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Editör veya yardımcıları tarafından, etik kurul onayı alınması zorunluluğu olan klinik araştırmalarda onay belgesi talep edilecektir. Yazıların içeriğinden ve kaynakların doğruluğundan yazarlar sorumludur.
Yazarlar, gönderdikleri çalışmanın başka bir dergide yayınlanmadığı ve/veya yayınlanmak üzere incelemede olmadığı konusunda garanti vermelidir. Daha önceki bilimsel toplantılarda 200 kelimeyi geçmeyen özet sunumlarının yayınları, durumu belirtilmek koşulu ile kabul edilebilir. Tüm otörler bilimsel katkı ve sorumluluklarını bildiren formu doldurarak yayına katılmalıdırlar.
Tüm yazılar, editör ve ilgili editör yardımcıları ile en az üç danışman hakem tarafından incelenir. Yazarlar, yayına kabul edilen yazılarda, metinde temel değişiklik yapmamak kaydı ile editör ve yardımcılarının düzeltme yapmalarını kabul etmiş olmalıdırlar.
Makalelerin formatı 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication' (http://www.icmje.org) kurallarına göre düzenlenmelidir.
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Bu sistem ile toplanan makaleler ICMJE-www.icmje.org, Index Medicus (Medline/PubMed) ve Ulakbim-Türk Tıp Dizini kurallarına uygun olarak sisteme alınmakta ve arşivlenmektedir. Yayına kabul edilmeyen yazılar, sanatsal resimler hariç geriye yollanmaz. Dergide yayınlanmak üzere editöre gönderilen yazılar A4 sayfasının bir yüzüne 12 punto, çift aralıkla, arial/times new roman karakteri ve kenarlarda 2,5 cm boşluk bırakılarak yazılmalıdır. Kullanılan kısaltmalar yazı içerisinde ilk geçtikleri yerde, parantez içinde, açık olarak yazılmalı, özel kısaltmalar yapılmamalıdır. Yazı içindeki 1-10 arası sayısal veriler yazıyla (Her iki tedavi grubunda, ikinci gün), 10 ve üstü rakamla belirtilmelidir. Ancak, yanında tanımlayıcı bir takısı olan 1-10 arası sayılar rakamla (1 yıl) cümle başındaki rakamlar da (Onbeş yaşında bir kız hasta) yazıyla yazılmalıdır. Yazının tümünün 5000 kelimeden az olması gerekmektedir. İlk sayfa hariç tüm yazıların sağ üst köşelerinde sayfa numaraları bulunmalıdır. Yazıda, konunun anlaşılmasında gerekli olan sayıda ve içerikte tablo ve şekil bulunmalıdır.
Başlık sayfası, kaynaklar, şekiller ve tablolar ile ilgili kurallar bu dergide basılan tüm yayın türleri için geçerlidir.
Hastalar mahremiyet hakkına sahiptirler. Belirleyici bilgiler, hasta isimleri ve fotoğraflar, bilimsel olarak gerekli olmayan durumlarda ve hasta (ebeveyn veya koruyucu) tarafından yayınlanmasına yazılı olarak bilgilendirilmiş bir onay verilmediği sürece yayınlanmamalıdır.
Bu amaçla, bilgilendirilmiş onay, hastanın yayınlanacak belirli bir taslağı görmesini gerektirir. Eğer gerekli değilse hastanın belirleyici detayları yayınlanmayabilir. Tam bir gizliliği yakalamak oldukça zordur ancak eğer bir şüphe varsa, bilgilendirilmiş onay alınmalıdır. Örneğin, hasta fotoğraflarında göz bölgesini maskelemek, yetersiz bir gizlilik sağlanmasıdır.
Haseki Tıp Bülteni'ne yayınlanmak amacıyla gönderilen ve etik kurul onayı alınması zorunluluğu olan deneysel, klinik ve ilaç araştırmaları için uluslararası anlaşmalara ve 2013'de gözden geçirilmiş Helsinki Bildirisi'ne uygun etik kurul onay raporu gereklidir (http://www.wma.net/en/30publications/10policies/b3/). Deneysel hayvan çalışmalarında ise "Guide for the care and use of laboratory animals (https://oacu.oir.nih.gov/regulations-standards) doğrultusunda hayvan haklarını koruduklarını belirtmeli ve kurumlarından etik kurul onay raporu almalıdırlar. Etik kurul onayı (onay numarası ile birlikte) ve "bilgilendirilmiş gönüllü olur formu" alındığı araştırmanın "Yöntemler" bölümünde belirtilmelidir. Yazarlar, makaleleriyle ilgili çıkar çatışması ve maddi destekleri bildirmelidirler.

Orijinal Makaleler

1) Başlık Sayfası (Sayfa 1): Yazı başlığının, yazar(lar)ın bilgilerinin, anahtar kelimelerin ve kısa başlıkların yer aldığı ilk sayfadır.
Türkçe yazılarda, yazının İngilizce başlığı da mutlaka yer almalıdır; yabancı dildeki yayınlarda ise yazının Türkçe başlığı da bulunmalıdır. Türkçe ve İngilizce anahtar sözcükler ve kısa başlık da başlık sayfasında yer almalıdır.
Yazarların isimleri, hangi kurumda çalıştıkları ve açık adresleri belirtilmelidir. Yazışmaların yapılacağı yazarın adresi de ayrıca açık olarak belirtilmelidir. Yazarlarla iletişimde öncelikle e-posta adresi ve mobil telefon kullanılacağından, yazışmaların yapılacağı yazara ait e-posta adresi ve mobil telefon mutlaka belirtilmelidir. Buna ek olarak sabit telefon ve faks numaraları da bildirilmelidir.
Çalışma herhangi bir bilimsel toplantıda önceden bildirilen koşullarda tebliğ edilmiş ya da özeti yayınlanmış ise bu sayfada konu ile ilgili açıklama yapılmalıdır.
Yine bu sayfada, dergiye gönderilen yazı ile ilgili herhangi bir kuruluşun desteği sağlanmışsa belirtilmelidir.
2) Özet (Sayfa 2): İkinci sayfada yazının Türkçe ve İngilizce özetleri (her biri için en fazla 200 sözcük) ile anahtar sözcükler belirtilmelidir.
Özet Bölümü: Amaç, Yöntemler, Bulgular, Sonuç şeklinde alt başlıklarla düzenlenir. Derleme, olgu sunumu ve eğitim yazılarında özet bölümü alt başlıklara ayrılmaz. Bunlarda özet bölümü, 200 kelimeyi geçmeyecek şekilde amaçlar, bulgular ve sonuç cümlelerini içermelidir.
Özet bölümünde kaynaklar gösterilmemelidir. Özet bölümünde kısaltmalardan mümkün olduğunca kaçınılmalıdır. Yapılacak kısaltmalar metindekilerden bağımsız olarak ele alınmalıdır.
3) Metin (Özetin uzunluğuna göre Sayfa 3 veya 4'den başlayarak)
Genel Kurallar bölümüne uyunuz.
Metinde Ana Başlıklar Şunlardır: Giriş, Yöntemler, Bulgular, Tartışma, Çalışmanın Kısıtlılıkları ve Sonuç.
Giriş bölümü çalışmanın mantığı ve konunun geçmişi ile ilgili bilgiler içermelidir. Çalışmanın sonuçları giriş bölümünde tartışılmamalıdır.
Yöntem bölümü çalışmanın tekrar edilebilmesi için yeterli ayrıntılar içermelidir. Kullanılan istatistik yöntemler açık olarak belirtilmelidir.
Bulgular bölümü de çalışmanın tekrar edilebilmesine yetecek ayrıntıları içermelidir.
Tartışma bölümünde, elde edilen bulguların doğru ve ayrıntılı bir yorumu verilmelidir. Bu bölümde kullanılacak literatürün, yazarların bulguları ile direkt ilişkili olmasına dikkat edilmelidir.
Çalışmanın Kısıtlılıkları bölümünde çalışma sürecinde yapılamayanlar ile sınırları ifade edilmelidir.
Sonuç bölümünde çalışmadan elde edilen sonuç, gelecek çalışmalara ilişkin öneriler ile vurgulanmalıdır.
Teşekkür mümkün olduğunca kısa tutulmalıdır. Çalışma için bir destek verilmişse bu bölümde söz edilmelidir. (Teşekkür yalnızca "Başlık Sayfası" içerisinde gönderilmelidir.)
Metinde fazla kısaltma kullanmaktan kaçınılmalıdır. Tüm kısaltılacak terimler metinde ilk geçtiği yerde parantez içinde belirtilmelidir. Özette ve metinde yapılan kısaltmalar birbirinden bağımsız olarak ele alınmalıdır. Özet bölümünde kısaltması yapılan kelimeler, metinde ilk geçtiği yerde tekrar uzun şekilleri ile yazılıp kısaltılmalıdırlar.
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c) Kitap Bölümü: Porter RJ, Meldrum BS. Antiepileptic drugs. In: Katzung BG, editor. Basic and clinical pharmacology. 6th ed. Norwalk, CN: Appleton and Lange; 1995. p. 361-80.
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The Medical Bulletin of Haseki

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The journal should be abbreviated as Med Bull Haseki when referenced.

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Manuscripts are accepted only online and can be submitted electronically through web site (http://hasekitip.dergisi.org) after creating an account. This system allows online submission and review.

The ORCID (Open Researcher and Contributor ID) number of the correspondence author should be provided while sending the manuscript. A free registration can create at http://orcid.org.

The manuscripts gathered with this system are archived according to ICMJE-www.icmje.org, Index Medicus (Medline/PubMed) and Ulakbim-Turkish Medicine Index Rules. Rejected manuscripts, except artworks are not returned.

Articles sent to the editor for publication should be written single-sided on A4 pages, double-spaced in 12-point, arial/times, new roman font and with 2.5 cm margins. Abbreviations must be explained clearly in parentheses in their first instance within the text and custom abbreviations should not be used. Numbers 1 to 10 should be given as text (In the two treatment groups the second day) and numbers 11 or bigger given as numbers. However, numbers 1-10 with a descriptive suffix should be given with numbers (1 year) while numbers that start sentences (Fifteen-year-old female patient) should be given as text.

The manuscript should not exceed 5000 words in total. All pages of the manuscript should be numbered at the top right-hand corner, except for the title page. Papers should include the necessary number of tables and figures in order to provide better understanding.

The rules for the title page, references, figures and tables are valid for all types of articles published in this journal.

Patients have a right to privacy. When not essential, identifying information, patient names and photographs should not be published, unless the written informed consent of the patient (parent or guardian) has been given.

The patient should, therefore, be given a draft of the paper in order to obtain written informed consent. When not necessary, any identifying details of the patient should not be published. Complete anonymity is difficult to attain, however, informed consent should be obtained if any doubt exists. For example, masking the eye region of a patient's photograph provides incomplete anonymity.

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The names, affiliated institutions and full addresses of the authors should be given. The author to whom correspondence is to be addressed should be indicated separately. As e-mail addresses will be used preferentially for communication, the e-mail address of the corresponding author should be stated. In addition, telephone and fax numbers must be notified.

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If any grants or other financial support has been given by any institutions or firms for the study, information must be provided by the authors.

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The Summary Should Consist of the Following Sub Sections: Aim, Methods, Results, Conclusion. Separate sections are not used in the summaries of the review articles, case reports and educational articles. For these articles, the summaries should not exceed 200 words and include the scope and aims of the study, the salient findings and conclusions.

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3) Text (From the Page 3 or 4, according to the length of the summaries)

Please follow the instructions in "general guidelines."

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The introduction should include the rationale for investigation and the background of the present study. Results of the study should not be discussed in this part.

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The Discussion section should provide a correct and thorough interpretation of the results. The references should be directly related to the findings of the authors.

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Conclusion section should provide highlighted and interpreted with the study's new and important findings.

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Original Article

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A Survey Analyzing Reflections of COVID-19 on Patients and Their Relatives

COVID-19'un Hasta ve Hasta Yakınları Üzerindeki Etkisi

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Abstract

Aim: In this study, we aimed to analyze the level of knowledge about Coronavirus disease-2019 (COVID-19) in patients and their relatives presented to the emergency department.

Methods: In this study, a 25-item questionnaire was applied to patients and their relatives. The participants were stratified into three groups as primary-secondary school, high school or university graduation. The responses were analyzed among education groups at a significant level of p<0.05.

Results: In this study, of the 212 participants, 62.7% were male. The proportion of the participants thinking "COVID-19 also affected younger individuals" was higher in participants having an education level of high school or higher (p=0.009). The willingness to receive the vaccine was significantly high among all education levels. The idea that traditional soups and gargling with salty water prevent disease was found to be more common among participants with an education level of high school or lower (p<0.05). The benefit from the opinion of the expert on media about protection against the virus was significant in participants with an education level below high school (p<0.05).

Conclusion: The revision of key messages of public health specialists according to education levels will have an important role in reorganizing inaccurate knowledge in the community.

Keywords: COVID-19, survey, Coronavirus, pandemics

Öz

Amaç: Biz bu çalışmada acil servise başvuran hasta ve hasta yakınlarının Koronavirüs hastalığı-2019 (COVID-19) ile ilgili bilgi düzeylerini analiz etmeyi amaçladık.

Yöntemler: Bu çalışmada hasta ve hasta yakınlarına 3'lü likert tip ölçeğe uygun hazırlanan 25 soru yöneltildi. Katılımcılar ilkokul-ortaokul, lise ve üniversite eğitim durumlarına göre 3 gruba ayrıldı. Eğitim grupları arasında sorulara verilen yanıtlar p<0,05 anlamlılık düzeyine göre analiz edildi.

Bulgular: Bu çalışmada 212 katılımcının %62,7'si erkekti. Katılımcıların eğitim durumuna göre cevapları incelediğimizde; COVID-19 enfeksiyonundan gençlerin de etkilendiğini düşünme oranı lise ve üzeri mezun grubunda daha yüksekti (p=0,009). COVID-19 aşısı yaptırma isteği ise tüm eğitim gruplarında anlamlı yüksek bulunmuştur. Geleneksel çorbaların tüketiminin ve tuzlu su ile gargara yapılmasının hastalığı önlediği fikri ise yine lise altı eğitim grubunda anlamlı bulunmuştur (p<0,05). Ekranlara çıkan uzman/doktorların virüsten korunmak için görüşlerinden faydalanma ise lise altı grupta daha anlamlı çıkmıştır (p<0,05).

Sonuç: Halk sağlığı uzmanlarının bilgilendirme mesajlarını eğitim gruplarına göre de revize etmesi toplumdaki yanlış ya da eksik bilgilerin düzeltilmesinde etkin rol oynayacaktır.

Anahtar Sözcükler: COVID-19, anket, Coronavirüs, pandemi

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Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) first emerged with findings of viral pneumonia in a group of patients at Wuhan Province, China (1). The Coronavirus disease-2019 (COVID-19), which was initially defined in a small group of patients, affected the whole Wuhan Province and the whole world thereafter (2). Currently, the COVID-19 has a mortality rate ranging from 1% to 5% (3). Although the mortality rate was lower when compared to SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) from betacoronavirus family (10% and 37%, respectively), it is apparent that SARS-CoV-2 affected far more people worldwide (4). Due to the rapid spread of viruses, the World Health Organization declared pandemics on January 30, 2020, and called for collaboration to fight against the virus (5).

The past experiences from outbreaks in the last two decades suggest that level of knowledge of the community is directed on prevention or disease transmission (6,7). In the current pandemics, governments have issued strict measures to fight pandemics and have made efforts to improve public awareness regarding the situation faced (6).

Despite all measures, the fight against COVID-19 is currently ongoing in Turkey as similar to the whole world. Determining the level of knowledge of patients and their relatives about virus will be beneficial in planning information meetings via public health organizations or mass media, allowing correcting false facts. Thus, in this study, we aimed to analyze the level of knowledge about COVID-19 disease in patients and their relatives presented to the emergency department (ED).

Materials and Methods

This study was conducted on patients and their relatives (aged >18 years) who presented to ED between May 1st, 2020 and May 30th, 2020. The participants declining participation, participants with incomplete data, participants lacking communication skills and participants requiring prompt intervention were excluded from this study. Thus, the final analysis included data from 212 participants. The items in the questionnaire were designed to identify the community's perception to COVID-19 by considering the public agenda. The first part of the questionnaire was prepared to collect data regarding sociodemographic characteristics of the participants while the second part to measure the level of knowledge about COVID-19. The questionnaire was rated using a 3-items Likert scale, "I agree," "I don't agree" and "I am indecisive." The participants were stratified into three groups according to education level as participants with primary-secondary school, high school and university graduation. The answers were analyzed among education groups. All participants gave written informed consent. This study was approved by Haydarpaşa Numune Training and Research Hospital and conducted in accordance with tenets of the Helsinki Declaration. University of Health Sciences, Haydarpaşa Numune Training and Research Hospital (Number: 2020/52-2143 Date: 04.06.2020).

Statistical Analysis

Was carried out using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). Descriptive analyses were presented using mean ± SD (minimum-maximum) or n (%), where appropriate. Categorical data were analyzed by the Pearson chi-square test. Cronbach's alpha coefficient was calculated for reliability analysis. A p-value of less than 0.05 was considered statistically significant.

Results

In this study, the mean age of the participants was 36.56±11.85 years ranging from 18 to 83 years. Of the 212 participants, 62.7% were men and 37.3% were women. Of the participants, 58 participants (27.4%) reported that they were primary or secondary school graduate, while 91 (42.9%) were high school graduate, and 63 (29.7%) were university or higher graduate. Of the participants, 48.1% presented to the hospital as they were ill, while 51.9% presented as patient relative (Table 1). The Cronbach alpha coefficient was calculated as 0.752 for 3-items Likert scale, indicating acceptable consistency (8).

Table 2-4 presents a comparison of responses of the participants according to education level. The findings obtained in this study showed that there were no significant differences among groups regarding responses to "this infection was transmitted by bats," "smoking aggravates the infection," "I will have the vaccine if

Table 1. General characteristics of participants

	N	%
Age (years). mean ± SD/min-max	36.56+11.85	18-83
Gender		
Male	133	62.7
Female	79	37.3
Education		
Primary-secondary school	58	27.4
High school-college	91	42.9
University or higher	63	29.7
Cause of presentation		
Patient	102	48.1
Patient's relative	110	51.9

SD: Standard deviation, Min: Minimum, Max: Maximum

it is available in Turkey" (p=0.209, p=0.116, p=0.059, respectively). The percent of the participants responding as "I don't agree" to the item "This infection does not affect younger individuals" was higher in participants with high school or university graduation than those with primary-secondary school graduation (p=0.009). It was seen that there was no significant difference among groups regarding responses to items "COVID-19 is a biological weapon," "Turkey is successful in the fight against the virus," and "stay at Home campaign is successful in Turkey" (p=0.168, p=0.338, p=0.059, respectively). The percent of the participants responding as "I don't agree" to the items "The infectivity of virus is eradicated by Beyran soup" and "Gargling with salty water prevents ascending of the virus to lungs" was higher in participants with high school or university graduation than participants with primary-secondary school graduation (p<0.001, p<0.001, respectively). It was seen that there was no significant difference according to education level regarding responses to the items on the use of a mask or hand disinfectant (p=0.657, p=0.207, respectively). The percent of the participants responding as "I agree" to the item "I benefit from opinions of experts/clinicians on TV" was higher in the group with primary-secondary school graduation than remaining groups (p=0.041). It was seen that the responses to the items "I approve broadcast with experts in the field," "The TV programs prompt unnecessary fear rather than informing people" and "I find the statement of health ministry as reliable and sufficient" were comparable according to education

Table 2. Comparison of responses according to educational level

	Education			
Questions	**Primary-secondary school**	**High school or college**	**University or higher**	**p**
This infection is transmitted from bats.				
I don't agree	16 (27.6)	35 (38.5)	19 (30.2)	0.209
I am indecisive	33 (56.9)	34 (37.4)	31 (49.2)	
I do agree	9 (15.5)	22 (24.2)	13 (20.6)	
This infection does not affect younger individuals.				
I don't agree	35 (60.3)	72 (79.1)	54 (85.7)	0.009
I am indecisive	18 (31)	15 (16.5)	9 (14.3)	
I do agree	5 (8.6)	4 (4.4)	0 (0)	
Smoking aggravates the infection.				
I don't agree	7 (12.1)	5 (5.5)	1 (1.6)	0.116
I am indecisive	8 (13.8)	14 (15.4)	6 (9.5)	
I do agree	43 (74.1)	72 (79.1)	56 (88.9)	
I will receive if the vaccine is available in Turkey.				
I don't agree	7 (12.1)	6 (6.6)	0 (0)	0.059
I am indecisive	21 (36.2)	33 (36.3)	20 (31.7)	
I do agree	30 (51.7)	52 (57.1)	43 (68.3)	
COVID-19 is a biological weapon.				
I don't agree	10 (17.2)	13 (14.3)	14 (22.2)	0.168
I am indecisive	23 (39.7)	32 (35.2)	30 (47.6)	
I do agree	25 (43.1)	46 (50.5)	19 (30.2)	
Turkey is successful in the fight against the virus.				
I don't agree	4 (6.9)	7 (7.7)	1 (1.6)	0.338
I am indecisive	7 (12.1)	18 (19.8)	13 (20.6)	
I do agree	47 (81)	66 (72.5)	49 (77.8)	
"Stay at Home" campaign is successful in Turkey				
I don't agree	8 (13.8)	11 (12.1)	4 (6.3)	0.059
I am indecisive	6 (10.3)	20 (22)	20 (31.7)	
I do agree	44 (75.9)	60 (65.9)	39 (61.9)	

Data are presented as n (%). Pearson chi-square test.
COVID-19: Coronavirus disease-2019

level (p=0.647, p=0.998, p=0.189, respectively). There was no significant difference in the percent of awareness about 14-Rules and adherence to 14-Rules according to education levels (p=0.170). No significant relationship was found between education level and item "I am aware of Advisory Board members and I find them sufficient" (p=0.398). There were differences in rates of fear from virus or think that virus is overestimated according to education level (p=0.167, p=0.557, respectively). It was seen that majority of participants in each education level reported that healthcare providers worked unselfishly during pandemics (p<0.001).

Discussion

By December 2019, initially in China and worldwide thereafter, COVID-19 has become one of the most common topics of discussion in both the scientific community and media, including mass media and social media. During this period, some limitations in public life have been instituted in Turkey and curfew was declared

Table 3. Comparison of responses according to educational level

	Education			
Questions	**Primary-secondary school**	**High school or college**	**University or higher**	**p**
The infectivity of the virus is eradicated by soup from the head and foot of sheep				
I don't agree	21 (36.2)	56 (61.5)	50 (79.4)	<0.001
I am indecisive	26 (44.8)	25 (27.5)	12 (19)	
I do agree	11 (19)	10 (11)	1 (1.6)	
The infectivity of the virus is eradicated by Beyran soup				
I don't agree	21 (36.2)	56 (61.5)	48 (76.2)	<0.001
I am indecisive	29 (50)	27 (29.7)	14 (22.2)	
I do agree	8 (13.8)	8 (8.8)	1 (1.6)	
Gargling with salty water prevents ascending of the virus to the lungs				
I don't agree	20 (34.5)	48 (52.7)	43 (68.3)	<0.001
I am indecisive	18 (31)	22 (24.2)	16 (25.4)	
I do agree	20 (34.5)	21 (23.1)	4 (6.3)	
Viral spread is decreased by wearing a mask				
I don't agree	2 (3.4)	7 (7.7)	2 (3.2)	0.657
I am indecisive	6 (10.3)	8 (8.8)	8 (12.7)	
I do agree	50 (86.2)	76 (83.5)	53 (84.1)	
Viral spread is decreased using hand disinfectants				
I don't agree	4 (6.9)	2 (2.2)	0 (0)	0.207
I am indecisive	7 (12.1)	11 (12.1)	10 (15.9)	
I do agree	47 (81)	78 (85.7)	53 (84.1)	
I benefit from the opinions of experts/clinicians on TV programs				
I don't agree	5 (8.6)	14 (15.4)	6 (9.5)	0.041
I am indecisive	3 (5.2)	18 (19.8)	13 (20.6)	
I do agree	50 (86.2)	59 (64.8)	44 (69.8)	
I approve TV programs involving experts in the field.				
I don't agree	6 (10.3)	9 (9.9)	5 (7.9)	0.647
I am indecisive	5 (8.6)	15 (16.5)	11 (17.5)	
I do agree	47 (81)	67 (73.6)	47 (74.6)	
TV programs prompt unnecessary fear rather than informing people				
I don't agree	25 (43.1)	40 (44)	29 (46)	0.998
I am indecisive	15 (25.9)	24 (26.4)	16 (25.4)	
I do agree	18 (31)	27 (29.7)	18 (28.6)	

Data are presented as n (%). Pearson chi-square test

Table 4. Comparison of responses according to educational level				
	Education			
Questions	Primary-secondary school	High School or College	University or higher	p
I find the statement of Ministry of Health as reliable and sufficient				
I don't agree	9 (15.5)	13 (14.3)	2 (3.2)	0.189
I am indecisive	15 (25.9)	24 (26.4)	17 (27)	
I do agree	34 (58.6)	54 (59.3)	44 (69.8)	
I am aware of 14-Rules and try to adhere				
I don't agree	8 (13.8)	4 (4.4)	3 (4.8)	0.170
I am indecisive	6 (10.3)	8 (8.8)	4 (6.3)	
I do agree	44 (75.9)	79 (86.8)	56 (88.9)	
I am aware of the Advisory Board members and I find them sufficient				
I don't agree	12 (20.7)	9 (9.9)	7 (11.1)	0.398
I am indecisive	12 (20.7)	20 (22)	15 (23.8)	
I do agree	34 (58.6)	62 (68.1)	41 (65.1)	
I feel fear about the virus transmission to me				
I don't agree	10 (17.2)	11 (12.1)	2 (3.2)	0.167
I am indecisive	8 (13.8)	14 (15.4)	11 (17.5)	
I do agree	40 (69)	66 (72.5)	50 (79.4)	
I think the virus is overestimated				
I don't agree	29 (50)	51 (56)	39 (61.9)	0.557
I am indecisive	10 (17.2)	19 (20.9)	10 (15.9)	
I do agree	19 (32.8)	21 (23.1)	14 (22.2)	
I think healthcare providers worked unselfishly during the pandemic				
I don't agree	6 (10.3)	3 (3.3)	0 (0)	<0.001
I am indecisive	2 (3.4)	8 (8.8)	4 (6.3)	
I do agree	50 (86.2)	80 (87.9)	59 (93.7)	
Data are presented as n (%). Pearson chi-square test.				

Table 5. 14 Rules against the novel coronavirus risk: Coronavirus Is Not Stronger Than Measures You Take!
1. Wash your hands frequently with soap and water for at least 20 seconds.
2. Keep a distance of at least 3 to 4 steps between people showing flu signs.
3. Cover your mouth and nose with disposable wipes during coughing or sneezing. If there is no wipe, use the inner part of your elbow.
4. Avoid close contact, such as handshaking or hugging.
5. Do not touch your hands to mouth, nose and eyes.
6. Postpone or cancel your travels abroad.
7. Isolate yourself at home for at least 14 days after returning abroad.
8. Ventilate your environments frequently.
9. Wash your clothes at 60-90 C using normal detergents.
10. Clean surfaces commonly used surfaces, such as door handles, armatures and sinks daily using water, disinfectant and detergent.
11. If you have cold symptoms, do not contact the elderly and people with chronic diseases. Do not go out without wearing a mask.
12. Do not share personnel belongings, such as a towel.
13. Consume sufficient fluid, follow a balanced diet, and pay attention to your sleep pattern.
14. If you have any complaints, such as persistent fever, cough and difficulty breathing, contact

for all individuals of all ages during weekends and bank holidays. In addition, continuous curfew was declared for individuals aged >65 years and those <20 years; public and private areas were closed to access; distance education programs were implemented, and areas where people can be present indiscrete were closed. Mass transportation was halted and permission was warranted for crossing between provinces. Extremely strict measures, such as quarantine for individuals with contact to infected people or isolation and provision of personal requirements of suspected individuals have been taken, which we had not experienced previously. Primary protection methods were expressed as 14-Rules (Table 5) by Advisory Board and a nationwide campaign "Stay at Home" was launched (9). Obviously, in addition to measures held by governments, the community has a great mission to lower spread. Although 14-Rules explain primary measures against coronavirus risk, potential false information should be revealed and correction of this false information will be helpful in the management of the pandemics.

Studies showed that novel coronavirus has >95% homology with bat coronavirus and >70% phylogenetic homology with SARS-CoV (10). In a survey on 453 healthcare providers, 58.7% of the participants confirmed COVID-19 transmission from bats (11). In our survey, the majority of the participants (46.2%) reported that they are indecisive about transmission from bats, while 40%1 of the participants reported that they are indecisive and 42.5% of participants reported that they agree to the item about being a biological weapon. The finding that there was no difference in responses according to education level in these items indicates that conspiracy theories are at the forefront for community and that community does not trust global forces and terrorist activities although coronavirus was proven to be zoonosis. Based on the results of an online survey, 23.9% of participants from USA and 18.4% from UK responded as "less likely," "likely" or "very likely" to the item "Is coronavirus a biological weapon" (12). The higher rate in our study may be because global forces and conspiracy theories are more commonly discussed in our society. Of the participants, 75.9% responded as "I don't agree" to the item "This infection does not affect younger individuals." The rate of the answer "I don't agree" to this item was higher in the participants with high school or university graduation than the participants with primary-secondary school graduation. In an online survey, 96.5% of participants from the US and 97.1% of participants from the UK did not agree to the following statement, "Only elder individuals are affected by virus" (12). Such an idea may lead that inadequate compliance to measures against the virus and overlooking transmission risk in the society by younger individuals. The rate of participants who responded as "I don't agree" was low among lower education levels suggests that public health specialists should inform society about this issue.

In our country, it is thought that some traditional soups enhance the immune system and their consumption is increased, particularly in respiratory tract infections. Even sometimes, some clinicians recommend these soups in the lists for healthy nutrition. Traditionally, the opinion that gargling with salty water will clean oropharynx is accepted in society. In our survey, the majority of participants responded as "I don't agree" to the items "The infectivity of virus is eradicated by the soup prepared from head and foot of sheep," "The infectivity of virus is eradicated by Beyran soup" and "gargling with salty water prevents ascending of the virus to lungs" (59.9%, 59.0% and 52.4%, respectively). When assessed according to education level, the rate of participants responded as "I don't agree" was higher among subjects with high school or university graduation than those with primary-secondary school graduation ($p<0.05$). The commitment of individuals with primary-secondary school graduation to traditional methods may be the cause of a higher rate of "I do agree" and "I am indecisive" in this group. It is recommended that public health interventions to inform society should target info pollution circulating on TV/video, press or social media (12,13). Thus, experts should continuously state that traditional soups or gargling are not effective protective measures against the virus.

Despite the proven efficiency of vaccines in the prevention of disease and disability, there are growing concerns about anti-vaccination or vaccine hesitancy, which has become a considerable challenge worldwide (14). In a survey on childhood vaccines in Turkey, 59.7% of the families declined all childhood vaccines, while 30.3% declined only some childhood vaccines (15). It is apparent that vaccine perception will change after coronavirus pandemics. In our survey, 50% of the participants reported that they were willing to receive the coronavirus vaccine, which did not differ according to education level. It is striking that 34.9% of participants are still indecisive about vaccination. Certainly, more information provided in public health programs will help to change minds in these indecisive individuals, and even it may offer a chance to prevent vaccine hesitancy. Trust in vaccines may be recovered in society, preventing the recurrence of many diseases associated with high morbidity and mortality.

It has been proposed that smokers are at higher risk for coronavirus during pandemics because of the harmful effects of smoking on immune and respiratory systems (16). In a survey by Klemperer et al. (16), the findings showed that to reduce the risk for COVID-19, 22.9% and 21.9% of the participants attempted to quit tobacco or

electronic cigar use, respectively. In our study, 80.7% of the participants stated that infection has a more severe course in smokers. Emphasizing this issue in public health programs will facilitate the prevention of smoking since 73.6% reported fear from virus transmission and 56.1% though that virus is not overestimated. When discussing the harmful effects of smoking, one should not only emphasize the increased incidence of cancer in smokers but also explain that it affects the course of infections due to its impact on the immune system.

Of the participants, 76.4% reported that government is successful in the fight against the virus and 67.5% approved that campaign Stay at Home played an effective role in reducing viral spread while 62.3% found statements of government reliable and sufficient and 84.4% reported that they are aware of 14-Rules and attempt to adhere these rules. Of the participants, 64.6% reported that they were aware of the advisory board and found the work of board sufficient. The finding that there was no difference according to education level in these items suggests that the majority of society trusts the government.

During pandemics, many television programs were on air and experts responded questions from the public. Of participants in our survey, 75.9% approved television programs with experts and 72.8% reported that they benefit from opinions of experts/clinicians on television programs. In a survey on healthcare providers, approximately 30% of the participants reported that they followed information about COVID-19 from TV, video, press or social media (11). In our study, rates above 70% on the items regarding media suggest that televisions programs have an influence on the perception of society; in fact, accurate programs can help to improve awareness in many issues in society. It was striking that the responding as "I agree" to item "I benefit from opinions of experts/clinicians on TV programs" was higher among participants with primary or secondary school graduation when compared to the remaining group (p=0.041). These findings suggest that updating the content of TV programs to appeal to individuals with lower education levels will be beneficial in improving the level of knowledge of society. In an online survey, including 6,910 participants, the findings showed that designing TV programs appealing to participants with low education levels would substantially improve knowledge about COVID-19 (6).

The increased physical and verbal violence against healthcare providers is a non-negligible fact worldwide. About one-third of the healthcare providers experience physical violence at least once and more experience verbal abuse or threat throughout a professional career (17). The healthcare providers subjected to violence will experience decreased motivation, negatively influencing his/her performance and decreasing the quality of healthcare services provided (18). In the literature, the incidence of violence against healthcare providers has been reported as 0.4-91% (19). In our study, 89.2% of the participants thought that healthcare providers work unselfishly during pandemics. While 73.6% of the participants reported fear about virus transmission, healthcare providers working actively in the hot zone led an empathy and recovery of esteem to healthcare providers.

The single-center design is a major limitation of our study. Multicenter studies with more patients and relatives can make clearer observations about the level of knowledge of society on novel coronavirus. This may help revealing interventions performed and deficiencies, leading improved awareness in society. These interventions are highly important in the fight against the outbreak.

Conclusion

We aimed to analyze the reflections of the novel coronavirus in society through a questionnaire completed by patients and their relatives. It was seen that participants were indecisive about the likelihood that the virus could be a biological weapon rather than being a virus transmitted naturally. It was also observed that society is trusting to the Turkish Ministry of Health and advisory board and adheres to recommendations and statements by these organizations. Given that there is a consensus that Turkey is successful in the fight against the virus, this indicates an environment of confidence. It is obvious that TV programs can affect the level of knowledge in society. Thus, awareness will be improved by accurate messages via media, given that society takes these messages seriously.

Author contributions

Concept: B.G.Y, S.Ç., R.G., Design: B.G.Y, S.Ç., R.G., Data Collection or Processing: B.G.Y., S.Ç., R.G., A.Ü., D.S., İ.A., Analysis or Interpretation: B.G.Y., S.Ç., R.G., A.Ü., D.S., İ.A., Literature Search: B.G.Y., S.Ç., R.G., A.Ü., D.S., İ.A., Writing: B.G.Y.

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Use of Cerebral Oximetry in Elective Cesarean Section Procedures Performed Under Spinal Anesthesia: A Randomized Prospective Study

Spinal Anestezi ile Yapılan Elektif Sezaryen Vakalarında Serebral Oksimetre Kullanımı: Randomize Prospektif Çalışma

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Abstract

Aim: To compare the effect of bupivacaine and bupivacaine/fentanyl combination on cerebral oxygenation values with the Near-infrared spectroscopy (NIRS) technique in elective cesarean sections performed under spinal anesthesia.

Methods: Fifty patients who underwent cesarean section under spinal anesthesia were randomly divided into two groups. 7.5-10 mg 0.5% hyperbaric bupivacaine was administered to the bupivacaine group (n=25) and 7.5-10 mg 0.5% hyperbaric bupivacaine+20-25 mcg fentanyl was given to the combination group (n=25). Heart rate, mean arterial pressure, peripheral oxygen saturation, mean values of regional cerebral oxygen saturation after spinal anesthesia were recorded preoperatively and the 1st, 5th, 10th, 15th and 20th minutes after anesthesia. The presence of perioperative nausea and vomiting was assessed with the Verbal Descriptive Scale.

Results: Significant difference was observed in mean arterial pressure values between groups (p=0.001). There was a statistically significant change in cerebral oxygenation values during surgery in both groups (p=0.001). The frequency of nausea and vomiting was lower in the combination group (p=0.009).

Conclusion: The non-invasive NIRS technique can be safely applied in the monitoring of cerebral oxygenation and hemodynamics in elective cesarean section procedures undergoing spinal anesthesia.

Keywords: Pregnancy, sesarean section, spinal anesthesia, cerebral oxygenation, intraoperative monitoring, near-infrared spectroscopy.

Öz

Amaç: Spinal anestezi ile yapılan elektif sezaryen vakalarında bupivakain ve bupivakain/fentanil kombinasyonunun serebral oksijenizasyon değerlerine etkisini Near-infrared Spektroskopi (NIRS) tekniği ile karşılaştırmak.

Yöntemler: Spinal anestezi ile sezaryen operasyonu olan 50 hasta rastgele yöntemle iki gruba ayrıldı. Hastalardan bupivakain grubuna (n=25) 7,5-10 mg %0,5 hiperbarik bupivakain ve kombine grubuna (n=25) 7,5-10 mg %0,5 hiperbarik bupivakain+20-25 mcg fentanil uygulandı. Hastaların, spinal anestezi uygulaması sonrası kalp atım hızı, ortalama arteriyel basıncı, periferik oksijen satürasyonu, rejyonel serebral oksijen satürasyonunun ortalama değerleri preoperatif ve anestezi uygulamasının 1, 5, 10, 15, 20 dk sonrasında kaydedildi. Peroperatif bulantı kusma varlığı Verbal Deskriptif Skala ile takip edildi.

Bulgular: Her iki grupta ortalama arter basıncı değerleri arasında anlamlı değişim gözlendi (p=0,001). Gruplarda cerrahi süresince serebral oksijenizasyon değerleri arasında istatistiksel olarak anlamlı değişim oldu (p=0,001). Kombine grupta bulantı-kusma görülme sıklığı daha az saptandı (p=0,009).

Sonuç: Spinal anestezi uygulanan elektif sezaryen vakalarında serebral oksijenizasyon ve hemodinami takibinde girişimsel olmayan NIRS tekniği güvenle uygulanabilir.

Anahtar Sözcükler: Gebelik, sezaryen yöntemi, spinal anestezi, serebral oksijenasyon, intraoperatif izleme, yakın kızıl ötesi spektroskopi

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Introduction

Cesarean delivery, which is becoming increasingly common worldwide, should have a frequency of around 10-15% of births; however, its use is rapidly increasing, especially in developing countries (1). In our country, the frequency of cesarean section reached 53.1% in 2016 (2). Spinal anesthesia for cesarean section has various advantages over general anesthesia, such as the lack of influence on mental functions, continuation of spontaneous breathing, enabling the patient to stay awake, reductions in thromboembolic complications and blood loss, early mobilization, and shortening the duration of hospitalization. In spinal anesthesia, local anesthetics are used either alone or in combination with adjuvant compounds. The most commonly used adjuvant agents are opioids. The addition of opioids to local anesthetics decreases the dose of local anesthetic required, the incidence of side effects on the central nervous system and cardiovascular system, while also shortening the onset of anesthetic action (3-5).

Non-invasive Near-infrared spectroscopy (NIRS) devices, such as the INVOS (Covidien, Somanetics, Troy, MI) device, can be used to measure the saturation of critical watershed areas in which circulation consists of a mixture of 1/3 arterial and 2/3 venous blood (6). In recent years, non-invasive NIRS has also begun to be widely used in surgeries wherein regional anesthesia is applied (7).

In our study, we aimed to compare intrathecal hyperbaric bupivacaine and intrathecal hyperbaric bupivacaine with fentanyl adjuvant in patients undergoing elective caesarean section, with regard to their effects on hemodynamic parameters and cerebral oxygenation values during surgery.

Methods

Study Design

Fifty patients between the ages of 18-40 years who underwent caesarean section with spinal anesthesia between 01.08.2013 and 31.12.2013 were included in our study. The ethical approval for the study was obtained from the local ethics committee (decision protocol number: 2013/0037), and informed consent was obtained from each patient included in the study. The patients were randomly divided into 2 groups with the closed envelope technique: those that received 7.5-10 mg 0.5% hyperbaric bupivacaine (bupivacaine group, n=25) and those that received 7.5-10 mg 0.5% hyperbaric bupivacaine +20-25 mcg fentanyl (combination group, n=25). The patient exclusion criteria of the study were as follows: refusal of spinal anesthesia administration, presence of bleeding diathesis, determination of infection at the intervention site, having neurological or cardiac comorbidities, documented or suspected allergy to any of the drugs used, history of psychiatric illness, having any type of pregnancy complication (preeclampsia, gestational diabetes, presence of fetal anomaly, etc.), being diagnosed with placenta previa, ablatio placenta or HELLP, and receiving anticoagulant treatment. After the exclusion criteria was applied 74 patients were initially enrolled in the study after signing informed consent forms. However, due to various reasons, such as switching to general anesthesia as a result of unsuccessful spinal anesthesia (n=6), massive bleeding during surgery (>2000 cc) (n=2), development of respiratory depression after spinal block (n=1), and transition to general anesthesia as a result of bowel injury during surgery (n=1), a total of 10 patients were excluded from the study (Figure 1).

The demographic and examination data of the patients (age, weight, height, ASA class, gestational weeks), the average values of heart rate (HR) after spinal anesthesia, mean arterial pressure (MAP), peripheral oxygen saturation (sPO_2) and the mean values of regional cerebral oxygen saturation (rSO_2) measured from the right-left hemispheres were recorded preoperatively and the 1st, 5th, 10th, 15th and 20th minutes after anesthesia. In case the MAP fell below 80% of baseline value, intravenous (iv) ephedrine (5-10 mg) was administered. The time of first ephedrine administration and total ephedrine amounts were recorded. In case of bradycardia (HR <50 beats/min), iv atropine 0.5 mg was administered. The presence of preoperative nausea and vomiting was assessed with the Verbal Descriptive Scale (VDS) (15) (0=no nausea, 1=mild nausea, 2=moderate nausea, 3=frequent vomiting, 4=severe vomiting).

Spinal Anesthesia Technique

Before the intervention, 20 mL/kg/hour iv crystalloid was administered in 30 minutes, and then spinal anesthesia was performed with a pen-tipped (M. Schilling) 25 G needle from the L3-4 gap in an appropriate position under sterile conditions. Patients were randomly divided into two equally-sized groups, the bupivacaine group and the combination group, according to the administered drug (s). The bupivacaine group (n=25) was administered 0.5% hyperbaric bupivacaine 7.5-10 mg via the intrathecal route, whereas the combination group (n=) was administered fentanyl 20-25 mcg+0.5% hyperbaric bupivacaine via the intrathecal route. After the applications, 4 L/min O_2 was provided to all patients with a face mask. Pin-prick test was used to evaluate the presence of sensory blockade. Surgery was initiated after reaching a sensory blockade at the T4-T6 level.

The NIRS Technique

The NIRS device was used to monitor intraparenchymal and microcirculatory oxygenation in the frontal cortex,

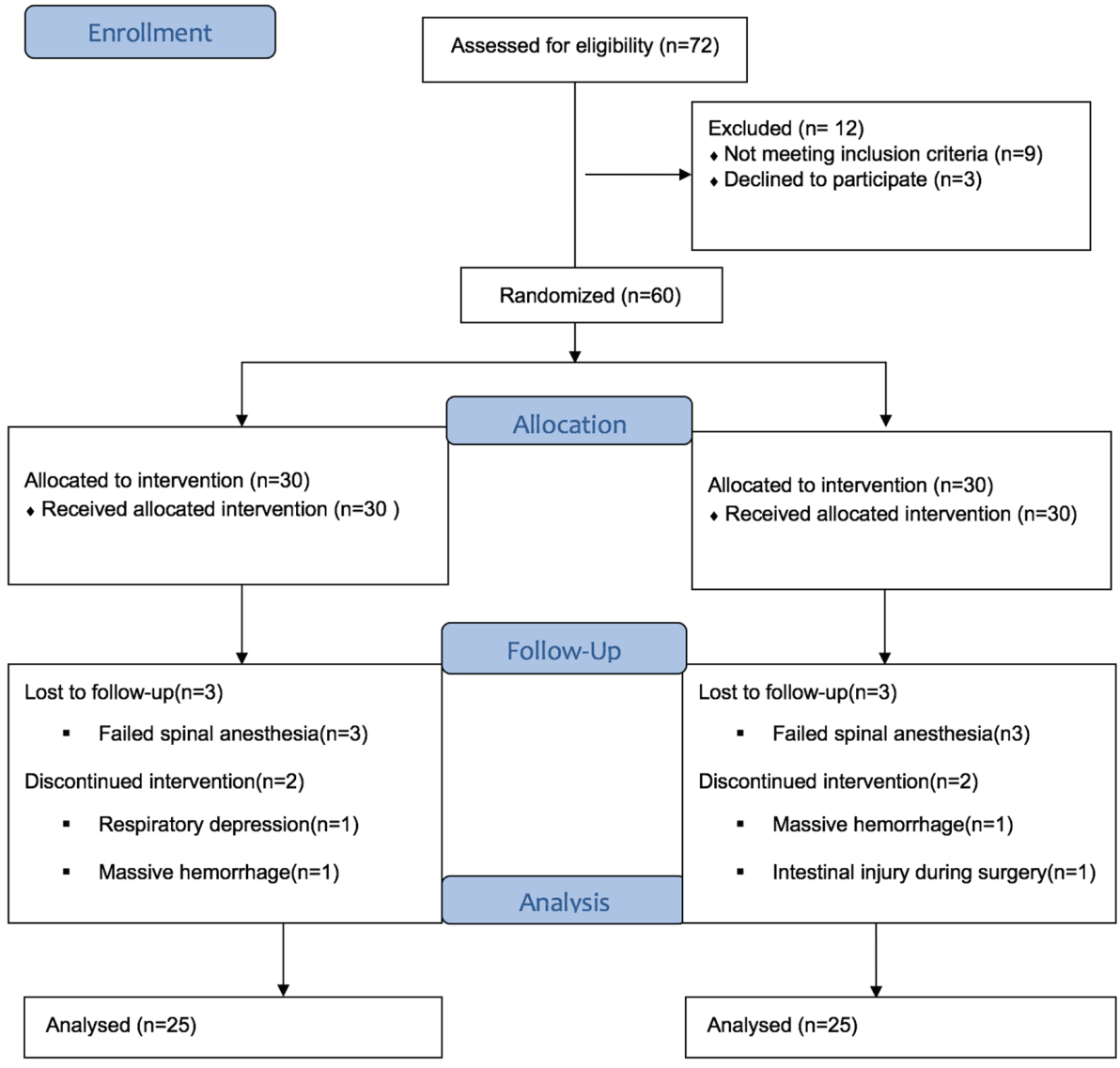

Figure 1. CONSORT 2010 flow diagram

and thereby was utilized as a measure of cerebral tissue oxygenation. The INVOS monitor has a light source and a probe with two photodetectors placed in the right and left anterior hemispheres of the forehead. The photodetector closest to the light source absorbs superficial rays (from skin, bone and fat tissue), while the other photodetector absorbs rays from deep brain tissues. The rSO_2 measurement, in which the oxygen saturation values of the right and left hemispheres are expressed in percent (%), measures the ratio of oxyhemoglobin of the area under the sensor to total hemoglobin based on the difference in the relative transmittance of biological tissue to near infrared light. This ratio is expressed as the percentage value of rSO_2. Its reference value ranges from 58% to 82% in healthy individuals. During hypoxia, hypocapnia, hypercapnia and arterial hypotension, rSO_2 index values change and can be used to assess cerebral oxygenation.

Statistical Analysis

Data analysis was done using the IBM SPSS 22.0 statistics package program. Quantitative data were presented as mean and standard deviation, and qualitative data were presented as numbers and percentages. For quantitative data, the repeated measures analysis of variance test was used for the temporal comparison of multiple groups, and the independent samples student t-test was used for comparison of the two subject groups. chi-square (X^2) tests were used for the comparison of qualitative data.

Table 1. Comparison of age. height. weight. gestational week values of the groups (mean ± SD)

	Group bupivacaine	Group combination	p*
Age	29.56±3.82	29.84±4.09	0.804
Weight (kg)	75.72±8.15	77.6±6.98	0.385
Height (cm)	161.6±3.61	162.32±5.09	0.556
Gestational week	38.8±0.99	39.08±0.91	0.143
*Student t-test, SD: Standart deviation			

Table 2. Total fluid replacement given in the groups. the amount of ephedrine use. the mean time of first ephedrine administration and the number of patients administered ephedrine within the group (n: mean ± SD)

	Group bupivacaine	Group combination	p*
Total fluid replacement (Crystalloid) (ml)	1352±82.26	1368±69.04	0.460
Amount of ephedrine used (mg)	10±4.08	9±2.11	0.501
Time of first ephedrine administration (min)	7.30±4.79	7.19±4.77	0.955
Number of patients that received ephedrine (n)	10	11	0.774
*Student t-test SD: Standart deviation			

The Spearman rho correlation coefficient was calculated to analyze correlations. Analysis results with a probability (P) a less than 0.05 were accepted as significant, whereas higher values were accepted to be insignificant.

Results

There were no differences between the two groups in terms of age, weight, height, gestational week, total fluid replacement, amount of ephedrine use, time of first ephedrine administration, and sPO_2 values (Table 1-3). All patients were accepted as ASA II. Ephedrine administration was needed at an average of 7-8 minutes after spinal anesthesia. An average of 10 mg of ephedrine was administered to 10 patients in the bupivacaine group and to 11 patients in the combination group.

MAP and HR values of the groups are shown in Table 3. In both groups, the initial MAP values were found to be higher than all other values during surgery (p=0.001), the MAP values recorded during skin incision were higher than the MAP values recorded at the 5th minute after the skin incision in both groups (p=0.048, p=0.012).

There was a statistically significant change in rSO_2 values recorded during surgery in both groups (p=0.001). The decrease in rSO_2 values (compared to baseline) during skin incision, at the 5th minute after incision, and at the moment of delivery were statistically significant (p<0.001). There was no significant difference between the two groups in terms of rSO_2 values recorded during surgery (p>0.05, Table 3).

A significant difference in VDS values between measurement time-points during the surgery was identified in the bupivacaine group (p=0.009); however, there was no significant difference in the combination group (p=0.108). The VDS values of the bupivacaine group at the 5th minute after skin incision and at the moment of baby delivery were found to be higher than the respective values of the combination group (p=0.027 and p=0.003, respectively; Table 3).

Correlation analyses revealed weak positive correlations between rSO_2 and MAP values measured at the time of skin incision (r=0.326; p=0.021), at the 5th minute after skin incision (r=0.326; p=0.021), and at the 5th minute after baby delivery (r=0.352; p=0.012) (Table 4).

Discussion

In our study, we compared a group receiving hyperbaric bupivacaine to a group in which fentanyl was added to hyperbaric bupivacaine, in terms of cerebral oxygenation and various other characteristics. Although significant decreases were observed in rSO_2 according to baseline values in both groups (until baby delivery), rSO_2 values were similar between the groups. Ephedrine was generally required in the first 10 minutes of surgery in both groups. The incidence of nausea and vomiting was lower in the combination group.

Hypotension is the most common complication after spinal anesthesia (8). Hypotension should not be allowed to develop during caesarean section, as it may cause changes in the physiology of both the new-born and the mother. Since hemodynamic instability and hypotension may develop rather frequently in relation with the use of local anesthetics during spinal anesthesia, opioid addition has emerged as a reliable method to prevent such occurrences (9). In addition, it is known that the combination of opioids with local anesthetics shortens the onset time of sensory and motor block, and facilitates more effective and long-term anesthesia (10). There is no definite instruction regarding the intrathecal dose of local anesthetics and opioids. The lowest effective fentanyl dose reported to be used in caesarean section is 6.25 mcg (11). There are studies suggesting that 20-30 mcg of fentanyl should be added to bupivacaine (12,13). Kang et al. (14) compared the combination of 8 mg 0.5% hyperbaric bupivacaine and 5 mg 0.5% hyperbaric bupivacaine with 25 mcg fentanyl, and showed that the combination of bupivacaine and fentanyl provided better hemodynamic stability. Meyer et al. (15) studied patients who underwent spinal anesthesia in caesarean section procedures by forming two groups according to drug administration

Table 3. Comparison of HR, MAP, SpO_2, rSO_2, VDS values of the groups during surgery (mean ± SD)

		T0	T1	T2	T3	T4	T5	T6	p-value
HR	Bupivacaine group Combination group p*	92.36±9.53 93.2±13.03 0.79	98.28±17.24 96±18.63 0.65	99.76±19.56 95.76±19.08 0.46	98.86±18.45 98.28±16.08 0.71	105±19.46 99±15.63 0.23	96.32±14.7 94.8±14.86 0.71	95.48±18.18 91.43±13.2 0.37	p>0.05 p>0.05
MAP	Bupivacaine group Combination group p*	92.72±11.83 91.4±10.48 0.67	82.48±14.79 82.56±12.43 0.98	77.72±15.19 75.8±12.52 0.62	80.08±19.35 81±13.59 0.84	79.12±12.2 81±11.39 0.68	80.96±7.86 81±11.39 0.98	81.92±9 78.92±10.09 0.27	T1-T2 p=0.048 Other p>0.05 T1-T2 p=0.012 Other p>0.05
SpO_2	Bupivacaine group Combination group p*	99±1.08 98.96±0.79 0.88	99.16±0.75 98.92±1.22 0.41	98.8±0.96 99.44±0.94 0.18	98.96±1.24 99.44±0.65 0.09	99.32±0.75 99.28±1.02 0.87	99.6±0.58 99.4±0.76 0.31	99.56±0.58 99.36±0.76 0.32	p>0.05 p>0.05
rSO_2	Bupivacaine group Combination group p*	63.84±7.96 65.12±6.46 0.53	60.4±8.04 61.32±6.54 0.65	59.52±9.36 59.32±8.8 0.93	60.16±9.36 60.24±7.76 0.97	66.64±8.25 66.96±9.8 0.91	65.92±7.06 66.36±10.3 0.86	67.68±8.51 66.44±9.9 0.63	T0-T3:p<0.001 T0-T3:p<0.001
VDS	Bupivacaine group Combination group p*	- - -	0.12±0.33 0.12±0.33 1	0.28±0.61 - 0.027	0.44±0.71 - 0.003	0.36±0.57 0.16±0.47 0.18	0.24±0.66 0.12±0.33 0.42	0.08±0.28 0.04±0.2 0.56	p=0.009 P>0.05

*Student-t test, **Student-t test, HR: Heart rate, MAP: Mean artery pressure, SpO_2: Peripheral oxygen saturation rSO_2: Cerebral oxygen saturation, VDS: Verbal descriptive scales. T0: anesthesia onset, T1: Skin incision, T2: 5th minute after skin incision, T3: Moment of baby delivery, T4: 5th minute after baby delivery, T5: 10th minute after baby delivery, T6: 20th minute after baby delivery

Table 4. Correlation of rSO2 and MAP values of groups

			rSO_2						
			T0	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**
MAP	T0	r	0.067						
		p	0.645						
	T1	r		0.370					
		p		0.008*					
	T2	r			0.326				
		p			0.021*				
	T3	r				0.128			
		p				0.376			
	T4	r					0.352		
		p					0.012*		
	T5	r						0.26	
		p						0.068	
	T6	r							0.229
		p							0.110

* p<0.05, r: Spearman-rho correlation.
MAP: Mean artery pressure, rSO_2: Cerebral oxygen saturation, T0: Anesthesia onset, T1: Skin incision, T2: 5th minute after skin incision, T3: Moment of baby delivery, T4: 5th minute after baby delivery, T5: 10th minute after baby delivery, T6: 20th minute after baby delivery

(15 mg bupivacaine and 12 mg bupivacaine+15 mcg fentanyl), similar to our study design. While there was no difference between blockade characteristics between the groups, they found that the incidence of nausea/vomiting

and hypotension were more common in the bupivacaine group (15). In our study, while nausea and vomiting were also found to be more common in recipients of bupivacaine only, no difference was observed between the groups according to hemodynamic parameters. In both groups, the lowest MAP was seen at the time of delivery and during the first 5 minutes following delivery. This situation has been associated with sympathetic blockade in relation with the use of spinal anesthesia. The sensory block in both groups was at the T4-T6 level, and the average time it took to develop adequate block was 3.5-4.5 minutes. Phenylephrine and ephedrine are routinely administered to increase MAP and cerebral perfusion in anesthesia-related hypotension that develops during perioperative processes (16). Since ephedrine is an agent with positive chronotropic and inotropic effects, it has become the preferred agent in hypotension that develops during regional anesthesia (17). In our study, the frequency and amount of ephedrine administration and hemodynamic responses were found to be similar in both groups. rSO_2 reflects the balance between cerebral oxygen delivery and oxygen requirements, is affected by changes in blood oxygenation, cerebral blood flow, hemoglobin concentration and cerebral metabolism. Cerebral oximetry, which is widely used in neurosurgery and cardiovascular surgery because it provides critical information pertaining to the oxygenation level in cerebral tissue, is recently being used in surgeries where regional anesthesia is applied. A previous study reported a 5% decrease in rSO_2 value compared to baseline with NIRS-based measurements in 38 patients who underwent caesarean section under spinal anesthesia (18). The sensitivity of the NIRS technique to predict hypotension in caesarean sections performed with the use of spinal anesthesia was determined to be 100% and the specificity was 85%. The study by Fassoulaki et al. (19) reported rSO_2 changes during the operation in 35 pregnant women undergoing elective caesarean section with spinal anesthesia. In the study, 1.8-2 mL 0.75% ropivacaine+10 mcg fentanyl were administered intrathecally to the patients. In about half of the patients, especially in the 5^{th} and 10^{th} minutes after spinal anesthesia administration, a decrease in rSO_2 values from 65% (baseline) to 55% was observed, and it was stated that the clinical effects of these decreases could be investigated in detail in the long term. In another study, 42 patients who underwent caesarean section were divided into two groups as isobaric bupivacaine recipients and hyperbaric bupivacaine recipients and the effects on rSO_2 were compared. It was concluded that hemodynamic parameters remained stable and cerebral oxygenation was preserved in the group receiving isobaric bupivacaine (20). Kaori Yamazaki et al. (21) recorded perioperative rSO_2 values of 18 pregnant women who underwent caesarean section. In patients with placenta previa or massive bleeding, rSO_2 rapidly decreased from 67.2% to 54.2%, while there was no change in sPO_2 measured simultaneously. In the same study, the average rSO_2 before induction in pregnant women with preeclampsia was found to be significantly higher than normotensive women. In the study conducted by Van Noord et al. (22), while a decrease in MAP was observed in 19.5% of patients who were scheduled for general anesthesia and had undergone surgery with controlled hypotension due to major bleeding, the rSO_2 decrease was measured as 21.5% on the left and 14.7% on the right. Hypotension and cerebral desaturation were observed in the transition to a semi-sitting position in 42% of shoulder arthroscopy cases in which the risk of developing hypotension was increased due to surgical position (23). In a study involving patients undergoing shoulder surgery, a decrease in cerebral oxygenation associated with controlled hypotension was identified together with a decrease in cerebral blood flow in simultaneous Doppler measurements; however, the sPO_2 values of these patients had not demonstrated any significant change throughout surgery (24). Similarly, in our study, a decrease in rSO_2 values was found to be associated with a decrease in MAP values, especially in the measurement time-points with sympathetic blockade. The absence of simultaneous sPO_2 changes indicates that cerebral oximetry monitoring is more sensitive than sPO_2 monitoring, especially when it is considered that cerebral oxygenation level is critical in such surgeries.

Ephedrine was administered to prevent the decrease in cerebral perfusion associated with hypotension in patients whose right-left rSO_2 average fell below 50%. In a study conducted in patients undergoing cardiac surgery, there was observational evidence that decreased intraoperative and preoperative cerebral oximetry levels gave an idea of poor postoperative outcomes, and that intra-operatively decreased cerebral oximetry levels could be reversed by interventions aimed at optimizing cerebral oxygenation (25). Especially in patients with increased risk for hypotension, such as pregnant women, those undergoing surgeries requiring non-supine positioning, patients with advanced age, those with risks for bleeding, and individuals undergoing cardiac surgery, cerebral oximetry measurements may be crucial in terms of enabling timely intervention(s) to prevent reduced cerebral perfusion.

Study Limitations

Since we did not measure the amount of fluids administered before and after surgery and the amount of urine output, we could not analyze our data with regard to these variables, indicating a limitation in the assessment

of overall hemodynamic stability of the patients. Secondly, our study was conducted on a small number of patients due to financial limitations that affected the number of patients that could be included enrolled. Lastly, the effect of hypotension and rSO_2 reduction on cognitive functions were not assessed in the postoperative period. Future studies would benefit from including a higher number of patients.

Conclusion

We think that cerebral oximetry can be used as an effective and reliable perioperative method of monitoring in patients undergoing cesarean section with spinal anesthesia, especially in cases with a high probability of developing hypotension.

Authorship Contributions

Concept: M.G.Ç., T.O., Design: T.O., M.G.Ç., Data Collection or Processing: T.O., Analysis or Interpretation: T.O., Literature Search: T.O., Ü.K., Writing: T.O., Ü.K.

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Kalıtsal Kolorektal Kanser Tanılı Hastaların APC, MLH1 ve MSH2 Mutasyonlarının Araştırılması: Tek Merkez Deneyimi

Investigation of APC, MLH1 and MSH2 Mutations in Patients with Hereditary Colorectal Carcinoma: A Single Center Experience

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Öz

Amaç: Kolorektal kanser (KRK) dünyada en sık görülen üçüncü kanserdir. Tüm KRK'lerin yaklaşık %5-6'sı germline mutasyonlar sonucunda ortaya çıkmaktadır. Ailesel KRK'lerin daha etkin yönetilebilmesi için gen panelleri ile mutasyon taraması yapılmaktadır. Bu çalışmada herediter polipozis koli tanılı hastalarda APC ve herediter non-polipozis koli tanılı hastaların MLH1/MSH2 genlerinde mutasyon taraması yapılmış, tespit edilen mutasyon dağılımları ve özellikleri incelenmiştir.

Yöntemler: Çalışmaya Türkiye genelinden 152 polipozis koli, 123 non-polipozis koli hastası dahil edilmiş olup, APC, MLH1 ve MSH2 gen analizleri değerlendirilmiştir.

Bulgular: Ailesel polipozis koli tanılı hastaların 39'unda (%25) *APC* geninde, herediter non-polipozis koli tanılı hastaların 24'ünde (%18,8) MLH1 ya da MSH2 genin de mutasyon tespit edilmiştir. Tespit edilen mutasyonlardan APC genindeki 5, MLH1 geninde 2, MSH2 genindeki 2 varyant patojenik/olası patojenik değerlendirilmiş olup literatürde daha önce bildirilmemiş varyantlardır.

Sonuç: Bu çalışma ülkemizde ailesel KRK'lerin moleküler genetik etiyolojilerinin ortaya konulduğu en kapsamlı çalışmadır. Ailesel KRK etiyolojisinin ortaya konulması ile mutasyon tespit edilen ailelerde kapsamlı genetik danışma alabilmesine ve hasta/asemptomatik bireylerin ailesel kanser yönetim rehberlerine uygun takip edilebilmesine imkân sağlayacaktır.

Anahtar Sözcükler: Herediter kolon kanseri, *APC, MLH1, MSH2,* mutasyon

Abstract

Aim: Colorectal cancer (CRC) is the third most common cancer in the world. About 5-6% of all CRCs have a hereditary inheritance related with germline mutations. Mutation screening is carried out with gene panels for CRCs to manage family against to CRCs more effectively. In this study, mutation screening was performed by sequencing of APC in patients with hereditary polyposis coli and of MLH1/MSH2 in patients with hereditary non-polyposis coli and the detected mutation distributions and their properties were investigated.

Methods: One hundred-fifty two patients with hereditary polyposis coli and 123 patients with hereditary non-polyposis coli were included to the study from Turkey and APC, MLH1 and MSH2 analysis were performed.

Results: Thirty nine (25%) patients with hereditary polyposis coli and 24 (18.8%) patients with hereditary non-polyposis coli had mutation in APC and MLH/MSH2, respectively. Among the evaluated as pathogenic/likely pathogenic variants, 5 of them in APC, 2 of them in MLH1 and 2 of them in MSH2 have not been previously reported in the literature.

Conclusion: This study is the most comprehensive study demonstrated that molecular genetic etiology of familial CRC in Turkey. With the explanation of familial CRC etiology, it will enable comprehensive genetic counseling and follow-up of patients/asymptomatic individuals in accordance with familial cancer management guidelines.

Keywords: Hereditary colorectal cancer, APC, MLH, MSH2, mutation

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Giriş

Kolorektal kanser (KRK) dünyada en sık görülen üçüncü kanserdir. Her sene ABD'de 100.000'den fazla olgu KRK tanısı almaktadır. Tedavi seçeneklerinin çoğalması, yeni tedavi yaklaşımları ve tarama programlarının rutine girmesiyle KRK ölüm oranları %54'lere kadar gerilemiştir (1). KRK'lerin yaklaşık %5-6'sı germline mutasyonlar sonucunda ortaya çıkar ve bu grup herediter KRK sendromları olarak adlandırılır (2). Bu grubun içerisinde antigen-presenting (APC) ile ilişkili ailesel adenomatöz polipozis koli (FAP, MIM: 175100), zayıflamış FAP, lynch sendromu (LS, MIM: 120435), *MUTYH* ile ilişkili adenomatöz polipozis koli sendromları (MAP, MIM: 608456) bulunmaktadır.

LS; mikrosatellit instabilite KRK'ye eşlik eden gastrik kanser, kadınlarda endometrium kanseri ile karakterize otozomal dominant bir kalıtsal kanser sendromudur (3). FAP ise kolon ve rektumda binlerce adenömatöz polip ile karakterize otozomal dominant geçişli bir hastalıktır. FAP'de KRK dışında ekstrakolonik klinik bulgularda görülebilir. Özellikle gastrik veya duodenal polipler, desmoid tümörler, tiroid ve beyin tümörleri, retina pigment epitelinin hipertrofisi, fazla diş, osteoma ve epidermoid kistler görülmektedir (4). LS, tüm KRK olguların yaklaşık %2-3'ünü oluştururken FAP ise yaklaşık %1'ini oluşturmaktadır (2). LS'de monoallelik germline mutasyonlar mismatch (yanlış eşleşme) tamir (*MMR*) genlerinde (*MLH1*, *MSH2*, *MSH6*, *PMS2* ve *EPCAM/TACSTD1*) görülmektedir. FAP kliniğine ise germline monoallelik APC mutasyonları neden olmaktadır (5). Günümüzde National Comprehensive Cancer Network'un (NCCN) yayımladığı kriterlere göre hastaların klinik, aile öyküsü ve histopatolojik bulguları değerlendirilerek yukarıda ifade edilen genler ve bunların yanında bu hastalığa neden olabileceği düşünülen aday genlere yönelik analizler yapılmaktadır (6).

Kalıtsal KRK sendromların tanı, tedavi ve takibinde birçok branşın yer aldığı multidisipliner yaklaşımlar gerekmektedir. Bu sendromların tespit edilebilmesi, hastalık ortaya çıkan bireylerde uygun tedavinin ve takiplerin planlanmasına, hastalık ortaya çıkmadıysa kanseri önlemek için uygun takip ve asemptomatik dönemde müdahale etme fırsatı sunar. Bunun neticesinde mutasyona sahip ailelerde mortalite ve morbiditenin oranları düşürülür (2,3).

Bugüne kadar Türkiye'de herediter polipozis koli ve non-polipozis koli tanılı hastaların tanılarının moleküler genetik yöntemlerle doğrulandığı geniş çalışmalar yapılmamış olup belirtilen genlerdeki mutasyon sıklığı, dağılım bölgeleri ve özellikleri hakkında literatürde yeterli veri bulunmamaktadır. Bu çalışmada ülkemizde herediter polipozis koli ile takip edilen hastalarda *APC* geninde mutasyon sıklığı ve mutasyon çeşitlerinin dağılımı; herediter non-polipozis koli ile takip edilen hastalarda ise *MLH1* ve *MSH2* genlerinde mutasyon sıklığı ve mutasyon çeşitlerinin dağılımını saptamak ve bunların klinik takipleri üzerindeki etkilerini tartışmak ve bu bilgilerin literatüre kazandırılması amaçlanmıştır.

Yöntemler

2018-2020 yılları arasında Sağlık Bilimleri Üniversitesi Haseki Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu, Genetik Hastalıklar Tanı Merkezi'ne *APC*, *MLH1* ve *MSH2* genlerinin dizi analizlerini yaptırmak amacıyla yönlendirilen hastaların dosyaları incelenmiş olup, sonuçları retrospektif olarak düzenlenmiştir. Bu çalışma Sağlık Bilimleri Üniversitesi Haseki Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu Etik Kurulu tarafından onaylanmıştır (tarih: 10.06.2020) (dosya numarası: 2020-75). Genetik Hastalıklar Tanı Merkezi'ne numunesi yönlendirilen hastaların tamamından onam formu alınmıştır. *APC* geni analizi 152 herediter polipozis tanılı hastada, *MLH1/MSH2* gen analizleri ise 127 herediter non-polipozis koli tanılı hastada yapılmıştır. Tüm hastalardan üretici firmanın önerileri göz önüne alınarak DNA izolasyonu yapılmıştır (QIAamp DNA blood Maxi kit, Qiagen, Hilden, Almanya). *APC*, *MLH1* ve *MSH2* genlerinin amplifikasyonu amacıyla Primer 3 programında tasarlanan primerler (talep olması halinde dizileri paylaşılacaktır), PrimerBlast programının önerilerine göre amplifikasyon gerçekleştirildi. Sekans reaksiyonlarında BigDye 3.1 (Life Technologies, CA, ABD) kullanıldı, ardından ABI-3730xl kapiller dizi cihazında (Life Technologies, CA, ABD) yürütüldü. Sonuçlar SeqScape V3 programında analiz edildi (Applied Biosystems, Foster City, CA).

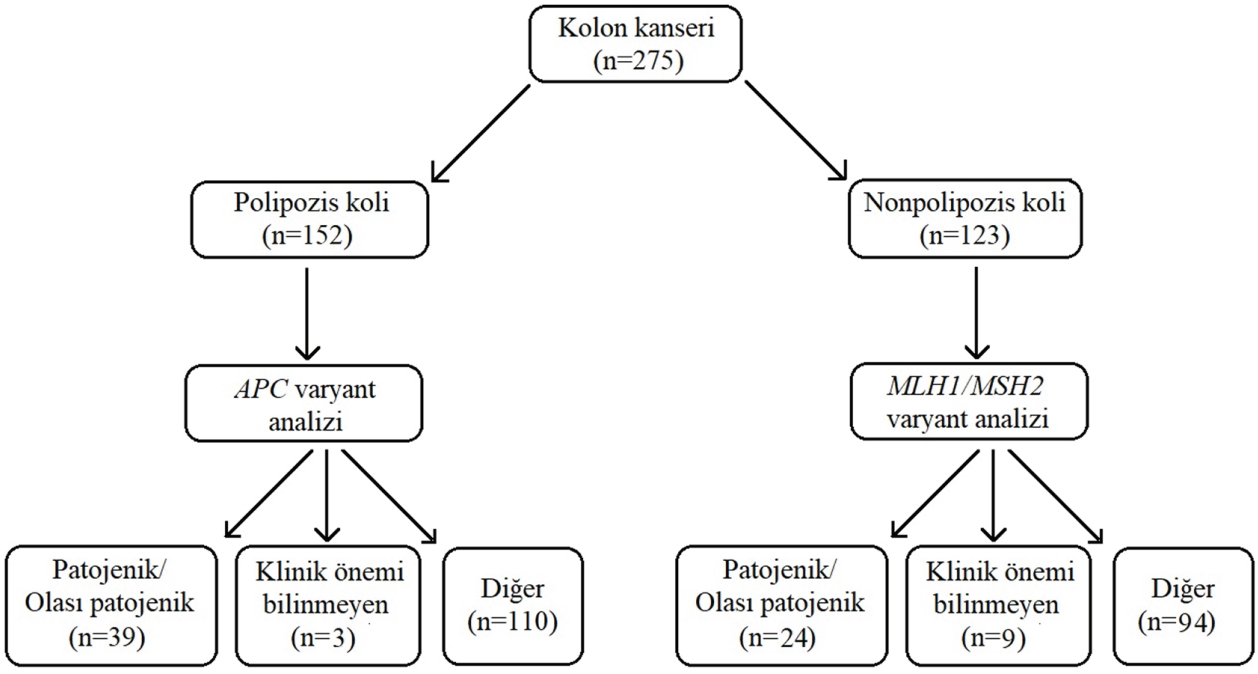
Elde edilen varyantlar ACMG 2015 kriterleri ışığında benign, muhtemel benign, klinik önemi bilinmeyen, muhtemel patojenik ve patojenik olmak üzere 5 başlıkta sınıflandırıldı (7). Herhangi varyant bulunamayan veya benign ve/veya muhtemel benign olarak sınıflandırılan varyantlar bu çalışma içerisinde tartışılmadı ve diğer varyantlar olarak adlandırılan havuzunun içinde değerlendirilerek istatistikler yapıldı.

Bulgular

Çalışmaya dahil edilen toplam 275 hastadan, 112'si kadın 163'ü erkekti. Bu hastalardan 152'sine *APC* analizi, kalan 127 hastaya ise *MLH1* ve *MSH2* analizi yapıldı. 38 herediter polipozis tanılı hastalarda klinik tabloyu açıklayabilecek *APC* mutasyonu saptanırken, 24 herediter non-polipozis koli tanılı hastada klinik tabloyu açıklayabilecek *MLH1/MSH2* mutasyonu saptandı. Çalışmanın tasarımı ve bulguların özeti Şekil 1'de gösterilmiştir.

Herediter polipozis koli hastaları ve *APC* analizi

APC ile ilişkili polipozis koli sendromu tanısı alan hastaların 12'si erkek, 26'sı kadındı. Erkek hastaların yaş ortalaması 38,33±6,24 iken kadınlarda bu ortalama



Şekil 1. Çalışmanın tasarımı, dahil edilen hastalar ve sonuçlarının özeti

34,26±2,95 idi. Herediter polipozis koli tanılı 152 hastadan yapılan *APC* analizinde hastaların 41'inde hastalıkla ilişkisi olabilecek varyant bulundu. Bunların 38'inde (%25,6) patojenik/olası patojenik, 3'ünde (%0,01) klinik önemi belirsiz varyant saptandı. Kalan 110 (%72,3) hastada ise herhangi bir varyant saptanmadı ya da saptanan varyant benign olarak değerlendirildi. Herediter polipozis koli tanılı hastaların demografik özellikleri ve APC mutasyonlarının analizi sonuçları Tablo 1'de gösterildi.

Herediter non-polipozis koli hastaları ve *MLH1/MSH2* analizi

Herediter non-polipozis koli tanısı alan erkek hastaların yaş ortalaması 38,33±6,24 iken kadınlarda bu ortalama 34,26±2,95 idi. Herediter non-polipozis koli tanılı 127 hastadan yapılan *MLH1* ve *MSH2* analizinde hastaların 24'ünde (%18,8) patojenik/olası patojenik, 9'unda (%0,07) klinik önemi belirsiz varyant saptandı. Kalan 94 (%74) hastada ise herhangi bir varyant saptanmadı ya da saptanan varyant benign olarak değerlendirildi. Herediter non-polipozis koli tanısı alan hastaların 17'si erkek, 16'sı kadındı. *MLH1* geninde 10 patojenik/olası patojenik, 3 klinik önemi bilinmeyen varyant tespit edilirken, *MSH2* geninde 13 patojenik/olası patojenik, 5 klinik önemi bilinmeyen varyant tespit edildi. Herediter non-polipozis koli tanılı hastaların demografik özellikleri ve *MLH1* gen analizi sonuçları Tablo 2'de, *MSH2* gen analizi sonuçları Tablo 3'te gösterildi.

Tartışma

A. Herediter polipozis koli ve *APC* analizi

Tümör süpresör gen olarak işlev gören *APC* genindeki monoallelik mutasyonlar hastalığın ortaya çıkmasına neden olur. Mutasyon taşıyıcısı bir bireyde sıklıkla ergenlik veya erken erişkin dönemde polipler ortaya çıkmaya başlar. Cerrahi yapılmadığı durumlarda kolonda binler hatta on binlerce polipten oluşan ciddi bir yük meydana gelir ki bu durumda %90 ve üzerinde KRK tablosu oluşur (3). FAP hastalarının en sık ölüm sebebi KRK olup bunu duodenal ve ampuller adenokarsinomalar takip etmektedir (8). Bu nedenle FAP tanılı bir hastaya total kolektomi yapılmış olsa bile hayat boyunca gastrointestinal sistem endoskopisi ile takip edilmelidir (9).

APC geni 5q22.2'de yer alan, primer transkribi NM_000038.5 olan 15 ekzondan ve 2.843 amino asitten oluşmaktadır. Gen ürünü *APC* proteini ise 311,8 kd'lik bir büyüklüğe sahiptir. Son ekzonu en büyük ekzon olup kodlanan toplam bölgenin 3/4'ünden fazlasını oluşturmaktadır (10). Şu ana kadar *APC*'de 1200'den fazla hastalıkla ilişkilendirilmiş patojenik/olası patojenik varyant bildirilmiştir. Patojenik varyantlar gen boyunca dağılmış olarak bulunurken, bunlar ağırlıklı olarak genin 5 ucunda bulunur (11).

APC analizinin yapıldığı geniş kohortlara bakıldığı zaman mutasyonların çoğunlukla çerçeve kaymasına neden olduğu görülmüştür. Nagase ve ark. (12) 176 mutasyonun

tanımladığı çalışmada olguların 106'sında çerçeve kayması bildirilirken 68'in de nokta mutasyonu tespit edilmiştir. Nokta mutasyonlara ise kendi içinde bakıldığında 57'sinin non-sense (anlamsız) mutasyon, 6'sında missense (yanlış anlamlı) mutasyon ve kalan 5'inde ise splicing (kırpılma) mutasyonları tanımlanmıştır. Çerçeve kayması ve non-sense mutasyonları ACMG 2015 kriterlerine göre PVS1 (pathogenic very strong) patojenik olarak sınıflandırılması bu mutasyonların patojenik veya olası patojenik olarak değerlendirilmesi açısından önemlidir. Bu çalışmada

Tablo 1. Herediter polipozis koli tanılı hastaların demografik özellikleri ve APC mutasyonlarının analizi

Olgu	Yaş	Cinsiyet	Nükleotid değişimi	Protein etkisi	Yerleşim	ACMG	Referans
APC1	68	E	c.450_453delAGAA	p.Glu151Lysfs*18	Ekzon 5	P	(26)
APC2	64	K	c.531+1 G>A	-	İntron 5	MP	(27)
APC3	44	E	c.531+1 G>A	-	İntron 5	MP	(27)
APC4	58	K	c.667 delC	p.Gln223Lysfs*70	Ekzon 7	MP	Yeni mutasyon
APC5	45	K	c.847C>T	p.Arg283*	Ekzon 9	P	(28)
APC6	82	E	c.994 C>T	p.Arg332*	Ekzon 9	P	(29)
APC7	16	K	c.1269 G>A	p.Trp423*	Ekzon 10	P	(30)
APC8	27	K	c.1312+1 G>T	-	İntron 10	MP	(31)
APC9	41	E	c.1312+3 A>G	-	İntron 10	P	(32)
APC10	42	K	c.1660 C>T	p.Arg554*	Ekzon 14	P	(33)
APC11	41	K	c.1690C>T	p.Arg564*	Ekzon 14	P	(32)
APC12	31	K	c.1690C>T	p.Arg564*	Ekzon 14	P	(32)
APC13	66	K	c.1743+1 G>T	-	İntron 14	MP	(34)
APC14	58	E	c.1743+1 G>T	-	İntron 14	LP	(34)
APC15	25	K	c.1748 C>A	p.Ser583*	Ekzon 15	LP	(35)
APC16	30	K	c.1748 C>A	p.Ser583*	Ekzon 15	LP	(35)
APC17	31	K	c.1748 C>A	p.Ser583*	Ekzon 16	LP	(35)
APC18	17	E	c.2222A>G	p.Asn741Ser	Ekzon 16	KÖB	(36)
APC19	50	K	c.2249insC	p.Ser751Ilefs*5	Ekzon 16	MP	Yeni mutasyon
APC20	28	E	c.2249insC	p.Ser751Ilefs*5	Ekzon 16	MP	Yeni mutasyon
APC21	24	K	c.2896dupA	p.Ser966Lysfs*	Ekzon 16	MP	Yeni mutasyon
APC22	24	K	c.2896dupA	p.Ser966Lysfs*	Ekzon 16	MP	Yeni mutasyon
APC23	52	E	c.3220A>G	p.Thr1074Ala	Ekzon 16	KÖB	(32)
APC24	40	E	c.3324_3325insAA	p.Gly1109Lysfs*18	Ekzon 16	MP	Yeni mutasyon
APC25	29	K	c.3340 C>T	p.Arg1114*	Ekzon 16	P	(37)
APC26	22	K	c.3927_3931del AAAGA	p.Glu1309Aspfs*4	Ekzon 16	P	(38)
APC27	51	E	c.3927_3931del AAAGA	p.Glu1309Aspfs*4	Ekzon 16	P	(38)
APC28	29	E	c.3927_3931del AAAGA	p.Glu1309Aspfs*4	Ekzon 16	P	(38)
APC29	6	E	c.3927_3931del AAAGA	p.Glu1309Aspfs*4	Ekzon 16	P	(38)
APC30	30	K	c.3927_3931del AAAGA	p.Glu1309Aspfs*4	Ekzon 16	P	(38)
APC31	14	K	c.3927_3931del AAAGA	p.Glu1309Aspfs*4	Ekzon 16	P	(38)
APC32	20	E	c.3927_3931del AAAGA	p.Glu1309Aspfs*4	Ekzon 16	P	(38)
APC33	16	K	c.3927_3931del AAAGA	p.Glu1309Aspfs*4	Ekzon 16	P	(38)
APC34	33	K	c.3927_3931del AAAGA	p.Glu1309Aspfs*4	Ekzon 16	P	(38)
APC35	30	K	c.3927_3931del AAAGA	p.Glu1309Aspfs*4	Ekzon 16	P	(38)
APC36	15	K	c.4391_4394 delAGAG	p.Glu1464Valfs*8	Ekzon 16	P	(39)
APC37	19	E	c.4391_4394 delAGAG	p.Glu1464Valfs*8	Ekzon 16	P	(39)
APC38	20	E	c.4688 delT	p.Leu1563Hisfs*2	Ekzon 16	MP	Yeni mutasyon
APC39	24	K	c.4688 delT	p.Leu1563Hisfs*2	Ekzon 16	MP	Yeni mutasyon
APC40	62	K	c.4688delT	p.Leu1563Hisfs*2	Ekzon 16	MP	Yeni mutasyon
APC41	42	K	c.7399C>A	p.Pro2467Thr	Ekzon 16	KÖB	(40)

Tablo 2. Herediter non-polipozis koli tanılı hastaların demografik özellikleri ve *MLH1* (NM_000249) mutasyonlarının analizi

Olgu	Yaş	Cinsiyet	Nükleotid değişimi	Protein etkisi	Yerleşim	ACMG	Referans
ML1	39	K	c.289 T>G	p.Tyr97Asp	Ekzon 3	KÖB	(18)
ML2	26	E	c.289 T>G	p.Tyr97Asp	Ekzon 3	KÖB	(18)
ML3	32	K	c.293 G>C	p.Gly98Ala	Ekzon 3	KÖB	(17)
ML4	45	K	c.589 C>T	p.Gln197*	Ekzon 8	P	Yeni mutasyon
ML5	41	K	c.676 C>T	p.Arg226*	Ekzon 8	P	(41)
ML6	44	K	c.677G>A	p.Arg226Gln	Ekzon 8	P	(23)
ML7	55	E	c.677G>A	p.Arg226Gln	Ekzon 8	P	(23)
ML8	63	E	c.728A>G	p.Asn243Ser	Ekzon 9	KÖB	(19)
ML9	23	K	c.790+1G>A	-	İntron 9	P	(32)
ML10	54	K	c.1649 T>C	p.Leu550Pro	Ekzon 14	P	(42)
ML11	28	K	c.1690_1693 delCTCA	p.Leu564Phefs*26	Ekzon 15	P	(23)
ML12	45	E	c.1752_1765 del14	p.Ala586Argfs*2	Ekzon 16	MP	Yeni mutasyon
ML13	32	E	c.1852_1854 delAAG	p.Lys618del	Ekzon 16	P	(43)
ML14	63	E	c.1852_1854delAAG	p.Lys618del	Ekzon 16	P	(43)
ML15	51	E	c.1852_1854delAAG	p.Lys618del	Ekzon 16	P	(43)

Tablo 3. Herediter non-polipozis koli tanılı hastaların demografik özellikleri ve *MSH2* (NM_000251) mutasyonlarının analizi

Olgu	Yaş	Cinsiyet	Nükleotid değişimi	Protein etkisi	Yerleşim	ACMG	Referans
MS1	26	K	c.244A>T	p.Lys82*	Ekzon 2	P	(44)
MS2	45	E	c.433A>G	p.Ile145Val	Ekzon 3	KÖB	(24)
MS3	46	E	c.435T>G	p.Ile145Met	Ekzon 3	KÖB	(23)
MS4	41	E	c.435T>G	p.Ile145Met	Ekzon 3	KÖB	(23)
MS5	44	E	c.801_802delTT	p.Ser268Ilefs*15	Ekzon 5	MP	Yeni mutasyon
MS6	16	E	c.970 C>G	p.Gln324Glu	Ekzon 6	KÖB	Yeni mutasyon
MS7	40	E	c.1165 C>T	p.Arg389X	Ekzon 7	P	(45)
MS8	53	K	c.1565_1568delACTT	p.Tyr522Phefs*3	Ekzon 10	P	(46)
MS9	43	E	c.1565_1568delACTT	p.Tyr522Phefs*3	Ekzon 10	P	(46)
MS10	24	K	c.1609delA	p.Asn538Thrfs*5	Ekzon 10	MP	Yeni mutasyon
MS11	23	E	c.1787A>G	p.Asn596Ser	Ekzon 12	KÖB	(25)
MS12	16	E	c.2074 G>A	p.Gly692Arg	Ekzon 13	P	(47)
MS13	28	E	c.2074 G>A	p.Gly692Arg	Ekzon 13	P	(47)
MS14	26	K	c.2074 G>A	p.Gly692Arg	Ekzon 13	P	(47)
MS15	37	K	c.2131 C>T	p.Arg711X	Ekzon 13	P	(48)
MS16	50	K	c.2362dupA	p.Thr788Asnfs*11	Ekzon 14	P	(49)
MS17	10	K	c.2634+5G>C	-	İntron 15	P	(50)
MS18	39	K	c.2634+5 G>C	-	İntron 15	P	(50)

saptadığımız 38 varyanttan 22'si çerçeve kaymasına neden olurken, 13'ü nokta mutasyonu kalan 6'sı ise splicing mutasyonuydu. Nokta mutasyonlarının içerisinde 10 mutasyon ile non-sense en sık görülendi. Elde ettiğimiz veriler literatür bilgi ise ile birebir örtüşmekteydi. *APC* geninde en sık görülen patojenik varyant ise 16. ekzonda bulunan c.3927_3931delAAAGA, p.Glu1309AspfsTer4 çalışmamızda mutasyon tespit edilen 38 hastadan 10'unda (%26,3) mevcut olup en sık tespit edilmiş mutasyondur (3).

Çalışmada en az görülen mutasyon çeşidi missense mutasyonlar olup bunların tamamı ACMG 2015 kriterlerine göre klinik önemi bilinmeyen olarak sınıflandırılmıştır. Elde edilecek daha geniş aile hikayesi, varsa KRK pozitif olgularda APC analizi, tespit edilen mutasyonlara ilişkin fonksiyonel çalışmalar yapılması ve varyantların benign ya da patojenite açısından değerlendirilmesi daha sağlıklı sınıflama yapılmasına katkı sağlayacaktır. Bu mutasyonlardan *in silico* algoritmalara göre c.3220A>G polimorfizm olarak değerlendirilirken c.2222A>G ve

c.7399C>A hastalık yapıcı olarak değerlendirilmiştir (13).

Bu çalışmada saptanan 5 varyant daha önce literatürde bildirilmemişti. ACMG 2015 kriterleri ışığında bu varyantlar değerlendirildiğinde tümü muhtemel patojenik olarak sınıflandırıldı. Beş varyanttan 2'si ≤2 baz insersiyonu, 2'si tek baz delesyonu kalan bir mutasyon ise tek baz duplikasyonu olup bu mutasyonların tamamı çerçeve kaymasına neden olmaktadır. *In silico* analizlerde hasar verici ve tolerans düzeyinin düşük olması, mutasyonların genin yüksek korunmuş bölgesinde yer alması benzer şekilde fenotipe yol açmasını destekleyici faktörlerdendir (13).

Herediter polipozis koli ön tanılı 110 hastada *APC* geninde kliniği açıklayabilecek herhangi bir varyant tespit edilememiştir. *APC* geninin dizi analizinde hastaların %90'ına tanı konulurken, büyük delesyon/duplikasyon analizleri neticesinde yaklaşık %8-12 oranında tanı konulmaktadır. Bu çalışmada dizileme yapılmış olup *APC* genini ilgilendiren büyük delesyon/duplikasyonların tespit edilebilmesi mümkün değildir. Bu nedenle klinik şüphesi kuvvetli olan olgulara MLPA ya da yüksek çözünürlüklü array ile analiz yapılmalıdır (3). Bunun dışında literatürde herediter polipozis ile takip edilen hastaların %20-30'unda *APC* geninde mutasyon tespit edilememektedir. Bu bir kısmında *MUTYH* geninde mutasyonlar bildirilmiş olup *MUTYH* ilişkili polipozis koli (MAP) tanısı almışlardır (14).

B. Herediter Non-polipozis Koli ve *MLH1/MSH2* analizi

LS, herediter KRK sendromları içerisinde en sık görülen alt tip olup tüm KRK olguların yaklaşık %2-3'ünü oluşturmaktadır (14). Bu sendrom otozomal dominant kalıtım modeline sahiptir. KRK yanı sıra endometrium kanseri, mide kanseri, over kanserleri de ortaya çıkabilmektedir. Germline mutasyonlar mismatch tamir (MMR) genlerinde *MLH1*, *MSH2*, *MSH6*, *PMS2* ve *EPCAM/TACSTD1'de* görülmektedir (3).

MLH1

3p22.2 bölgesinde yer alan *MLH1* geni yaklaşık 57 kb büyüklüğünde olup kodlanan 19 ekzon toplam 756 amino asitten oluşmaktadır (15). Bugüne kadar 700'den fazla germline mutasyon bildirilmiştir. Bunlardan yaklaşık %5-10'u delesyon/duplikasyonlardan oluşmaktadır (16). Ayrıca dokularda *MLH1*'in metilasyonu ile somatik heterozigosite kaybı da olguların yaklaşık %0,6'sında gösterilmiştir. Mlh1 proteini *PMS2* gen ürünü ile birlikte dimerize olarak DNA polimeraz, tek zincir DNA bağlanma proteini (RPA), hücre proliferasyonu nükleer antijen (PCNA), helikaz gibi MMR'de görevli proteinlerin bağlanmasını koordine eder (3). Bu çalışmada herediter non-polipozis koli ile takip edilen hastalardan 15'inde *MLH1* geninde varyant bulunmuştur. Bu varyantlardan 11'i patojenik/olası patojenik, kalan 4'ü ise klinik önemi bilinmeyen olarak sınıflandırılmıştır. Tespit edilen 2 patojenik varyant ise daha önce literatürde bildirilmemiştir.

MLH1 geninde 4 hastada toplam 3 farklı missense klinik önemi belirsiz varyant saptanmıştır. Dominguez-Valentin ve ark. (17) c.289 T>G değişimini ve Tunca ve ark. (18) c.293 G>C değişimini *in silico* analiz programlarına dayanarak hastalık yapıcı etkileri olduğunu öne sürmüştür. Ancak ACMG 2015 kriterlerine göre hastalık yapıcı etkileri lehine yeterli kanıt bulunamamıştır. *MLH1* geninde saptanan c.728A>G değişimi ise daha önce ClinVar veri tabanında bildirilmiş olup hasta veya değişiminin etkileri hakkında yeterli veri paylaşılmadığından klinik önemi belirsiz varyant olarak sınıflandırıldı (19).

c.589 C>T ve c.1752_1765 del14 varyantları literatürde daha önce bildirilmemiş olup ACMG 2015 kriterlerine göre muhtemel patojenik olarak sınıflandırılmıştır. İlk mutasyon neticesinde erken durdurma kodonu, ikinci mutasyonda çerçeve kayması buna bağlı olarak iki kodon sonrasında erken durdurma kodonu meydana gelmesi nedeniyle güdük protein ortaya çıktığı düşünülmektedir. Bunun yanı sıra bu bölge evrimsel süreçte yüksek derecede korunmuş bir bölge olması nedeniyle bu noktalarda olabilecek mutasyonların tolere edilme ihtimali oldukça düşüktür (13).

MSH2

MSH2 geni 2p21p16 yer alır, kodlanan 16 ekzonu olup gen ürünü toplam 934 aminoasitten meydana gelir (20). Bu gende literatürde bildirilmiş 170'den fazla mutasyon bulunur ve bunların yaklaşık %20'si ekzonik/multiekzonik delesyonlardır (11). *MSH2* gen ürünü MSH2 MMR proteinlerinden MSH6 veya MSH3 ile heterodimer oluşturarak yanlış eşleşmeleri tespit eder. Bu çalışmada herediter non-polipozis koli ile takip edilen hastalardan 18'inde *MSH2* geninde varyant bulunmuştur (3). Bu varyantlardan 14'ü patojenik/olası patojenik, kalan 4'ü ise klinik önemi bilinmeyen olarak sınıflandırılmıştır. Tespit edilen 2 olası patojenik ve klinik önemi bilinmeyen bir varyant ise daha önce literatürde bildirilmemiştir.

c.433A>G ve c.435T>G değişimleri sonucunda 145. pozisyondaki izolösin amino asidinin sırasıyla valin ve metiyoninde değişmesine neden olmaktadır. Literatürde bu varyantın *MLH1* geni üzerinde fonksiyon bozucu bir etkisi gösterilememekle beraber herediter non-polipozis koli hastada gösterilmiştir (21-24). c.1787A>G değişikliği LS ön tanılı hastalarda saptanmış ancak benzer klinik bulguları olan diğer aile bireylerinde bu varyant tespit edilememiş, bu nedenle aile içi segregasyon uyumsuzluğu sebebiyle klinik önemi belirsiz olarak sınıflanmıştır (25).

MSH2 geninde tespit edilmiş olan 3 varyant literatürde daha önce bildirilmemiştir. ACMG 2015 sınıflamasına göre bunlardan ikisi (c.801_802delTT ve c.1609delA) muhtemel

patojenik olarak değerlendirilirken diğer varyant (c.970 C>G) ise klinik önemi bilinmeyen olarak sınıflandırılmıştır. Muhtemel patojenik olan her iki varyantta çerçeve kaymasına sebep olarak güdük protein oluşmasıyla sonuçlandığı düşünülmektedir (13).

Herediter non-polipozis koli, herediter KRK tanılı hastalarda *MLH1* ve *MSH2* genlerinin hem dizileme hem de delesyon/duplikasyon analizi ile hastaların yaklaşık %90'ında mutasyon tespit edilebiliyor. Kalan kısım için ise dağılım MSH6'da %7-10, PMS2'de <%5, EPCAM'da <%1 şeklindedir. Bu görülen oranların sadece dizileme teknolojileri ile tespiti mümkün değildir. Bu genlere yönelik büyük delesyon/duplikasyon analizleri önerilmektedir. MLH1'de %5-10, MSH2'de >%20, MSH & <%5, EPCAM %100 oranında bu analizler neticesinde mutasyon saptanabilmektedir (3). Çalışmamızda 94 hastada herhangi bir mutasyon saptanamadığında yukarıda belirtilen bilgiler ışığında kalan genlerin hem dizileme hem de delesyon/duplikasyon açısından analiz edilmesi gerekmektedir.

Sonuç

Gelişen dizileme teknolojileri, tanımlanan yeni genlerin yanı sıra kanser genetiğindeki yeni çalışmalar ve yaklaşımlar tanının moleküler olarak doğrulanması gerekliliğini ortaya koymuştur. Herediter KRK tanısının doğrulanması ve mutasyonun tespit edilebilmesi multidisipliner hasta yönetiminin daha başarılı olması, tıbbi genetik uzmanlarının daha doğru ve kapsayıcı genetik danışma vermesine imkan sağlayacağı ve bu durumunda mortalite ve morbiditenin düşürülmesine katkı sunacağı düşünülmektedir.

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The Relationship Between the Long-Term Non-Rehabilitated Benign Paroxysmal Positional Vertigo and Vestibular Hypofunction

Uzun Süre Rehabilite Edilmemiş Benign Paroksismal Pozisyonel Vertigo ve Vestibüler Hipofonksiyon İlişkisi

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Abstract

Aim: Recurrent Benign paroxysmal positional vertigo (BPPV) and vestibular hypofunction (VH) can be co-diagnosed in some patients. We aimed to sight the relationship between the recurrent BPPV and VH, and to evaluate the change in the VH prevelance according to recurrent BPPV duration.

Methods: We conducted a retrospective chart review of 416 patients who were diagnosed with recurrent BPPV. Demographic features of the patients, co-diagnosis frequency of recurrent BPPV and VH, and the change in the VH prevelance according to recurrent BPPV duration were recorded. Patients were divided into two groups for having BPPV attacks for more than 12 months or less than 12 months. Both groups were compared in terms of VH prevalence.

Results: VH was co-diagnosed in 61.7% of patients with BPPV. The age of the recurrent BPPV patients with VH was significantly higher than the patients without VH ($p<0.05$). VH positivity was directly correlated with the duration of recurrent BPPV. VH prevelance was significantly higher in the group that the BPPV duration was above 12 months than in the group that the recurrent BPPV duration was under 12 months ($p<0.05$).

Conclusion: VH is common in patients with recurrent BPPV. There is may be a causal relationship between BPPV and VH.

Keywords: Benign paroxysmal positional vertigo, peripheral vestibulopathy, vestibular hypofunction, BPPV, vestibulopathy

Öz

Amaç: Benign paroksismal pozisyonel vertigo (BPPV) ve vestibüler hipofonksiyon (VH) bazı hastalarda birlikte görülebilir. Çalışmamızda, BPPV ve VH arasındaki ilişkiyi gözlemlemeyi ve tekrarlayan BPPV süresine göre VH görülme sıklığındaki değişimi araştırmayı amaçladık.

Yöntemler: BPPV tanısı almış 416 hastanın geriye dönük dosya incelemesi yapıldı. Hastaların demografik özellikleri, BPPV ve VH birlikteliğindeki sıklık ve de BPPV süresine göre VH görülme sıklığındaki değişim kaydedildi. Hastalar 12 aydan daha uzun süredir tekrarlayan ve son 11 ay içinde gelişen ve/veya tekrarlayan BPPV'li olmak üzere iki gruba ayırıldı. Her iki gruptaki hastalar VH sıklığı açısından karşılaştırıldı.

Bulgular: BPPV'li hastaların %61,7'sinde ayrıca VH tanısı konuldu. VH ile birlikte olan BPPV'li hastaların yaş ortalaması, VH ile birlikte olmayan BPPV'li hastaların yaş ortalamasına göre anlamlı olarak yüksekti (PC 0,05). VH ile birlikte olan veya olmayan BPPV'li hastaların cinsiyet dağılımında anlamlı fark yoktu ($p<0,05$). VH pozitifliği ile tekrarlayan BPPV süresi doğru orantılı idi. Tekrarlayan BPPV süresi 12 aydan uzun olan gruptaki VH sıklığı, BPPV süresi 12 aydan kısa olan gruba göre anlamlı olarak yüksekti ($p<0,05$).

Sonuç: Uzun süredir tekrarlayan BPPV'li hastalarda VH görülmesi yaygındır. VH ile BPPV'nin bir sebep-sonuç ilişkisi olabilir.

Anahtar Sözcükler: Benign paroksismal pozisyonel vertigo, periferik vestibülopati, vestibüler hipofonksiyon, BPPV, vestibülopati

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Introduction

Peripheral vestibular dysfunction is one of the most common reasons for applying to the hospitals. The most common cause of peripheral vestibular dysfunction is benign paroxysmal positional vertigo (BPPV) (1). BPPV is characterized by short (seconds to minutes) recurrent episodes of positional vertigo and dizziness provoked by changes in head position. Displaced otoconia (canalolithiasis or cupulolithiasis) are thought to cause BPPV by mechanically stimulating the vestibular receptors within the semicircular canals (2,3).

The second most common cause of peripheral vestibular dysfunction is vestibular hypofunction (VH), which can be described as a disturbance of the vestibulo-ocular reflex (VOR) in one or both of the inner ears (4). The VOR assists in maintaining gaze stability, which allows the eyes to maintain focus on a target while the head is moving. As the VOR is disturbed in VH, tracking of moving objects becomes difficult, which is an important symptom of VH (1,5).

Among patients with BPPV or VH who have not undergone appropriate medical treatment, intentional movement restriction and hypodynamics are often experienced due to fear of falling (6). Previous studies have shown that leading a sedentary lifestyle and hypodynamics have negative effects on the balance system, while sports and movement have positive effects on it (7,8). In our clinical experiences, we often observe VH symptoms in BPPV patients even after successful canalith repositioning. Thus, we speculated that prolonged movement restriction may cause secondary VH.

We aimed to investigate the frequency of co-diagnosis of BPPV and VH and also to find the relationship between the VH prevelance and recurrent BPPV duration.

Methods

Patients who were admitted to our audio-vestibular center between January 2016 and January 2020 and underwent detailed vestibular examination were recruited for this study. The study protocol was approved by the Ethics Committee of İstanbul Aydın University, Faculty of Medicine (number: 2020/240). Patients between 18 and 65 years of age who were diagnosed with BPPV were included in the study. The diagnosis of BPPV was made according to the 2015 Barany Society criteria (9). The onset of dizziness of every subject was determined by examining the history of the selected patients. The patients were divided into two groups depending on for how long the recurrent BPPV had been troubling, as less than 12 months (control group) and 12 months or more (study group). The both groups patients were investigated in terms of VH. During the evaluation of VH, the Dizziness Handicap Inventory Questionnaire (validated Turkish version) was completed by patients according to their anamnesis (10). Videonystagmography (VNG) recorded vestibular examination, including saccade test, tracking test, optokinetic test, gaze test, Dix-Halpike maneuver, air-stimulated binaural bithermal caloric test, fixation suppression test, baseline shift, gain asymmetry were taken into consideration. VNG equipment from Otometrics (ICS Chartr 200; Taastrup, Denmark) and a computerized system were used for VH diagnosis. PC-VNG software was used for automatic analysis of the recordings. The following criterias were used to diagnose VH.

A. Chronic vestibular syndrome with the following symptoms:

1. Unsteadiness when walking or standing plus at least one of 2 or 3.

2. Movement-induced blurred vision or oscillopsia during walking or quick head/body movements and/or.

3. Worsening of unsteadiness in darkness and/or on uneven ground.

B. No symptoms while sitting or lying down under static conditions

C. Bilateral weakness in the caloric response was considered based on the 2017 Barany Society criteria (11): Bilaterally reduced or absent angular VOR function documented by reduced caloric response (sum of bithermal maximum peak Slow-phase velocity on each side <6◦/sec).

D. Unilateral weakness in the caloric response was quantified according to the Jongkees formula. A value greater than or equal to 25% was pathological according to our normative data. Additionally, the directional preponderance (DP) was measured using the formula DP=[(RW+LC)-(LW+RC)]/(RW+LW+RC+LC)x100. Normal absolute values in our lab are below a DP of 30%.

E. Not better accounted for by another disease

The both groups patients were statistically compared in terms of VH frequency. The demographic characteristics of the patients, relationship between BPPV duration and VH prevelance, involved semicircular canal, and involved ear were investigated and analyzed.

Patients with any additional otologic pathologies that can cause VH (including endolymphatic hydrops, history of labyrinthitis, vestibular neurinitis, trauma, and meningitis), patients with additional neurologic or orthopedic pathologies, patients less than 18 or more than 65 years of age, patients with incomplete anamnesis and/or questionnaire, and patients who had not undergone VNG recorded vestibular examination were excluded from the study. Patients whose anamnesis suggested that VH developed before BPPV occurred were also excluded from the study.

Statistical Analysis

Mean, standard deviation, median, lowest and highest frequency, and ratio values were used as descriptive statistics of the data. The distribution of variables was measured using the Kolmogorov-Smirnov test. In the analysis of quantitative independent data, the Mann-Whitney U test was used. The chi-square test was used for the analysis of qualitative independent data. The Statistical Package for the Social Sciences (SPSS) 22.0 program was used in the analysis.

Results

Of the 416 patients diagnosed with BPPV who matched our study criteria, 257 (61.7%) had VH, and 159 (38.2%) did not have VH. The demographic features and VNG records of the BPPV patients are shown in Table 1. The age of the patients with VH was significantly higher than the age of the patients without VH ($p<0.05$). There was no significant difference in gender distribution between the BPPV patients with and without VH ($p<0.05$). There was no significant difference between the groups in terms of saccade positivity, gaze positivity, tracking test positivity, and optokinetic test positivity ($p>0.05$) (Table 2). In the patients with VH, the duration of the BPPV was significantly longer than in the patients without VH ($p<0.05$) (Figure 1). We found that the duration of BPPV was directly correlated with VH positivity (Figure 2). In the study group (BPPV duration ≥12 month), VH positivity was significantly higher than in the control group (BPPV duration <12 month) ($p<0.05$) (Figure 3). The age of the patients with bilateral VH was significantly higher than the age of the patients with unilateral VH ($p<0.05$). There were no statistically significant differences in patients with bilateral or unilateral VH ($p<0.05$) in terms of gender distribution, duration of BPPV, and optokinetic test results (Table 3).

Discussion

BPPV has been shown to be related with otologic disorders, including sudden idiopathic hearing loss, vestibular neuritis, and Meniere's disease (12-14). BPPV may develop after head trauma or inner ear surgery (stapes surgery, cochlear implantation, or when repairing superior canal dehiscence) (15). Patients with an acute

Table 1. Demographic features and videonystagmography records of the BPPV patients

		Min-Max			Median	Mean ± SD/N-%		
Age (years)		7.0	-	91.0	50.0	49.0	±	16.0
Sex	Female					280		67.5%
	Male					136		32.8%
BPPV time (months)		0.1	-	420.0	5.3	30.7	±	60.8
Saccade	(-)					383		92.3%
	(+)					33		8.0%
Gaze	(-)					416		100.2%
	(+)					0		0.0%
Tracking	(-)					298		71.8%
	(+)					118		28.4%
Optokinetic	(-)					299		72.0%
	(+)					117		28.2%
ROLL test	(-)					389		93.7%
	(+)					27		6.5%
DIX hallpike right	(-)					123		29.6%
	(+)					293		70.6%
DIX hallpike left	(-)					136		32.8%
	(+)					280		67.5%
Vestibular hypofunction	(-)					159		38.3%
	(+)					257		61.9%
-	Right					107		25.8%
-	Left					101		24.3%
-	Bilateral					49		11.8%

Min: Minimum value, Max: Maximum value, ± SD/N: Standart deviation/number, BPPV: Benign paroxysmal positional vertigo

Table 2. Comparison of the patients regarding BPPV duration and VH positivity											
		Vestibular Hypofunction (-)				Vestibular Hypofunction (+)				p	
		Mean ± SD/n-%			Median	Mean ± SD/n-%			Median		
Age (years)		46.3	±	16.5	47.5	50.6	±	15.4	51.0	0.015	m
Sex	Female	110		69.2%		170		66.1%		0.521	X²
	Male	49		30.8%		87		33.9%			
BPPV time (months)		17.7	±	43.9	1.0	38.8	±	68.1	12.0	0.000	m
BPPV time (monhts)	≤12 >12	120 39		75.5% 24.5%	1.0	139 118		54.1% 45.9%		0.000	X²
BPPV	(-) (+)	0 159		0% 100%		0 257		0.0% 100%		1.000	X²
Saccade	(-)	148		93.1%		235		91.4%		0.547	X²
	(+)	11		6.9%		22		8.6%			
Gaze	(-)	159		100.0%		257		100.0%		1.000	X²
	(+)	0		0.0%		0		0.0%			
Tracking	(-)	114		71.7%		184		71.6%		0.982	X²
	(+)	45		28.3%		73		28.4%			
Optokinetic	(-)	115		72.3%		184		71.6%		0.872	X²
	(+)	44		27.7%		73		28.4%			
ROLL test	(-)	146		91.8%		243		94.6%		0.272	X²
	(+)	13		8,2%		14		5,4%			
DIX hallpike right	(-)	55		34.6%		68		26.5%		0.077	X²
	(+)	104		65.4%		189		73.5%			
DIX hallpike left	(-)	60		37.7%		76		29.6%		0.085	X²
	(+)	99		62.3%		181		70.4%			

Min: Minimum value, Max: Maximum value, ± SD/N: Standart deviation/number, m: Mann-whitney u test, x2: Chi-square test, BPPV: Benign paroxysmal positional vertigo, VH: Vestibular hypofunction

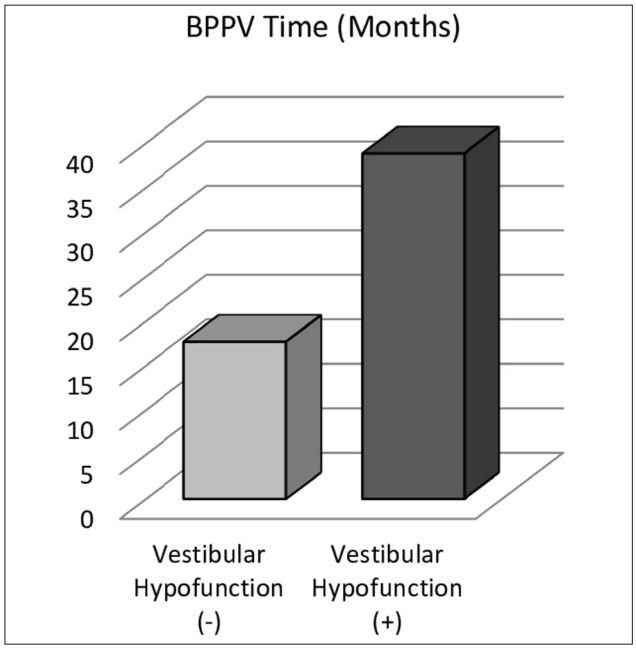

Figure 1. The duration of BPPV between the patients with and without vestibular hypofunction
BPPV: Benign paroxysmal positional vertigo

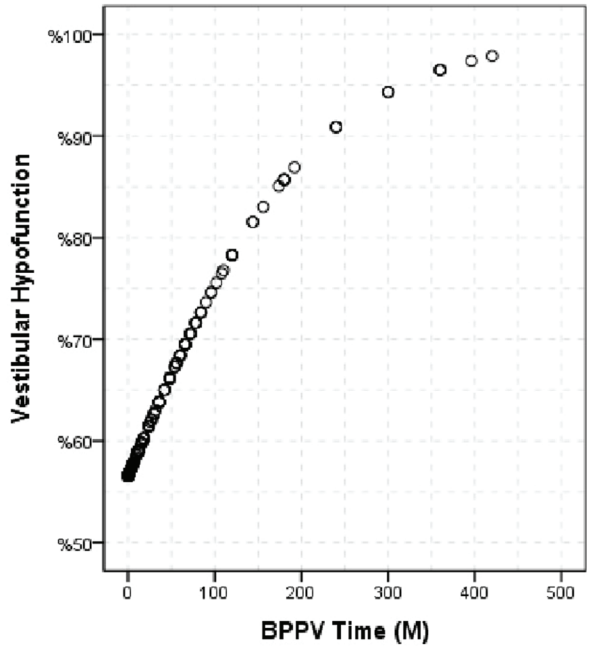

Figure 2. The correlation between duration of BPPV and VH
BPPV: Benign paroxysmal positional vertigo, VH: Vestibular hypofunction

and/or chronic unilateral peripheral vestibulopathy can develop recurrent posterior canal BPPV in the same ear (16,17).

In a recent study, it was reported that patients with a history of BPPV and otologic disease were more likely to have VH than those without a history of otologic disease (18). However, the relationship between VH and BPPV has not been comprehensively described in the literature. There is only one study, conducted by Summer et al. (19) in 2012, in which the rate of co-diagnosis of VH and BPPV,

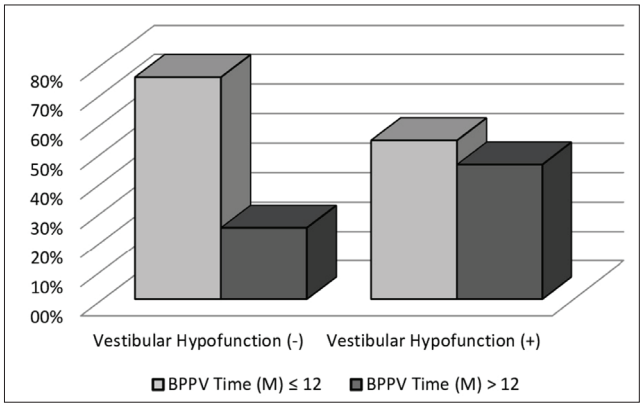

Figure 3. Comparison of vestibular hypofunction prevelance between the patients who have BPPV more than 12 months and less than 12 months
BPPV: Benign paroxysmal positional vertigo

the frequency of admission to physical therapy, and the relationship with patients' ages were determined. They retrospectively reviewed 500 medical records of patients diagnosed with VNG. They found that 38% of their patients had a single diagnosis, and 6.6% of their patients had a co-diagnosis. They also found a positive relationship between VH-BPPV co-diagnosis and increased age. We also found significantly higher ages in BPPV patients with VH than in patients without VH (19). However, it is possible that the increase in co-diagnosis with age may simply be due to the increased incidence of both VH and BPPV in the elderly.

Physical activity including head and body movements is important factor for recovering from vestibular dysfunctions. On the other hand, prolonged dizziness caused by vestibulopathies including BPPV is a risk factor for developing anxiety (20). Therefore, patients with untreated BPPV tend to be less active as a result of balance problems and anxiety (6,20). Morimoto et al. (6) reported a study in which they provided objective measures of physical activity in patients with chronic unilateral vestibular hypofunction. They found direct correlation between physical activity and postural stability (6).

In the study by Summer M. and San Lucas (19), they did not determine the time course of VH and BPPV. It is possible that patients may have had VH years prior to VNG testing and developed BPPV near the time of VNG testing.

Table 3. Demographic features and videonystagmography records of the patients regarding unilateral and bilateral VH

		Vestibular hypofunction unilateral			Vestibular hypofunction bilateral				p	
	Mean ± SD			Median	Mean ± SD			Median		
Age (years)		51.9	±	15.2	52.0	45.3	±	15.4	44.0	0.009	m
Sex	Female	136		65.4%		34		69.4%		0.594	X²
	Male	72		34.6%		15		30.6%			
BPPV Time (months)		37.7	±	67.6	12.0	43.7	±	70.5	12.0	0.803	m
Saccade	(-)	191		91.8%		44		89.8%		0.648	X²
	(+)	17		8.2%		5		10.2%			
Gaze	(-)	208		100.0%		49		100.0%		1.000	X²
	(+)	0		0.0%		0		0.0%			
Tracking	(-)	151		72.6%		33		67.3%		0.464	X²
	(+)	57		27.4%		16		32.7%			
Optokinetic	(-)	151		72.6%		33		67.3%		0.464	X²
	(+)	57		27.4%		16		32.7%			
ROLL test	(-)	200		96.2%		43		87.8%		0.020	X²
	(+)	8		3.8%		6		12.2%			
DIX-hallpike right	(-)	57		27.4%		11		22.4%		0.479	X²
	(+)	151		72.6%		38		77.6%			
DIX-hallpike left	(-)	67		32.2%		9		18.4%		0.056	X²
	(+)	141		67.8%		40		81.6%			

Min: Minimum value, Max: Maximum value, ± SD/N: Standart deviation/number, m: Mann-whitney v test, x2: Chi-square test, BPPV: Benign paroxysmal positional vertigo

In our study, we recruited only BPPV patients. Out of the 416 BPPV patients, 257 (61.7%) had VH, and 159 (38.2%) did not have VH. These remarkably different results may be due to the fact that our clinic is a referral center, and specific patients are admitted oftenly. For the same reason, we have had many BPPV cases that have not been treated for a long time.

We analyzed the correlation between the duration of recurrent BPPV and the frequency of VH in order to investigate the duration of recurrent BPPV as a risk factor for VH. It was remarkable that we found a positive correlation. Since our audio-vestibular center is a tertiary center, we noted that most of our patients had previous examinations and treatments in other clinics and had not benefited or had recurrences. Thus, we excluded patients when it was revealed that they had developed VH before BPPV. However, this exclusion was provided based on the patients' history. Conversely, Summer M. and San Lucas (19), reported that they found a significant association between peripheral vestibular dysfunction and non-referral to physical therapy after BPPV treatment. This data suggests that non-rehabilitated BPPV may contribute to the occurrence of VH.

In order to distinguish long- and short-term BPPV, we chose a relative period of 12 months. Statistical analysis could not prove its usefulness as a cut-off time. If a patient has multiple sources of dizziness and only one source is treated, it is likely that the treatment will be incomplete. Accurate identification of BPPV and VH comorbidities will provide an appropriate treatment strategy. In cases of co-diagnosis of BPPV and VH, it is recommended that BPPV, which can be resolved in one to three sessions, be treated first (21). Then, rehabilitation procedures can be initiated to treat VH.

The mean age of patients with VH was found to be significantly higher compared to those without VH (Table 2). It is known that vestibular response decreases with increasing age and old age is a risk factor for VH. But, considering the follow-up periods of our patients, the average age of the group with VH is 50 years, the average follow-up period is 38 months (three years), while the average age of those without VH is 46 years and the average follow-up period is 17 months (1 year). In other words, we see that the ages at which the first BPPV attack developed in both groups are close to each other. Therefore, although there appears to be a statistical age difference between the patient group with VH and the group without VH, we believe that this did not affect negatively our study results.

In conclusion, VH, which is very common in the elderly population, quite often diagnosed together with BPPV. Further investigations are needed regarding possible causal relationship of these conditions. We speculate that VH can develop because of prolonged movement restriction due to fear of falling. From this point of view early rehabilitation of BPPV can prevent VH development.

Authorship Contributions

Concept: D.T., Design: D.T., Data Collection or Processing: G.K., Analysis or Interpretation: E.S., Literature Search: D.T., E.S., Writing: E.S

Conflict of Interest: There is not any financial and personal relationships with other people or organisations. Also there is not any funding source.

Informed Consent: Consent form was filled out by all participants.

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Original Article / *Özgün Araştırma*

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Factors that Increase the Need for Surgery in Chiari Malformation Type 1 Patients Morphometric Analyses in Chiari Patients

Tip 1 Chiari Malformasyonlu Hastalarda Ameliyat Gereksinimini Artıran Faktörler Chiari Hastalarında Morfometrik Analiz

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Abstract

Aim: The causes of the syringomyelia in Chiari are not certainly defined. We have done morphometric analyses which can be useful to understand natural course and causes which increase the surgery requirement of patients.

Methods: Eighty nine patients (operated) and 41 patients (non-operated) were included the study. Investigations were done as randomized. Accompanying syringomyelia, area of foramen magnum, herniated tonsil volume and clivo-dental angle were compared between operated and control groups.

Results: Syringomyelia was seen in 50%. The mean values of FMA were 765.2±119.5 mm^2. The mean value of critical discourse analysis (CDA) was 139.5±10.6°. Mean of the hydrophobicity (HTV) were found to be 54.5±24.1 mm^3. The mean of age was 27±11.1, FMA was 876.5±131.9 mm^2, CDA was 141.1±10.2° and HTV was 57.6±20.7 mm3 in the patients with syringomyelia. The mean of age was 33.9±12, FMA was 704.3±99.6 mm^2, CDA was 137,8±10,8° and HTV was 51,4±26,8 mm^3 in the patients who had not syringomyelia.

Conclusion: Younger age, larger FMA and CDA increase the HTV and the rate of accompanying syringomyelia. As a result, the need for surgery increases. We think that it may be beneficial to consider these parameters in patients who are evaluated for surgery.

Keywords: Arnold-Chiari malformation type 1, syringomyelia, morphometric analysis

Öz

Amaç: Hastalığın doğal seyri halen tam anlaşılamamıştır. Siringomiyelinin oluşum sebepleri de belirsizliğini kısmen korumaktadır. Biz bu çalışmada, hastalığın doğal seyrine, operasyon gereksinimine neden olan sebeplere açıklık getirmede fayda sağlayacağını düşündüğümüz morfometrik analizler yaptık.

Yöntemler: Seksen dokuz opere ve 41 opere olmayan incelendi. İncelemelerimiz randomize, retrospektif ve radyolojik olarak özel formüller vasıtasıyla yapıldı. Opere olanlarla olmayanlar arasında siringomyeli eşlik etme oranına, foramen magnum alanı (FMA), herniye tonsil hacmi (HTH) ve klivo-dental (KD) açı farklarına bakıldı. Siringomyeliye sebep olan parametrelerin oranı ayrı ayrı incelendi. HTH hesaplamasında sferoid hacim formülü ile hesaplandı. İstatistik analizi için veriler toplandı. Analizler sonrası anlamlılık değeri p<0,05 olarak gösterildi.

Bulgular: Siringomyeli eşlik etme oranı %50 idi. FMA ortalaması 765,2 ± 119,5 mm^2, KD açı 139,5±10,6, THH ortalaması 54,5±24,1 olarak ölçüldü. Siringomiyeli mevcut olan hastalarda ortalama yaş 27±11,1 iken FMA ortalaması 876,5 ± 131,9, KDA ortalaması 141,1±10,2 ve THH ortalaması 57,6±20,7 olarak bulunmuştur. Siringomiyeli olmayanlarda ise ortalama yaş 33,9±12, FMA 704,3 ± 99,6, KD açı 137,8±10,8, ve THH 51,4±26,8 olarak bulunmuştur.

Sonuç: Daha genç yaş, büyük foramen magnum ve klivus-dens açısı, tonsil herniasyon hacmi miktarını ve siringomiyeli eşlik etme oranını artırmakta ve bunlara sekonder operasyona gidişi daha sık hale getirmektedir. Operasyon gereksinimi açısından değerlendirilen hastalarda bu parametrelerin de gözönüne alınmasının, yararlı olabileceğini düşünmekteyiz.

Anahtar Sözcükler: Arnold-Chiari malformasyonu tip 1, siringomiyeli, morfometrik analiz

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Introduction

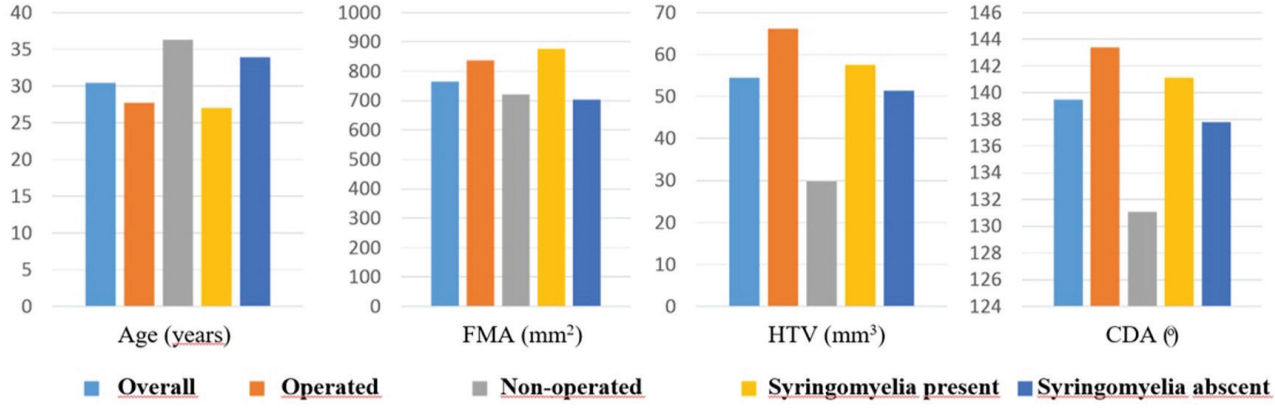
Chiari malformations (CM) is a group of diseases which includes anatomical abnormalities of craniovertebral junction, cerebellum and brainstem (1). The most common form of this disease group is Chiari malformation type 1 (CM1). It was first described as "migration of conic-shaped cerebellar tonsils and caudal portions of cerebellum to the spinal canal with medulla oblongata" by Hans Chiari. CM1 is one of the most controversial issue in neurosurgery practice because of its definition, prognosis, treatment indications, selection of surgical procedure, accompanying abnormalities and diseases (2). Although one of the defined mechanisms is depletion of normal sized hindbrain to the inferior because of crowded posterior fossa caused by inadequate development of posterior cranial fossa which is derived from paraxial mesoderm; neutral progression of disease is still unclear. Although there are studies investigating the natural course of CM-1 which is less common in adults, sufficient data could not be obtained (3,4). Although the symptomatic patients mostly require surgery, there is no sufficient data for asymptomatic CM-1 cases (5,6). The causes of the syringomyelia are not certainly defined (7). In this study, we have done morphometric analyses which can be useful to understand natural course of CM-1 and causes which increase the surgery requirement of patients.

Methods

This retrospective study was carried out with the collaboration of Şişli Hamidiye Etfal Training and Research Hospital and Haseki Training and Research Hospital's Neurosurgery clinics. 89 patients (operation group) had surgery because of CM-1 and 41 patients (control group) followed due to the CM-1 malformation between the years 2001 and 2018 were included the study. Investigations were done as randomized and by using special radiological formulas. Accompanying syringomyelia, area of foramen magnum (FMA), herniated tonsil volume (HTV) and clivo-dental angle (CDA) were compared between operated and control groups. Parameters which cause syringomyelia were investigated separately. HTV were calculated with $4/3\times\varpi\times(X_{/2}\times Y_{/2}\times Z_{/2})$ spheroidal volume formula by using the largest cross-sections in three planes. The longest cross sections of herniated tonsils were measured in axial, coronal, sagittal planes and noted as X, Y, Z respectively. The angle between posterior line of clivus and dens in sagittal plane was used to determine CDA (Figure 1, 2). Length of the largest anterior-posterior (A-P) and lateral sections of foramen magnum were multiplied in axial plane to calculate FMA (Figure 1, 3, 4). All data was collected for statistical analysis and range, mean and standard deviation values were calculated for each measurement parameters. Independent sample student's t test was used for normally distributed age, volume and measurements. The Spearman correlation test was used to evaluate the correlation between two continuous variables. Statistically significance value was found as $p<0.05$ (Figure 1, 5, 6).

Findings

The mean age of all patients was 30.4±12.0. While the mean age of patients who had surgery was 27.7±10.4, mean value of the age was found to be 36.3±10.3 in the control group. Accompanying syringomyelia was seen in 50% of all patients, but operated patients had higher syringomyelia incidence than control group (60.6% vs. 28.5%). The mean values of FMA in all, operated and control patients were 765.2±119.5 mm^2, 838.2 ± 119.8 mm^2 and 721.9±108.2 mm^2 respectively. While the mean value of CDA was 139.5±10.6° in all patients, the mean CDA was 143.4±10.3° in operated group and 131.1±5.2° in control group. Mean of the HTVs were found to be



Graphic 1. Age and morphometric values of all patients. Fma: foramen magnum area, htv: herniated tonsil volume, cda: clivo-dental angle

54.5±24.1 mm^3, 66.2±19.9 mm^3 and 29.8±8.4 mm^3 in the all, operated and control groups respectively (Table 1). The mean of age was 27±11.1, FMA was 876.5 ± 131.9 mm^2, CDA was 141.1±10.2° and HTV was 57.6±20.7 mm^3 in the patients with syringomyelia. The mean of age was 33.9±12, FMA was 704.3 ± 99.6 mm^2, CDA was 137,8±10,8° and HTV was 51,4±26,8 mm^3 in the patients who had not syringomyelia (Table 2, Graphic 1).

Discussion

When we analyze our results, we found higher mean values for FMA (p<0.001), CDA (p<0.001), HTV (p<0.001) in the operated group. Increasing of FMA causes the facilitation of downward herniation of tonsils.

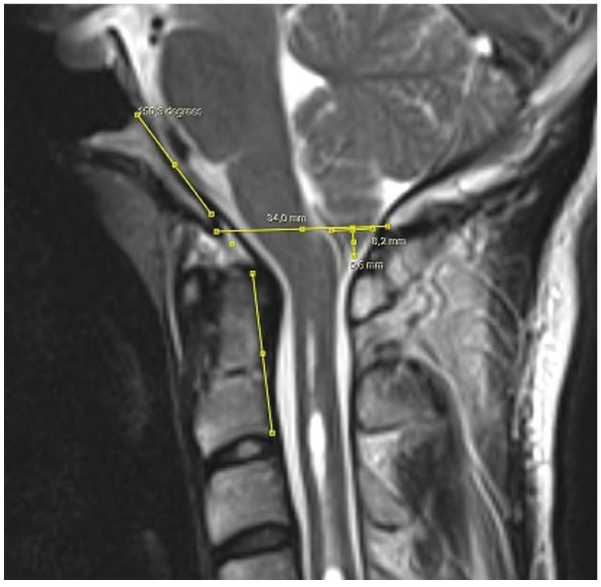


Figure 1. Measurements of clivo-dental angle, foramen magnum area and herniated tonsil volume at saggital plane

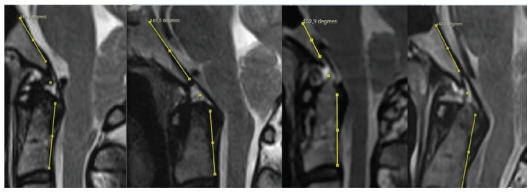


Figure 2. Examples of measurements of clivo-dental angle

The underlying mechanism is that the expansion of the foramen magnum facilitates the downward movement of the tonsils. Tonsils, which move to inferior, pull the anatomic structures they are attached to down. Arachnoid bands and adhesions at the level of tonsils may induce this process. Another facilitating factor is the effect of CDA. The higher CDA facilitates the movement of brainstem to the inferior. Additionally to this movement, tonsillar herniation together causes the compression around the foramen magnum, which is one of the reasons of syringomyelia.

Although the pathophysiology of the formation of syringomyelia has not been fully explained, defects of the CSF flow are important (8). Massive syringomyelia had been

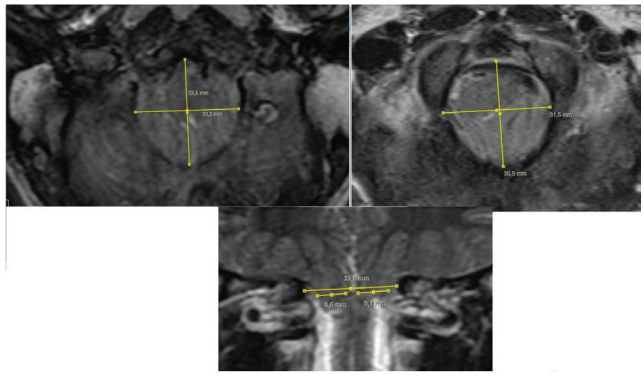


Figure 4. Examples of measurements of foramen magnum area at coronal and axial planes

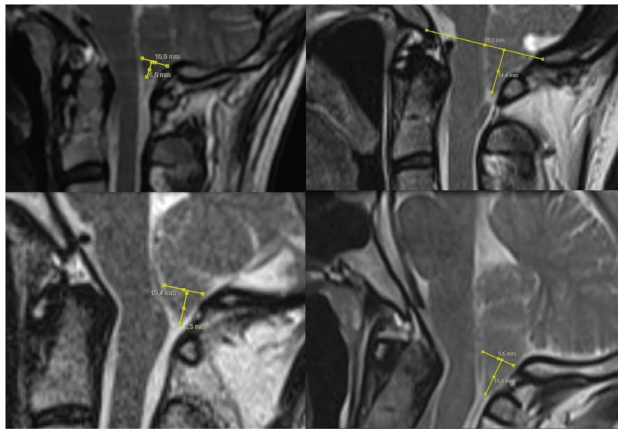


Figure 5. Examples of measurements of herniated tonsil volume at saggital plane

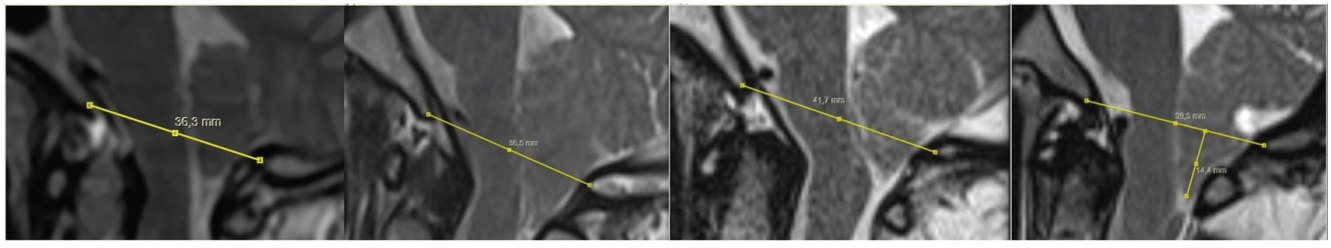


Figure 3. Examples of measurements of foramen magnum area at saggital plane

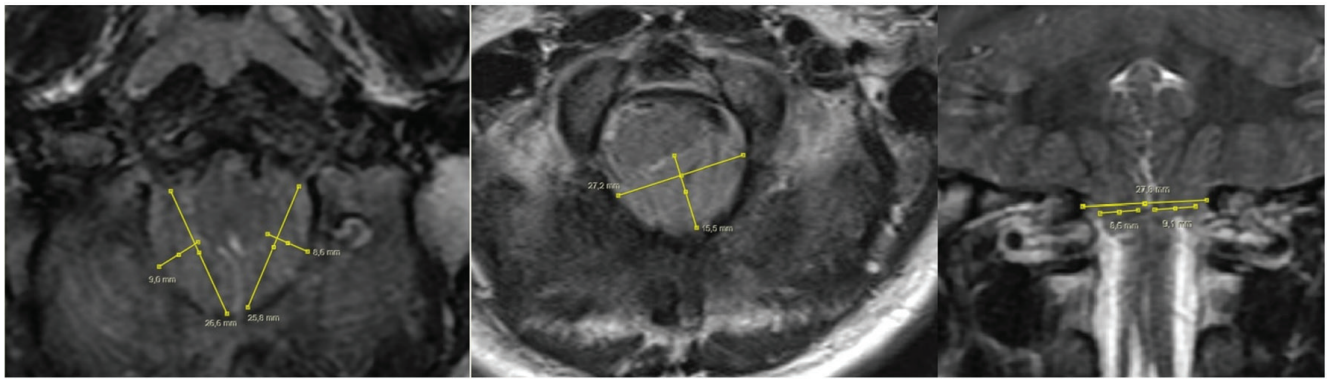


Figure 6. Examples of measurements of herniated tonsil volume at coronal and axial planes

Table 1. Age and morphometric values of operated and non-operated patients					
	Age (years)	**FMA (mm^2)**	**HTV (mm^3)**	**CDA (°)**	**Syringomyelia (%)**
Overall	30.4±12.0	765.2±119.5	54.5±24.1	139.5±10.6	50
Operated	27.7±10.4	838.2±119.8	66.2±19.9	143.4±10.3	60.6
Non-operated	36.3±10.3	721.9±108.2	29.8±8.4	131.1±5.2	28.5
FMA: Foramen magnum area, HTV: Herniated tonsil volume, CDA: Clivo-dental angle					

Table 2. Age and morphometric values according to syringmyelia presence				
	Age (years)	**FMA (mm^2)**	**HTV (mm^3)**	**CDA (°)**
Patients with syringomyelia	27±11.1	876.5±131.9	57.6±20.7	141.1±10.2
No syringomyelia	33.9±12	704.3±99.6	51.4±26.8	137.8±10.8
Overall	30.4±12.0	765.2±119.5	54.5±24.1	139.5±10.6
FMA: Foramen magnum area, HTV: Herniated tonsil volume, CDA: Clivo-dental angle				

reported in acute worsening patients (9). We found the incidence of syringomyelia was 50% in all patients which is parallel to the literature (8). We also found HTV and accompanying syringomyelia were inversely proportional with age ($p<0.001$) and were directly proportional with CDA ($p<0.001$) and FMA ($p<0.001$).

Growing anatomical structures which continues in younger patients and comes to an end in elder patients, may be responsible this negative correlation. One of another effect may be the mobility of neural structures in young patients. In this study tonsil herniation and syringomyelia were found to be more frequently in younger patients. Younger patients consist the majority of the cases who need surgery (10). Even if the older patients diagnosed as CM1, progressive disease and accompanying syringomyelia are very rare.

We found the young patients need surgery than older patients because of the tonsil herniation and accompanying syringomyelia. Also we found the increasing FMA and CDA cause more tonsil herniation and cooccurrence of syringomyelia.

It has been previously reported that the presence of syringomyelia is a factor that strengthens the indication for operation (7,11). These findings may clarify the natural course of the disease and which factors are more frequent in operated patients. In addition, further studies are needed with more and different demographic people.

Conclusion

Younger age, larger FMA and CDA increase the HTV and the rate of accompanying syringomyelia. As a result, the need for surgery increases. We think that it may be beneficial to consider these parameters in patients who are evaluated for surgery.

Authorship Contributions

Concept: E.A., Design: A.K., Data Collection or Processing: E.A., A.K., Analysis or Interpretation: E.A., Literature Search: A.K., Writing: E.A., A.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Neonatal Prognosis and Outcomes in Adolescent Pregnancies

Adölesan Gebeliklerin Neonatal Prognoz ve Sonuçları

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Abstract

Aim: The study aims to determine features, morbidities and mortality of adolescent pregnants and their hospitalized newborns in the neonatal period.

Methods: Six hundred forty-one adolescent pregnants were enrolled and compared to 309 non-adolescent pregnants. Demographic characteristics of mothers and complications of delivery, demographic characteristics of newborns, morbidities, and mortality of infants admitted to hospital during neonatal period were recorded.

Results: The mean age of adolescent and non-adolescent pregnants were 17.2±0.8 and 27.0±4.3 years, respectively. Education levels, being housewife, extramarital birth-giving, cesarean section rate, and twin pregnancy were higher in adolescent pregnants. The mean height, head circumference, and weight of newborns in adolescent pregnants were significantly lower. Even though neonatal mortality was similar in both pregnants, early neonatal morbidities were more common in adolescent pregnants. Duration and rate of hospitalization, and morbidities causing hospitalization during the neonatal period were similar in the babies of both pregnants. Among babies admitted to the neonatal intensive care unit, mortality rates were higher in babies born to non-adolescent mothers.

Conclusion: Worse neonatal outcome of babies born to adolescent pregnants, and higher mortality in the neonatal period in non-adolescent pregnants were found. But characteristics and morbidities of babies hospitalized in the neonatal period were similar in both groups.

Keywords: Adolescent pregnancy, hospitalization, neonatal morbidity, neonatal mortality, newborn

Öz

Amaç: Çalışmamızın amacı, adolesan gebelerin ve yenidoğan döneminde hastaneye yatırılan bebeklerinin özelliklerini, morbidite ve mortalitelerini araştırmaktır.

Yöntemler: Çalışmaya 641 adolesan ve 309 adolesan olmayan gebe dahil edildi. Anne ve bebeklerin demografik özellikleri, doğum komplikasyonları, yenidoğan döneminde hastaneye yatırılan bebeklerinin morbidite ve mortaliteleri kaydedildi.

Bulgular: Adolesan olan ve olmayan gebelerin ortalama yaşı sırasıyla 17,2±0,8 ve 27,0±4,3 yıldı. Adolesan gebelerde eğitim düzeyleri, ev hanımı olma oranı, evlilik dışı doğum oranı, sezaryen doğum oranı ve ikiz gebelik oranı daha yüksekti. Adölesan anne bebeklerinde ortalama boy, baş çevresi ve ağırlık anlamlı düzeyde daha düşüktü. Neonatal mortalite her iki grupta benzer saptanmışken, erken neonatal morbiditeler adolesan gebe bebeklerinde daha sık saptanmıştı. Hastane yatış oranı, süresi ve yatışa neden olan yenidoğan dönemi morbiditeleri her iki grup bebeklerinde benzerdi. Yenidoğan yoğun bakıma yatan bebekler arasında, mortalite kontrol grubunda daha yüksekti.

Sonuç: Çalışmamızda adolesan anne bebeklerinde doğum özellikleri daha düşük saptanmışken, hastaneye yatan adolesan olmayan anne bebeklerinde ise neonatal mortalite yüksek bulunmuştur. Yenidoğan döneminde yatırılan bebeklerin özellikleri ve morbiditeleri her iki grupta benzer saptanmıştır.

Anahtar Sözcükler: Adolesan gebelik, hastane yatışı, neonatal morbidite, neonatal mortalite, yenidoğan

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Introduction

Adolescent period involves a frame of time when the individual goes through biological, psychological and social changes. As the definition of World Health Organization states, it is a nine years period between ages of 10-19. Because of the biological immaturity, being an adolescent pregnant is an important factor which poses a risk for both the mother and the newborn (1). Becoming pregnant during adolescence can greatly alter young women's life prospects and those of their children. Complications of pregnancy and childbirth are the second leading cause of death among 15-19-year-old women (2). Malnutrition, smoking and alcohol use, emotional stres and suboptimal prenatal care are observed more in adolescents (3,4). Stillbirth, death within the first week and month are higher in newborns born to adolescent mothers compared to mothers between ages of 20-29 years and the risk increases as the age of the mother decreases. Although preterm birth, low birth weight and asphyxia rates are higher in adolescent mothers, all of which increase risks for the infants, morbidities and mortality of the babies born to adolescent pregnants who needs to be hospitalized during neonatal period have not been clearly identified in our population.

The aim of our study was to determine the features and problems related to adolescent pregnancies for the mothers and the newborns during delivery and their newborns having problems during neonatal period in our country.

Methods

Study Population

The single center, retrospective, observational, cohort study protocol was approved by the local Ethics Committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Ethical clearance was obtained from the Ethics Committee of the Bakirkoy Maternity and Children Hospital. 950 pregnants having no missing data of patient files and whose babies were followed up in neonatal period were enrolled to our study during two years in our hospital. Pregnants below 15 years and above 35 years, patients with missing data, pregnants with in utero ex fetus and babies who could not be followed up in our hospital during neonatal period were excluded from the study. The adolescent mothers consisted of pregnants aged between 15 and 19 years and the non-adolescent pregnants consisted of mothers aged between 20 and 35 years. Six hundred and forty-one adolescent pregnants and three hundred and nine non-adolescent pregnants were enrolled to the study. Patient files and hospital database records were provided via newborn database by the researcher.

Maternal Characteristics

Maternal charactetristics included age, marital status, duration of marriage, consanguineous marriages, smoking history, occupation, educational status, mode of delivery, cesarean indication, and obstertric complication.

Neonatal Features

Last menstruation date or new Ballard score with ultrasound were used to determine the gestational age and preterm delivery (gestation <37 weeks). Neonatal characteristics included gender, APGAR score (1^{st} and 5^{th} minutes), low 1^{st} and 5^{th} minutes APGAR score (less <7), birth weight (gram), low birth weight (less than 2.500 g), very low birth weight (less than 1.500 g), birth height (cm), head circumference (cm), congenital abnormalities, intrauterine growth retardation (IUGR), the presence of neonatal respiratory problems respiratory distress syndrome (RDS) and/or transient tachyphnea of newborn (TTN), meconium aspiration syndrome, hypoglycemia, Rh incompatibility, polycythemia, hyperbilirubinemia, and presence of resuscitation.

Features of Newborns Admitted to Hospital

Rate of prematurity, presence of accompanying congenital malformation, duration of hospitalization, level of hospitalization, ventilatory support, duration of total parenteral nutrition, the reasons for hospitalization, mortality rates during hospitalization of babies in neonatal period were recorded.

Data analysis

The analyses were performed by using the SPSS software (Statistical Package for the Social Sciences, version 20.0, SPSS Inc, Chicago Illinois, USA). Data are expressed as mean ± standard deviation. Parametric variables were compared with student's t-test between dependent variables and with Mann-Whitney U test between undependent variables. Categorical variables were compaired by using Pearson's chi-square test and Fisher's exact test was used parameters that were not normally distributed. The results were evaluated with a confidence interval of 95% and a significance level of $p<0.05$.

Results

Maternal Outcomes

Demographic characteristics of adolescent and non-adolescent pregnants were given in Table 1. The cesarean rate was significantly higher in the adolescent pregnants

compared to non-adolescent pregnants (52.9% and 42.7%; p=0.003). The most common cesarean indications were fetal distress, cephalopelvic disproportion and breech presentation in adolescent pregnants, however the most common indication was a previous cesarean section in the non-adolescent pregnants. 529 (82.5%) of the adolescent pregnants did not have any obstetric complications and the most common reason was bleeding among 112 (17.5%) of adolescent pregnants having complication. Whereas in non-adolescent pregnants; 235 pregnancies (76%) did not develop obstetric complications and 74 (24%) of the pregnants had bleeding as the most common complication. Preeclampsia rates were also similar (2.2% vs 3.9%, p=0.133, respectively). While 96 (15%) of the adolescents had premature birth, 53 (17.2%) of the non-adolescent pregnants had premature birth (p=0.388). Pregnant women in the adolescent age group stayed 1.9±1.2 days in the hospital, while the hospitalization duration of the pregnant women in the non-adolescent group was 1.8±1.2 days (p=0.19).

Table 1. Demographic characteristics of adolescent and non-adolescent pregnants

	Adolescent pregnant (n=641)	Non-adolescent pregnant (n=309)	p
Age (year) (mean±SD)	17.2±0.8	27.0±4.3	<0.001
Married (%)	93.3%	99.7%	<0.001
Duration of marriage (years) (mean±SD)	1.6±0.9	6.1±4.1	<0.001
Consanguineous marriage (%)	9.7%	13.3%	0.09
Smoker (%)	0.9%	0.6%	0.488
Unemployment rate (%)	99.5%	93.3%	<0.001
Education level (%)	16.7% Illiterate 42.3% PSG 34.2% SSG 6.7% HSG	20.6% Illiterate 44% PSG 17.2% SSG 14.6% HSG 3.9% Bachelor	<0.001

PSG: Primary school graduate, SSG: Secondary school graduate, HSG: High school graduate

Table 2. Neonatal characteristics of newborns born to the adolescent and non-adolescent mothers

	Adolescent mothers' babies (n=666)	Non-adolescent mothers' babies (n=313)	p
Gestational week (week)	37.8±2.3	37.7±2.1	0.526
Gender (male)	50.2%	49.2%	0.782
1st min. Low APGAR (<7)	19.7%	5.1%	<0.001
5th min. Low APGAR (<7)	1.1%	0.3%	0.216
Birth weight (gr)	3033±660	3202±587	<0.001
Birth height (cm)	49.2±3.5	49.9±2.7	0.002
Birth head circumference (cm)	34±2.1	34.7±2.1	<0.001

Neonatal Outcomes

Six hundred and sixty-six babies were delievered from 641 adolescent women, 313 babies were delivered from 309 non-adolescent women. One hundred and six (16.1%) of the babies born to adolescent mothers had a birth weight below 2500 g, while 31 (9.9%) of the infants born to non-adolescent mothers had a birth weight below 2500 g (p=0.01). 18 (2.7%) of the babies born to adolescent mothers had a birth weight below 1500 g, while 5 (9.9%) of the infants born to non-adolescent mothers had a birth weight below 1500 g (p=0.281).

There were no congenital anomalies of any system among 614 (92.2%) of the infants born to adolescent mothers, and 270 (86.3%) of the infants born to non-adolescent mothers, however the genitourinary and central nervous system anomalies were significantly higher in the babies of the non-adolescent group (p=0.01 and p=0.03, respectively). Demographic characteristics of newborns born to adolescent and non-adolescent mothers are given in Table 2.

Four hundred and twent one (63.2%) of babies born to adolescent mother had no any problem while 242 (77.3%) of the babies born to non-adolescent pregnants were all well during neonatal period. Early neonatal morbidities are summarized in Table 3. Among the morbidities resulted with hospitalization; meconium aspiration syndrome (MAS), respiratory distress syndrome, and hypogylycemia were significantly higher in the adolescent group compared to the non-adolescent group. The rate of resuscitation was 12.5% (n=83) in babies born to adolescent mother whereas 9.3% (n=29) in babies born to non-adolescent mothers (p=0.143).

Outcomes of Newborns Admitted to Hospital

In adolescent group, one hundred and twelve of six hundred and sixty six (17%) babies were hospitalized in the neonatal period however only fourty of three hundred and thirteen (13%) babies were hospitalized in the non-adolescent mothers (p=0.104). The reasons of hospitalization of babies admitted to neonatal intensive care unit are given in Table 4. Hospitalization due to MAS was significantly higher in the babies born to adolescent mothers. Among the hospitalized babies; twenty-nine (25.9%) of 112 babies born to adolescent mothers were premature while 9 (22.5%) babies were premature in non-adolescent mothers (p=0.671). And 13 (11%) babies in the adolescent group and 3 (7%) babies in the control group had no any congenital malformation (p=0.962). While the hospitalized infants born to adolescent mother had an

Table 3. Neonatal morbidities in newborns born to adolescent and non-adolescent pregnants

	Adolescent pregnants' babies (n=666)	Non-adolescent pregnants' babies (n=313)	OR (95% CI)	p
Respiratory problems	74 (11.1%)	14 (4.5%)	0.375 (0.208-0.674)	0.001
MAS	52 (7.8%)	9 (2.9%)	0.350 (0.170-0.719)	0.003
Hypoglycemia	44 (6.6%)	10 (3.2%)	0.467 (0.232-0.940)	0.029
Rh incompatibility	34 (5.1%)	23 (7.3%)	1.474 (0.853-2.548)	0.162
IUGR	17 (2.6%)	8 (2.6%)	1.001 (0.427-2.346)	0.998
Polycythemia	8 (1.2%)	3 (1%)	0.796 (0.210-3.021)	0.737
Hyperbilirubinemia	8 (1.2%)	2 (0.6%)	0.529 (0.112-2.505)	0.415

MAS: Meconium aspiration syndrome, IUGR: Intrauterine growth retardation

Table 4. Reasons of hospitalization and morbidities of babies admitted to the neonatal intensive care unit

	Adolescent pregnants' babies (n=112)	Non-adolescent pregnants' babies (n=40)	p
Hypogylcemia	12 (10.7%)	2 (5%)	0.232
TTN	20 (17.9%)	6 (15%)	0.680
MAS	10 (8.9%)	0	0.042
Hyperbilirubinemia	44 (39.3%)	14 (35%)	0.632
Septicemia	27 (24.1%)	15 (37.5%)	0.104
Respiratory Distress Syndrome	12 (10.7%)	4 (10%)	0.583
Bronchopulmonary Dysplasia	3 (2.7%)	1 (2.5%)	0.717
Retinopathy of Prematurity	5 (4.5%)	2 (5%)	0.592
Necrotizing Enterocolitis	2 (1.8%)	1 (2.5)	0.603
Intraventricular hemorrage	5 (4.5%)	2 (5%)	0.592

TTN: Transient tachypnea of newborn, MAS: Meconium aspiration syndrome

average of 9.1 days, the mean hospitalization period of the infants was 8.2 days in the non-adolescent mothers. (p=0.707). When the level of hospitalization was evaluated; 80 (71.4%) of the babies born to adolescent mothers were in the first level, 18 (16.1%) were in the second level and 14 (12.5%) were in the third level intensive care unit whereas 28 (70%) of the babies born to non-adolescent mothers were in the first level, 6 (15%) were in the second level and 6 (15%) were in the third level intensive care unit. There was no significant difference between the groups in terms of hospitalization level (p=0.919). Twelve(10.7%) of the hospitalized babies born to adolescent mothers needed mechanical ventilation support while 4 (10%) of the infants were needed for the mechanical ventilation support in the control group. While the infants born to adolescent mothers who connected to the ventilator needed an average of 8.1±9.2 days of ventilator support during their hospitalization, it was observed that in, the infants born to non-adolescent mothers spent 14.2±8.0 days of ventilator support (p=0.261). While 27 (24.1%) of the hospitalized adolescent mothers needed total parenteral nutrition support for 10.5 days during the hospitalization period, 9 (22.5%) of their babies needed an average of 10.3 days during their hospitalization. 27 (24.1%) of the infants born to adolescent mother were fed with total parenteral nutrition t for 10.5 days while 9 (22.5%) of the babies born to non-adolescent mothers needed an average of 10.3 days of total parenteral nutrion during hospitalization (p=0.949).

Three (2.7%) infants who were hospitalized in the adolescent group and two (5%) of the infants born to non-adolescent mothers died during hospitalization. Mortality rate among hospitalized infants born to non-adolescent mothers was significantly higher (p=0.002).

Discussion

We evaluated the outcomes of babies born to adolescent mother who gave birth in our hospital which is one of the important tertiary referral hospital in our country. Babies born to adolescent mother had worse fetal outcome during antenatal period, despite the results of those hospitalized babies in the first 28-day period were similar compared to babies born to non-adolescent mothers. Although there are studies examining the results of adolescent pregnancies in our country, our study is the first study that compared the babies born to adolescent pregnant with the non-adolescent pregnants who were hospitalized in the neonatal period.

Adolescent pregnancy is usually an unintended pregnancy mostly seen among women who have an unsteady lifesytle and were unmarried in the western countries. In our country, adolescent pregnancy is usually seen as a result of early marriage especially in low socio-economic groups. However, these pregnancies are mostly intended and planned according to the expectations of the families of the parents. In our study, the rate of extramarital pregnancy in adolescents was 5.5% and was significantly higher than non-adolescent pregnants. However, this rate was found to be lower compared to other studies (5-7). According to the World Health Organization, low level of education and living in rural areas increase the incidence

of adolescent pregnancy and childbirth. In our study, the educational level of adolescent pregnant women was significantly lower (p<0.001) compared to adult pregnant women. Similarly, there are studies reporting low education level in the adolescent pregnant women in the literature (6,8). A large proportion of pregnant women in our country were married and have a regular daily life. Drug use or alcoholic beverage consumption were almost never present.

Gestational week and birth weight are important in neonatal morbidity and mortality. In our study, there was no difference in the rate of preterm birth in adolescent and adult group. The findings of Suparp Thaitha and Thato (9), Raatikain et al. (10) and Chen et al. (5) were in agreement with our study. However, in many other studies; the rates of preterm delivery were found to be higher in the adolescent pregnants compared to the non-adolescent pregnants (6-8,11-13). In our country, according to the Demographic and Health Survey of Turkey; the rate of low birth weight babies was found to be 12.2% in born to mother <20 year, 11.9% in born to mother between 20-34 years, and 11.8% in born to mother between 35-49 years (14). In the present study, birth weights of infants born to adolescent mothers were found to be significantly lower compared to infants born to adult mothers. In another study conducted in our hospital, Sultan Kavuncuoğlu et al. (15) reported the ratio of low birthweight as 9%. There are several studies reporting similar results to our study (7,10,12,13). However, some of the studies reported no significant difference between the groups (5,9). Similar to the study conducted by Shrim et al. (13) in our study, the rate of low APGAR scores (1st minute) was found to be significantly higher in the adolescent pregnants compared to the non-adolescent pregnants. Chen et al. (5) and Kongnyuy et al. (6) reported lower 5th minute APGAR scores in the babies of adolescent mothers compared to those of the non-adolescent mothers However, Thaithae and Thato (9), Rasheed et al. (10) and Rahheed et al. (8) showed no statistically significant difference in terms of 1st and 5th minute APGAR scores between the adolescent and the non-adolescent pregnants.

In our study, hospitalization rates and average hospitalization day among newborns did not differ between the groups (p=0.104 and p=0.707). There are varying findings in the literature. Rasheed et al. (10), found no significant difference among hospitalization rates while Shrum et al. (13) and Rasheed et al. (9) reported higher hospitalization rates in the adolescent group (p<0.001 and p<0.01, respectively).

There were some limitations of the study. Our study was designed as single center and retrospective. And also this study reported the short duration of follow-up to identify morbidities and mortality, as some outcomes may take a longer duration to develop. The findings from our study hopefully lend itself to form a template for further and prospective, multicentre clinical study.

Conclusion

Our results showed that 1st minute Apgar scores and birth weight, height and head circumference were lower and cesarean delivery rate, early neonatal morbidities (respiratory distress, MAS, hypoglycemia) and hospitalization rates were higher in the newborns born to the adolescent mothers compared to the non-adolescent mothers. Prematurity rate was similar in both groups, and among hospitalized patients, there was no difference in the duration of hospitalization when the level of hospitalization and the etiologies were taken into account. Our study is the first comprehensive study including adolescent pregnants and outcomes of their babies in neonatal period. Also, there is still urgent need of multi-centered studies evaluating long-term outcomes and morbidities related to growth, development and neurodevelopmental prognosis of these infants.

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Authorship Contributions

Concept: B.C., Design: B.C., M.Ç., S.K., Data Collection or Processing: BC., Analysis or Interpretation: B.C., T.E.E., Z.E., M.Ç., S.K., Literature Search: B.C., Writing: B.C.

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Effectiveness of Algan Hemostatic Agent in Bleeding Control: An Experimental Kidney Incision Model

Algan Hemostatik Ajanın Kanama Kontrolündeki Etkinliği: Deneysel Bir Böbrek İnsizyon Modeli

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Abstract

Aim: The purpose of this study is to evaluate the hemostatic efficacy of a novel plant originated blood stopper which is called Algan Hemostatic Agent (AHA) in uncontrolled kidney incision bleeding model.

Methods: The study was conducted with thirty-two rats 5-7 weeks old. The rats were randomly divided into 4 groups, each consisting of eight rats (Group 1: heparinized saline, 2: heparinized AHA, 3: non-heparinized saline, 4: non-heparinized AHA). Experimental kidney incision was made, and saline soaked sponge was applied to the control group and AHA to the study group.

Results: The duration of bleeding was significantly shorter in the AHA group compared to the control group. The AHA has controlled the bleeding in the heparinized and non-heparinized groups 5±1.19 and 3±0.91 seconds respectively ($p<0.001$). In the control group, hemorrhage was controlled in the heparinized and non-heparinized group 180.6±25.4 and 125.4±21 seconds respectively.

Conclusion: This study demonstrated that the AHA is useful in controlling bleeding in the Rat kidney incision model.

Keywords: Algan hemostatic agent, hemostasis, rats, kidney, bleeding

Öz

Amaç: Çalışmanın amacı Algan kanama durdurucu ajanın böbrek insizyon rat modelinde etkinliğini araştırmaktır.

Yöntemler: Çalışma 5-7 haftalık otuz iki sıçan ile yapıldı. Sıçanlar rastgele her biri sekiz sıçandan oluşan 4 gruba ayrıldı (Grup 1: heparinize salin, 2: heparinize AHA, 3: non-heparinize salin, 4: non-heparinize AHA). Deneysel böbrek insizyonu yapıldı ve kontrol grubuna salin emdirilmiş spanç, çalışma grubuna AHA uygulandı.

Bulgular: AHA grubunda kanama süresi kontrol grubuna göre anlamlı olarak daha kısaydı. AHA, heparinize ve heparinize olmayan gruplarda kanamayı sırasıyla 5±1,19 ve 3±0,91 saniyede kontrol etmiştir. Kontrol grubunda heparinize ve heparinize olmayan grupta kanama sırasıyla 180,6±25,4 ve 125,4±21 saniyede kontrol edildi.

Sonuç: Bu çalışma, AHA'nın sıçan parsiyel nefrektomi modelinde kanamayı kontrol etmede faydalı olduğunu göstermiştir.

Anahtar Sözcükler: Algan hemostatik ajan, hemostaz, sıçan, böbrek, kanama

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Introduction

Bleeding is one of the major complications of partial nephrectomy and there are some difficulties in providing homeostasis in surgical procedures. For this reason, many new techniques, tools and agents have been used in recent years to control bleeding in renal surgery during partial nephrectomy (1,2).

The Algan Hemostatic Agent (AHA) is an herbal polysacrid-based extract derived from the standardized blend of six different plants (3,4). Each of the plants that form AHA has a content which is effective in hemostasis by alone or in combination (5). AHA contains tannins, phenolic components, polysaccharide. It has been determined that the AHA contains 57% polysaccharides. In addition, the phenolic content of 50 mg AHA sample was found to be equivalent to 3.015 mg GAE/g (gallic acid). There are polysaccharide-based hemostats on the market. However, phenolic compounds have not been previously tested in bleeding control. This study is the first study in the control of bleeding in the kidney incision model of AHA in rats.

All biocompatibility tests such as sensitization, cytotoxicity and irritation and hemodynamic tests of the AHA were performed, and the results supported its safety and efficacy as a hemostatic agent. It was shown that AHA did not cause more damage on rat liver tissue than in the control in the hepatectomy, liver laceration skin wound models (6-8).

AHA is easily applied locally. Further, it has a low cost, and does not require special storage. When AHA used in moist environment, it quickly polymerizes into a thin elastic film which has high tensile strength and firmly adheres to the anatomy of the tissue on which it is applied. Today, there are many products used in bleeding control, and a product that can effectively control bleeding has not been produced yet (9,10). The purpose of this study is to assess the hemostatic efficacy of the AHA kidney incision model.

Methods

This study was approved by the Institutional Animal Experiments Local Ethics Committee of Kırıkkale University (number, 2018/07). All animal studies conformed to the animal experiment guidelines of the Committee for Humane Care. All animals received care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the US National Academy of Sciences and published by the US National Institute of Health (NIH Publications, No: 80-23).

In the literature, the kidney incision method has not been used, but in this study, the effectiveness was evaluated according to the partial nephrectomy model (11). Thirty-two 180-210 gram 5-7-week-old Sprague Dawley rats were included in this study. Rats were fed ad libitum and examined under standard laboratory conditions according to a 12-hour dark-light period. The rats were randomly divided into 2 groups as heparinized and non-heparinized; each of the group has 16 rats. The rats were then randomly selected and divided into 4 groups of 8 rats in each group. Dose of 640 IU/kg heparin was administered intraperitoneal to heparinized group three times a day for 3 days. The same amount of saline was given to the other group. The groups were formed as follows. 1st group (Heparinized control group), 2nd group (Heparinized AHA liquid group), 3rd group (Non-Heparinized control group), 4th group (Non-Heparinized AHA liquid group. Procedures were performed under general anesthesia with ketamine hydrochloride (100 mg/kg) and xylazine hydrochloride (10 mg/kg).

Rat Kidney Incision Model

All operations will be performed under anesthesia. The renal artery and venous hilum were determined by vascular dissection for each rat. The renal artery and vein were not compressed with a vascular clamp. Deep incision was made in the lower third of the left kidneys with an amputation knife, and then AHA and saline were applied to the groups.

Partial nephrectomy models have been used in the literature. In this study, we used the kidney incision method. Considering the difficulty of applying AHA in partial nephrectomy, we made an incision. In this way, more contact with the bleeding surfaces in the area where AHA was applied was provided.

Bleeding Test

The kidneys of rats were surgically exposed and, the left kidney was resected from the lower pit (Figures 1, 2).

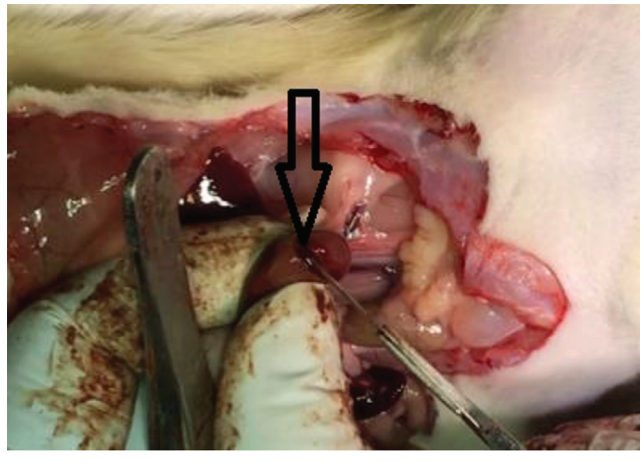

Figure 1. Application of kidney incision

Immediately after the bleeding started, the first blood was cleaned with a dry sponge and the area was treated with 2 cc volumes of AHA liquid and 2 cc saline. AHA liquid and saline were applied on the bleeding surface. Bleeding time was measured by chronometer. After stopping the bleeding (at the earliest 10 minutes after the end of the experiment) rats were euthanized by high intra-abdominal bleeding.

Statistical Analysis

SPSS software version 22.0 (SPSS Inc., Chicago, IL) was used to analyze the data of this study. Weights, bleeding time was calculated and was compared among the four groups using analysis of variance (ANOVA). When differences were found, the difference group was determined by Duncan's multiple range tests. The results were assessed at a 95% confidence interval and a significance level of $p<0.05$.

Results

There was no difference in body weight between the groups. The duration of bleeding in the control group was longer than in the experimental groups.

The AHA liquid form has controlled the bleeding in the heparinized and non-heparinized groups 5±1.19 and 3±0.91 seconds respectively. In the control group, hemorrhage was controlled in the heparinized group at 180.6± 25.4 and in the non-heparinized group at 125.4± 21 seconds. There was a statistically significant difference in bleeding control efficacy of the AHA compared to the control group (Table 1). AHA contributes to bleeding control by creating a mechanical barrier where it is applied (Figure 3).

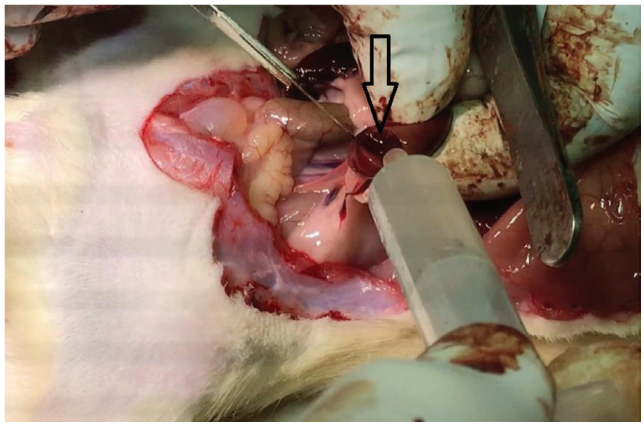

Figure 2. Application of the AHA liquid form
AHA: American Hispital Association

Discussion

AHA had rapidly controlled bleeding in the kidney incision bleeding model. AHA liquid form stopped the bleeding in the first application both the heparin and non-heparinized group.

There was a statistically significant difference in the bleeding control efficacy of the AHA compared to the control group. These results have shown that AHA is a highly effective product in controlling bleeding.

Today, many hemostatic agents are used for internal and external bleeding control (9-17). In addition, cyanoacrylates are used safely in many clinical urology fields (18).

Traditionally, some plants are known to be used as bleeding arrestors. The mechanism of hemostatic action of these plants is based more on the astringency nature of the more common type of polyphenolic phytochemicals. Astringent, any of a group of substances that cause the contraction or shrinkage of tissues and that dry up secretions. However, some hemostatic plants have been shown to shorten the coagulation time and increase the coagulation of platelets in the area of bleeding, reducing the risk of infection and inflammation that can lead to infiltration and damage to vessels (19).

There are a lot of literature studies about AHA content plants (5). It has been shown that Polyphenolic-polysaccharide conjugates in the combination of Achillea millefolium and some Asteraceae plants have protective effects against oxidative damage on blood platelet proteins (20). Juglans regia L. contains tannin and leaves

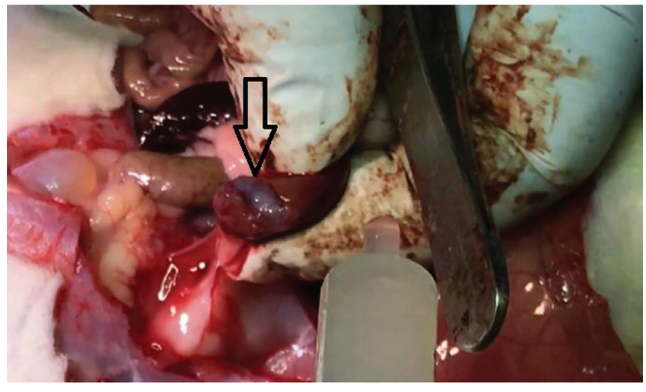

Figure 3. Barrier formation of the AHA application

Table 1. Mean bleeding time, body weight distribution of the groups.

	Group 1 (Heparinized Control)	Group 2 (Heparinized *AHA*)	Group 3 (Non-Heparinized Control)	Group 4 (Non-Heparinized AHA)	p
Weight (grams)	190.6±5.5	189.5±7.3	175.6±10.5	182.4±7.5	p=0.94
Bleeding time (sec.)	180.6±25.4 sec.	5±1.19 sec.	125.4±21.2 sec.	3±0.91 sec.	p<0.001

are used as astringent in external bleeds. Tannins cross-link with damaged cells to accelerate healing (21).

Rubus coreanus in the AHA formulation has anti-aggressive activity. This plant can also play a role in preventing the formation of platelets by common organic acids, resulting in systemic clogging of vessels due to excessive clotting (22,23). Rubus coreanus in the AHA has antithrombotic activity and is important for the prevention of systemic thrombotic effect against the possibility of systemic circulation of AHA after topical application. It shows the AHA effect locally by creating a physical barrier. The blood outside the vein forms a physical barrier by forming a polymeric network after the AHA is in contact with the fluid (5,6). The blood clotted in this polymeric network rapidly solidifies with the clotting enhancing effect of AHA and the physical effect soon becomes a permanent barrier. In the event of possible systemic circulation, the systemic aggravating effect is eliminated by the anti-agonist effect of Rubus coreanus.

Viscum album L. Leaves of the plant (Herba Visci albi) are used for internal bleeds and many purposes. No adverse effects were observed in acute, subchronic and genotoxicity tests (24).

The amount of tannin from Vitis vinifera L. leaves is high and infusion (5%) is used as an astringent and blood-blocker; fresh leaves are used externally as wound healers (25).

AHA was obtained by brewing from a standard mixture of six different plants. AHA biocompatibility tests were conducted and converted into the final product. AHA is produced in many forms such as liquid, powder and sponge (3,4,6,7,26).

However, AHA has an easy-to-apply feature, as well as an advantage over other products in terms of hemostasis in a much shorter time.

There are few studies in the literature investigating the efficacy of hemostatic agents in the nephrectomy model. In one study, Glubran2®, FloSeal®, and Celox™ were compared in rats with partial nephrectomy hemostatic efficacy (12). In this study hemostasis time was found to be 32, 40, 55 seconds.

In another study, after partial nephrectomy, the mean bleeding time with BloodSTOP iX and Surgicel treatment was found 83.70±13.73 seconds and 168.8±19.41 seconds, respectively (27).

In another study, it was shown that local hemostatic agent shortens the nephrectomy time (28). All the forms of the AHA differ greatly from these results. Because of the many factors such as animal weight, the experience of the practitioner, technical differences, vessel variations, laboratory conditions, etc., this comparison needs to be compared with other products in the same experiment to assess bleeding effectiveness of other bleeding arrestors.

Limitations of the Study

A limitation of this study is that only the acute stage effects of the AHA are assessed.

The fact that histopathological effects have not been investigated is a cause of limitation. The difference in the amount of bleeding between rats is one of the other limitations of this study.

In addition, the method used in this study is not a standard method used in the literature and may need to be improved.

Conclusion

This study has shown that AHA is a candidate for use as an effective product in hemostasis in nephrectomy operations. According to the results of this study, although AHA is the effective hemostatic agent available in the kidney incision bleeding, the actual difference can only be demonstrated by comparative studies. This situation will be clearer with future work.

The advantages of AHA when compared with other products that are readily available include effectiveness, ease of application.

Authorship Contributions

Concept: A.M., A.K., H.E., Design: A.M., A.K., H.E., Data Collection or Processing: A.M., A.K., H.E., Y.K., Analysis or Interpretation: A.M., Y.K., R.Ö., Literature Search: A.M., Y.K., R.Ö., Writing: A.M., Y.K., R.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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İnterstisyel Akciğer Hastalıkları Tanısında Videotorakoskopiden Beklenmedik Torakotomiye Dönüş Başarısızlık mıdır?

Is it a Failure From Videothoracoscopy Convert to an Unexpected Thoracotomy in Interstitial Lung Disease Diagnosis?

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Öz

Amaç: Bizim bu çalışmadaki amacımız, kliniğimizde interstisyel akciğer hastalıkları nedeniyle tanısal video yardımlı toraks cerrahisi (VATS) yapılan hastalar ile torakoskopik başlayıp torakotomiye dönülen hastaların preoperatif risk faktörlerinin değerlendirilmesi ve komplikasyonlarının karşılaştırılmasıdır.

Yöntemler: Kliniğimizde Ocak 2010 ile Aralık 2019 tarihleri arasında, interstisyel akciğer hastalığı nedeniyle VATS yapılan hastalar çalışmaya alındı. Çalışmada hastalar 2 grup altında değerlendirilmiştir. VATS ile wedge (Grup-V) yapılan 159 hasta, VATS ile başlanıp intraoperatif beklenmedik komplikasyonlar nedeniyle torakotomiye dönülen (Grup-T) 29 hasta bulunmaktadır.

Bulgular: VATS ve torakotomi grupları arasında tüberküloz öyküsü dışında demografik özellikler açısından anlamlı fark saptanmadı. Postoperatif en sık saptanan patoloji unusual interstisyel pnömoni (n=56, %28) idi. On yedi hastada (%9) komplikasyon izlendi. Beş hastada uzamış hava kaçağı, 3 hastada postoperatif dren çekilmesi sonrasında pnömotoraks, 3 hastada revizyon gerektiren yara yeri enfeksiyonu, 6 hastada non-invaziv mekanik ventilasyon ihtiyacı gerektiren solunum yetersizliği gelişmiştir. 5 hastada (%2,7) postoperatif ilk 30 günde mortalite meydana gelmiştir. VATS'dan torakotomiye dönüş, geçirilmiş tüberküloz öyküsü ve yaygın yapışıklıklar nedeniyle meydana geldi.

Sonuç: Videotorakoskopik cerrahide açığa dönmek her ne kadar başarısızlık olarak düşünülse de, postoperatif komplikasyon ve mortalite oranları VATS ile benzer olarak saptanmıştır. Torakotomiye dönmedeki başlıca risk faktörleri preoperatif toraks BT'de izlenen tüberküloz sekelleri ve peroperatif saptanan plevral yaygın yapışıklıklar olarak saptandı. Bu nedenle interstisyel akciğer hastalıklarında (İAH), VATS güvenilir ve uygulanabilir bir yöntemdir. Preoperatif dönemde dikkatli hasta seçimi ile açığa dönme olasılığının azalacağı düşüncesindeyiz.

Anahtar Sözcükler: İntertisyel Akciğer Hastalığı, torakotomiye dönüş, VATS

Abstract

Aim: In this study is to evaluate the preoperative risk factors and compare the complications of patients who underwent diagnostic VATS for interstitial lung diseases in our clinic and patients who started thoracoscopic and converted to thoracotomy.

Methods: Patients who underwent VATS due to interstitial lung disease between January 2010 and December 2019 in our clinic were included in the study. In the study, patients were evaluated under 2 groups. There are 159 patients who underwent VATS wedge (Group-V) and 29 patients who started with VATS and converted to thoracotomy (Group-T) due to unexpected intraoperative complications.

Results: There was no significant difference between VATS and thoracotomy groups in terms of demographic characteristics, except for a history of tuberculosis. The most common postoperative pathology was unusual interstitial pneumonia (n=56, 28%). Complications were observed in 17 patients (9%). Prolonged air leak in 5 patients, pneumothorax after postoperative drain removal in 3 patients, wound infection requiring revision in 3 patients, respiratory failure requiring non-invasive mechanical ventilation in 6 patients developed. Mortality occurred in 5 patients (2.7%) in the first 30 days postoperatively. Conversion from VATS to thoracotomy occurred due to a previous history of tuberculosis and widespread pleural adhesions.

Conclusion: Although revealing in videothoracoscopic surgery is considered to be a failure, postoperative complication and mortality rates were found to be similar to VATS. The main risk factor for conversion to thoracotomy is tuberculous sequelae observed in preoperative thoracic CT and perioperative pleural diffuse adhesions. Therefore, VATS is a reliable and applicable method in interstitial lung disease (ILD). We think that careful patient selection in the preoperative period will reduce the probability of the thoracotomy.

Keywords: Interstitial Lung Disease, conversion to thoracotomy, VATS

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Giriş

İnterstisyel akciğer hastalıkları (İAH), tedavi seçenekleri ve prognozda farklılıklar gösteren, heterojen bir akciğer parankim bozukluğudur. Bu nedenle ayırıcı tanıya ulaşmak oldukça önemlidir (1). Heterojen bir grup hastalık olması nedeniyle klinik ve radyolojik değerlendirmeler ile tanı konulması oldukça zordur. Görüntüleme yöntemleri ve solunum fonksiyon testleri sonucunda İAH'dan şüphe edilen hastalarda kesin tanıya ulaşabilmek için invaziv yöntemlere gereksinim duyulmaktadır. Cerrahi açık akciğer biyopsisi, diffüz interstisyel akciğer hastalığında detaylı tanı için önerilen altın standart yöntemdir. Videotorakoskopik yardımlı torasik cerrahisi (VATS) ise İAH tanısı koymada güvenilir ve etkili bir yöntemdir. VATS cerrahisinin açık cerrahi yaklaşıma oranla daha az ağrı, kısa yatış süresi, pulmoner fonksiyonların korunması ve daha az morbidite gelişmesi gibi avantajları bulunmaktadır (2,3). Ancak tüm bu avantajlarının yanında torakoskopik cerrahide eğitim sürecinde torakotomiye dönülme oranları da sık olarak izlenmektedir. Küçük insizyonlar ve kısıtlı kamera açıları nedeniyle torakoskopik cerrahide teknik zorluklar gelişebilmektedir. İAH'de torakoskopik yaklaşımdan torakotomiye dönüşüm ile ilgili çalışmalar literatürde çok sık rastlanmamakla birlikte, bu çalışmalarda torakotomiye dönme oranı %2,5-20 arasında değişmektedir (4-6).

Bizim bu çalışmadaki amacımız, kliniğimizde İAH nedeniyle tanısal VATS yapılan hastalar ile torakoskopik başlayıp torakotomiye dönülen hastaların preoperatif risk faktörlerinin değerlendirilmesi ve komplikasyonlarının karşılaştırılmasıdır.

Yöntemler

Çalışmaya kliniğimizde Ocak 2010 ile Aralık 2019 tarihleri arasında, interstisyel akciğer hastalığı nedeniyle VATS yapılan hastalar dahil edildi. Hastaların bilgileri, kliniğimizin prospektif olarak girilen veritabanından retrospektif olarak değerlendirildi. Çalışmada hastalar 2 grup altında değerlendirildi. Birinci grupta VATS ile wedge (Grup V) yapılan 159 hasta, 2. grupta ise VATS ile başlanıp intraoperatif beklenmedik komplikasyonlar nedeniyle torakotomiye dönülen (Grup T) 29 hasta bulunmaktadır. Videotorakoskopik olarak başlanan 183 hasta çalışmada değerlendirildi. Verilerine ulaşılamayan ve torakotomi yapılan hastalar çalışma dışı bırakılmıştır. Çalışmanın etik kurul onayı İstanbul Eğim ve Araştırma Hastanesi'nin lokal etik kurulundan (Karar No: 2379 Tarih :29/05/2020) alındı.

Preoperatif Değerlendirme

Çalışmadaki tüm hastalara preoperatif yüksek rezolüsyonlu bilgisayarlı toraks tomografisi (HRCT) istenmiştir. Hastalara rutin biyokimyasal testler ve solunum fonksiyon testleri yapıldı. Solunum fonksiyon testleri sınırda olan olgularda ise karbon monoksit difüzyon testi yapıldı. Kardiyak açıdan yüksek riskli ve 65 yaşın üzerindeki hastalar preoperatif kardiyoloji tarafından değerlendirilmiştir. Elektrokardiyogram ve ekokardiyografi ile hastaların kardiyak fonksiyonları değerlendirildi. Tüm hastalara preoperatif dönemde bronkoskopi ve bronkoalveoler lavaj (BAL) yapıldı. BAL tanı gelmeyen hastalar İnterstisyel Akciğer Hastalıkları Konseyi tarafından cerrahi biyopsi için yönlendirildi. Pulmoner arteryel basınç <40 mmHg olan hastalara tanısal cerrahi tedavi uygulandı. Komorbiditeleri değerlendirmek amacıyla Charlson komorbidite indeksi (CCI) kullanıldı (7).

Cerrahi Prosedür

Çift lümenli entübasyonu takiben lateral dekübit pozisyondan anterior aksiller hattın 8. interkostal aralık hizasından 10 mm'lik kamera portu açıldı. 30°, 10 mm torakoskop (Logic HD, Wolf, Knittlingen, Almanya) kamerası ile toraks içerisindeki patoloji, yapışıklıklar ve diyafragma seviyesi değerlendirildi. Ardından 5 cm'lik utility insizyonu latissimuss dorsi kasının anterior hizasından 4. veya 5. interkostal aralıktan açıldı. Plevral yapışıklıklar için ultrasonik enerji cihazıları kullanıldı (Harmonic, Etichon, USA). İki farklı lobdan (üst ve alt) wedge rezeksiyon uygulandı. Wedge rezeksiyon için endoskopik kapatma aletleri kullanıldı (endoGIA, Covidien plc, Norwalk, USA).

Planlanmamış açığa dönme, geçirilmiş tüberküloz ve yaygın yapışıklıklar nedenleriyle meydana geldi. VATS lobektomiden torakotomiye dönülen hastalarda utiliy kesisi posteriora uzatılarak yaklaşık 15-20 cm'lik kesi yapıldı. Standart açık teknik ile komplikasyonlar düzeltilerek operasyonlar tamamlandı.

Postoperatif Takip

Morbiditeler hastaların yatış süresince meydana gelen komplikasyonlar olarak kabul edildi. Morbiditeler pnömoni, solunum yetersizliği, deri altı amfizemi, atrial fibrilasyon, dren çekilmesi sonrasında pnömotoraks, uzamış hava kaçağı (>7 gün), yara yeri revizyonu gerektiren enfeksiyonlar, postoperatif hemoraji olarak kabul edildi.

Yatış süresince veya operasyonu takiben bir ay içerisinde meydana gelen ölümler mortalite olarak kabul edildi. İntraoperatif ölümler mortaliteye dahil edildi. Postoperatif patoloji sonucu ile hastaların medikal tedavileri göğüs hastalıkları tarafından verildi. Tanı konulamayan 3 hasta ise takibe alındı. Hastalarının dataları hastanın bilgi sisteminden retrospektif olarak taranarak elde edildi.

İstatistiksel Analiz

İstatistiksel analizler IBM SPSS Windows 22.0 kullanılarak yapıldı. Sayısal değişkenler ortalama±standart sapma ve medyan (min-maks) ile kategorik değişkenler ise sayı ve yüzde ile değerlendirildi. Gruplar sayısal değişkenler bakımından karşılaştırılmadan önce parametrik test varsayımları (normallik ve varyansların homojenliği)

kontrol edildi. Gruplar arasında fark olup olmadığı bağımlı gruplarda t testi ile incelendi. Kategorik değerler Fisher'in kesin testi ile analiz edildi. Sürekli değişkenlerin karşılaştırılmasında Mann-Whitney U testi kullanıldı. Çalışmada anlamlılık düzeyi p<0,05 olarak alındı.

Bulgular

Yüz seksen sekiz hastanın 98'i erkek (%52,1), 90'ı kadın cinsiyette (%47,9) idi. Hastaların ortalama yaşı 52,87±13,05 (aralık: 16-79) yıl idi. Seksen bir hastanın (%43,1) sigara öyküsü mevcuttu. Ortalama 36,98±55,78 paket/yıl sigara öyküsü mevcuttu. Hastaların ortalama FEV1 değeri 1,95±0,76L, FVC değeri ise 2,31±0.87 L idi. CCI "0"skoru olan 93 hasta (%49,5),"1"skoru olan 59 hasta (%31,4),"2"skoru olan 21 hasta (%11,2),"3"skoru olan 11 hasta (%5,9),"4"skoru olan 3 hasta (%1,6) ve 5 skoru olan 1 hasta (%0,5) mevcuttu. Hastaların 159'una (%84,6) VATS ile operasyon yapılırken, 29 hastaya (%15,4) torakotomi ile operasyon yapıldı. Yüz elli iki hastada (%80,9) sağ taraftan işlem yapılırken, 36'sına (%19,1) sol taraftan tanısal işlem yapıldı. VATS ve torakotomi grupları arasında tüberküloz öyküsü dışında demografik özellikler açısından anlamlı fark saptanmadı. Grup T'de intraoperatif cerrahi süresi 76,67±9,77 dk iken, Grup V'de cerrahi süresi 33,70±11,52 dk idi. İki grup arasında istatistiksel anlamlı fark vardı (p<0,001). Tablo 1'de gruplara göre demografik özelliklerin karşılaştırması yer almaktadır. Postoperatif en sık saptanan patoloji "unusual" interstisyel pnömoni (n=56, %28) olarak saptandı. VATS ile wedge rezeksiyon yapılan 3 hastada postoperatif tanı saptanmadı. Üç hastada "destroyed" akciğer dokusu olarak raporlandı. Bu hastalara postoperatif interstisyel konsey tarafından takip önerildi. Tablo 2'de hastaların postoperatif kesin tanıları yer almaktadır.

On yedi hastada (%9) komplikasyon izlendi. Beş hastada uzamış hava kaçağı, 3 hastada postoperatif dren çekilmesi sonrasında pnömotoraks, 3 hastada revizyon gerektiren yara yeri enfeksiyonu, 6 hastada non-invaziv mekanik ventilasyon ihtiyacı gerektiren solunum yetersizliği gelişti. Bu hastaların 3'ünde pnömoni meydana geldi. Bir hastada revizyon gerektiren hemoraji, 1 hastada spontan regresyon gösteren deri altı amfizemi, 1 hastada atrial fibrilasyon saptandı. Uzamış hava kaçağı gelişen hastaların 2'si spontan olarak düzelirken, 3 hastada kan plöredezis uygulama sonrasında düzelme oldu. Tablo 3'de komplikasyonlara etki eden prognostik faktörler saptandı.

Beş hastada (%2,7) postoperatif ilk 30 günde mortalite meydana geldi. İntraoperatif mortalite saptanmadı. Bu hastaların 3'üne postoperatif erken dönemde solunum yetersizliği sonrasında entübasyon gerekti. Entübasyon gereken bu 3 hasta postoperatif pnömoni gelişmesi nedeniyle ex oldu. Bir hasta taburculuk sonrası 10. günde miyokard infarktüsü nedeniyle, vaskülit tanısı alan 1 hasta da postoperatif 3. haftada masif hemoptizi sonrasında ex oldu. Torakotomi yapılan 1 hastada (%3,4) ve VATS yapılan 4 hastada (%2,5) mortalite gelişti (p=0,774).

Tartışma

İAH tanısı genellikle HRCT, klinik muayeneler ve histopatolojik doku tanısı yardımıyla gerçekleştirilmektedir.

Tablo 1. Gruplara göre demografik özelliklerin karşılaştırılması

Değişkenler		Grup T		Grup V		p-Değeri
		n	%	n	%	
Yaş (Yıl) Ort ± SS		51,21±12,27		53,18±13,20		0,306
Yaş	<65	27	93,1	132	83,0	0,167
	>65	2	6,9	27	17,0	
Cinsiyet	Erkek	13	44,8	85	53,5	0,392
	Kadın	16	55,2	74	46,5	
Sigara	Yok	18	62,1	89	56,0	0,542
	Var	11	37,9	70	44,0	
CCI	0	11	37,9	82	51,6	0,177
	>1	18	62,1	77	48,4	
Taraf	Sağ	24	82,8	128	80,5	0,776
	Sol	5	17,2	31	19,5	
Geçirilmiş Tbc Öyküsü	Yok	22	75,9	147	92,5	<0,014
	Var	7	24,1	12	7,5	
Tanı	Yok	0	0,0	4	2,5	0,388
	Var	29	100,0	155	97,5	
Dren Kalış Süresi		3,00±2,09		2,40±1,48		0,072
Yatış Süresi		4,51±3,61		3,55±2,01		0,077

CCI: Charlson Komorbidite indeksi, SS: Standart sapma, Tbc: tüberküloz

Tablo 2. Hastaların postoperatif kesin tanıları

Değişkenler	Grup T	Grup V	Total
	n	n	%
Alveolar proteinozis	0	1	0,5
Amfizem	1	4	2,7
Bal paterni	2	5	3,7
Bronşiolit	0	15	8,0
Eozinofilik pnömoni	0	2	1,1
Hipersensitivite pnomonisi	0	31	16,4
Histiyositozis x	1	3	2,1
İnterstisyel fibrozis	5	16	11,2
Lenfanjiyoleimiyomatozis	0	2	1,1
Nekrotizan granülomatöz enflamasyon	4	3	3,7
Nonnekrotizan granülomatöz enflamasyon	1	11	6,4
Organiza pnömoni	0	10	5,3
Tip 2 pnömosit proliferasyonu	0	9	4,8
Usual interstisyel pnömoni	15	42	30,3
Wegener vasküliti	1	1	1,1

Tablo 3. Komplikasyonlara etki eden prognostik faktörlerin değerlendirilmesi

Değişkenler n		Komplikasyon Yok		Komplikasyon Var		p-Değeri
		%	n	%		
Yaş (Yıl) Ort ± SS		53,09±13,08		50,71±12,84		0,316
Yaş	<65	144	84,5	15	88,2	0,661
	>65	27	15,8	2	11,8	
Cinsiyet	Erkek	87	50,9	11	64,7	0,278
	Kadın	84	49,1	6	35,3	
Sigara	Yok	97	56,7	10	58,8	0,868
	Var	74	43,3	7	41,2	
Tüberküloz öyküsü	Yok	153	89,5	16	94,1	0,545
	Var	18	10,5	1	5,9	
CCI	0	84	49,1	9	52,9	0,774
	>1	87	50,9	8	47,1	
Taraf	Sağ	140	18,1	12	70,6	0,259
	Sol	31	18,1	5	29,4	
Rezeksiyon	Grup T	25	14,6	4	23,5	0,332
	Grup V	146	85,4	13	76,5	

CCI: Charlson Komorbidite indeksi, SS: Standart sapma

Cerrahi biyopsi ile tanı alan hastalara en iyi tedavi seçenekleri sunulmaktadır. VATS ile açığa dönme oranları genel olarak literatürde %1-20 arasında değişmektedir (6,8,9). Özellikle gelişmekte olan ve sosyoekonomik düzeyi düşük ülkelerde geçirilen yaygın enfeksiyonlar, yanlış antibiyotik kullanımı ve sağlık hizmetine ulaşımdaki sorunlar nedeniyle hastalarda yaygın yapışıklıklar izlenebilmektedir. Ülkemizdeki sosyoekonomik koşulların düşük olması tüberküloz prevalansının yüksek olması plevral yapışıklıkların fazla olmasına neden olmaktadır (6,10,11). VATS günümüzde yaygın olarak teröpatik ve tanısal operasyonlarda kullanılsa da, dar bir kesi alanından çalışılma zorluğu ve peroperatif saptanan yapışıklıklar nedeniyle ameliyatlarda beklenmeyen durumlar meydana gelmektedir.

Torakotomiye dönüş intraoperatif komplikasyonlar dışında, cerrahın deneyimi ve hastanın durumu ile ilişkilidir. Literatürde VATS lobektomi yapılan hastalarda torakotomiye dönüşte en sık nedenler arasında antrakotik lenf nodları, vasküler yaralanmalar sayılmaktadır (12-16). Gazala ve ark. (17) torakotomiye dönüş ile ilgili başlıca nedenleri şu şekilde sınıflandırmıştır. Vasküler yaralanmalar, anatomik nedenler, adezyonlar, lenf nodları ve teknik problemlerdir (stapler hatası ve ekipman sorunları). Mason ve ark. (14) ise preoperatif detaylı bir şekilde yapılan radyolojik değerlendirmelerin oluşabilecek komplikasyonları azaltabileceğini saptamıştır. Özellikle toraks BT'deki fibrotik, sekel değişikliklerin, fibrokalsifikasyonların önceden değerlendirilmesi, VATS komplikasyonlarını azaltacağını belirtmiştir. Bizim çalışmamızda da interstisyel akciğer hastalıklarında torakotomiye dönüş oranı %15,4 olarak saptandı. Özellikle de torakotomiye dönülen hastalarda tbc sekeli ve plevral yaygın yapışıklıklar daha fazla olarak izlendi.

Çalışmamızda torakotomiye dönülen hastalarda yatış süresi ve dren kalma süresi VATS ile kıyaslandığında istatistiksel olarak anlamlı fark saptandı. Ayrıca postoperatif gelişen komplikasyon oranları arasında istatistiksel fark saptanmadı (p>0,05). Postoperatif komplikasyon olarak solunum yetersizliğinin çalışmamızda daha fazla olmasının nedeninin İAH'da akciğer parankimindeki patolojik değişikliklere bağlı olarak gelişen uzamış hava kaçağı olduğunu düşünüyoruz.

Jagelavicius ve ark. (18) VATS ile yapılan ampiyem cerrahisi çalışmasında mortalite oranını %1,4 olarak saptamışlardır. Mortalite gelişmesinde özellikle postoperatif gelişen enfeksiyon sorumlu tutulmuştur. Marra ve ark. (19) ise plevral ampiyemlerde enfeksiyona bağlı mortalite saptamamıştır. Sawada ve ark.'nın (20) çalışmasında VATS lobektomi yapılan ve torakotomiye dönülen hastalarda intraoperatif mortalite ve mortal bir komplikasyon saptamamıştır. Bizim çalışmamızda ise mortalite nedeni olarak komplikasyonlara bağlı gelişen solunum yetersizliği saptandı.

Çalışmanın Kısıtlılıkları

Çalışmanın retrospektif olması, hastaların preoperatif performans durumlarının değerlendirilememiş olması, birden fazla cerrah tarafından operasyonların gerçekleştirilmesi ve deneyimlerinin farklı olması başlıca kısıtlılıklardandır.

Sonuç

Videotorakoskopik cerrahide açığa dönmek her ne kadar başarsızlık olarak düşünülse de, postoperatif komplikasyon ve mortalite oranları VATS ile benzer olarak saptanmıştır. Torakotomiye dönüşteki başlıca risk faktörleri preoperatif toraks BT'de izlenen tüberküloz sekelleri ve peroperatif saptanan yaygın yapışıklıklardır. Bu nedenle İAH'da VATS güvenilir ve uygulanabilir bir yöntemdir. Preoperatif dönemde dikkatli hasta seçiminin, açığa dönme olasılığını azaltacağı düşüncesindeyiz.

Yazarlık Katkıları

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Chronotype and Sleep Quality Assessment of Patients with Polycystic Ovary Syndrome

Polikistik Over Sendromu Olan Hastalarda Kronotip ve Uyku Kalitesi Değerlendirmesi

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Abstract

Aim: Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder among women during the reproductive ages. The purpose of this study was to investigate the chronotype and sleep quality of PCOS patients.

Methods: Volunteering nulliparous participants who were diagnosed with PCOS and a convenience sample of healthy controls without accompanying chronic medical conditions who presented to the Bezmialem University gynecology outpatient clinic were enrolled in the study. Participants were asked to fill out the Turkish versions of Morningness Eveningness Questionnaire (MEQ) and Pittsburgh Sleep Quality index Questionnaire (PSQIQ).

Results: There were 111 participants in the PCOS group and 108 participants in the healthy control group. Both groups were similar in age (p=0.24) and body mass index (p=0.9). The prevalance of hirsutism (mFG ≥8) was 33.3% among PCOS patients. Subjective sleep quality (<0.001), sleep latency (<0.001), habitual sleep efficiency (0.003), utilization of sleep medication (0.03) and daytime dysfunction (<0.001) scores were significantly different between the groups. In the PCOS group, MEQ score was inversely correlated with the mFG score and fT levels. There was a negative correlation between MEQ-mFG (r=-0.59, p<0.001).

Conclusion: PCOS patients were more prone to eveningness chronotype and had worse sleep quality compared to controls. Furthermore PCOS patients with hirsutism were more evening oriented and had more difficulty falling asleep compared to those without hyperandrogenism.

Keywords: PCOS, sleep, chronotype, hirsutism, PSQIQ, MEQ

Öz

Amaç: Polikistik Over Sendromu (PKOS) reprodüktif çağdaki kadınlarda en sık izlenen endokrin problemdir. Bu çalışmamızdaki amacımız PKOS hastalarının kronotipini belirlemek ve uyku kalitelerini değerlendirmektir.

Yöntemler: Daha önce doğum yapmamış PKOS hastaları ve herhangi bir kronik sağlık problemi bulunmayan Bezmialem Üniversitesi jinekoloji polikliniğine başvuran gönüllü erişkinler çalışmaya dahil edilmişlerdir. Çalışmaya dahil edilenlerden Türkçe validasyonu olan Sabahçıl Akşamcıl (MEQ) ve Pittsburgh Uyku Kalitesi indeksi (PSQIQ) ölçeklerini doldurmaları istenmiştir.

Bulgular: PKOS grubunda 111, kontrol grubunda 108 gönüllü yer almıştır.Her iki grup da yaş (p=0,24) ve vücut kitle indeksi (VKİ) (p=0.9) açısından benzerdi. PKOS hastaları arasında hirsutizm prevalansı (mFG>8) %33,3 idi. Subjektif uyku kalitesi (p<0,001), uykuya dalama süresi (p<0,001), alışılmış uyku etkinliği (p=0,003), uyku ilacı kullanımı (p=0,03) ve gündüz işlev bozukluğu (p<0,001) anlamlı olarak PCOS grubunda daha kötüydü. PKOS grubunda MEQ skoru mFG skoru ile negatif korelasyon MEQ-mFG (r=-0,59, p<0,001) gösteriyordu.

Sonuç: PKOS kontrol grubu ile karşılaştırıldığında akşamcıl kronotipe daha yatkındılar. Hirsutizm mevcut olan PKOS hastaları ise hirsutizm olmayan hastalara göre daha fazla akşamcıl kronotipe sahipti ve uykuya dalma konusunda daha fazla problem yaşıyordu.

Anahtar Sözcükler: PKOS, uyku, kronotip, hirsutizm, PSQIQ, MEQ

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Introduction

Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder among women during the reproductive ages. Epidemiological investigations have shown that 6-8% of women are affected by PCOS (1). The disorder is defined by polycystic ovaries on ultrasound examination, clinical and/or biochemical hyperandrogenemia, oligomenorrhea and/or amenorrhea (2). The diagnosis of PCOS has long-lasting associations including obesity, metabolic syndrome, diabetes mellitus and increased risk of endometrial carcinoma (3,4).

The timing of physiological functions, such as core body temperature, hormone secretion, and wake onset, differs between individuals. Based on these individual differences, humans can be classified as the earlier-timed morning types, the intermediate types or the later-timed evening types (5-7). Several studies have demonstrated that circadian preference towards eveningness is associated with an unhealthy lifestyle, including an unhealthy diet, various health problems, and psychopathology (8). We also have recently demonstrated that in pregnancy evening-types were significantly greater compared to morning-types in high risk pregnancies such as preterm birth and preeclampsia (9).

Sleep quality is associated with general well being (10) and metabolic syndrome (11,12). Sleep deprivation as well as prolonged sleep, or long-term circadian misalignment between the sleep-wake cycle and circadian rhythms, alter the hormonal regulation and metabolism (13,14). Sleep disturbances in PCOS patients have been examined before. Most of the literature until now focuses on increased prevalance of sleep apnea among PCOS patients (15-17). The purpose of our study was to investigate the chronotype and sleep quality of PCOS patients.

Methods

This study was conducted at Bezmialem University Hospital. Institutional review board approval was attained (Number: 11/213/2019).

Partipant Selection

Volunteering nulliparous participants who were diagnosed with PCOS and a convenience sample of healthy controls without accompanying chronic medical conditions who presented to the Bezmialem University gynecology outpatient clinic were enrolled in the study. Parous women and night shift workers were excluded. PCOS diagnosis was made according to the Rotterdam consensus as two of the following three criteria: oligoovulation/anovulation, biochemical or clinical hyperandrogenism and the presence of polycystic ovaries on ultrasound. Polycystic ovarian morphology was defined as one or more ovaries with a volume >10 cm^3 (18). Oligomenorrhea was defined as less than 10 menstrual cycles annually. Amenorrhoea was defined as the lack of menstruation for 6 months or longer (19). Clinical hyperandrogenism was defined as the presence of hirsutism (mFG score >8) (20). None of the participants were taking any medications including oral contraceptives.

Assessing Sleep Quality and Chronotype

All participants were asked to fill out the Turkish versions of Morningness Eveningness Questionnaire (21) and Pittsburgh Sleep Quality Index Questionnaire (PSQIQ) (22). The Morningness Eveningness Questionnaire (MEQ) was developed by Horne and Ostberg (23). MEQ is a 19-item assay tool analysing habitual wakefulness, sleep times, favored times of mental/physical performance and subjective vigilance after waking up and before going to sleep. Total scoring ranges between 16-86. High scores indicate morningness chronotype and low scores indicate eveningness chronotype.

The PSQIQ is composed of 19 scoring items which assess sleep disordes in 7 categories: (P1)-subjective sleep quality, (P2)-sleep latency, (P3)-sleep duration, (P4)-habitual sleep efficiency, (P5)-sleep disturbance, (P6)-utilization of sleeping medication and (P7)-daytime dysfunction. Each of the 19 items are designated scores ranging between 0-3. Zero score indicates no difficulty; 3 indicates severe difficulty. A total score above 5 indicates poor sleep quality.

Biochemistry Assays

For the PCOS patients only; blood samples were obtained between 08.00-08.30 a.m after overnight fasting in the early follicular phase of the spontaneous menstrual cycle (days 2-5) or following progesterone-induced withdrawal bleeding. Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Thyroid Stimulating Hormone (TSH), Estradiol (E2) prolactin, free testesterone (fT), Dehydroepiandrosterone (DHEAS), total cholesterol, low density lipoprotein (LDL), triglyceride (TG), insulin, glucose and Homeostatic Model Assessment for Insulin Resistance index (HOMA-IR) was assessed. The formula used for HOMA-IR was: fasting blood glucose (mmoL/L)×fasting serum insulin (mU/mL)/22.5.

Plasma FSH, LH, prolactin and DHEAS and insulin concentrations were measured by a direct chemiluminescence immunoassay. E2, fT concentrations were determined by a competitive chemiluminescent immunoassay (ADVIA Centaur, Siemens Healthcare Diagnostics). LDL and TG were determined by calorimetric methods. Serum glucose concentrations were analysed by an enzymatic UV method (Roche/Hitachi cobas c system).

Statistical Analysis

The statistical analysis was performed using R statistical software (version 3.3.3). Data were expressed

as mean±standard deviation or number and percentage, A p value of <.05 was considered statistically significant. The distribution of data was assessed with histogram analysis and the Kolmogorov-Smirnov test. Comparisons for sleep disturbance between women with and without PCOS in the analysis sample were made using chi-square tests of association, independent samples t-tests and Mann-Whitney U test, for categorical, normally distributed and skewed continuous variables, respectively. Comparisons were performed for PCOS patients according to their hirsutism status determined by their mFG score. For the group of women with PCOS logistic regression was used to quantify associations between sleep disturbance and other factors that are potentially influential.

Results

1-The demographic characteristics of PCOS and healthy control groups

There were 111 participants in the PCOS group and 108 participants in the healthy control (HC) group. The patients in the PCOS group were aged 25.12±5.81. The mean BMI for PCOS patients was 26.47±5.10. The control group was aged 26.37±9.4. The mean BMI of the control group was 26.46±4.95. Both groups were similar with regards to age (p=0.24) and BMI (p=1). The prevalance of hirsutism (m-FG ≥8) was 37/111 among PCOS patients (33.3%).

2- PSQIQ scoring and chronotype analysis of groups

For the analysis sample, comparisons between PCOS and HC group are presented in Table 1. The mean of PSQIQ scores for the PCOS and HC groups were calculated as: 7±4.5 and 4±3, respectively. There was a significant total PSQIQ score difference between the groups (p<0.001). In terms of the subcategories of sleep disorder; P1 (<0.001), P2 (<0.001), P4 (0.003), P6 (0.03) and P7 (<0.001) scores were higher for the PCOS group. P3 (p=0.3) and P5 (p=0.09) scores were not different. Statistically significant differences between the groups were also observed in relation to MEQ (p<0.001).

Table 1. Characteristics of Polycystic Ovary Syndrome and healthy control groups

Characteristics	PCOS group n=111	HC group n=108	p-value
Age	25.13±5.82	26.4±9.4	0.2
BMI	26.47±5.10	26.5± 5.0	0.9
Total PSQI	7.0±4.5	4±3	<0.001
P1. Subjective Sleep Quality	1.69±0.92	1.36±0.71	<0.001
P2. Sleep Latency	3.34±0.87	1.45±0.91	<0.001
P3. Sleep Duration	1.72±1.3	1.66±0.8	0.3
P4. Habitual Sleep Efficiency	1.52±0.8	1.32±0.8	0.03
P5. Sleep Disturbance	1.18±1.12	1.02±1.17	0.09
P6. Utilization of Sleeping Medication	1.2±0.8	0.9±0.1	0.03
P7. Daytime Dysfunction	1.72±0.81	1.29±0.83	<0.001
MEQ	48.26±7.25	55.2±7.7	<0.001

BMI: Body Mass Index, PSQI: Pittsburgh Sleep Quality index Questionnaire, MEQ: Morningness Eveningness Questionnaire, PCOS: Polycystic Ovary Syndrome, HC: Healthy Control

3- Correlation anaysis

In the PCOS group, we conducted a correlation analysis, for PSQI and dependent variables. In the correlation test, the PSQI score was positively associated with age (r=0.199, p=0.042); and MEQ (r=0.187, p=0.049). For the other factors (BMI, mFG, PSQI, glucose, insulin, HOMA.IR, cholesterol, LDL, TG, fT) no linear effect on PSQI score was observed. Moreover, MEQ score was inversely correlated with the mFG score and fT levels. The significant correlations are as follows: negative correlations between MEQ-fT (r=-0.5, p<0.001) and MEQ-mFG (r=-0.59, p<0.001), and positive correlation between mFG-fT (r=0.52, p<0.001) (Figure 1).

In the PCOS group, we conducted a correlation analysis, for PSQI and dependent variables. In the correlation test, the PSQI score was positively associated with age (r=0.199, p=0.042); and MEQ (r=0.187, p=0.049). For the

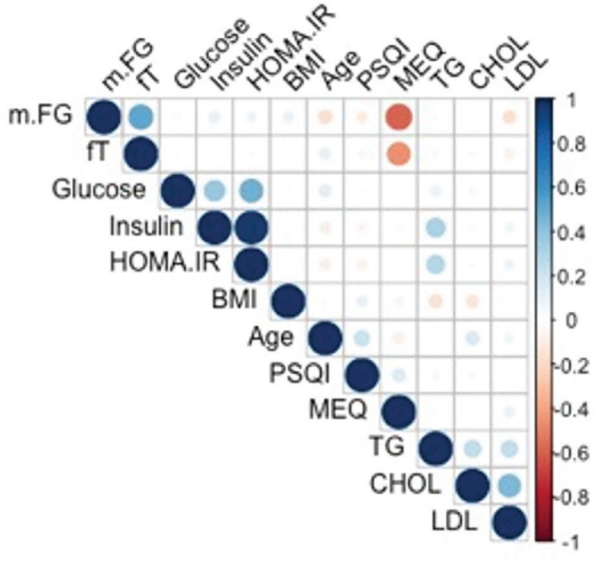

Figure 1. Correlation plot. In this plot higher correlations are represented by larger dots. Blue symbolizes positive correlation and red symbolizes negative correlation. (mFG: modified Ferriman Gallwey Score

fT: Free testesterone, HOMA.IR: Homeostatic Model Assessment for Insulin Resistance index, BMI: Body Mass Index, PSQI: Pittsburgh Sleep Quality index. MEQ: Morningness Eveningness Questionnaire, TG: Triglyceride, CHOL: Total cholesterol, LDL: Low density lipoprotein

other factors no linear effect on PSQI score was observed. Moreover, MEQ score was inversely correlated with the mFG score: MEQ-mFG (r=-0.59, p<0.00).

For the PCOS group we built a backward stepwise regression model for PSQI and confounding factors. The final regression model with the smallest Akaike's entropy-based Information Criterion score (140) includes age, BMI, and MEQ variables. The model indicates that, sleep quality is associated with age (p=0.002) and MEQ (p=0.001).

Discussion

Our results show that PCOS patients tend to be more evening-type oriented and have worse sleep quality compared to the control group. Within the PCOS group sleep quality was inversely correlated with age. The mFG score was inversely correlated with the MEQ score.

It has been suggested that evening types are more prone to unhealthy diet, less activity, increased alcohol tobacco consumption; all of which are related to general health disturbances (24). Additionally; eveningness chronotype has been studied in the literature as being associated with unfavorable metabolic outcomes such as higher prevalence of obesity, metabolic syndrome and insulin resistance (25). PCOS patients are prone to increased visceral fat and higher BMI. Considering that the evidence for the treatment of sleep and circadian problems to improve metabolic health is emerging it is of upmost importance to urge our patients to attain healthier lifestyle habits.

Our cohort was constituted of relatively young patients with normal median BMI indexes thus metabolic dysfunction was not as evident as it would have been in an older more diabetic-prone population. The association between PCOS and sleep disturbances is complex and not just due to the tendency of women with PCOS to be obese. Most associations are still evident after adjustment for BMI.

Sleep disturbances in patients with PCOS have been reported before (26,27). Sleep acts as an important modulator of several aspects of endocrine function, making the relationship between these factors difficult to elucidate (28). In the study conducted by Vgontzas and colleaugues; PCOS patients frequently reported more daytime sleepiness than did controls (80.4% vs. 27.0%) (29). In another study Moran et al. (30) have concluded that sleep disturbances were twice as common in women with PCOS compared to a retrospectively established control group and that PCOS was associated with a higher probability of difficulty falling asleep.

Interestingly, in our present study; we found that participants with hirsutism had more difficulty falling asleep (longer sleep latency-P2 score) compared to PCOS patients without hirsutism. Few studies have investigated the potential role of hyperandrogenemia in sleep disturbance in women. Sleep apnea is more commonly encountered in men; whose testesterone levels are higher than women. Testosterone is associated with upper airway collapsibility in patients with sleep apnea (31). Increased androgen levels in adolescent girls are often associated with obstructive sleep apnea (32). Testosterone levels in female patients with PCOS are known to be generally elevated. The underlying mechanism of this phenomonon is the excess testosterone production in the ovary in response to LH (33). Elevated androgen levels may affect body composition, visceral fat tissue, airway anatomy, and ventilatory flow during sleep (34). These findings have led us to the belief that testosterone abnormalities may play a role in the pathogenesis of sleep disorders in PCOS patients especially in those who show clinical signs of hyperandrogenism.

The strength of our study is; as far as we are aware it is the first record to find an association with PCOS patients with eveningness chronotype. The limitations of our study was that we analysed biological chronotypes and sleep disturbances based on data derived from self-reported questionnaires. Measuring sleep profiles more accurately by using clinical polysomnography, which is a gold standard test might have contributed to the reliability of our results,

Conclusion

PCOS patients are more prone to eveningness-chronotype and have worse sleep quality compared to controls. Furthermore PCOS patients with evident clinical hyperandrogenism are more evening oriented and have more difficulty falling asleep compared to those without overt hyperandrogenism. Testosterone abnormalities may play a role in the pathogenesis of sleep disorders in PCOS patients especially in those who show clinical signs of hyperandrogenism.

Authorship Contributions

Concept: A.F.G.K., Ç.D.Ş., Design: A.F.G.K., Ç.D.Ş., Data Collection or Processing: A.F.G.K., T.T., H.Ç., B.T., Analysis or Interpretation: A.F.G.K., Literature Search: A.F.G.K., T.T., Writing: A.F.G.K.

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İmatinibin Sıçan Karaciğerine Etkisi

Effects of Imatinib on Rat Liver

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Öz

Amaç: İmatinib antikanserojen ilaç olarak kullanılan bir protein-tirozin kinaz inhibitörüdür. Kullanımı sırasında karaciğer fonksiyon testlerinde bozulmalara neden olabilmektedir. Çalışmamızda imatinibin farklı dozlarda, sıçan karaciğeri üzerine olan etkilerinin biyokimyasal ve elektron mikroskobik düzeyde incelenmesi amaçlanmaktadır.

Yöntemler: Çalışmamızda 200-250 g ağırlığında 8-12 haftalık Wistar cinsi 30 olgun erkek sıçan kullanıldı. Sıçanlar 5 gruba ayrıldıktan sonra, deney gruplarına sırasıyla 10, 50, 100 ve 200 mg/kg imatinib gavaj yoluyla günde tek doz 21 gün uygulandı. Beşinci grup kontrol grubu olup serum fizyolojik verildi. Deney sonunda alınan kan örneklerinde karaciğer transaminazları, bilirubin, alkalen fosfataz değerlerine bakıldı, karaciğer üzerine olan morfolojik etkileri ise elektron mikroskobik düzeyde incelendi.

Bulgular: 10 mg/kg ve 50 mg/kg imatinib uygulanan deney gruplarındaki sıçanların karaciğer kesitlerinde hepatositlerin çekirdek ve sitoplazmik yapılarının, perisinuzoidal ve sinuzoidal alanların kontrol grubunda olduğu gibi normal histolojik görünüme sahip oldukları izlendi. 100 mg/kg imatinib uygulanan deney grubunda ise bazı hepatositlerin sitoplazmik densitelerinin arttığı, sitoplazmada yer yer litik alanların oluştuğu ve bu hücrelerin sitoplazmalarında lipid birikimi olduğu gözlendi. 200 mg/kg imatinib uygulanan grupta ise hücrelerin sitoplazmasında litik değişikliklerin belirginleştiği ve lipid birikiminin arttığı dikkati çekti.

Sonuç: Protein-tirozin kinaz inhibitörü olan imatinibin dozla bağlantılı olarak karaciğerde dejeneratif değişikliklere neden olabileceği ve tedavi sürecinde hastaların karaciğer fonksiyonlarının izlenmesi gerektiği sonucuna varılmıştır.

Anahtar Sözcükler: İmatinib, karaciğer, ince yapı

Abstract

Aim: Imatinib is a protein tyrosine kinase inhibitor that's used as an anticancer drug. In this study, evaluation the effects of different doses of imatinib on liver ultrastructurally and biochemically was aimed.

Methods: 200-250 g, 8-12 weeks old, 30 mature male Wistar rats were used. Rats were divided in 5 groups; 10, 50, 100 and 200 mg/kg imatinib daily were administered by gavage during 21 days to the experimental groups respectively. Fifth group was control; saline was given. Serum levels of liver transaminases, bilirubin, alkaline phosphatase were examined, morphological effects were investigated via electron microscopy.

Results: In 10 mg/kg and 50 mg/kg imatinib applied experimental groups, the nuclear and cytoplasmic structures, sinusoidal and perisinusoidal areas were similar to the control group. In 100 mg/kg imatinib applied group cytoplasmic density was increased, lytic areas and lipid accumulation in cytoplasm of some hepatocytes were seen. In 200 mg/kg imatinib applied experimental group lytic changes and lipid accumulation were prominent.

Conclusion: It is concluded that, protein-tyrosine kinase inhibitor imatinib may cause dose related degenerative changes in the liver, and liver functions should be monitored in patients during treatment.

Keywords: Imatinib, liver, ultrastructure

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Giriş

İmatinib bazı kanser türlerinde tedavi amacıyla kullanılan, Bcr-Abl tirozin kinazı inhibe eden bir protein tirozin kinaz inhibitörüdür (1). İmatinib, trombosit kaynaklı büyüme faktörü (PDGF) reseptörünü ve kök hücre faktörü (SCF) reseptörü olan c-kit'i de inhibe etmektedir (2). Hedefe yönelik tedavilerde öncü ilaç olan imatinib kronik miyeloid lösemi (KML) tedavisinde çok önemli gelişmeler sağlamıştır (3,4). Gastrointestinal sistem stromal tümör (GIST) hücrelerinde proliferasyonu inhibe edip apopitozu uyardığı bildirilmektedir (5,6). Rezekte edilemeyen metastatik GIST'lerinde kemoterapiye kötü cevap veren hastalarda dahi etkinliği gösterilmiştir (7). Kliniklerde fibrozisi azaltıcı etkilerinden dolayı da kullanılmaktadır. Wang ve ark. (8) imatinibin böbrekte fibrozisi azalttığını bildirmişlerdir. Schellings ve ark. (9) yaptıkları in vitro çalışmada, imatinibin kalp ve böbrek fibrozisini azalttığını rapor etmektedirler. Yapılan çalışmalarda, imatinibin karaciğer fibrozisinde rol alan PDGF'nin etkisini azalttığı immünohistokimyasal olarak gösterilmiştir (10,11).

İmatinib, karaciğerde p450 enzim sistemi ile metabolize edilmektedir (2). Tedavide kullanımı sırasında ödem, sitopeni ve karaciğer fonksiyon testlerinde bozulmalara neden olduğu için bazen tedaviye ara verilmekte veya ilaç tamamen kesilebilmektedir (2). Birçok çalışmada imatinibin karaciğer transaminazları, bilirubin, alkalen fosfataz değerlerinde değişikliklere neden olduğu rapor edilmektedir. Guilhot (12) yaptığı klinik çalışmalarda ödem, alerjik deri reaksiyonları, miyalji, kas krampları, karaciğer transaminazlarında artış ve miyelosupresyon tespit edilmiştir. Miyelosupresyonu ve karaciğer transaminazlarında artışı olan hastalarda tedavi kesilmektedir (12).

İmatinibin karaciğere olan etkilerini araştırmak için canlı hücre kültürü, immünohistokimyal ve ışık mikroskobik çalışmalar yapılmış olup, karaciğerin ince yapısı üzerindeki etkileri bu güne kadar gösterilmemiştir. Bu çalışmada, antikanserojen ilaç olan imatinibin farklı dozlarda uygulanmasının, sıçan karaciğeri üzerine olan etkilerinin biyokimyasal ve elektron mikroskobik düzeyde incelenmesi amaçlanmıştır.

Yöntemler

Deney sırasında yapılan tüm işlemler 1986 Uluslararası Strasbourg Hayvan Hakları Evrensel Beyannemesine uygun olarak, etik kurul onayı (toplantı sayısı 8, toplantı tarihi 06 Ekim 2009) ile veteriner hekim kontrolünde Çukurova Üniversitesi Bilimsel Araştırma Merkezi'nde gerçekleştirilmiştir.

Çalışmamızda 200-250 g ağırlığında 8-12 haftalık Wistar cinsi 30 olgun erkek sıçan kullanıldı. Sıçanlar 5 gruba ayrıldıktan sonra, deney gruplarına sırasıyla 10, 50, 100 ve 200 mg/kg dozlarında imatinib gavaj yoluyla 21 gün, günde tek doz uygulandı. Beşinci grup kontrol grubu olup aynı doz ve sürede gavaj yolu ile serum fizyolojik verildi. Çalışma sonunda, deney ve kontrol gruplarından alınan kan örneklerinde karaciğer transaminazları, bilirubin, alkalen fosfataz serum değerlerine bakıldı, karaciğer üzerine olan morfolojik etkileri ise rutin yöntemlere göre takip edilerek elde edilen kesitlerde elektron mikroskobik düzeyde incelendi.

Biyokimyasal Analizler

Serum alanin aminotransferaz (ALT), aspartat aminotransferaz (AST), total bilirubin (TBIL) ve alkalen fosfataz (ALP) seviyeleri Çukurova Üniversitesi Merkez Laboratuvarında, E170 immunoassay (Roche, Almanya) yöntemi ile ölçüldü.

Elektron Mikroskobik Doku Hazırlama Yöntemi

Elektron mikroskobik değerlendirme için alınan karaciğer doku örnekleri Millonig fosfat tamponu ile hazırlanmış, %5'lik glutaraldehit solusyonu içerisinde 4 saat süre ile tespit edildi. Elde edilen doku bloklardan Reichert Ultracut S ultramikrotomu ile yarı ince kesitler alınarak Toluidin mavisi ile boyandı ve ışık mikroskobunda değerlendirildi. Belirlenen alanlardan 50 nanometre kalınlığındaki alınan ince kesitler Jeol JEM 1400 Transmisyon Elektron Mikroskobu ile incelendi ve mikrografları elde edildi.

İstatistiksel Analizler

Çalışma verilerinin değerlendirilmesinde GraphPad Prism 5 (GraphPad Software Inc. USA) programı kullanıldı. Gruplar arasındaki farklılıklar Mann-Whitney U testi kullanılarak değerlendirildi. 0,05'ten küçük p değerleri anlamlı kabul edildi.

Bulgular

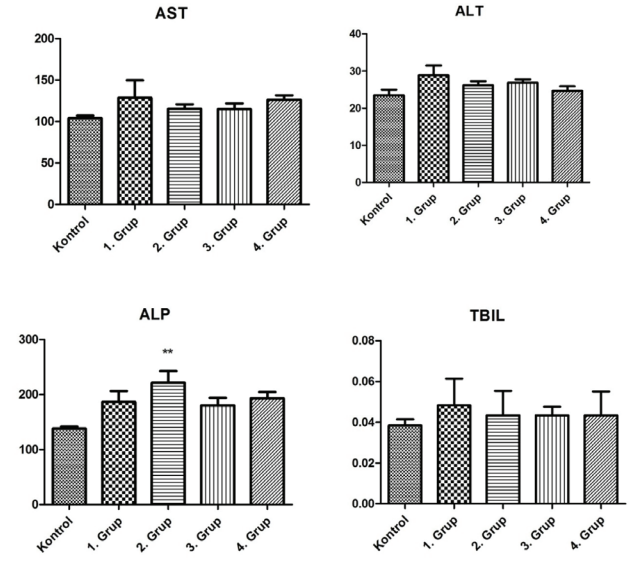
Biyokimyasal Analizler

Bütün deney gruplarında serum AST, ALT, ALP ve TBIL serum değeri yükselmekle birlikte kontrol grubu ile kıyaslandığında istatistiksel olarak anlamlı bir fark bulunmadığı gözlendi. Biyokimyasal analizlerden sadece Grup 2'deki ALP değerindeki yükselme istatistiksel olarak anlamlı bulundu (Şekil 1).

Elektron Mikroskobik Bulgular

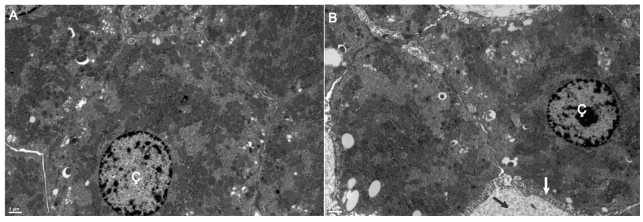
Kontrol grubunda hepatositlerin çekirdek ve sitoplazmik yapılarının, perisinuzoidal ve sinuzoidal alanların normal histolojik görünüme sahip oldukları izlendi (Şekil 2). 10 mg/kg ve 50 mg/kg imatinib uygulanan deney gruplarındaki sıçanların karaciğer kesitlerinde hepatositlerin çekirdek ve sitoplazmik yapılarının, perisinuzoidal ve sinüzoidal alanların kontrol grubunda olduğu gibi normal histolojik görünüme sahip oldukları izlendi (Şekil 3,4). 100 mg/kg imatinib uygulanan deney grubunda ise bazı hepatositlerin

sitoplazmik densitelerinin arttığı, sitoplazmada yer yer litik alanların oluştuğu ve bu hücrelerin sitoplazmalarında lipid damlacıklarının arttığı gözlendi (Şekil 5). 200 mg/kg imatinib uygulanan deney grubunda sitoplazmik densitelerin arttığı, granüler endoplazmik retikulum sisternalarının elektron dens görünümlü mitokondriyonların arasında kümeleştiği ve lipid damlacıklarının arttığı dikkati çekti (Şekil 6).

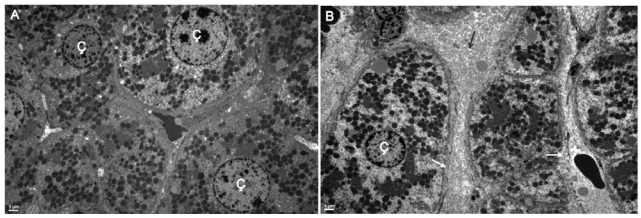


Şekil 1. Kontrol, Grup 1 (10 mg/kg imatinib), Grup 2 (50 mg/kg imatinib), Grup 3 (100 mg/kg imatinib) ve Grup 4 (200 mg/kg imatinib) deneklerinin AST, ALT, ALP ve TBIL seviyelerinin değerlendirilmesi. **p=0.0238

AST: Aspartat aminotransferaz, ALT: Alanin aminotransferaz, ALP: Alkalen fosfataz TBIL: Total bilirubin



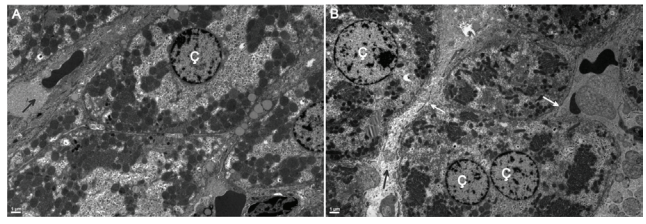
Şekil 2. A, B) Kontrol grubu. Hepatositlerin çekirdek (Ç) ve sitoplazmik yapılarının, perisinüzoidal (beyaz ok) ve sinüzoidal alanların (siyah ok) normal histolojik görünüme sahip oldukları izlenmekte. Bar=1 µm.



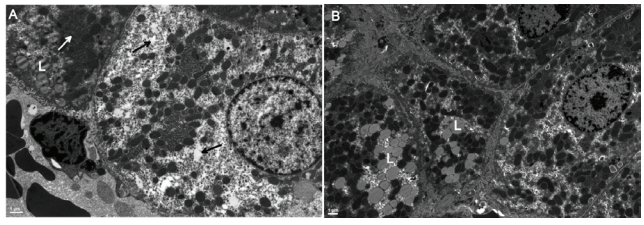
Şekil 3. A, B) Grup 1. 10 mg/kg imatinib uygulanan deney gruplarındaki sıçanların karaciğer kesitlerinde genellikle hepatositlerin çekirdek (Ç) ve sitoplazmik yapılarının, perisinuzoidal (beyaz oklar) ve sinuzoidal alanların (siyah ok) kontrol grubunda olduğu gibi normal histolojik görünüme sahip oldukları izlenmekte. Bar=1 µm.

Tartışma

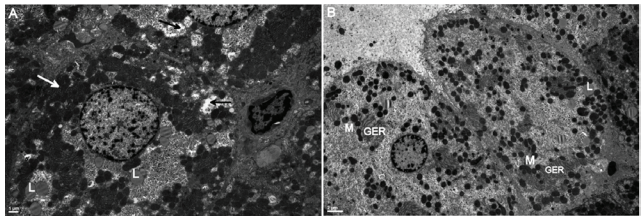
Günümüzde moleküler onkolojideki heyecan verici gelişmeler sonucu, hedefe yönelik anti-kanser tedavisinde önemli gelişmeler kaydedilmiş ve onkoloji kiniklerinde yeni ilaçlar kullanılmaya başlanmıştır (13). Hedefe yönelik tedavilerde hedeflenmiş moleküller arasında tirozin kinaz sinyal sistemi, tümör hücre yüzey antijenleri, epitelyal büyüme faktör reseptör sistemi, vasküler endotel büyüme



Şekil 4. A, B) Grup 2. 50 mg/kg imatinib uygulanan deney gruplarındaki sıçanların karaciğer kesitlerinde genellikle hepatositlerin çekirdek (Ç) ve sitoplazmik yapılarının, perisinuzoidal (beyaz oklar) ve sinuzoidal alanların (siyah oklar) kontrol grubuna yakın histolojik görünüme sahip oldukları görülmekte. Bazı hücrelerde ise organellerin sitoplazmik dağılımlarının değiştiği ve hücre periferinde toplandıkları gözlenmekte. Bar=1 µm.



Şekil 5. A, B) Grup 3. 100 mg/kg imatinib uygulanan deney grubunda bazı hepatositlerin sitoplazmik densitelerinin arttığı (beyaz ok), sitoplazmada yer yer litik alanların oluştuğu (siyah oklar) ve bu hücrelerin sitoplazmalarında lipid (L) birikimi olduğu gözlenmekte. Bar=1 µm.



Şekil 6. A, B) Grup 4. 200 mg/kg imatinib uygulanan grupta, hepatositlerin sitoplazmik densitelerinin arttığı (beyaz ok), hücrelerin sitoplazmasında litik değişikliklerin belirginleştiği (siyah oklar), granüler endoplazmik retikulum sisternalarının elektron dens görünümlü mitokondriyonların arasında kümeleştiği ve lipid birikiminin varlığı dikkati çekmekte. Bar (A)=1 µm, Bar (B)=2 µm. GER: Granüler endoplazmik retikulum sisternaları, M: Mitokondriyon, L: Lipid

faktör reseptörü, matriks metalloproteinazlar, siklin bağımlı kinazlar, apoptozis sürecinde görev alan moleküller, proteazom yolundaki moleküller, Ras onkojeni ve ısı şok proteinleri bulunmaktadır (14). Hedefe yönelik terapötikler, özgül moleküler defekti olan kanser hücrelerini seçici olarak etkilemekte, kanser hücresini öldürürken normal hücrelerin sağlıklı kalmalarına imkan sağlamaktadır (15). Hedefe yönelik tedavide imatinib, öncü ilaçlar içerisindedir. İmatinib, kronik miyelositer lösemi ve gastrointestinal stromal tümörlerini diğer antineoplastik terapötiklerle kıyaslandığında çok daha etkin bir şekilde kontrol altına almaktadır (3-7).

Protein tirozin kinazlar büyüme, metabolizma, farklılaşma, adhezyon ve apopitozis gibi birçok fizyolojik olayda rol alır. Tirozin kinazlar reseptör protein kinazlar veya reseptör olmayan (non reseptör) protein kinazlar olarak bulunurlar (16). Pirimidin (imatinib, dasatinib, nilotinib ve pazopanib), piridin (sorafenib) ve pirol (sunitinib) tirozin kinaz inhibitörleri çok hedefli tirozin kinaz inhibitörleridir; anjiogenezisde, tümör büyümesinde ve kanser metastazında görev alan birçok reseptör ve non-reseptör tirozin kinazla etkileşirler (17). Oral olarak kullanılan bu ilaçların içerisinde imatinibin biyoyararlanımı %100'dür. İmatinibin insanlarda merkezi sinir sistemine çok az geçtiği bildirilmektedir. Bütün tirozin kinaz inhibitörleri, plazmada %90'ın üzerinde plazma proteinlerine (α1-asid glikoprotein ve/veya albümin) bağlanırlar ve karaciğerde sitokrom p450 (CYP) 3A4 ile metabolize edilirler. İmatinib ve sunitinibin aktif metabolitlerinin de anti tümör etkisi olduğu bildirilmektedir. İmatinib, sorafenib ve pazopanibin sistemik kullanımında karaciğer fonksiyonlarının bozulduğu ve bu durumlarda tedavi dozunun azaltılması veya tamamen kesilmesi gerektiği bildirilmektedir. Böbrek yetmezliği olan hastalarda da imatinibin başlangıç dozlarının azaltılması önerilmektedir (17).

İmatinib, onkoloji kliniklerindeki kullanımının yanında, antifibrotik etkilerinden dolayı da birçok klinik tarafından tedavi edici ajan olarak önerilmektedir. İmatinibin PDGR üzerine olan inhibe edici etkilerinden yola çıkılarak, vazorelaksasyona neden olacağı düşünülmekte ve pulmoner hipertansiyonda da tedavi edici ajan olarak kullanılabileceği bildirilmektedir (18). İmatinibin, PDGF ve transforme edici büyüme faktörünün aktivitesini azaltarak hipertansiyon modeli oluşturulmuş sıçanlarda miyokardial fibrozisi azalttığı rapor edilmiştir (19). Dermatologlar kortikosteroide dirençli eozinofilik fasiitte alternatif terapötik olarak imatinibi kullanmaktadırlar (20).

İmatinibin kullanımı sırasında hastanın genel durumuna, hastalığın türüne, kullanılan ilacın dozu ve süresine, birlikte kullanılan diğer ilaçlara da bağlı olarak ağırlığı değişen yan etkiler ortaya çıkabilmektedir; ödem, alerjik deri reaksiyonları, miyalji, kas krampları, karaciğer toksisitesi ve miyelosupresyon bunlar içerisinde en iyi bilinenlerdir. İmatinibin kullanımı sırasında hastanın düzenli aralıklarla kontrol edilmesi ve karaciğer fonksiyon testleri ile takip edilmesi tavsiye edilmektedir (21). Yan etkilerin ağırlığına bağlı olarak ilacın dozunun azaltılması veya tedavinin tamamen kesilmesi önerilmektedir.

Çalışmamızda biyokimyasal analizlerde serum AST, ALT, ALP ve TBIL değerinde yükselme olmuş ancak kontrol grubu ile kıyaslandığında istatistiksel olarak anlamlı bir fark bulunmadığı görülmüştür. Literatürde birçok çalışmada, oluşacak yan etkilerin derecesinin hasta genel durumu, ilacın dozu, süresi gibi nedenlere bağlı olarak değişebileceği bildirilmektedir (22). Sunulan çalışmamızdaki biyokimyasal sonuçlar birçok araştırmacı tarafından bildirilmiş önceki raporlarla uyumlu bulunmuştur.

Çalışmamızda, 21 gün süreyle farklı dozlarda imatinib uygulamasına maruz kalan sıçanların karaciğer dokuları elektron mikroskobik düzeyde değerlendirildiğinde, 10 mg/kg ve 50 mg/kg imatinib uygulanan deney gruplarındaki sıçanların karaciğer kesitlerinde genellikle hepatositlerin çekirdek ve sitoplazmik yapılarının, perisinuzoidal ve sinuzoidal alanların kontrol grubuna yakın histolojik görünüme sahip oldukları ve önemli oranda etkilenmedikleri ancak bazı hücrelerde sitoplazmik organellerin yapı ve dağılımlarında değişiklikler olduğu görüldü. 100 mg/kg ve 200 mg/kg imatinib uygulanan deney gruplarında ise bu değişikliklerde belirginleşme, hepatositlerin sitoplazmik densitelerinde artma, sitoplazmada yer yer litik alanların ve lipid birikiminin varlığı dikkat çekiciydi. Son yapılan çalışmalar, axitinib, crizotinib, nilotinib ve imatinib gibi günümüzde birçok kanser türünde tedavi amacıyla kullanılan tirozin kinaz inhibitörü ilaçların farmakolojik aktiviteleri sonucu reaktif oksijen türlerinin (ROS) açığa çıkmasına neden olduklarına ve bu yola toksik etkilere neden olduklarına dikkat çekmektedirler (23). ROS'lerinin açığa çıkmasının karaciğerde akut ve kronik hepatotoksisiteye neden olduğu birçok araştırmacı tarafından rapor edilmektedir. Karaciğerde metabolik olaylar sırasında açığa çıkan artmış serbest radikallerin oksidatif stresin artmasına ve bu yolla lipid peroksidasyonuna, DNA, RNA, protein hasarına ve sonuçta hücresel hasara neden olduğu bildirilmektedir (24). Tirozin kinaz inhibitörü ilaçların kullanımı sırasında meydana gelen oksidatif stresin azaltılması amacıyla tedavide antioksidanların eklenmesinin yararlı etkileri olabileceği düşünülmektedir (23). İmatinibin kullanımı sırasında oluşabilecek akut karaciğer yetersizliğinde kortikosteroidlerin tedaviye eklenmesi gerektiği de bildirilmektedir (25).

Sonuç

Hepatositlerdeki ultrastrüktürel değişiklikler dikkate alındığında, protein tirozin kinaz inhibitörü olan imatinibin dozla bağlantılı olarak karaciğerde dejeneratif değişikliklere

neden olabileceği ve tedavi sürecinde hastaların karaciğer fonksiyonlarının izlenmesi gerektiği sonucuna varılmıştır.

Yazarlık Katkıları

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Karotis Aterosklerozu Tinnitus Oluşumunda Bir Neden midir?

Does Carotid Atherosclerosis Cause Tinnitus?

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Öz

Amaç: Ateroskleroz, orta ve büyük çaplı arterlerin intima tabakalarını etkileyen bir hastalıktır. Bu çalışmada tinnitusta etiyolojik faktör olarak düşünülen ateroskleroz, karotis aterosklerozu araştırılarak gösterilmek istendi.

Yöntemler: Çalışmaya 39'u kadın, 34'ü erkek olmak üzere toplam 73 hasta dahil edildi. Doppler sonucunda skleroz derecesine göre 4 gruba ayrıldı. Hastalardan rutin olarak trigliserid, total kolesterol, yüksek yoğunluklu lipoprotein (HDL) ve düşük yoğunluklu lipoprotein (LDL) incelemesi yapıldı. Hastalar tinnitusu olan ve olmayan olarak ayrıldı. Tümüne odyometrik tetkik yapıldı. Sonuçlar karşılaştırıldı.

Bulgular: Olguların %79,5'ünde tinnitus görülürken, %20,5'inde tinnitus yoktur. Olguların %31,5'ünde karotis darlığı görülmezken, %16,4'inde %1-49 arasında, %21,9'unda %50-69 arasında ve %30,1'inde %70'ten fazla karotis darlığı görülmektedir. Tinnitus görülen olgular ile görülmeyen olguların kolesterol, trigliserid, HDL ve LDL ortalamaları arasında anlamlı bir farklılık bulunmamaktadır. Tüm hastalarda karotis darlığı ile tinnitus varlığı arasında anlamlı bir ilişki bulunmamaktadır. Karotis darlığı %1-49 arasında olan olguların HDL düzeyleri, darlığı olmayanlardan anlamlı düzeyde yüksek bulunmuştur. Karotis darlığına göre odyogram parametreleri değerlendirildiğinde karotis darlık düzeylerine göre olguların odyogram düzeyleri arasında istatistiksel olarak anlamlı bir farklılık bulunmamaktadır.

Sonuç: Sonuç olarak karotis darlığı ile tinnitus arasında anlamlı ilişki bulunamamıştır. Karotis darlığı %1-49 arasında olanlarda HDL düzeyleri yüksek bulunmuştur.

Anahtar Sözcükler: Tinnitus, ateroskleroz, karotis arteri, odyogram

Abstract

Aim: Atherosclerosis is a disease affecting the intimas of arteries. We aimed to investigate the presence of carotid atherosclerosis in patients with tinnitus as an etiologic factor of tinnitus.

Methods: A total of 73 patients were included. The patients were divided into 4 groups according to the degree of sclerosis. Triglyceride, total cholesterol, high-density lipoprotein (HDL) and low-density lipoproteins (LDL) levels were investigated. Tinnitus was questioned in patients. All patients have undergone a pure tone audiometry. Comperative statistical analysis was performed.

Results: Tinnitus was seen in 79.5% of the patients and 20.5% of the patients had no tinnitus. Carotid stenosis of 1-49% degree was present in 16.4%, of 50-69% degree was present in 21.9%, and of 70% degree was present in 30.1% of the patients while 31.5% of the patients had no carotid stenosis. No significant association was present between carotid stenosis and the presence of tinnitus. HDL levels in patients with carotid stenosis of 1-49% degree were significantly higher than in those without stenosis. No significant difference was found between audiogram data and the level of carotid stenosis.

Conclusion: There was no significant relationship between the degree of carotid stenosis and the presence of tinnitus. Mean HDL levels were higher in carotid artery stenosis of a 1-49% degree.

Keywords: Tinnitus, atherosclerosis, carotid artery, audiogram

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Giriş

Tinnitus, herhangi bir işitsel uyaran yokluğunda sesin algılanmasıdır (1). Tinnitus, kulak burun boğaz (KBB) hastalarında en yaygın görülen semptomlardan biridir. Belirtiler genellikle pulsatil ve non-pulsatil olarak sınıflandırılır (2).

Pulsatil kulak çınlaması nedenleri anevrizma, arteriyovenöz şantlar, arteriyo-arteriyel anastomozlar ve karotid sistemin intraluminal düzensizlikleri aberan karotid arter, kalp üfürümleri ve orta kulak vasküler neoplazmlarıdır (1).

Vasküler olmayan nedenler Östaki tüpünün anormal açıklığı, temporomandibular eklem rahatsızlığı, arteriyovenöz anastomoz, orofaringeal, stapedius ve tensör timpanik kasların miyoklonusunu içerir (2).

Artmış karotid duvar kalınlığının koroner ve serebrovasküler hastalıkların belirteçlerinden biri olduğu gösterilmiştir (3-5).

Ateroskleroz plak oluşumu ile mekanik olarak daralmaya neden olmakla kalmaz, aynı zamanda endotel disfonksiyonuna ve vasküler kompliyansta değişikliğe neden olur (6,7).

Doppler sonografi, karotis hastalığının tanısı için yapılan en yaygın görüntüleme çalışmasıdır. Internal carotid artery peak systolic velocity (ICA PSV) ve Internal carotid artery end diastolic velocity (ICA EDV), Internal carotid artery (ICA) stenozunun saptanmasında kullanılan Doppler parametreleridir (8).

Ateroskleroz, tipik lezyonu ateroma plakları olan orta ve büyük çaplı arterlerin intima tabakalarını etkileyen bir hastalıktır. Endotel disfonksiyonu aterosklerotik süreçteki temel mekanizmalardan biridir. Klasik ve yeni belirlenen risk faktörleri endotelde vazodilatatör cevabın azalmasına yol açan kronik hasarlanma oluştururlar. Böylece endotelde oluşan vazokonstriksiyon, enflamatuvar hücrelerin birikimi, düz kas hücrelerinin migrasyonu, sitokin üretiminin artışı gibi olaylar aterosklerotik plak oluşumuna neden olurlar. Hiperkolesterolemi, ateroskleroz patogenezinde rol oynayan en önemli faktördür (9).

Bu çalışmada tinnitusta etiyolojik faktör olarak düşünülen ateroskleroz, karotis aterosklerozu araştırılarak ortaya koymaya çalışıldı. Hastalar karotid arter Doppler ultrasonografi ile değerlendirildi. Tinnitusu olan hastalarda internal karotid arter lümen çapları ölçüldü. Ayrıca, trigliserid, kolesterol, yüksek yoğunluklu lipoprotein (HDL) ve düşük yoğunluklu lipoprotein (LDL) düzeyleri de incelendi. Bu değerler ile ateroskleroz ve tinnitus arasındaki ilişki ortaya konmaya çalışıldı.

Yöntemler

Bu çalışmanın etik kurulu üçüncü basamak hastane etik kurulundan (2016-245) alındı. Çalışmaya 39'u (%53,4) kadın ve 34'ü (%46,6) erkek olmak üzere toplam 73 hasta dahil edildi. Tüm hastalar etik kurallara uygun olarak bilgilendirildi ve onamları alındı. Dışlama kriteri olarak doğuştan işitme kaybı olanlar, daha önce kulaktan cerrahi geçirenler veya kronik otiti olanlar, daha önce bir yüksek sese maruz kalma hikayesi olanlar, ototoksik ilaç kullanma hikayesi olanlar dahil edildi.

Kalp ve damar cerrahiye başvurup karotis aterosklerozu tanısı konan hastalar yapılan Doppler ultrasonografi (Toshiba Applio 300 Japan) sonucunda skleroz derecesine göre 4 gruba ayrıldı. Grup 1 stenoz olmayan hastalar, grup 2 %1-49 arası, grup 3 %50-69 arası ve grup 4 %70 den fazla olanlar olarak sınıflandırıldı. Hastalardan rutin olarak trigliserid, total kolesterol, HDL ve LDL incelemesi yapıldı. Sonra tüm hastalar KBB muayenesinden geçirildi. Dışlama kriterleri haricinde olan hastalara tinnitus varlığı sorgulandı. Hastalar tinnitusu olan ve olmayan olarak ayrıldı. Ayrıca hepsine odyometrik tetkik yapıldı. Sonuçlar istatistiksel incelemelerle karşılaştırıldı.

Çalışmada elde edilen bulgular değerlendirilirken, istatistiksel analizler için IBM SPSS Statistics 22.0 (IBM SPSS, Türkiye) programı kullanıldı. Çalışma verileri değerlendirilirken parametrelerin normal dağılıma uygunluğu Shapiro-Wilks testi ile değerlendirilmiştir. Çalışma verileri değerlendirilirken tanımlayıcı istatistiksel metotların (ortalama, standart sapma) yanı sıra niceliksel verilerin karşılaştırılmasında normal dağılım gösteren parametrelerin gruplar arası karşılaştırmalarında tek yönlü Anova testi ve farklılığa neden olan grubun tespitinde Tukey HDS testi kullanıldı. Normal dağılım göstermeyen parametrelerin gruplar arası karşılaştırmalarında Kruskal-Wallis testi kullanıldı. Normal dağılım gösteren parametrelerin iki grup arası karşılaştırmalarında student t-testi, normal dağılım göstermeyen parametrelerin iki grup arası karşılaştırmalarında Mann-Whitney U testi kullanıldı. Niteliksel verilerin karşılaştırılmasında ise ki-kare testi ve Continuity (Yates) düzeltmesi kullanıldı. Anlamlılık $p<0,05$ düzeyinde değerlendirildi.

Bulgular

Çalışma Ocak 2016-Nisan 2018 Tarihleri arasında yaşları 44 ile 90 arasında değişmekte olan, 39'u (%53,4) kadın ve 34'ü (%46,6) erkek olmak üzere toplam 73 olgu üzerinde yapılmıştır. Olguların yaş ortalaması 63,65±10,16 yıldır.

Stenoz gruplarına bakılınca grup 1'de 23 hasta, grup 2'de 12 hasta, grup 3'de 16 hasta ve grup 4'te 22 hasta bulundu.

Olguların %79,5'inde tinnitus görülürken, %20,5'inde tinnitus yoktur. Olguların %31,5'ünde karotis darlığı görülmezken, %16,4'ünde %1-49 arasında, %21,9'unda %50-69 arasında ve %30,1'inde %70'den fazla karotis darlığı görülmektedir (Tablo 1).

Tinnitus görülen olgular ile görülmeyen olguların yaş ortalamaları ve cinsiyet dağılımları arasında istatistiksel olarak anlamlı bir farklılık bulunmamaktadır (p>0,05) (Tablo 2).

Kolesterol değerlerine bakınca tinnitus olanlarda kolesterol ortalaması 201,16 mg/dL iken tinnitus olmayanlarda 214,13 mg/dL olarak bulundu. Trigliserid değerlerine bakınca tinnitus olanlarda trigliserid ortalaması 133,78 mg/dL iken tinnitus olmayanlarda 133 mg/dL olarak bulundu. HDL değerlerine bakınca tinnitus olanlarda HDL ortalaması 61,53 mg/dL iken tinnitus olmayanlarda 53,53 mg/dL olarak bulundu. LDL değerlerine bakınca tinnitus olanlarda LDL ortalaması 113,64 mg/dL iken tinnitus olmayanlarda 127,4 mg/dL olarak bulundu. Tinnitus görülen olgular ile görülmeyen olguların kolesterol, trigliserid, HDL ve LDL ortalamaları arasında istatistiksel olarak anlamlı bir farklılık bulunmamaktadır (p>0,05) (Tablo 3).

Tinnitus görülen olgular ile görülmeyen olguların 500-1000-2000-4000-8000 frekansta odyogram düzeyleri arasında istatistiksel olarak anlamlı bir farklılık bulunmamaktadır (p>0,05) (Tablo 4).

Tablo 1. Tinnitus bilgilerinin dağılımları

		N (Sayı)	%
Tinnitus	Tinnitus Var	58	79,5
	Tinnitus Yok	15	20,5
Karotis Darlık	Yok	23	31,5
	1-49	12	16,4
	50-69	16	21,9
	>70	22	30,1

Tablo 2. Tinnitus varlığına göre yaş ve cinsiyet değerlendirilmesi

Tinnitus				
		Var	Yok	p
Yaş (Ort ± SS)		63,0±9,42	66,2±12,67	[1]0,280
Cinsiyet (n,%)	Kadın	32 (%55,2)	7 (%46,7)	[2]0,765
	Erkek	26 (%44,8)	8 (%53,3)	

[1]Student t test, [2]Continuity (Yates) düzeltmesi
SS: Standart sapma

Tablo 3. Tinnitus varlığına göre kolesterol parametrelerinin değerlendirilmesi

Tinnitus			
	Var	Yok	p
	Ort ± SS	Ort ± SS	
Kolesterol	201,16±48,39	214,13±45,36	0,352
Trigliserid	133,78±75,72	133±65,17	0,971
HDL	61,53±28,48	53,53±21,46	0,314
LDL	113,64±40,2	127,4±46,58	0,257

Student t-test, HDL: Yüksek yoğunluklu lipoprotein, LDL: Düşük yoğunluklu lipoprotein, SS: Standart sapma

Karotis darlığına göre grup 1'de tinnitus olanların sayısı 15 iken tinnitus olmayanların sayısı 8 olarak bulundu. Grup 2'de tinnitus olanlar 9, olmayanlar 3, grup 3'te tinnitus olanlar 13, olmayanlar 3 ve grup 4'te tinnitusu olanlar 21, olmayanlar 1 olarak bulundu.

Tüm hastalara bakıldığında karotis darlığı ile tinnitus varlığı arasında istatistiksel olarak anlamlı bir ilişki bulunmamaktadır (p=0,090; p>0,05) (Tablo 5).

Hastaların yaşı ve cinsiyetlerine göre karotis darlık düzeylerine bakıldığında olguların yaş ortalamaları ve cinsiyet dağılımları arasında istatistiksel olarak anlamlı bir farklılık bulunmamaktadır (p>0,05) (Tablo 6).

Karotis darlığına göre kan yağ parametrelerinin değerlendirildiğinde, karotis darlık düzeylerine göre olguların kolesterol, trigliserid ve LDL ortalamaları arasında istatistiksel olarak anlamlı bir farklılık bulunmamaktadır (p>0,05).

Karotis darlık düzeylerine göre olguların HDL ortalamaları arasında istatistiksel olarak anlamlı farklılık bulunmaktadır (p:0,007; p<0,05). Anlamlılığın hangi karotis darlık düzeyinden kaynaklandığının tespiti için yapılan ikili karşılaştırmalar sonucunda; karotis darlığı %1-49 arasında olan olguların HDL düzeyleri, karotis darlığı olmayan olgulardan anlamlı düzeyde yüksek bulunmuştur

Tablo 4. Tinnitus varlığına göre odyogram parametrelerinin değerlendirilmesi

Tinnitus			
	Var	Yok	p
Ort ± SS (ortanca)		Ort±SS (ortanca)	
R 500	22,62±13,16 (20)	22,13±13,88 (15)	0,814
R 1000	22,93±14,78 (20)	25,67±20,95 (15)	0,978
R 2000	25,57±18,58 (20)	32±29,64 (20)	0,445
R 4000	42,84±24,71 (40)	43±31,89 (30)	0,579
R 8000	48,05±28,24 (45)	113,47±250 (40)	0,603
L 500	21,55±11,82 (20)	20,47±10,97 (20)	0,693
L 1000	21,72±13,65 (20)	23±13,2 (20)	0,618
L 2000	27,98±19,54 (20)	27,33±18,89 (20)	0,962
L 4000	40,31±22,47 (35)	40,33±31,19 (25)	0,565
L 8000	47,84±26,01 (45)	46,67±27,56 (45)	0,843

Mann-Whitney U test, SS: Standart sapma

Tablo 5. Karotis darlığı ile tinnitus ilişkisi

Karotis darlık						
		Yok	1-49	50-69	>70	p
		n sayı (%)	n sayı (%)	n sayı (%)	n sayı (%)	
Tinnitus	Var	15 (%25,9)	9 (%15,5)	13 (%22,4)	21 (%36,2)	0,090*
	Yok	8 (%53,3)	3 (%20)	3 (%20)	1 (%6,7)	

Ki-kare test, *p<0,05

Tablo 6. Karotis darlığına göre yaş ve cinsiyet değerlendirilmesi					
Karotis darlık					
	Yok	**1-49**	**50-69**	**>70**	**p**
Yaş (Ort±SS)	62,20±9,87	64,31±11,42	61,55±9,72	69,25±9,07	[1]0,182
Kadın	22 (%56,4)	7 (%53,8)	5 (%55,6)	5 (%41,7)	[2]0,844
Erkek	17 (%43,6)	6 (%46,2)	4 (%44,4)	7 (%58,3)	
[1]Tek yönlü ANOVA testi, [2]Ki-kare testi, SS: Standart sapma					

(p:0,003; p<0,05). Diğer karotis darlık düzeyleri arasında HDL ortalamaları açısından istatistiksel olarak anlamlı bir farklılık bulunmamaktadır (p>0,05). Karotis darlığına göre odyogram parametreleri değerlendirildiğinde karotis darlık düzeylerine göre olguların odyogram düzeyleri arasında istatistiksel olarak anlamlı bir farklılık bulunmamaktadır (p>0,05).

Tartışma

Tinnitus KBB alanında çok görülen bir şikayettir (2). Etiyolojisinde birçok neden mevcuttur (1). Bu nedenlerden bazıları önlenebilir nedenler iken bazılarının önüne geçilemez. Ateroskleroz oluşumunun insanın doğumuyla birlikte başladığı ve artışının birçok faktöre bağlı olduğu biliniyor. Aterosklerozun artması damar lümen çapını azaltarak damarın kan akımını sağladığı bölgeye daha az kan gitmesine neden olur. Bu da o bölgenin fonksiyonunu etkiler. Yine ateroskleroz sadece bir damarda sınırlı kalmayıp tüm damar sistemini etkilemektedir. Dolayısıyla karotiste görülen ateroskleroz tüm damar sisteminin de habercisi olabilir. İç kulak da arteriyel sistemle vaskülarize olduğundan bu damardaki bir ateroskleroz da kanlanmayı etkileyebilir. Bunun sonucunda tinnitus gelişebilir.

Tinnitus varlığına göre yağ parametrelerinin değerlendirildiğinde anlamlı bir fark bulunmamıştır. Bu da kan parametrelerinin tinnitus etiyolojisinde bir etken olmadığını ortaya koymaktadır.

Bu çalışmada karotis ateroskerozu mevcut olan hastalarda tinnitus varlığının skleroz olmayanlarla kıyaslaması yapılmak istendi. Yapılan istatistiki sonuçlara göre karotiste skleroz ile tinnitus arasında ilişki bulunamadı. Aterosklerozda yağ parametrelerinin önemini ortaya koymak için yapılan tetkiklerde ise karotis darlığına göre kan yağ parametrelerinin değerlendirilmesinde, karotis darlık düzeylerine göre olguların kolesterol, trigliserid ve LDL ortalamaları arasında istatistiksel olarak anlamlı bir farklılık bulunmadı. Bu da bize aterosklerozda beslenmenin ve kan yağ değerlerinin dışında başka etiyolojik faktörlerin daha önemli olduğunu ortaya koydu.

Karotis darlık düzeylerine göre olguların HDL ortalamaları arasında istatistiksel olarak anlamlı farklılık bulunmaktadır. Anlamlılığın hangi karotis darlık düzeyinden kaynaklandığının tespiti için yapılan ikili karşılaştırmalar sonucunda, karotis darlığı %1-49 arasında olan olguların HDL düzeyleri, karotis darlığı olmayan olgulardan anlamlı düzeyde yüksek bulunmuştur. Diğer karotis darlık düzeyleri arasında HDL ortalamaları açısından istatistiksel olarak anlamlı bir farklılık bulunmamaktadır. Oysa tinnitus görülen olgular ile görülmeyen olguların kolesterol, trigliserid, HDL ve LDL ortalamaları arasında anlamlı bir farklılık bulunmamaktadır. Bu sonuç da tinnitusun etiyolojisinde direkt olarak yağ parametreleri arasında bir ilişki bulunmadığını ortaya koymaktadır.

Bizim hastalarımızda ateroskleroz gelişiminde rol oynayabilecek kolesterol paneli dışındaki yeni risk faktörleri değerlendirilmemiştir. Kolesterol paneli normal laboratuvar değer aralıkları bizim hastanemizde şu şekildedir: Kolesterol: 0-200 mg/dl, trigliserid: 0-200 mg/dL, HDL: 45-65 mg/dL, LDL: 0-130 mg/dL. Çalışmaya katılan hastalarda kolesterol paneli değerleri istatistiksel anlamlı bulunmamıştır. Bunun kolesterol dışı diğer faktörlere bağlı olabileceği düşünülmektedir. HDL'nin anti-enflamatuvar, anti-oksidatif, anti-apopitotik, anti-enfeksiyöz ve anti-trombotik özellikleri de iyi bilinmektedir (10). HDL'nin istenen seviyelerde tutulması klinik öneme sahiptir. HDL'nin 60 mg/dL'den fazla olması yüksek kabul edilir. Bu değerin kadınlarda 50 erkeklerde 40 dan az olması HDL düşüklüğü olarak ifade edilir (11) .

Bizim hastalarımızda en yüksek HDL değeri 126 mg/dL'dir. HDL'nin normalden yüksek olması HDL partikül metabolizmasının bozulduğunu göstermektedir. Bu durumda HDL kolesterol partikülleri sürekli çok iyi olarak tanımlansalar da kanda kolesterol ester transfer proteini eksik olduğundan HDL partiküllerinin kandan uzaklaştırılamıyor olduğu anlaşılır. Damar darlığı %1-49 arasında olan 12 hastadan 7'si kadın, 5'i erkekti. Bu kadınlarda HDL yüksekliğine sebep minör risk faktörleri olabileceği düşünüldü.

Tinnitus görülen olgular ile görülmeyen olguların 500-1000-2000-4000-8000 frekansta odyogram düzeyleri arasında istatistiksel olarak anlamlı bir farklılık bulunmamaktadır. Bu sonuç bizim olgularımızda tinnitusun etiyolojisinde işitme kaybı olmadığını ortaya koymaktadır. Ancak yüksek frekans odyometri yapılmaması bu çalışmanın eksikliğidir. Zira daha önce tinnitus ile yapılan çalışmalarda tinnitusu olan hastalarda özellikle yüksek frekanslarda işitmede düşüş olduğunu ortaya koymaktadır (12).

Koo ve ark. (13) yaptıkları çalışmada periferik arter tıkayıcı hastalıkları ile tinnitus arası ilişki bulamadıklarını bildirmiştir. Terzi ve ark. (14) ise tinnituslu hastlarda karotis arterin intima kalınlığının kontrol grubuna göre daha kalın olduğunu bildirilmişlerdir.

Bizim çalışmamızda karotis darlığı ile tinnitus arasında anlamlı ilişki bulunamamıştır. Çalışmamızda tinnitus görülen olgular ile görülmeyen olguların yaş ortalamaları ve cinsiyet dağılımları arasında istatistiksel olarak anlamlı bir farklılık bulunmamaktadır Bu çalışmadaki kısıtlılığımız 50 yaştan küçük hasta sayımızın çok az olmasıdır.

Sonuç

Sonuç olarak karotis darlığı ile tinnitus arasında anlamlı ilişki bulunamamıştır. Karotis darlığı %1-49 arasında olanlarda HDL düzeyleri yüksek bulunmuştur. Daha geniş hasta sayıları ile değişik yaş gruplarının da çalışmaya dahil edildiği yeni çalışmalara ihtiyaç vardır.

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Macular Optical Coherence Tomography Angiography Parameters in Central Retinal Vein Occlusion and Differentiation of Ischemic and Non-Ischemic Types

Santral Retinal Ven Tıkanıklığında Makuler Optik Koherens Tomografi Anjiyografi Parametreleri ve İskemik ile İskemik Olmayan Tiplerin Ayrımı

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Abstract

Aim: To evaluate the macular microvascular parameters in central retinal vein occlusion (CRVO) and to differentiate its ischemic and non-ischemic types.

Methods: This study included 32 affected and 32 unaffected eyes of patients with unilateral CRVO and 32 age and sex-matched healthy control eyes. All participants had 6x6 scan pattern macular optical coherence tomography, optical coherence tomography angiography (OCTA) imaging. Vessel density (VD), perfusion density (PD), and foveal avascular zone area measurements of the superficial capillary plexus (SCP) were automatically calculated.

Results: There were statistically significant differences among the affected and unaffected eyes of CRVO patients and the control eyes in terms of the mean VD of the central ring and the median PD of the central and inner ring. There was a significant decrease in the mean VD and PD values of the inner and outer ring in the ischemic CRVO types compared to the non-ischemic types.

Conclusion: The results of this study showed that VD and PD in SCP were significantly affected CRVO. The alterations were more pronounced in ischemic type of CRVO. OCTA imaging may provide valuable information on early prediction of ischemic and non-ischemic CRVO types.

Keywords: Ischemia, perfusion, retinal vein occlusion

Öz

Amaç: Santral retinal ven tıkanıklığında (SRVT) makuler mikrovasküler parametrelerin değerlendirmesi ve iskemik ile iskemik olmayan tiplerin ayırt edilmesi

Yöntemler: Bu çalışmaya, tek taraflı SRVT'li olguların 32 etkilenmiş ve 32 etkilenmemiş gözü ile yaş ve cinsiyet uyumlu 32 sağlıklı kontrol gözleri dahil edilmiştir. Tüm katılımcılara 6x6 tarama paterninde makuler optik koherens tomografi anjiyografi (OKTA) görüntülemesi yapılmıştır. Yüzeyel kapiller pleksusta (SCP) damar yoğunluğu (VD), perfüzyon yoğunluğu (PD) ve foveal avasküler bölge (FAZ) alanı ölçümleri otomatik olarak hesaplanmıştır.

Bulgular: SRVT'li gözler, SRVT olgularının etkilenmeyen gözleri ve kontrol gözleri arasında santral bölge VD'si ile santral ve iç halkanın ortanca PD'si açısından istatistiksel olarak anlamlı farklılık saptandı. İç ve dış halkanın ortalama VD ve PD ölçümlerinde, iskemik olmayan tipe kıyasla, iskemik tipteki ölçümlerde istatistiksel anlamlı bir azalma saptanmıştır.

Sonuç: Bu çalışma, SRVT olgularında SCP'de VD ve PD ölçümlerinin anlamlı olarak etkilendiğini göstermiştir. Değişiklikler SRVT'nin iskemik tipinde daha belirgin saptanmıştır. OKTA görüntüleme, iskemik ile iskemik olmayan SRVT tipinde erken tahmin konusunda değerli bilgiler sağlayabilir.

Anahtar Sözcükler: İskemi, perfüzyon, retinal ven tıkanıklığı

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Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disease causing permanent loss of vision following diabetic retinopathy (1). Visual prognosis and outcomes are dependent on the presence of retinal ischemia and macular edema. Severe retinal ischemia causes increased vascular endothelial growth factor (VEGF) levels, which may lead to neovascularization, vitreous hemorrhage, neovascular glaucoma, and retinal detachment (2).

RVO is classified into ischemic and non-ischemic types based on non-perfused areas in fluorescein angiography (FA). FA is the gold standard for evaluating the extent of retinal ischemia and neovascularization in RVO (3). That imaging technique requires intravenous fluorescein dye injection for the acquisition of retinal images. In addition, the procedure also has side effects including renal function impairment, vomiting, nausea, and life-threatening severe allergic anaphylactoid reactions due to the fluorescein (4,5).

Optical coherence tomography angiography (OCTA) is a novel, reproducible and non-invasive imaging technique that enables clinicians to visualize the retinal microvascular circulation. Moreover, different OCTA platforms also provide quantitative data of macular microvasculature. In a previous study, Casselhomde Salles et al. (6) analyzed the foveal avascular zone (FAZ) area in central retinal vein occlusion (CRVO) and observed FAZ enlargement both in superior capillary plexus (SCP) and deep capillary plexus (DCP). Koulisis et al. (7) showed a reduced vascular density of SCP in cases with macular edema due to RVO compared to that in eyes without edema. A recent study revealed decreased parafoveal vascular density values in SCP and DCP of eyes with CRVO (8). OCTA seems like a promising method for clarification of changes in macular microcirculation and evaluation of the ischemic status of RVO.

In the present study, we aimed to investigate the macular vascular parameters in SCP using OCTA and to determine whether these changes may be used in differentiation between the ischemic and non-ischemic characteristics of RVO.

Methods

Study Design

This single-center, retrospective case-control study was conducted from October 2019 to April 2020 in a tertiary referral center for retinal diseases. Informed consent was obtained from the participants before the examination, and all measurements were taken from each patient before enrollment. The study was carried out in accordance with the Declaration of Helsinki and approved by the Hamidiye Ethics Committee of the University of Health Sciences (20/218, 12.6.2020).

Participants and Examination

This retrospective study included 32 affected and 32 fellow eyes of patients with CRVO, and 32 healthy eyes from normal subjects.

Unilateral CRVO patients with clear ocular media and a healthy fellow eye and no history for an intraocular surgical procedure or invasive intervention were included in the study. The exclusion criteria were as follows; spherical equivalent (SE) >6 diopters, axial length (AL) >26 mm, media opacities preventing high-quality imaging, uncontrolled diabetes and hypertension, history of neurological diseases, myocardial infarction and stroke, history of intraocular inflammation, history of intraocular surgery other than uncomplicated cataract surgery, eye trauma, the presence of ocular hypertension, glaucoma, or any other retinal or optic disc pathology or congenital anomaly.

CRVO was diagnosed based on clinical examination findings, and retinal images. All eyes, including the healthy eyes, underwent a comprehensive ophthalmological evaluation, comprising best-corrected visual acuity (BCVA) assessment with a Snellen chart, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement using Goldman applanation tonometry, axial length (AL) measurements, and fundus examination in the dilated pupil. FA was only performed in the CRVO group. BCVA was converted to the logarithm of the minimal angle of resolution (logMAR) for statistical analysis.

Fundus Fluorescein Angiography

FA imaging was performed using Spectralis (Heidelberg Engineering, Heidelberg, Germany) FA module. All CRVO patients were administered a 5 mL intravenous injection of 20% sodium fluorescein for the evaluation of the dye pattern and thereby the determination of non-perfused areas of retinal tissue. Angiographic photographs were taken 15-40 seconds after the injection. The presence of a non-perfused area ≥10 optic disc diameter (DD) was defined as peripheral ischemia for patients with central retinal vein occlusion, and ≥5 DD non-perfused area was defined as peripheral ischemia for branch retinal vein occlusion. All FA procedures were performed after the complete resolution of retinal findings in retinal vein occlusion.

Optical Coherence Tomography Angiography Image Acquisition

All CRVO subjects had OCTA on the same day with FA imaging using Cirrus 5000 HD OCT with AngioPlex (Carl Zeiss, Dublin, USA) device. Macular microvasculature was evaluated using a 6x6 volume angiography scan

pattern centered on the fovea. Vessel density (VD), perfusion density (PD), and FAZ area measurements in the superficial capillary plexus (SCP) of the macula were automatically calculated based on an ETDRS grid using the manufacturer's software. In the ETDRS grid, inner and outer rings correspond to the parafoveal and perifoveal regions. Images with ≥8 signal strength during scanning were recorded.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0. The conformity of the variables to normal distribution was assessed with the Kolmogorov Smirnov test. For variables that were normally distributed, the Independent samples t-test was used to compare the groups, and for variables that did not show normal distribution, the Mann-Whitney U test was used. The chi-square test was applied in comparisons of the proportions of the groups. For data with normal distribution, ANOVA was used to compare the means of the study groups and the Tukey test to test the significance of pairwise differences. The Mann-Whitney U-test was performed to test the significance of pairwise differences using Bonferroni correction adjusted for multiple comparisons. The relationships between measurements were assessed with Spearman's Correlation test. A 5% type-I error level was accepted as statistical significance.

Results

Demographic Data

There were 18 male and 14 female participants both in CRVO and control groups. The mean age was 60.7±11.6 years in CRVO group and 63.3±11.8 years in the control group. No significant differences were determined in the mean age between the CRVO patients and the healthy subjects (p=0.39). There were no significant differences between the CRVO and control group in terms of mean BCVA, IOP, AL, and SE (Table 1).

Optical Coherence Tomography Angiography Analysis

The mean central macular (CMT) and ganglion cell-internal plexiform layer (GC-IPL) thicknesses were 390±134.7 µm and 62.8±19.5 µm in CRVO eyes, 248.2±27.1 µm and 79.6±9.5 µm in the fellow eyes of CRVO patients, and 258.4±23 µm and 79.1±14.7 µm in the control eyes, respectively. The mean GC-IPL was determined to be statistically significantly thinner, and the mean CMT was statistically significantly thicker in eyes with CRVO compared to the fellow and control group eyes (p<0.001 for all comparisons).

VD and PD in the SCP were calculated as the central, inner, and outer ring in the macular region. There were statistically significant differences among the affected and fellow eyes of CRVO patients, and the control eyes in terms of the mean VD of the central ring and the median PD of the center and inner ring measurements (p<0.001, p<0.001 and p=0.04, respectively). The comparisons of OCTA measurements and the p values of eyes with CRVO, the fellow eyes of the CRVO patients, and the control eyes are presented in Table 2.

Subgroup Analysis of Ischemic and Non-Ischemic Types of CRVO

The patients were classified into ischemic and non-ischemic subgroups of CRVO. There was a significant decrease in the mean VD of the inner ring and outer ring, and in the mean PD of the inner ring and outer ring measurements in the ischemic types of CRVO compared to the non-ischemic form (p<0.001 for all comparisons). The subgroup analysis of OCTA measurements in the CRVO eyes and the p values are given in Table 3.

Discussion

With the increasing availability of OCTA, there has been a recent interest of researchers in the assessment of the effects of RVO on macular microvascular circulation. OCTA is a useful non-invasive method to assess vascular density, non-perfused vessels, SCP and, and macular morphology in retinal vein occlusion (9,10). The results of the current study showed that the mean VD of the central ring was significantly lower, whereas the median PD in the central and inner rings of the macular SCP was found to be significantly higher.

CRVO affects both the superficial and deep plexuses of the macula. Macular capillary network abnormalities, such as capillary disruption or dilatation, mainly occurs in the DCP. The SCP is directly bonded to retinal arterioles with greater perfusion pressure and oxygen supply, which could explain why the SCP is less affected than the DCP in RVO. The other plexus, DCP is mainly comprised of venous

Table 1 . Demographic data of CRVO patients and control subjects

	CRVO group n=32	Control group n=32	p-value
Age, years	60.7±11.6	63.3±11.8	0.39**
BVCA, logMAR¥	0.00±0.05	0.00±0.07	0.62**
IOP, mmHg¥	13.16±1.66	13.35±2.41	0.72**
AL, mm¥	23.25±0.6	23.37±0.6	0.92**
SE, diopters¥	-0.24±0.6	-0.25±0.5	0.73**

Values are presented as mean ± SD
¥Values were collected from the fellow eyes in the RVO patients.
*Chi-square test
**Independent samples t-test
CRVO: Central retinal vein occlusion, logMAR: Logarithm of the minimal angle of resolution, IOP: Intraocular pressure, AL: Axial length, SE: Spherical equivalent, SD: Standard deviation

Table 2. Comparison of macular OCTA parameters among study groups				
	CRVO eyes	**CRVO fellow eyes**	**Control eyes**	**p-value**
Vessel density (mm/mm²)				
Central	9±5	6.5±4.6	3.6±2.2	<0.001* CRVO-Control: <0.001 Fellow-Control: 0.02
Inner ring	13.1±4.5	13.9±5.1	12.1±3.5	0.27*
Outer ring	13.3±4.8	12.1±3.5	15.2±3.4	<0.20*
Perfusion density (%)				
Central	19.3 (0.2-41.7)	13.9 (1.6-32.6)	8.2 (0.4-17.3)	<0.001† CRVO-Control : <0.001 Fellow-control : 0.02
Inner ring	33.5 (5.7-46.1)	38.3 (9.3-45.7)	30.5 (6-36.3)	0.04† CRVO-Control : 0.04 Fellow-Control : 0.02
Outer ring	39.9 (6-49.1)	44.5 (12.5-48.3)	38.9 (12.5-46.3)	0.20†
Faz Area (mm²)				
	0.25±0.1	0.24±0.1	0.25±0.1	0.69*

Values are presented as mean ± SD and median (minimum-maximum) values
*One-Way ANOVA test and Bonferonni multiple comparisons
†Kruskal-Wallis test and pairwise comparisons
OCTA: Coherence tomography angiography, CRVO: Central retinal vein occlusion, SD: Standard deviation

Table 3. Analysis of macular OCTA parameters in ischemic and non-ischemic CRVO eyes determined via FA imaging			
	CRVO eyes		
	Ischemic (n=18)	**Non-ischemic (n=14)**	**p-value**
Vessel density (mm/mm²)			
Central ring	8.2±5.7	10.1±3.8	0.25*
Inner ring	10.8±4.6	16.2±1.9	<0.00*
Outer ring	10.6±4.3	16.8±2.7	<0.001*
Perfusion density (%)			
Central ring	14.2 (0.2-41.7)	20.7 (10.5-38.0)	0.20**
Inner ring	28.6 (5.7-44.7)	41.0 (30.4-46)	<0.001**
Outer ring	27.0 (6.0-43.0)	44.0 (26.4-49.1)	<0.001**

Values are presented as mean ± SD and median± minimum and maximum values
*By independent t test
**By Mann-Whitney U test
OCTA: Coherence tomography angiography, CRVO: Central retinal vein occlusion, SD: Standard deviation

collecting channels. When a venous occlusion occurs, hydrostatic pressure elevates, and perfusion decreases, and retinal hypoxia develops (11-13). In accordance with the current study, Seknazi et al. (14) reported macular microvascular abnormalities in both the SCP and DCP on OCTA, although it was also stated that the DCP seems to be more vulnerable than the SCP in RVO. Lee et al. (15) noted that the mean VD of the SCP was lower in both CRVO and BRVO eyes. The study also highlighted that the VD in SCP was most significantly associated with collateral formation, which is strongly linked to retinal ischemia. A recent study revealed a significant decrease in both SCP and DCP in BRVO and reported that the non-perfusion area in the DCP tends to be greater than that in the SCP (16). Studies that have investigated macular microcirculation in the SCP and DCP of RVO patients suggest that both the superficial and deep plexuses are affected at different levels. Moreover, reduction in vascular perfusion and density of the DCP are more frequent and pronounced in RVO. However, the changes in the SCP and DCP VD in both ischemic and non-ischemic forms of RVO have not yet been fully elucidated (17,18).

FA is the most commonly preferred technique to detect peripheral and macular ischemia in RVO, however, the DCP may not adequately be seen on FA. The evaluation of the retinal non-perfused areas is the main determining factor in the diagnosis of ischemic RVO. The presence of diffuse peripheral ischemia in RVO may cause a significant

visual impairment due to the development of retinal and anterior segment neovascularization (3). To evaluate the retinal ischemia optimally with FA, the disease should be in a coalescent phase and intra and sub-retinal hemorrhages should regress. However, that requires a follow-up period. In the present study, the subgroup analysis of CRVO eyes demonstrated that the mean VD and PD of SCP in the inner and outer ring were significantly decreased in the ischemic type of CRVO compared to the non-ischemic type. Consistent with these results, Khodabandeh et al. (8), also reported significantly lower VD and reduced flow density in the parafoveal macular region in ischemic CRVO compared to non-ischemic CRVO. Pellegrini et al. (19) determined a negative correlation between the extent of the non-perfused area and VD, and explained that VD reduction is associated with an increase in non-perfusion areas. Collateral vessels develop in RVO as a response to vein occlusion, and this collateral formation has strongly been associated with retinal ischemia and the extent of the non-perfused area (15). The severity of peripheral ischemia in CRVO may be associated with the grading of the decrease in the OCTA parameters. Nevertheless, vascular dilation and telangiectasias can give a false sense of increased perfusion density in CRVO eyes. That can be overcome by vessel length analysis which accepts all the vessels as having the same caliber.

The margin of the central ring in the foveal capillary network corresponds to an avascular capillary region, known as the FAZ. In the current study, no significant difference was determined in the mean FAZ measurement in the SCP on OCTA, among study groups. The FAZ measurements of the superficial capillary layer on OCTA could not be compared with the FA images because of the lack of automatized analysis in the angiography device. Other studies have revealed that the FAZ area of SCP values in OCTA is significantly larger than FA measurements and also can be easily delineated (17,20). The discrepancy in the study results may have arisen from the different OCTA platforms that are used in studies.

Study Limitations

There were several limitations to this study. First, our study is limited by its retrospective design and small sample size. Secondly, a longitudinal study would be more appropriate when evaluating retinal ischemia in CRVO. Because it has been proven that 13-18 % of eyes with non-ischemic CRVO at baseline may convert to ischemic type at 6-18 months (21). The third limitation is the imaging artifacts with OCTA. This is particularly essential in eyes with poor visual acuity in which the artifacts may affect accurate quantification of parameters. Finally, because of the software used, a 6x6 scan pattern was used and only SCP parameters were obtained. However, this scan pattern may not provide quantitative information in the non-perfused areas. In addition, a 3x3 scan pattern would have delineated the FAZ border more accurately (22).

Conclusion

The current study demonstrated that macular microvascular parameters such as the VD and PD are significantly affected in patients with CRVO. The changes in SCP was more pronounced in the ischemic type of CRVO compared to the non-ischemic type. Thus, OCTA may be able to provide valuable information for the early prediction of the ischemic type CRVO at the initial examination before fluorescein angiography is performed. Nevertheless, further studies are needed to confirm these results.

Authorship Contributions

Analysis and Data collection: Ş.Ö., Y.Ö., Writing: Ş.Ö., Y.Ö., Peer-review: Ö.A.

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Comparisson of Different Cardiovascular Risk Scores in Newly Diagnosed Hyperlipidemia Patients and Their Relations with Metabolic Syndrome

Yeni Tanı Almış Hiperlipidemili Hastalarda Farklı Kardiyovasküler Risk Skorlamalarının Karşılaştırılması ve Bunlarin Metabolik Sendromla İlişkileri

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Abstract

Aim: Today, there are many risk calculation methods. In this study, we aimed to compare SCORE, QRISK2, BNF, ASSIGN and Framingham risk scorings for patients who have been first detected that they have hyperlipidemia and to evaluate the relation between metabolic syndrome criteria and cardiovascular risk scorings for the same group patients.

Methods: We included 216 female, 84 male newly diagnosed hyperlipidemic patients. Lipid levels measured using enzymatic calorimetric methods. We also measured weight, height, waist circumference of patients. We used NCEP ATP III for metabolic syndrome identification. For 10 years cardiovascular risk assessment we performed Framingham, SCORE, QRISK 2, ASSIGN, BNF score systems.

Results: The difference between these four different methods found statistically significant with Friedman test (p<0.001). With post-hoc dual analysis, we found that Framinghan score was different from the other 3 methods, QRISK2 score was different from Framingham and ASSIGN score results, ASSIGN score was different from other 3 score results and BNF score was also different from Framingham and ASSIGN score results. Only between BNF-QRISK2 scores we could not find difference.

Conclusions: This study showed that when four different cardiovascular risk score methods are compared in newly diagnosed hyperlipidemia patients, only BNF and QRISK2 scorings revealed similar results but Framingham and ASSIGN scorings resulted differently either from each other or BNF and QRISK2

Keywords: Metabolic syndrome, hyperlipidemia, cardiovascular risk scores

Öz

Amaç: Günümüzde çok sayıda kardiyovasküler risk hesaplama sistemi bulunmaktadır. Biz bu çalışmada ilk kez hiperlipidemi saptanan hastalarda SCORE, QRISK2, BNF, ASSIGN, Framingham risk skorlamalarını karşılaştırmayı ve aynı grup hastalarda metabolik sendrom kriterlerinin varlığı ile kardiyovasküler risk skorlamaları arasındaki ilişkiyi değerlendirmeyi amaçladık.

Yöntemler: Yeni hiperlipidemi tanısı almış 216 kadın, 84 erkek hastayı çalışmaya dahil ettik. Kan lipid seviyeleri için enzimatik kalorimetrik yöntemler kullanıldı. Hastaların kilosu, boyu, bel çevresi de ölçüldü. Metabolik sendrom tanımlaması için NCEP ATP III kriterlerini kullandık. 10 yıllık kardiyovasküler risk değerlendirmesi için de Framingham, SCORE, QRISK 2, ASSIGN, BNF skor sistemleri uyguladık.

Bulgular: Bu dört farklı yöntem arasındaki fark, Friedman testi ile istatistiksel olarak anlamlı bulundu (p<0,001). Post-hoc ikili analiz ile Framinghan skor sisteminin diğer 3 skor sisteminden, QRISK2 skor sisteminin Framingham ve ASSIGN skor sistemlerinden farklı olduğunu, ASSIGN skor sisteminin, diğer 3 skor sisteminden farklı olduğunu ve BNF skor sisteminin de Framingham ve ASSIGN'den farklı olduğunu bulduk. Sadece BNF ile QRISK2 skor sistemleri arasında fark bulamadık.

Sonuç: Bu çalışma ile yeni tanı konmuş hiperlipidemili hastalarda dört farklı kardiyovasküler risk skorlama sistemi karşılaştırıldığında; sadece BNF ve QRISK2 skorlarının benzer sonuç verdiği ancak FRAMINGHAM ve ASSIGN skorlarının hem birbirinden hem de BNF ve QRISK2'den farklı sonuçlar verdiği ortaya konuldu.

Anahtar Sözcükler: Metabolik sendrom, hiperlipidemi, kardiyovasküler risk skorları

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Introduction

Atherosclerotic cardiovascular diseases (ASCVD) continue to be the leading cause of morbidity and mortality worldwide, especially in developing countries, despite significant advances in this area in recent years (1). Lifelong coronary heart disease (CHD) risk was determined as 49% for men and 32% for women aged 40 years old in the Framingham Heart Study which included 7733 people between the ages of 40-94 who did not have a history of CHD. Even in persons with no known disease at the age of 70, the lifetime risk has been calculated as 35% for men and 24% for women (2). The situation in our country is not different from the global status. According to the Heart Disease and Risk Factors in Turkish Adults (HDRFTA) study, CHD mortality between the ages of 45-74 was 9.1 per 1000 among men and 2.34 among women. It has been shown that both CHD mortality and the prevalence of new coronary events in Turkish adults have an increasing trend compared to neighboring countries, and the study emphasized the need for preventive measures against coronary disease (3).

Age, gender, high blood pressure, smoking, dyslipidemia and the presence of diabetes mellitus are accepted as the major risk factors for ASCVD (4). Stroke, thromboembolism, heart failure, are the most important results of ASCVD that cause morbidity, mortality and decrease quality of life (5). The combination and interaction of these risk factors has been shown to accelerate the risk of vascular disease (6); therefore, risk prediction algorithms assessing the risk of developing ASCVD have been developed in order to be able to reduce the mortality and morbidity of those with high risk and to maintain low risk by encouraging the maintenance of a healthy lifestyle in those with low risk (7).

In order to prevent cardiovascular diseases, current guidelines recommend the calculation of 10-year atherosclerotic cardiovascular disease (ASCVD) risk of individuals aged 40-75 years and performing risk assessment before starting pharmacological treatments (antihypertensive, lipid lowering, antiplatelet, etc.) (1).

There are many risk calculation systems available today, and the oldest and most well-known of these is the Framingham scoring system. Other well-known systems are SCORE, PROCAM, QRISK, WHO/ISH, and various other national risk calculation systems. Since hyperlipidemia is a condition associated with cardiovascular risk, lipid level is included in all risk calculation systems. In our study, we aimed to compare the SCORE, QRISK2, BNF, ASSIGN, Framingham risk scores in patients with hyperlipidemia for the first time, and to evaluate the relationship between the presence of metabolic syndrome criteria and cardiovascular risk scores in the same group of patients.

Methods

The study was approved by the ethics committee on 23/10/2012. Written and verbal informed consent was obtained from each participant for the study. A total of 216 female and 84 male patients who received their initial diagnosis of hyperlipidemia after applying to the internal diseases outpatient clinic between January and April 2014 (and had not received any treatment for this reason) were included in the study.

Diagnosis of Metabolic Syndrome

Participants were evaluated for metabolic syndrome using the NCEP ATP III criteria:

1. Central obesity (waist circumference; female >88 cm, male >102 cm)
2. Fasting triglyceride ≥150 mg/dL
3. Low HDL cholesterol (men <40 mg/dL, women <50 mg/dL)
4. High blood pressure (≥130/≥85 mm Hg) or medication use for hypertension
5. Fasting blood glucose elevation (≥100 mg/dL)

Metabolic syndrome was diagnosed in patients who met 3 of these criteria.

Calculating Cardiovascular Risk

The Framingham, SCORE, QRISK2, ASSIGN, and BNF risk systems were used to evaluate the 10-year coronary artery disease risk of the participants. Framingham, ASSIGN, and BNF were automatically calculated from the website https://www.bloodpressureclinic.ed.ac.uk/calculating-cardiovascular-risk using Joint National Comittee (JNC)-VIII blood pressure categories, NCEP total cholesterol categories, and LDL cholesterol categories. SCORE was calculated automatically from the website http://www.heartscore.org.

Statistical Analysis

For continuous variables, compliance with normal distribution was examined using the Shapiro-Wilk test. Descriptive statistics used to define continuous variables were mean, standard deviation, minimum, median and maximum. Frequency (n) and percentages (%) were used to describe discrete variables. The Wilcoxon signed-rank test was used to compare dependent variables of 2 groups that did not show normal distribution. The Friedman test was used to compare dependent variables with more than 2 groups that did not show normal distribution. Post-hoc evaluations were performed using the Wilcoxon signed-rank test for significant results. Statistical significance level was set at 0.05. All analyses were conducted by the use of the MedCalc Statistical Software version 12.7.7 (MedCalc Software Bvba, Ostend, Belgium; http://www.medcalc.org).

Results

Patient characteristics are shown in Table 1. A statistically significant difference was found between the risk scores of the patients measured by 4 different methods, as determined by the Friedman test (p<0.001).

As a result of post-hoc pairwise comparisons:

- Framingham score was significantly different from scores calculated by the other 3 methods,
- QRISK2 score was significantly different from scores calculated with the Framingham and ASSIGN methods,
- The ASSIGN score was significantly different from the scores calculated by the other 3 methods,
- BNF score was significantly different from Framingham and ASSIGN,
- It was seen that there was no statistically significant difference between BNF and QRISK2 (Table 2).

A statistically significant and high level of correlation was found between all scoring methods (Table 3).

There was a statistically significant difference between the risk scores measured by different methods in groups formed according to the presence/absence of metabolic syndrome (Friedman test, p<0.001). In the post-hoc evaluation, it was seen that each measurement method had significantly different results from each other (Table 4).

When risk scoring systems were compared among themselves (Table 5):

Table 1. General characteristics of the patients

		Mean ± SD	n	%
Age (year)		54.1±11		
Age (year)	<50		111	37
	≥50		189	63
Gender	Female		216	72
	Male		84	28
BMI (kg/m^2)		29.4±5.1		
BMI (kg/m^2)	<25		57	19
	25-30		121	40.3
	≥30		122	40.7
DiabetesMellitus	Yes		69	23
	No		231	77
Hypertension	Yes		98	32.7
	No		202	67.3
Familyhistory	Yes		88	29.3
	No		212	70.7
Smoking	Yes		94	31.3
	No		206	68.7
Metabolic syndrome	Yes		109	36.4
	Mo		191	63.6

BMI: Body mass index, SD: Standard deviation

- Among subjects who were defined to have high-risk according to the Framingham criteria, the QRISK2, BNF and ASSIGN scores identified that 62.5% (n=35), 46.4% (n=26) and 96.4% (n=54) of these were individuals at high risk, respectively.
- Among subjects who were defined to have high-risk according to the QRISK2 criteria, the Framingham, BNF and ASSIGN scores identified that 71.4% (n=35), 46.9% (n=23) and 91.8% (n=45) of these were individuals at high risk, respectively.
- Among subjects who were defined to have high-risk according to the BNF criteria, the Framingham, QRISK2 and ASSIGN scores identified 86.7% (n=26), 76.7% (n=23) and 100% (n=30) of these were individuals at high risk, respectively.
- Among subjects who were defined to have high-risk according to the ASSIGN criteria, the Framingham, QRISK2 and BNF scores identified that 47.8% (n=54), 39.8% (n=45) and 26.5% (n=30) of these were individuals at high risk, respectively.

While the ASSIGN scoring system tended to assign patients to a higher risk group, the BNF and QRISK2 systems showed a tendency for categorizing patients into lower risk categories.

Discussion

In our study, we evaluated the results of different cardiovascular risk scoring systems in patients with newly diagnosed hyperlipidemia, and the relationships between the presence of metabolic syndrome and cardiovascular risk scores in the same group. Our findings revealed that when all patients with hyperlipidemia are considered (without distinction for metabolic syndrome), only the BNF and QRISK2 scores of these 4 cardiovascular risk scoring system provided similar results, and the Framingham and each on risk score often produced different results as well Ncho IS Different results. It has been shown that patients with hyperlipidemia with metabolic syndrome have higher cardiovascular risk than patients without metabolic syndrome.

As of the year 2000, 9.2 million people aged older than 30 years have been identified to have metabolic

Table 2. Comparison of different cardiovascular risk scores (Post-hoc analysis)

Post-hoc analysis	p
Framingham vs QRISK2	<0.001
Framingham vs ASSIGN	<0.001
Framingham vs BNF	<0.001
BNF vs QRISK2	0.648
BNF vs ASSIGN	<0.001
ASSIGN vs QRISK2	<0.001

Table 3. Correlation between different cardiovascular risk scores

	Framingham	QRISK2	ASSIGN	BNF
	r (p)	r (p)	r (p)	r (p)
Framingham	1.00	0.881 (<0.001)	0.894 (<0.001)	0.891 (<0.001)
QRISK2	0.881 (<0.001)	1.00	0.845 (<0.001)	0.808 (<0.001)
ASSIGN	0.894 (<0.001)	0.845 (<0.001)	1.00	0.882 (<0.001)
BNF	0.891 (<0.001)	0.808 (<0.001)	0.882 (<0.001)	1.00

Table 4. Comparison of differentcardiovascular risk scores in patients with or without metabolic syndrome (Post-Hoc analysis)

	Metabolic syndrome (+)	Metabolic syndrome (-)
Framingham vs QRISK2	<0.001	<0.001
Framingham vs ASSIGN	<0.001	<0.001
Framingham vs BNF	<0.001	<0.001
QRISK2 vs ASSIGN	<0.001	<0.001
QRISK2 vs BNF	0.001	0.019
ASSIGN vs BNF	<0.001	<0.001
*Wilcoxon Signed-rank test		

Table 5. Distribution of patients according to risk status using different scoring methods

	Low Risk	Moderate Risk	High Risk	Total
	n (%)	n (%)	n (%)	N(%)
Framingham	148 (49.5)	95 (31.8)	56 (18.7)	299 (100)
QRISK2	173 (58.1)	76 (25.5)	49 (16.4)	298 (100)
ASSIGN	123 (41.0)	64 (21.3)	113 (37.7)	300 (100)
BNF	179 (59.9)	90 (30.1)	30 (10)	299 (100)

syndrome in Turkey. On the other hand, 53% of individual who developed coronary artery disease wereals patients with metabolic syndrome (8). In the retrospective study, in which they conducted a 10-year cardiovascular risk assessment, Lee et al. (9) revealed that Framingham had a low sensitivity (37%) in patients younger than 40 years. Although young patients were not differentiated in our study, Framingham and other risk models gave similar results in the general patient group, unlike the findings of Lee et al. (9) Furthermore, unlike the findings of Ghandehari et al. (10) showed that Framing ham results were significantly associated with body mass index (BMI) and abdominal obesity. Similar to our results, the aforementioned study demonstrates that the selection of risk assessment models is critical for accurate analysis of patients in terms of cardiovascular risks, since this diseases have been shown to be associated with obesity and metabolic syndrome and the fact that the incidence of cardiovascular diseases can be reduced even with lifestyle changes (11). Marsh et al. (12) stated in their study that the risk of cardiovascular disease increases in direct proportion to thein crease in risk factors, concluding that individuals' future cardiovascular risk can be predicted via such risk factors. Although the results of our study support the argument of Marsh et al. (12), it is evident that choosing a valid model specific to population characteristics in each region is required for better assessment of cardiovascular risk.

A study from Canada aimed at identifying individuals with cardiovascular risk who may need statin therapy, John Mancini et al. (13) compared the Framingham, ATP III, Reynolds, and score risk models in a massive cohort study including one million individuals. As a result of the study (in which individuals with diabetes and familial cardiovascular risk were excluded), they showed that SCORE results were compatible with Framingham, especially in men. All other risk algorithms, except for the high-risk SCORE model, gave similar results to Framingham. In our study, it was determined that the Framingham and ASSIGN models resulted in greater risk estimations compared to the BNF and QRISK2 models in the whole group. In addition, it was revealed that the predicted risk score in the presence and absence of metabolic syndrome differed in all risk models. G B John Mancini, et al. (13) found that a sudden transition from the Framingham model to other risk models, such as the ATP III Reynolds, would put low-risk groups into a higher-risk category, which would significantly alter the treatment protocol to be applied. According to the results of our study, our suggestion is to carry out a gradual transition to a new model after determination of reliability via population-based studies, rather than attempting a rigid change into a pre-determined model. In a study involving 40,000 people conducted in the Netherlands, Scheltens et al. (14) examined the Framingham and SCORE risk models in terms of distinctiveness, ability to measure, and the number of people that would require treatment according to the new treatment guidelines. They found that both models were similar in distinguishing patients, based on the resulting ROC curve analysis. However, the measurement capability of both models was found to be low. According to the treatment guidelines applied in the Netherlands, 0.7% of the participants required treatment according to Framingham, while this value was found to be 0.4% for SCORE. As a result, while they reported the results of the two models to be similar, they also

concluded that attempts to procure newer models should pay attention to providing better measurement capability, since the measurement capabilities of both methods were limited (14). Scheltens et al. (14) evaluated two risk models similar to the work of Mancini and colleagues; whereas we assessed four risk models in a specific patient group. In our study, differently, the distinctiveness and measurement ability of the risk models were compared over the probability values predicted by risk models in the low, medium and high-risk groups. Cardiovascular risk estimates for the hyperlipidemia and metabolic syndrome groups were found to differ in all four risk models.

In the study by Simmonds et al. (15), which included 500,000 individuals, the Framingham 1991, Framingham 2008, Reynolds, ASSIGN, SCORE and QRISK2 cardiovascular risk models were used to ascertain the risk of cardiovascular events in England. Sensitivity and specificity criteria were emphasized in evaluating the performance of the models. The correct measurement values of all six algorithms were found between 72-79% with a 20% margin of error. Simmonds et al. (15) reported that, different from our study results, all tests yielded similar results at the end of the study. In our study, it was found that the QRISK2, BNF and ASSIGN scores respectively estimated high risk among 62.5%, 46.4% and 96.4% of subjects who were defined to have high-risk according to the Framingham criteria. Additionally, among the subjects who were defined to have high-risk according to the QRISK2 criteria, the Framingham, BNF and ASSIGN scores identified that 71.4%, 46.9% and 91.8% of these were individuals at high risk, respectively.

One of the most important limitations of our study is the absence of cardiovascular risk assessment via coronary angiography and the lack of atherosclerosis evaluation or follow-up studies. As such, we can no tinder superiority any of the models. As a consequence, any risk assessment method can be preferred depending on its applicability to the patients, the features of the institution that is utilizing the measures, and possibly, the ease of application. The presence or absence of metabolic syndrome does not appear to have an effect size that could alter the reference of scoring models. However, in our study, we showed that all of the four scoring systems provided significantly different results in both groups with and without metabolic syndrome.While the BNF and QRISK2 scores were similar in the whole group, these risk scores gave different results in the two subgroups formed according to the presence of metabolic syndrome. It was thought that the reason for this might be the different parameters evaluated in these two risk scores and the homogenous absence of these parameters in the groups with and without metabolic syndrome. In order to understand which of these risk scores has a higher diagnostic and prognostic predictive value in both the whole group and the group with metabolic syndrome, it is necessary to perform follow up for cardiovascular events and to investigate cardiovascular disease with a highly reliable method (such as coronary angiography, or carotid intima media thickness measurement) in prospective studies.

Conclusion

When four different risk scores were compared in newly diagnosed hyperlipidemia patients without differentiation of metabolic syndrome, it was revealed that only BNF and QRISK2 scores gave similar results, while the Framingham and ASSIGN scores provided different results from each other, as well as from BNF and QRISK2. In the literature, a cardiovascular risk probability model for the metabolic syndrome and hyperlipidemia patient group has not been determined yet; therefore, we believe that the results of our study will contribute to literature in this regard. However, our data should be supported by further objective evaluations and prospective studies.

Authorship Contributions

Concept: S.U., Design: S.U., Data Collection or Processing: A.İ., Analysis or Interpretation: O.B., S.U., Literature Search: N.D., Y.A., Writing: A.İ.

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The Fate of the Gallbladder in Patients Admitted to Bariatric Surgery

Bariatrik Cerrahiye Kabul Edilen Hastalarda Safra Kesesinin Kaderi

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Abstract

Aim: Obesity has become a rapidly increasing public health problem all over the world. Obesity itself is a risk factor for cholelithiasis, and the fast weight loss period after bariatric surgery is a situation that increases this risk. The fact that both obesity and surgical treatment of obesity increases the formation of stones in the gall bladder has made it even defendible that cholecystectomy should be performed routinely during the bariatric surgery at one stage, even if there is no cholelithiasis. In this study, we aimed to evaluate our gallbladder approach in patients who were decided to undergo bariatric surgery in our center, together with the literature reviews.

Methods: In our study, the data of 185 patients who underwent bariatric surgery due to obesity in the University of Health Sciences Kanuni Sultan Suleyman the in Istanbul Training and Research Hospital Clinic of, Department of General Surgery, between 2018 and 2020 were retrospectively obtained. A total of 185 patients were included in the study. The patients were divided into group 1 (sleeve gastrectomy) and Group 2 (gastric bypass) according to their operation techniques.

Results: The average age was 36.43 ± 9.52, the ratio of women/men was 151 (81.6%)/34 (18.4%). Mean body mass index (BMI) was determined as 44.16±5.09. In the postoperative period, gallstones were formed in 27 (14.6%) patients, whereas gallstones were not detected in 158 (85.4%) patients. There was no significant difference between the groups in terms of postoperative gallstone formation.

Conclusion: In the light of the literature and after our clinical experience, we do not require routine imaging of the gallbladder before bariatric surgery in asymptomatic patients, and we recommend performing concomitant cholecystectomy only in symptomatic patients.

Keywords: Obesity, bariatric surgery, cholelithiasis, cholecystectomy, gallstone

Öz

Amaç: Obezite, tüm dünyada hızla artan bir toplum sağlığı problemi haline gelmiştir. Obezitenin kendisi safra kesesi taşı oluşumu için bir risk faktörü olup, bariatrik cerrahi sonrası hızlı kilo verme dönemi de bu riski artıran bir durumdur. Hem obezitenin hem de obezitenin cerrahi tedavisinin safra kesesinde taş oluşumunu artırması, bariatrik cerrahi sırasında kesede taş olmasa bile kolesistektominin de rutin olarak yapılması gerektiğini bir dönem savunulur hale getirmiştir. Biz bu çalışmamızda merkezimizde bariatrik cerrahi kararı verilen hastalarda safra kesesi yaklaşımımızı literatür değerlendirmeleri ile beraber ele almayı amaçladık.

Yöntemler: Çalışmamızda 2018-2020 yılları arasında İstanbul Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi Genel Cerrahi Kliniği'nde obezite nedeni ile bariatrik cerrahi operasyonu geçiren toplan 185 hastanın bilgileri retrospektif olarak değerlendirildi. Çalışmaya toplam 185 hasta dahil edildi. Hastalar operasyon tekniklerine göre grup 1 (sleeve gastrektomi) ve grup 2 (gastrik bypass) olacak şekilde ayrıldı.

Bulgular: Yaş ortalaması 36,43±9,52 yıl, kadın/erkek oranı ise 151 (%81,6)/34 (%18,4) idi. Ortalama vücut kitle indeksi (VKİ) 44,16±5,09 olarak tespit edildi. Postoperatif dönemde 27 (%14,6) hastada safra kesesi taşı oluşurken, 158 (%85,4) hastada safra kesesinde taş tespit edilmedi. Gruplar arasında postoperatif safra kesesi taşı oluşumu açısından anlamlı fark yoktu.

Sonuç: Literatür ışığında ve klinik tecrübelerimiz sonrası, bariatrik cerrahi öncesi safra kesesi görüntülemesinin asemptomatik hastalarda rutin yapılmasını gerek görmemekte, sadece semptomatik hastalarda eşzamanlı kolesistektomi yapılmasını önermekteyiz.

Anahtar Sözcükler: Obezite, bariatrik cerrahi, safra kesesi taşı, kolesistektomi, safra taşı

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Introduction

Obesity has become a rapidly increasing public health problem all over the world. This problem has serious consequences due to the comorbid diseases it brings. For this reason, many studies have been conducted on obesity treatment all over the world. Studies have shown that the gold standard in the fastest, permanent and long-term treatment of obesity is bariatric surgery (1). Bariatric surgical procedures such as Roux-en-Y gastric bypass (RYGB), laparoscopic sleeve gastrectomy (LSG), single anastomotic gastric bypass (OAGB), biliopancreatic diversion-duodenal switch (BPD-DS) and laparoscopic adjustable gastric band (LAGB) are the modern techniques used nowadays. It is a fact that bariatric surgery has benefits for the improvement of comorbid diseases (2).

In addition to all the benefits of these surgeries, there are also problems that may occur after surgery. One of these is the increased risk of gallstones formation, as stated in the literature (3). Obesity itself is a risk factor of cholelithiasis, and the period of rapid weight loss after bariatric surgery also increases this risk (4). The rate of cholelithiasis in the first year after bariatric surgery has been reported to be 35% (5).

Rapid weight loss causes an increase in bile cholesterol concentration, the major metabolic counterpart of cholesterol, which is the main reason for the formation of gallstones (6,7). Gallbladder hypomotility, increase in calcium secretion, impaired enterohepatic circulation of arachidonic acid derivatives, biliary mucin and bile salts also contribute to gallstone formation (8,9). As a result, after bariatric surgery, patients are at risk of developing stone complications such as biliary colic, acute cholecystitis, acute pancreatitis, and gallstone migration.

The risk of gallstone formation is very high in patients who have a high body mass index (BMI) before bariatric surgery and will lose weight in a short time after surgery (10).

For these reasons, there is no consensus in the literature regarding the investigation of gallstones with bariatric pre-surgical imaging, how to approach the gallbladder in patients with asymptomatic gallstones and in symptomatic patients, and there are various meta-analyzes regarding those above.

In this study, we aimed to evaluate our gallbladder approach in patients who were decided to have bariatric surgery in our center, together with the literature reviews.

Methods

In our study, the data of 200 consecutive patients who underwent bariatric surgery due to obesity in the General Surgery Clinic of Istanbul Kanuni Sultan Suleyman Training and Research Hospital between 2018 and 2020 were retrospectively obtained. Ethics committee approval of the study was obtained from the local ethics committee with the number of KAEK-2020.12.220 on 10.12.2020. Patients who underwent bariatric surgery for obesity were included in the study. Those who had cholecystectomy before bariatric surgery, those who underwent concomitant cholecystectomy (CC) during bariatric surgery, those with concomittant gall stoness and those who did not attend their follow-up regularly were excluded from the study. Patients' age, gender, pre-operative BMI, pre-operative comorbid diseases, pre-operative hepatobiliary ultrasonography (USG) findings, which surgical procedure they underwent, postoperative BMI, postoperative complications, and ultrasound findings 6 months after surgery were recorded. The patients were divided into two groups according to the bariatric surgical procedure. The patients who underwent LSG were included in the first group, and the patients who had laparoscopic RYGB in the second.

Statistical Analysis

Frequency and percentage for categorical variables, mean and standard deviation values for continuous variables were given. The normality of the variables was checked with the Shapiro-Wilk test. Mann-Whitney U test was used for the analysis of continuous variables not distributed normally. Chi-square test was used for comparison of categorical variables. All analyzes were performed with the Social Sciences Statistics Package for Windows 22.0 (SPSS Inc., Chicago, Illinois, USA) and results with $p<0.05$ were considered significant.

Results

A total of 185 patients were included in the study. The average age was 36.43±9.52 years and, the ratio of women/men was 151 (81.6%)/34 (18.4%). Mean BMI was determined as 44.16±5.09. When comorbidities were evaluated, 116 (62.7%) patients had comorbidity, while 69 (37.3%) patients did not. There were no preoperative gallstones in any patient. The mean BMI at the postoperative 6th month was found to be 32.30±3.98 (Table 1). The patients were divided into group 1 (sleeve gastrectomy) and group 2 (gastric bypass) according to their operation techniques. There were 138 (74.6%) patients in group 1, and 47 (25.4%) patients in group 2. The mean age of the groups was 36.28±9.58 and 36.87±9.44 years, respectively, there was no significant difference between the groups in terms of mean age ($p=0.567$). The female/male ratio was 120 (87.0%)/18 (13%) in group 1, and 31 (66.0%)/16 (34.0%) in group 2. There was a significant difference in gender between the groups ($p=0.002$). In group 1, female gender was significantly higher. In group 1, 89 (64.5%) patients had

Table 1. Demographic data of patients	
Age	36.43±9.52 (20-60)
Gender	
Female	151 (81.6%)
Male	34 (18.4%)
BMI	44.16±5.09
Comorbid disease	
Yes	116 (62.7%)
No	69 (37.3%)
Sixth month BMI	32.30±3.98

Frequency and percentage values for categorical variables, mean and standard deviation values for continuous variables are given.
BMI: Body mass index

Table 2. Comparison of groups			
	Group 1 (n=138)	**Group 2 (n=47)**	**p**
Age	36.28±9.58	36.87±9.44	0.567
Gender			
Female	120 (87.0%)	31 (66.0%)	0.002
Male	18 (13%)	16 (34.0%)	
BMI	45.31±4,77	40.76±4.45	<0.001
Comorbid disease			
Yes	89 (64.5%)	27 (57.4%)	0.389
No	46 (35.5%)	20 (42.6%)	
Sixth month BMI	32.44±4.31	31.91±2.78	0.895
Cholelithiasis			
Yes	24 (17.4%)	3 (6.4%)	0.092
No	114 (82.6%)	44 (93.6%)	

Frequency and percentage for categorical variables, mean and standard deviation values for continuous variables are given. Chi-square and Mann-Whitney U tests were used in group comparisons. P<0.005 was considered significant. BMI: Body mass index

additional disease, while 46 (35.5%) patients did not. While additional disease was detected in 27 (57.4%) patients in Group 2, it was not detected in 20 (42.6%) patients. There was no significant difference between the groups in terms of comorbidity (p=0.389). The mean BMI of the groups were 45.31±4.77 and 40.76±4.45, respectively. BMI was significantly different between groups (p<0.001). BMI was significantly higher in group 1. The mean BMI of the groups in the postoperative 6th month was 32.44±4.31, 31.91±2.78, respectively. There was no significant difference between the groups in terms of 6th month BMI (p=0.895). In the postoperative period, gallstones were formed in 27 (14.6%) patients, whereas gallstones were not detected in 158 (85.4%) patients. There was no significant difference between the groups in terms of postoperative gallstone formation (p=0.092) (Table 2).

Discussion

It is known that the risk of gallstone formation increases considerably after bariatric surgery, and its incidence varies between 10% and 38% (11). This also carries the risks of biliary complications.

Prophylactic cholecystectomy along with bariatric surgery prevents gallstone formation and stone-related complications. In addition, CC will reduce additional costs and hospitalization. However, simultaneous cholecystectomy is technically difficult during laparoscopic bariatric surgery due to, suboptimal port placement, visceral obesity, difficulty in accessing the gallbladder by the large liver, and prolonged surgery (12). In conclusion, while the place of prophylactic cholecystectomy in morbidly obese patients remains unclear, the timing of cholecystectomy in these patients remains a concern (13).

Gallstone migration becomes a difficult situation to manage in cases of BPD or gastric bypass (GB). Changes in anatomy prevent standard treatment with endoscopic retrograde choledochopancreaticography (13).

Many randomized studies have shown that the administration of ursodeoxycholic acid (UDCA) after bariatric surgery reduces gallstone formation and cholecystectomy rates after bariatric surgery (14-17). Sugerman et al. (18) showed that the use of UDCA (600 mg per day) for 6 moths after bariatric surgery reduces the formation of gallstones (cholelithiasis was detected in 2% of patients using UDCA and in 32% of patients who did not). Especially with UDCA prophylaxis (for 6 months), the risk of postoperative biliary complications appears low, and CC can be avoided (13).

In our clinic, we did not start UDCA in our patients after surgery. In our series, gallstones were observed in 14.6% of the patients (27 patients) in the postoperative 6th month. Laparoscopic cholecystectomy was performed in 3 of these patients because they were symptomatic, and no complications were observed during and after the operation. These 3 patients were excluded as described previously.

Sakorafas et al. (19) and Patel et al. (20) in their studies, they reported that asymptomatic gallstones became symptomatic after bariatric surgery as less than 5%. In the light of such studies, surgical treatment of asymptomatic gallstones after bariatric surgery is not routinely performed.

In a review study, routine gallbladder imaging before LSG, LAGB, RYGB operations and CC with surgery were not recommended in asymptomatic patients (4).

Studies in the literature report that performing CC together with bariatric surgery brings high morbidity and long hospitalization periods (21). The addition of cholecystectomy to bariatric surgery is associated with

an increased risk of postoperative complications and an additional mean operative time of 32.84 minutes. Technically, the difficulty of accompanying cholecystectomy and bariatric surgery may increase the risk of complications (22,23).

In our series, 10 patients underwent CC, and it did not cause any complications or prolonged hospitalization.

In a study, while the rate of patients with symptomatic bile mud or stones after RYGB was 8.7%, this rate was reported as 3.8% after LSG (24).

According to a meta-analysis, increases in complication rates such as anastomotic leakage and stricture formation were observed in patients who underwent RYGB+CC compared to the patient group who underwent RYGB alone (24). However, the same study, on the other hand, stated that bariatric surgery increased the risk of gallstone formation, and stated that controlled randomized large-series studies are needed (24).

In one study, it was reported that the procedure with the lowest rate of cholecystectomy in the 10-year follow-up period after bariatric surgery was LAGB (6.5%), followed by RYGB (9.7%) and LSG (10.1%), respectively (25).

In a meta-analysis, the risk of postoperative complications from cholecystectomy was lower than with post- or pre-bariatric surgery when performed with bariatric surgery. In addition, the risk of reoperation was lower for CC (13). In the same study, the authors stated that prophylactic cholecystectomy could be avoided because they reported that bariatric surgery patients had a low incidence of biliary complications, and CC increased the risk of postoperative complications and the mean operation time. However, they noted that if cholecystectomy is not performed during bariatric surgery, patients should be followed with special care for biliary complications. In the same study, it was stated that bariatric surgery and CC could be considered in patients with complaints about the gall bladder (13).

Although the vast majority of the stones are formed within 6 months after surgery, lenghtening of the follow-up period might have increased the number of patients with newly formed stones which may be interpreted as the weak point limiting the study.

In summary, we can mention the effects of bariatric surgery on other comorbid diseases and other undesirable effects such as kidney stones. LSG has a positive impact on hypothyroidism. Ruiz-Tovar et al. (26) found significant decrease in TSH level after LSG. The impact of LSG on hypertension is variable. Abelson et al. (27) also reported similar rates of 31% remission at 5 and 7 year follow up respectively. Regarding type 2 diabetes mellitus, Golomb et al. (28) who demonstrated only 20% remission rate at 5 years. Abelson et al. (27) who found marked decline in the need of insulin therapy and mean number of oral hypoglycemic drugs in 132 diabetic patients undergoing LSG at 5 year follow-up. Another problem is kidney stones after bariatric surgery. From a review of a database of private insurance claims which contained 4639 patients who were matched to obese controls. Over a median follow-up of about 4 years, 7.65% of bariatric patients had a stone compared to 4.63% of obese controls (29).

Conclusion

In the light of the literature and after our clinical experience, we do not require routine imaging of the gallbladder before bariatric surgery in asymptomatic patients, and we recommend performing CC in symptomatic patients. We think that in symptomatic gallstones occurring after bariatric surgery, surgery does not bring about a serious increase in complications due to previous bariatric surgery.

Authorship Contributions

Concept: M.C.K., Design: M.C.K., Data Collection or Processing: M.C.K., Analysis or Interpretation: S.Y., Literature Search: M.C.K., Writing: M.C.K.

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Impact of Admission, Fasting Glucose and HbA1c Levels on in-stent Restenosis in The Patients Treated with Primary Percutaneous Coronary Intervention in 5-Year Follow-up

Beş Yıllık Izlemde HbA1c, Başvuru ve Açlık Kan Şekeri Düzeylerinin Primer Perkütan Koroner Girişim Yapılan Hastalarda in-Stent Restenozuna Etkisi

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Abstract

Aim: Despite advances in-stent technology, in-stent restenosis (ISR) is still a major problem following percutaneous coronary intervention (PCI) and its reasons have not been fully revealed. In the presented study, we investigated the effect of admission blood glucose (ABG), fasting blood glucose (FBG) and glycated hemoglobin A1c (HbA1c) levels on coronary ISR patients with ST-elevation myocardial infarction (STEMI) who underwent primary PCI in five-year follow-up.

Methods: From 2.900 patients who underwent coronary stent implantation for STEMI from January 2008 through December 2012 were retrospectively analyzed through the hospital digital recording system. Of these, 264 patients who underwent control coronary angiography during the five-year follow-up were included in the study. Patients were divided into two main group ISR and non-ISR; were divided into two subgroups diabetic and non-diabetic groups were compared with HbA1c, ABG, FBG and angiographic parameters.

Results: There were 127 patients in the ISR group (diabetic: 36 non-diabetic: 91) and 137 patients in the non-ISR group (diabetic: 43 non-diabetic: 94). Regardless of the patients diabetes status, no significant difference was found between the groups with and without ISR in terms of HbA1c, FBG and ABG. A significant relationship was found between the baseline HbA1c value and having ISR only in the diabetic subgroup (p=0.01).

Conclusion: This study results showed that in diabetic STEMI patients who underwent primary PCI, higher HbA1c levels were associated with higher ISR rates, but not with FBG and ABG levels.

Keywords: ST elevation myocardial infarction, blood glucose, glycated hemoglobin A1c, percutaneous coronary intervention, coronary angiography, coronary restenosis, diabetes mellitus

Öz

Amaç: Stent teknolojisindeki ilerlemelere rağmen perkütan koroner girişimi (PKG) takiben gelişen in-stent restenozu (ISR) halen önemli bir sorundur ve nedenleri tam olarak ortaya konulamamıştır. Sunulan çalışmada primer PKG uygulanmış ST-segment yükselmeli akut miyokard enfarktüsü (STEMI) hastalarında başvuru kan şekeri (BKŞ), açlık kan şekeri (AKŞ) ve HbA1c düzeylerinin 5 yıllık izlemde koroner ISR üzerine etkisi analiz edildi.

Yöntemler: Ocak 2008-Aralık 2012 tarihleri arasında STEMI nedeniyle koroner stent implantasyonu uygulanan 2.900 hasta, hastane dijital kayıt sisteminden geriye dönük olarak incelendi. Bunlardan beş yıllık takipte kontrol koroner anjiyografisi yapılan 264 hasta çalışmamıza dahil edildi. Hastalar ana grup olarak ISR ve non-ISR; alt grup olarak ise diyabetik ve diyabetik olmayanlar olarak ayrıldı ve gruplar HbA1c, BKŞ, AKŞ ile birlikte anjiyografik parametreler açılarından karşılaştırıldı.

Bulgular: ISR grubunda toplam 127 hasta (diyabetik: 36 non-diyabetik 91) ve non-ISR grubunda toplam 137 hasta (diyabetik: 43 non-diyabetik: 94) mevcuttu. Hastaların diyabetik olup olmamasına bakılmaksızın, ISR olan ve olmayan gruplar arasında AKŞ, BKŞ ve HbA1c değerleri açısından anlamlı fark saptanmadı. Sadece diyabetik alt grupta HbA1c değeri ile ISR arasında anlamlı ilişki saptandı (p=0,01).

Sonuç: Çalışma sonuçlarımız, primer PKG uygulanan diyabetik STEMI hastalarında yüksek HbA1c düzeylerinin daha yüksek ISR oranlarıyla ilişkili olduğunu, fakat BKŞ ve AKŞ düzeyleri ile ilişkili olmadığını gösterdi.

Anahtar Sözcükler: ST yükselmeli miyokard enfarktüsü, kan glukozu, glikozile hemoglobin A1c, perkütan koroner girişim, koroner anjiyografi, koroner restenoz, diabetes mellitus

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Introduction

Restenosis is defined as a decrease in the luminal diameter after the percutaneous coronary intervention (PCI), regarding if the stent is implanted or not. In-stent restenosis (ISR) is often defined as the restenosis anywhere between 5 mm from the proximal or distal edges of the stent associated with the loss of more than 50% of the diameter of the vessel which had been successfully treated (1-2). The most important limitations of the successful treatment of stenotic coronary artery through PCI are acute or late stent thrombosis and ISR.

Despite significant advances in interventional techniques such as new-generation bare-metal stents (BMS), drug-eluting stents (DES), drug-coated balloons, and drug therapies, ISR remains a significant problem in interventional cardiology, especially in diabetic patients (3-6). Diabetes mellitus (DM) is a critical patient-related cause in the pathogenesis of ISR (7). Glycosylated hemoglobin is a biomarker for the time-integrated average blood glucose and is assessed clinically with glycated hemoglobin A1c (HbA1c). HbA1c is used increasingly and more commonly for screening during the management of diabetes. HbA1c is more closely related to the total risk of complications in DM than other (single or intermittent) measurements of blood glucose level (8). HbA1c provides a simple method to assess a patient's DM status and prognosis of coronary stent implantation in terms of ISR and other cardiovascular outcomes (9,10).

In the last century, although many studies have been conducted on ISR, but it has not been clearly revealed which patients are susceptible to ISR both in diabetic and non-diabetic patients. This study aimed to evaluate the relationship between ISR and HbA1c, admission blood glucose (ABG), and fasting blood glucose (FBG) in diabetic and non-diabetic patients.

Methods

Patient Population

The study protocol was in accordance with the Declaration of Helsinki and approved by the local Dr. Siyami Ersek Hospital) Ethics Committee (13.08.2013 date and 2. number decision). We accessed hospital digital records retrospectively for the patients who underwent coronary stent implantation for ST-segment elevation myocardial infarction (STEMI) from January 2008 through December 2012 from a total of 2.900 patients. Among these patients, 2.636 patients who did not have control coronary angiography during the five-year follow-up were excluded. In those patients, we included 264 patients whose control coronary angiography was performed because of a stable angina pectoris, unstable angina pectoris, non-STEMI, and STEMI during the five-year follow-up. ISR was detected in 127 patients, and no-ISR was detected in 137 patients.

Those who had a history of diabetes and used a restrictive diet, oral hypoglycemic medication, or insulin or those with an FBG level of ≥126 mg/dL on two occasions during hospitalization or an HbA1c level ≥6.5% were evaluated as diabetic. DM was detected in 79 patients (HbA1c ≥6.5%); 185 patients were non-diabetic (HbA1c <6.5%).

The patients' clinical and demographic characteristics were noted, including age, gender, and histories of DM, arterial hypertension, hyperlipidemia, coronary artery disease (CAD), tobacco use, and medications.

Laboratory Tests

For each patient, FBG, ABG, HbA1c, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, total cholesterol, white blood cell count (WBC), hemoglobin, platelet count, and peak creatine kinase MB isoenzyme (CKMB) were measured in the first 24 hours of hospital admission. HbA1c was examined by immuno-turbidimetric method (Modular P800i, Roche, Germany) with the Tina-quant HgA1c II kit.

Angiographic Parameters

Current practice guidelines were followed for coronary interventions, and the data were recorded in digital storage for quantitative analysis. Access site for PCI was femoral with the Judkins technique. Two experienced interventional cardiologists estimated the degree of coronary stenosis visually. Significant stenosis was defined as a luminal narrowing of >50% in a major subepicardial vessel (left anterior descending, left circumflex, or right coronary artery). After stent placement, clopidogrel was used for at least one year, and aspirin was used indefinitely. All treatments were given following the European Society of Cardiology guidelines. The patient adherence to medical therapy was standardized. Coronary angiography was performed secondarily during routine clinical follow-up in the patients with stable angina pectoris, unstable angina pectoris, non-STEMI, and STEMI. The Judkins technique was used to record control coronary angiograms. Two independent cardiologists who were blinded to the patients' data interpreted the angiograms. In coronary angiography, a narrowing of >50% in 5-mm proximal and the distal of the stent edge in an otherwise normal diameter was accepted as stent restenosis.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS Windows version 20.0, IBM Corp, USA) was used in all analyses. Quantitative variables with a normal distribution were given as the mean ± standard deviation, and those

with non-normal distribution were given as the median (minimum and maximum). Chi-square test and Fisher exact test were used for categorical variables to compare the groups. Mann-Whitney U test was used to compare the instruments of the two groups that were not normally distributed and the normal distributions were compared using the student's t-test. A p-value of <0.05 was considered statistically significant.

Results

Of the 264 patients in this study, 127 patients were diagnosed with ISR over 50% stenosis. There were 79 diabetic patients: 36 in the ISR group and 43 non-ISR group. The demographic characteristics of the patients and the risk factors were given in Table 1. Their baseline clinical characteristics were similar except they are more likely to be male in in ISR group and history of coronary artery disease is more common in non-ISR group. The vessels implanted with a stent in the primary PCI, the number of vessels involved, and the restenosis treatment were shown in Table 2. The average stent diameter and length were 3.0±0.42 and 20.0±6.1 in the ISR group and 2.98±0.75 and 17.7±6.0 in the non-ISR group, respectively. The two groups did not differ significantly in terms of target vessel, lesion type classified according to American College of Cardiology/American Heart Association, and implanted stent type, size except length. Of the patients who developed ISR, 63 underwent repeat PCI, 46 underwent coronary bypass operation, and 18 were followed up with drug treatment.

The laboratory parameters of the patients were detailed in Table 3. For the whole patient group, the mean FBG, ABG, and HbA1c values were 121±5, 171±85, and 6.65±1.69 in the ISR group and 118±41, 169±83, and 6.39±1.29 in the non-ISR groups, respectively. The difference between the ISR and non-ISR groups was not statistically significant (p>0.05). When these parameters were examined in the diabetic subgroup, there was no significant difference between the ISR and non-ISR groups regarding the FBG (164±82 vs.152±53, p=0.44) and ABG (245±100 vs. 229±105, p=0.53). However, a significant difference was found between the ISR and non-ISR groups regarding the HbA1c values (7.47±1.57 vs. 8.60±1.82, p=0.01) (Figure 1). The differences between the ISR and non-ISR groups in the diabetic patients regarding the demographic, angiographic, and laboratory parameters were given in Table 4.

Table 1. Baseline demographic characteristics of the study population

	ISR (n=127)	Non-ISR (n=137)	p
Age (years), mean ± SD	56.1±10.2	56.8±10.8	0.54
Gender male, n (%)	113 (89%)	69 (50.4%)	0.01
Female, n (%)	14 (11%)	68 (49.6%)	0.01
Hypertension, n (%)	64 (50.4%)	57 (41.6%)	0.37
Diabetes mellitus, n (%)	36 (28.3%)	43 (31.4%)	0.59
Insulin user, n (%)	2 (5.5%)	17 (39.5%)	0.01
Oral anti-diabetic user, n (%)	34 (94.4%)	26 (60.4%)	0.13
Hyperlipidemia, n (%)	54 (42.5%)	39 (28.5%)	0.18
Smoker, n (%)	71 (55.9%)	63 (46%)	0.31
History of coronary artery disease, n (%)	19 (15%)	79 (57.7%)	0.01

SD: Standard deviation, ISR: In-stent restenosis

Table 2. Baseline angiographic parameters of the study population and treatment modality of ISR group

	ISR (n=127)	Non-ISR (n=137)	p
Culprit artery			
LAD, n (%)	66 (51.9%)	73 (53.2%)	
CX, n (%)	18 (14.1%)	29 (21.1%)	0.18
RCA, n (%)	43 (33.8%)	35 (25.5%)	
Number of diseased vessels, mean±SD	1.80±0.79	1.68±0.80	0.23
Stent diameter (mm), mean±SD	3.0±0.42	2.98±0.75	0.72
Stent length (mm), mean ± SD	20.0±6.1	17.7±6.0	0.01
Treatment of stent restenosis			
Medical, n (%)	18 (14.1%)	-	-
PCI, n (%)	63 (49.6%)	-	-
CABG, n (%)	46 (36.2%)	-	-

LAD: Left anterior descending artery, CX: Circumflex artery, RCA: Right coronary artery, CABG: Coronary artery by-pass grafting, SD: Standard deviation, ISR: In-stent restenosis

Table 3. Admission laboratory parameters of study population

	ISR (n=127) Mean ± SD	Non-ISR (n=137) Mean ± SD	p
Hemoglobin (mg/dL)	14.1±1.4	14.0±1.6	0.21
Platelet (103/μL)	295±80	235±75	0.25
WBC (103/μL)	12.1±3.9	11.9±4.6	0.79
Creatinine (mg/dL)	0.89±0.31	0.88±0.22	0.65
Peak-CKMB (IU/L)	160±120	195±140	0.05
Total cholesterol (mg/dL)	189±53	184±43	0.40
LDL cholesterol (mg/dL)	116±41	110±36	0.20
HDL cholesterol (mg/dL)	37±9	39±10	0.09
Triglyceride (mg/dL)	130±108	141±100	0.77
Fasting blood glucose (mg/dL)	121±5	118±41	0.61
Admission blood glucose (mg/dL)	171±85	169±83	0,82
HbA1c (%)	6.65±1.69	6.39±1.29	0.17

SD: Standard deviation, WBC: White blood cell, CKMB: peak Creatine kinase MB isoenzyme, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, HbA1c: Glycated hemoglobin A1c, ISR: In-stent restenosis

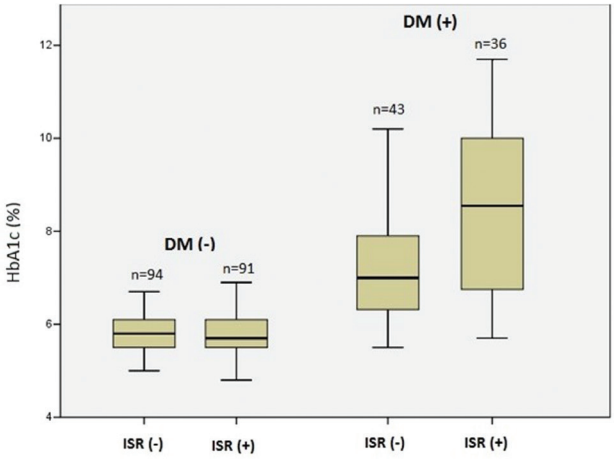

Figure 1. Comparison of in-stent restenosis with HbA1c level in diabetic patients and non-diabetic group
ISR: In-stent restenosis, DM: Diabetes mellitus, HbA1c: Glycated hemoglobin A1c

Table 4. Demographic characteristics and laboratory and angiographic parameters in the diabetic sub-group

	ISR (n=36)	Non-ISR (n=43)	p
Age (years) mean ± SD	55.8±11.3	58.1±8.8	0.33
Gender male (n) (%)	32 (88.8%)	18 (41.8%)	0.01
Female (n) (%)	4 (11.1%)	25(58.1%)	0.01
Hypertension (n) (%)	25 (69.4%)	22 (51.1%)	0.20
Hyperlipidemia (n) (%)	20 (55.5%)	15 (34.8%)	0.06
History of coronary artery disease (n) (%)	6 (16.6%)	30 (69.7%)	0.01
Hemoglobin (mg/dL) mean±SD	13.9±1.4	13.7±1.9	0.61
WBC (103/µL) mean ± SD	12.1±3.9	11.9±4.6	0.79
Creatinine (mg/dL) mean ± SD	0.89±0.31	0.88±0.22	0.46
Peak CKMB (IU/L) mean ± SD	115±84	205±150	0.02
Total cholesterol (mg/dL) mean ± SD	192±48	189±49	0.79
LDL cholesterol (mg/dL) mean ± SD	112±44	115±39	0.71
HDL cholesterol (mg/dL) mean ± SD	36±10	38±9	0.31
Triglyceride (mg/dL) mean ± SD	151±109	159±121	0.48
Fasting blood glucose (mg/dL) mean ± SD	164±82	152±53	0.44
Admission blood glucose (mg/dL) mean ± SD	245±100	229±105	0,53
HbA1c (%) mean ± SD	8.60±1.82	7.47±1.57	0.01
Stent diameter (mm) mean ± SD	3.02±0.32	2.96±0.78	0.69
Stent length (mm) mean ± SD	20.41±5.48	18.53±5.69	0.15

SD: Standard deviation, WBC: White blood cell count, CKMB: peak creatine kinase MB isoenzyme, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, HbA1c: Glycated hemoglobin A1c, ISR: In-stent restenosis

Discussion

It is well known that DM is associated with an increased of cardiovascular mortality and plays a main role in ISR development (11). Additionaly, it is shown that ISR was an independent risk factor for mortality (12). The results of this study evaluated the effects of FBG, ABG, and HbA1c on the long-term ISR rate in both diabetic and non-diabetic patients who underwent primary PCI. Our study shows that admission HbA1c levels are associated with higher ISR rates in a diabetic STEMI population treated with primary PCI. Our findings are supported with several previous studies reporting increased rates of ISR following PCI in uncontrolled diabetic patients (13-15).

Measurement of HbA1c levels with ABG and FBG levels in non-diabetic patients may improve risk assessment in patients presenting with acute STEMI. Our study showed no association between these parameters and ISR rates in non-diabetic patients. Naito et al. (13) investigated the effects of ABG and HbA1c on the long-term PCI outcomes in 452 non-diabetic patients presenting with acute coronary syndrome (ACS). They showed that the ABG and HbA1c values were independently correlated with the clinical outcomes in non-diabetic ACS patients treated with PCI (13). This association is supported by some other works (16,17). Our investigation could not demonstrate this association. The reason of this can be low number of study patients in this study and glucose variability.

In an other study high HbA1c levels were suggested to predict cardiovascular disease frequency and mortality in non-diabetic patients, independent of FBG (18). Pai et al. (19) showed in their study that increasing HbA1c levels increases the risk of coronary artery disease in patients with diabetes and non-diabetic patients. In a meta-analysis by Cavero-Redondo et al. (10), a relationship was found between HbA1c levels and mortality and cardiovascular outcomes in both diabetic and non-diabetic patients. In their analysis, all-cause mortality was higher when HbA1c levels were over 6% and 8% in non-diabetic and diabetic patients, respectively (10).

The development of ISR is a complex and multifactorial process; there are patient-, vessel-, and procedure-related factors involved (20). Among the identified factors associated with the patient, DM was considered one of the high-risk clinical predictors for ISR, which was found to be 30-50% following BMS implantations (21). Although the rate of ISR in DES was found to be lower than that in BMS, it was higher in diabetic patients compared to non-diabetic patients (22,23). In a meta-analysis, an association was found between HbA1c level and cardiovascular outcomes in diabetic patients after PCI (24). Anatomically, both lesion length and lesion diameter are predictors of ISR. Generally, the length of the lesion and the narrow

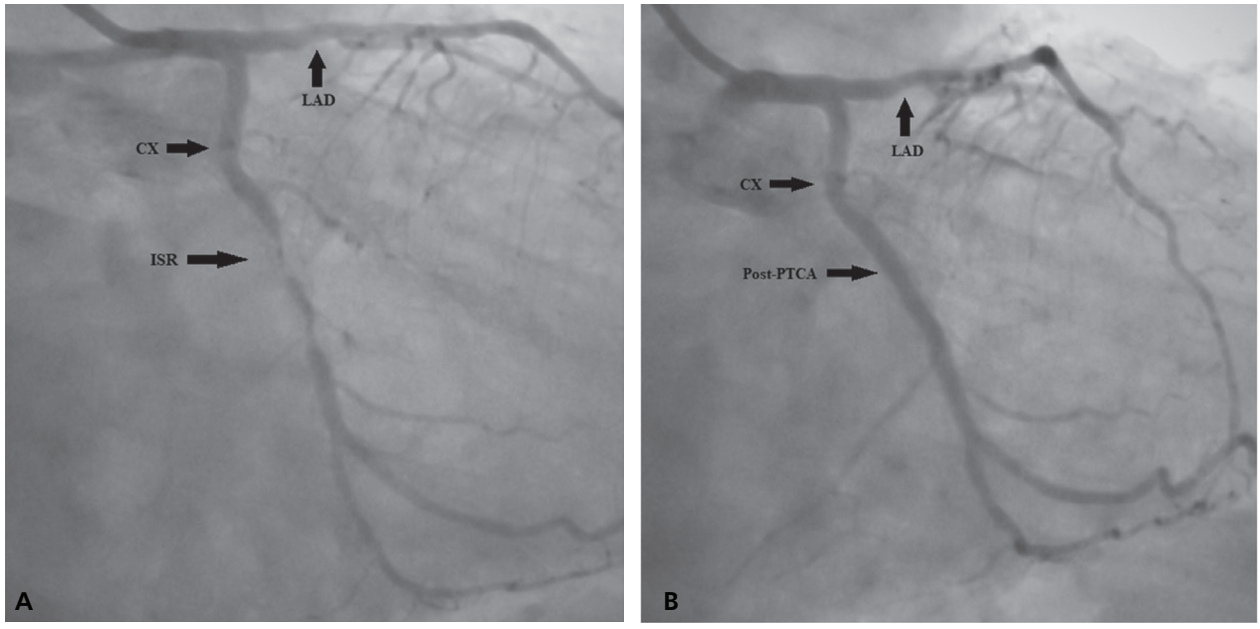

Figure 2. A) In-stent critical lesion in CX coronary artery, B) After treatment with PTCA in stenotic CX coronary artery
Example of ISR case report: 65 years old patient presented with chest pain. He had a history of hypertension, diabetes mellitus and primary PCI to CX coronary artery due to acute inferior MI two years ago. His HbA1c, ABG and FBG levels were 10.1%, 187 mg/dL, 150 mg/dL respectively during admission. A control CAG was performed with the diagnosis of non-STEMI. The control CAG revealed 95% ISR in CX coronary artery. Percutan transluminal coronary angioplasty is performed into restenotic segment and full openness was achieved.
LAD: Left anterior descending artery, CX: Circumflex artery, PTCA: Percutaneous transluminal coronary angioplasty

diameters have been shown to increase the incidence of ISR (22). In the diabetic subgroup in our study, no significant difference was found between the ISR and non-ISR groups in terms of stent length and diameter. Since our hospital is a tertiary center for cardiovascular diseases and all angiographies are performed by two experienced cardiologists, the factors related to ISR procedures were standardized.

HbA1c is an important marker revealing the long-term glycemic follow-up of diabetic patients. Increased HbA1c levels are associated with microvascular and macrovascular complications. In our study, the reasons for not finding a significant relationship between the ISR and ABG or FBG, as opposed to HbA1c, could be that HbA1c does not require fasting, its biological variability and irregularity before analysis is less, and it is not affected by acute changes in blood glucose levels. In previous studies, microvascular and macrovascular symptoms of diabetes were observed above the limit value of 6.5%; an HbA1c cut-off value of ≥6.5% was established for the diagnosis of DM in the last report of the American Diabetes Association (9). For this reason, we took the HbA1c cut-off as 6.5% in this study.

The clinical manifestation of ISR commonly includes recurring angina symptoms or ACS, and it may lead to a re-intervention either with coronary artery bypass or repeat PCI (25). We presented an example case about ISR (Figure 2A-B)

Study Limitations

This study analyzed the data derived from a single center. An important limitation of our study is the low number of study patients. In addition, since our study was retrospective, the patients' glycemic control during their long follow-up period could not be corroborated. Although the restenosis rates of DESs were found to be lower in diabetic patients in recent studies, a BMS was applied in our study. Although the HbA1c level was affected in the patients with low hemoglobin levels and hemoglobinopathy, the patients with anemia were excluded from our study, and the measuring device we used did not interact with abnormal hemoglobin.

Conclusion

HbA1c is strong independent predictor of ISR in patients with DM after coronary stent implantation. Our findings supported that strict diabetes control such as prescribing aggresive glucose lowering medication will reduce ISR rates in the subpopulation of DM patients. This relationship was not observed in non-diabetic patients. Extensive, randomized studies are needed to further demonstrate this relationship both in non-diabetic patients.

Authorship Contributions

Concept: F.Ö.K., Design: F.Ö.K., M.E., Data Collection or Processing: F.Ö.K., Y.K., Analysis or Interpretation: B.G., Literature Search: F.Ö.K., Writing: F.Ö.K., Y.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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