: Kronik böbrek yetmezliği, Hemodiyaliz, Sentetik greft, Arteriyovenöz fistül

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Introduction

Hemodialysis is one of the most common renal replacement methods in patients with end-stage renal failure. Despite the modern methods and techniques used, the average life expectancy of these patients is higher than deaths due to malignancy [1].

Arteriovenous fistula (AVF) applications, described and developed by Brescia and Cimino in 1966, remain popular in hemodialysis patients [2].

Some patients are not suitable for creating arteriovenous fistulas with autologous veins. Although various methods are developed for renal replacement in such patients, such as jugular, subclavian, femoral transient or permanent hemodialysis catheters and peritoneal dialysis catheters, they are not as healthy as native vein AVFs [3].

Specially manufactured artificial polytetrafluoroethylene (PTFE) grafts are used for long-term vascular access in patients with or without depletion of autologous vascular access in the upper extremities [4]. In 1976, Baker LD et al. studied PTFE grafts for dialysis, after which the use of these grafts increased gradually [5].

Our aim in this study was to examine the AVFs we opened with synthetic grafts in patients whose veins were depleted due to multiple AVFs or those whose autologous veins were not suitable and share our experiences.

Materials and methods

This retrospective cohort study started after the approval of Adıyaman University Non-Interventional Clinical Research Ethics Committee was obtained (Date: 1/14/2020, number 2020/1-4). Patients who had AVF opened to the upper extremities between December 2012 and December 2018 were reviewed. None of our patients died during the procedure. However, patients who died during the 6-year follow-up due to comorbid conditions were excluded from the study. The data were gathered electronically from patient files in the hospital registry. Demographic data, surgical complications, physical examination findings, target vascular structures (artery and vein structure where the graft was interposed) were identified and defined. The most frequently used vascular structures, the reasons for the choice of vessel and its differences were investigated technically.

Definitions

Radiocephalic Straight AVF: AVF in which the graft is interposed between the radial artery at the wrist level and the cephalic vein or antecubital vein in the antecubital region (Figure 1A).

Brachiocephalic Straight AVF: AVF where the graft is interposed between the brachial artery in the antecubital region and the region where the cephalic vein pours into the axillary vein (Figure 1B).

Brachiocephalic distal loop AVF: AVF, where the graft is interposed between the brachial artery and the brachial vein in the antecubital region and opened by creating a distal loop (Figure 1C).

Brachioaxillary distal loop AVF: AVF in which the graft is interposed between the brachial artery and the axillary vein in the axillary region and opened by creating a distal loop AVF (Figure 1D).

Primary and secondary patency rates of grafts were recorded. The primary patency rate was defined as the time between the date when the AVF was first opened and when it became dysfunctional for several reasons. Secondary patency rate was defined as the time when the graft was re-functionalized and the time until the second intervention.

Statistical analysis

Statistical analysis to determine patency rates was performed with the Kaplan-Meier method using Graphpad Prism 8.0.2 (La Jolla, CA: GraphPad Software, Inc., accessed at http://www.graphpad.com/scientific-software/prism/). SPSS 22.0 program was used for data analysis. Continuous variable results were reported as mean (standard deviation (SD)). Categorical variables were compared using chi-square homogeneity test and expressed as count and percentage. *P*-value <0.05 was considered statistically significant.

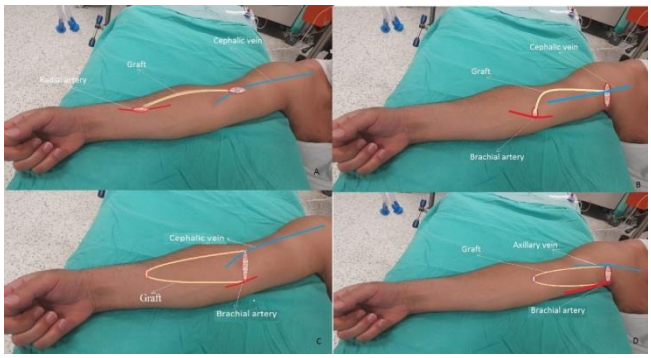

Figure 1: Graft localization. A: Arteriovenous fistula (AVF) with radiocephalic (RC) straight graft, B: AVF with brachiocephalic (BC) straight graft, C: AVF with brachiocephalic (BC) distal loop graft, D: AVF with Brachioaxillary (BA) distal loop graft

Results

The 72-month follow-up results of the patients were examined by scanning patient files. It was determined that a total of 33 patients (15 men, 18 women) had AVFs opened with polytetrafluoroethylene (PTFE) early dialysis grafts to the upper extremity by a single surgical team. The demographic and operative features of the patients are given in Table 1. The mean age was 59.2 (17) years. All patients had at least 3 previous AVFs opened to both upper extremities and none had a chance of native AVF. In AVFs opened with a native vein before the graft, basilic vein transposition was performed. The patients were homogeneously distributed in terms of gender (P=0.273).

Two (6.06%) patients had left-RC AVF, 12 (36.36%) patients, left-BC straight graft AVF, 13 (39.39%) patients, left-BC distal loop AVF, 1 (3.03%) patient, right-BA distal loop AVF, 3 (9.09%) patients, left-BA distal loop AVF and 2 (6.06%) patients had AVF with right BA distal loop graft.

There was no homogeneous distribution in terms of graft localization and position (P<0.001). The rate of left forearm AVFs (84.84%) were significantly higher than left upper arm AVFs (6.06%) and right forearm AVFs (9.09%) (P<0.001). The rate of left BC straight AVFs (36.36%) and left BC distal loop AVFs (39.39%) were significantly higher than other graft positions (P<0.001).

It was understood from the file screening that hypertension, diabetes mellitus and glomerulonephritis were the causes of kidney failure (Table 1). Comorbid features of the

patients are summarized in Table 2. The most common accompanying diseases were atherosclerosis and hypertension.

Table 1: Demographic and operative features

	Mean (SD)	*P*-value
Age(year)	59.2 (17)	
	n (%)	*P*-value
Gender		
Male	15 (45.45%)	0.273
Female	18 (54.54%)	
Graft localization		
Left upper arm	2 (6.06)	
Left forearm	28 (84.84)	<0.001
Right forearm	3 (9.09)	
Graft position		
Left RC AVF	2 (6.06)	
Left BC straight graft AVF	12 (36.36)	
Left BC distal loop AVF	13 (39.39)	<0.001
Right BC distal loop AVF	1 (3.03)	
Left BA distal loop AVF	3 (9.09)	
Right BA distal loop AVF	2 (6.06)	
The cause of kidney failure		
Diabetes mellitus	16 (48.48)	
Hypertension	20 (60.60)	0.024
Glomerulonephritis	6 (18.18)	

* Chi square homogeneity test was used, RC: Radiocephalic, BC: Brachiocephalic, BA: Brachioaxillary, AVF: Arteriovenous fistula

Table 2: Comorbid features of patients

	n
Hypertension	20
Diabetes mellitus	16
Coronary artery disease	12
Morbid obesity (BMI >40)	7
Hyperlipidemia	5
Atherosclerosis	24

n: Frequency, BMI: Body mass index

Early and late complications are summarized in Table 3. The most common early complication was edema. It was found that 2 patients were taken for revision and thrombectomy within the early period (first 48 hours) due to bleeding and 3 patients due to graft thrombosis. Two patients presented to the outpatient clinic in the first 3 months with ischemic pain and were followed up with medical treatment. In the eighth month, one of our patients developed steal syndrome (Figure 2) and AVF was closed due to high flow (Figure 3) on Doppler ultrasonography. Another patient developed pseudoaneurysm (Figure 4) and underwent pseudoaneurysm repair (Table 3).

Table 3: Early / late complications and treatment

Early (first 48 hours)	n	Treatment
Bleeding /hematoma	2	Follow-up
Graft thrombosis	3	Thrombectomy/revision
Edema	6	Follow-up
In the first 2 months		
Graft thrombosis	5	Thrombectomy
Infection	1	Antibiotics
Cellulite	1	Antibiotics
Ecchymosis	4	Follow-up
Ischemic pain	2	Medical treatment
Late (6 months-2 years)		
Graft thrombosis	16	Thrombectomy
Pseudoaneurysm	1	Repair
Steal syndrome	1	Closure of AVF

AVF: Arteriovenous fistula

In the 72-month follow-up of the patients, the cumulative primary patency rates were as follows: 72% at 3 months, 65% at 6 months, 42% at 12 months, 33% at 24 months, 12% at 60 months. There was no open fistula at the 72nd month (Figure 5). Cumulative secondary patency rates were 96.96% for 12 and 24 months, 90.28% for 36 and 48 months, 59.12% for 60 months, and 43.11% for 72 months (Figure 6).

Figure 2: Steal Syndrome in brachiocephalic (BC) distal loop graft fistula

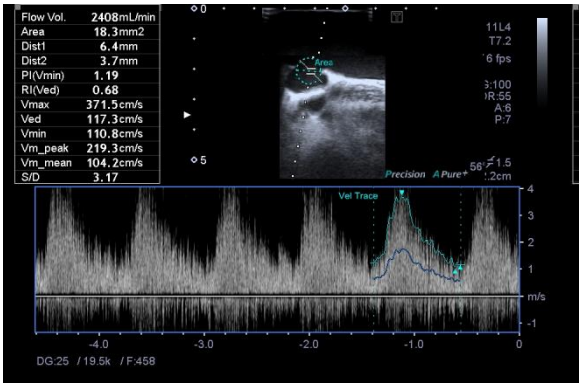

Figure 3: High flow on Doppler ultrasonography in arteriovenous fistula (AVF)

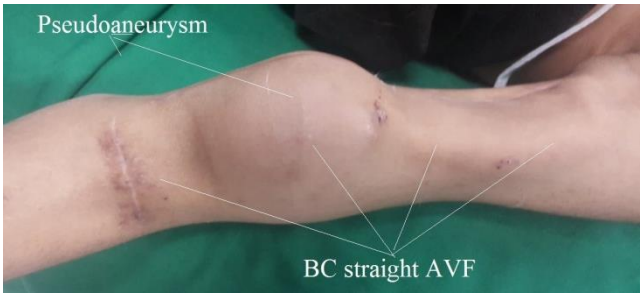

Figure 4: Pseudoaneurysm in brachiocephalic (BC) straight graft arteriovenous fistula (AVF)

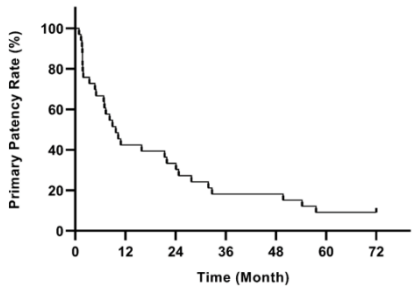

Figure 5: Primary graft patency rates

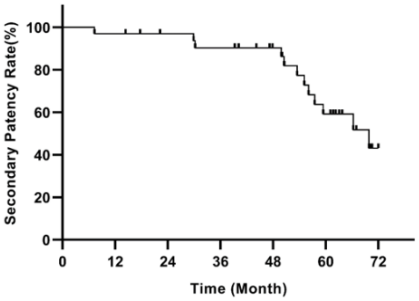

Figure 6: Secondary graft patency rates

The patients in this study consisted of those who had multiple previous AVFs opened to their upper extremities, which all became dysfunctional for several reasons over time, and there was no chance of opening an AVF with other appropriate native veins in the upper extremities. Early dialysis grafts with 4 mm in the arterial side and 7 mm in the venous side were used to prevent ischemia in the hands and fingers. All patients underwent under local anesthesia, 5000 IU heparin was applied before vascular clamps were placed, and no patients were started on prophylactic antibiotics.

Discussion

The preferred vascular access route for hemodialysis is an AVF. For this reason, arteriovenous fistulas, which can be used for a long time for hemodialysis, are vitally important in patients whose lives are dialysis-dependent [6].

However, AVFs cannot be created with native veins in every patient. In the absence or inadequacy of native vessels, artificial grafts can be used for AVF creation in these patients, as needed [7,8].

Patients with end-stage renal disease face multiple AVF openings to the upper extremity throughout their lifetime. The reason for this is that AVFs that open become dysfunctional over time due to thrombosis, infection, and aneurysm. When opening AVFs, the most distal part of the nondominant arm is preferred. RC AVFs created between cephalic vein and radial artery at wrist level are the most preferred routes due to high patency rates [2,9].

Parenteral treatments applied in chronic diseases or repeated multiple vascular interventions for hemodialysis destroy the vessels. For this reason, surgeons have searched for new ways. Microstructured ePTFE grafts with biological structures are the most frequently used artificial grafts for this purpose [10]. These grafts are interposed by passing through a tunnel formed under the skin and forming a straight or U-shaped loop between the artery and vein [11]. While creating AVF with a graft, although there are individual factors, the most preferred artery in the antecubital region is the brachial artery. The most preferred veins include the cephalic vein in the antecubital region and cephalic vein at the axillary region, just before pouring into the axillary vein [11,12].

In our series, 31 of 33 patients had BC AVF. Twelve of these were straight BC grafts, 14 were distal loop BC grafts and 5 were distal loop BA grafts. Our reason for choosing BA distal loop in the last 5 patients was the intense scar tissue which developed due to multiple AVFs that were opened and thrombosed on the forearm. The antero-lateral part of the upper arm was preferred for comfortable cannulation while creating a loop in this region.

The most common complication in PTFE grafts is venous stenosis and thrombosis due to neointimal hyperplasia [13,14].

Dialysis patients must be dialyzed 2 or 3 times a week. For this purpose, complications such as hematoma, bleeding or pseudoaneurysm may also occur due to repeated needle injections to the grafts [7].

The most common early complications were edema and graft thrombosis in our study series. Three patients underwent thrombectomy in the first 48 hours due to graft thrombosis, 2 of which had AVFs opened with RC straight grafts. Thrombosis was associated with a diameter mismatch between the graft and artery. These two patients were observed to use these fistulas for more than two years (secondary patency rates were 50% at 36 months) after thrombectomy and revision. The other patient had a distal loop BA AVF and the graft was thrombosed due twisting in the loop region. For this reason, we believe that such complications can be avoided if the loop area is formed with a wide angle while the graft is passed through the tunnel created under the skin.

Another important complication that required the closure of AVF in our series was steal syndrome in 1 patient, in whom the fistula was closed because of severe ischemia in the outpatient control at the 8th month. The fistula flow rate was measured at 2408 ml/min on colored venous doppler ultrasonography.

Infection rates in PTFE grafts have been reported between 1% and 13% in various series. This is due to compliance with asepsis-antisepsis rules during nursing care and graft cannulation. In our series, our infection rate was 3%, compatible with the literature [15,18].

Pseudoaneurysm is usually caused by degenerative damage to the graft due to repeated cannulations. This complication presents with difficult cannulation, severe pain, and cosmetic problems. While pseudoaneurysm has not been reported in some studies, it has been reported as 23% in others [17,19,20].

In our study, the rate of pseudoaneurysm was limited to 1 patient (3%), who was underweight and had developmental retardation. Surgical repair of the pseudoaneurysm failed due to graft infection, and the graft had to be removed.

Hematoma and edema may occur in the relevant extremity when the graft is passed through the created tunnel under the skin. For this reason, there are publications defending that cannulation should begin after 2-3 weeks of maturation period [17].

However, all patients in our series were cannulated within the first week. The reason for this was attributed to the feature of the used graft. We used 4x7 mm early dialysis grafts, which allow cannulation within the first week [14].

The rate of thrombosis in artificial grafts is 6 times higher than that of native vein AVFs despite the advances in graft technology [7].

Early thrombosis that develops in PTFE grafts is usually caused by surgical technique. In the late period, it is due to intimal hyperplasia, stenosis in venous anastomosis, poor blood flow, hypercoagulability, inappropriate pressure on the graft after dialysis, hypovolemia, and hypotension. The risk increases in diabetic individuals [21]. The one-year primary patency rates of PTFE grafts are between 46% and 68% in the literature [7,22,23].

The primary patency rates were 100% in the first 3 months in BC straight graft patients in our study, 91.6% at 6 months, 75% at 9 months, and 66.7% at 12 months. This rate was 78.5% in the 3rd month, 71.4% in the 6th, 50% in the 9th and 42.8% in the 12th month in BC distal loop AVF, all of which were coherent with the literature [23]. The primary patency rates were 25% at the 3rd, 6th and 9th months in patients with BA distal loop AVF and there was no open fistula at the 12th month. The secondary patency rates of patients in this group were 60%. The RC straight graft patients had 50% patency at the 3rd and 6th months, and there was no primary open fistula at the 9th month. The cumulative primary patency rates in our series were 72% in the 3rd month, 65% in the 6th month, 42% in the 12th month, 33% in 24th and 12% in the 60th month. There was no open primary fistula in the 72nd month. Our secondary cumulative patency rates were 96.96% at the 12th and 24th months, 90.28% at the 36th and 48th months, 59.12% at the 60th month, 43.11% at the 72nd

month, all of which were similar to those reported in the literature. It would be safe to say that our late results were better. The decreased primary patency rates in the first year, compared to the literature, were related with the low rates in RC straight and BA distal loop graft AVFs. This was because of the low opening rates of RC fistulas due to the incompatibility of radial artery diameter with the graft and difficult cannulation in BA distal loop AVFs [24]. Patients in this group had cannulation problems due to morbid obesity.

We believe that nurses should be able to reach vascular maps during dialysis after the AVF is created with a graft. Otherwise the errors in arterial and venous cannulation will result in inadequate dialysis while the patient is connected to the hemodialysis machine and the patient will require multiple vascular interventions, both of which will decrease the life of the graft.

Our study center is the only one which provides venous access to dialysis patients in the area, along with dialysis services. Surgeries are usually performed by a single surgical team and patient records are kept digitally. Considering factors such as timely and necessary intervention of complications and patient follow-up, we think it is important both to open the patient's fistula and to perform dialysis in a single center.

Limitations

The most important limitation of our study is its single-centered design. Compared to similar studies, the number of patients was sufficient, and we did not find any similar studies in the literature reporting 6-year follow-up results in a single center, which is the strength of our study.

Conclusion

When forming an AVF with a graft, we recommend preferring the brachial artery and cephalic vein in the antecubital region, followed by the cephalic vein in the axillary region. We believe that PTFE grafts can be used with low complications for long-term vascular access with correct surgical technique, appropriate vessel selection and proper cannulation for hemodialysis patients.

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Morphometric evaluation of acetabulum

Acetabulum'un morfometrik olarak incelenmesi

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Ethics Committee Approval: This study does not contain human participants or experiments on animals. There is no identifying information regarding the participants.
Etik Kurul Onayı: Bu makale, yazar tarafından yapılan insan katılımcılar veya hayvanlar hakkında herhangi bir çalışma içermemektedir. Katılımcıların tanımlayıcı bilgisi yoktur.

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Abstract

Aim: The acetabulum is a pit located on the outer surface of the hip bone and articulates with the femur head. It consists of three bones: *Os Ilium, Os Ischii, Os Pubis*. The joining of these three bones starts at 14-16 years and continues until the age of 23. The purpose of this study is to assist clinicians in hip operations by performing morphometric measurements of the acetabulum.

Methods: In this observational study, *Os Coxae* in the bone collection were measured in the anatomy laboratory. 96 *Os Coxa* (50 right, 46 left) were used in the Anatomy Department of Erciyes University. With the help of a digital caliper, the following nine parameters were measured on the left and right dry bones separately and evaluated: The mean length between *Corpus Ischii* acetabulum edge and the acetabulum anterior edge (CIAE-AAE), transverse diameter of *Incisura Acetabulum* (IATD), *Incisura Acetabulum* length (IAU), mean acetabulum depth (AD), mean length between the edge of the acetabulum on the inferior side of *Spina Iliaca Anterior* and the posterior edge of the acetabulum (SIAIAK-AKU), *facies lunata* area, *Limbus Acetabuli* length, mean length between the midpoints of *Incisura Acetabuli* and limbus, and the shape of the acetabulum. The images obtained from the dry bones were transferred to the computer and the area of *Facies Lunata* and the length of *Limbus Acetabuli* were calculated with ImageJ program.

Results: The parameters measured on the right and left sides, respectively, were as follows: CIAE-AAE: 53.04-54.67 mm, IATD: 50.57-51.44 mm, IAU:18.08-20.25 mm, AD: 24.87-22.85 mm, SIAIAK-AKU: 52.38-45.63 mm, mean *Facies Lunata* area 13.25-13.65 cm^2, *Limbus Acetabuli* length 13.65-3.61 cm (mean 13.63 cm), mean distance between the midpoints of *Incisura Acetabuli* and limbus: 56.45-57.12 mm. The acetabulum was straight in 41 bones, irregular in 8, inclined in 27 and angular in 20.

Conclusion: We think that these index values of acetabulum we obtained will contribute to clinicians and the literature in hip dislocation and total hip surgeries.

Keywords: Acetabulum, Morphometry, ImageJ

Öz

Amaç: Kalça kemiğinin dış yüzünde bulunan ve femur başı ile eklem yapan çukura acetabulum denir. Acetabulum os ilium, os ischii, os pubis olmak üzere üç kemikten oluşur. Bu üç kemiğin birleşmesi 14–16 yaşlarında başlar ve 23 yaşına kadar devam eder. Bu çalışmanın amacı, acetabulum'un morfometrik ölçümlerini yaparak, kalça operasyonlarında klinisyenlere yardımcı olmaktır.

Yöntemler: Bu gözlemsel çalışmada Erciyes Üniversitesi Anatomi Anabilim Dalındaki 96 adet os coxae (50 sağ, 46 sol) kullanıldı. Kuru kemik üzerinde dijital kumpas yardımı ile sağ ve sol ayrı ayrı olmak üzere, corpus ischii acetabulum kenarı ile acetabulum ön kenarı arası uzunluğu (CİAK-AÖK) ortalama, incisura acetabulum'un transvers çapı (ATÇ), incisura acetabuli (IAU) uzunluğu, acetabulum'un derinliği (AD) ortalama, spina iliaca anterior inferior tarafındaki acetabulum kenarı ile acetabulum arka kenarı arası uzunluk ortalama (SİAİ), facies lunata alanı, limbus acetabuli uzunluğu, incisura acetabuli orta noktası ile limbus orta noktası arası mesafe ortalama, acetabulum'un şekli hesaplanarak 9 parametre değerlendirildi. Kuru kemik üzerinden alınan görüntüler bilgisayar ortamına aktarıldı ve ImageJ programı ile facies lunata'nın alanı ve limbus acetabuli'nin uzunluğu hesaplandı.

Bulgular: Yapılan ölçümler sonucunda ortalama değerleri, sağ-sol olarak CİAK-AÖK 53,04-54,67 mm, ATÇ 50,57-51.44 mm, IAU 18,08-20,25 mm, AD 24,87-22,85 mm, SİAİ mesafe 52,38-45,63 mm, facies lunata alanı ortalama 13,25-13,65 cm2, limbus acetabuli uzunluğu 13,65-3,61 cm (ortalama 13,63 cm), incisura acetabuli orta noktası ile limbus orta noktası arası mesafe ortalama 56,45-57,12 mm hesaplandı. Acetabulum'un şekli ise 41 kemikte düz şekilli, 8 kemikte düzensiz, 27 kemikte eğimli ve 20 kemikte açısal şekilde hesaplandı.

Sonuç: Elde ettiğimiz acetabulum'a ait bu indeks değerlerininin kalça dislokasyonu ve total kalça ameliyatlarında klinisyenlere ve aynı zamanda literatüre katkı sağlayacağını düşünmekteyiz.

Anahtar kelimeler: Acetabulum, Morfometri, ImageJ

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Introduction

Hip joint is an important anatomical structure that has been researched by various clinical branches such as surgery, orthopedics, radiology, rheumatology, physical therapy for many years [1]. This irregular and flat joint, connecting the lower extremity to the axial skeleton, resides on the pelvic skeleton. The structures that make the joint so important are the acetabulum located on the femur head and pelvis. Acetabulum is the pit which joins the femur head on the outer surface of the hip bone, and it is joined by three bones that make up os coxae: *Os Ilium, Os Ishii, Os Pubis* [2]. Y cartilage indicates the joining of three separate bones, which begins between the ages of 14-16 years and continues until the age of 23 years. Inside the acetabulum is a horse-shaped joint cartilage and *Fossa Acetabulu* (cotyloid cavity), which is filled with fibroadipose tissue and covered with synovial tissue in the middle. There is a transverse acetabular ligament at the lower edge of this pit. Normally, the acetabulum angles forward by 20–40° and its inclination ranges between 40–50°. Bony acetabulum is wrapped with a fibrocartilage labrum. It has been determined that the labrum contributes 22% to the articulating face of the hip and increases the volume of Acetabulum by 33% [7]. Acetabulum is also becoming important in terms of gender prediction and age determination [3]. Acetabular index, defined by Hilgenreiner in 1925, is a common method for evaluating the Acetabulum roof. In this measurement, the lowest side point of the ilium's Y cartilage, and the most lateral point of the sclerotic Acetabulum are determined. If the anterior and posterior edges seem separate due to pelvic slope, the point where both lines intersect should be taken as the side point of the Acetabulum. The angle between the line that combines these two points and the line (Hilgenreiner) that combines both ilium points is defined as the acetabular index [4,5]. The hip joint is one of the most important anatomical structures which provides the continuous regular movements of the lower extremity.

The acetabulum is an especially important structure for the interventions in the region [1]. Morphology of the front protrusion of acetabulum in total hip arthroplasty carries much clinical importance [6,8]. When total hip arthroplasty (prosthesis) is planned, acetabulum's bone measurement values are needed, which can affect the position and stability of the acetabular component [3]. The diameter and depth of acetabulum are considered during surgical treatment of acetabular fractures [8]. We herein presented the morphometric measurements of the acetabulum and aimed to provide clinical benefit in hip replacement surgeries and hip dislocation treatments with these data.

Materials and methods

In our study, *Os Coxae* from the bone collection were measured in the anatomy laboratory. We used 96 *Os Coxae* (50 right, 46 left) in the Department of Anatomy at Erciyes University. With the help of a digital caliper, the following nine parameters were measured on the left and right dry bones separately and evaluated: The mean length between *Corpus Ischii* acetabulum edge and the acetabulum anterior edge (CIAE-AAE), transverse diameter of *Incisura Acetabulum* (IATD), *Incisura Acetabulum* length (IAU), mean acetabulum depth (AD), mean length between the edge of the acetabulum on the inferior side of *Spina Iliaca Anterior* and the posterior edge of the acetabulum (SIAIAK-AKU), *facies lunata* area, *Limbus Acetabuli* length, mean length between the midpoints of *Incisura Acetabuli* and limbus and the shape of the acetabulum. The images obtained from the dry bones were transferred to the computer and the area of *Facies Lunata* and the length of *Limbus Acetabuli* were calculated with ImageJ program.

Statistical analysis

All data obtained from the acetabulum were entered into SPSS Statistics Software (IBM, version 15.0) to obtain mean, maximum, and minimum values. No comparisons could be made between genders because the genders were unknown. Since no two bones belonged to the same individual, the differences between the right and left bones were not statistically analyzed.

Results

The parameters measured on the right and left sides, respectively, were as follows: CIAE-AAE: 53.04-54.67 mm, IATD: 50.57-51.44 mm, IAU:18.08-20.25 mm, AD: 24.87-22.85 mm, SIAIAK-AKU: 52.38-45.63 mm, mean *Facies Lunata* area 13.25-13.65 cm^2, *Limbus Acetabuli* length 13.65-3.61 cm (mean 13.63 cm), mean distance between the midpoints of *Incisura Acetabuli* and limbus: 56.45-57.12 mm. The acetabulum was straight in 41 bones, irregular in 8, inclined in 27 and angular in 20 (Figure 1).

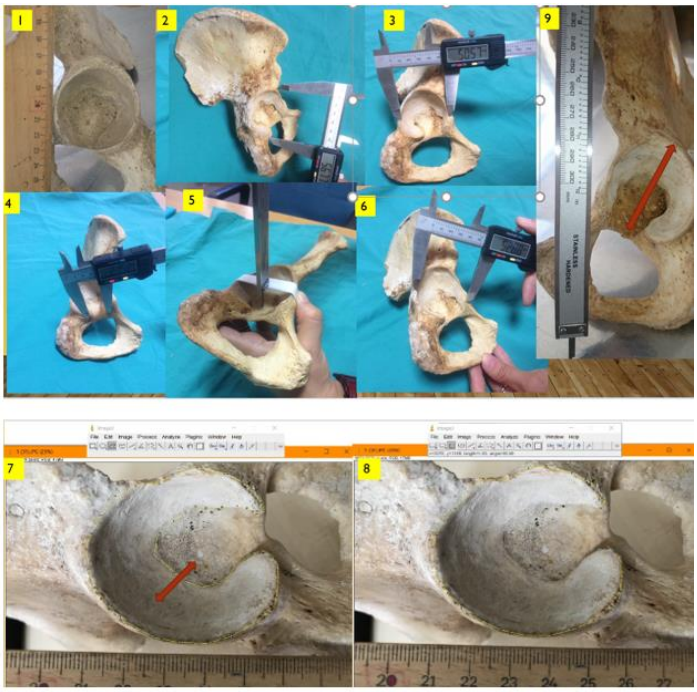

Figure 1: Parameters measured from acetabulum with the help of digital caliper on dry bone 1: Anterior acetabular ridge 2: CİAE-AAE, 3: IATD 4. IAU 5: AD 6: SIAIAK-AKU 7: Area of *Facies Lunata* 8: *Limbus Acatebulum* length 9: Length between the midpoint of *Incisura Acetabuli* and the midpoint of *Limbus Acetabuli*

Discussion

Acetabulum is one of the most important structures of the hip joint. Deformation and ischemic necrosis of the femur head are two of its clinically significant pathologies [9]. When planning a total hip arthroplasty (prosthesis), the dimensions of acetabulum, which can affect its the size, position, and stability, are considered [3]. The diameter and depth of acetabulum are also of importance in surgical treatment of its fractures [6]. The

transverse diameter of the acetabulum was reported as 50.99 ± 1.99 mm, 54.29±3.8 mm and 42.54 ± 3.6 mm by Devi et al. [6], Taştekin et al. [8] and Parmara et al. [12], respectively. The shape of the acetabulum was mostly curved in the studies of Maruyama et al. [10], Devi et al. [6], Taştekin et al. [8], and Parmara et al. [12]. In our study, acetabulum was rarely irregular. The least found shapes of acetabulum in the study of Taştekin et al. [8], Maruyamada et al. [10], Govsa et al. [11], and Thoudam et al. [14] were irregular, flat, flat, and flat, respectively. Thoudam et al. [14] reported the most common shape of acetabulum as curved. The mean values of AD in various studies were as follows: Salomon et al. [13]: 30±3.2 mm, Devi et al. [6]: 28.32±1.32 mm, Taştekin et al. [8]: 29.49 ± 4.2, Parmara et al. [12]: 19.07 ±2.47, Dhindsa et al. [16], on the right: 26. 7 + 2.7, on the left 26.4+3.0 mm. The length of incisura acetabulum reported by Taştekin et al. [8] was 16.60-4.01 mm. The values we found in our study were similar to those reported. Gangavarapu and Muralidhar reported the mean AD values as 24.09±2.69 mm on the right and 25.16±2.84 mm on the left. The AD values are important in diagnosing acetabulum-related disorders [15]. Dhindsa [16] also found that values on the right and left sides were close to each other, just as in our study.

Limitations

Being unable to discriminate between the genders of the bones limited our study.

Conclusion

We believe that the values of acetabulum we measured will be of use to the clinicians during hip disposition and total hip surgeries and valuable additions to the literature.

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Clinical characteristics and short-term outcome of dialysis-requiring acute kidney injury in critically ill patients

Kritik hastalarda diyaliz gerektiren akut böbrek yetmezliğinin klinik özellikleri ve kısa dönemli sonuçları

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Abstract

Aim: Dialysis-requiring acute kidney injury (D-AKI) in intensive care unit (ICU) continues to be associated with adverse outcomes of high mortality and dialysis-dependent chronic kidney disease (CKD). This retrospective study aimed to identify clinical characteristics of dialysis-requiring AKI and renal replacement therapy (RRT) which replaces the normal blood-filtering function of the kidneys in current ICU practice.

Methods: This retrospective cohort study was conducted in a 20-bed, third level ICU of a University Hospital between 2011 and 2017. In total, 145 D-AKI patients who underwent RRT were identified. Hospital records of patients with D-AKI were retrospectively analyzed for demographics, medical history, clinical characteristics, details of RRT modality, and short-term outcome.

Results: Of the 1689 patients investigated, 145 had D-AKI. The median age of the patients included in the study was 73 years. Septic etiology was the most common suspected cause for D-AKI development. Fifty-two patients (35.9%) underwent continuous RRT (CRRT) while intermittent hemodialysis was used in 93 patients (64.1%). Mechanical ventilation and inotropic support were more commonly used in CRRT patients than IHD patients (P=0.03). In total, in-hospital mortality rate was 73.1% while rate of dialysis-dependent CKD on discharge was 6.2%. Mortality rate was significantly higher in CRRT (84.6%) patients than in IHD patients (66.7%, P=0.019).

Conclusion: Our study results reveal that sepsis appears to be the most important cause of D-AKI in intensive care patients. D-AKI was observed more frequently in elderly patients and associated with an increased risk of short-term mortality.

Keywords: Critically ill patients, Acute kidney injury, Dialysis, Continuous renal replacement therapy, Intermittent hemodialysis

Öz

Amaç: Diyaliz gerektiren akut böbrek hasarı yoğun bakım ünitelerinde yüksek mortalite ve diyalize bağımlı kronik böbrek hastalığı gibi olumsuz sonuçları ile ilişkilidir. Bu retrospektif çalışma günümüz yoğun bakım pratiğinde diyaliz gerektiren akut böbrek hasarının klinik özelliklerini ve renal replasman tedavi yöntemlerini tanımlamayı amaçlamıştır.

Yöntemler: Bu retrospektif kohort çalışma, bir üniversite hastanesinin 20 yataklı üçüncü basamak yoğun bakım ünitesinde 2011-2017 arasında gerçekleştirilmiştir. Toplamda, renal replasman tedavisi uygulanan 145 diyaliz gerektiren akut böbrek hasarı hastası tanımlanmıştır. Diyaliz gerektiren akut böbrek hasarı hastalarının hastane kayıtları demografi, tıbbi öykü, klinik özellikler, renal replasman tedavisi detayları ve ısa dönemli sonuçlar için retrospektif olarak analiz edilmiştir.

Bulgular: İncelenen 1689 hastanın 145'inde diyaliz gerektiren akut böbrek hasarı mevcuttu. Dahil edilen hastaların ortanca yaşı 73 idi. septik etiyoloji, diyaliz gerektiren akut böbrek hasarı gelişiminde en sık şüphelenilen nedendi. Elli iki hasta (%35,9) sürekli renal replasman tedavisi hastaya uygulanmışken 93 hastaya (%64,1) aralıklı hemodiyaliz uygulanmıştır. Sürekli renal replasman tedavisi uygulanan hastalarda mekanik ventilasyon ve inotrop desteği daha sık kullanılmıştır (P=0,03). Toplamda, hastane içi mortalite oranı %73,1 iken taburculukta diyaliz bağımlı kronik böbrek hastalığı oranı %6,2 idi. mortalite oranı sürekli renal replasman tedavisi uygulanan hastalarda anlamlı olarak daha yüksekti (%84,6'ya karşılık %66,7, P=0,019).

Sonuç: Çalışmamızın bulguları yoğun bakım hastalarında diyaliz gerektiren akut böbrek hasarının en önemli nedeninin sepsis olduğunu göstermektedir. Diyaliz gerektiren akut böbrek hasarı yaşlı hastalarda daha fazla görülmüştür ve kısa dönemli mortalite riskinde artış ile ilişkilidir.

Anahtar kelimeler: Kritik hasta, Akut böbrek hasarı, Diyaliz, Sürekli renal replasman tedavisi, Aralıklı hemodiyaliz

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Introduction

Acute kidney injury (AKI) is a common and serious problem of intensive care unit (ICU) patients, related with high in-hospital mortality rates and dialysis-dependent chronic kidney disease [1-4]. Advanced age, increased AKI severity, dialysis requirement, infections or sepsis, oliguria, number of failing organs, mechanical ventilation requirement and cardiovascular failure are associated with increased mortality of AKI patients in the ICU [1,5-8]. Management of AKI is variable and includes renal replacement therapy (RRT) with hemodialysis (HD) [9]. While intermittent HD (IHD) continues to be in use, continuous veno-venous HD or continuous RRT (CRRT) has been increasingly adapted since 2000, mostly in ICU setting [10].

We aimed to determine the demographic and clinical characteristics, dialysis modalities (IHD or CRRT), and short-term outcomes of dialysis-requiring AKI (D-AKI) patients in a tertiary hospital ICU within routine medical practice for providing exploratory epidemiological evidence. The secondary aim was to compare IHD and CRRT modalities in terms of patient populations and outcomes in routine ICU practice.

Materials and methods

This study protocol was conducted in accordance with principles of Declaration of Helsinki and good clinical practice. In this observational retrospective study, consecutive adult (≥18 years) patients who were admitted to the third level, 20-bed ICU of a University Hospital with D-AKI were included. Patients who underwent kidney transplantation, those requiring chronic dialysis before ICU admission, and patients with incomplete medical records were excluded from the study.

AKI was determined with KDIGO criteria [11]. By definition of the study population, all patients had KDIGO stage 3 AKI. D-AKI was defined as acute dialysis in patients without previously registered end-stage renal disease [10]. Patient records between 2011-2017 were searched, and those with AKI who underwent RRT and stayed in the ICU for more than 24 hours were noted. Electronic data codes, keywords and matching records were obtained. All patient-level data were obtained and analyzed without personally identifying information. Variables of age, sex, comorbidities, indications for ICU admittance and primary suspected cause of AKI, Acute Physiology and Chronic Health Evaluation (APACHE II) Score calculated within 24 hours of ICU admission [12], vasopressor requirement and mechanical ventilation use at the beginning of dialysis, length of stay (LOS) in ICU and hospital, in-hospital mortality, and HD requirement for kidney failure following discharge (i.e. stage 5 chronic kidney disease as defined by Kidney Disease: Improving Global Outcomes [KDIGO]) [13] were recorded. Charlson Comorbidity Index (CCI) score [14] was calculated with age and comorbidity history of patients and classified as low (0-1) or high (≥2). Values of laboratory parameters for hemoglobin, serum albumin, creatinine, blood urea nitrogen (BUN), and glomerular filtration rate (calculated with Modification of Diet in Renal Disease formula) [15] first obtained at initial hospital admission and before the first HD session were also noted.

Patients were classified according to RRT type employed for the treatment of AKI into two groups as IHD and CRRT to compare baseline characteristics and outcomes.

RRT was performed solely as IHD or CRRT, a decision taken by nephrologists and ICU attending physicians considering the hemodynamic stability of the patient. IHD was performed within 3 to 5 hours with AKI 96 dialysis machine (Gambro Lundia AB, Sweden) with bicarbonate-based dialysate and polysulfone hollow-fiber dialyzer (F8 High Performance Steam, Fresenius Medical Care, Germany). CRRT was administered with Prismaflex System (Baxter, IL, United States) as continuous veno-venous hemofiltration with bicarbonate-based dialysate, saline-based replacement fluid, and AN 69 dialyzer membrane. All HD modalities were performed through a venous access dialysis catheter using the anticoagulant agent of heparin.

Statistical analysis

Demographical and clinical characteristics were presented as number (%) or median (range). Non-parametrical statistical tests of Mann-Whitney U and Pearson χ^2 or Fisher's exact tests were used for continuous and categorical variables, respectively, for comparisons between IHD and CRRT groups. Data analysis was carried out with IBM SPSS Statistics (version 20; IBMCorp., Armonk, NewYork) software. A two-sided *P*-value of <0.05 was regarded as significant.

Results

A total of 1689 patients were screened within a seven-year period and 145 patients with the diagnosis of D-AKI and complete medical records were found. IHD was used in 93 patients (64.1%) whereas CRRT was used in 52 (35.9%). Median age was 73 (20-93) years with male population predominance (55.9%). Based upon their medical history, 118 patients (81.4%) (79 IHD patients [84.9%] and 39 CRRT patients [75.0%]) had comorbidities. Age, gender, CCI categories, and selected comorbidities of the patients were similar between IHD and CRRT groups except for coronary artery disease (28.0% vs 13.5%, respectively; *P*=0.046). A surgical indication for ICU admission was found in 52 patients (35.9), mostly as postoperative need for follow-up in an ICU setting (n=44, 84.6%). Respiratory failure was the most common overall cause for ICU requirement (n=56, 38.6%). Prevalence of selected indications for ICU admission and median APACHE II scores were similar between IHD and CRRT patients. CRRT patients had higher vasopressor (94.2% vs. 81.7%) and mechanical ventilation (100% vs. 91.4%) needs than IHD patients at the beginning of dialysis (*P*=0.036 and 0.030, respectively). Septic etiology was the most common cause (57.9%) in the patient population who developed D-AKI. In addition, the number of patients with septic etiology in the CRRT group was higher than in the IHD group (71.2% vs. 50.5%, *P*=0.053). Detailed demographical and clinical patient characteristics are presented in Table 1.

Diagnostic laboratory values of blood parameters are presented in Table 2. CRRT group had lower median BUN and higher median GFR than in the IHD group at hospital admission (46 vs 50 mg/dL and 65.5 vs 57.0 mL/min/1.73 m^2, respectively; *P*=0.046 for both). Prior to initiation of HD, CRRT patients had lower median creatinine (2.4 vs 3.3 mg/dL) and BUN (120.5 vs

144 mg/dL) levels and higher median GFR (25.5 vs 18 mL/min/1.73 m^2; P=0.003 for all) than those in the IHD group.

Among the patient population of D-AKI, median LOS in the ICU and hospital were 17 and 22 days, respectively. LOS in the ICU and hospital were longer in IHD group (20 vs 9.5 days and 26 vs 18.5 days, respectively; P=0.008 for both). In-hospital mortality rate was 73.1% for all patients. Mortality rate was higher in CRRT patients (84.6 vs 66.7%, P=0.019) while dialysis-requiring kidney failure rates at discharge were similar, albeit the patient numbers were small (Table 3).

Table 1: Clinical and demographical characteristics of patients admitted to intensive care unit with dialysis-requiring acute kidney injury

Characteristic	All patients (n=145)	Hemodialysis modality IHD (n=93)	CRRT (n=52)	*P*-value
Median age (years), (range)	73 (20-93)	74 (20-93)	71 (26-89)	0.095
Sex, No. (%)				
Female	64 (44.1)	45 (48.4)	19 (36.5)	0.168
Male	81 (55.9)	48 (51.6)	33 (63.5)	
Charlson comorbidity index, No. (%)				
Low (0-1)	22 (15.2)	11 (11.8)	11 (21.2)	0.133
High (≥2)	123 (84.8)	82 (88.2)	41 (78.8)	
Selected comorbidities, No. (%)				
Hypertension	80 (55.2)	56 (60.2)	24 (46.2)	0.102
Coronary artery disease	33 (22.8)	26 (28.0)	7 (13.5)	0.046
Atrial fibrillation	9 (6.2)	5 (5.4)	4 (7.7)	0.722b
Chronic heart failure	19 (13.1)	14 (15.1)	5 (9.6)	0.352
Diabetes	37 (25.5)	28 (30.1)	9 (17.3)	0.090
Chronic obstructive pulmonary disease	19 (13.1)	11 (11.8)	8 (15.4)	0.543
Dementia	13 (9.0)	9 (9.7)	4 (7.7)	0.771b
Cerebrovascular disease	17 (11.7)	13 (14.0)	4 (7.7)	0.296b
Other	22 (15.2)	9 (9.7)	9 (17.3)	NA
Primary indication type, No. (%)				
Medical	93 (64.1)	62 (66.7)	31 (59.6)	0.396
Surgical	52 (35.9)	31 (33.3)	21 (40.4)	
Selected primary indication for ICU admission, No. (%)				
Respiratory failure	56 (38.6)	36 (38.7)	20 (38.5)	0.97
Postoperative admission	44 (30.3)	28 (30.1)	16 (30.8)	0.934
Sepsis	14 (9.7)	8 (8.6)	6 (11.5)	0.566
Other	31 (21.4)	21 (22.6)	10 (19.2)	NA
Median APACHE II score, (range)	30 (11-48)	29 (11-48)	33 (16-48)	0.134
Vasopressor need, No. (%)	125 (86.2)	76 (81.7)	49 (94.2)	0.036
Mechanical ventilation use, No. (%)	136 (93.8)	85 (91.4)	52 (100.0)	0.030
Suspected primary cause for AKI				
Septic	84 (57.9)	47 (50.5)	37 (71.2)	0.053
Cardiovascular	54 (37.2)	41 (44.1)	13 (25.0)	
Other	7 (4.8)	5 (5.4)	2 (3.8)	

a: 93 patients (64.1%) (65 IHD [69.9%] and 28 CRRT [53.8%] patients) had more than one comorbidity, b: Fisher's exact test was used, AKI: acute kidney injury, APACHE II: acute physiology and chronic health evaluation, CRRT: Continuous renal replacement therapy, ICU: intensive care unit, IHD: intermittent hemodialysis, NA: not applicable.

Table 2: Values of blood diagnostics of patients at hospital admission and prior to hemodialysis initiation in intensive care unit

Parameter, Median (range)	All patients (n=145)	Hemodialysis modality IHD (n=93)	CRRT (n=52)	*P*-value
Creatinine (mg/dL)				
At admission	1.1 (0.4-2.6)	1.2 (0.4-2.6)	1.1 (0.6-2.1)	0.239
Before hemodialysis	3.0 (1.0-8.0)	3.3 (1.0-8.0)	2.4 (1.0-8.0)	0.013
Blood urea nitrogen (mg/dL)				
At admission	48 (13-160)	50 (16-160)	46 (13-94)	0.017
Before hemodialysis	138 (34-342)	144 (35-342)	120.5 (34-279)	0.015
Glomerular filtration rate (mL/min/1.73 m2)				
At admission	59 (26-124)	57 (31-121)	65.5 (26-124)	0.046
Before hemodialysis	19 (6-89)	18 (8-66)	25.5 (6-89)	0.003
Albumin (g/dL)				
At admission	3.2 (2.0-4.8)	3.2 (2.0-4.7)	3.3 (2.1-4.8)	0.475
Before hemodialysis	2.5 (1.0-4.0)	2.5 (1.6-4.0)	2.5 (1.0-3.6)	0.341
Hemoglobin (g/dL)				
At admission	11.0 (7.1-18.0)	11.0 (7.7-18.0)	12.0 (7.1-17.0)	0.071
Before hemodialysis	8.0 (7.0-16.0)	8.0 (7.0-15.0)	8.0 (7.0-16.0)	0.682

CRRT: Continuous renal replacement therapy, IHD: intermittent hemodialysis

Table 3: Length of stays and clinical outcomes of dialysis-requiring acute kidney injury patients

Parameter	All patients (n=145)	Hemodialysis modality IHD (n=93)	CRRT (n=52)	*P*-value
Median LOS in ICU (days), (range)	17 (2-156)	20 (2-156)	9.5 (2-154)	0.001
Median total LOS in hospital (days), (range)	22 (2-157)	26 (2-157)	18.5 (2-154)	0.008
In-hospital mortality, n (%)	106 (73.1)	62 (66.7)	44 (84.6)	0.019
Chronic RRT need on discharge, n (%)	9 (6.2)	8 (8.6)	1 (1.9)	0.157

CRRT: Continuous renal replacement therapy, ICU: intensive care unit, IHD: intermittent hemodialysis, LOS: length of stay, RRT: renal replacement therapy

Discussion

This study was conducted to determine factors associated with D-AKI patients followed up in a single-institution ICU. Our study population comprised of patients with advanced age (median age over 70 years), high burden of comorbidities, and high proportion of septic etiology for D-AKI along with extensive need for ventilator and vasopressor support. Therefore IHD was the preferred method of RRT in two-thirds of the patients. Sepsis was present in less than ten percent of the patients at ICU admission whereas over the course of ICU stay, D-AKI developed due to septic etiologies in over half of the patients. This finding indicates the importance of prevention of hospital-acquired infections in critically ill patients. Given our patient population with these high-risk AKI characteristics, observed in-hospital mortality in nearly three-quarters of the overall study population was considered to be in line with previous studies [1,16,17]. Hoste et al. [9] reported a median age of 65 in their AKI cohort with sepsis and hypovolemia being the most common etiologies for AKI development. About half of their AKI patients had KDIGO stage 3 disease, which was significantly associated with increased risk of mortality when compared with the group without AKI. Majority (75%) of RRT sessions were reported to have been conducted with CRRT, yet association of RRT modalities with mortality was not analyzed in their study [1]. Wilson et al. reported significantly increased in-hospital mortality (64%) in D-AKI group when compared with AKI patients who did not require RRT (22%) [16]. AKI was classified with Acute Kidney Injury Network staging system in their study [16]. In the extension phase of a randomized trial for RRT intensity for AKI, Gallagher et al. [17] reported around 60% of mortality with long-term follow-up. Increasing age was found to be predictive of increasing mortality.

While rates of mortality and/or chronic kidney failure associated with an in-hospital episode of AKI decreased over the years [18-21], critically ill patients with high risk factors and dialysis-requiring AKI continue to have a poor prognosis. A subgroup of AKI patients (6%) were discharged with a diagnosis of dialysis-requiring chronic kidney disease in our patient cohort, an expected outcome after AKI with a frequency increasing with AKI severity [22,23]. Depending on the patient cohort and duration of follow-up, crude rates of chronic kidney failure or end-stage renal disease development following AKI range from 1% to 8% [2,17,18,24-26].

Baseline clinical characteristics and outcomes of our patients differed according to the RRT modality of choice. Significantly higher numbers of CRRT patients had a need for mechanical ventilation and vasopressor support with a trend for higher number of patients with a suspected septic cause for AKI development. Additionally, CRRT patients had a higher in-hospital mortality rate when compared to the IHD group. An earlier observational study with relatively younger AKI patients who underwent RRT in the ICU also noted higher diagnosis of sepsis, use of mechanical ventilation and inotropic agents, and in-hospital mortality rates among CRRT patients compared to the IHD group, although probability of survival at 12 months were similar between these groups [27].

Requirement for mechanical ventilation [5,28], vasopressors [28], and acute cardiovascular failure [6] have been

associated with increased mortality in AKI patients. KDIGO guidelines recommend CRRT as the modality of RRT choice in hemodynamic instability, based mostly on theoretical advantage for better fluid balance control and circumstantial evidence of improvement of cardiovascular parameters [14]. While randomized controlled trials comparing IHD and CRRT in AKI consistently found no difference for survival outcomes [29,30], these trials largely excluded patients with severe illness and hemodynamic instability and involved crossover between RRT modalities [14,31]. Therefore, causal relation between risks related to underlying diseases, ICU-specific treatment modalities, and mortality remains to be investigated in dialysis-requiring AKI patients within ICU setting [9]. Shorter LOS in ICU and hospital observed in CRRT group could also be attributed to more severe state of illness and earlier death. Regarding these complex interactions and inherent limitations for trial design, selection of patient subgroups most likely to benefit from different HD methods and sequential or hybrid use of RRT modalities have been proposed as investigational areas instead of head-to-head comparisons of different RRT modalities [31-33].

While creatinine levels at HD initiation were almost three times of the baseline values in all patients, significantly lower levels of creatinine and BUN was detected at HD initiation in the CRRT group. This finding could be explained by the different nutritional or metabolic state of RRT groups and the dilutional effect of volume overload to correct severe hypotension or hypovolemia in the CRRT patients [34]. Unfortunately, further interpretation is not possible as reliable data for fluid admission and nutritional interventions were not available in our patient records.

Limitations

Limitations of this study include absence of data for urine output, fluid administration, and nutritional management, lack of long-term follow-up for survival and development of kidney failure, and finally a possible patient selection bias as this study was conducted in a single tertiary institution.

Conclusion

We found that patients admitted to the ICU with D-AKI suffered from considerable risk factors with poor prognosis and preference of CRRT, as RRT could be an indicator for increased in-hospital mortality. Prospective studies with large groups to investigate dialysis-requiring high-risk AKI in critical illness are required. Prevention of infectious complications and sepsis may lower the burden of morbidity and incidence of D-AKI and hereby improve outcome in AKI patients admitted to the ICU.

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The role of serum cystatin C level in detection of early onset kidney injury after coronary artery bypass surgery

Koroner arter baypas cerrahisi sonrası erken dönemde gelişen böbrek hasarının saptanmasında serum sistatin C düzeyinin rolü

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Ethics Committee Approval: The study protocol was approved by the Harran University Ethics Committee (date: 07.06.2018 no: 06) (ACTRN Trial ID: ACTRN12619000061134). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
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Abstract

Aim: Acute kidney injury (AKI) is an important condition after coronary artery bypass graft (CABG) surgery. Precautions can be taken to prevent AKI by recognizing the risky patients in the preoperative period. In this study, we investigated the relationship between the serum cystatin C (CyC) levels and AKI after CABG surgery.

Methods: A total of 42 patients (mean age 59.33 (6.66) and 69% male) who underwent isolated on-pump CABG between June 2018 and January 2019 were included in this prospective cohort study. Creatinine and CyC levels were evaluated at the preoperative period, postoperative 2nd and 24th hours. Patients were assessed for the development of AKI according to the Acute Kidney Injury Network criteria and divided into two groups as those with and without AKI in the postoperative period.

Results: Based on the creatinine level at the postoperative 24th hour, 9 (21.4%) patients developed AKI. Compared to patients who did not develop AKI, it was found that CyC level was significantly higher at the postoperative 2nd hour in patients who developed AKI (1.06 (0.26) vs 0.87 (0.19), P=0.023). In patients who developed AKI, the duration of cross-clamp was significantly longer (P=0.038), and erythrocyte suspension (P<0.001) and the number of fresh frozen plasma infusions (P<0.001) were significantly higher.

Conclusion: Increased CyC levels were associated with the development of AKI in the early postoperative period. CyC measurements performed in the initial period after CABG can be used in the diagnosis of cardiac surgery related AKI.

Keywords: Coronary artery bypass graft surgery, Serum cystatin C, Acute kidney injury

Öz

Amaç: Akut böbrek hasarı (AKI), koroner arter baypas greft (KABG) ameliyatından sonra gelişebilen önemli bir klinik durumdur. Preoperatif dönemde riskli hastaları tanıyarak AKI'nın önlenmesi için önlemler alınabilir. Bu nedenle, AKI için risk faktörlerini belirlemek çok önemlidir. Bu çalışmada, serum sistatin C (CyC) düzeyleri ile CABG cerrahisi sonrası gelişen AKI arasındaki ilişkiyi araştırdık.

Yöntemler: Haziran 2018-Ocak 2019 tarihleri arasında kardiyopulmoner bypass eşliğinde yapılan KABG cerrahisi yapılan toplam 42 hasta (ortalama yaş 59,33 (6,66) ve %69 erkek) bu prospektif kohort çalışmasına dahil edildi. Acut Kidney İnjury Network (AKİN) kriterlerine göre AKI gelişimi değerlendirildi. Hastalar postoperatif dönemde AKI olan ve olmayanlar olmak üzere iki gruba ayrıldı.

Bulgular: Postoperatif 24. saatte kreatinin düzeyine göre 9 (%21,4) hastada AKI gelişti. AKI gelişmeyen hastalarla karşılaştırıldığında, AKI gelişen hastalarda postoperatif 2. saatte CyC düzeyinin kreatinin düzeyine göre anlamlı derecede yüksek olduğu bulundu (1,06 (0,26) vs 0,87 (0,19), P=0,023). AKI gelişen hastalarda krosklemp süresi anlamlı olarak daha uzun (P=0,038), eritrosit süspansiyonu (P<0,001) ve taze donmuş plazma (P<0,001) kullanımı AKI gelişmeyen hastalardan anlamlı olarak daha yüksekti.

Sonuç: Artmış CyC düzeyleri, postoperatif erken dönemde AKI gelişimi ile ilişkili bulunmuştur. CABG sonrası erken dönemde yapılan CyC ölçümleri, kalp cerrahisi ile ilişkili AKI tanısında kullanılabilir.

Anahtar kelimeler: Koroner arter baypas greft cerrahisi, Serum sistatin C, Akut böbrek hasarı

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Introduction

Development of kidney failure after coronary artery bypass graft (CABG) surgery is one of the significant causes of morbidity and mortality [1]. Cardiac surgery-associated acute kidney injury (CSA-AKI) affects approximately 30% of the cases who undergo cardiac surgery. CSA-AKI development is related with lengthened hospital stays and increased mortality rates [2-4]. Various inflammatory parameters have been extensively studied in the diagnosis and prediction of the prognosis of cardiovascular diseases [5,6]. One of them, cystatin C (CyC) is a 13kD endogenous cysteine proteinase inhibitor that plays an important role in the intracellular catabolism of proteins and peptides. Some studies have shown that, in comparison to creatinine, CyC is a better marker in terms of the detection of kidney injury [7,8]. In patients who had cardiac surgery, it was shown that CyC measurement made within the first 24 hours following the operation could detect AKI development earlier [9]. In bypass surgeries, preoperative CyC levels were associated with postoperative kidney injury development [10]. To prevent CSA-AKI formation, studies are carried out on modifiable risk factors. Operation time and cross-clamp duration have special significance [1]. The relationship between an increase in early-term CyC levels and AKI development has not been reported yet. This study investigated the relationship between the postoperative change of blood CyC levels in patients receiving CABG surgery and early-developing CSA-AKI, and the effect of cross-clamp duration.

Materials and methods

Patient selection

After approval of the ethics committee from Harran University (2018 74059997-050.04.04), the trial was registered on ANZCTR with Id of ACTRN12619000061134. Written consent was obtained from the patients. This prospective cohort study included forty-two consecutive patients between the ages of 18-80 years who underwent CABG surgery between June 2018 and January 2019. Patients were divided into two groups as those with and without AKI. Renal failure after the operation was determined according to the Acute Kidney Injury Network (AKIN) criteria, as shown below [2]:

Stage 1: Increase in serum creatinine ≥1.5 × baseline or ≥0.3 mg/dL, or decrease in glomerular filtration rate (GFR) ≥25%

Stage 2: Increase in serum creatinine ≥2.0 × baseline or decrease in GFR ≥50%

Stage 3: Increase in serum creatinine ≥3.0 × baseline or ≥4.0 mg/dL (354 μmol/L), or decrease in GFR ≥75%, or initiation of renal replacement therapy

Patients with kidney disease (preoperative creatinine level >2 mg/dl), hemodialysis patients, those who were planned to undergo cardiac valve surgery with CABG surgery, pregnant patients, those to receive revision surgery, patients in whom normotension could not be achieved with inotropic support after development of hypotensive attack, and patients who had emergency surgery (those taken into surgery within 24 hours following coronary angiography application) were excluded. The demographic data (age, gender, height, weight) of the patients and their preoperative left ventricular ejection fraction (LVEF) were recorded. Written informed consent was obtained from all patients.

Blood sampling

Preoperatively and at the 2nd and 24th postoperative hours, blood samples were collected for BUN, creatinine and CyC. For CyC measurements, 5-ml serum separator tubes were used, and the obtained blood samples were centrifuged and kept at -80°C until analyzed. The serum CyC analyses were carried out by the "immunonephelometric method" in a Siemens BN ProSpec analyzer by using the Siemens N Latex Cystatin C commercial kits (Dade-Behring, Germany) (reference range: 0.62-1.11 mg/L).

Statistical analysis

The data were analyzed with SPSS 20.0 software (SPSS Inc. an IBM Company, Chicago, USA). Kolmogorov-Smirnov test was used to check the normality of distribution of the variables. The normally distributed continuous variables were compared with student's t-test and represented as mean ± standard deviation. The non-normally distributed continuous variables were compared by Mann Whitney-U test and represented as median (25-75th quartiles). The categorical variables were represented as frequency (percentage) and compared with chi-square or Fisher's exact tests. Pearson's or Spearman's correlation coefficient was used for correlation analysis. *P*-values<0.05 were considered statistically significant.

Results

The preoperative basal characteristics of 42 patients who were included in the study are shown in Table 1. The mean age of the patients was 59.33 (6.66) years, and 69% (29) of the patients were male. Seventeen patients (40.5%) had a history of hypertension, while 16 (38.1%) had a history of diabetes mellitus. The mean LVEF was 53.7% (5.4).

The postoperative basal characteristics of the patients are presented in Table 2. While the median cross-clamp duration was 95 (80-120) minutes, the median bypass duration was 127 (100-146) minutes. The mean extubation time after the operation was 5.83 (0.96) hours. Inotropic agent support was used in 17 patients. Considering the creatinine level at the 24th postoperative hour, acute kidney injury (AKI) developed in 9 (21.4%) patients.

Table 1: Preoperative basal characteristics of patients

Variables	(n=42)
Age, years, mean(sd)	59.33 (6.66)
Male gender (%)	29 (69.0)
Hypertension (%)	17 (40.5)
Diabetes mellitus (%)	16 (38.1)
Smoking (%)	14 (33.3)
Ejection Fraction (%),mean(sd)	53.7 (5.4)
Preoperative urea, mg/dL, mean(sd)	33.41 (12.85)
Preoperative creatinine, mg/dL, mean(sd)	0.75 (0.18)
Preoperative Cystatin C, mean(sd)	0.87 (0.20)

Table 2: Postoperative basal characteristics of patients

Variables	(n=42)
Cross-clamp duration, min.	95 (80-120)
Cardiopulmonary Bypass duration, min.	127 (100-146)
Number of grafts	3.17 (0.76)
Extubation hour	5.83 (0.96)
Mediastinal drainage amount, ml	300 (237-400)
Thorax drainage amount, ml	300 (200-400)
Number of erythrocyte suspensions given	2 (1-3)
Number of fresh frozen plasma given	2 (2-3)
Inotropic support (%)	17 (40.5)
Acute kidney injury development (%)	9 (21.4)

min: minutes, ml: milliliters

Table 3 shows the comparison of the preoperative characteristics of the patients who developed AKI and those who did not. There was no statistically significant difference between the groups in terms of preoperative characteristics. Table 4 shows the comparison of postoperative characteristics of these patients. In comparison to the patients who did not develop AKI, those who did had longer cross-clamp durations (P=0.038) and higher amounts of erythrocyte suspension (P<0.001) and fresh frozen plasma infused (P<0.001). These differences were all statistically significant. The patients who developed AKI had significantly higher cystatin levels at the 2nd postoperative hour (1.06 (0.26) vs 0.87 (0.19), P=0.023). Furthermore, as expected, the 24th-hour creatinine levels in the patients who developed AKI were significantly higher than those who did not (0.99 (0.30) vs 0.71 (0.21), P=0.003). However, there was no statistically significant difference between the groups in terms of the 2nd-hour creatinine levels (P=0.167).

Creatinine level in 3 patients, and cystatin levels in 9 patients increased significantly at the 2nd postoperative hour compared to basal levels. Table 5 shows the comparison of the patients who did and did not develop AKI in terms of significant creatinine and cystatin increase at the 2nd postoperative hour. Among 9 patients who developed AKI, only 2 had significant creatinine and 8 had significant CyC increase at the 2nd postoperative hour. There was no significant difference between the groups in terms of creatinine increase (P=0.111), however, CyC increase was significantly higher in the AKI- developing group (88.9% vs 33.3%, P=0.006). The correlation analysis revealed that cross-clamp duration was positively correlated with the postoperative 2nd hour cystatin (r=0.406, P=0.008), postoperative 2nd hour creatinine (r=0.400, P=0.009) and postoperative 24th hour creatinine (r=0.385, P=0.012) levels. Additionally, postoperative 2nd hour CyC level was positively corelated with the postoperative 2nd hour creatinine (r=0.425, P=0.005) and postoperative 24th hour creatinine (r=0.531, P<0.001) levels (Figure 1).

Table 3: Comparison of the preoperative characteristics of patients who developed AKI and those who did not

	AKI [-] (n=33)	AKI [+] (n=9)	*P*-value
Age, years	58.36 (6.48)	62.89 (6.41)	0.084
Male gender (%)	22 (66.7)	7 (77.8)	0.695
Hypertension (%)	16 (48.5)	1 (11.1)	0.060
Diabetes mellitus (%)	13 (39.4)	3 (33.3)	1.000
Smoking (%)	9 (27.3)	5 (55.6)	0.133
Ejection Fraction (%)	54.24 (5.46)	51.67 (5.00)	0.201
Preoperative urea, mg/dl	33.18 (12.29)	34.29 (15.54)	0.821
Preoperative creatinine, mg/dl	0.77 (0.16)	0.66 (0.19)	0.070
Preoperative Cystatin C	0.86 (0.20)	0.87 (0.20)	0.909

AKI: Acute kidney injury, mg: milligrams, dl: deciliters

Table 4: Comparison of the postoperative characteristics of patients who did and did not develop AKI

	AKI [-] (n=33)	AKI [+] (n=9)	*P*-value
Cross-clamp duration, min.	88 (71-114)	113 (96-124)	0.038
Cardiopulmonary Bypass duration, min.	117 (95-143)	143 (120-159)	0.052
Number of grafts	3.15 (0.83)	3.22 (0.44)	0.809
Extubation hour	5.73 (1.01)	6.22 (0.67)	0.174
Mediastinal drainage amount, ml	300 (225-400)	300 (250-375)	0.857
Thorax drainage amount, ml	300 (250-400)	200 (125-350)	0.056
Number of erythrocyte suspensions given	1.79 (0.65)	3.78 (0.67)	< 0.001
Number of fresh frozen plasma given	2.24 (0.50)	3.33 (0.87)	< 0.001
Inotropic support (%)	11 (33.3)	6 (66.7)	0.124
Postoperative 2nd hour urea, mg/dl	35.92 (9.15)	41.96 (15.11)	0.139
Postoperative 2nd hour Creatine, mg/dl	0.75 (0.20)	0.85 (0.23)	0.167
Postoperative 2nd hour Cystatin C	0.87 (0.19)	1.06 (0.26)	0.023
Postoperative 24th hour urea, mg/dl	36.08 (12.38)	45.22 (18.55)	0.281
Postoperative 24th hour Creatinine, mg/dl	0.71 (0.21)	0.99 (0.30)	0.003
Postoperative 24th hour Cystatin c	0.93 (0.20)	1.09 (0.28)	0.143

AKI: Acute kidney injury, mg: milligrams, dl: deciliters, ml: milliliters

Table 5: Comparison of the patients who did and did not develop AKI based on postoperative 2nd hour significant creatine and cystatin increase

	AKI [-] (n=33)	AKI [+] (n=9)	*P*-value
2nd hour significant creatinine increase n(%)	1 (3)	2 (22.2)	0.111
2nd hour significant cystatin increase n(%)	11 (33.3)	8 (88.9)	0.006

AKI: Acute kidney injury, Significant creatinine increase: Any stage of the Acute Kidney Injury Network criteria, Significant cystatin increase: At least 15% increase compared to basal value

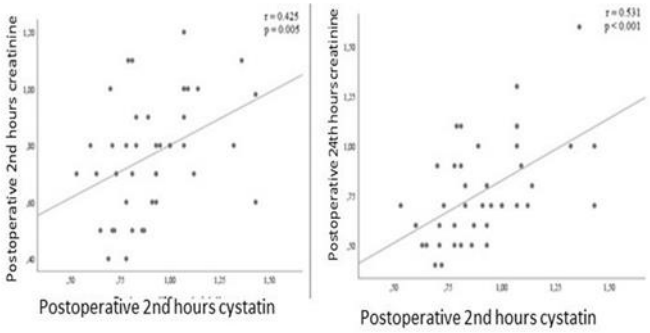

Figure 1: Comparison of Cystatin C and Creatinine values

Discussion

The main finding obtained in this study is that a relationship was determined between early postoperative period CyC levels and AKI. CyC is a protein with a low molecular weight. Although the serum concentrations of many proteins with low molecular weights increase in inflammatory, immunological, and neoplastic disorders, CyC concentrations remain unaffected. Many studies have shown that its disposal from the body occurs only by glomerular filtration, it does not vary based on age, gender, or body muscle mass, and it is better than creatinine as a glomerular filtration rate (GFR) indicator. CyC is not bound by any protein and is freely filtered from the glomerulus. Differing from creatinine, it does not undergo tubular secretion, and its half-life (90-120 min – 4 h) is shorter [8]. The production rate of CyC is highly stable, and its plasma concentration may be used as a reliable measurement of the glomerular filtration rate. In comparison to other biomarkers, it was reported that measurement of blood CyC levels provided the best results in determining AKI development in postoperative care patients in the intensive care unit after cardiac surgery [11]. In a study they conducted with 1246 patients, Wasen et al. showed that increases in CyC and creatinine levels are highly associated with AKI development [12]. In our study, we examined CyC levels in the postoperative early period and observed an increase, which was related to AKI development. This suggests that CyC measurement may be useful in predicting a kidney injury that starts during an operation.

One important finding of our study is the positive correlation between cross-clamp duration and AKI, where more AKI development was observed in cases with prolonged cross-clamp duration. In physiological conditions, until the average blood pressure drops under 80 mmHg, the glomerular filtration rate (GFR) is preserved by autoregulation. During cardiac surgery, the average blood pressure progresses under the critical limit. It was shown that there is a noticeable decrease (25-70%) in kidney blood flow, as well as a reduction in glomerular filtration rate in patients undergoing cardiac surgery. Patients' exposure to angiotensin-converting enzyme, angiotensin receptor blockers, non-steroid anti-inflammatory drugs and nephrotoxic drugs such as radiocontrast agents increases their risk of kidney failure. During CPB, low perfusion pressure and non-pulsatile

flow reduce kidney blood flow and increase renin secretion and angiotensin-II production. During CPB, patients are exposed to strong systemic inflammatory response. Inflammation is a major risk factor for ischemic kidney injury [2]. A retrospective study which investigated 669 patients between the ages of 18-40 years who underwent cardiac surgery due to congenital heart disease reported that a mean cross-clamp duration of 52 minutes was associated with increased AKI [13]. Another study conducted in 145 pediatric cardiac surgery cases reported that CPB and long aortic cross-clamp duration were effective in development of AKI [14]. A study on 45 patients who received off-pump CABG reported that AKI developed in 24%, and CPB and aortic cross-clamp durations were significantly longer in patients who developed AKI in comparison to those who did not [15]. In our study, cross-clamp durations were noticeably longer in 21.4% of the patients that developed AKI, which suggests that increased cross-clamp duration in CABG patients plays a role in AKI development.

The mechanisms where perioperative anemia and RBC transfusions could lead to AKI in cardiac surgery have not been clarified. The latest proteomic studies suggest that all patients who experience cardiac surgery with CPB developed the early stages of ischemia-reperfusion kidney damage, but whether or not they developed AKI was dependent on not only the revelation of other renal effects but also the following inflammatory response and the severity of hypoxia and oxidative stress. Anemia and RBC transfusion may lead to AKI by directly harming the kidney or increasing the susceptibility of patients to simultaneous kidney damage [16]. During storage, RBCs experience various changes that may harm the kidney after transfusion. These changes include reduction in 2,3-Diphosphoglycerate, adenosine triphosphate and S-nitroso-hemoglobinase and increased concentrations of lactate, potassium, cytokines, iron, and free hemoglobin in the supernatant [17-21]. Red blood cells may also be even more deformed in a time-dependent manner during storage and become more fragile. This leads to accumulation of hemoglobin-loaded microvesicles in the supernatant, while causing approximately 25% of RBCs to become susceptible to early hemolysis within the hour following transfusion [22-24]. Cumulatively, these changes may lead to a disruption in the transmission of oxygen to the tissue after transfusion, increased severity of inflammatory response and oxidative stress, and thus, kidney damage. Based on this hypothesis, some retrospective studies have found a relationship between the age of blood and negative outcomes.

There are different views on the indication of blood transfusion. Some authors transfused blood when the Hb level was 9 gr/dl, while some others waited until it decreased to 7.5 gr/dl. However, the meta-analysis carried out by Mazer et al. [25] that was published recently reported that transfusion made based on the Hb level in cardiac surgery patients carrying a moderate-high risk of mortality did not affect morbidity, and there was no difference between the restrictive and liberal approaches in terms of mortality, myocardial infarction, stroke or newly-onset kidney failure requiring dialysis. A liberal strategy was followed in our study, and the Hb levels were aimed to be kept at 8.5 gr/dL or higher. It was observed that more AKI developed in patients who received blood transfusion than those who did not; however, none of these patients developed kidney failure. In order to understand better the extent to which blood transfusion affects AKI in these patients, it may be necessary to conduct broader-scale studies. In the meta-analysis by Chen et al. [26] on patients who underwent cardiac surgery, it was reported that the restrictive transfusion strategy did not have lower rates of 30-day mortality, pulmonary morbidity, postoperative infection, cerebrovascular event, AKI or acute myocardial infarction in comparison to the liberal strategy.

A retrospective study including 1444 cardiac surgery patients investigated the relationship between preoperative, intraoperative anemia and erythrocyte suspension transfusion and AKI. The researchers reported that one or more of these risk factors were found in more than a third of the patients, AKI developed in 16% of the patients, and there was an increase of 2.6 times in the risk of AKI development in these patients in comparison to individuals who did not have any of the risk factors [3]. Stover et al. [27] suggested that the frequency of blood transfusion in patients who receive CABG surgery is between 27% and 92%, but this variability cannot be explained solely by the preoperative characteristics of patients, CPB time or perioperative bleeding amounts. It was argued that this difference may be dependent on the clinic, and excessive blood transfusion is made at some clinics in proportion to perioperative blood loss. A study by Koch et al. [28] on approximately 12000 patients who received CABG surgery showed that erythrocyte suspension transfusion is a risk factor for postoperative cardiac complications, severe infections, kidney failure, neurological complications, total morbidity, prolonged ventilator support and in-hospital mortality depending on the number of units. A retrospective study carried out by Güven et al. [29] on 407 patients who had CABG surgery demonstrated that blood and blood product transfusion in patients having CABG surgery increased postoperative complications and mortality in relation to the number of units. In that study, it was reported that fresh frozen plasma transfusion noticeably increased mortality in patients who received CABG surgery. The effects of erythrocyte suspension and fresh frozen plasma transfusion on morbidity are not completely known. The finding in our study that more AKI developed in the patients who received blood transfusion may lead one to think that transfusion causes kidney damage. However, it would be appropriate to investigate the issue of whether this damage is caused by transfusion or the clinical situation that required the transfusion with further studies with larger number of patients.

Limitations

Its single-center design and the fact that operations were conducted by multiple surgical teams are some of the limitations of our study. Also, our number of patients was relatively low. Further studies involving larger populations are needed to confirm these findings.

Conclusion

We observed that increased serum CyC levels in the early postoperative period was associated with AKI development. As AKI can be diagnosed and treated early, we believe that CyC measurements in initial period after CABG may

be helpful for early diagnosis of CSA-AKI. Further studies involving larger populations are needed to confirm this finding.

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Effects of alpha-lipoic acid on skeletal muscle ischemia-reperfusion injury in mice

Farelerde iskelet kasında iskemi reperfüzyon hasarında alfa lipoik asidin etkileri

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Abstract

Aim: The main problem in the treatment of cardiovascular diseases, which is the most common cause of death in the world today, is reperfusion injury. In our study, we investigated the effects of alpha-lipoic acid on lower limb ischemia-reperfusion injury.

Methods: In this study, 30 male Swiss breed albino mice weighing 45-65 g were used. Mice were randomly divided into 5 groups (Control group (C), Dimethyl Sulfoxide (DMSO) group, ischemia-reperfusion (IR) group, alpha-lipoic acid control group (ALA), alpha-lipoic acid - IR group (ALA+IR)), 6 mice in each group. All groups were administered 100 IU/kg intravenous heparin bolus 30 minutes before the procedure. Lower limb ischemia (2 hours) and reperfusion (2 hours) protocols were applied to the IR and ALA+IR groups by clamping the main femoral artery. Alpha-lipoic acid was administered to ALA and ALA+IR groups 1 hour before the experimental procedure (100 mg/kg intraperitoneal). After the experiment protocol, the lower limb gastrocnemius muscles were collected from the sacrificed mice and total antioxidant status (TAS), total oxidant status (TOS), oxidative stress index (OSI), Myeloperoxidase (MPO) and Malondialdehyde (MDA) levels were determined in the tissue. In addition, edema, necrosis, and inflammatory cell infiltration levels in the skeletal muscle were determined by histologic grading, and apoptosis was determined by terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) method.

Results: TAS measurements of ALA group subjects were higher than the control group (P=0.01). The TOS level of the ALA+IR group was lower than the IR group (P=0.01), but higher than the C, ALA, and DMSO groups. The OSI index of the IR group was significantly higher than the ALA+IR group (P=0.01). It was observed that the IR group was at higher levels than the ALA+IR group (P=0.01). MDA measurements of IR group subjects were higher than that of the C, ALA, DMSO, ALA+IR groups (P=0.01). Edema of the IR and ALA+IR group subjects were higher than the C, ALA, DMSO groups (P=0.01). Necrosis measurements of IR and ALA+IR group subjects were higher than C, ALA, DMSO groups (P=0.01). Inflammatory cell infiltration measurements of IR and ALA+IR group subjects were higher than C, ALA, DMSO groups (P=0.01). Apoptosis level was significantly lower in the ALA+IR group than in the IR group. (P=0.01).

Conclusion: The results showed us that alpha-lipoic acid has a protective effect against oxidative damage, inflammation, and apoptosis in the tissue in lower limb ischemia-reperfusion.

Keywords: Alpha-lipoic acid, Ischemia-reperfusion injury, Skeletal muscle

Öz

Amaç: Günümüzde dünya üzerinde en sık ölüm nedeni olan kardiovasküler hastalıkların tedavisnde temel sorun reperfüzyon hasarıdır. Çalışmamızda alfa lipoik asid'in alt ekstremite iskemi reperfüzyon hasarında etkilerini araştırdık.

Yöntemler: Çalışmada ağırlıkları 45-65 gr arasında değişen 30 adet, erkek Swiss cinsi albino fare kullanıldı. Fareler her grupta 6 tane olmak üzere, rastgele 5 gruba ayrıldı (Kontrol grubu (C), Dimethyl Sulphoxyde (DMSO) grubu, iskemi- reperfüzyon (İR) grubu, alfa-lipoik asid kontrol grubu (ALA), alfa-lipoik asid - İR grubu (ALA+İR)). Tüm gruplara işlemden 30 dakika önce 100 IU/kg heparin intravenöz bolus olarak uygulandı. İ-R ve ALA+İR gruplarına ana femoral arter klemplenerek alt ekstremite iskemisi (2 saat) ve reperfüzyon (2 saat) protokolü uygulandı. ALA ve ALA+İR gruplarına deney prosedüründen 1 saat önce alfa lipoic asid uygulaması (100 mg/kg intraperitoneal) yapıldı. Deney protokolü sonrası farelerin alt ekstremite gastroknemus kası sakrifiye edildi ve dokudan totalantioksidan status (TAS), total oksidan status (TOS), oksidatif stress indexi (OSI), Myeloperoxidase (MPO) ve Malondialdehyde (MDA) düzeyleri bakıldı. Ayrıca iskelet kasından histolojik gradeleme ile ödem, nekroz ve inflamatuar hücre infiltrasyon düzeyleri ile Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) yöntemi ile apoptozis tayini yapıldı.

Bulgular: ALA grubu deneklerinin TAS ölçümlerinin kontrol grubunda göre daha yüksek düzeylerde olduğu tespit edilmiştir (P=0,01). ALA+İR grubunun TOS seviyesi IR grubuna göre daha düşük çıkmış (P=0,01) ancak C, ALA ve DMSO gruplarına göre yüksek olarak tespit edilmiştir. IR grubunun OSI indeksi, ALA + İR grubunda anlamlı derecede yüksek çıkmıştır (P=0,01). İR grubun ALA+İR grubundan daha yüksek düzeylerde olduğu görülmüştür (P=0,01). İR grubu deneklerinin MDA ölçümlerinin C, ALA, DMSO, ALA+İR gruplarına göre daha yüksek düzeylerde olduğu tespit edilmiştir (P=0,01). İR ve ALA+İR grubu deneklerinin ödem ölçümlerinin C, ALA, DMSO gruplarına göre daha yüksek düzeylerde olduğu tespit edilmiştir (P=0,01). İR ve ALA+İR grubu deneklerinin nekroz ölçümlerinin C, ALA, DMSO gruplarına göre daha yüksek düzeylerde olduğu tespit edilmiştir (P=0,01). İR ve ALA+İR grubu deneklerinin inflammatory cell infiltration ölçümlerinin C, ALA, DMSO gruplarına göre daha yüksek düzeylerde olduğu tespit edilmiştir (P=0,01). Apoptozis düzeyi ALA+İR grubunda İR grubuna göre anlamlı olarak düşük çıkmıştır (P=0,01).

Sonuç: Sonuçlar bize alfa lipoik asid'in alt ekstremite iskemi reperfüzyonunda dokuda oluşan oksidan hasara ve inflamsyona ve apoptozise karşı koruyucu etkinliğinin olduğunu gösterdi.

Anahtar kelimeler: Alfa lipoik asit, İskemi reperfüzyon hasarı, İskelet kası

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Introduction

Ischemia-reperfusion injury is common in many clinical conditions such as acute coronary syndromes, peripheral vascular diseases, and organ transplant procedures [1]. Ischemia-reperfusion (IR) injury is the damage caused by the return of blood flow to the tissue, especially after the lack of oxygen. The lack of oxygen and nutrients during ischemia induces many events related to oxidative damage and inflammation. The main mechanism of cardiovascular diseases, the most common cause of death worldwide, is ischemia-reperfusion injury [2]. For these reasons, ischemia reperfusion injury has been an area of interest for researchers [3,4].

Alpha-lipoic acid (α-LA) is a short-chain fatty acid that occurs naturally and contains 2 sulfur molecules [5]. Although alpha-lipoic acid is sufficiently found in the human diet, it is synthesized de novo by lipoic acid synthase in mitochondria. It dissolves in both lipid and aqueous media is easily absorbed and transported to the cells and reduced to DHLA [6]. It is the dithiolane ring that provides the chemical reactivity of α-LA and its reduced form, DHLA. This structure makes α-LA unique among other known biomolecules containing thiol [7]. Due to its low redox potential and unique reduction capacity, α-LA, which is involved in the capture of reactive oxygen derivatives and the reduction of oxidized forms of other antioxidants, is called the 'antioxidant of antioxidants' [8].

In our study, we investigated the effects of alpha-lipoic acid on changes caused by skeletal muscle ischemia-reperfusion injury.

Materials and methods

The study was conducted at Gazi University Laboratory Animal Breeding and Experimental Researches Center (GÜDAM) with the permission obtained from Gazi University Animal Experiments Local Ethics Committee with the code number G.Ü.ET-20.004. Alpha-lipoic acid used in the study was provided from Sigma-Aldrich company without any institutional or company support. The study protocol was drawn up with the permission obtained from Gazi University Faculty of Medicine Animal Experiments Ethics Committee with the code number G.Ü.ET-20.004. All procedures were carried out in accordance with the Standards for the Care and Use of Laboratory Animals.

Technical procedure

General anesthesia was achieved with Ketamine (90 mg/kg) + Xylazine (10 mg/kg) before surgery. All groups were administered 100 IU/kg intravenous heparin bolus 30 minutes before the procedure. Subsequently, the abdominal area was shaved and excess hair was removed. The surgical area was cleaned with an antiseptic solution. Before starting the surgical procedure, it was tested whether anesthesia was sufficient. The surgical procedure was performed under a heat lamp while the mice were in the supine position. A longitudinal skin incision was made on the mice in the inguinal region. Common-superficial and profundal femoral artery were explored. An atraumatic microvascular clamp was placed on the common femoral artery. Following the 120-minute ischemic period, the microvascular clamp on the common femoral artery was removed and reperfusion was achieved for 120 minutes. The same time (240 minutes) was awaited by applying an inguinal incision on the mice forming the control group, but IR was not generated in these groups.

In the study, 30 male Swiss breed albino mice weighing 45-65 g were used. Mice were randomly divided into 5 groups, 6 mice in each group. (Control group (C), Dimethyl Sulfoxide (DMSO) group, ischemia-reperfusion (IR) group, alpha-lipoic acid control (ALA) group, alpha-lipoic acid - IR (ALA+IR) group)

Control group (Gr-I, n=6): After heparin administration, only an inguinal incision was made and closed without ischemia in this group of mice. The mice were sacrificed under anesthesia four hours after the procedure.

DMSO group (Gr-II, n=6): After heparin administration, Dimethyl Sulfoxide (DMSO), in which alpha-lipoic acid is dissolved, was intraperitoneally administered to mice in this group without ischemia, only an inguinal incision was made and closed, and four hours after the procedure the mice were sacrificed under anesthesia.

Ischemia-Reperfusion group (Gr-III, n=6): After heparin administration to the mice in this group, an inguinal incision was made without injection of alpha-lipoic acid. Atraumatic microvascular clamp was placed on the main femoral artery, and mice were sacrificed under anesthesia after 120 minutes of ischemia and 120 minutes of reperfusion.

Alpha-lipoic acid group (Gr-IV, n=6): After heparin administration to the mice in this group, a dose of 100 mg/kg alpha-lipoic acid was administered intraperitoneally without ischemia, only an inguinal incision was made and closed, and four hours after the procedure the mice were sacrificed under anesthesia.

Alpha-lipoic acid Ischemia-Reperfusion group (Gr-V, n=6): In this group, alpha-lipoic acid was administered intraperitoneally at a dose of 100 mg/kg 1 hour before ischemia. An inguinal incision was made 30 minutes after heparin administration. Atraumatic microvascular clamp was placed on the main femoral artery, and mice were sacrificed under anesthesia after 120 minutes of ischemia and 120 minutes of reperfusion.

Tissue homogenization

The hind limb tissue was collected in a sterile Eppendorf tube and was stored at −80°C until total antioxidant/oxidant status and oxidative stress index analysis. Tissues were quickly weighed on a precision scale without allowing them to dissolve. These frozen tissue samples were ground in a porcelain mortar by adding liquid nitrogen. The pulverized tissue was transferred to the homogenization tube adding 140 mM KCl solution per gram of tissue, with a dilution of 1/10. To prevent temperature rise during homogenization, the tube was kept in a glass beaker filled with ice for 2 minutes at 50 rpm rotation speed before and after homogenization with homogenizer. Homogenates were transferred to Eppendorf tubes and the tubes were covered with paraffin and then centrifuged at 3,000 rpm for 10 minutes. After centrifugation, the supernatant was collected in another Eppendorf tube and made suitable for the measurement of total oxidative status (TOS) and total antioxidant status (TAS) [9].

TAS measurement

Samples were studied on the fully automated Mindray BS300 device with the Relassay® kit. 300 µL of reagent 1 (measuring buffer) and 18 mcL of the sample were taken and mixed in the cuvette. The first reading was made at 660 nm after 30 seconds. Next, 45 µL of reagent 2 (colored 2,2-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) was added to the mixture, and absorbance was measured at 660 nm after 5 minutes of incubation. For standard measurement, the Trolox Eq solution at a concentration of 1 mmol/L was equally used instead of the sample. The first and second measurements were performed three times, and their average were calculated. The absorbance change (ΔAbs) was calculated by subtracting the first absorbance value (A1) from the second absorbance value (A2). TAS levels were calculated using the formula given in the kit and expressed as mmol Trolox Eq/L. TAS=ΔAbsH_{2nd}O - Abs sample / ΔAbsH_{2nd}O - Abs standard

TOS measurement

Samples were studied on the fully automated Mindray BS300 device with the Relassay® kit. 300 µl of reagent 1 (measuring buffer) and 45 µl of the sample were taken and mixed in the cuvette. After 30 seconds, the first reading was obtained at 530 nm. Subsequently, 15 µl of reagent 2 (Pro-chromogenic solution) was mixed and left for 5 minutes in the incubator and the second reading was taken at 530nm. A standard solution containing 10 µmol/L hydrogen peroxide (H_20_2) equivalent/liter supplied in the kit was used for standard measurement. The first and second measurements were performed three times, and their averages were calculated. The absorbance change (ΔAbs) was calculated by subtracting the first absorbance value (A1) from the second absorbance value (A2). TOS levels were calculated using the formula provided in the kit and expressed as mmol H202 Eq/L. TOS= Δ Abs sample /Δ Abs standard X Standard Concentration 10 µmol/L

Oxidative Stress Index (OSI)

The ratio of TOS to TAS was accepted as the oxidative stress index (OSI). For calculation, the resulting TAS unit was converted to µmol/L and the OSI value was calculated according to the formula below. OSI (arbitrary unit) =TOS (µmol H2O2 equivalent/L)/ TAC (µmol Trolox equivalent/L) [10-12].

Myeloperoxidase (MPO) measurement

MPO possesses various catalytical activities. It exhibits the main catalytical activity by the production of hypochlorous acid (HClO) from hydrogen peroxide (H2O2) and chloride anion, Cl- (or halide). MPO also exhibits peroxidase activity that catalyzes the oxidation of several substrates by H_2O_2. These reaction categories have been widely used to assess the activities of MPO [13].

The Relassay Myeloperoxidase Chlorination Activity Assay Kit and the Relassay Myeloperoxidase Peroxidation Activity Assay Kit are quantitative and colorimetric assay kits for measuring the myeloperoxidase activity within a sample. In the Relassay Myeloperoxidase Chlorination Activity Assay Kit, MPO catalyzes the formation of hypochlorous acid, which reacts with taurine to form taurine chloramine. Taurine chloramine reacts with the chromophore TNB, resulting in the formation of the colorless product DTNB. One unit of MPO activity is defined as the amount of enzyme that hydrolyzes the substrate and generates taurine chloramine to consume 1.0 µmole of TNB per minute. In the Relassay Myeloperoxidase Peroxidation Activity Assay Kit, MPO catalyzes o-dianisidine to colored o-dianisidyl radical using H2O2. The increasing absorbance is monitored at 412 nm and the activity is measured kinetically. This kit can be used manually and is easily adapted to automated analyzers.

Malondialdehyde (MDA) measurement

The MDA level is an end-product of lipid peroxidation at the end of the reperfusion process and an indication of increased free radical production [14]. MDA has been an important biochemical parameter measured in many experimental animal studies to evaluate the oxidative stress level [15].

The tissue MDA level was determined by a method based on the reaction with thiobarbituric acid (TBA) at 90-100°C. In the TBA test reaction, MDA or MDA-like substances and TBA react with the production of a pink pigment with maximum absorption at 532 nm. The reaction was performed at pH 2–3 at 90°C for 15 min. The sample was mixed with two volumes of cold 10% (w/v) trichloroacetic acid for the precipitation of protein. The precipitate was pelleted by centrifugation, and an aliquot of the supernatant was reacted with an equal volume of 0.67% (w/v) TBA in a boiling water bath for 10 min. After cooling, the absorbance was read at 532 nm. The results were expressed as nmol/g wet tissue.

Histopathological analysis

Tissue samples taken from the patient were rapidly thrown into 10% neutral buffered formalin. Routine histopathological processing steps were performed after 48 hours of fixation. At the end of processing, tissue samples were embedded in paraffin blocks. 5-micron sections from the blocks were stained with Hematoxylin-Eosin. Stained sections were graded according to necrosis, edema, and inflammatory cell infiltration criteria as follows (0: No damage, 1: Slight damage, 2: Moderate damage, 3: Severe damage) [16,17]. The evaluation of the stained sections prepared from the tissues was performed with the microscope with Olympus CX43 camera attachment.

Determination of Apoptosis by TUNEL (Terminal deoxynucleotidyl transferase dUTP nick end labeling) Method: 4-micron sections from paraffin blocks were painted using commercial TUNEL kit (ApopTag® Plus Peroxidase In Situ Apoptosis Detection Kit, LOT: 2789455 Merc) after deparaffinization and hydration procedures. In order to determine the apoptotic index (AI), 5 randomly selected regions of each section were chosen under x400 magnification. Cells stained brown or black were considered TUNEL-positive apoptotic cells. The AI of hepatocytes was determined as the percentage of TUNEL positive cells with respect to the total number of cells counted using the

Formula: Apoptotic index (AI)= (Number of positive cells / Total number of cells counted) x100

Statistical analysis

In the analysis of the data, descriptive statistics were presented with mean, and standard deviation values. In the study, the Kruskal-Wallis test was used to analyze the difference between the measurement values of 6 different groups. Mann-Whitney U test was used for each pair to identify the groups which differ. In the study, p values less than 0.05 were

considered statistically significant. All analyses were made using SPSS 22.0 software package.

Results

TAS measurements differed among the study groups (P=0.01): That of the ALA group subjects were higher than that of the C group (P=0.01).

TOS measurements differed among the study groups (P=0.01). TOS measurements of the IR group were higher than the C, ALA, DMSO, ALA+IR groups (P=0.01). Besides, the TOS level of the ALA+IR group was lower than the IR group (P=0.01), and higher than C, ALA, and DMSO groups.

OSI measurements differed among the study groups (P=0.01). OSI measurements of the IR group were higher than the C, ALA, DMSO, ALA+IR groups (P=0.01). The OSI index of the IR group was significantly higher than the ALA+IR group (P=0.01).

MPO measurements differed according to the study groups (P=0.01). MPO measurements of the IR group were higher than the C, ALA, DMSO, ALA+IR groups (P=0.01). Besides, that in the IR group was higher than that in the ALA+IR group (P=0.01).

MDA measurements differed according to the study groups (P=0.01). MDA measurements of the IR group subjects were higher than the C, ALA, DMSO, ALA+IR groups (P=0.01).

Edema measurements differed according to the study groups (P=0.01). Edema levels of the IR and ALA+IR group subjects were higher than those of the C, ALA, DMSO groups (P=0.01). There was no significant difference between IR and ALA+IR groups (P=0.06) (Table 1)

Necrosis differed with the study groups (P=0.01). Necrosis in the IR and ALA+IR group subjects were higher than those in the C, ALA, DMSO groups (P=0.01). There was no significant difference between IR and ALA+IR groups (P=0.06).

Inflammatory cell infiltration measurements differed with the study groups (P=0.01). Inflammatory cell infiltration measurements of IR and ALA+IR group subjects were higher than those in the C, ALA, DMSO groups (P=0.01).

TUNEL measurements were different among the study groups (P=0.01). TUNEL measurements of the IR and ALA+IR group subjects were higher than those in the C, ALA, DMSO groups (P=0.01). Apoptosis was significantly lower in the ALA+IR group than in the IR group (P=0.01) (Table 2, Figure 1, 2).

Table 1: TAS (mmol/L), TOS, OSI, MPO, MDA, and groups

Group	Control (1) X (SD)	Alfa lipoic acid (2) X (SD)	DMSO (3) X (SD)	Mouse ischemia reperfusion (4) X (SD)	Alfa lipoic acid + IR (5) X (SD)	*P*-value
TAS mmol/L	0.27 (0.02)	0.44 (0.03)	0.31 (0.04)	0.30 (0.03)	0.35 (0.03)	0.01
	Difference: 1-2 (P=0.01)*, 1-3 (P=0.46), 1-4 (P=0.49), 1-5 (P=0.08), 2-3 (P=0.12), 2-4 (P=0.11), 2-5 (P=0.21), 3-4 (P=0.86), 3-5 (P=0.36), 4-5 (P=0.51)					
TOS µmol/L	3.29 (0.41)	3.31 (0.11)	3.54 (0.9)	7.17 (0.8)	4.22 (0.31)	0.01
	Difference:1-2 (P=0.56), 1-3 (P=0.32), 1-4 (P=0.01)*, 1-5 (P=0.10), 2-3 (P=0.27), 2-4 (P=0.01)*, 2-5 (P=0.12), 3-4 (P=0.01)*, 3-5 (P=0.14), 4-5 (P=0.01)*					
OSI	1.21 (0.12)	0.76 (0.06)	1.25 (0.25)	2,43 (0.27)	1.21 (0.1)	0.01
	Difference: 1-2 (P=0.12), 1-3 (P=0.67), 1-4 (P=0.01)*, 1-5 (P=0.92), 2-3 (P=0.09), 2-4 (P=0.01)*, 2-5 (P=0.13), 3-4 (P=0.01)*, 3-5 (P=0.81), 4-5 (P=0.01)*					
MPO U/L	54.42 (4.19)	55.55 (4.39)	53.71 (1.34)	80.34 (2.82)	61.92 (4.15)	0.01
	Difference: 1-2 (P=0.74), 1-3 (P=0.63), 1-4 (P=0.01)*, 1-5 (P=0.01)*, 2-3 (P=0.58), 2-4 (P=0.01)*, 2-4 (P=0.01)*, 3-4 (P=0.01)*, 2-4 (P=0.01)*, 4-5 (P=0.01)*					
MDA nmol/L	0.43 (0.04)	0.38 (0.19)	0.45 (0.03)	0.69 (0.04)	0.55 (0.03)	0.01
	Difference: 1-2 (P=0.16), 1-3 (P=0.32), 1-4 (P=0.01)*, 1-5 (P=0.10), 2-3 (P=0.37), 2-4 (P=0.01)*, 2-5 (P=0.06), 3-4 (P=0.01)*, 3-5 (P=0.12), 4-5 (P=0.01)*					

** Kruskal-Wallis test, * shows significant difference, ** Mann-Whitney U test as difference test, SD: Standard deviation

Table 2: TUNEL, inflammatory cell infiltration, edema, necrosis measurements by groups

Group	Control (1) X (SD)	Alfa lipoic acid (2) X (SD)	DMSO (3) X (SD)	Mouse ischemia reperfusion(4) X (SD)	Alfa Lipoic acid + IR(5) X (SD)	*P*-value
Edema	0 (0)	0 (0)	0 (0)	2.5 (0.55)	2.17 (0.98)	0.01
	Difference: 1-2 (P=0.99), 1-3 (P=0.99), 1-4 (P=0.01)*, 1-5 (P=0.01)*, 2-3 (P=0.99), 2-4 (P=0.01), 2-5(P=0.01)*, 3-4 (P=0.01)*, 3-5 (P=0.01)*, 4-5 (P=0.18)					
Necrosis	0.17 (0.41)	0.50 (0.55)	0.17 (0.41)	2.67 (0.52)	1.83 (1.17)	0.01
	Difference: 1-2 (P=0.13), 1-3 (P=0.99), 1-4 (P=0.01)*, 2-3 (P=0.13), 2-4 (P=0.01)*,2-5 (P=0.01)*, 3-4 (P=0.01)*, 3-5 (P=0.01)*, 4-5 (P=0.06)					
Inflammatory cell infiltration	0 (0)	0.33 (0.52)	0.17 (0.41)	2.67 (0.52)	1.83 (0.75)	0.01
	Difference: 1-2 (P=0.01)*, 1-3 (P=0.01)*, 1-4 (P=0.01)*, 1-5 (P=0.01)*, 2-3 (P=0.18), 2-4 (P=0.01), 2-5 (P=0.01)*, 3-4 (P=0.01)*, 3-5 (P=0.01)*, 4-5 (P=0.07)					
TUNEL	1 (1.17)	7 (1.41)	6.58 (3.14)	3.5 (2.17)	30.17 (6.79)	0.01
	Difference: 1-2 (P=0.01)*, 1-3 (P=0.01)*, 1-4 (P=0.01)*, 1-5 (P=0.01)*, 2-3 (P=0.41), 2-4 (P=0.08), 2-5 (P=0.01)*, 3-4 (P=0.09), 3-5 (P=0.01)*, 4-5 (P=0.01)*					

** Kruskal-Wallis test, * shows significant difference, ** Mann-Whitney U test as difference test, SD: Standard Deviation

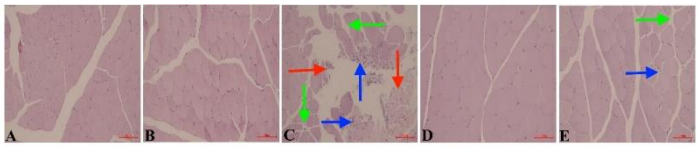

Figure 1: H&E stained photographs of histological sections of experimental groups. A, B, C, D, and E belong to the Control, DMSO, IR, ALA, and ALA+IR groups, respectively. The photographs show areas of necrosis (red arrow), edema (green arrow), and inflammatory cell infiltration (blue arrow) (Magnification x200).

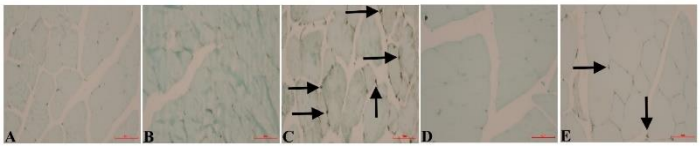

Figure 2: Photographs of sections stained with the TUNEL method for the evaluation of apoptosis in experimental groups. A, B, C, D, and E belong to the Control, DMSO, IR, ALA, and ALA+IR groups, respectively. In the photos, arrows show apoptotic cells (Magnification x400).

Discussion

Alpha-lipoic acid, a naturally occurring thiol compound, has long been known as an essential cofactor for mitochondrial bio-energetic enzymes. Alpha-lipoic acid and its reduced form of dihydrolipoic acid (DHLA) have been observed to strongly cleanse reactive oxygen radicals in vitro experiments [18]. However, more in vivo studies are needed to determine whether ALA and DHLA act directly as antioxidants [19]. Therefore, we investigated the effects of alpha-lipoic acid on lower limb ischemia-reperfusion injury, which is very common among cardiovascular diseases, on the animal model. We found that alpha-lipoic acid therapy has protective effects in lower limb ischemia-reperfusion injury, especially against oxidative damage and inflammation and apoptosis in skeletal muscle.

In total antioxidant status (TAS) measurements, the antioxidant levels of the ALA group were significantly higher than of the control group. However, although the TAS level of the ALA group was numerically higher than the TAS level of the other groups, no statistically significant difference was observed. Though not statistically significant, the level of TAS in the ALA+IR group being higher than the IR and ALA groups may be an indicator of the antioxidant activity of alpha-lipoic acid.

In total oxidant status (TOS) measurements, the TOS level of the IR group was significantly higher than the other groups. Also, the TOS level of the ALA+IR group was significantly lower than that of the IR group. These results show us that alpha-lipoic acid reduces the oxidative status in the tissue.

The oxidative stress index (OSI), which is the ratio of total oxidative status and total anti-oxidative status in the tissue, is a better indicator for the level of tissue damage associated with reperfusion compared to TAS and TOS as it reflects the balance between the oxidants and antioxidants in the tissue. The fact that the OSI level was significantly lower in the ALA+IR group

compared to the IR group indicates that alpha-lipoic acid shifts the balance between oxidants and antioxidants formed in the tissue in reperfusion injury in favor of antioxidants. According to these results, it can be claimed that alpha-lipoic acid protects the tissue against oxidative damage in reperfusion injury.

In a study, it was observed that MDA and MPO levels increased in all periods of reperfusion in ischemia-reperfusion. In addition, it has been determined that the longer the reperfusion period, the higher the damage to the skeletal muscle [20]. Therefore, measuring the MDA and MPO, both products of lipid peroxidation that occur during ischemia-reperfusion injury, can give an idea about the degree of reperfusion injury. As a matter of fact, in this study, MDA and MPO measurements were made to evaluate reperfusion injury [21].

In our study, the fact that the MDA level was significantly higher in the IR group compared to the ALA+IR group shows that alpha-lipoic acid has protective effects against lipid peroxidation in reperfusion injury. The fact that the MDA level of the ALA+IR group is significantly higher than DMSO and ALA groups shows that alpha-lipoic acid decreases the MDA level in reperfusion injury but cannot decrease it to a level close to the control groups.

The values of MPO secreted from leukocyte and mononuclear cells, which is an inflammatory indicator, in the treatment group were significantly lower than that detected in the IR group. The low level of MPO in the treatment group shows that alpha-lipoic acid also prevents leukocyte and mononuclear cell migration into ischemic-reperfused muscle tissue and thus may create an anti-inflammatory effect. These effects that reduce inflammatory cell migration show that alpha-lipoic acid can also be effective in reducing damage in muscle cells in reperfusion injury.

In the case of ischemia-reperfusion, reactive oxygen molecules are produced, and the oxygenation and nutrient intake of the cell decreases, and eventually necrosis develops in the cells [22]. In one study, it was found that alpha-lipoic acid reduced cardiac dysfunction by reducing necrosis, inflammation, and apoptosis after myocardial ischemia-reperfusion injury [23]. In another study on people with type II diabetes mellitus, the effects of oral alpha-lipoic acid therapy on oxidative stress and inflammation were investigated. Patients receiving alpha-lipoic acid therapy were similar to those receiving placebo treatment. It is stated that this result may be dose-dependent [24]. However, the route of drug administration is important in the anti-inflammatory activity of alpha-lipoic acid. The effectiveness of oral administration of treatment is questioned [25,26].

In our study, histologic grading was performed on skeletal muscle and edema, necrosis, inflammatory cell infiltration parameters were examined. In histologic grading, it was observed that the ALA+IR group had numerically lower edema, necrosis, and inflammatory cell infiltration values than the IR group. However, no statistically significant difference was observed. Evaluating our pathology results together with tissue MPO in the evaluation of inflammatory cell infiltration, it can be claimed that alpha-lipoic acid reduces inflammation in reperfusion injury.

In the assessment of apoptosis with the TUNEL method, the significant difference between the number of apoptotic cells in the ALA+IR group and those in the IR group indicates that the alpha-lipoic acid has antiapoptotic activity in reperfusion injury.

Similar to our study on skeletal muscle, in another study, it was found that alpha-lipoic acid treatment reduced the production of reactive oxygen radicals, MDA production, and apoptosis in cardiac myocytes [27].

Limitations

The fact that edema, necrosis, and inflammation were numerically high but not statistically significant in histologic grading showed us that more animals should be used in the study groups.

Conclusion

It can be claimed that alpha-lipoic acid has a protective effect against oxidant damage, inflammation, and apoptosis in the tissue in lower limb ischemia-reperfusion injury. An important aspect of our study is that it was conducted in vivo. However, larger doses and clinical studies of the protective effect of alpha-lipoic acid against reperfusion injury are needed.

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Estimation of renal scarring in children with lower urinary tract dysfunction by utilizing resampling technique and machine learning algorithms

Alt üriner sistem disfonksiyonu olan çocuklarda böbrek skarının yeniden örnekleme tekniği ve makine öğrenme algoritmaları kullanılarak tahmini

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Ethics Committee Approval: The study protocol was approved by the Eskisehir Osmangazi University Non-interventional Clinical Researches Ethics Committee (10/9/2018-07). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma protokolü Eskişehir Osmangazi Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu (09.10.2018-07) tarafından onaylanmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

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Abstract

Aim: Classical database methods may be inadequate for large data sets accumulating continuously. Machine learning (ML), one of the main subsets of artificial intelligence, may solve this problem and find the best solution for future problems by gaining experience from the present data in medical studies. A method that may show the correlation between clinical findings and renal scarring (RS) with high accuracy in patients with lower urinary tract dysfunction (LUTD) is needed. In this study, the aim is to establish a model for the prediction of RS in children with LUTD by using ML.

Methods: Patients older than three years of age (n=114) who needed urodynamic study were included in the study. There were 47 variables in the data set. Variables such as symptomatic urinary tract infection, vesicoureteral reflux, bladder trabeculation, bladder wall thickness, abnormal DMSA scintigraphy, and the use of clean intermittent catheterization were recorded. Several ML techniques (MLT) were applied to estimate RS.

Results: As a result of the comparisons, the highest accuracy rate according to the confusion matrix was obtained by the Extreme Gradient Boosting (XGB) algorithm (91.30%). In the balanced (SMOTE) data set, the highest accuracy rate was obtained by the Artificial Neural Network (ANN) algorithm (90.63%). According to the Receiver Operating Characteristic (ROC), the highest success rate was obtained by the ANN algorithm in the balanced (SMOTE) data set (90.78%).

Conclusion: High accuracy rates obtained by MLT may suggest that MLT might provide a faster and accurate evaluation process in the estimation of RS in patients with LUTD.

Keywords: Artificial intelligence, Machine learning, Renal Scar, Lower urinary tract dysfunction, Children

Öz

Amaç: Klasik veritabanı yöntemleri, sürekli biriken büyük veri kümeleri için yetersiz olabilir. Yapay zekanın ana alt kümelerinden biri olarak makine öğrenme (MÖ) bu sorunu çözebilir ve tıbbi çalışmalarda mevcut verilerden deneyim kazanarak özellik problemleri için en iyi çözümü bulabilir. Alt üriner sistem disfonksiyonu (AÜSD) olan hastalarda klinik bulgularla renal skar (RS) arasında yüksek doğrulukla korelasyonu gösterebilecek bir yönteme ihtiyaç vardır. Bu çalışmada, AÜSD'lu çocuklarda MÖ kullanarak böbrek skarının tahmini için bir model oluşturmak amaçlanmıştır.

Yöntemler: Ürodinamik çalışmaya ihtiyaç duyan üç yaşından büyük hastalar (n=114) çalışmaya dahil edildi. Veri seti 47 değişkenden oluştu. Semptomatik idrar yolu enfeksiyonu, vezikoüreteral reflü, mesane trabekülasyonu, mesane duvarı kalınlığı, anormal DMSA sintigrafisi, temiz aralıklı kateterizasyon kullanımı gibi değişkenler kaydedildi. RS tahmini için farklı MÖ teknikleri (MÖT) uygulandı.

Bulgular: Karşılaştırmalar sonucunda, Karışıklık Matrisi'ne göre en yüksek doğruluk oranı (%91,30), dengesiz veri kümesinde Extreme Gradient Boosting algoritması ile elde edilmiştir. Dengeli (SMOTE) veri setinde ise, en yüksek doğruluk oranı (%90,63) Yapay Sinir Ağı (YSA) algoritması ile elde edilmiştir. Alıcı İşleme Karakteristiği'ne (ROC) göre, en yüksek başarı oranı (%90,78), SMOTE veri setinde YSA algoritması ile elde edilmiştir.

Sonuç: MÖT tarafından elde edilen yüksek doğruluk oranları, MÖT'lerin AÜSD'lu hastaların RS tahmininde daha hızlı ve doğru bir değerlendirme süreci sağlayabileceğini düşündürmektedir.

Anahtar kelimeler: Yapay zeka, Makine öğrenme, Renal skar, Alt üriner sistem disfonksiyonu, Çocuk

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Introduction

Most healthy children achieve daytime bladder control at the age between 9 months and 5.25 years (mean of 2.4 years of age) [1]. Urinary incontinence, which is defined as involuntary urination, is a frequent problem affecting children at different ages. It has a negative effect on the quality of life of children and their families [2]. According to the International Children's Continence Society (ICCS), anatomic, neurologic, and functional conditions can cause lower urinary tract dysfunction (LUTD). Congenital anomalies of kidney and urinary tract (CAKUT) such as posterior urethral valves, and ectopic ureter can cause sphincter dysfunction and urinary incontinence [3]. The disorders involving innervation of bladder and pelvic sphincter can lead to impairment of storage and emptying functions of the bladder. Spina bifida is the most common cause of neurogenic bladder dysfunction (NBD) in children. Incomplete bladder emptying and increased intravesical pressures may cause the development of renal damage or failure [4]. Functional incontinence (FI) is defined as the involuntary loss of urine in children who do not have anatomic or structural neurologic lesions [5]. LUTD is often associated with urinary tract infections (UTI), and vesicoureteral reflux (VUR). Recurrent UTI (RUTI) may lead to the development of damage and loss of renal function in children with LUTD [6].

Machine learning (ML) is used to classify multivariate data. ML first separates the data as a training dataset and is a group of multivariate analytical methods that then define these data properties or patterns to the test dataset for data classification or estimation. ML can learn and predict from large data sets in many areas such as healthcare [7-9]. ML was applied in the emergency room for triage decisions and kidney transplantation [10]. ML is being applied increasingly in the biomedical field [11, 12]. Despite the increasing availability of data sets containing a large number of variables and patients, no study has applied machine learning techniques for predicting outcomes in children with LUTD.

In this study, we aimed to evaluate the correlations between urodynamic study, bladder ultrasound (US) and 99Tc-dimercaptosuc-cinic acid (DMSA) scintigraphy findings in children having LUTD, using ML resampling technique. We also aimed to estimated permanent kidney damage, and the renal scar in children by investigating the risk factors via ML.

Materials and methods

The data from children older than three-years-old who needed urodynamic study between 12/1/2011 and 12/1/2016 were included in the study. Data on episodes of symptomatic UTI, the presence of VUR, bladder trabeculation, bladder wall thickness (BWT), abnormal DMSA scintigraphy, the use of clean intermittent catheterization (CIC) were recorded.

Positive urine culture was defined as one species of bacteria when 50,000 CFU (CFU) per milliliter of urine reproduced in sterile bladder catheterization, or 100,000 CFU/mL of urine reproduced in the urine collected by urinary bag [13]. RUTI was defined as two or more episodes of acute pyelonephritis or acute pyelonephritis plus one or more episode of cystitis or three or more episodes of lower urinary tract infection. Bladder US was done in all patients. DMSA scintigraphy was performed in patients with abnormal US findings, RUTI, and small-sized kidney. A urodynamic study was performed for any clinical symptoms of lower urinary tract dysfunction refractory to urotherapy for at least 1 year and suspicion of neurogenic or non-neurogenic bladder dysfunction or infravesical obstruction.

Post voiding residual volume (PVR), trabeculation, bladder volume and wall thickness were determined in all patients by bladder US. BWT of 3 mm in filled bladder was defined as increased thickness. Detrusor hyperactivity was defined as involuntary detrusor contractions during the filling phase. Expected bladder capacity was defined as (age in years x 30+30) mL. Reduced bladder capacity was defined as <65% of the expected bladder capacity. Compliance was defined as the increase in detrusor pressure per unit of volume change in detrusor pressure (V / P) [3]. In children <6 years, post voiding residual urine volume greater than 20 mL was defined as an increased residual volume. In children >7 years, post voiding residual urine volume >10 mL was considered elevated [14]. The detrusor leak point pressure (DLPP) was defined as the lowest detrusor pressure causing leakage of urine in the absence of increased abdominal pressure [15]. The differential function of less than 40% or the presence of renal scarring and/or atrophy were considered renal damage.

Abnormal urodynamic test results were detected in 60 (80%) patients. The most frequent [n=45 (60%)] pathologic urodynamic finding was reduced bladder capacity, and median bladder capacity was 319 mL (203-384). Thirty-nine (52%) patients had elevated PVR with a median of 10 mL (0-95). Forty-five (60%) patients had hypocompliant bladder. Thirty (40%) patients had unstable detrusor contraction. VCUG was performed in 50 patients. Twenty-three (46%) patients had VUR. Renal damage was detected in 26 (34.7%) patients. Twenty-five patients (33.3%) performed clean intermittent catheterization (CIC).

Data pre-processing

There were 106 patients and 47 features (variables) in the data set. Before the machine learning techniques were applied, the dataset was analyzed using the following steps (Table 1).

1- User Name was not included in the training.

2- Variables with more than 15% missing values were eliminated. At the end of this process, 75 (22-scar true, 53-scar false) people and 24 variables remained.

3- Variables with a correlation coefficient of 0.6 and above were determined and the appropriate variables were eliminated. At the end of this process, 75 people and 18 variables remained.

4- Machine learning algorithms were run with unbalanced data set and results were obtained.

5- The machine learning algorithms were run by balancing the data set with the smote technique (At the end of this process, the data set included 106 people (53-scar true, 53-scar false)) and the results were obtained.

6- The ratio of test and training sets was 30-70%, respectively. For Cross Validation, k value was selected as 5.

7- Comparing the results of three techniques.

Table 1: Outcomes of group-projects coursework

Scar	The number of cases	
	Imbalanced	SMOTE
0	53	53
1	22	53

Machine learning

Machine learning is the science of computational statistics, which based on making predictions by using computers. Machine learning focuses on estimations from the learned data based on known features [15]. In this study, Artificial Neural Networks (ANN), Decision Tree (DT), Support Vector Machine (SVM), Naive Bayes (NB), Logistic Regression (LR), k-Nearest Neighbor (KNN), Random Forest (RF) and Extreme Gradient Boosting (XGBoost) were used as MLT.

Resampling techniques

The imbalance is that the sample size of one class is much higher than the other class or classes. Therefore, data samples belonging to small classes are misclassified more often than those belonging to common classes. Some techniques have been developed to balance the unbalanced data set [13].

Synthetic minority oversampling technique

Smote is a statistical technique for increasing the number of cases in your dataset in a balanced way. The module works by generating new instances from existing minority cases that you supply as input. This implementation of Smote does not change the number of majority cases [14].

Statistical analysis

Confusion Matrix contains information about actual and predicted classifications made by a classification system. The performance of such systems is generally evaluated using the data in the matrix. The Accuracy Rate (ACC), a commonly used success evaluation method, was used in our study. The accuracy method is the rate of the sample number the system classifies as trues (True Positive (TP) and True Negative (TN)) to all sample number. Error rate is the rate of the sample number calculated false (False Positive (FP) and False Negative (FN)) to all sample number. It is expected that the accuracy rate is higher than the false rate at the end of the study. NPV means Negative Predictive Value [15]. Success scores are calculated with the help of the confusion matrix (Table 2).

Table 2: Distribution of scar variable

Scar		Actual		Total
		1	0	
Prediction	1	TP	FP	Precision Score
	0	FN	TN	NPV
Total		Recall Score, Sensitivity	Specificity	ACC

The success measures and formulas used in our study, which were calculated with the help of Confusion Matrix;

ACC = (TP + TN) / (TP + TN + FP + FN)

Precision = TP / (TP + FP)

NPV = TN / (TP + FP)

Recall = TP / (TP + FN)

Specificity = TN / (FP + TN)

There are several more accuracy scores calculated with the help of confusion matrix. In addition to the power of the study, type II error, type I error are calculated respectively via TP value, FN value and FP value.

In statistics, the ROC (receiver operating characteristic) curve is a graphical plot showing the diagnostic capability of the dual classification system. AUC (Area Under the Curve) shows the classification performance of the installed model and takes a value between 0 and 1. AUC value close to 1 means that the classification performance of the model is high [15].

K-fold cross validation is a popular procedure for estimating the performance of a classification algorithm or comparing the performance between two classification algorithms on a data set. This procedure randomly divides a data set into k disjoint folds with approximately equal size, and each fold is in turn used to test the model induced from the other k1 folds by a classification algorithm. The performance of the classification algorithm is evaluated by the average of the k accuracies resulting from k-fold cross validation, and hence the level of averaging is assumed to be at fold [12].

For all analysis and processing, a computer with Windows 10 64-bit operating system, quad-core Intel Skylake Core i5-6500 CPU with 3.2 GHz 6MB Cache and 8GB 2400MHz DDR4 Ram was used.

Results

In this study, we used machine learning to retrospectively analyze data from patients with LUTD. The records of 114 patients who underwent urodynamic study were retrospectively investigated in this study. The data of 39 patients were excluded from the study due to the missing information.

The mean age of 75 patients [48 (64%) girls, 27 (36%) boys] was 8.7 (3.78) years. Of 75 patients, 24 (32%) had NBD, 25 (33.3%) FI and 26 (34.7%) CAKUT. Fifty-one (68%) patients had RUTI (22 patients with UTI due to extended-spectrum beta-lactamase-producing Enterobacteriaceae). There was renal parenchymal thinning in 6 (8%) patients on US examination. Hydronephrosis was detected in 19 (25.3%) patients. US examination showed bladder wall thickening in 26 (34.7%) patients. The trabeculated bladder was present in 15 (20%) patients. Table 3 shows the results obtained by MLT. Table 4 shows the best scores of the study. Figure 1 shows ROC AUC Graphs for Imbalanced and Smote Dataset.

Table 3: The results obtained by MLT

(%)	Alg.	LR	KNN	SVM	NB	DT	RF	XGB	ANN
Specificity	Smote	80.00	66.67	76.19	76.19	88.24	88.24	93.33	93.75
	Imb.	100.0	28.57	100.0	57.14	50.00	50.00	100.0	80.0
Sensitivity	Smote	91.67	58.87	90.91	90.91	86.67	86.67	82.35	87.50
	Imb.	80.95	75.00	80.95	87.50	82.35	85.00	89.47	88.89
NPV	Smote	94.12	58.82	94.12	94.12	88.24	88.24	82.35	88.24
	Imb.	33.33	33.33	33.33	66.67	50.00	50.00	66.67	66.67
Precision	Smote	73.33	66.67	66.67	66.67	86.67	86.67	93.33	93.33
	Imb.	100.0	70.59	100.0	82.35	82.35	100.0	100.00	94.12
ROC AUC	Smote	83.73	62.75	80.39	80.39	87.45	87.45	87.84	90.78
	Imb.	66.67	51.96	66.67	74.51	66.18	75.00	83.33	80.39
ACC	Smote	84.38	62.50	81.25	81.25	87.50	87.50	87.50	90.63
	Imb.	82.61	60.87	82.61	78.26	73.91	86.96	91.30	86.96
Cross Validation	Smote	75.27 (6.92)	72.82 (6.94)	75.18 (12.42)	73.55 (4.74)	75.55 (8.72)	80.45 (10.39)	78.27 (9.94)	81.27 (9.82)
	Imb.	78.42 (5.75)	61.19 (5.8)	63.87 (7.52)	74.13 (9.21)	68.88 (10.86)	66.38 (10.08)	73.06 (8.42)	79.93 (9.94)

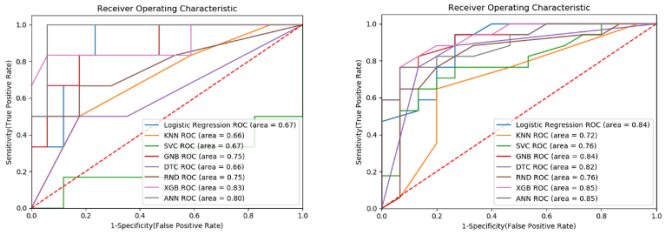

Figure 1: ROC AUC Graphs for Imbalanced and Smote Dataset

Table 4: The best scores of the study

(%)	Imbalanced (ANN)			Imbalanced (XGB)			Smote (ANN)			Smote (XGB)		
Predict\Actual	1	0	ACC	1	0	ACC	1	0	ACC	1	0	ACC
1	16	1	94.12	17	0	100.00	14	1	93.33	14	1	93.33
0	2	4	66.67	2	4	66.67	2	15	88.24	3	14	82.35
ACC	88.89	80.00	86.96	89.47	100.00	91.30	87.50	93.75	90.63	82.35	93.33	87.50
Cross Validation Score	79.93 (6.12)			73.06 (8.42)			81.27 (9.82)			78.27 (9.94)		
ROC AUC	80.39			83.33			90.78			87.84		

Discussion

The highest success rate according to the ACC value in the Confusion Matrix was obtained by the XGB algorithm in the unbalanced data set (91.30%). However, the Cross-Validation method and ROC AUC results are more reliable, especially because of the small number of data. When the ROC AUC values were examined, the highest success rate was obtained by ANN algorithm (90.78%). When cross-validation results (k=5) were examined, it was found that it supports ROC AUC results and the highest success rate was achieved with ANN algorithm (81.27%). In addition, by performing smote the data set, the number of samples (data) was increased and the data was balanced, the result was higher than the balance of the data.

When all these findings are evaluated together, it can be said that ANN algorithm with (90.63%), Cross Validation score (81.27%) and ROC AUC value (90.78%) can give high results in estimating renal scar in children with lower urinary tract dysfunction. In this case, patients with truly scarring are estimated correctly (93.33%) and in fact, non-scar patients are more accurately estimated (82.35%). However, higher number of data (sample size) would lead to a better result.

Abnormalities of the bladder wall by muscular hypertrophy and abnormal collagen in the detrusor muscle could result in bladder wall thickness and trabeculation in LUTD. The children with LUTD have an increased risk for RUTI infections due to the presence of PVR and other alterations of lower urinary tract dynamics. The incidence of breakthrough infection is higher in LUTD than in patients without voiding dysfunction [16]. The adequate blood flow of the bladder is very important for the host defense mechanism. Bladder ischemia due to over-distension or poor compliance may lead to an increased risk of UTI. PVR urine is especially important in the diagnosis of LUTD dysfunction. There is a positive association between elevated PVR and an increased risk of UTI [17]. The disorders of bladder emptying and drainage of the pelvicalyceal system may lead to the development of renal scarring by UTI. Also, elevated PVR may increase the risk for upper urinary tract damage [18]. Upper urinary tract deterioration and renal scarring are the most threatening problems in patients with lower urinary tract dysfunction (LUTD), occurring in 5–50% [19].

Follow-up studies of children with LUTD defined a subset at risk for urinary tract deterioration focused on disadvantageous urodynamic parameters, which include dyssynergia between the detrusor and the external urethral sphincter, detrusor pressure at maximal cystometric capacity (PMCC) greater than 40 cm water, and decreased bladder compliance [20].

Sonography is an important imaging modality with some remarkable advantages to follow the renal scar. It can be performed rapidly and in multiple settings, costs less, and saves patients from ionizing radiation and anesthesia. Major disadvantages are its lower resolution and inter- and intra-operator variability. Normal USG could not exclude the renal parenchymal lesion [21]. However, previous reports have proven a low correlation between RBUS and renal scarring, compared to the gold standard DMSA scintigraphy, with sensitivity ranging from 5 to 47% [22, 23]. It can substitute Tc-DMSA scintigraphy, especially in patients requiring follow-up scanning and, accordingly, remarkable radiation exposure [24].

Hydronephrosis is thought to cause renal functional deterioration. DeLair et al. [25] reported that hydronephrosis did not correlate with kidney damage. Vega et al. [21] reported that the reduced bladder capacity was the most frequent finding in children with RUTI and bilateral renal damage. Arora et al. [26] showed that the frequency of decreased bladder capacity was higher in patients with renal scarring. They had greater leak pressures compared to patients without renal damage.

It is particularly important to protect kidney function in patients with LUTD. Clean intermittent catheterization is one of the treatment methods in patients with difficulty emptying their bladder due to neurogenic and non-neurogenic causes. The majority of patients to whom CIC was performed are at an increased risk for RUTI. The use of urine catheters can lead to increase the risk of UTI due to decreased protective effect of urethral length, chronic inflammation, and alterations in defense mechanisms [25]. CIC has been performed to decrease hydronephrosis, VUR, bladder trabeculation, and renal scarring. In recent years, controversial results have been reported regarding the benefit of CIC to decrease renal scarring, trabeculated bladder, and VUR. DeLair et al. [26] reported that delayed initiation of CIC was associated with renal cortical deterioration, but there was no statistically significant difference in their study. In another study, it was shown that early CIC might not prevent renal scarring in children with NBD. Moreover, early initiation of CIC was associated with the development of abnormal findings on DMSA scintigraphy. Also, the performing of CIC is one of the most important risk factors for UTI in patients with LUTD [27]. CIC facilitates the entry of bacteria into the bladder. Also, bacteria can reach the kidney more easily in patients VUR.

Limitations

There are several limitations in our study. Firstly, this is a retrospective analysis. Secondly, the numbers of patients are small. Nevertheless, the first time, the estimation model for renal scarring in children was tested by using ML.

Conclusion

In conclusion, our data may suggest that ML is a useful method of predicting a diagnosis of renal damage in children with LUTD. In addition, the use of ML method could be helpful to prevent unnecessary DMSA scintigraphy and radiation exposure.

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Neutrophil to lymphocte ratio and mean platelet volume may predict the development of the pressure ulcers

Nötrofil lenfosit oranı ve ortalama trombosit hacmi bası yarası oluşumu öngörebilir

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Ethics Committee Approval: Ethics Committee and the institutional review board of Health Sciences University Sureyyapasa Chest Diseases and Chest Surgery Training and Research Hospital approval was obtained (116.2017.184/2020). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
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Abstract

Aim: Inflammation may have deleterious effects on tissue healing. Pressure ulcers impair the quality of life of the patients admitted to intensive care unit (ICU) besides increasing the health costs. Neutrophil to lymphocyte ratio (NLR) and mean platelet volume (MPV) are simple and readily available markers proinflammatory state. This study aimed to investigate whether measurement of admission NLR and MPV could be useful in identification of the patients who are at elevated risk for the development of the pressure ulcers.

Methods: This retrospective cohort study evaluated 104 patients admitted to the intensive care unit of a tertiary center. Patients were divided into two groups according to the presence of pressure ulcers as follows: Patients without pressure ulcers throughout hospitalization and patients who developed pressure ulcers while hospitalized. The two groups were compared with respect to the demographic features and complete blood count parameters at admission.

Results: The NLR [8.8 (6.6) vs. 5.3 (2.6), $P<0.001$], platelet to lymphocyte ratio [322(125) vs. 234(116), $P=0.023$] and MPV [10.5 (1.5) fl vs. 9.8 (1.1) fl, $P<0.001$] were significantly higher, and length of ICU stay was significantly longer in patients with pressure ulcers than those without [16.1 (3.8) days vs. 12.5 (2.9) days, $P<0.001$]. Logistic regression analysis revealed that age ($P=0.03$), length of ICU stay ($P=0.01$), NLR ($P=0.01$) and MPV ($P=0.01$) were significantly predictive for the presence of pressure ulcers.

Conclusions: Our findings indicate that age, length of ICU stay, and NLR, and MPV, which are indicative for the preexisting inflammatory state, are independent predictors for the development of pressure ulcers in patients admitted to the ICU.

Keywords: Intensive care unit, Pressure ulcer, Neutrophil to lymphocyte ratio, Mean platelet volume, Inflammation

Öz

Amaç: İnflamasyonun doku iyileşmesi üzerinde olumsuz etkileri olabilir. Basınç ülserleri, yoğun bakım ünitesine (YBÜ) kabul edilen hastaların yaşam kalitesini bozmanın yanı sıra sağlık maliyetlerini de arttırır. Nötrofil/lenfosit oranı (NLR) ve ortalama trombosit hacmi (MPV) basit ve kolayca temin edilebilen proinflamatuar belirteçlerdir. Bu çalışma, NLR ve MPV giriş ölçümünün, basınç ülserlerinin gelişimi için yüksek risk altında olan hastaların tanımlanmasında faydalı olup olmadığını araştırmayı amaçlamıştır.

Yöntemler: Bu retrospektif kohort çalışması ile üçüncü basamak bir merkezin yoğun bakım ünitesine başvuran 104 hastanın değerlendirilmesi yapıldı. Basınç ülseri varlığına göre hastalar şu şekilde iki gruba ayrıldı: Hastanede yatış boyunca basınç ülseri olmayan hastalar ve hastanede yatış döneminde basınç ülseri gelişen hastalar. İki grup demografik özellikler ve geliş tam kan sayımı parametreleri açısından karşılaştırıldı.

Bulgular: NLR [8,8 (6,6) / 5,3 (2,6), $P<0,001$], trombosit-lenfosit oranı [322 (125) / 234 (116), $P=0,023$] ve MPV [10,5 (1,5) fl / 9,8 (1,1) fl, $P<0,001$] basınç ülseri olan hastalarda olmayanlara göre anlamlı olarak daha yüksekti. YBÜ'de kalış süresi de basınç ülseri olanlarda basınç ülseri olmayanlardan anlamlı olarak daha uzundu [16,1 (3,8) güne karşı 12.5 (2,9) gün, $P<0,001$]. Lojistik regresyon analizi yaş ($P=0,03$), YBÜ kalış süresi ($P=0,01$), NLR ($P=0,01$) ve MPV'nin ($P=0,01$) basınç ülserlerinin varlığı için anlamlı olduğunu göstermiştir.

Sonuçlar: Bulgularımız, önceden var olan enflamatuar durumu gösteren yaş, YBÜ kalış süresi ve NLR ve MPV'nin YBÜ'ye kabul edilen hastalarda basınç ülseri gelişimi için bağımsız belirteçler olduğunu göstermektedir.

Anahtar kelimeler: Yoğun bakım ünitesi, Bası yarası, Nötrofil lenfosit oranı, Ortalama trombosit hacmi, Enflamasyon

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Introduction

Intensive care refers to the combination of the methods used to maintain the vital functions of the patients who are critically ill. Since these patients require extensive monitorisation and catheterization, majority are prone to the development of the pressure ulcers resulting from immobilization. A pressure ulcer is defined as a new or established area of skin and/or tissue discoloration or damage which persists after the removal of pressure and which is likely due to the pressure on the tissues [1]. These ulcers usually occur over bony prominences such as the base of the spine, hips, and heels of the elderly and immobile patients, or those with acute illnesses who are admitted to the intensive care unit (ICU). The reported incidence of pressure ulcers among patients admitted to the ICU varies between 3.3% and 39.3% [2,3].

Development of pressure ulcers in a patient admitted the ICU not only increases health costs but also represent a major burden of sickness and reduced quality of life for patients. Several scales have been introduced to identify the subjects who are at high risk for the development of pressure ulcers. However, the benefits of using a pressure ulcer risk scale are of question. Some previous data indicate that clinical judgment provides similar outcomes with these scales in the identification of the high-risk patients for pressure ulcers. Therefore, there is still need for simple indicators for the detection of the patients who are potential candidates for the development of the pressure ulcers.

Complete blood count (CBC) parameters, including neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), mean platelet volume (MPV), and red blood cell distribution width (RDW) have previously shown to be useful in predicting poor wound healing in various clinical settings [4-6]. However, the roles of the aforementioned CBC parameters in prediction of the pressure ulcer development has not been studied yet.

The present study aimed to investigate whether the CBC parameters, including NLR, PLR, MPV and RDW could be useful in identification of the patients who are at elevated risk for the development of the pressure ulcers.

Materials and methods

We retrospectively evaluated 104 patients admitted to the intensive care unit of a tertiary center between September 2018 and August 2019. Written informed consent was obtained for all subjects. This study complied with the Declaration of Helsinki and was approved by the Ethics Committee and the institutional review board of Health Sciences University Sureyyapasa Chest Diseases and Chest Surgery Training and Research Hospital (116.2017.184/2020).

Those with peripheral arterial disease, recent or previous cerebrovascular event, spinal cord injury, intracranial mass, length of ICU stay > 30 days, mean arterial pressure<70 mmHg, subjects requiring vasopressors and patients with pressure ulcers at admission to ICU were excluded. Patients were divided into two groups according to the presence of pressure ulcers as follows: Patients without pressure ulcers throughout the hospitalization period and patients who developed pressure ulcers while hospitalized. Demographic and clinical data, and laboratory test values at admission were retrieved from the institutional database and the patient charts. The two groups were compared with respect to the demographic features and complete blood count parameters at admission (LH-750, Beckman Coulter, USA).

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 17 (SPSS, Chicago, IL, USA). Shapiro-Wilk test was used for normality check. Data are presented as mean (standard deviation) or median (minimum-maximum) for continuous variables regarding normality and as frequency for categorical variables. Normally distributed continuous variables were compared using the Student's t-test. Categorical variables were compared with the Pearson chi-square test. Logistic regression analysis was carried out to identify the predictors for the development of the pressure ulcers. A two-sided $P<0.05$ was considered statistically significant.

Results

A total of 104 patients, 66 males (63.5%) and 38 females (36.5%), with a mean age of 67 (14) years were included in the study. Among all, 52 had pressure ulcers and 52 did not. Demographic features and laboratory values at admission are presented in Table 1.

There were no significant differences between the groups with respect to age, gender, BMI, presence of diabetes, hypertension, coronary artery disease and smoking habit ($P>0.05$ for all). Hemoglobin, reticulocyte distribution width, platelet count and leukocyte count were also similar in the two groups. However, NLR [8.8 (6.6) vs. 5.3 (2.6), $P<0.001$], platelet to lymphocyte ratio [322 (125) vs. 234 (116), $P=0.023$] and MPV [10.5 (1.5) fl vs. 9.8 (1.1) fl, $P<0.001$] were significantly higher, and length of ICU stay was significantly longer in patients with pressure ulcers than those without [16.1 (3.8) days vs. 12.5 (2.9) days, $P<0.001$]. As shown in Table 2, variables for which the *P*-value was <0.01 were included in the binary logistic regression. Logistic regression analysis revealed that age (OR:1.038, 95% CI: 1.002-1.075, $P=0.039$), length of ICU stay (OR:1.183, 95% CI: 1.034-1.353, $P=0.015$), NLR (OR:1.206, 95% CI: 1.032-1.411, $P=0.019$) and MPV (OR:1.456, 95% CI: 1.064-1.992, $P=0.019$) were significantly predictive for developing pressure ulcers.

Table 1: Comparison of the clinical features and laboratory measurements of the study groups

	Pressure ulcer (-) n=52	Pressure ulcer (+) n=52	*P*-value
Age, years	63.2 (15.8)	70.8 (12.2)	0.064
Gender, male	34 (65.4%)	32 (61.5%)	0.684
BMI, kg/m^2	28.6 (1.5)	28.9 (1.7)	0.441
Diabetes, n	14 (26.9%)	18 (34.6%)	0.395
Hypertension, n	25 (48.1%)	20 (38.5%)	0.322
Smoking, n	16 (30.8%)	19 (36.5%)	0.534
CAD, n	12 (23.1%)	14 (26.9%)	0.651
ICU stay, days	12.5 (2.9)	16.1 (3.8)	<0.001
Hemoglobin, g/dl	10.7 (2.0)	10.9 (1.6)	0.911
NLR	5.3 (2.6)	8.8 (6.6)	<0.001
Mean platelet volume, fl	9.8 (1.1)	10.5 (1.5)	0.012
RDW, %	14.4 (1.0)	14.1 (0.8)	0.788
Platelet count, 10^3/ul	194 (68)	221 (83)	0.080
PLR	234 (116)	322 (125)	0.023
Leukocyte count, 10^3/ul	10.1 (2.7)	10.9 (2.6)	0.098

BMI: Body mass index, CAD: Coronary artery disease, ICU: Intensive care unit, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, RDW: Red cell distribution width, Data are presented as mean (standard deviation (SD)) for continuous variables, and frequency (percentage) for the categorical variables.

Table 2: Predictive value of the selected variables on the development of the pressure ulcer

	Odds ratio	95% CI	*P*-value
Age	1.038	1.002 - 1.075	0.039
ICU stay	1.183	1.034 - 1.353	0.015
NLR	1.206	1.032 - 1.411	0.019
MPV	1.456	1.064 - 1.992	0.019
Platelet count	1.001	0.995 - 1.008	0.705
PLR	1.002	0.999 - 1.005	0.268
Leukocyte count	1.075	0.893 - 1.293	0.446

ICU: Intensive care unit, MPV: Mean platelet volume, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio

Discussion

The present study investigated whether several components of CBC could prove successful in identification of subjects who are at high risk for the development of the pressure ulcers during their stay in the ICU. Our findings show that NLR, PLR, and MPV are higher and length of ICU stay is longer in patients with pressure ulcers than those without. Our results also indicate that age, NLR, MPV and length of ICU stay are independent predictors of the development of pressure ulcers in patients admitted to the ICU. Pressure ulcers, which are also known as decubitus ulcers, usually develop in subjects who are unable to change position regularly. Huge majority of the patients admitted to ICU are, therefore, at considerable risk for the development of pressure ulcers [7]. Although the development of the pressure ulcer does not likely increase the mortality rate during hospital admission, it is associated with several other complications including increased risk of infection, in-hospital malnutrition, increased length of stay, increased workload for healthcare professionals and increased healthcare costs [8,9]. Patients admitted to ICU do not perceive the increased tissue pressure and consequently cannot react to it properly due to all sedative agents they receive. Moreover, underlying diseases and deterioration of the tissue perfusion due to the altered hemodynamics or hypoxia increases the risk of pressure ulcers [10-12].

Several preventative measures have been introduced to reduce the magnitude and/or duration of pressure between a patient and the supporting surface and to treat the wound which results from the pressure [13, 14]. However, non-selective application of these measures for all patients admitted to the ICU is not only time consuming but also costly.

Thus, various scales have been developed to identify the patients who are at high risk for development of pressure ulcers [15]. However, the evidence indicating the accuracy of risk assessment scales for pressure sores is vague, and it is not clear that these scales are better than clinical judgement or that they improve outcomes [16].

A recent prospective cohort study of 335 patients who were hospitalized in ICU revealed that presence of diabetes, treatment with vasopressors, endotracheal intubation, length of stay on ICU, and level of consciousness were associated with the development of pressure ulcers [17].

However, a recent meta-analysis of 17 studies and 19,363 patients have reported that there was no single factor which could explain the occurrence of pressure ulcers among the risk factors including age, length of ICU stay, diabetes, time of MAP <60-70 mmHg, mechanical ventilation, length of mechanical ventilation, intermittent hemodialysis or continuous veno-venous hemofiltration therapy, vasopressor support, sedation and turning [16,18].

Nevertheless, the need for a simple, readily available, and costless biomarker for the identification of the risk for the development of pressure ulcer is continuing. We, therefore, investigated whether CBC parameters could facilitate the identification of those at elevated risk for pressure ulcers and found out that age, NLR, MPV and length of ICU stay were predictive for the development of pressure ulcers. Older age and longer ICU stay as predictors of pressure ulcers is somewhat consistent the evidence derived from the previous studies [19-21]. However, high NLR and MPV have been established as predictors for pressure ulcer development for the first time. Platelets are enucleated cells which are traditionally considered to be solely involved in primary hemostasis and coagulation as a response to various kinds of physiologic triggers. However, emerging evidence indicates that platelets have additional roles in other physiopathological processes including inflammation, tissue regeneration and wound healing [22-24]. Recent findings from in-depth platelet signaling studies show that platelets actively participate in immunity and may exhibit deleterious effects in certain conditions such as in systemic inflammatory response syndrome and acute vascular diseases. Mean platelet volume is a measurement of the average size of platelets found in the blood stream which is universally available with routine blood counts by automated hemograms. An elevation in MPV level has been shown in several clinical conditions with chronic inflammation including ankylosing spondylitis, rheumatoid arthritis, chronic cardiovascular diseases, hypertension, and dyslipidemia [25-27].

Moreover, higher MPV was associated with poor wound healing in patients undergoing total abdominal hysterectomy [28]. In addition to MPV, NLR is another marker for pro-inflammatory state and has been associated with several diseases presenting with subclinical inflammation including peripheral vascular disease and coronary artery disease [29-31].

With this in mind, we speculate that the preexisting inflammatory state, as indicated by the presence of high MPV and NLR in our subjects with pressure ulcers, complicates tissue healing and gives rise to the development of decubitus ulcers. We suggest that clinicians should pay attention to the admission levels of NLR and MPV, which are widely available, easily derived, and reproducible markers of inflammation, to identify the subjects at elevated risk for the development of pressure ulcers.

Limitations

This study also has some limitations. First, our results represent the analysis of retrospective data. Therefore, we cannot reach accurate conclusions to recommend NLR and MPV as a routine part of the evaluation of patients admitted to the ICU. However, we concur that our findings are encouraging for future prospective and randomized trials investigating the predictive role of inflammatory markers in the development of pressure ulcers.

Conclusions

Results of the present study show that NLR, PLR, and MPV are higher and length of ICU stay is longer in patients with pressure ulcers than those without. Our findings also indicate that age, NLR, MPV and length of ICU stay are independent predictors for the development of pressure ulcers in patients

admitted to the ICU. The preexisting inflammatory state indicated by the high NLR and MPV might have contributed to the development of the pressure ulcers. We suggest that clinicians should pay attention to the admission levels of NLR and MPV, which are widely available, easily derived, and reproducible markers of inflammation, to identify the subjects at elevated risk for the development of pressure ulcers.

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Treatment of fistula-in-ano: Outcome comparison between traditional surgery and novel approaches. A retrospective cohort study in a single center

Perianal fistül tedavisi: Geleneksel cerrahi yöntem ile yeni yaklaşımlarının sonuçlarının karşılaştırılması. Tek merkezli bir retrospektif kohort çalışması

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Ethics Committee Approval: The study was approved by the Ethical Committee of the Province of Ferrara on 14 July 2016 with the number 160597. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
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Abstract

Aim: Fistula-in-ano is a well described disease but no definitive surgical technique has been developed. We conducted a retrospective cohort study in a single center to evaluate patients who underwent surgical treatment of a perianal fistula from 2012 to 2018 in our hospital. The aim of the study was to compare the outcome of different surgical techniques (Fistulotomy/fistulectomy and seton, Video-Assisted Anal Fistula Treatment (VAAFT), Micro-fragmented adipose tissue injection, Lipogems®).

Methods: A cohort of 103 patients with anal fistula who qualified for elective surgery between 2012 and 2018 were recruited at Sant'Anna Hospital in Ferrara. All patients underwent a digital rectal examination and preoperative magnetic resonance imaging (MRI) to identify the fistula tract and internal opening. Patients were divided into 4 groups, one for each type of surgery they underwent: Fistulotomy/fistulectomy and seton, Video-Assisted Anal Fistula Treatment (VAAFT), Micro-fragmented adipose tissue injection, Lipogems®). Numerical rating scale (NRS) was used to assess subjective pain one week after surgery and documented. The scale ranged from 0 to 10, where 0 stands for no pain and 10 stands for worst pain ever faced. Primary end point was fistula recurrence at 1 year of follow-up. Secondary end point was evaluation of post-operative pain.

Results: There were 71 males and 32 females, with a median age of 50 years (range 21-89 years). Among them, 79 patients were newly diagnosed, the other 24 patients had undergone previous surgery and had recurrence. In total, 118 surgical operation were performed for anal fistula. During the follow-up period, anal fistula recurrence was observed in 13 patients after VAAFT, 3 patients after Micro-fragmented adipose tissue injection, 4 after fistulotomy, 12 after fistulectomy, 10 after seton placement and 8 after Lipogems® technique. One week after surgery, pain was evaluated by all patients on a scale from 0 to 10. The mean scores of patients who underwent VAAFT, micro-fragmented adipose tissue injection, fistulotomy, fistulectomy, seton placement and Lipogems® technique were 1 (0-5), 1.5 (0-8), 5 (3-8), 6.8 (5-9), 4.2 (2-6) and 0 (0-2), respectively.

Conclusion: This study presents the difficulties in managing anal fistulas and the variety of surgical options. VAAFT and Micro-fragmented adipose tissue injection appear to be safe and feasible options in the management of anal fistula, and short-term healing rates are acceptable with no sustained effect on continence. There is, however, a paucity of robust data with long-term outcomes. These techniques are thus welcome additions. Lipogems ® technique is a safe and reproducible procedure, unfortunately according to our experience, it does not promote fistula healing in patients with recurrent inter-sphincteric anal fistula. We do not suggest the use of this technique as a first-line treatment.

Keywords: Anal fistula, Fistulotomy, Fistulectomy, Seton, VAAFT, Lipogems®, Micro-fragmented adipose tissue

Öz

Amaç: Anal fistül iyi tanımlanmış bir hastalıktır ancak kesin bir cerrahi teknik geliştirilmemiştir. Hastanemizde 2012-2018 yılları arasında perianal fistül nedeniyle cerrahi tedavi uygulanan hastaları değerlendirmek için tek merkezli, retrospektif bir kohort çalışması yürüttük. Çalışmanın amacı, farklı cerrahi tekniklerin (Fistülotomi / fistülektomi ve seton, Video Destekli Anal Fistül Tedavisi (VAAFT), Mikro-parçalanmış yağ dokusu enjeksiyonu, Lipogems®) sonuçlarını karşılaştırmaktı.

Yöntemler: Elektif cerrahi için uygun olan anal fistüllü 103 hastadan oluşan bir kohort, 2012 ve 2018 yılları arasında Ferrara'daki Sant'Anna Hastanesi'nde opere edildi. Tüm hastalara fistül traktını ve iç açıklığı belirlemek için ameliyat öncesi rektal tuşe ve manyetik rezonans görüntüleme (MRI) uygulandı. Hastalar, geçirdikleri her ameliyat için birer tane olmak üzere 4 gruba ayrıldı: Fistülotomi / fistülektomi ve seton, Video Destekli Anal Fistül Tedavisi (VAAFT), Mikro parçalı yağ dokusu enjeksiyonu, Lipogems®). Ameliyattan bir hafta sonra öznel ağrıyı değerlendirmek için sayısal derecelendirme ölçeği (NRS) kullanıldı ve sonuçlar kaydedildi. Puanlar, 0, hiç ağrı yok, ile 10, karşılaşılan en şiddetli ağrı, arasında değişmekteydi. Birincil sonlanım noktası, 1 yıllık takipte fistül rekürrensiydi. İkincil sonlanım noktası, ameliyat sonrası ağrının değerlendirilmesiydi.

Bulgular: Ortanca yaşı 50 olan (aralık 21-89 yaş) 71 erkek ve 32 kadın çalışmaya dahil edildi. Bunlardan 79 hastaya yeni teşhis konulmuş, diğer 24 hasta daha önce ameliyat olmuş ve nüksetmişti. Anal fistül için toplam 118 cerrahi operasyon yapıldı. Takip süresince VAAFT sonrası 13 hastada, Mikro parçalı yağ dokusu enjeksiyonu sonrası 3 hastada, fistülotomi sonrası 4 hastada, fistülotomi sonrası 12 hastada, seton yerleştirme sonrasında 10 hastada ve Lipogems® tekniğinden sonra 8 hastada anal fistül rekürrensi gözlendi. Ameliyattan bir hafta sonra ağrı tüm hastalar tarafından 0 ile 10 arasında bir ölçekte değerlendirildi. VAAFT, mikro parçalı yağ dokusu enjeksiyonu, fistülotomi, fistülektomi, seton yerleştirme ve Lipogems® tekniği uygulanan hastaların ortalama skorları sırasıyla 1 (0- 5), 1.5 (0-8), 5 (3-8), 6.8 (5-9), 4.2 (2-6) ve 0'dı (0-2).

Sonuç: Bu çalışma anal fistül yönetimindeki zorlukları ve çeşitli cerrahi seçenekleri sunmaktadır. VAAFT ve Mikro-parçalanmış yağ dokusu enjeksiyonu, anal fistül yönetiminde güvenli ve uygulanabilir seçenekler gibi görünmektedir ve kısa süreli iyileşme oranları, kontinans üzerinde kalıcı bir etki olmaksızın kabul edilebilirdir. Bununla birlikte, uzun vadeli sonuçları olan güvenilir veri yetersizliği olduğundan, bu teknikler, bu nedenle memnuniyetle karşılanmaktadır. Lipogems ® tekniği güvenli ve tekrarlanabilir bir işlemdir, ancak ne yazık ki deneyimlerimize göre, tekrarlayan sfinkterik anal fistülü olan hastalarda fistül iyileşmesini desteklememektedir. Bu tekniğin birinci basamak tedavi olarak kullanılmasını önermiyoruz.

Anahtar kelimeler: Anal fistül, Fistülotomi, Fistülektomi, Seton, VAAFT, Lipogems®, Mikro parçalanmış adipoz doku

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Introduction

Anal fistula is one of the most common conditions in surgical clinics dealing with anorectal diseases. Anal fistula is an epithelized communication of infectious origin between the rectum or anal canal and the perianal region. One of the most widely accepted etiologic factors for the formation of fistulae is when an infected perianal gland develops an abscess and ruptures into anal canal on one side and perianal skin on the other side. Patients with anal fistulae typically complain of pain, drainage of pus or stool, pruritus, and excoriation of adjacent tissue. Though not life-threatening, these symptoms often significantly impact patients' social, intimate, and work lives. There are several types of fistulae with respect to their course through the anal sphincter:

- Submucosal: the fistula track passes superficially beneath the submucosa and does not involve any sphincter muscle
- Inter-sphincteric fistula: the track passes through the internal sphincter and continues in the inter- sphincteric plane to the perianal skin, not including the external anal sphincter
- Trans-sphincteric fistula: the track cross through the internal and external anal sphincter on its exit towards the perianal area.
- Supra-sphincteric fistula: the fistulous tract passes through the internal sphincter but traverses the external sphincter below the puborectalis muscle;
- Extra-sphincteric fistula: the fistulous track may pass outside the sphincter complex through the ischiorectal fossa to the perianal skin [1].

A fistula-in-ano can be "simple" or "complex."

Simple fistulae are inter-sphincteric and low trans-sphincteric, with less than 30% of the external and internal anal sphincter involved.

It is termed "complex" when the tract crosses more than 30% to 50% of the external sphincter (high trans-sphincteric, supra-sphincteric and extra-sphincteric fistulas), is located anteriorly, found in a female, is recurrent, has multiple tracks or the patient has pre-existing incontinence, was exposed to local irradiation or the patient has Crohn's disease. Complex fistulas pose a higher risk of incontinence after surgical management [2].

Fistulotomy/fistulectomy is still considered the gold standard for the treatment of the simple type, but has lot of postoperative pain, takes more time to heal and poses another important problem: Anal sphincter injury which can result in incontinence. On the other hand, the treatment of the complex type is still very challenging, and a gold standard procedure is not available. Studies have shown that complex, branched, or recurrent fistulas are at a higher risk of treatment failure and complications [3].

To date, only a few studies with surgical comparison for treatment of anal fistula are published in the English literature. The aim of our study is to compare outcome and pain control of different surgical procedures for the treatment of anal fistula in a well-defined territorial cohort of a single hospital with dedicated surgeons.

Materials and methods

This is a retrospective cohort study was designed to compare clinical outcome data on the use of different surgical techniques in the treatment of anorectal fistula.

From 2012 to 2018, a total of 103 patients with anal fistula who qualified for elective surgery were recruited at Sant' Anna Hospital in Ferrara. All patients underwent a digital rectal examination and preoperative magnetic resonance imaging (MRI) to identify the fistula tract and internal opening. Every patient was informed of the procedure and consents were obtained. The plan of the study was approved by the ethical committee of the Province of Ferrara on 14 July 2016 with the number 160597. Prior informed consent was obtained from all patients included in the study.

Patients were divided into 4 groups, one for each type of surgery they underwent:

- Fistulotomy/fistulectomy and seton
- Video-Assisted Anal Fistula Treatment (VAAFT)
- Micro-fragmented adipose tissue injection
- Lipogems®

All patients operated with Lipogems technique were affected by simple perianal fistula and all were previously treated unsuccessfully with seton placement.

Some patients operated with the traditional technique (seton with or without fistulectomy) underwent the same or different type of surgery and for this reason they were included in more groups. All patients with first presentation or recurrent fistula were included in the study.

Numerical rating scale was used to assess subjective pain one week after surgery and documented. The scale ranged from 0 to 10, where 0 stands for no pain and 10 stands for worst pain ever faced. After discharge, all patients were followed for one year and any recurrence of the disease was noted. Any complications occurring in the postoperative period and during follow-up were noted. Recurrence was defined as the persistence of fistula at the same site or reappearance of any new fistula at the operated site.

Surgical procedures performed

Traditional surgery

- **Fistulotomy:** To perform fistulotomy, the internal and external sphincters are divided, accessory tracts are excised, and eventually overlapping sphincter reconstruction is performed.
- **Fistulectomy:** A keyhole skin incision is made over the fistulous tract and the external opening is encircled. The incision is deepened through the subcutaneous tissue, and the tract is removed from surrounding tissues.
- **Seton:** There are two types of setons used in treating anal fistulas. A cutting seton is used to slowly cut through the tissue allowing for healing from inside to outside thus minimizing the risk of incontinence. The second type of seton, the non-cutting seton, is used primarily for draining, especially in the acute setting, where it provides rapid and safe relief of the infection, with no compromise to the sphincter complex, providing time for the inflammation to resolve, and better assessment and decision-making. [1] After the removal of the seton, the fistula was closed by performing an anorectal flap.

VAAFT

Video-assisted anal fistula treatment is performed with a kit which includes a fistuloscope, an obturator, a unipolar electrode, an endobrush and 0.5 mL of synthetic cyanoacrylate glue. The fistuloscope has an 80° angled eyepiece and is equipped with an optical canne and a working and irrigating channel. Its diameter is 3.3 mm × 4.7 mm and its operative length is 18 cm.

The fistuloscope has two channels, one of which is connected to the irrigation fluid and the other which introduces the instruments. VAAFT consists of a diagnostic phase, followed by an operative phase. In the diagnostic phase, after proper cleaning and draping of the anal area, an obturatoris is introduced in the anal canal and fistuloscopy is performed to correctly locate the internal opening of the fistulous tract, secondary tracts, and abscess cavity if any. The running glycine-mannitol solution helps to open the fistulous tract.

The scope is then advanced forward slowly and the tract is straightened by maneuvering the scope. The next step is visualization of the internal opening, which is identified by the exit of the fistuloscope through it. Narrow openings are identified as a beam of illumination through the rectal mucosa or the exit of irrigating fluid through them. Both primary and secondary os and tracts are explored via fistuloscope. After the internal opening is located, absorbable sutures are put at its site in the rectum or anal canal for traction.

During the next operative phase, the aim is to destroy the fistula tract from the inside, curette it and close the internal opening. For this purpose, the electrode replaces the obturator from the external opening, under direct vision. The fistula wall is cauterized, and all wasted material is eliminated into the rectum through the internal opening. The internal opening is then closed with an anorectal flap. [4]

Micro-fragmented adipose tissue injection

Adipose tissue is collected via liposuction. Collected adipose tissue is centrifuged, and the aqueous fraction is subsequently expelled. The remaining adipose tissue is homogenized by shifting it between 2 connected syringes.

Epithelium and granulation tissue are removed by curettage, and a thin catheter is placed through the fistula. The mucosal edges are lifted before closing the internal opening, including the internal anal sphincter and the mucosa. The adipose tissue is injected around the internal opening and the fistula tract, creating a doughnut shape, until a firm swelling surrounds the fistula tract. [5]

Lipogems®

The initial procedure includes two phases: Lipo-aspiration (harvesting) and processing. Lower or lateral abdomen are chosen as the donor site. Before harvesting the fat, the area is injected with a local anesthetic (20 ml lidocaine 20 mg/ml and diluted with 1 ml adrenaline for vasoconstriction). After infiltration, the adipose tissue is harvested using standard liposuction technique, a 19cm 13G blunt cannula is used to prevent additional trauma to cells during the aspiration process. The harvested fat is then processed in the Lipogems ® processing kit, a disposable device that gradually reduces the size of the adipose tissue clusters while eliminating oily substances and blood residues with pro-inflammatory properties. The entire process is performed in complete immersion in saline solution minimizing any traumatic action on cell products. The resulting microfragmented adipose tissue is collected in a 10-ml syringe and positioned to empty the excess of saline solution. At the end, the product is transferred to several 1-ml syringes with a 22G and 30-mm length needle to be injected into the patient. The entire process takes between 15-20 minutes.

The first step of the surgical procedure is the debridement of the internal opening, and then, the closure of the muscular layer is carried out with 2/0 polydioxanone (PDS) stitches after undermining the mucosal edges in order to raise an amount of tissue 1 cm wider than the size of the enlarged tract. The product is injected into the submucosal layer surrounding the inner orifice and along the walls of the fistula's tract. [6]

Statistical analysis

Based on the size of the patient sample we performed a descriptive statistical analysis of the data collected. A total of 103 patients with anal fistulae were included in this study. There were 71 males and 32 females, with a median age of 50 years (range 21-89 years). Among them, 79 patients were newly diagnosed, the other 24 patients had undergone previous surgery and had recurrent conditions. In total, 118 surgical operations for anal fistula treatment were performed.

Results

Most of the perianal fistulas treated in our study were of the trans-sphincteric type 36 (35%), of which 25 were firstly diagnosed and 11 were recurrences (Table 1, figure 1).

Table 1: Types of fistula in ano

Type of fistula	First Diagnosis	Recurrent Fistula	Total
Complex fistula	3	2	5
Extrasphinteric	9	6	15
Transsphincteric	25	11	36
Intersphincteric	18	1	19
Submucosal	10	1	11
Not classified	14	3	17
Total	79 (77%)	24 (23%)	103

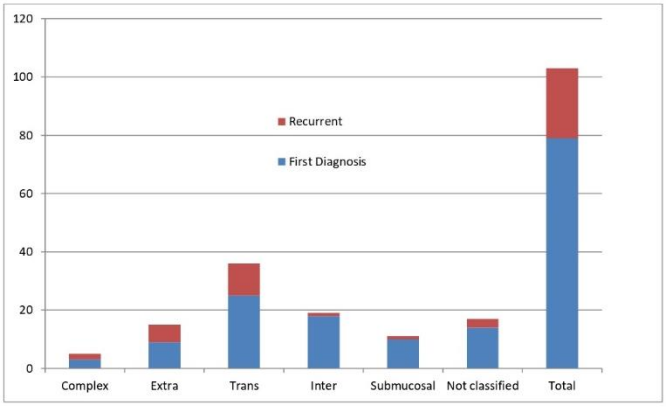

Figure 1: Groups of perianal fistulas, classified by type and first diagnosis\recurrence. Complex, Extra (extrasphinteric fistula), Trans (trans-sphinteric fistula), Inter (intersphinteric fistula), Submucosal, Not classified, Total (total of cases). First diagnosis of fistula in ano are blue and Recurrent fistula are red. Sant'Anna Hospital, Ferrara (2012-2018)

Video-Assisted Anal Fistula Treatment (VAAFT) group consisted of 24 patients, constituting 20% of surgeries. Micro-fragmented adipose tissue injection was performed in 25 patients, 21% of surgeries. Fistulotomy was performed in 21 patients, 18% of surgeries, fistulectomies were performed in 19 patients, 16% of surgeries and Setons were placed in 21 patients, making up 18% of all surgeries. Lipogems® technique was performed in 8 patients, adding up to only 6% of the total

number of surgeries. The outcomes of surgeries are summarized in Table 2 and Figure 2. During the follow-up period, anal fistula recurrence was observed in 13 (54%) patients after VAAFT, 3 (12%) patients after Micro-fragmented adipose tissue injection, 4 (19%) after fistulotomy, 12 (63%) after fistulectomy, 10 (48%) after seton placement and 8 (100%) after the Lipogems® technique. 3 cases who underwent fistulotomy and 1 patient who underwent seton application developed fecal soiling after the treatment. One week after surgery, pain was assessed by all patients on a scale (NRS) ranging from 0 to 10. One week after surgery, pain was evaluated by all patients on a scale from 0 to 10. The mean scores of patients who underwent VAAFT, micro-fragmented adipose tissue injection, fistulotomy, fistulectomy, seton placement and Lipogems® technique were 1 (0-5), 1.5 (0-8), 5 (3-8), 6.8 (5-9), 4.2 (2-6) and 0 (0-2), respectively.

Table 2: Outcomes of surgeries

Prognosis at 12-months follow-up	Healing	Recurrences	Total
VAAFT	11 (46%)	13 (54%)	24
Micro-fragmented adipose tissue injection	22 (88%)	3 (12%)	25
Fistulotomy	17 (81%)	4 (19%)	21
Fistulectomy	7 (37%)	12 (63%)	19
Seton	11 (52%)	10 (48%)	21
Lipogems	0 (0%)	8 (100%)	8
Total	68 (58%)	50 (42%)	118

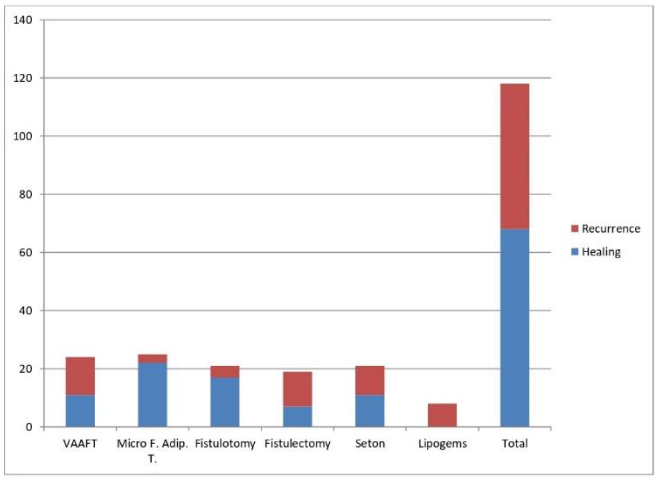

Figure 2: Type of surgery and outcomes (healing in blue and recurrence in red), Sant'Anna Hospital, Ferrara (2012-2018)

Discussion

The treatment of anal fistula is still challenging, although many attempts with new minimally invasive techniques have been made over the decades, it continues to be one of the most complex clinical problems in anorectal surgery [7].

The success rate of each technique varies, as reported in recent systemic reviews [8,9]. Fistulotomy remains the best option when solely addressing the chance of cure, although a third to a quarter of patients will experience mild leakage of flatus and mucus or fecal incontinence [10,11].

The goal of curing the disease whilst minimizing the risk of functional impairment has fueled the development of sphincter-preserving techniques.

VAAFT technique

VAAFT provides a minimally invasive technique with the ability to view the fistula from the inside so that all extensions can be identified and eradicated under direct vision using a fistuloscope [12]. Review demonstrates variable success rates with short-term (< 1 year) healing rates ranging from 67% [13]to 100% [14].

In our VAAFT group the recurrences were 13 (54%) out of 24. However, out of the total of 13 recurrences after VAAFT, 8 were trans-sphincteric fistulas. Some of the patients who had recurrence after VAAFT underwent autologous micro-fragmented adipose tissue injection. Only 1 patient out of 7 had another recurrence at 12 months of follow- up.

Micro-fragmented adipose tissue injection

It is well known that, besides being multipotent, mesenchymal stem cells (MSCs) can promote tissue repair through the release of bioactive [15] and immunomodulatory molecules [16]. Adipose tissue is an optimal source of MSCs because of easier access and greater abundance than other sources such as the bone marrow. Panès and colleagues reported a 50% combined remission rate in the intention-to-treat group treated with MSCs, compared to 34% success rate in those who received placebo in a randomized, double-blind, parallel group, placebo-controlled study. The treatment-related adverse events rate was 17% in the group treated with MSCs versus 29% in those treated with placebo [17].

In our experience Micro-fragmented adipose tissue injection had the lowest number of recurrences. Out of 25 patients treated with autologous micro-fragmented adipose tissue injection, 12 had trans-sphincteric fistulas (48%), 9 patients had recurrences (5 trans-sphincteric, 2 complex fistulas, 1 extra-sphincteric and 1 submucosal). 3 recurrences were recorded in patients injected with autologous micro-fragmented adipose tissue, 2 were complex fistulas and 1 was inter-sphincteric. All-trans sphincteric fistulas had healed at the 12-month follow-up visit.

Lipogems technique

Based on our experience, patients treated with Lipogems® do not require numerous post-operative medications. Postoperative pain and discomfort reported by our patients was limited when compared with patients treated with other techniques like seton with and without fistulectomy.

Furthermore, using autologous adipose tissue always allows compatible material to be available and ready to be used without major complications or adverse events.

The reduced amount of adipose tissue needed for each patient does not limit the use of this technique to patients with high BMI only. However, the high recurrence rate that occurred in our experience and the high cost of the product doesn't allow us to suggest its use as a first-line treatment for anal fistula. However, it could be taken into consideration as a possible second-line treatment after informing the patient about the advantages and risks. The high recurrence rate after treatment with Lipogems® technique could be explained by the type of fistula treated. In fact, all patients had already been treated with seton placement unsuccessfully.

Despite the limited cases in our study, the distribution of type of surgery within the individual arms of the study is homogeneous. The percentage of total recurrences in our hospital is 42%. As reported in literature, as well as in our study, the treatment of simple fistulas resulted in less recurrences (1 sub-submucosal; 1 inter-sphincteric). It is interesting to note that the only recurrences of this type of fistula were those treated with non-traditional surgery (1 submucosal recurrence after VAAFT; 1 inter-sphincteric recurrence after lipoaspirate). The surgical

procedure that had the highest number of recurrences was Fistulectomy (63%) followed by Seton application (48%). However, these groups of patients were not selected by type of fistulas; therefore, it is possible that many complex fistulas were subjected to this surgery. Furthermore, these types of interventions have been proposed to some patients who already underwent surgery.

The present study has several limitations. Firstly, there is significant heterogeneity in the population studied, fistula morphology and etiology, with no standardized population. Follow-up times is relatively short; high initial success rates (many lacking radiological assessment) may be misleading, and recurrences may develop more than a year after surgery.

However, the choice made by our center was to have all the operations performed by a single experienced surgeon, to standardize the surgical procedure as much as possible, reducing any bias. The paucity of patients on VAAFT and Micro-fragmented adipose tissue injection makes it difficult to comment accurately on success rates, but early results are promising. Notable advantages of these techniques are their avoidance of sphincter injury, minimal morbidity, and the ability to repeat them or perform other surgical techniques following failure.

Despite many treatment modalities, anal fistula disease remains an important problem. High recurrence rates have been reported in the surgical treatment of complicated anal fistulas [18].

The cost of the procedures is an important consideration. All new techniques involve the use of novel medical devices with an associated cost which is not a consideration when performing procedures like fistulotomy. No studies assessed cost-effectiveness. This needs to be further investigated.

Conclusion

This study is a picture of the difficulties in managing anal fistulas and of the variety of surgical options. VAAFT and Micro-fragmented adipose tissue injection appear to be safe and feasible options in the management of anal fistula, and short-term healing rates are acceptable with no sustained effect on continence. There is, however, a paucity of robust data with long-term outcomes. These techniques are thus welcome additions.

Lipogems® technique is a safe and reproducible procedure; unfortunately, according to our experience, it does not promote fistula healing in patients with recurrent inter-sphincteric anal fistula. We do not suggest the use of this technique as a first-line treatment.

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Research article
Araştırma makalesi

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The protective effect of sildenafil on liver sinusoidal obstructive syndrome after oxaliplatin-based chemotherapy: An experimental animal study

Sildenafil'in oksaliplatin esaslı kemoterapi sonrası karaciğerde gelişen sinüsoidal obstruktif sendrom üzerine koruyucu etkisi: Deneysel bir hayvan çalışması

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Ethics Committee Approval: The study protocol was approved by the Ankara University Animal Experiments Ethics Committee (Approval no: 201-2-11, dated 11/22/2014). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma protokolü Ankara Üniversitesi Hayvan Deneyleri Etik Kurulu tarafından onaylanmıştır (22.11.2014 tarih, 201-2-11 sayılı onay). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

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Abstract

Aim: Sinusoidal obstructive syndrome (SOS) that develops due to oxaliplatin-based chemotherapy influences morbidity and mortality following surgical treatment of colorectal liver metastases. The aim of this study was to evaluate the protective effect of sildenafil on liver damage (sinusoidal obstructive syndrome (SOS)) that develops due to oxaliplatin-based chemotherapy.

Methods: An experimental animal study was conducted and a total of 42 rats were randomly separated into 4 groups as Sham, intraperitoneal chemotherapy (ipCT), ipCT+low-dose sildenafil treatment, and ipCT +high-dose sildenafil treatment. The ipCT was applied once a week for 5 weeks. Histochemical analysis was made in the livers removed from rats.

Results: Parenchymal, stromal, and vascular changes were examined, and no statistically significant difference was determined between the groups with respect to the severity of sinusoidal dilatation (P=0.243). The groups significantly differed with regards to centrilobular, peliotic changes and hepatocellular changes (P<0.001).

Conclusion: Sildenafil has a protective effect against liver damage that develops due to oxaliplatin-based chemotherapy and prevents the development of SOS during chemotherapy in colorectal cancer patients. Therefore, it could be considered as a treatment strategy.

Keywords: Oxaliplatin, Sinusoidal obstructive syndrome, Sildenafil, Colorectal cancer, Liver metastasis

Öz

Amaç: Oksaliplatin bazlı kemoterapinin karaciğer metastazlı kolon kanserli hastalarda kullanımı karaciğer hasarına (sinüsoidal obstruktif sendrom (SOS)) neden olarak; metastaz rezeksiyonu sonrasında mortalite ve morbiditeyi arttırır. Bu çalışmamızda; sildenafilin kolorektal kanserlerin karaciğer metastazları için oksaliplatin bazlı kemoterapi sonucunda gelişen karaciğer hasarı, (SOS) üzerindeki koruyucu etkisini değerlendirmeyi amaçladık.

Yöntemler: Deneysel bir hayvan çalışması yürütüldü ve toplam 42 rat rastgele Sham, intraperitoneal kemoterapi (ipCT), ipCT + düşük doz sildenafil tedavisi ve ipCT +yüksek doz sildenafil tedavi grupları olarak 4 gruba ayrıldı. İpCT, 5 haftalık bir süre boyunca haftada birkez uygulandı. Ratlardan çıkarılan karaciğerlerde histopatolojik analiz yapıldı.

Bulgular: Parankimal, stromal ve vasküler değişiklikler incelendi ve sinüzoidal dilatasyonun şiddeti açısından gruplar arasında istatistiksel olarak anlamlı bir fark bulunmadı (P=0,243). Dört grup arasında sentrolobüler değişiklikler açısından istatistiksel olarak anlamlı fark saptandı (P<0,001). Peliotik ve hepatosellüler değişikliklerin değerlendirilmesinde gruplar arasındaki fark istatistiksel olarak anlamlı bulundu (P<0,001).

Sonuç: Sildenafil, kolorektal kanser hastalarında kemoterapi sırasında oksaliplatin bazlı kemoterapinin bir sonucu olarak gelişen SOS gelişimini önleyerek karaciğer hasarına karşı koruyucu bir etkiye sahip olması nedeniyle, kemoterapi esnasında tedaviye eklenmelidir.

Anahtar kelimeler: Oxaliplatin, Sinüsoidal obstrüktif sendrom, Sildenafil, Kolorektal kanser, Karaciğer metastaz

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Introduction

Colorectal cancer remains one of the most frequent cancers throughout the world and it is related with high mortality rates. An important prognostic factor is the presence of metastases. The liver is the most common site of metastasis. It develops in approximately 50% of colorectal cancer patients and 25% have liver metastases at diagnosis [1]. The best treatment method in patients with metastasis in the liver only is liver resection, which aims to remove all metastatic lesions [2]. Unfortunately, surgery is not appropriate for many patients due to a combination of factors such as size, localization, and the number of liver metastases. Neoadjuvant chemotherapy is currently applied to these patients who are initially considered inoperable to shrink the metastases, so the patient becomes eligible for surgery [3]. Chemotherapy regimens which are widely used for this purpose consist of a combination of thymidylate synthase inhibitors (5-FU/folinic acid or capecitabine), oxaliplatin (FOLFOX) or irinotecan (FOLFIRI). In the recent years, bevacizumab or cetuximab antibody treatments have been added to these regimens [4]. However, all these options are associated with chemotherapy-related liver damage (CTRLD), regarding which 3 forms have been defined: Steatosis, steatohepatitis, and sinusoidal obstructive syndrome (SOS) [5,6]. In the development of regimen-specific liver damage, the use of oxaliplatin was found to associate with SOS and nodular regenerative hyperplasia, and the use of irinotecan, with steatohepatitis [7-9].

The aim of this study was to evaluate the protective effect of sildenafil citrate against chemotherapy-related liver damage and determine the inflammatory response in tissue healing and micro-circulatory hemodynamics.

Materials and methods

Study design

A total of 42 male Wistar Albino rats, each weighing 200-250 gr were used in the study. The animals were obtained from the Experimental Animal Breeding and Research Laboratory of Ankara University. Guidelines for the Care and Use of Laboratory Animals' published by the National Institute for Health (NIH publication no.85-23, 1996 revised) were followed. The procedures used and the care of animals were approved by the Ankara University Animal Experiments Local Ethics Committee (Approval no: 201-2-11, dated 11/22/2014).

In vivo chemotherapy model

Four groups were created: Sham group, Folfox group, Folfox+ low dose sildenafil group, and Folfox+ high dose sildenafil group. To create direct toxicity on the liver, oxaliplatin 6mg/kg, followed by 5FU (50mg/kg) and folinic acid (90mg /kg) were administered intraperitoneally to all rats in the study groups once a week for 5 weeks (FOLFOX regime). To determine the effects of sildenafil on oxaliplatin-related liver damage, rats in the low and high-dose groups were administered 1mg/kg/day and 20mg/kg/day sildenafil, respectively, with oral gavage. The doses applied were determined according to previous studies [6,7]. The Sham group was used as a comparison group only and comprised 6 rats. Each of the study groups comprised 12 rats. During the study period, 1 rat in the oxaliplatin group, 4 in the oxaliplatin+low-dose sildenafil group and 3 in the oxaliplatin+high-dose sildenafil group died. All rats were kept in standard laboratory conditions and fed standard laboratory rat food for the duration of the experiment. At 5 days after the final dose of oxaliplatin, all the rats were administered ketamine HCL (80mg/kg) and xylazine hydrochloride (12mg/kg) for anesthesia and muscle relaxant. A laparotomy was made to each animal with a 2.5cm-long midline incision. After laparotomy, hepatectomy was performed, after which the animals were sacrificed. The livers removed from the rats were placed in formalin for pathological examination.

Histological examination

The tissue samples were fixed in formalin and embedded in paraffin blocks. Sections, 5µm in thickness, were cut and stained with hematoxylin and eosin (H&E). Category classification of sinusoidal dilatation, nodular regeneration, centrilobular or portal vein lesions, centrilobular vein and perisinusoidal fibrosis and steatosis was made as follows: For sinusoidal dilatation, 0= None, 1= Mild (involvement limited to one-third of the centrilobular area), 2= Moderate (two-thirds of the centrilobular area), 3= Severe (full involvement of the lobular area or centrilobular involvement extending with congestion to adjacent lobules), for nodular regeneration, 0= None, 1= Mild (focal nodular hyperplasia, not evident with H&E staining but evident with reticular staining) 2= Moderate (focal nodular hyperplasia, evident with both H&E and reticular staining), 3= Severe (widespread nodular hyperplasia on both reticular and H&E staining), for centrilobular or portal vein lesions, and centrilobular perisinusoidal and vein fibrosis, 0= None, 1= Mild (<50% of veins and sinusoids in 20 areas at x 200 magnification), 2= Moderate (>50% of veins and sinusoids in 20 areas at x 200 magnification), for steatosis, 0= None, 1= Mild (10%-30% of hepatocytes), 2= Moderate (in 30%-60% of hepatocytes), 3= Severe (>60% of hepatocytes). Peliosis, perisinusoidal hemorrhage and hepatocellular changes were evaluated as absent or present.

Statistical analysis

Data were analyzed using SPSS-16 software (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.). Differences between the groups with respect to the severity of the lesions formed after different regimens were assessed with the Pearson Chi-square test. A value of $P<0.05$ was considered statistically significant.

Results

The type of histopathological lesions according to the groups were summarized in Tables 1 and 2. The analysis of distribution of pathological lesions in the groups were presented in Table 3.

Table 1: Distribution of lesions according to groups

Pathology lesions	Sham group (n=6)				Folfox group (n=11)				Folfox+low-dose sildenafil group (n=8)				Folfox+high-dose sildenafil group (n=9)				*P*-value
	N	M	Mod	S	N	M	Mod	S	N	M	Mod	S	N	M	Mod	S	
Sinusoidal dilatation	3	3	0	0	0	5	4	2	2	2	3	1	1	5	3	0	X2=11.6. *P*=0.243
Nodular regeneration	6	0	0	0	11	0	0	0	8	0	0	0	9	0	0	0	
Centrilobular changes	6	0	0	0	0	6	5	0	5	3	0	0	0	9	0	0	X2=49.9 *P*<0.001
Steatosis	6	0	0	0	11	0	0	0	8	0	0	0	11	0	0	0	

N: None, M: Mild, Mod: Moderate, S: Severe

Table 2: Analysis of the distribution of the pathology lesions in groups

Groups	Sinusoidal dilatation	Centrilobular changes	Hepatocellular changes	Peliosis (Perisinusoidal hemorrhage)	Nodular regeneration	Steatosis
Sham(n=6)	3(50%)	-	-	1(16.6%)	-	-
Folfox(n=11)	11(100%)	11(100%)	10(90.9%)	5(45.4%)	-	-
Folfox+low-dose sildenafil (n=8)	6(75%)	3(37.5%)	1(12.5%)	-	-	-
Folfox+ high-dose sildenafil(n=9)	8(88.8%)	9(100%)	-	-	-	-
P-value	0.243	<0.001	<0.001	<0.001	-	-

Table 3: Hepatocellular and peliotic changes according to the groups

Pathology lesions	Sham group (n=6)		Folfox group (n=11)		Folfox+low-dose sildenafil group (n=8)		Folfox+high-dose sildenafil group(n=9)		*P*-value
Hepatocellular changes	+	-	+	-	+	-	+	-	x2=63.7
	0	6	10	1	1	7	0	9	*P*<0.001
Peliosis (Perisinusoidal hemorrhage)	1	5	5	6	0	8	0	9	x2=46.7 *P*<0.001

+ : present - : absent

Sinusoidal dilatation (Figure 1) was determined in all groups at different degrees of severity (Table 1). Centrilobular changes were lowest (37.5%) in the Folfox+ low dose sildenafil group. Nodular regeneration and steatosis were not observed in any of the groups (Table 1). Hepatocellular changes (Figure 2), and perisinusoidal hemorrhage were observed highest in the Folfox group (P<0.001).

Peliosis (Figure 3) was observed in both sildenafil groups. Although sinusoidal dilatation and centrilobular changes were observed in all 3 groups, it was seen less in the sildenafil groups and primarily at a lower rate in the FOLFOX+low-dose sildenafil group (P<0.001).

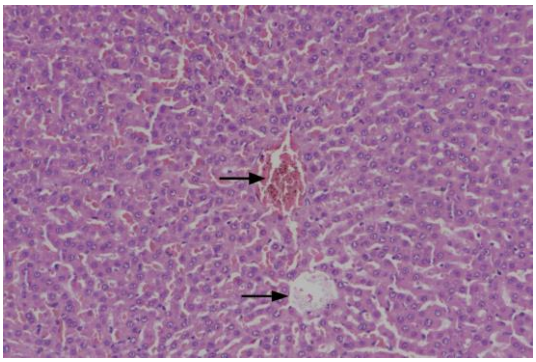

Figure 1: Widespread dilatation in the sinusoids

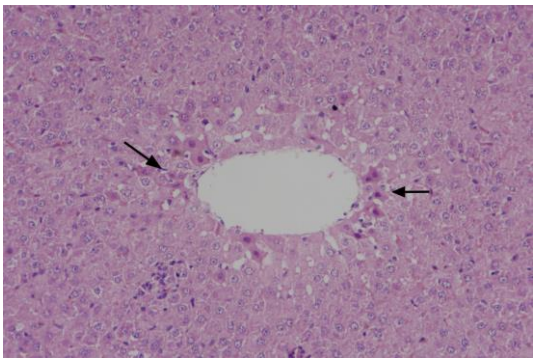

Figure 2: Degenerated Hepatocytes

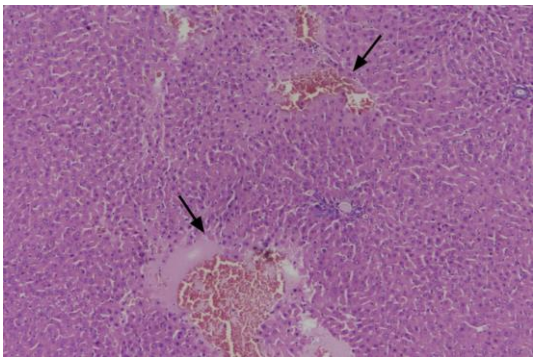

Figure 3: Foci of perisinusoidal hemorrhage

Discussion

Until the development of modern chemotherapy regimens, the only known reason for SOS was the use of pyrrolizidine alkaloids. SOS has been noted in patients who received myeloablative chemotherapy before bone marrow transplantation and recently in colorectal cancer patients with liver metastasis, following the application of platinum-based chemotherapy [8]. In addition, some studies have reported that there is a relationship with SOS in the tumor-free area of the liver in approximately 45% of patients with who received oxaliplatin-based chemotherapy before resection of colorectal liver metastasis [9]. In patients receiving oxaliplatin-based chemotherapy, an association was found between the development of SOS and increased need for perioperative transfusion (especially in major hepatectomies), high perioperative morbidity, a longer postoperative stay in hospital and increase in complications, such as post-hepatectomy liver failure characterized by cholestasis, ascites and prolonged prothrombin time [10, 11]. Using a model of liver damage which developed after oxaliplatin -based chemotherapy, Tamandl et al. demonstrated a relationship between SOS and a short survival period after liver resection performed due to early recurrence of the disease and colorectal liver metastasis [9]. Vreuls et al. determined a correlation between SOS and significantly low tumor response in oxaliplatin treatment [12]. Therefore, when surgeons are planning liver resections after systemic chemotherapy, they must ensure that there is sufficient preoperative liver functional reserve to avoid postoperative complications.

Various risk factors have been related to the development of SOS: Patients with an abnormal preoperative g-glutamyl transferase level, advanced age, female gender, tumor size>5cm, the 15-minute retention rate of indocyanine green, increased number of chemotherapy cycles and a short period between the end of chemotherapy and liver resection [9]. Previous studies have reported that some non-invasive blood tests can be used such as preoperative platelet count (<167,000), aspartate aminotransferase platelet ratio index (APRI) or FIB-4 scoring system (calculated with a formula based on AST, platelet count and age) to predict high-grade lesions of SOS [10]. Although results have been promising, further evaluation is required for the routine use of these tests, because SOS lesions are heterogenous, the reliability of liver biopsy is reduced, and false negative results may occur.

Sinusoidal endothelial cells (SECs) play a significant role in maintenance of normal sinusoid structure. SECs express metalloproteinases (MMP), enzymes responsible for extracellular remodeling. SECs maintain hepatic stellate cells (HSCs) in a quiescent state through VEGF stimulated NO production, and promote reversion of activated collagen–producing HSCs to a quiescent state [13]. SECs are a major cellular target for several toxins. One explanation for this is their location, which results in their direct exposure to drugs absorbed by the intestinal tract and transported to the liver by portal circulation [14]. Over activation or injury of SEC exerts proinflammatory, proadhesive, and procoagulant properties.

SOS develops because of a spectrum of lesions including sinusoidal dilatation following toxic liver damage

primarily targeting sinusoidal endothelial cells (SEC), perisinusoidal fibrosis, nodular regenerative hyperplasia (NRH) and peliosis [3, 12]. Previous experimental studies have shown that more toxic damage is formed earlier in the SECs than in the hepatocytes. In the pathogenesis of SOS development, there is a reduction in SEC glutathione level and NO levels, an increase in the expression of matrix metalloproteinases (MMP), and vascular endothelial growth factor (VEGF) as well as activation of clotting factor [15]. DeLeve et al. showed that NO level reduced in the hepatic veins of rats during SOS induction [16]. In another study of SOS induction by DeLeve et al, the severity was seen to increase with the application of N(G)-nitro-L-arginine methyl ester (L-NAME), which is a non-selective inhibitor of NO synthase and ameliorate with an infusion of V-YRRO/NO, which is a liver selective NO donor pre-medication [17].

It has been difficult to identify patients at risk of developing parenchymal damage following preoperative chemotherapy. It has been shown in rats that the administration of MMP -2/-9 inhibitors or a glutathione infusion has prevented the development of SOS by reducing SEC damage [18]. In hematopoietic stem cell transplantation, when treatment is given with glutamine, which is a probable glutathione synthesis stimulant, hepatic functions of patients were protected [19, 20]. On the other hand, it has been researched as to whether anticoagulants such as heparin and defibrotide, prostaglandin E1, plasminogen activator, ursodeoxycolic acid and pentoxifylline are sufficient to prevent the development of SOS related to hematopoietic stem cell transplant [21].

Oxaliplatin is a third-generation platinum compound consisting of a platinum atom conjugated to diamino cyclohexane and oxalate groups [22]. Some platinum compounds, such as OX, lead to generation of reactive oxygen species (ROS) and glutathione depletion in SEC, resulting increased oxidative stress in SECs [23,24]. Thrombocytopenia and alteration in platelet function have recently been observed with severe OX-related SOS [25].

Sildenafil was developed in 1985 for the treatment of hypertension and is a phosphodiesterase-5 inhibitor (PDE5i) drug. The PDE5i effect is usually to provide relaxation of the blood vessels by increasing the NO level while inducing guanyl monophosphate (cGMP) degradation [26]. Previous animal and clinical studies have shown that by inhibiting vasodilation, thrombocyte aggression and adhesion, sildenafil had positive effects on anastomosis, bone and skin healing and systemic inflammation, such as an increase in microcirculatory hemodynamics and an amelioration of the inflammatory process [27].

Liver damage was created using an oxaliplatin-based chemotherapy regimen in the current study. Centrilobular, peliotic and hepatocellular changes significantly differed between the groups. No steatotic or nodular regenerative changes were observed in any of the groups, which was most likely because the sinusoidal changes seen in liver damage were not severe, and chemotherapy dosage and duration may have affected the process. When the treatment groups were compared with the control group, peliosis was observed in both sildenafil groups. Although sinusoidal dilatation and centrilobular changes were observed in all 3 groups, it was seen less in the sildenafil groups and primarily at a lower rate in the FOLFOX+low-dose sildenafil group. Hepatocellular changes were not observed at all in the FOLFOX+ high-dose sildenafil group and seen at a lower rate in the sildenafil groups, compared to the control group.

The results obtained in this study are encouraging on the topic of prevention against liver damage that develops as a result of oxaliplatin-based chemotherapy. Further supportive clinical studies of drugs to be used against the active mechanisms in SOS pathophysiology may yield more successful results. Confirming the results with biochemical analyses may strengthen the results. We studied only one (sildenafil) drug to prevent SOS, which could be a potential bias.

Conclusion

The ideal strategy for patients with colorectal cancer liver metastasis receiving preoperative FOLFOX-based chemotherapy is the administration of drugs to prevent SOS development throughout chemotherapy. This approach could be of value to those with a large tumor burdens requiring prolonged preoperative chemotherapy.

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Duodenal GIST: Surgical treatment based on the location. A single center experience with review of the literature

Duodenal GIST: Lokasyona göre cerrahi tedavi. Literatür derlemesi ile tek merkez deneyimleri

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Abstract

Aim: Gastrointestinal stromal tumors (GIST) are the most common digestive tract mesenchymal neoplasms, but only 1 to 5% of GISTs occur in the duodenum. Consequently, clinical manifestations, management and surgical treatment and their results remain poorly defined. The aim of this study is to expose the surgical experience in our institution, analyze surgical procedures according to the location of the tumor in the duodenum, and review the surgical management of GISTs in this anatomically complex region.

Methods: Patients with duodenal GISTs who were surgically treated with curative intention in our center during the last 5 years (January 2014 - December 2019) were included in this retrospective cohort study. Demographic data, clinical presentation, GIST location, diagnostic evaluation, oncologic treatment, surgical procedure, mortality and morbidity, pathological and morphological GIST characteristics, pathological risk category, follow up and survival were noted.

Results: Five patients diagnosed with duodenal GIST were operated in our center during the last 5 years. Four surgeries were performed with intent to cure and negative margins of resection. Only one was performed by laparoscopic approach. Limited resection R0 was done in all cases. None of the patients received neoadjuvant treatment before surgery. All patients were women with a mean age of 63 years (52-70 years). Clinical manifestations consisted of abdominal pain and upper gastrointestinal bleeding. One of the cases was incidentally diagnosed. There was no postoperative mortality. Mean length of stay was of 8 days (4-26 days). The median follow-up time was 33 months (6 months - 8 years). During the follow up, 2 patients passed away due non-GIST related causes, and one patient was operated for resectable peritoneum metastasis 29 months after the initial surgery.

Conclusion: Tumor biology is more important than the surgical procedure for oncologic results of duodenal GIST. GIST located in duodenum with surgical indication is a challenge for the surgeon due to the complex duodenum anatomy.

Keywords: Gastrointestinal stromal tumor, Duodenum, Surgery procedures

Öz

Amaç: Gastrointestinal stromal tümörler (GIST) en yaygın sindirim yolu mezenkimal neoplazileridir, ancak GIST'lerin sadece% 1-5'i duodenumda görülür. Klinik belirtiler, yönetim, cerrahi tedavi ve bunların sonuçları tam olarak tanımlanmamıştır. Bu çalışmanın amacı, kurumumuzdaki cerrahi deneyimi ortaya koymak, duodenumdaki tümörün konumuna göre cerrahi prosedürleri analiz etmek ve anatomik olarak karmaşık olan bu bölgedeki GIST'lerin cerrahi yönetimini gözden geçirmektir.

Yöntemler: Son 5 yılda (Ocak 2014 - Aralık 2019) merkezimizde küratif amaçla cerrahi olarak tedavi edilen duodenal GIST'li hastalar bu retrospektif kohort çalışmaya dahil edildi. Demografik veriler, klinik tablo, GIST yeri, tanısal değerlendirme, onkolojik tedavi, cerrahi prosedür, mortalite ve morbidite, patolojik ve morfolojik GIST özellikleri, patolojik risk kategorisi, takip ve sağkalım not edildi.

Bulgular: Merkezimizde son 5 yılda duodenal GIST tanısı alan 5 hasta ameliyat edildi. İyileştirme amaçlı ve negatif rezeksiyon sınırları ile dört ameliyat yapıldı. Sadece biri laparoskopik yaklaşımla yapıldı. Tüm vakalarda sınırlı rezeksiyon R0 yapıldı. Hiçbir hasta ameliyattan önce neoadjuvan tedavi almadı. Tüm hastaların ortalama yaşı 63 yıldı (52-70 yıl) ve hepsi kadındı. Klinik belirtiler karın ağrısı ve üst gastrointestinal kanamadan oluşuyordu. Vakalardan biri tesadüfen teşhis edildi. Postoperatif mortalite olmadı. Ortalama hastanede kalış süresi 8 gündü (4-26 gün). Ortanca takip süresi 33 aydı (6 ay - 8 yıl). Takip sırasında 2 hasta GIST dışı nedenlerle kaybedildi ve bir hasta ilk ameliyattan 29 ay sonra rezektabl periton metastazı nedeniyle ameliyat edildi.

Sonuç: Tümör biyolojisi, duodenal GIST'nin onkolojik sonuçları için cerrahi işlemden daha önemlidir. Duodenumda görülen, cerrahi rezeksiyon endikasyonu olan GIST, karmaşık duodenum anatomisi nedeniyle cerrah için zordur.

Anahtar kelimeler: Gastrointestinal stromal tümör, Duodenum, Cerrahi işlemler

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Introduction

Gastrointestinal stromal tumors (GIST) originate in the interstitial cells of Cajal, which are mesenchymal cells located in the myenteric plexus of the gastrointestinal wall. Around 80-85% of these tumors have mutations in the gene encoding Tyrosine Kinase Protein Receptor (c-KIT) and 5-7% in the Platelet Derived Growth Factor Receptor Alpha (PDGFREA) gene. Remaining 10-15% of GISTs do not present with KIT / PDGFRA detectable mutations (*wild type GIST*) [1].

GISTs are the most common mesenchymal neoplasms in the gastrointestinal tract, although they represent less than 1% of digestive tumors. The main locations for GISTs are stomach (60-70%), small intestine (20-30%), colon and esophagus (<5%). They are less frequently seen in the peritoneum, mesentery and omentum [2]. Presentation in duodenum is rare (1-5% of all GIST), however, GISTs represent 30% of all primary duodenal tumors [3].

The ideal treatment for GIST is surgical excision with an intact psuedocapsule and negative surgical margins. Surgical excision with wide margins and lymphadenectomy are not generally indicated because GISTs do not extend further than the submucosal layer or present with lymphatic invasion [4].

Unlike other locations where surgical treatment is established, the clinical manifestations, diagnosis and treatment are not well defined in duodenal GISTs, since they are based on case reports or studies with limited sample sizes [5].

The purpose of this study is to analyze the results of duodenal GISTs operated in our center during the last 5 years and review the surgical management of GISTs in this anatomically complex region.

Materials and methods

This is a retrospective analysis of patients with duodenal GISTs surgically treated with curative intention in our center during the last 5 years (January 2014 - December 2019). Incidentally diagnosed cases in surgical specimen during another surgery and initially metastatic cases were excluded.

Demographic data, clinical presentation, GIST location, diagnostic evaluation, oncologic treatment, surgical procedure, mortality and morbidity, pathological and morphological GIST characteristics, pathological risk category, follow up and survival were noted.

Risk assessment was calculated according to the *Armed Forces Institute of Pathology* (AFIP) [1] and TNM 8th edition classifications [6]. Low risk GISTs were smaller than 2 cm and had less than 5 mitosis / 50 high power fields (HPF), intermediate risk GISTs presented with a size between 2 and 5 cm and more than 5 mitosis /50 HPF or more than 10 cm but less than 5 mitosis / 50 HPF, and high risk GISTs were >5cm in size with more than 5 mitosis / 50 HPF.

All operations were performed with curative intention following the current guidelines [7]. Surgeries were classified based on the duodenal location (first, second, third or fourth duodenal portion).

Postoperative complications were categorized according to the Clavien-Dindo classification [8].

Follow up protocol included physical examination, blood test and imaging every 6 months until 5 years of follow up, then yearly afterwards for low-risk GIST, every 3-4 months for high-risk GIST until 3 years, then every 6 months until 5 years, and annually after 5 years of follow up.

Results

Five patients diagnosed with duodenal GISTs were operated in our center during the last 5 years. Four of them had curative intention surgery with clear margins, one of the surgeries had palliative intention, which was reason for exclusion.

Patients' demographic and disease characteristics are presented in Table 1. All patients were female with a mean age of 63 years (52-70 years) at the time of surgery. Clinical manifestations included abdominal pain and upper gastrointestinal bleeding. One of the cases was incidentally diagnosed. All cases of duodenal GISTs were detected with abdominal computed tomography (Figure 1-4).

Table 1: Patients' demographics and disease characteristics

Characteristics	Duodenal location			
	D1	D2	D3	D4
Age (years)	52	70	57	69
Sex	Female	Female	Female	Female
Size (cm)	3	4	5	14
Mitosis	<5	0	>5	>5
Clinical presentation	Anemia	Incidental finding	Abdominal Pain	Abdominal Pain
Recurrence risk	Low	Low	Intermediate	High
Neoadjuvant treatment	No	No	No	No
Adjuvant treatment	No	No	No	Yes
Diagnosis	CT/ endoscopy	CT/ endoscopy	CT/ endoscopy	CT
Follow up (months)	6	14	51	100

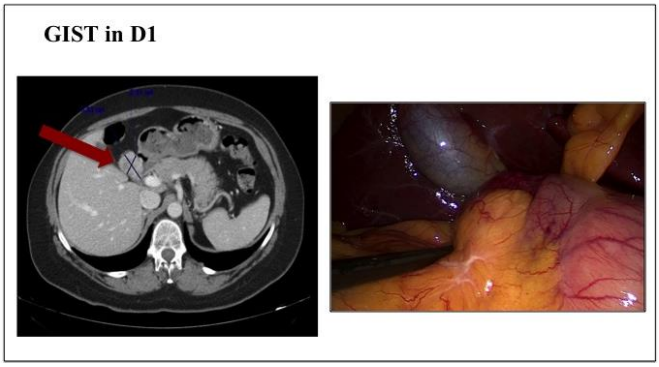

Figure 1: CT images of duodenal GIST depending on duodenal location, GIST in D1 (First duodenal portion), Arterial CT and tumor image during laparoscopic surgery

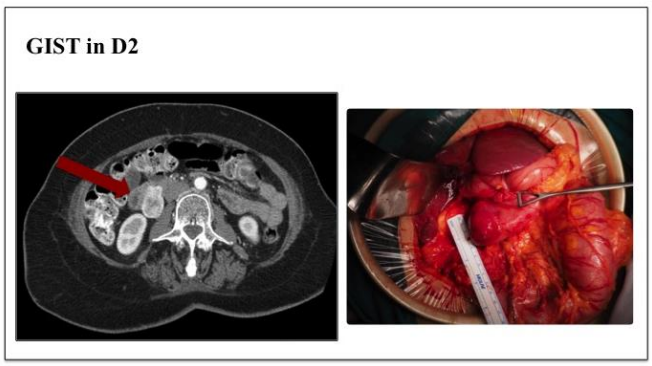

Figure 2: GIST in D2-infrapapillary portion (Second duodenal portion). Arterial CT and tumor image during open surgery

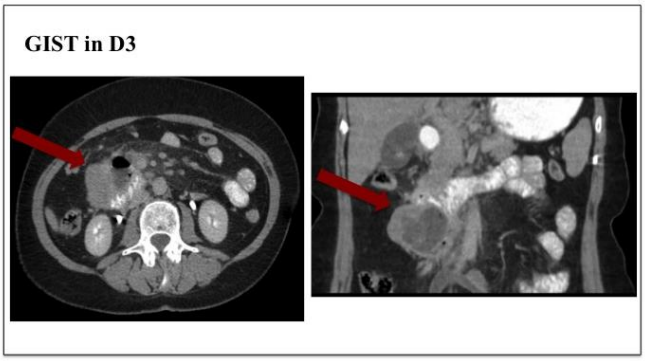

Figure 3: GIST in D3 (Third duodenal portion) CT in arterial and venous phases

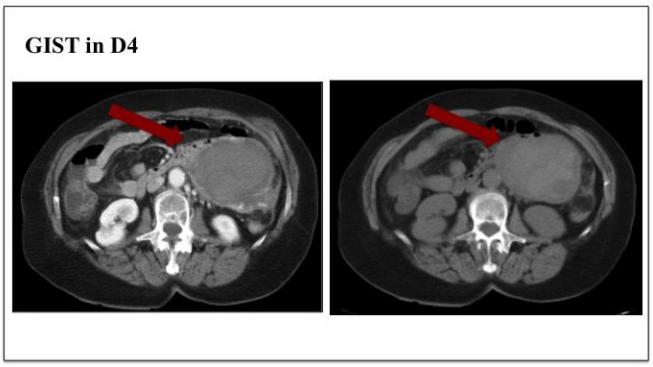

Figure 4: GIST in D4 (Fourth duodenal portion), CT in arterial and venous phases

Only one surgery was performed by laparoscopic approach. Limited resection R0 procedure was performed in all cases without capsule break. Details of the surgical procedure are described in Table 2 and Figure 5. Histopathological findings of our series are shown in Table 3.

There was no postoperative mortality. Morbidity was based on Clavien-Dindo classification, also described in Table 2. Mean length of stay was of 8 days (4-26 days).

The median follow-up time was 33 months (6 months - 8 years). During the follow up, 2 patients passed away due to non-GIST related causes, and one patient was operated for resectable peritoneum metastasis 29 months after the initial surgery. This patient presented with disease progression during adjuvant treatment with Imatinib, ineligible for surgical treatment.

None of the patients received neoadjuvant treatment before surgery.

Table 2: Surgical procedures according to GIST location in the duodenum

Surgery	Duodenal location			
	D1	D2	D3	D4
Procedure	Segmental Duodenectomy	Segmental Duodenectomy	Local Resection	Segmental Duodenectomy
Anastomosis	End-to-side Duodenojejunal	Side-to-end Duodenojejunal	Side-to-side Duodenojejunal	End-to-end Duodenojejunal
Approach	Laparoscopy	Laparotomy	Laparotomy	Laparotomy
Duodenal Side	Antimesenteric Anterolateral	Antimesenteric Posterolateral	Antimesenteric Lateral	Antimesenteric Posterolateral
Size (cm)	3	4	5	14
Morbidity	No	Yes	Yes	No
Clavien-DIndo classification	-	IIIa (Intra-abdominal abscess)	II (Anemic syndrome)	-
Length of stay (days)	4	26	8	8
Recurrence (location)	No	No	No	Peritoneal
Time to recurrence (months)	-	-	-	29

D1: First duodenal portion, D2: Second duodenal portion, D3: Third duodenal portion, D4: fourth duodenal portion

Table 3: Histopathologic features according to GIST location in the duodenum

Histopathologic features	Duodenal location			
	D1	D2	D3	D4
Cell type	Fusocelular	Fusocelular	Fusocelular	Fusocelular
Atypia	No	Moderate	No	Severe
Necrosis	No	No	Yes	Yes
Resection margins	Clear	Clear	Clear	Clear
CD34	NA	Positive	NA	Positive
CD-117	Positive	Positive	Positive	Positive
Mutation	c-KIT exon 11	NA	NA	c-KIT exon 11
TNM classification	T2NxM0	T2NxM0	T2NxM0	T4NxM0

NA = not applicable, D1: First duodenal portion, D2: Second duodenal portion, D3: Third duodenal portion, D4: fourth duodenal portion

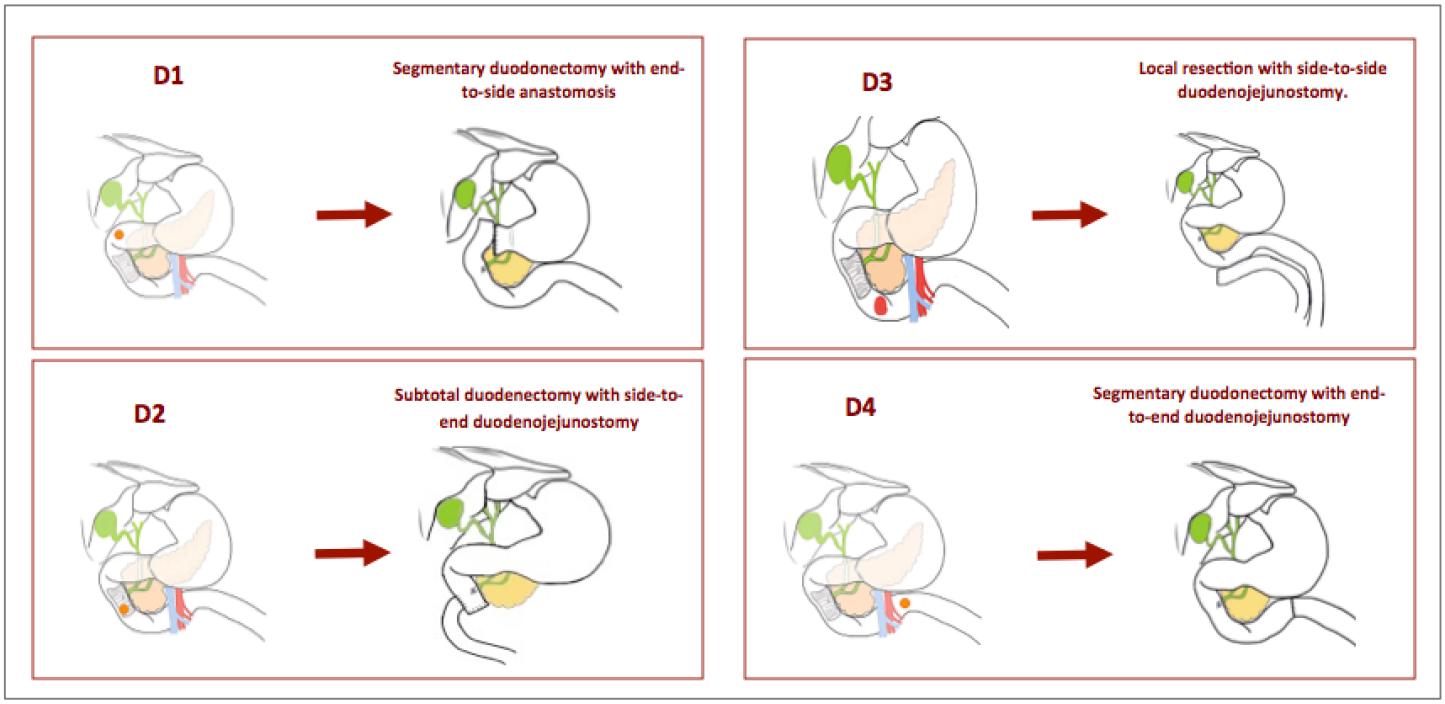

Figure 5: D1 (First duodenal portion): GIST in D1 with resected area marked. Surgical procedure: segmental duodenectomy with end-to-side anastomosis. D2 (Second duodenal portion): GIST in D2 (infrapapillary) with resected area marked. Surgical procedure: subtotal duodenectomy with side-to-end duodenojejunostomy. D3 (Third duodenal portion): GIST in D3 with resected area marked. Surgical procedure: local resection with side-to-side duodenojejunostomy. D4 (Fourth duodenal portion): GIST in D4 with resected area marked. Surgical procedure: segmental duodenectomy with end-to-end duodenojejunostomy.

Discussion

The most common duodenal portion affected by GIST is the second part, followed by the third and first parts [3,9]. This is in coherence with our results (40% GISTs were located in the second part of the duodenum).

In our series, all our patients were females, with a mean age of 63 years (52-70 years), which is also consistent with the literature [7,10]. Most patients had clinical manifestations such as hemorrhage and abdominal pain, which are the most common presentation of duodenal GISTs [9,10].

Contrast-enhanced abdominal and pelvic computed tomography (CT) scan is the investigation of choice for staging and follow-up. GISTs are hypervascular tumors appearing as well-defined endophytic or exophytic masses on contrast enhanced images, the tumor is strongly enhanced in the arterial phase and this enhancement may last until the delayed venous phase [9]. In our study, all patients were diagnosed by CT.

The differential diagnosis includes other soft tissue tumors including leiomyoma adenocarcinoma, leiomyoma, leiomyosarcoma, fibrosing mesenteritis, lipoma, mesenteric lymphangioma, plexiform neurofibromatosis, ectopic pancreas, Brunner's gland cyst, schwannoma, vascular tumors, and neuroendocrine tumors [9,11].

Upper endoscopy should be the first procedure of choice, it can even be therapeutic as the most frequent clinical manifestation of duodenal GIST is bleeding [11]. Duodenal GIST usually shows as a submucous elevated lesion. Endoscopy also allows exploration of the first and second duodenal parts. Endoscopic biopsies usually do not provide enough material for GIST diagnosis due to its location in the submucous layer. Endoscopic ultrasound assessment (EUS) is a better tool to define GIST-suspicious lesions, which are round or oval shaped, hypoechogenic, and originate from muscular propria. EUS allows localizing the lesion with precision and its relationship with surrounding structures (pancreatic head, ampulla of Vater) [7,9].

In our series, EUS was not performed because it was not available. Upper endoscopy was performed in tumors located in D1, D2 and D3, biopsy confirming the diagnosis in half of the cases.

There are many histopathologic and biological factors associated with prognostic value (tumor line, cell density, ulceration, mucous layer invasion, necrosis, cell atypia, KIT/PDGFRA mutation). However, it is difficult to distinguish the real importance of these factors because relevant studies include small number of patients and are usually retrospective in design [12].

In the published series, the recurrence risk is low and very low in 50-64% of cases [10,13]. The disease-free survival and the disease-specific survival of duodenal GISTs are significantly worse than those of gastric GISTs [10].

The case in our series with the worst prognosis (high recurrence risk) presented with tumoral progression in peritoneum, one of the most frequent locations for metastasis, together with the liver. The guideline of European Society of Medical Oncology (ESMO) proposes EUS evaluation and follow up for duodenal tumors <2cm, and excision if tumor growth is noticed or linked with symptomatology. In lesions ≥2cm, biopsy or excision is recommended due to worse prognosis if GIST [7].

The decision to obtain a biopsy should be based on the grade of suspected tumor type, and disease extension. Biopsy is needed before starting neoadjuvant treatment. The National Comprehensive Cancer Network (NCCN) guidelines suggest that EUS fine needle guided biopsy is better than percutaneous biopsy due to high bleeding risk and intra-abdominal dissemination. Percutaneous biopsy would be appropriate to confirm cases with metastasis [1,14].

The duodenal GIST cases analyzed in our series presented with a tumoral size ≥ 2 cm. Endoscopic biopsy confirmed diagnosis in 2 cases and the therapeutic procedure was limited resection with curative intention (R0) in all cases.

The published series describe 2 main surgical procedures: Limited resection (LR), which includes duodenectomy preserving pancreas, segmental duodenectomy or local excision with primary closure and duodenopancreatectomy (DP).

Selection of any of these options depends on tumor size, location in mesenteric or anti-mesenteric side in the duodenum and distance to essential structures (Vater's papilla).

In a revision of more than 300 cases [10], 66,3 % were treated with LR and 26% with DP. In multivariate analysis the technical procedure was not an independent prognostic factor.

Miettinen et al. [3] published a revision of duodenal GIST where 45% of cases were treated with segmental resection, 34% with local excision and the remaining 20% with DP. In the published series, between 20-80% of patients are treated with DP [2,15,16].

A meta-analysis suggests that LR is the best procedure for duodenal GIST whenever it is technically possible, due to its good oncologic results and low morbidity compared to DP [2]. When comparing both procedures, one should be cautious on account of proximity to essential structures such as the papilla of Vater, pancreas, mesenteric vessels, common biliary duct, and pancreatic duct, which can be a selection bias. The choice of the surgical approach should depend on the anatomical location and tumor size [17].

GISTs located on the anti-mesenteric side (lateral wall) in D2 and those not located in the periampullary region can be limitedly resected with local resection or segmental duodenectomy depending on the circumferential extension. Primary closure of the duodenal wall can be achieved through transverse suture, and if there is risk of duodenum lumen stenosis, side-to-end duodenojejunostomy or Roux-en-Y side-to-side duodenojejunostomy [9,18].

Tumors localized in D2, surrounding Vater's ampulla, and in the mesenteric border (medial wall) could be candidates for local resection with ampullectomy, duodenectomy with pancreatic preservation or cephalic duodenopancreatectomy depending on tumor size [19].

Options for GISTs located in lateral wall of D1, D3 or D4 are local resection or segmental duodenectomy with end-to-end / end-to-side / side-to-side anastomosis. If a large tumor is located on the medial wall, an aggressive surgery may be needed [9,11,20].

Limitations

We do not pretend to describe new or relevant aspects about the pathophysiology of the disease or its diagnosis. Our aim is to propose different surgical approaches with low morbidity in a complex anatomical location, such as the duodenum.

Some of the limitations include the retrospective design and the small sample size of this study. This happens because duodenal GISTs are uncommon tumors. It´s acknowledged that most of the publications are based on case reports or small sample studies, although there are available meta-analyses and systematic reviews that can help understand the current evidence in surgical treatment. Since it is an uncommon pathology, a review of these articles is necessary when facing these tumors.

We could not compare different surgical procedures (LR vs. DP) due to small sample size and because we did not have the chance to perform DP in our series.

Conclusion

The second duodenal portion is the most common location for duodenal GISTs. Placement in duodenal wall (mesenteric o anti-mesenteric side), tumor size and relation to critical structures in the duodenal-pancreatic anatomy are the most important key factors for surgical procedure selection. Tumor biology is more important than the surgical procedure for oncologic results of duodenal GIST. Surgical procedure (LR or DP) is not an independent prognostic factor.

GISTs located in duodenum with surgical indication are a challenge for the surgeon due to the complex duodenum anatomy. Our first option is limited resection with R0 margins in opposition to more aggressive options with high morbidity and mortality.

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Visceral variations in adult intestinal malrotation: A case-series study

Erişkin bağırsak malrotasyonunda iç organ varyasyonları: Olgu serisi çalışması

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Ethics Committee Approval: The study protocol was approved by the Adıyaman Clinical Research Ethics Committee (Date: 01/14/2020, No: 2020/1-36). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
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Abstract

Aim: Intestinal malrotation (IM) is a very rare rotational anomaly of the midgut. Although uncommon, failure to diagnose IM may lead to devastating consequences. It is important that radiologists and surgeons are made aware of the diagnosis of adult IM and accompanying variations. Since IM is usually reported as a case report, it is important to note the frequency of the accompanying variations. It is aimed to present radiological findings of intestinal malrotation, increase awareness of abdominal variations and pathologies accompanying adult IM and reduce diagnostic failure.

Methods: Thirty-two patients aged over 18 years, who underwent computed tomography (CT) and received a diagnosis of IM, were retrospectively evaluated in terms of CT findings. Aplasia or hypoplasia of the uncinate process of the pancreas, focal thickening areas that may cause suspicion of a pseudomass, location of the superior mesenteric vein relative to the superior mesenteric artery, localization of the cecum, and the frequency of a redundant sigmoid colon were determined.

Results: The frequency of IM in adults undergoing CT was 1/5,375. In two of 32 cases, the cause of acute abdomen was identified while the other cases were detected incidentally. Aplasia or hypoplasia of the uncinate process of the pancreas and a redundant sigmoid colon were detected in 21 (65.6%) and 23 (71.9%) cases, respectively. The cecum was in the normal location in eight patients (25%), and there was a normal superior mesenteric artery-vein relationship in six (18.8%).

Conclusion: Intestinal malrotation is rarely encountered in adults and most cases are incidentally detected. IM is often accompanied by aplasia or hypoplasia of the uncinate process of the pancreas. A normal superior mesenteric artery-vein relationship and the cecum in the normal position are seen in one out of every four to five cases.

Keywords: Intestinal malrotation, Computed tomography, Redundant colon, Uncinate process

Öz

Amaç: İntestinal malrotasyon (IM), midgutta çok nadir görülen rotasyonel bir anomalidir. Nadiren de olsa, IM tanısı koyamamak yıkıcı sonuçlara yol açabilir. Radyologların ve cerrahların erişkin IM tanısı ve eşlik eden varyasyonlar hakkında bilgilendirilmesi önemlidir. IM genellikle bir vaka raporu olarak bildirildiğinden, eşlik eden varyasyonların sıklığını not etmek önemlidir. İntestinal malrotasyonun radyolojik bulgularını sunmak, erişkin intestinal malrotasyona eşlik eden abdominal varyasyonlara ve patolojilere farkındalığı artırmak ve tanı başarısızlığını azaltmak amaçlanmaktadır.

Yöntemler: Bilgisayarlı tomografi çekilen ve intestinal malrotasyon tanısı alan 18 yaş üzerindeki 32 olgunun BT'leri retrospektif olarak değerlendirildi. Pankreasta unsinat proses aplazisi veya hipoplazisi, psödomass şüphesi uyandırabilecek fokal kalınlaşma alanları, süperior mezenterik venin süperior mezenterik artere göre konumu, çekumun lokalizasyonu, sigmoid kolon redunsansisinin sıklığı belirlenecektir.

Bulgular: Bilgisayarlı tomografi çekilen erişkinlerde intestinal malrotasyon sıklığı 1/5375'tir. 32 olgunun 2'sinde akut batın nedeni saptanmış olup diğer olgular insidental olarak saptanmıştır. Pankreas unsinat proses aplazi veya hipoplazisi 21(%65,6) olguda ve sigmoid kolon redunsansisi 23 (%71,9) olguda rastlandı. Normal konumda çekum 8 (%25) olguda ve normal superior mesenterik arter-ven ilişkisi 6 (%18,8) olguda saptandı.

Sonuç: Erişkin intesitnal malrotasyona nadir olarak rastlanmaktadır. Karşılaşılan olguların büyük kısmına insidental olarak rastlanmaktadır. Erişkin intesitnal malrotasyona sıklıkla pankreas unsinat proses aplazi veya hipoplazisi eşlik etmektedir. Normal superior mesenterik arter-ven ilişkisi ve normal konumda çekum 4-5 olguda bir görülmektedir.

Anahtar kelimeler: İntestinal malrotasyon, Bilgisayarlı tomografi, Redundan kolon, Unsinat proses

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Introduction

Any rotation of the midgut of less than 270 degrees around the superior mesenteric pedicle is defined as intestinal malrotation (IM) [1], which also presents with malfixation and predisposes patients to various conditions, such as volvulus and intestinal obstruction. In childhood, IM is often diagnosed based on the volvulus and intestinal obstruction it causes [2]. IM is rarely encountered and the true incidence of IM is not known in adults. In the diagnosis of IM, the gold standard is to see the duodenojejunal junction in abnormal localization during the imaging of the upper gastrointestinal tract [3]. However, in suspicious cases in daily practice, the superior mesenteric vein (SMV) localized on the left of the superior mesenteric artery (SMA) or vertical on ultrasound and the misplaced cecum on direct radiography suggests the presence of IM, but can also cause false positive and negative diagnoses.

A redundant sigmoid colon is defined as the presence of the sigmoid colon over bilateral iliac crests on barium colon radiographs [4]. Defined nearly a century ago, this condition has once more gained importance due to the difficulties it causes during colonoscopy [5]. In addition, it predisposes patients to sigmoid colon volvulus [6]. As in IM, malfixation is considered in a redundant sigmoid colon. Since the rotation of the duodenojejunal loop covers the pancreatic primordium, IM can also be accompanied by the hypoplasia of the uncinate process of the pancreas [7]. The coexistence of heterotaxy syndrome and IM has also been reported [8].

Adult IM is usually described in case reports [9-11]. The current study aimed to evaluate the incidence of adult IM in patients that underwent computed tomography (CT), identify the causes of concomitant acute abdomen, and the incidence of abdominal abnormalities accompanying IM.

Materials and methods

The abdominal CT images of the patients aged over 18 years were screened from the radiology archives of Adiyaman and Evliya Celebi Education and Research Hospitals between January 2013 and April 2020. Among 172,000 CT images of adults obtained from the two centers, those of 39 cases diagnosed with IM were reevaluated. Seven patients with a history of surgery were excluded from the study. The localization of the cecum, presence of a redundant sigmoid colon, location of SMV relative to SMA, the morphology of the pancreatic uncinate process were evaluated for all patients included in the study. In addition, variational conditions, such as heterotaxy and polysplenia, and other factors that could cause abdominal pain were noted. All cases were assessed by two radiologists with 10 and 11 years of experience with consensus.

Ethical statement

The study protocol was approved by Adıyaman Clinical Research Ethics Committee (Date: 01/14/2020, No: 2020/1-36), and conducted in accordance with the principles of Declaration of Helsinki.

Statistical analysis

For the statistical analyses, SPSS for Windows (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY) was used. The continuous variables were expressed as mean and standard deviation (SD), and the categorical variables, as frequency and percentage.

Results

In this study, IM was detected in one of every 5,375 adult cases according to the abdominal CT findings. The mean age of the cases was 45.53 (21.69) years, ranging from 18 to 89 years. Seventeen patients were male and 15 were female. While eight patients presented to the emergency department with the complaint of abdominal pain, 24 cases were incidentally detected during an abdominal CT performed for other reasons. Internal herniation, midgut volvulus, polysplenia, and heterotaxy syndrome were determined in one patient each. In the remaining 28 cases, no pathology was found. The cecum was located on the right in eight cases (25%), in the middle in 14 (43.8), and on the left in 10 (31.3), (Figure 1). A redundant sigmoid colon was found in 23 (71.9%) of cases while the remaining nine patients (28.1) had normal sigmoid colon (Figure 2). SMV was located to the left of SMA in 11 (34.4%) cases, to the immediate anterior of SMA in 15 (46.9%), and to the right of SMA in six (18.8%), (Figure 3). Aplasia and hypoplasia of the uncinate process of the pancreas were seen in 17 (53.1%) and four (12.5%) cases, respectively while uncinate process was normal in the remaining 11 (34.4%) cases (Table 1). An increase in the thickness, which gave the appearance of a pseudomass, was present in the pancreatic head in 10 cases (31.3%) and pancreatic tail in four (12.5%). In addition, 6 cases (18.8%) presented with a short pancreas.

Table 1: Localization of cecum and superior mesenteric vein and uncinate process morphology in cases with intestinal malrotation

Cecum			Localization of SMV			Uncinate process		
Right	Middle	Left	Right	Anterior	Left	Normal	Hypoplasia	Aplasia
8	14	10	6	15	11	11	4	17

SMV: Superior mesenteric vein

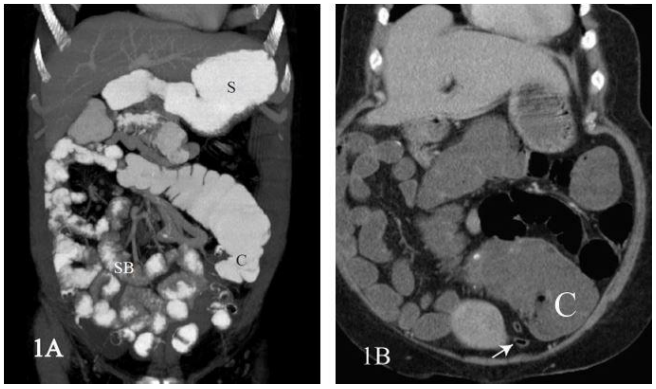

Figure 1: A: Oral and IV-contrast enhanced CT performed on a 36-year-old male patient due to abdominal pain, coronal reformatted MIP images shows cecum on the left side and small bowel loops on the right side of the abdomen, B: Abdominal non-contrast CT performed due to renal colic in a 51-year-old woman shows cecum and appendix (arrow) in the left side of the abdomen (S: stomach, SB: small bowel, C: cecum, IV: intravenous, MIP: maximum intensity projection)

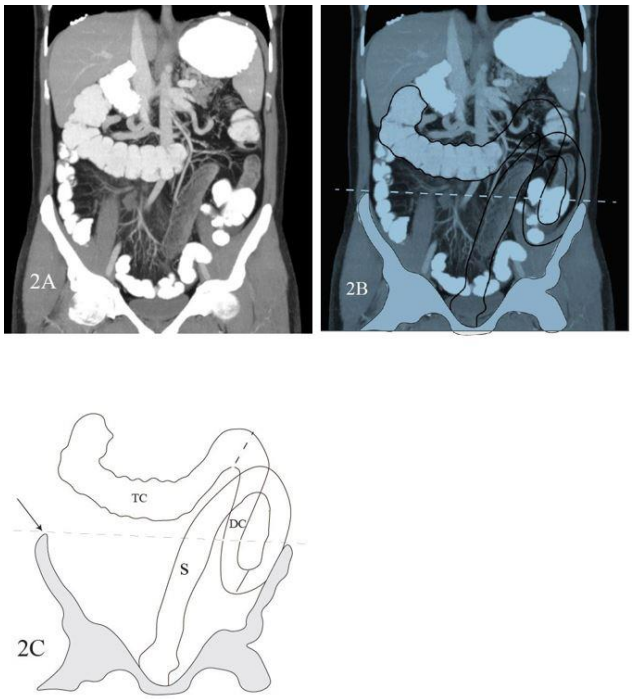

Figure 2: The coronal reformatted MIP images of a 41-year-old male patient who received oral and IV contrast enhanced abdominal CT after unsuccessful colonoscopy, the sigmoid colon (S) goes on the line passing through the bilateral iliac crests (arrow) (IV: intravenous, CT: computed tomography, MIP: maximum intensity projection, DC: descending colon, TC: transverse colon).

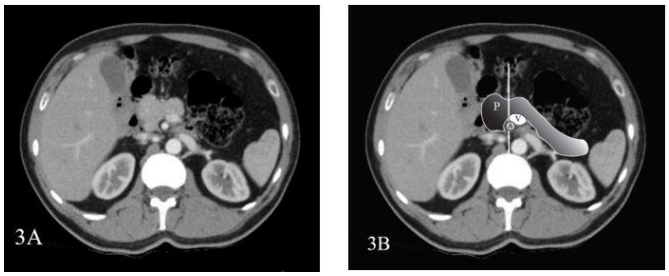

Figure 3: In contrast-enhanced abdominal CT performed to a 29-year-old male patient due to lymphoma, the SMV (V) is located to the left of the SMA (A). Uncinate process aplasia in the pancreas (P), there is no pancreatic tissue on the posterior of SMV at the left of the imaginary line crossing the right edge of the SMV.

Discussion

Intestinal malrotation is seen in one of every 200-500 births [12]. In this study, the incidence of IM among adult cases that underwent CT was one in 5,375. Of the 32 diagnosed cases, only two had acute abdomen, six had abdominal pain and the other cases that were incidentally detected. The incidence of IM was 72% in children with heterotaxy [13] while the frequency of heterotaxy in adult patients with IM is 6.2%.

It is reported that the cecum is in the right lower quadrant in 20% of cases with IM [7]. In the current study, consistent with the literature, the cecum was found in its normal localization in 25% of cases. The rate of a redundant sigmoid colon has been shown to range from 16% to 20.5% [5,14,15], and it was determined as 71.9% in the current study, which also probably suggests that the malfixation of the sigmoid colon is also a common condition accompanying IM.

The location of SMA is fixed but that of SMV changes according to the localization of the small intestine [7]. The starting point for success in diagnosing IM is the presence of an abnormal SMV-SMA relationship. However, there may be exceptions that are not few in number. In a previous study, a normal SMV-SMA relationship was found in 30% of pediatric IM cases [16]. In the current study, a normal SMV-SMA relationship was detected in 18.8% of the adult IM cases.

Pancreatic abnormalities may be encountered in IM as a result of the close developmental relationship between the pancreas and small intestines. Aplasia or hypoplasia of the uncinate process of the pancreas has been identified in 86% of cases with IM [17]. In the current study, aplasia or hypoplasia of the pancreatic uncinate process was detected in 65.6% of the cases, which is lower than previously reported. Shape variations that may cause suspicion of a mass at the pancreatic head have been described in 35% of the general population [18]. In a study evaluating patients with IM, the contour abnormality of the pancreatic head was 48% [17]. In the current study, the contour abnormality of the pancreatic head was determined as 31.3%, and there was no significant difference compared to the values reported for the general population in the literature.

Limitations

The value of this study was limited by its retrospective design, which may have resulted in overlooking mild IM cases.

Conclusion

IM is rarely encountered in adults and most cases are incidentally detected. Adult IM is often accompanied by the aplasia or hypoplasia of the pancreatic uncinate process. A normal SMA-SMV relationship and the cecum in the normal position are seen in one out of every four to five cases.

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Review
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Do the clinical outcomes of Covid-19 differ in pregnancy?

Covid-19'da gebeliğin klinik sonuçları farklı mıdır?

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Abstract

In this brief review, we aimed to assess Covid-19 infection from a different aspect and emphasize the advantages of patients during pregnancy. Therefore, the course of Covid-19 infection and chronic diseases during pregnancy were evaluated. The disease seems to have a positive effect on fetomaternal circulation during pregnancy. Our hypothesis on this matter is that the regulation of the host immune system which occurs due to pregnancy may reduce the cytokine storm and multiple organ failure-related mortality in Covid-19 infected pregnant women.

Keywords: Corona virus disease, Covid-19, Pregnancy, Maternal-fetal conflict

Öz

Bu kısa derlemede gebelikte Covid-19 enfeksiyonuna farklı yönden bakmak ve hastaların hamilelik sırasında avantajlarını vurgulamak istedik. Bu amaçla, hamilelikte Covid-19 enfeksiyonunun seyri ve hamilelik sırasındaki kronik hastalıklar değerlendirildi. Covid-19 enfeksiyonunun çoğu gebe hastada fetomaternal dolaşım üzerine olumlu etkisi mevcut gibi görünmektedir. Bu konudaki hipotezimiz, gebelikte konakçının immün sisteminde gelişen düzenlemenin, Covid-19 ile enfekte gebelerde sitokin fırtınası ve çoklu organ yetmezliğini azaltıcı yönde bir etki yarattığı yönündedir.

Anahtar kelimeler: Korona virüs hastalığı, Covid-19, Gebelik, Maternal-fetal çıkar

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Introduction

Corona virus disease-2019 (Covid-2019) pandemic started in the Chinese city of Wuhan within the last days of 2019 with a prominent level of person-to-person transmission rate. Mortality rate was reported as 2.67% [1]. Clinical results of a small group of pregnant women who tested positive for Covid-19 in RT-PCR were published in a preliminary study. In this series, computed thorax tomography revealed ground glass appearance in many of positive pregnant cases. Fever was seen in 13 of 15 cases with pneumonia and 2 patients were asymptomatic. Following the delivery of Covid-19 positive pregnant women, ground glass appearance disappeared in thorax CT. Clinical statuses improved in 4 cases who were still pregnant without any antiviral therapy. It was found that pregnancy and delivery did not exacerbate the disease or affect CT findings negatively [2].

Pregnancy is a state of partial immune suppression which makes pregnant women more vulnerable to viral infections, and in case of seasonal flu, mortality and morbidity may be higher. Physiological adaptations in pregnancy, such as edematous mucous membranes, elevated diaphragm, decreased lung capacity and tachypnea may render pregnant women more vulnerable to respiratory infections [3]. Therefore, the Covid-19 pandemic may have potential grave consequences for pregnant women. Previous data and knowledge of H1N1 and SARS pneumonias showed us that pregnant patients needed more advanced respiratory support and medical care in the intensive care unit. In SARS, mortality rates reached 25%. However, pregnant women with Covid-19 pneumonia and normal adult patients show clinically similar findings. Cough and fever are the most common clinical findings of the disease and lymphopenia is marked [4].

Various drugs including hydroxychloroquine, antivirals (Remdesivir, Oseltamivir, Ritonavir plus Lopinavir), cytokine antagonists and azithromycin were tried for the treatment of Covid-19 pneumonia in addition to respiratory support. No uniform treatment was suggested for Covid-19-related clinical problems. Recently it is discussed that human umbilical cord stem cells (Human Umbilical Mesenchymal Stem Cell; hUMSC) may play a role in the treatment [5].

Immune response to the virus can cause exaggerated inflammatory response and cytokine storm in the pathogenesis of the Covid-19 disease. This cytokine storm can cause edema, ARDS, cardiac injury, secondary bacterial infections, multiple organ failure and death.

Can avoiding or preventing this excess immune response be a way to reduce mortality from Covid-19 infection? The fetomaternal circulation and immune modulation during pregnancy may play roles in the different clinical courses between other viral pneumonias and pneumonia of Covid-19. Cytokine levels are regulated by two different mechanisms in pregnancy:

1) Pregnancy is a major source of mesenchymal stem cells, which have lower immunogenic properties and pluripotent differentiation potentials [6]. hUMSC are widely used in various branches of medicine such as ophthalmology due to their anti-inflammatory and immunomodulatory properties [7].

2) Higher blood progesterone levels affect cytokine levels during pregnancy.

As a steroid hormone, progesterone has a critical role in the implantation and maintenance of early pregnancy. Control of the immune response to the semi-allogeneic embryo is the cornerstone of the early development of the embryo. The role of cytokine network starts with ovulation. Local inflammatory response begins with secretion of prostaglandin, IL-6 and IL-8 during ovulation [8]. Progesterone modulates the immune system by inducing NF-kB expression which affects a number of proinflammatory factors (IL-1 beta, IL-2, TNF-alpha, INF-gamma), anti-inflammatory factors (IL-4, IL-10, TGF-beta) and IL-6 (both proinflammatory and anti-inflammatory). NF-kB is the key step in the activation of signaling pathways of cytokines [8,9]. To prevent the rejection of the allogeneic embryo, inflammatory reactions should be suppressed. In the implantation and early development process, progesterone shifts the Th1-Th2 balance to Th2 dominance. This physiologic shift helps the ongoing pregnancy by decreasing Th1-secreted IFN-γ TNF-a. IL-4 and IL-6 secretion increase, and IL-10 secretion remains unchanged [10]. Progesterone has an immunosuppressive or immunostimulatory effect on macrophages depending on the microenvironment in the pregnancy [11]. It also exerts an immunosuppressive effect on the human umbilical cord fetal T lymphocytes (Both CD4 and CD8 T lymphocytes) [12]. The use of umbilical cord stem cells in Covid-19 treatment was tried and reported by Atluri et al. [5].

Another important observation is that older mothers have improved clinical outcomes in chronic and inflammatory diseases during pregnancy. Placenta is a wonderful source of fetal stem cells which retain low immunogenicity along with immunomodulatory and anti-inflammatory activities [13]. The fetal stem cells are of great interest in regenerative medicine due to their easy collection and reliability. Although elevated levels of chimerism occurs rarely, microchimerism could be seen in the organism with a placenta. Invasion depth of placenta is the critical source of both substrate and fetomaternal cellular exchange between two different organisms.

Fetal microchimerism was documented in humans. There are many studies about fetal microchimerism: One well-known example is fetal cells which induce wound healing in the murine model. In this model, fetal cells accumulated in the maternal wound participated in maternal angiogenesis. Also, in humans, fetal cells which express markers of cytokeratin and collagen were detected in healed cesarean section scars. This finding suggests that fetal cells actively participate in maternal wound healing [13].

Inflammation mediators and cytokines such as IL-6, IL-1beta, TNF-alpha secretion increases from the aged cells. Permanent and low-grade inflammation accelerates the aging process and causes many diseases. The production and levels of these cytokines are high in cardiovascular and autoimmune diseases such as rheumatoid arthritis and multiple sclerosis [14,15].

Previous animal studies revealed that amniotic fluid cells accelerated wound healing and decreased adhesion formation [16]. The regenerative potential of pregnancy was also observed in other previous studies [17].

Conclusion

In the light of this literature data, we concur that fetal microchimerism may protect the mother from a more severe process of Coronavirus infection, which causes extensive inflammatory reaction and cytokine storm. Less severe clinical progression of Covid-19 infection in the pregnant women might be related to the progesterone effect on T lymphocyte function and immunomodulatory feature of fetal umbilical cord stem cells by microchimerism. Observations and results from small series comprise limited number of Covid-19 positive pregnant women. Maternal adaptation during pregnancy could limit extensive inflammatory reaction. Our hypothesis on this matter is that the regulation of the host immune system which occurs due to pregnancy may reduce the cytokine storm and multiple organ failure-related mortality in Covid-19 infected pregnant women.

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Review
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Can mesenchymal stem cells ameliorate testicular damage? Current researches

Mezenkimal kök hücreler testis hasarını iyileştirebilir mi? Güncel çalışmalar

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Abstract

Many recent studies have demonstrated the therapeutic effects of mesenchymal stem cells (MSC) in different disease models. Infertility is a global disease with a high prevalence. Non-obstructive azoospermia may occur due to genetic factors, exposure to toxic substances, anticancer treatments such as radiotherapy and chemotherapy and testicular torsion. Many experiments have been conducted to determine the efficacy of MSCs in the treatment of male infertility due to their differentiation capacity and paracrine effect. In these studies, the differentiation capacities of MSCs, obtained from diverse sources, to male germ cells were determined in vitro and their effects on testis niche were assessed by injection of MSCs into the testis. In this review, we addressed a few of the causes of non-obstructive azoospermia and summarized the current studies to determine the therapeutic effects of MSCs on testicular injury.
Keywords: Azoospermia, Male infertility, Mesenchymal stem cells, Stem cell therapy, Testicular damage

Öz

Son zamanlarda yapılan birçok çalışma, farklı hastalık modellerinde mezenkimal kök hücrelerin (MKH) terapötik etkilerini göstermiştir. İnfertilite, yüksek prevalansa sahip global bir hastalıktır. Obstrüktif olmayan azospermi, genetik faktörler, toksik maddelere maruz kalma, radyoterapi, kemoterapi gibi antikanser tedavileri ve testis torsiyonu nedeniyle ortaya çıkabilir. MKH'lerin farklılaşma kapasiteleri ve parakrin etkileri nedeniyle erkek infertilitesinin tedavisinde etkinliğini belirlemek için birçok çalışma yapılmıştır. Araştırmalarda, farklı kaynaklardan elde edilen MKH'lerin erkek germ hücrelerine farklılaşma kapasiteleri in vitro olarak belirlenmesinin yanı sıra bu hücrelerin testis nişi üzerindeki etkileri MKH'lerin testis içine enjekte edilmesiyle belirlenmiştir. Bu derlemede, obstrüktif olmayan azosperminin nedenlerinden birkaçına değindik ve MKH'lerin testis yaralanması üzerindeki terapötik etkilerini belirlemek için mevcut çalışmaları özetledik.
Anahtar kelimeler: Azospermi, Erkek infertilitesi, Mezenkimal kök hücreler, Kök hücre tedavisi, Testis hasarı

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Introduction

Infertility is a global public health problem, characterized by failure to achieve pregnancy after 12 months of unprotected sexual intercourse, which affects about 10-15% of couples worldwide. The contribution of the male factor is estimated to be 50-60%. The male factor alone is responsible in 20% of couples who cannot conceive [1-4]. Environmental, physiological, and genetic factors are effective in male infertility. Environmental factors include smoking, radiation, infections, injuries, exposure to toxic substances, and the use of chemotherapeutic drugs [5]. Semen volume, sperm motility, morphology and count are essential. In 2010, the World Health Organization (WHO) published a guide to report normal values [6]. It is termed normozoospermia if all semen analysis parameters are within normal range, oligozoospermia if sperm count is reduced (5-20 million /ml, severe: <5 million /ml) and azoospermia if there is no viable sperm in the semen. Azoospermia is divided into 3 types: Pretesticular, testicular and post testicular azoospermia [7]. Recent advances in assisted reproductive techniques (ART) have been a great hope for infertile couples to have a baby. The use of in vitro fertilization, which is one of the ART, can increase birth defects during fertilization and thus may lead to genetic or epigenetic abnormalities in the child. In addition, current ART has not been able to help infertile couples without functional gametes unless donor gametes are used. However, the development of stem cell technology may provide new therapeutic strategies for infertile couples [8,9] . In this review, we aimed to summarize the current studies on the role of therapeutic mesenchymal stem cells (MSCs) in the treatment of testicular damage.

Reasons of non-obstructive male testicular damage

Environmental Factors - Cigarette and alcohol

It is known that cigarettes contain a lot of toxic chemicals. Smoking leads to an increase in reactive oxygen species, thereby escalating oxidative stress, leading to DNA damage and apoptosis. Consequently, spermatogenesis, maturation of sperm, and sperm function all deteriorate, which may lead to infertility [10,11]. In addition, maternal smoking could be injurious on the fertility of the male offspring. Germ cell DNA damage and defective sperm production were detected in the male offspring with prenatal smoke exposure [12].

Excessive alcohol intake has a negative effect on the male reproductive system, because it decreases testosterone levels and increases FSH, LH and E2 levels, while impairing Sertoli and Leydig cell functions. It also deteriorates sperm motility and morphology, and reduces sperm concentration and count [13].

ROS and male infertility

Oxidative stress occurs when the defense of the antioxidant mechanism is inadequate in the face of an excessive increase in oxidants or reactive oxygen species (ROS) [14]. Excessive ROS impair sperm function and sperm morphology due to sperm membrane lipid peroxidation, and cause reduced motility and ineffective sperm-oocyte fusion [15,16]. When oxidative stress elevates, peroxidation of polyunsaturated fatty acids (PUFA) in sperm plasma membrane prevents the realization of normal fertilization in male germ line [14]. Lipid peroxidation disrupts membrane integrity, leading to enzyme inactivation, DNA structural damage and cell death. Oxidative stress not only affects the fluency of the sperm plasma membrane, but also the integrity of the DNA in the sperm nucleus and mitochondria. Oxidative damage causes DNA chain breaks, base degradation, DNA fragmentation, DNA lesion, and protein crosslinking. The rate of DNA fragmentation has been shown to increase in the ejaculate of infertile men. Changes in spermatogenic events lead to the elimination of abnormal immature sperm in the ejaculate. Immature sperm, on the other hand, leads to excessive ROS production and DNA damage. [17-20]. High levels of ROS disrupt the inner and outer membranes of the mitochondria. This leads to the release of cytochrome c from mitochondria, activating caspases and causes apoptosis [17].

Cancer Treatment and male infertility

The success of cancer treatment has increased with the combination of surgery, radiotherapy and chemotherapy. Radiotherapy and chemotherapy are gonadotoxic for testes in all age groups of men. In particular, the testicular germinal epithelium is highly sensitive to radiation damage with regards to total dose, fraction and treatment site. Radiotherapy can adversely affect the testes when targeted for malignancies in the retroperitoneum or pelvis before bone marrow or stem cell transplantation. Even low dose irradiation (such as 0.1 Gray) reduces spermatogenesis. Doses over 2 Gy result in oligospermia or azoospermia [21,22].

Chemotherapeutic drugs such as alkylating agents, procarbazine and cisplatin have a negative effect on spermatogenesis because they induce azoospermia and their effects persist for a long time after chemotherapy. Azoospermia occurs in treatments (such as Ewing Syndrome) using one or both alkylating agents, such as cyclophosphamide or ifosfamide. Furthermore, the combination of cisplatin with one of the alkylating agents causes oligospermia or azoospermia. Different combinations of chemotherapeutic agents used for the treatment of Hodgkin's disease also cause azoospermia. Although successful results are obtained with mechlorethamine, oncorin/vincristine, procarbazine, prednisone (MOPP / MVPP) in patients with hematopoietic malignancies, these chemotherapeutic drugs taken in childhood may cause azoospermia and hypogonadism in 85% of patients, and the effects may last up to 15 years [23-25].

Testicular torsion

Testicular torsion may reduce blood flow in the testis, thereby causing infertility in a 1/4000 male population younger than 25 years. Ischemia-reperfusion (I / R) injury occurs even if detorsion is performed as an emergency surgical intervention to prevent testicular damage. I / R injury can lead to infertility in men due to disrupted spermatogenesis and increased apoptosis of germ cells. The duration of testicular ischemia in torsion and the severity of twisted cord are important. When the twisted cord is intervened within 6 hours, the testicular damage is less, and if the severity of the twist is high, cell necrosis begins within 4 hours. Severe testicular atrophy is inevitable if a torsion of more than 360 degrees lasts more than 24 hours [26,27].

Mesenchymal Stem Cells (MSCs)

Multipotent stem cells self-replicate, differentiate and provide tissue integrity. These cells have the potential to renew themselves, maintaining homeostasis in tissues and organs. In addition, they proliferate throughout life and meet the number of cells required for the tissue. Mesenchymal stem cells have multipotent stem cells properties [28]. Mesenchymal stem cells are heterogeneous cells and it is not enough to identify only specific cell surface markers for the isolation of MSCs. Instead, the characters of MSCs, their differentiation into multiple cells and their phenotypic markers should be fully defined. In short, in order to evaluate the cells as MSCs, the cells must have plastic adherence and differentiate into various cells such as osteocytes, chondrocytes and adipocytes. Furthermore, the expression rate of cell surface markers such as CD105, CD73 and CD90 should be greater than 95%, and the expression rate of markers such as CD34, CD45, CD14, Cd11b, CD79, CD19 and HLA-DR should be less than 5% [29,30].

When MSCs are administered systemically to the body, they not only treat the damaged region by differentiation, but also affect other cells by inducing regulatory paracrine effects, such as stimulants and inhibitors. MSCs are determined to secrete various growth factors and cytokines such hepatocyte growth factor (HGF), insulin-like growth factor 1 (IGF-1), vascular endothelial growth factor (VEGF) , platelet-derived growth factor, interferon gamma, fibroblast growth factor (FGF) and interleukin IL-6, IL-8, IL-10 [31,32].

Differentiation of MSCs to germ cells - *in vitro* experiments

Recent advances in stem cell technology have also brought a new perspective to treatment of infertility. Nowadays, infertility is no longer a desperate disease due to the studies on obtaining germ cells from cells of different origins [33]. It is thought that infertility will be treated by transplanting germ cells obtained from differentiated stem cells in vitro to gonads in patients of non-obstructive azoospermia [34].

Huang et al. [35] investigated whether human umbilical cord MSCs (HUCMSC) differentiate into germ cells. For this, the HUCMSCs in retinoic acid (RA), testosterone and testicular cell conditioned medium were incubated separately for 3, 7 and 14 days, respectively, and expressions of germ cell specific genes (Oct-4, Ckit, CD49, Stella, and Vasa) were determined with RT-PCR and immunocytochemistry [35]. RA is a polar molecule that is a derivative of vitamin A and binds to retinoid receptors in the spermatogonia nucleus, thereby increasing the expression of tyrosine kinase required for spermatogonia differentiation [36]. In this case, while the expression of Oct-4 gene was high in both control and differentiation medium-treated cells, expression of the other genes (except Vasa) was increased both on days 3 and 7 after incubation. Vasa expression was determined in 14 days by immunocytochemistry, and it was determined that HUMSCs could differentiate into germ cells [35]. In study of Ghasemzadeh-Hasankolaei et al. [37], the efficacy of transforming growth factor beta 1 (TGFβ1), BMP4 and BMP8 on the conversion of BM-MSCs to germ cells was investigated. These agents were administered to individual BM-MSCs for 21 days. Differentiation to germ cells was demonstrated by determining the expression of Germ cell specific markers by RT-PCR. After use of TGFβ1 in BM-MSC culture, spermatogonial stem cells (SSC) and spermatogonia-like cells were obtained, while BMP4 and BMP8b were shown to induce primordial germ cell formation in BM-MSCs. Thus, it was determined that TGFβ1 could play a prominent role in infertility and spermatogenesis [37]. In another study, RA and BMP4 were combined and applied to both BM-MSCs and adipose tissue-derived MSCs (AD-MSC) to compare their differentiation potency to germ cells by determining the expression levels of Mvh, Dazl, Stra8 and Scp3 germ cell specific genes. Although there was an increase in the expression of these genes in both BM-MSCs and AD-MSCs, the expression rate in BM-MSCs was higher than in AD-MSCs, indicating that the potential for BM-MSCs to differentiate into germ cells is stronger [33]. The properties of AD-MSCs such as antioxidants and immune modulators are known. The secretomes of these cells are therefore very valuable. Oxidative stress has a major role in the development of male infertility. Therefore, oxidative stress in human sperm was induced by H_2O_2 in a study. These cells were then incubated for 24, 48 and 72 hours with conditioned medium of AD-MSCs (ADMSC-CM) to investigate the effects of ADMSC-CM on sperm vacuolation, DNA fragmentation, and oxidative stress levels. Sperm vacuolization and DNA fragmentation decreased significantly in the samples incubated for 24 hours, while other parameters remained stable [38].

Application of MSC in testicular damage - in vivo experiments

In recent years, after in vitro studies, in vivo studies have been accelerated and MSC application studies on damaged testicular tissues have increased. For this reason, many researchers have investigated the differentiation potential of MSCs obtained from various sources to germ cells and whether MSCs settle in testis and ameliorate testicular damage (Table 1). According to these studies, MSCs from different sources can restore spermatogenesis and the testicular niche (Figure 1).

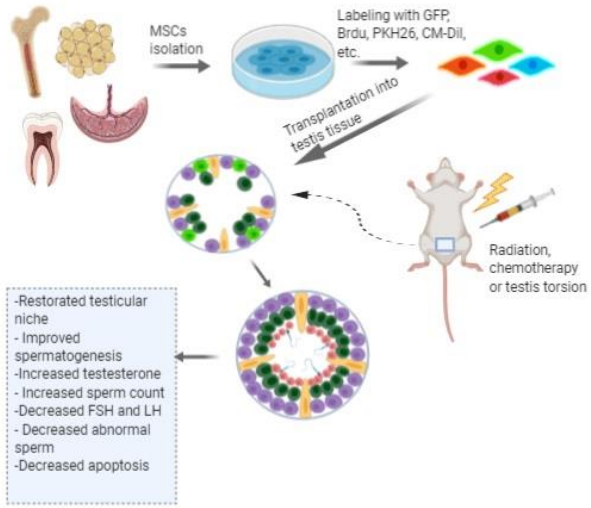

Figure 1: Mesenchymal stem cell isolation and transplantation into rat or mice with azoospermia. MSCs isolated from various sources such as bone marrow, adipose tissue, umbilical cord, placenta, and tooth. Isolated MSCs transplanted into testis (seminiferous tubules, rete testis or efferent duct) after labeling with Green fluorescent protein (GFP), Bromodeoxyuridine (Brdu), Paul Karl Horan 26 (PKH26), CM-Dil and etc. MSCs can restore spermatogenesis and testicular niche.

Table 1: Recent in vivo studies of MSCs application for male infertility

MSC Source	Number of cells	Used animals	Disease model	Period of MSCs Treatment	Results	Reference
Rat ADMSC	$1x10^6$ cells	Rat	Busulfan induced azoospermia	12 weeks	$GFP^+/Vasa^+$ and $GFP^+/SCP1^+$ cells were determined. Full spermatogenesis recovery and proliferation	[39]
Rat BMMSCs	$1x10^6$ cells	Rat	Lead (Pb) induced gonado-toxicity	21, 30 and 60 days	BMMSCs can differentiate into germ cells and Leydig cells. BMMSCs modulated testosterone levels and DNA apoptosis	[47]
Human UCMSC	$2,5x10^5$ cells	Mice	Busulfan induced infertility	3,9,18 and 20 days	HUCMSCs differentiated into germ cells and restored tubules	[40]
Induced BM-MSCs by co-culture with testicular cell conditioned medium	$1 x10^5$ cells	Rat	Busulfan induced azoospermia	8 weeks	BMMSCs can transdifferentiate into spermatogenic cells but after 8 weeks meiosis was not determined	[48]
Rat BMMSCs	$2,5x10^5$ cells	Rat	Busulfan induced infertility	4, 6 and 8 weeks	BMMSCs migrated to the germinal epithelium and expressed spermatogonia markers so these cells differentiated into spermatogonia	[49]
Human UCMSCs	$1 x10^5$ cells	BALB/c mice	Busulfan induced azoospermia	12 weeks	After transplantation of UCMSCs, increased expressions of meiosis-associated genes. UCMSCs (CD34-) restored testicular injury and decrease FSH and LH levels.	[41]
Rat BMMSCs	$5x10^6$ cells	Rat	Cadmium-induced testis injury	2 weeks	BMMSCs can prevent mitochondrial apoptosis and repair testis injury	[42]
Rat BMMSCs	$1x10^6$ cells	Rat	Doxorubicin-induced testicular toxicity	8 weeks	BMMSCs reduced rate of abnormal sperm and testicular oxidative stress	[44]
Human orbital fat tissues (OFSC)	$3x10^4$ cells	Rat	3 hours 720^0 torsion and detorsion	7 days	OFSCs can prevent intrinsic apoptosis and oxidative stress	[45]

Cakici et al [39] obtained ADMSC from rat adipose tissue and transplanted them into busulfan-induced azoospermic rats by labeling with GFP. The detection of GFP / Vasa and GFP / SCP1 positive cells showed the presence of ADMSCs in the tissue and these cells differentiated into spermatogenic cells after 12 weeks. Bromodeoxyuridine-labeled human UC-MSCs (HUMSCs) were transplanted in another azoospermia model using chemotherapeutic busulfan and detected in the tubule even after 120 days. It was determined that these cells settled, proliferated and differentiated into germ cells (via Oct-4, α6 integrin, C - kit, VASA expressions) [40]. A comparison study of the effects of stem cells on testicular injury was also conducted. Researchers isolated stem cells from umbilical cord origin. Umbilical cord blood-derived hematopoietic stem cells (HSC, CD34 + cells) and UCMSCs (CD 34-cells) were transplanted into mice with busulfan-induced azoospermia, and increased expression of meiosis-associated genes were determined in the MSC transplanted group (Vasa, SCP3 and PgK2). The MSC group (CD34-) restored testicular injury by increasing spermatogenic gene expression, whereas the CD34 + group showed no activity [41]. Cadmium is a heavy metal used in industrial and agricultural production and may cause infertility by reducing the number of sperm on people exposed to this toxic substance. Researchers transplanted 10^7 BM-MSC and studied whether BM-MSCs could restore cadmium-induced rat testicular damage and the role of mitochondrial apoptosis in this process. Expression of apoptosis-related proteins (Bim, Bax, Cytochrome C, Caspase-3, active Caspase-3 and AIF increased, Bcl-2 decreased) was determined 2 weeks after transplantation. Thus, it has been shown that mitochondrial apoptosis may be highly associated with BM-MSCs repairing damaged testicular tissue damage in rats [42].

Researchers are turning to different sources of MSC for the treatment of testicular injury. For example, Maghen et al [43] evaluated the first trimester human umbilical cord perivascular cells (FTM HUCPVCs), a new source of MSC. These cells have been shown to express and secrete factors known as important regulators of the testicular cell line such as FGF2, GDNF, LIF and BMP4. In addition, FTM HUCPVCs were found to have supportive properties for testicular regeneration in vitro and in vivo. After transplanting FTM HUCPVC to testicular injury models, induced by mono-2-ethylhexyl phthalate (MEHP), these cells were demonstrated to promote germ cell regeneration by the presence of Daz1 and acrosin positive cells. It has been reported that FTM HUCPVCs are capable of repairing the human testicular niche in case of testicular damage.

Chemotherapy causes irreversible damage and loss of fertility, especially in children and young men. For instance, although Doxorubicin (Dox) is an effective and widely used anti-cancer drug, its gonadotoxicity is quite high. Rats were injected intravenously with BM-MSC (2×10^6 cells) to investigate the effect of BM-MSCs against doxorubicin (Dox) induced toxicity in the assays. After 8 weeks of treatment, BM-MSCs reduced the high level of malondialdehyde caused by Dox and increased antioxidant levels to reduce testicular oxidative stress. Morphologically, testicular atrophy due to Dox, diameter of seminiferous tubules and germinative cell layer thickness were significantly reduced after BM-MSC transplantation. BM-MSCs were effective in restoring the structural efficiency of the reproductive system in testicular injury [44].

Hsiao and his team [45] transplanted 3×10^4 MSCs obtained from human orbital adipose tissue into 720^0 Torsion-Detorsion (T/D) rats by local injection into the testis. The effects of MSCs on oxidative stress and apoptosis mechanisms were investigated by superoxide dismutase 2, Bax, Caspase-3, P450, Sox-9 and malondialdehyde (MDA) test in T/D rats. MSCs were shown to reduce I/R-induced intrinsic apoptosis and oxidative stress. In addition, in their other study, they determined that T / D reduced sperm motility, sperm content, ATP content in sperm and F-actin expression, while MSCs injected to the testis increased ATP production by regulating glycolysis imbalance and Akt / GSK3 pathway. Sperm motility and energy were

increased with the help of MSCs in T/D induced-testicular damage thus, sperm function was repaired [45,46].

Conclusion

Male infertility is a fundamental problem and different treatments are investigated. Today, ART is widely used in couples who cannot have children. However, ART may be insufficient in some cases. For example, patients who received chemotherapy and / or radiotherapy in childhood may encounter azoospermia. Researches have focused on regenerative medicine and the development of stem cell technology has raised hope for infertility. MSCs from many sources have attracted the attention of researchers because of their high potential for both proliferation and differentiation. Although stem cells obtained from various sources are identified as MSC, their differentiation potentials to germ cells were different. Studies comparing the differentiation potentials of MSCs from different sources in testicular tissue are limited. Apparently, MSCs can improve testicular damage. In addition to proliferation in the damaged region, their paracrine properties can also improve the damaged tissue. MSCs secrete chemokines, cytokines, and growth factors, which may affect the testicular niche and restore the process of spermatogenesis. MSCs have brought a new perspective in the treatment of male infertility.

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Case report
Olgu sunumu

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A rare cause of steal phenomenon and ischemic pain: A radial artery pseudoaneurysm

Çalma fenomeni ile iskemi ağrısının nadir bir nedeni: Radial arter psödoanverizması

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Abstract
Catheter insertion and forearm arteriovenous shunts are the main reasons for pseudoaneurysms in the practice of cardiovascular surgery. Radial artery pseudoaneurysm from arterial wall disruption is an extremely rare complication of arterial approach. Herein, we report a case of radial pseudoaneurysm repair leading to steal phenomenon and ischemic pain which occurred following the closure of the arteriovenous fistula located between the radial artery and cephalic vein in the medial aspect of the right forearm in a 37-year-old male receiving regular hemodialysis for chronic renal failure.
Keywords: Radial pseudoaneurysm, Arteriovenous fistula, Steal phenomenon

Öz
Kalp ve damar cerrahisinde psödoanevrizmaların en önemli nedeni, kateter uygulamaları ve ön kolda açılan arteriyovenöz şantlardır. Arteriyel duvar bozulmasından kaynaklanan radyal arter psödoanevrizması, arteriyel yaklaşımın oldukça nadir görülen bir komplikasyonudur. Bu yazıda, kronik böbrek yetmezliği nedeniyle rutin hemodiyalize giren 37 yaşında erkek bir olguda, efektif çalışmayan sağ ön kol medial yüzde radial arter ve sefalik ven arasında arteriyovenöz fistülün kapatılması sonrasında oluşan ve çalma fenomeni nedeniyle iskemi ağrısı oluşturan radial arter psödoanevrizma tamiri sunuldu.
Anahtar kelimeler: Radial psödoanevrizma, Arteriyovenöz fistül, Çalma fenomeni

Introduction

Pseudoaneurysms usually occur at the site of needling/puncture or at the anastomoses and can be defined as hematomas communicating with the vascular lumen. They may develop into a fibrotic sac over time, which is devoid of an endothelium or vascular wall structure [1].

Risk factors include advanced age, diabetes, female sex, hypertension, fibrinolytic or anticoagulant therapy, peripheral vasculopathy, regular hemodialysis, repeated percutaneous interventions, long catheterization time, large catheter diameter, coagulation disorder, incomplete hemostasis, multiple puncture attempts, inadequate compression after the procedure, and vascular site infection [2-4].

In the few reported cases of radial artery pseudoaneurysms, surgical repair is the most commonly used treatment [5]. We herein report a case of radial pseudoaneurysm leading to steal phenomenon and ischemic pain which occurred following the closure of the arteriovenous fistula (AVF) located between the radial artery and cephalic vein in the medial aspect of the right forearm in a patient receiving regular hemodialysis for chronic renal failure.

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Case presentation

A 37-year-old male patient was admitted to our outpatient clinic with a swollen wrist and severe pain in the right arm for one week. His medical history revealed renal transplantation a decade ago and rejection two years ago. The patient underwent several operations previously for the creation of an AVF in the right arm for hemodialysis, and the last AVF where the wrist swell was closed surgically four years ago. He was receiving clopidogrel 75 mg/kg/day, doxazosin 8 mg/day, and prednisolone 5 mg/day. Laboratory test results were as follows: Urea: 155 mg/dL, creatinine: 9,06 mg/dL, and erythrocyte sedimentation rate: 17/mm/h. Electrocardiography and chest X-ray showed normal findings. Visual inspection of the right arm demonstrated surgical scars including a 2-cm transverse scar in the snuffbox region, a 10-cm vertical scar in the radial aspect, and a 6-cm transverse scar in the antecubital region (Figure 1). Physical examination revealed a 3x3 cm pulsatile swelling in the radial aspect of the right hand above the surgical scar. Radial pulse was present proximal and distal to the swelling; however, no ulnar pulse was documented. On auscultation, there were murmur and a palpable thrill.

Superficial ultrasonography revealed a 15-mm pseudoaneurysm originating from the radial artery, mostly with a thrombosed lumen. Upper limb arteriography was performed to obtain a definite diagnosis of the pseudoaneurysm, probably located in the former AVF line, and evaluate its relationship with other vascular structures. According to the arteriography findings, there was a pseudoaneurysm in the fistula line of the radial artery, the palmar arch was filled by the radial artery, and ulnar artery was occluded (Figure 2). As the radial artery is the only source of arterial blood flow to the hand, closure using interventional radiological procedures was not preferred. Surgical repair of the pseudoaneurysm was decided and a written informed consent was obtained from the patient.

Skin incision was performed under local anesthesia and the pseudoaneurysm sac was reached. The radial artery, released from the proximal and distal ends, was rotated, and clamped after intravenous administration of heparin 80 IU/kg. The arterial continuity was disrupted in the distal segment. Dissection was performed and a vascular clamp was placed to the distal segment. The pseudoaneurysm sac was then excised. Specimens from both solid and fluid material inside the sac were collected for pathological and microbiological examination. As the proximal and distal ends of the radial artery were unable to be repaired in an end-to-end fashion, saphenous vein graft interposition was performed (Figure 3). The vascular clamps were released, and it was observed that radial artery was pulsatile with adequate microcirculation on palpation. No microorganism was isolated in the culture. Clinical diagnosis was confirmed by the pathological examination. The patient was uneventfully discharged from the hospital on postoperative day 2.

Figure 1: A preoperative image of surgical scars and swollen radial pseudoaneurysm in the right forearm (red circle)

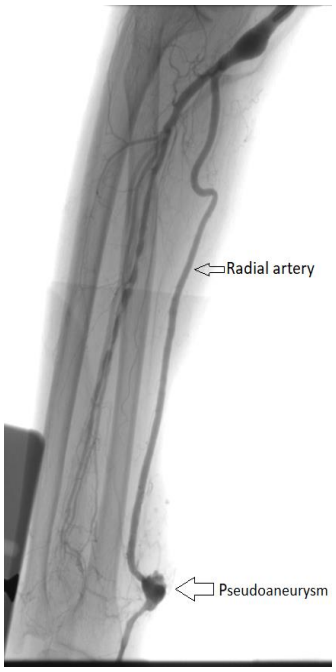

Figure 2: An arteriography image showing a radial pseudoaneurysm in the right upper limb

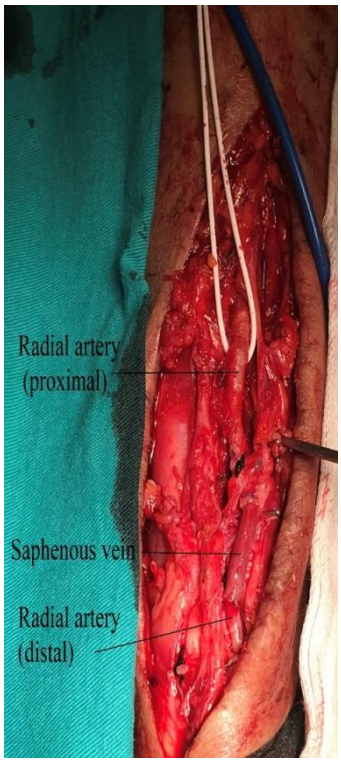

Figure 3: An intraoperative image of saphenous vein graft interposition of the radial artery after the excision of pseudoaneurysm sac

Discussion

Regular puncture and anticoagulation make pseudoaneurysms and true aneurysms relatively common complications in patients receiving hemodialysis [5]. Vascular access is essential to ensure effective hemodialysis treatment in dialysis patients. Unfortunately, vascular access complications are common, and many complications can threaten vascular access [1]. Pseudoaneurysms are one of these complications.

Clinical presentation of pseudoaneurysm varies depending on the localization, size, and growth rate of the pseudoaneurysm. The main goal of treatment of a radial pseudoaneurysm is to repair the wall lesion or discontinue the flow communication between the artery and the parenchymal

hematoma. In general, treatment depends on the etiology, location, symptoms, presence of thrombi, distal circulation, and collateral formation [3].

Surgical options to recover the AVF should be considered in AVF aneurysms. If the aneurysm is small and discrete in a tortuous AVF, it may reconstruct the AVF with a direct end-to-end anastomosis [6]. In case of larger aneurysms, either a bypass with a graft or an aneurysmorrhaphy can be performed [7,8]. To ensure the vascular continuity immediately in acute arterial pathologies which are not eligible for primary repair, autogenous veins with higher long-term patency rates that are highly resistant to infections should be preferred [9]. The small saccular pseudoaneurysms with narrow necks may be suitable to thrombin injection [10] or ultrasound compression [11]. This non-invasive technique can be attempted before the initiation of surgical or endovascular alternatives. In recent years, endovascular techniques have been also used widely in the treatment of AVF aneurysms [12].

In our case, there was a small, but a suddenly and rapidly growing pseudoaneurysm originating from the single artery which filled the palmar arch and, thereby, led to steal phenomenon and ischemic pain. Since the radial artery was the only source of arterial blood flow to the hand, non-surgical closure was not considered feasible. Therefore, the pseudoaneurysm sac was resected and the proximal and distal vascular defect was repaired using a saphenous vein graft.

Vascular complications such as pseudoaneurysms can easily occur in patients undergoing multiple vascular operations due to chronic renal failure, resulting in severe ischemic pain. In addition, patients should be educated and trained on modifiable risk factors after surgery, which is as important as the treatment itself.

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A case of sebaceous carcinoma in the eyelid: The results of chemoradiotherapy after recurrence

Göz kapağında sebase karsinom olgusu: Nüks sonrası kemoradyoterapi sonuçları

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Abstract
Sebaceous carcinoma of the eyelid, a rare and locally aggressive malignant neoplasm, can metastasize via the lymphatic and hematogenous route. The diagnosis and treatment can be delayed because of the similarity of the tumors with benign lesions. We herein present a 65-year-old male patient who was diagnosed with sebaceous carcinoma of the left upper eyelid 7 years ago, after which surgical resection was performed. Regional recurrence developed in left cervical nodes two years later. Left neck dissection was performed and adjuvant radiotherapy was administered. The patient has no evidence of recurrence or metastasis after radiotherapy during 5 years of follow-up.
Keywords: Sebaceous carcinoma, Radiotherapy, Eyelid

Öz
Göz kapağının sebase karsinomu nadir ve lokal-agresif malign neoplazmıdır. Lenfatik ve hematojen metastaz görülebilir. Benign lezyonlara benzerliği nedeniyle tanı ve tedavi gecikebilir. Bu olgu, 7 yıl önce sol üst göz kapağında sebase karsinom tanısı konulan 65 yaşında erkek hastadır. Cerrahi rezeksiyon yapıldıktan 2 yıl sonra sol servikal lenf nodunda nüks gelişti. Sol boyun diseksiyonu ve daha sonra adjuvan radyoterapi uygulandı. Hastanın 5 yıllık gözlem sırasında radyoterapiden sonra nüks veya metastaz bulgusu yoktur.
Anahtar kelimeler: Sebase karsinom, Radyoterapi, Göz kapağı

Introduction

Sebaceous carcinoma (SC) arises from the sebaceous gland of the skin for which there is no standard treatment. In general, it occurs in the periorbital and head and neck regions (extraocular). Due to similarities with benign lesions, it can be misdiagnosed. Early treatment is significant for locoregional control. Lymph node metastasis is common (30%) [1]. We aimed to share the results of a case in which multiple treatment modalities were applied.

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Case presentation

A 65-year-old male presented with complaint of a mass in the left upper eyelid. It was decided to evaluate the orbital region with contrast-enhanced MRI for preliminary diagnosis, which revealed a 24x18x10 mm heterogeneous hyperintense lesion in the left upper eyelid. Ultrasonographic evaluation of the cervical region was negative for any metastatic lymph nodes. Local excision was performed without sentinel lymph node biopsy (SLNB) or lymph node dissection. Pathological diagnosis was sebaceous carcinoma with a 1 mm surgical margin and a tumor size of 22 mm. After 2 years, the patient presented with left upper cervical mass. Relapse was considered and ^{18}F fluorodeoxyglucose positron emission tomography/computed to mography (FDG PET/CT) was performed for re-staging, which showed left upper jugular (12 mm) (SUVmax=14) and left submandibular (23x16 mm) (SUVmax=14) hypermetabolic lymphadenopathies. The patient then underwent left selective neck dissection. The pathology report showed a total of 5 lymph node metastases, 4 of which were level I and 1 of which was level II. After surgery, radiotherapy (RT) was administered along with weekly cisplatin treatment. EBRT was delivered to the left level I-IV, preauricular and intraparotid lymph node regions with 6MV X-rays using Intensity Modulated Radiotherapy (IMRT). The patient was treated with a median radiation dose of 60 Gy to level I-II nodal regions and 54 Gy to elective nodal regions (level III-IV, preauricular and intraparotid lymph nodes) in 2 Gy fraction doses.

He was followed-up at 3-6 months intervals for 5 years after RT. During follow up, there was no local regional progression or distant metastasis.

Discussion

Ocular SC is a rare tumor with poor prognosis arising from the Meibomian glands of the upper eyelid. The incidence varies among ethnic groups. Although it is exceedingly rare in the Western world, its incidence is quite high in China, Japan, India.

It is emphasized in the literature that these cases can be overlooked due to misdiagnosis. In a study by Lam SC et al. [2], it was noted that the delay of treatment had a negative effect on DFS. In this study, 5-year survival rates were better in cases with a disease history of less than 6 months. Our patient was followed up after being misdiagnosed as hordeolum for more than 6 months until the correct diagnosis.

SC is common in older female individuals, while our case was an old male patient. Older age is a negative factor for DFS [2]. T and N stage, location (upper-lower lid), grade are correlated with DFS in periocular SC. In addition, large tumor size (20 mm <), diffuse pattern, multicentric origin, lobular pattern, pagetoid spread negatively affect local recurrence and distant metastasis [3].

Regional lymph node metastasis rate is 8-28% [1,4,5], the most commonly affected nodes being the preauricular, parotid, submandibular, and cervical lymph nodes.

The rate of local-regional lymph node metastasis in ocular SC is reportedly higher than that of extraocular SC [6]. Lam et al. stated that stage T2b and higher (Tumor diameter >10 mm) were related to lymph node metastasis [2], and recommended sentinel lymph node biopsy for periorbital sebaceous carcinomas >10 mm in diameter.

The recommended standard treatment is surgical excision with wide margins [7]. A minimum margin of 5 mm is considered adequate. The 5-year local recurrence rates range from 9% to 36% at 4 mm margins [8]. In case of advanced stage tumors, orbital exenteration is suggested. In addition to surgery, the roles of RT and chemotherapy (CT) have been investigated. RT was required after positive surgical margin, local-regional recurrence and/or orbital exenteration [9,10]. While studies evaluating the effectiveness of chemotherapy are limited, it can be recommended in recurrent cases [11]. In our case, no additional treatment was performed after wide local excision 7 years ago. 2 years after initial treatment, the patient presented with ipsilateral cervical lymph node recurrence. Adjuvant RT was performed with chemotherapy following regional lymph node dissection. In the literature, the rates of recurrence are 4-37% for periorbital SC [2]. The mean recurrence time is 18 months.

Conclusions

The primarily recommended treatment of the eyelid SC is wide surgical excision. Prognostic factors should be well assessed for the use of additional treatment modalities.

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Giant fibroadenoma of the breast: A case report of a 37-year-old woman during the second trimester of pregnancy

Memenin dev fibroadenomu: Gebeliğin ikinci trimesterinde olan 37 yaşında kadın olgu sunumu

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Abstract
Fibroadenomas are the most common benign breast tumors in young women aged between 20-30 years. Giant fibroadenomas are often larger than 5 cm, weigh more than 500 g or occupy 80% of the breast. They can mimic malignant tumors because they grow rapidly and cause breast deformity. We present a young female patient, in the second trimester of her pregnancy, who had a rapidly growing giant fibroadenoma. Since the mass was suspected of malignancy and caused deformity in the breast, surgical excision was indicated. The operation was performed without complications and the patient was discharged on the second postoperative day. Although the second trimester is suitable for semielective surgeries that cannot be postponed, the timing of the operation is decided by a multidisciplinary team including surgeons, anesthesiologists, obstetricians and perinatologists.
Keywords: Fibroadenoma, Phyllodes tumor, Pregnancy

Öz
Fibroadenomlar, 20-30 yaş arası genç kadınlarda en sık görülen benign meme tümörleridir. Dev fibroadenomlar genellikle 5 cm'den daha büyük boyuta sahip, 500 g'dan daha ağırdır veya memenin % 80'ini kaplarlar. Büyüme hızları ve meme deformitesine neden olabilmeleri nedeniyle malign tümörleri taklit edebilirler. Hamileliğin ikinci trimesterinde ve hızla büyüyen dev fibroadenomu olan genç bir kadın hastayı sunuyoruz. Kitlenin malignite şüphesi olması ve memede deformiteye yol açması nedeniyle cerrahi eksizyon önerildi. Ameliyat komplikasyonsuz gerçekleşti ve hasta ameliyat sonrası ikinci gününde taburcu edildi. İkinci trimester ertelenemeyen semielektif cerrahiler için uygun olsa da, operasyonun zamanlamasına cerrahlar, anestezistler, kadın doğum uzmanları ve perinatologlar dahil olmak üzere multidisipliner bir ekip tarafından karar verilir.
Anahtar kelimeler: Fibroadenom, Filloid tümör, Gebelik

Introduction

Fibroadenomas, the most common benign tumors of the breast, contain stromal and epithelial elements. The overall incidences of fibroadenomas in adolescents and women older than 30 years are 2.2% and 18%, respectively, and account for nearly 70% of all breast masses [1,2]. Fibroadenomas are generally small breast lumps that can increase in size but rarely to greater than 3 cm [3]. Spontaneous regression is also possible after menopause. The size of the adenoma can change as a response to the hormonal changes during menstrual cycles and pregnancy. The clinical presentation is most commonly an asymptomatic, painless breast mass. Giant fibroadenomas are rare benign lesions usually found in patients under 20 years of age and defined as fibroadenomas >5 cm in size, heavier than 500 g, or occupying more than 80% of the breast [4]. Although it is a benign lesion, its dimensions suggest a possible malignancy and a differential diagnosis from malignant breast masses should be made. We present a 37-year-old pregnant woman in the 17th gestational week who had a giant fibroadenoma in her right breast, which showed an approximately two-fold increase in size within 6 months.

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Case presentation

A 37-year-old, 17-weeks-pregnant woman presented to the general surgery outpatient clinic with a giant mass in the right breast, which she noticed 6 months ago. She had no known additional diseases. Breast ultrasonography revealed a solid mass lesion with lobulated contours, 6 cm in diameter, which could not be distinguished from a phyllodes tumor. Follow-up was decided.

The patient re-applied 6 months later due to rapid growth of the mass with pregnancy. In clinical examination, a mass larger than 10 cm was detected, which met the criteria of a benign mass lesion. Ultrasonographic examination revealed a solid mass, 10x94x70mm in size, containing microcystic areas with lobulated contours filling the periphery of the right outer lower quadrant. The ultrasound and biopsy examination did not distinguish the mass from phyllodes tumor for certain.

Due to the rapid growth and progressive deformation of the breast, lumpectomy was recommended, and surgery was performed without any perioperative and postoperative complications, considering the stage of the pregnancy. Pathological examination reported the tumor size as 13x11x5 cm (Figure 1). Histopathological examination of the mass was compatible with fibroadenoma with increased stromal tissue, and cellularity and proliferation in epithelial cells (Figure 2). Safety of the fetus was ensured by perioperative and postoperative follow-up. At the third month follow-up, bilateral breasts were symmetrical and wound healing was rapid without any infection or complications. Written informed consent was obtained from the patient.

Figure 1: Large, well-circumscribed, nodular right breast mass measuring 13x11x5 cm in size on physical examination

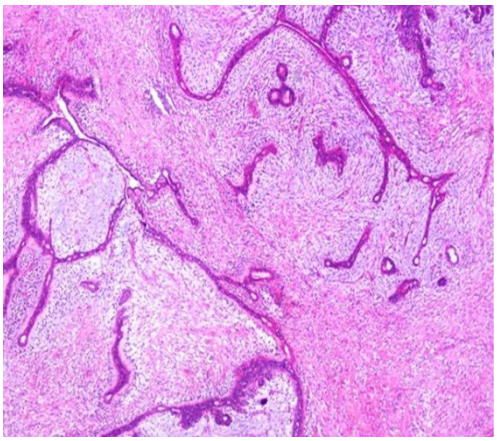

Figure 2: Histopathological examination of the mass was compatible with fibroadenoma with typical stromal and epithelial proliferation (hematoxylin and eosin, magnification ×100).

Discussion

Fibroadenomas arise from the terminal ductal lobular unit. The etiology is not clear, but it is believed result from an abnormal response to hormonal stimulation. With hormonal changes during pregnancy, proliferative changes occur in the ductal and alveolar elements. There is lobular hyperplasia, hyperemia and fluid retention in breast tissue. Milk synthesis in the mammary gland begins in the second trimester of pregnancy. Towards the end of pregnancy, secretion begins from the alveoli and the parenchyma largely replaces the stromal tissue. The increase in the size and incidence of fibroadenomas during pregnancy seems to be linked to increased estrogen, progesterone, placental prolactin, and other growth factors levels. Fibroadenomas may undergo spontaneous infarction and necrotic-calcified degeneration, especially due to their rapid growth during pregnancy and lack of vascularity. A history of oral contraceptive use before the age of 20 also causes an increase in incidence [5,6]. Fibroadenomas are divided into simple, complex, giant, and juvenile types. Those greater than 5 cm in diameter or 500 g in weight are named giant fibroadenomas. If seen in patients between 10-18 years old, they are called juvenile fibroadenomas [7]. They tend to grow fast but may shrink after adolescence. Phyllodes tumor should be suspected in fast growing palpable breast masses over 3 cm [8].

Ultrasonography is the preferred diagnostic method for fibroadenomas. Distinct features include a round or ovoid, well-circumscribed, macrolobulated hypoechoic mass. Mammography demonstrates a well-circumscribed macrolobulated mass, sometimes with a classic or popcorn calcification, especially in older women. Due to the use of gadolinium in breast MRI (magnetic resonance imaging) and the radiation exposure during mammography, the diagnostic imaging method is primarily ultrasonography in pregnant women. Mammography should be performed with a lead shield to ensure the safety of the fetus. Gold standard for histopathological diagnosis of a fibroadenoma is core needle biopsy. The incidence of malignancy development from fibroadenomas is less than 1%. The low incidence of cancer development and slowly growing or shrinking nature of fibroadenomas support observation of the mass, particularly in biopsy-proven cases [9].

Phyllodes tumors are rare, fibroadenoma-like structures which should be handled carefully. They may be confused with breast fibroadenomas clinically, radiologically and histopathologically [10]. They constitute less than 1% of all breast tumors and can be seen at any age but are mostly observed starting from the fourth decade [11]. They tend to grow quickly. Most of the phyllodes tumors are benign but malignant and borderline tumors can also be seen. Approximately 20% of phyllodes tumors emerge as a non-palpable mass revealed by screening mammography. Diagnosis can be obtained with a core needle or excisional biopsy. Core needle biopsy sometimes isn't adequate to diagnose phyllodes tumors [12]. Surgical treatment of benign, borderline or malignant phyllodes tumors comprises wide excision of the tumor with at least 1 cm negative surgical margin [13].

Fibroadenomas of typical appearance emerging during pregnancy can be monitored closely by clinical examination and ultrasound imaging. Biopsy may be performed according to the

size of the fibroadenoma. Fibroadenomas of atypical appearance detected during pregnancy should be biopsied first. Close monitoring is not necessary if fibroadenomas detected before pregnancy remain stable during pregnancy. Clinical and ultrasound follow-up is recommended if there is no more than 20% increase in size compared to previous imagings and in case of benign appearance. Biopsy is performed in the presence of significant increase in size and suspicious morphological changes. Close monitoring is recommended for multiple fibroadenomas of typical appearance, but biopsy should be performed in case of a suspicious nodule [14].

In our case, since the possibility of malignancy could not be eliminated with preoperative examinations, the mass was managed with a multidisciplinary team to protect the fetus and apply the correct approach during the treatment. The first trimester is the initial phase of fetal organogenesis, during which drug-induced fetal defect is higher. Preterm delivery risk is increased in the third trimester. Second trimester is considered the optimal time for elective surgery in pregnant patients [14,15]. The fetus should be monitored closely due to potential teratogenic effect of anesthetic agents administered during pregnancy.

Conclusions

We presented a rare case of a young female patient who is in the second trimester of pregnancy and has a fast growing giant fibroadenoma. Treatment decisions are best made with the guidance of a multidisciplinary team and should include discussions about specific approaches to breast masses and protecting the fetus during the treatment.

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Management of iatrogenic left main coronary artery dissection in a center without onsite cardiac surgery back up

Açık kalp cerrahi desteği olmayan bir merkezde iatrojenik sol ana koroner arter diseksiyon yönetimi

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Abstract
Catheter-related iatrogenic left main coronary artery dissection is an extremely rare complication that can cause fatal outcomes if not recognized and treated early. In the current approach, conservative follow-up, bailout stenting with percutaneous intervention and bypass surgery treatment options are available. However, in some centers, coronary angiography and interventional applications are performed without surgical support. Management of such rare but important complications becomes more complex in these centers. In this experience, we wanted to share after her approval, how we managed catheter-induced iatrogenic left main coronary artery dissection in a 72-year-old female patient with bailout stenting and conservative approach in a center without surgical back up.
Keywords: Coronary artery dissection, Stent, Angiography

Öz
Katatere bağlı iatrojenik sol ana koroner arter diseksiyonu son derece nadir görülen ancak erken fark edilip tedavi planlaması yapılmadığında ölümcül sonuçlara sebep olabilen bir komplikasyondur. Güncel yaklaşımda konservatif izlem, perkutan girişimle bailout stentleme, bypass cerrahisi tedavi seçenekleri mevcuttur. Ancak bazı merkezlerde cerrahi destek olmadan koroner anjiografi ve girişimsel uygulamalar yapılmaktadır. Bu gibi nadir ama önemli komplikasyonların yönetimi bu merkezlerde daha karmaşık hale gelmektedir. Bu konuda yaşadığımız bu tecrübede stent implante edebilmek için kateteri derin entübasyon yapmak durumunda kaldığımız 72 yaş bayan hastada katetere bağlı gelişen iatrojenik sol ana koroner arter diseksiyonunu cerrahi destek olmayan merkezde bailout stentleme ve konservatif yaklaşımla nasıl yönettiğimizi kendisinin onayı alındıktan sonra paylaşmak istedik.
Anahtar kelimeler: Koroner arter diseksiyonu, Stent, Anjiografi

Introduction

Catheter-induced iatrogenic left main coronary artery (LMCA) dissection is an exceedingly rare complication (0.071%) that can be fatal if not recognized and treated early [1]. In the current approach, conservative follow-up, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) treatment options are available [2]. However, in some centers, coronary angiography and interventional procedures are performed without surgical support. We herein report how we managed catheter-induced LMCA dissection with both PCI (bailout stenting) and conservative approach in a center without on-site cardiac surgery back up.

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Hasta Onamı: Yazarlar çalışmada görüntüleri ile sunulan hastalardan yazılı onam alındığını ifade etmiştir.

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Case presentation

A 72-year-old woman with a previous history of hypertension (HT) and atrial fibrillation (AF) was admitted to the emergency department with typical chest pain and was taken for emergency coronary angiography with elevated cardiac biomarkers. Physical examination was unremarkable and transthoracic echocardiogram showed mild anterior hypokinesia with an ejection fraction of 50%. Coronary angiography performed with 6 French catheters in the right femoral pathway revealed a 90% critical stenosis in the left anterior descending artery (LAD) with dense calcific eccentric structures in the proximal-mid region (Figure 1a). The stenosis of the LAD was passed with 0.014-inch soft type floppy wire (BMV, Abbott Vascular, Santa Clara, CA, USA). Subsequently, the lesion was predilated with 1.25×12 mm and 2.0×12 mm compliant balloons at 12 atm. 3.0×18 mm drug eluting stent (Xıence Pro, Abbott Vascular, Santa Clara, CA, USA) was advanced to the lesion with deep intubation of Left Judkins 4.0 catheter (Launcher, Medtronic, Minneapolis MN, USA) because the lesion could not be passed despite repeated attempts (Figure 1b). After the stent passed, it was implanted at 13 atm. Catheter-induced type B dissection (NHLB-I classification) in the LMCA region was observed in the control images (Figure 1c-1d).

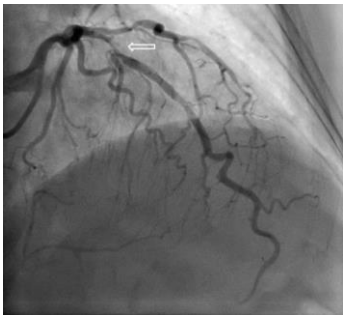

Figure 1a: Calcified lesion in the proximal-mid part of LAD (arrow)

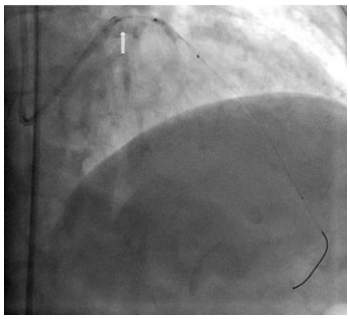

Figure 1b: Deep catheter intubation (arrow) into LMCA

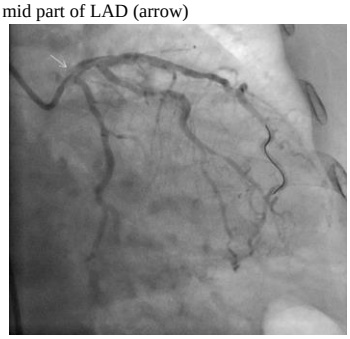

Figure 1c: Dissection of LMCA (arrow) with antegrade extension to LAD

Figure 1d: Dissection line (arrow) extension to LAD

Afterwards, 4.0×9 mm bare metal stent (Ephesos II, Alvimedica**,** Istanbul, Turkey) was implanted at 12 atm (Figure 2a) to the area where the intimal dissection line had begun. In the control pose, the initial dissectıon line at LMCA was closed (Figure 2b). The patient remained hemodynamically stable after the development of main coronary artery dissection and did not have any symptoms. However, there was no surgical back up in our clinic, and in case of deterioration and retrograde progression of dissection, the closest surgical center was 60 km away. Therefore, retrograde progression of dissection was prevented by spot stenting of the intimal flap insertion site instead of conservative follow-up. Due to the presence of stents, conservative follow-up was planned for the minimal dissection line between two stents. The patient was discharged after 3 days of follow-up. Patient's written consent was obtained.

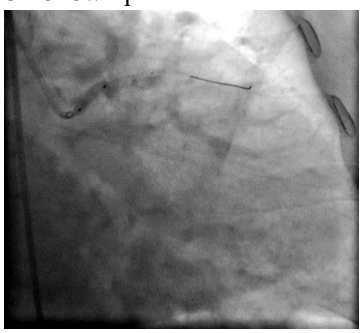

Figure 2a: Urgent stenting of LMCA

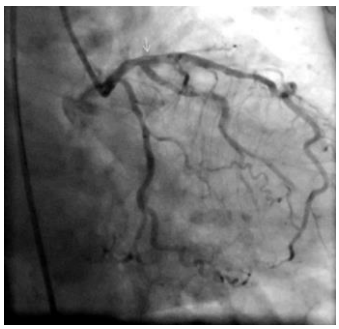

Figure 2b: Starting point of the dissection line is closed and the minimal dissection line (arrow) remains in LAD

Discussion

Especially in cases of very intense intracoronary calcification and severe atherosclerosis, or abnormal anatomic output of LMCA, LMCA dissections may occur due to subintimal passage of rigid and hydrophilic wires used during the procedure, inappropriate small diameter catheter selection, excessive manipulation of catheter, use of left amplatz and extra back up catheters and deep intubation of catheters, rapid and excessive contrast applications and operator-dependent reasons [3-5]. LMCA dissection management depends on the patient's clinical condition, the causative factor, antegrade flow and hemodynamic status and the character of the dissection line progression. In some cases, previously reported in the literature, the conservative approach of 'Watchful waiting' is sufficient when the dissection line is minimal and does not block flow [6,7]. Although bailout stenting is the most logical strategy in cases where dissection is more severe and obstructs flow, cases where stenting failed and the dissection line advanced antegrade or retrograde to the aorta have been reported [8,9]. We believe that we were lucky, because the treatment we performed was sufficient for the patient. Although our patient was clinically stable, the nearest surgical center was 60 km away thus bailout stenting was more reasonable than the conservative approach to prevent further deterioration.

Conclusion

Interventional cardiologists should always consider the physical conditions of the medical center, their own clinical experience and their complication management experience in cases requiring deep catheter intubation and excessive catheter manipulation.

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