e-ISSN: 2564-6567

ACEM

Archives of Clinical and Experimental Medicine

2019;4(1)

Cilt: 4 - Sayı: 1

İçindekiler

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS (http://www.icmje.org/conflicts-of-interest/)

ICMJE COI Form (http://www.icmje.org/conflicts-of-interest/)

Formlar

Copyright Transfer / Conflict of Interest / Financial Disclosure Statements
(http://dergipark.gov.tr/uploads/submissionfiles/b450/33a0/d9c4/5894f31f5826f.pdf)

(https://publicationethics.org/)

C O P E

Publication ethics (https://publicationethics.org/)

(https://publicationethics.org/)

2018 Yılındaki Hakemlerimize Teşekkürler

2018 yılında, **Archives of Clinical and Experimental Medicine** (ACEM) dergisi'ne gönderilen bilimsel yazıların değerlendirme sürecinde hakemlik yapan akademisyenlere değerli katkıları için teşekkür eder, saygılarımızı sunarız. Listeye ulaşmak için tıklayınız. (http://dergipark.gov.tr/download/journal-file/8266)

Sosyal medya

(https://twitter.com/acem) (https://tr-tr.facebook.com/acem) (https://linkedin.com/share/acem)

Hızlı Erişim Kodu

ACEM (http://dergipark.gov.tr/acem)

ULAKBİM Dergi Sistemleri v 19.02.2 (//dergipark.gov.tr/)

ULAKBİM Dergi Sistemleri v 19.02.2 (//dergipark.gov.tr/)

Arch Clin Exp Med 2019;4(1):1-5. e-ISSN: 2564-6567

DOI:10.25000/acem.451394 Araştırma makalesi / Research article

Assessment of serum trace element levels in rheumatic heart disease: A case-control study

Romatizmal kalp hastalığında serum eser element seviyelerinin değerlendirilmesi: Bir vaka kontrol araştırması

Mehmet Hakan Öncel [1], Cemal Tuncer [2]

Abstract

Aim: Some trace elements play important roles in various heart diseases. In this study, we aimed to determine the changes in some trace element concentrations in the serum of patients with rheumatic heart disease (RHD).
Methods: Sixty-one patients with RHD and 60 healthy subjects were included in the study. Six subgroups were defined in the study group according to the Wilkins score, the degree of aortic involvement, and the presence or absence of pulmonary hypertension. Selenium (Se), Zinc (Zn), and Cupper (Cu) levels were measured, and transthoracic echocardiography was performed in all participants.
Results: Serum Se and Zn concentrations were significantly lower in the patients compared to the controls (mean±SD and p 43.08±1.83 µg/dL vs. 60.75±2.44 µg/dL; t=-5.305, p=0.001 and 64.65±2.77 µg/dL vs. 87.34±3.33 µg/dL; t=-5.458, p=0.001, respectively). However, the serum Cu concentration was significantly higher in the patient group than in the control group (84.50±3.50 µg/dL vs. 74.23±3.08 µg/dL; t=2.309, p=0.023). Similarly, the Cu/Zn ratio in the patient group was found to be significantly higher than the control group (1.4±0.09 µg/dL vs. 0.9±0.04 µg/dL; t=5.267, p=0.001). In the patient group, there was no significant relationship between the Wilkins score, aortic involvement, pulmonary hypertension, the serum trace element concentrations, and Cu/Zn ratio (p>0.05 for all).
Conclusions: We conclude that the changes in the concentrations of the measured trace elements can predispose to RHD and play a role in the formation of certain factors that leads to the development of the disease. Besides, serum Cu levels and Cu/Zn ratio can be used as inflammatory process markers.

Keywords: rheumatic heart disease; trace elements; selenium; zinc; copper

Öz

Amaç: Değişik kalp hastalıklarında bazı eser elementlerin önemli olduğu bilinmektedir. Bu çalışmada Romatizmal Kalp Hastalığı (RKH) olan hastaların serumunda bazı eser element konsantrasyonlarındaki değişiklikleri belirlemek ve bunun kronik RKH ve kapak tutulumunun şiddetiyle olan ilişkisinin ortaya konması amaçlanmıştır.
Metod: RKH olan 61 hasta ve 60 sağlıklı birey çalışma kapsamına alındı. Bu çalışmaya alınan hasta grup, Wilkins skoruna, aort tutulumunun derecesine ve ayrıca pulmoner hipertansiyonun varlığı ve yokluğuna göre olmak üzere toplam altı alt gruba daha ayrıldı. Hastalara ayrıntılı fizik muayene ve laboratuvar incelemesinin yanında kan Se, Zn ve Cu analizleri yapıldı. Hasta ve kontrol guruplarına transtorasik ekokardiografi ile ölçümler standart görünümleri üzerinden yapıldı.
Bulgular: Hasta grubunda serum Se ve Zn konsantrasyonu kontrol grubuna göre anlamlı ölçüde düşük bulundu (sırasıyla 43,08±1,83 µg/dL; 60,75±2,44 µg/dL; p<0,001) ve 64,65±2,77 µg/dL; 87,34±3,33 µg/dL; p<0.001). Serum Cu konsantrasyonu hasta grubunda kontrol grubuna göre anlamlı ölçüde yüksek bulunmuştur (84,5±3,5 µg/dL'ye karşılık 74,23± 3,08 µg/dL, p<0.05). Benzer şekilde Cu/Zn oranı hasta grubunda kontrol grubuna göre anlamlı ölçüde yüksek bulunmuştur (1,4±0,09 µg/dL'ye karşılık 0,9±0,04 µg/dL, p<0.001). Hasta grubunda serum eser element konsantrasyonları ve Cu/Zn oranı ile hastalığın tutulum şiddetini gösteren Wilkins skoru, aort tutulumu ve pulmoner hipertansiyon arasında anlamlı bir ilişki bulunmamıştır (p>0,05).
Sonuç: Eser element konsantrasyonundaki değişiklikler RKH'nı predispoze edebileceği gibi hastalığın gelişimine yol açan bazı faktörlerin ortaya çıkmasına da katkı sağlayabilir. Ek olarak artmış serum Cu seviyesi ve Cu/Zn oranı devam eden inflamatuvar proçes markırları olarak kullanılabilir.

Anahtar kelimeler: Romatizmal kalp hastalığı; eser element; selenyum; çinko; bakır.

[1] Şanlıurfa Mehmet Akif İnan Education Hospital, Department of Cardiology, Şanlıurfa, Turkey.
[2] Kahramanmaraş Sütçü İmam University, Medical Faculty, Department of Cardiology, Kahramanmaraş, Turkey.

Ethics Committee Approval: The study wass approved by the local ethical authority.
Etik Kurul Onayı: Çalışma lokal etik komite tarafından onaylanmıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Geliş Tarihi / Received: 06.08.2018
Kabul Tarihi / Accepted: 20.12.2018
Yayın Tarihi / Published: 15.03.2019

Sorumlu yazar / Corresponding author:

Mehmet Hakan Öncel
Şanlıurfa Mehmet Akif İnan Education Hospital, Department of Cardiology
Şanlıurfa, Turkey
e-posta: mhakanoncel@gmail.com
Tel/Phone: +905316703352

Introduction

Acute rheumatic fever (ARF) is classified as a connective or collagen tissue disease. In this ailment, there is damage in the collagen fibrils and connective tissue. The disease presents with inflammatory reactions in many organs, including the heart, joints, and the central nervous system [1]. The most significant complication of ARF is fibrosis in the heart valves, which may lead to hemodynamic disturbance and chronic heart disease, causing acquired heart disease in children and young adults [2].

The effects of antioxidant trace elements on the response of cardiac tissue to oxidative stress is long known [3]. It has been suggested that abnormal immunoglobulin inflammatory responses may be related to changes in the trace element levels [4].

The role of oxidative stress in the etiology of cardiovascular disease has been regarded as promising concerning antioxidant therapies [5]. Despite the huge accumulation of knowledge, there are still conflicting reports on the significance of trace elements. Antioxidant supplementations were reported to be associated with no effect or even adverse disease outcomes [6].

We hypothesized that the serum Selenium (Se), Zinc (Zn), and Cupper (Cu) levels are lower in patients with rheumatic heart disease. Thus, the aim of this study was to determine some trace element concentrations in the serum of patients with RHD and to demonstrate the association of chronic RHD and the severity of valvular involvement.

Material and methods

Study design

A retrospective case-control study was conducted. Study reporting was done according to the STROBE criteria [7]. Ethical permit for conducting the study was obtained from the local ethics committee at the Kahramanmaraş Sütçü İmam University Medical Faculty (IRB number: 2006/4-3, date: 06/04/2006). The Helsinki Declaration was followed during all study processes.

Setting

The study was executed at the Kahramanmaraş Sütçü İmam University, Department of Cardiology between June 2005 and June 2006. During the study period, a total of 12,375 outpatients were served by the department.

Participants

Sixty-one patients (Group I) who applied to the cardiology polyclinics within one year meeting the revised Jones criteria [8] and 60 healthy controls (Group II) were included in the study. Healthy controls were selected from the visitors or caregivers of the study group. All control cases were interviewed and examined concerning the absence of the outcome. Six subgroups were defined among the patients, consisting of two according to Wilkins score [9] (Wilkins score 1-8 and ≥9), two according to the degree of aortic involvement (no or mild involvement and moderate or severe involvement) [10], and two according to the state of pulmonary hypertension (present or absent).

Patients with known coronary artery disease, degenerative valve disease, congestive heart failure, cardiomyopathy, primary pulmonary hypertension, uncontrolled hyperthyroidism or hypothyroidism, chronic obstructive pulmonary disease, active ARF, active myocarditis, pericardial diseases, congenital heart diseases, renal or hepatic insufficiency, acute or chronic inflammation, infectious diseases, known malignancy, cerebrovascular disease, presence of major systemic disease, and age younger than 18 were excluded from the study. The study procedures were explained and written consent was obtained from all participants. The patients underwent a detailed physical examination and transthoracic echocardiography.

Variables

The main study outcomes were serum Selenium (Se), Zinc (Zn), and Cupper (Cu) levels. Samples for zinc (Zn) and copper (Cu) measurements were diluted with glycerol. Standards were prepared at concentrations of 50, 100, 200, and 400 μg/dL. Samples were measured and evaluated in a flame photometer against standard concentrations. Other variables studied were age, sex, systolic blood pressure (mmHg), diastolic blood pressure (mmHg), presence of hypertension or diabetes mellitus, smoking status, blood Ca (mg/dL), Mg (mg/dL), P (mg/dL), alanine aminotransferase (U/L), aspartate transaminase (U/L), glucose (mg/dL), creatinine (mg/dL), total cholesterol (mg/dL), triglycerides (mg/dL), high-density lipoprotein (mg/dL), low-density lipoprotein (mg/dL), hemoglobin (g/dL), and hematocrit (%) measurements.

Sample collection and storage was done while the participants were in the sitting position, drawing 10 ml of venous blood from the forearm cubital vein using vacutainer tubes. After being kept in the room temperature for 30 minutes, the blood samples were centrifuged at 4000 rpm for 15 minutes. Serum samples were transferred to another tube and stored in the deep freeze at -20◦C for analysis. For complete blood count (CBC), sufficient blood was obtained to an ethylenediaminetetraacetic acid (EDTA) tube. CBC, glucose, creatinine, aspartate transaminase (AST), alanine aminotransferase (ALT), total cholesterol, triglyceride, HDL (High-density lipoprotein), low-density lipoprotein (LDL), Ca, Mg, P, and Fe levels were analyzed in the same day with the Behring RXL autoanalyser.

Samples for selenium (Se) measurement were diluted with 5% Triton X 100. A mixture of palladium (Pd) and Mg (NO3)2 (magnesium nitrate) was used as matrix modifier. Standards were prepared at concentrations of 10, 20, 30, and 40 μg / L. Samples were run on an atomic absorption spectrophotometer using a graphite bath and the concentrations were evaluated according to the standard curve.

Transthoracic echocardiography was performed with the Acuson-Aspen® (Acuson Computer Sonography, Mountain View, California) device using a 3.5 MHz probe. Echocardiographic examinations were performed using standard parasternal long axis, parasternal short axis, apical two spaces, apical four space, and apical five space views. Measurements of left ventricular (LV) end-diastole diameter, end-systolic diameter, posterior wall thickness, interventricular septum thickness, ejection fraction, fractional shortening, left atrium (LA) and aortic root were done by the M-mode echocardiography as defined by the American Echocardiography Society [11]. The systolic pulmonary artery pressure was calculated from the tricuspid insufficiency jet flow using the Bernoulli equation by adding the right atrial pressure. In addition, grading of the mitral valve characteristics by echocardiographic examination was performed using the Massachusetts General Hospital Score for Mitral valve morphology (Wilkins scoring) [9]. Two-dimensional, M-mode and double echocardiography methods were used in the assessment of aortic involvement [12–15]. Transesophageal echocardiography (TEE) was performed in patients where transthoracic echocardiography was inadequate due to a poor acoustic window [16].

Study size

Sample size calculation revealed that a total sample of 120 cases (60 study+60 controls) would be enough to detect a

difference of 1.5 µg/dl difference in the serum Zn levels between the study and control groups using the Independent Samples t-test with a two-tailed hypothesis given a mean 1 of 60 µg/dl and mean 2 58.5 µg/dl, standard deviation of 2 (effect size 0.6), alpha error of 5% with a power of 90% [17].

Statistical methods

Clinical, laboratory, and echocardiographic data were compared between Group I and Group II. Data were presented as mean ± standard deviation (SD) or median (min-max). The numerical variables were checked for normal distribution. Variables with normal distribution were analyzed with the Independent Samples t-test whereas the Mann-Whitney U test was used for skewed data. The Chi-Square test was used for the comparisons between categorical variables. All statistical analyzes were done with the statistical package program SPSS (version 13.0). A p-value less than 0.05 was accepted as statistically significant.

Results

Participants

A total of 121 participants (Group I: n=61; Group II: n=60 controls) were included in the study. Of the 61 patients in Group I, 15 (24.6%) were males, and 46 (75.4%) were females, while from the 60 controls in Group II 18 (30%) were males and 42 (70%) were females.

Descriptive data

The mean age of the participants was 37.02 ± 1.25 years in Group I and 38.95 ± 1.44 years in Group II. There was no significant difference between the groups concerning the demographic and clinical characteristics (p> 0.05 for all) (Table 1).

Table 1: Comparison of demographic features and blood chemistry between Group I and Group II.

Variable	Group I (n=61)	Group II (n=60)	p
Age (years)¥	38.95±1.44 (18-64)	37.02±1.25 (18-61)	0.313
Male/female	15/46	18/42	0.508
Systolic blood pressure (mmHg)¥	119.18±1.83 (100-160)	120.08±1.80 (90-160)	0.855
Diastolic blood pressure (mmHg)¥	73.28±1.32 (50-100)	75.68±1.21 (60-100)	0.116
Hypertension β	5/61 (8.2)	4/60 (6.7)	0.751
Diabetes mellitus β	3/61 (4.9)	2/60 (3.3)	0.665
Smokers β	6/61 (9.8)	7/60 (11.7)	0.551
Ca (mg/dL)¥	8.96±0.06 (7.9-10)	9.03±0.06 (7.8-10)	0.381
Mg (mg/dL)¥	1.83±0.03 (1.20-2.30)	1.87±0.07 (1.40-5.70)	0.729
P (mg/dL)¥	3.47±0.08 (2.30-5.90)	3.29±0.06 (2.30-4.60)	0.090
ALT (U/L)¥	38.38±2.10 (15-105)	40.05±1.80 (16-93)	0.096
AST (U/L)¥	25.92±1.55 (14-72)	24.26±1.31 (12-66)	0.249
Glucose (mg/dL)¥	94.20±1.79 (69-137)	92.87±1.67 (75-134)	0.173
Creatinine (mg/dL)¥	0.79±0.03 (0.10-1.40)	0.74±0.02 (0.10-1.40)	0.093
Total cholesterol (mg/dL)¥	162.35±4.54 (95-240)	172.06±3.96 (117-228)	0.193
Triglycerides (mg/dL)¥	118.34±8.45 (26-339)	135.93±9.15 (33-306)	0.160
HDL (mg/dL)¥	43.62±1.45 (22-71)	42.00±1.53 (26-96)	0.444
LDL (mg/dL)¥	98.58±3.4 (45.8-189.2)	108.33±3.84 (44.8-175.2)	0.206
Hemoglobin (g/dL)	12.92±0.17 (8.7-17.1)	13.40±0.20 (9.03-16.50)	0.876
Hematocrit (%)¥	38.46±0.75 (24.37-47.30)	39.75±0.56 (27.70-46.90)	0.468

¥: Mean±standard deviation (range), β: n(%), RHD: Rheumatic Heart Disease; AST: Aspartate transaminase; ALT: Alanine aminotransferase; HDL: High-density lipoprotein, LDL: Low-density lipoprotein

Outcome data

The two groups were compared regarding cardiac functions. There was no significant difference in the LV end-diastole diameters, aortic root diameters, posterior wall and septum thicknesses between Group I and Group II with echocardiographic measurements (p> 0.05 for all). However, significantly higher values for LV end-systolic diameter, lower ejection fraction levels, lower fractional shortening, and higher left atrium diameters were observed in the Group I compared to the Group II (Table 2).

Table 2: Comparison of transthoracic echocardiography measurements between the groups.

Variable	Group I (n=61)	Group II (n=60)	p
LV end-diastole diameter (cm)¥	4.69±0.08 (2.24-6)	4.57±0.06 (3.66-5.36)	0.591
LV end-systole diameter (cm)¥	2.95±0.06 (2.00-4.40)	3.67±0.06 (1.90-3.51)	0.976
Ejection fraction¥	65.75±1.08 (45.0-79.0)	69.83±0.93 (58.0-83.0)	0.542
Fractional shortening¥	37.26±0.88 (25.0-48.0)	40.84±1.03 (31.0-51.0)	0.388
Interventricular septum thickness (cm)¥	1.03±0.02 (0.70-1.50)	0.98±0.02 (0.66-1.30)	0.758
LV posterior wall thickness (cm)¥	0.91±0.02 (0.64-1.40)	0.87±0.02 (0.58-1.10)	0.930
Left atrium diameter (cm)¥	3.84±0.14 (2.30-7.30)	2.90±0.07 (2.18-4.10)	0.546
Aorta diameter (cm)¥	2.62±0.05 (1.83-3.30)	2.68±0.05 (2.05-3.47)	0.907

¥: Mean±standard deviation (range), LV: the left ventricle

Serum Se and Zn concentrations in the Group I were significantly lower than in Group II. Se values for the patient and control groups were 43.08±1.83 and 60.75±2.44, respectively (t=-5.305, p<0.001), while the Zn values were 64.65±2.77 and 87.34±3.33, respectively (t=-5.458, p<0.001). Serum Cu concentrations were significantly higher in the Group I compared to the Group II (84.5±3.5 vs. 74.23±3.08, respectively) (t=2.309, p=0.023) (Figure 1). Similarly, the Cu/Zn ratio was significantly higher in the Group I than the Group II (1.4±0.09 vs. 0.9±0.04), (Z=4.588, p=0.001) (Table 3).

Figure 1: Comparison of the mean serum trace element values between the groups.

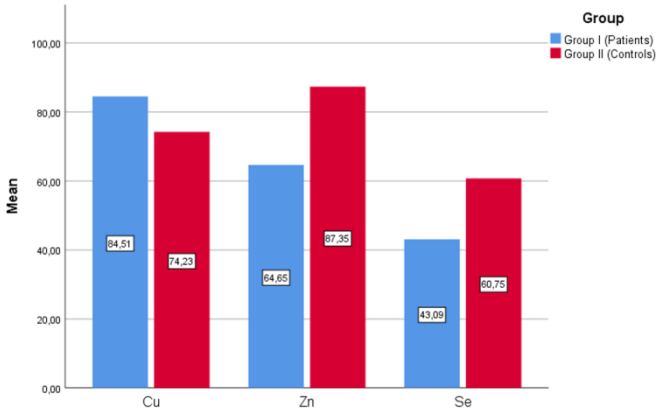

Table 3: Comparison of serum trace element levels between the groups.

Variable	Group I (n=61)	Group II (n=60)	p
Se (µg/dL)¥	43.08 ± 1.83 (9.77-79.65)	60.75±2.44 (10.77-107.88)	0.001
Zn (µg/dL)¥	64.65±2.77 (30.15-109.4)	87.34±3.33 (57.16-166.84)	0.001
Cu (µg/dL)¥	84.50±3.5 (37.32-167.92)	74.23±3.08 (38.20-133.10)	0.023
Cu/Zn (ratio)¥	1.40±0.09 (0.58-2.84)	0.90±0.04 (0.04-1.82)	0.001

¥: Mean±standard deviation (range)

Mean serum Se and Zn values were slightly higher (45.74 µg/dl vs. 42.29 µg/dl and 73.49 µg/dl vs. 61.98 µg/dl, respectively), while the serum Cu concentrations were slightly lower (85.53 µg/dl vs. 81.59 µg/dl) among the patients with a Wilkins score of >8. However, there was no significant relationship between the serum trace element concentrations and Cu/Zn ratio depending on the Wilkins score groups in the patients (p>0.05) (Table 4).

Table 4: Comparison of serum trace element levels between Wilkins score groups.

	Wilkins Score 1-8 (n=47)	Wilkins Score >8 (n=14)	p
Se (µg/dL)¥	42.29±2.06 (9.77-72.15)	45.74±4.06 (23.97-79.65)	0.444
Zn (µg/dL)¥	61.98±2.96 (30.15-109.40)	73.49±6.43 (43.68-108.44)	0.060
Cu (µg/dL)¥	85.53±4.48 (37.32-167.92)	81.59±4.41 (38.98-97.30)	0.263
Cu/Zn ratio¥	1.47±0.11 (0.58-2.84)	1.20±0.14 (0.72±2.22)	0.392

¥: Mean±standard deviation (range)

There was no significant relationship between the serum trace element concentrations and Cu/Zn ratio with aortic involvement in the Group I (p>0.05) (Table 5).

Table 5: Comparison of serum trace element levels in the Group I based on aortic involvement.

	No or mild aortic involvement (n=30)	Medium or severe aortic involvement (n=31)	p
Se (µg/dL) ¥	43.09±2.89 (9.77-72.15)	43.08±2.29 (17.12-79.65)	0.315
Zn (µg/dL) ¥	65.27±3.65 (30.15-108.64)	64.04±4.22 (32.63-109.40)	0.061
Cu (µg/dL) ¥	84.72±4.95 (40.70-157.14)	84.31±5.03 (37.32-167.92)	0.147
Cu/Zn ratio ¥	1.37±0.14 (0.65-2.84)	1.42±0.12 (0.58±2.57)	0.159

¥: Mean±standard deviation (range)

There was no significant relationship between serum trace element concentration and Cu/Zn ratio and pulmonary hypertension in the patient group (p>0.05) (Table 6).

Table 6: Comparison of serum trace element levels in the Group I based on pulmonary hypertension status.

Variable	Absence of pulmonary hypertension (n=29)	Presence of pulmonary hypertension (n=32)	p
Se (µg/dl) ¥	43.08±2.78 (15.78-79.65)	43.10±2.45 (9.77-72.15)	0.932
Zn (µg/dl) ¥	58.69±3.06 (34.00-103.04)	63.22±3.79 (30.15-99.48)	0.659
Cu (µg/dl) ¥	87.25±4.93 (40.70-157.14)	81.98±4.99 (37.32-167.92)	0.225
Cu/Zn ratio ¥	1.51±0.13 (0.65-2.84)	1.28±0.12 (0.58±2.66)	0.214

¥: Mean±standard deviation (range)

Discussion

This study demonstrated that rheumatic heart disease (RHD) is accompanied by decreased Se and Zn concentrations and increased Cu concentrations.

Deteriorated trace element levels in cardiac diseases such as atherosclerosis, idiopathic dilated cardiomyopathy, and chronic heart failure have been reported in the literature [18–21]. Likewise, possible changes in the trace element levels in rheumatic heart disease (RHD) have been reported [22,23]. However, serum trace element levels have not been studied in detail. Nutritional deficiencies and infectious diseases are common and show complex interactions leading to poor clinical effects. Such combinations are evident in developing countries, especially in rural areas. Many nutritional elements (such as Se, Cu, and Zn) modulate the immune function and affect the sensitivity of the host to the infection [24,25]. It is also essential for optimal functioning of organs and tissues. For this reason, trace elements can play a critical role in cardiovascular diseases.

Selenium is an essential trace element for protecting the immune system and oxidative functions. It acts as both an antioxidant and an anti-inflammatory agent. Because hydrogen reduces peroxide and phospholipid hydroperoxidase, it also reduces the levels of free radicals and reactive oxygen species [26].

Zn and Cu, like Se, have similar effects on immunological systems [24]. Increased Cu levels and Cu / Zn ratio are indicative of the severity of an inflammatory process, high levels demonstrating a more serious inflammatory process. It has been suggested that high levels of serum Cu and low Zn (therefore, high Cu/Zn ratio) are low-rate acute phase reactants in patients with sclerotic aortic valves. Studies with similar patient groups have also been supported by moderately elevated C-reactive protein levels [27]. Using serum trace element levels of healthy individuals, sclerotic aortic valves of operated patients, and aortic valves from autopsies, Nyström-Rosader et al. [28] supported that serum Cu and Zn concentrations are indicative of the severity of infection and inflammatory process.

Various immunologic and inflammatory changes have long been reported to play a key role in the pathogenesis and prognosis of RHD. According to many theories, the pathogenesis of RHD is explained by an abnormal immunological response [1, 29]. It was also stated that these responses are related to changes in trace element levels. Previous studies have focused on the trace element levels (especially Zn) in the tissue samples of RHD [22, 23]. These studies have shown that the Zn levels in the samples taken from heart valves of postmortem cases of RCC are significantly lower than those of the control group. Govindarajo et al. [22] have shown that low levels of Zn in RHD may affect cell-mediated immunity and increase rheumatic activity and patients' susceptibility to infections. Koşar F. and colleagues [4] observed that serum Zn and Se concentrations were lower and Cu and Cu / Zn ratios were significantly higher in RHD, and they observed that these were important parameters in the development of the rheumatic process, but they did not find a meaningful relationship with the severity of the functional class, which is indicative of the severity of the disease. Chlamydia pneumonia contributes to the development of atherosclerosis and RHD. Nyström-Rosader and colleagues observed that serum and sclerotic occult elemental levels play an important role in this contribution of Chlamydia pneumonia [30], facilitating the development of active infection by Chlamydia pneumonia and adversely affecting the immune system of the brain.

Low Se levels have been demonstrated in the inflamed heart in acute viral myocarditis [31]. Especially feeding with nutrients deficient from Se is known by its negative effect on the immune system. As a result, more virulent virus variants are selected and they contribute to a heavier disease transmission [32]. In addition, Se deficiency has been associated with many different cardiovascular diseases such as Keshan and Chagas [33].

In our study, it was determined that the serum concentrations of Se and Zn were significantly lower in patients with RHD than in the healthy control group, and that these patients had a significantly higher serum Cu level and a higher Cu/Zn ratio than the control group. However, there was no difference between the groups in which trace element concentrations and Cu/Zn ratios were classified according to the presence of Wilkins score, aortic valve involvement, and presence of pulmonary hypertension, which are echocardiographic findings showing the severity of patients' illnesses. We found that the echocardiographic parameters LV end-systolic diameter and left atrium diameters were significantly larger in the patient group than the control group, and the ejection fraction and fractional shortening were significantly lower.

However, we could not explain an underlying mechanism by which serum Zn and Se element levels could be reduced, and we could not detect a situation that would increase oxidative stress or inflammation and affect serum Zn or Se levels. Because RHD is an inflammatory condition, it is not surprising that low levels of Se and Zn are seen in our patients. In other words, it can be said that the changes in trace element levels in these patients may be the result of the current inflammatory process, as well as the inadequate intake of dietary trace elements. A second finding in this study is that the increase in serum Cu concentration and Cu/Zn ratio reflects an increased or persistent inflammatory process in this disease, because the Cu concentrations and Cu/Zn ratios are significantly higher in these patients compared to the control group. There was no significant relationship between the third trace element profile and the groups we classified according to Wilkins score, aortic valve involvement, and the presence of pulmonary hypertension, which were echocardiographic findings showing the severity of the disease. It is known and expected that among the echocardiographic parameters the left atrium diameter is significantly larger in the patient group than in the control group. Although the ejection fraction and fractional shortening measurements were significantly lower than the control group,

we observed that left ventricular function was maintained in the patient group.

As a result, we report that RHD is accompanied by decreased Se and Zn concentrations and increased Cu concentrations. We can say that changes in trace element concentration may predispose to RHD, but may also give rise to the development of some factors, which may lead to the disease. As they may contribute to the development of many cardiovascular diseases, the low serum levels of Se and Zn may have also significantly contributed to the development of RHD. In childhood, malnutrition and poor hygienic conditions contribute to the decrease of Se and Zn levels [32]. Of course, it is the most economical way to prevent the development of RHD, which is still a significant health problem in Turkey. Therefore, it can be expected that rich and balanced nutrition in terms of trace elements can contribute to the reduction of the incidence of RHD by providing support for a healthy immune system.

When we translate our results into clinical practice, some limitations of this study must be kept in mind. First, our sample is from a restricted area and a limited number of carefully selected participants. Although the results of a study from the same area [4] supports our findings, there is a need for a wider range of data to verify the accuracy and precision of these results. Secondly, the serum levels of the measured elements depend on the nutritional status and oral intake such as mineral supplements and medications. For this reason, it is difficult to make final conclusions by a one-time analysis. Also the time gap between data collection and study reporting, which was due to personal problems of the main author, can be mentioned as a limitation.

In conclusion, assessment of serum trace element levels in patients with well-settled RHD may not be clinically useful, but evaluation of serum trace element levels and providing nutritional trace element support in the acute phase may reduce the development of RHD. Besides, elevated serum Cu levels and Cu / Zn ratio can be used as ongoing inflammatory process markers. For this reason, evaluation of serum trace element levels seems feasible in patients with RHD.

References

1. Amigo MC, Martinez-Lavin M, Reyes PA. Acute rheumatic fever. Rheum Dis Clin North Am. 1993;19:333–50.
2. Licciardi F, Scaioli G, Mulatero R, Marolda A, Delle Piane M, Martino S, et al. Epidemiologic Impact of the New Guidelines for the Diagnosis of Acute Rheumatic Fever. J Pediatr. 2018;198:25-8.
3. Barandier C, Tanguy S, Pucheu S, Boucher F, De Leiris J. Effect of antioxidant trace elements on the response of cardiac tissue to oxidative stress. Ann N Y Acad Sci. 1999;874:138–55.
4. Kosar F, Sahin I, Acıkgöz N, Aksoy Y, Kucukbay Z, Cehreli S. Significance of Serum Trace Element Status in Patients with Rheumatic Heart Disease: A Prospective Study. Biol Trace Elem Res. 2005;107:1-10
5. Alissa EM. Antioxidants and Cardiovascular Disease: A summary of the Evidence. J Cardiovasc Dis. 2015;3:347–56.
6. Song Y, Cook NR, Albert CM, Van Denburgh M, Manson JE. Effects of vitamins C and E and β-carotene on the risk of type 2 diabetes in women at high risk of cardiovascular disease: a randomized controlled trial–. Am J Clin Nutr. 2009;90:429–37.
7. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. PLoS Med. 2007;4:1623–7.
8. Rhodes KL, Rasa MM, Yamamoto LG. Acute Rheumatic Fever: Revised Diagnostic Criteria. Pediatr Emerg Care. 2018;34:436–40.
9. Wilkins GT, Weyman AE, Abascal VM, Block PC, Palacios IF. Percutaneous balloon dilatation of the mitral valve: An analysis of echocardiographic variables related to outcome and the mechanism of dilatation. Heart. 1988;60:299–308.
10. Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, et al. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J. 2007;28:230–68.
11. Yamamoto K, Masuyama T, Tanouchi J, Uematsu M, Doi Y, Mano T, et al. Peak early diastolic filling velocity may decrease with preload augmentation: effect of concomitant increase in the rate of left atrial pressure drop in early diastole. J Am Soc Echocardiogr. 1993;6:245–54.
12. Karpuz H, Ikitimur B. [Echocardiographic evaluation of aortic stenosis]. Ana Kar Der. 2002;2:65-9.
13. Godley RW, Green D, Dillon JC, Rogers EW, Feigenbaum H, Weyman AE. Reliability of two-dimensional echocardiography in assessing the severity of valvular aortic stenosis. Chest. 1981;79:657–62.
14. Stoddard MF, Hammons RT, Longaker RA. Doppler transesophageal echocardiographic determination of aortic valve area in adults with aortic stenosis. Am Heart J. 1996;132:337–42.
15. Yeager M, Yock PG, Popp RL. Comparison of Doppler-derived pressure gradient to that determined at cardiac catheterization in adults with aortic valve stenosis: Implications for management. Am J Cardiol. 1986;57:644–8.
16. Bai AD, Steinberg M, Showler A, Burry L, Bhatia RS, Tomlinson GA, et al. Diagnostic accuracy of transthoracic echocardiography for infective endocarditis findings using transesophageal echocardiography as the reference standard: a meta-analysis. J Am Soc Echocardiogr. 2017;30:639–46.
17. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3:A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39:175–91.
18. Oster O, Prellwitz W. Selenium and cardiovascular disease. Biol Trace Elem Res.1990;24:91-103.
19. Bai-Song N, Chung-Seng L, Li-Hua C. Significance of low levels of blood selenium in dilated cardiomyopathy. Bio Trace Elem Res. 1986 Dec;99(12):948-9.
20. Klevay LM. The role of copper, zinc and other chemical elements in ischemic heart disease . eds. CRC, Boca Raton, FL, pp. 1984;129–157.. In: Rennert OM, Chan WY, editors. Metabolism of trace metals in man. Boca Raton: CRC; 1984. p. 129–57.
21. Yu X, Huang L, Zhao J, Wang Z, Yao W, Wu X, et al. The Relationship between Serum Zinc Level and Heart Failure: A Meta-Analysis. Biomed Res Int. 2018;2018:2739014.
22. Govindaraju V, Prabhudev N, Gurappa M, Jawali VS, Chandrasekhara PM, Manjunath CN. Zinc in rheumatic heart valves. J Assoc Physicians India. 1993;41:653–4.
23. Durak I, Akyol Ö, Es MU, Canbolat O, Akpoyraz M. Element structure in stenotic mitral valves. Am J Cardiol. 1993;71:355.
24. Chandra RK. Trace Element Regulation of Immunity and Infection. J Am Coll Nutr. 1985;4:5–16.
25. Rotruck JT, Pope AL, Ganther HE, Swanson AB, Hafeman DG, Hoekstra WG. Selenium: biochemical role as a component of glutathione peroxidase. Science. 1973;179:588–90.
26. El-Ghazaly MA, Fadel N, Rashed E, El-Batal A, Kenawy SA. Anti-inflammatory effect of selenium nanoparticles on the inflammation induced in irradiated rats. Can J Physiol Pharmacol. 2017;95:101–10.
27. Galante A, Pietroiusti A, Vellini M, Piccolo P, Possati G, De Bonis M, et al. C-reactive protein is increased in patients with degenerative aortic valvular stenosis. J Am Coll Cardiol. 2001;38:1078–82.
28. Nystrom-Rosander C, Lindh U, Friman G, Lindqvist O, Thelin S, Ilback N-G. Trace element changes in sclerotic heart valves from patients are expressed in their blood. Biometals. 2004;17:121–8.
29. Goldstein I, Halpern B, Robert L. Immunological relationship between streptococcus A polysaccharide and the structural glycoproteins of heart valve. Nature. 1967;213:44–7.
30. Nyström-Rosander C, Lindh U, Ilbäck NG, Hjelm E, Thelin S, Lindqvist O, et al. Interactions between Chlamydia pneumoniae and trace elements: A possible link to aortic valve sclerosis. Biol Trace Elem Res. 2003;91:97–110.
31. Funseth E, Lindh U, Friman G, Ilbäck NG. Relation between trace element levels in plasma and myocardium during coxsackievirus B3 myocarditis in the mouse. BioMetals. 2000;13:361–7.
32. Levander OA, Ager ALJ, Beck MA. Vitamin E and selenium: contrasting and interacting nutritional determinants of host resistance to parasitic and viral infections. Proc Nutr Soc. 1995;54:475–87.
33. Chen X, Yang G, Chen J, Chen X, Wen Z, Ge K. Studies on the relations of selenium and Keshan disease. Biol Trace Elem Res. 1980;2:91–107.

Arch Clin Exp Med 2019;4(1):6-9. e-ISSN: 2564-6567

DOI:10.25000/acem.451930 Araştırma makalesi / Research article

Assessment of relationship between serum magnesium and serum glucose levels and HOMA-IR in diabetic and prediabetic patients

Diyabetik ve prediabetik hastalarda serum magnezyum ve serum glukoz düzeyleri ile HOMA-IR arasındaki ilişkinin değerlendirilmesi

Gülçin Şahingöz Erdal [1], Faruk Karandere [1], Fuat Mısıroğlu [1], Işıl Özbaş Tevetoğlu [1], Yıldız Okuturlar [2], Hakan Koçoğlu [1], Mehmet Hurşitoğlu [1]

Abstract

Aim: In this study, we aimed to investigate the serum magnesium (Mg) levels in diabetic and prediabetic patients and its correlation with age, body-mass index, HOMA-IR, serum fasting glucose, HbA1c, and insulin levels.

Methods: In this retrospective study, a total of 130 patients consisted of newly diagnosed prediabetes (Group PD) (n=63) and type 2 diabetes mellitus (Group D) (n=67) were included. Patients' age, body mass index, serum Mg, glucose and insulin, HOMA-IR and HbA1c were recorded. The prediabetes and type 2 diabetes diagnoses had been made according to WHO criteria at the time of diagnosis.

Results: In group D, the mean Mg level (1.88 ± 0.17 mg/dl) was significantly lower than group PD (1.96 ± 0.17 mg/dl) (p = 0.007). Correlation analysis showed that there was a significant negative correlation between Mg and glucose (r = -0.390, p = 0.001) and HOMA-IR (r = -0.284; p = 0.022) in the group D. No correlation was found between serum Mg level and serum insulin, HbA1c, age, and body-mass index (p = 0.801, 0.087, 0.611 and 0.691, respectively). In group PD, serum insulin, HbA1c, glucose, HOMA-IR, age, and body-mass index were not corraleted with serum Mg levels (p = 0.801, 0.087, 0.939, 0.998, 0.611 and 0.691, respectively).

Conclusıon: We showed that while there was a negative correlation between magnesium levels and HOMA-IR and fasting blood glucose levels in diabetic patients, but this correlation was not present in prediabetic patients. Our results suggest that serum Mg level is associated with metabolic control of type 2 diabetes and thus it can be considered in these patients.

Key words: Magnesium, diabetes, prediabetes, insülin resistance, fasting glucose, HOMA-IR

Öz

Amaç: Bu çalışmada diyabetik ve prediyabetik hastalarda serum magnezyum (Mg) düzeyleri ile yaş, vücut kitle indeksi, HOMA-IR, serum açlık glukoz, HbA1c ve insülin düzeyleri arasındaki ilişkiyi inceledik.

Yöntemler: Bu retrospektif çalışmada, yeni tanı almış prediyabet (Grup PD) (n=63) ve tip 2 diabetes mellitus (Grup D) (n=67) olmak üzere toplam 130 hasta çalışmaya alındı. Hastaların yaşı, vücut kitle indeksi, serum Mg, glukoz ve insülin değerleri, HOMA-IR ve HbA1c kaydedildi. Prediabetes ve tip 2 diyabet tanısı, tanı anında WHO kriterlerine göre yapıldı.

Bulgular: Grup D'de ortalama Mg düzeyi (1,88 ± 0,17 mg/dl), grup PD'den (1,96 ± 0,17 mg/dl) anlamlı derecede düşüktü (p = 0,007). Korelasyon analizi, D grubunda Mg ve glukoz (r = -0,390, p = 0,001) ve HOMA-IR (r = -0,284; p = 0,022) arasında anlamlı negatif korelasyon olduğunu gösterdi. Serum Mg ile insülin, HbA1c, yaş ve vücut kütle indeksi (sırasıyla p = 0,801, 0,087, 0,611 ve 0,691) arasında korelasyon saptanmadı. Grup PD'de serum insülin, HbA1c, glukoz, HOMA-IR, yaş ve vücut kitle indeksi ile serum Mg düzeyleri arasında korelasyon yoktu (sırasıyla p = 0,801, 0,087, 0,939, 0,998, 0,611 ve 0,691).

Sonuçlar: Diyabetik hastalarda magnezyum düzeyleri ile HOMA-IR ve açlık kan glikoz düzeyleri arasında negatif bir ilişki olduğunu, ancak bu ilişkinin prediyabetik hastalarda mevcut olmadığını gösterdik. Çalışma sonuçlarımız serum Mg seviyesinin tip 2 diyabetin metabolik kontrolü ile ilişkili olduğunu ve bu nedenle bu hastalarda göz önüne alınabileceğini düşündürmektedir.

Anahtar Kelimeler: Magnezyum, diyabet, prediyabet, insülin direnci, açlık glikoz, HOMA-IR

[1] Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Department of Internal Medicine, Istanbul, Turkey

[2] Acibadem Mehmet Ali Aydinlar University, Atakent Education and Research Hospital, Department of Internal Medicine, Istanbul, Turkey

Ethics Committee Approval: The study wass approved by the local ethical authority.
Etik Kurul Onayı: Çalışma lokal etik komite tarafından onaylanmıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Geliş Tarihi / Received: 08.08.2018
Kabul Tarihi / Accepted: 11.12.2018
Yayın Tarihi / Published: 15.03.2019

Sorumlu yazar / Corresponding author:
Gülçin Şahingöz Erdal
Department of Internal Medicine, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey
e-posta: gulcinctf@hotmail.com
Tel/Phone: +90531 6427516

Introduction

Magnesium (Mg) is the second most abundant intracellular cation after potassium present in living cells and may influence the regulation of blood glucose metabolism by modulation of insulin secretion and insulin action [1]. Therefore, alterations in the metabolism of this mineral may influence these functions, contributing to the pathogenesis of obesity and insulin resistance [2, 3].

Studies and knowledge on the relationship between diabetes and Mg status are expanding. Hypomagnesemia is a common finding in type 2 diabetic patients (T2DM) [4]. It has been reported to occur in 13.5 to 47.7% of patients with T2DM compared with 2.5 to 15% among their counterparts without diabetes [5-8]. Some studies have demonstrated the action of Mg on insulin resistance in obesity and diabetes, and thus Mg deficiency has been proposed as a risk factor for T2DM [1, 9, 10].

Prediabetes, characterized by impaired fasting glucose and/or impaired glucose tolerance, is considered an important risk factor for the development of overt diabetes [11]. A few studies have investigated the association of serum Mg levels with prediabetes, but the findings were inconsistent [3, 12]

In this study, we have aimed to investigate the serum Mg levels in patients with T2DM and prediabetes and its correlation with serum fasting glucose, insulin, HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) and HbA1c levels.

Material and methods

In this retrospective study, patients with newly diagnosed prediabetes and T2DM who were admitted to Diabetes and Internal Medicine outpatient clinics of Bakirkoy Dr. Sadi Konuk Education and Research Hospital between February 2017 and January 2018 were evaluated. The study was approved by institutional ethical committee of the Bakirkoy Dr. Sadi Konuk Education and Research Hospital (2018/144), which complies with Helsinki Declaration.

A total of 130 patients with prediabetes and T2DM were included in this study. The study included 67 newly diagnosed T2DM (group D) and 63 newly diagnosed prediabetic patients (group PD). All patients were newly diagnosed patients and have not reported a history of diabetes and not used insulin or an oral antidiabetic agent at the time of diagnosis. At our outpatient clinics the prediabetes and T2DM diagnoses have been made according to WHO criteria [13].

Exclusion criterias were as follows: patients other than newly diagnosed diabetes and/or prediabetes; patients with hypertension, chronic renal failure, acute or chronic diarrhea, malabsorption syndrome, congenital diseases, immunologic diseases, acute/chronic pancreatitis, cirrhosis, malignancy, epilepsy and patients who were using alcohol, magnesium-containing antacids, magnesium-containing vitamin-mineral preparations.

Patients' age, weight, height, glucose, insulin, HOMA-IR, glycosylated hemoglobin (HbA1c), calcium (Ca), Mg, and 25 (OH) vitamin-D levels were recorded. Body mass indexes (BMI) [(weight (kg) / height (m²)] of all patients were calculated using height and weight measurements. HOMA-IR was measured to determine insulin resistance and calculated as the fasting insulin level (μU/mL) × early morning fasting blood glucose level (mg/dL)/405. In our clinical routine, blood samples were taken in the morning after at least 12 hours of nightly fasting.

Statistical analysis

For the statistical analysis, SPSS version 17 for Windows (Statistical Package for Social Sciences - SPSS, Chicago, IL, USA) was used. Student t test was used for comparison of descriptive statistical methods (mean and standard deviation) as well as quantitative data when study data were evaluated. Pearson correlation test was used when the relations between the parameters were examined. Chi-square test was used for comparison of qualitative data. The results were evaluated in a confidence interval of 95% and a significance level of $p < 0.05$.

Results

This study included 130 patients consisted of 67 newly diagnosed T2DM (group D) and 63 newly diagnosed prediabetic (group PD) patients. There was no statistically significant difference in mean age between the group D (44.89±7.67 years) and group PD (42.14±8.74 years) (p=0.058) patients. Only 7.7% (n = 10) of our study population was over 55 years of age.

Descriptive data of groups D and PD is shown in Table 1. In group D, the mean Mg level (1.88±0.17 mg/dL) was significantly lower than group PD (1.96±0.17 mg/dL) (p=0.007). Also, in group D, serum glucose, HOMA-IR and HbA1c levels were found to be statistically higher than group PD whereas BMI and magnesium levels in the group PD were found to be statistically higher than group D (Table 1).

Table 1. Descriptive data of diabetic and prediabetic patients and comparison between the groups.

	Group PD (n=63)¥	Group D (n=67) ¥	p
Age (year)	42.14±8.74	44.89±7.67	0.058
BMI (kg/m²)	34.41±6.46	28.77±5.21	0.0001
Glucose (mg/dl)	96.22±10.01	191.16±81.67	0.0001
Insulin (μu/ml)	14.95±6.50	15.60±16.64	0.205
HOMA-IR score	3.57±1.61	7.22±9.22	0.001
HbA1c (%)	5.70±0.40	8.40±2.46	0.0001
Ca (mg/dl)	9.62±0.46	9.43±0.42	0.012
Mg (mg/dl)	1.96±0.17	1.88±0.17	0.007
Vitamin D (ng/ml)	16.11±11.36	19.57±10.77	0.088

¥: Mean±standard deviation, BMI: Body mass index, HOMA-IR: Homeostatic Model Assessment - Insulin Resistance, Ca: Calcium, Mg: Magnesium, HbA1c: Glycosylated hemoglobin

Significant negative correlations were found between Mg and glucose levels (r=-0.390; p=0.001) and HOMA-IR values (r =-0.284; p=0.022) in group D, but the same correlations were not found in group PD. Also, age, BMI and serum insulin levels were not correlated with serum Mg levels in both groups (Table 2).

Table 2. Correlation analysis between Mg level and BMI, blood glucose, insulin, and HbA1c levels.

Magnesium	Prediabetes		Diabetes	
	r	p	r	p
Age (year)	0.065	0.611	0.083	0.506
BMI (kg/m²)	-0.051	0.691	-0.031	0.809
Glucose (mg/dl)	0.01	0.939	-0.390	0.001
Insulin (μu/ml)	-0.032	0.801	-0.108	0.393
HOMA-IR score	0.000	0.998	-0.284	0.022
HbA1c (%)	0.217	0.087	-0.240	0.051

BMI: Body mass index, HOMA-IR; Homeostatic Model Assessment - Insulin Resistance, HbA1c: Glycosylated hemoglobin

Discussion

This study shows the effect of serum magnesium levels on serum glucose and HOMA-IR values in T2DM patients which could have an impact on diabetes regulation in those patients in clinical routine.

Electrolyte disorders are common in diabetic patients and closely related to increased morbidity and mortality. In a study, a total of 5179 patients over 55 years old have been evaluated for electrolyte disturbance and at least one electrolyte imbalance has been observed in 776 cases (15%) [14]. Electrolyte imbalance is more commonly seen in patients with poor blood glucose regulation and those with renal dysfunction [8, 15]. In our study, patients with renal dysfunction were excluded from the study in order to exclude any conflict.

One of the common electrolyte disorders among diabetic patients is hypomagnesaemia. In a study published in 2004 in United States [16], in which participants who were consisted of 40,000 women aged 45 years and older, 918 subjects had diabetes mellitus and lower magnesium levels than non-diabetic subjects. Similar results have also been obtained in another study [14] aiming to determine the frequency of electrolytic impairment in the elderly population in 2013. Analysis of that study has shown that diabetes was an independent risk factor for hypomagnesaemia in people aged 55 years or older. A study by Odusan et al. [17] has shown that diabetic patients had a lower magnesium level than non-diabetics. In that study, about one-quarter of diabetic patients had hypomagnesemia. In our study, we have determined a significant negative correlation between serum magnesium and glucose level in diabetic patients but there was no correlation in prediabetic patients. However, we could not find a significant relationship between Mg level and age in our study. Similar result was found in the study by Arpaci et al. [18]. This could be caused from the younger age of the patient population taken into the our study.

Studies conducted by Dasgupta et al. [19] and Guerro-Romero et al. [20] have shown that hypomagnesemia increases the risk of complications in diabetic patients, affects glucose regulation badly. A study published in 2018 [21] has been suggested that magnesium might be important because of the antioxidant effect in providing metabolic control of type 2 diabetes. Reasons for the frequent occurrence of hypomagnesemia in diabetics include inappropriate magnesiumuria, incomplete magnesium intake, glomerular hyperfiltration, impaired insulin metabolism, diuretic usage, and recurrent metabolic acidosis [22, 23]. In our study, we have excluded the patients who were using any anti-hypertensive drugs and also patients with renal dysfunction. However, we did not determine the urinary Mg levels in our patients. And we also did not calculate the levels of eGFR (glomerular filtration rate) in our patients. In terms of metabolic acidosis, having a history of diabetes including diabetic ketoacidosis was also an exclusion criterion of our study. We found a significant negative correlation between Mg level and HOMA-IR values in diabetic patients but no correlation was found in prediabetic patients.

The detection and correction of altered Mg status in diabetic patients is clinically appropriate, although many physicians tend to ignore Mg status. The increased risk of developing impaired glucose tolerance and/or frank DM2 in persons with dietary or serum Mg deficits have suggested a potential benefit of Mg supplements in patients with DM2 or in the presence of risk factors for DM2. Mg supplements have been proposed as a complementary tool for the prevention of DM2 and its metabolic control [1].

T2DM is a condition in which the electrolyte disorders are frequently seen due to the pathophysiology of the disease as well as the drugs used and comorbid conditions. It is important to evaluate the electrolytes and to take measures to correct this condition if any disorder is detected [24]. Some benefits of Mg supplements on glycemic profiles have been found in most but not all studies. In our study, we showed a significant negative correlation between magnesium levels and HOMA-IR and fasting blood glucose levels in diabetic patients, but this correlation did not exist in prediabetic ones. Our study included newly diagnosed patients in order to avoid a possible interference between our results and 'disease other than diabetes-related' or drug-related Mg disturbance. As we did not investigate the effect of magnesium on diabetes regulation, we could not evaluate the clinical efficacy of magnesium replacement on T2DM patients.

In conclusion, our study results suggest that serum Mg level is associated with metabolic control of T2DM, and thus it can be considered in T2DM patients.

References

1. Barbagallo M. Magnesium and type 2 diabetes. World J Diabetes. 2015;6:1152-7.
2. Jahnen-Dechent W, Ketteler M. Magnesium basics. Clin Kidney J. 2012;5:i3-i14.
3. Simmons D, Joshi S, Shaw J. Hypomagnesaemia is associated with diabetes: Not pre-diabetes, obesity or the metabolic syndrome. Diabetes Res Clin Pract. 2010;87:261-6.
4. Ma J, Folsom AR, Melnick SL, Eckfeldt JH, Sharrett AR, Nabulsi AA, et al. Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: the ARIC study. Atherosclerosis Risk in Communities Study. J Clin Epidemiol. 1995;48:927-40.
5. Pham PC, Pham PM, Pham PA, Pham SV, Pham HV, Miller JM, et al. Lower serum magnesium levels are associated with more rapid decline of renal function in patients with diabetes mellitus type 2. Clin Nephrol. 2005;63:429-36.
6. Mather HM, Nisbet JA, Burton GH, Poston GJ, Bland JM, Bailey PA, et al. Hypomagnesaemia in diabetes. Clin Chim Acta. 1979;95:235-42.
7. de Lordes Lima M, Cruz T, Pousada JC, Rodrigues LE, Barbosa K, Cangucu V. The effect of magnesium supplementation in increasing doses on the control of type 2 diabetes. Diabetes Care. 1998;21:682-6.
8. Walti MK, Zimmermann MB, Spinas GA, Hurrell RF. Low plasma magnesium in type 2 diabetes. Swiss Med Wkly. 2003;133:289-92.
9. Mooren FC. Magnesium and disturbances in carbohydrate metabolism. Diabetes Obes Metab. 2015;17:813-23.
10. Tosiello L. Hypomagnesemia and diabetes mellitus. A review of clinical implications. Arch Intern Med. 1996;156:1143-8.
11. Nichols GA, Hillier TA, Brown JB. Progression From Newly Acquired Impaired Fasting Glusose to Type 2 Diabetes. Diabetes Care. 2007;30:228-33.
12. Fang C, Wang X, Wu W, Gu X, Ye T, Deng H, et al. Association of Serum Magnesium Level with Odds of Prediabetes and Diabetes in a Southern Chinese Population: a Prospective Nested Case-Control Study. Biol Trace Elem Res. 2015;172:307-14.
13. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia - Report of a WHO/IDF Consultation: WHO Press, World Health Organization, Geneva, Switzerland 2006 [cited 2018 June, 1st]. Available from: http://www.who.int/diabetes/publications/Definition and diagnosis of diabetes_new.pdf.
14. Liamis G, Rodenburg EM, Hofman A, Zietse R, Stricker BH, Hoorn EJ. Electrolyte disorders in community subjects: prevalence and risk factors. Am J Med. 2013;126:256-63.
15. Palmer BF, Clegg DJ. Electrolyte and Acid-Base Disturbances in Patients with Diabetes Mellitus. N Engl J Med. 2015;373:548-59.
16. Song Y, Manson JE, Buring JE, Liu S. Dietary magnesium intake in relation to plasma insulin levels and risk of type 2 diabetes in women. Diabetes Care. 2004;27:59-65.
17. Odusan OO, Familoni OB, Odewabi AO, Idowu AO, Adekolade AS. Patterns and Correlates of Serum Magnesium Levels in Subsets of Type 2 Diabetes Mellitus Patients in Nigeria. Indian J Endocrinol Metab. 2017;21:439-42.
18. Arpaci D, Tocoglu AG, Ergenc H, Korkmaz S, Ucar A, Tamer A. Associations of serum Magnesium levels with diabetes mellitus and diabetic complications. Hippokratia. 2015;19:153-7.
19. Dasgupta A, Sarma D, Saikia UK. Hypomagnesemia in type 2 diabetes mellitus. Indian J Endocrinol Metab. 2012;16:1000-3.
20. Guerrero-Romero F, Simental-Mendia LE, Hernandez-Ronquillo G, Rodriguez-Moran M. Oral magnesium supplementation improves glycaemic status in subjects with prediabetes and hypomagnesaemia: A

double-blind placebo-controlled randomized trial. Diabetes Metab. 2015;41:202-7.
21. Morakinyo AO, Samuel TA, Adekunbi DA. Magnesium upregulates insulin receptor and glucose transporter-4 in streptozotocin-nicotinamide-induced type-2 diabetic rats. Endocr Regul. 2018;52:6-16.
22. Liamis G, Liberopoulos E, Barkas F, Elisaf M. Diabetes mellitus and electrolyte disorders. World J Clin Cases. 2014;2:488-96.
23. Pham PC, Pham PM, Pham SV, Miller JM, Pham PT. Hypomagnesemia in patients with type 2 diabetes. Clin J Am Soc Nephrol. 2007;2:366-73.
24. Özsan M, Yaprak M, Özcan O, Kiriktir E, Turgut F. Tip 2 Diyabetli Hastalarda Elektrolit Bozuklukları. Turkish Nephrology Dialysis Transplantation. 2017;26:285-9.

Arch Clin Exp Med 2019;4(1):10-13. e-ISSN: 2564-6567

DOI:10.25000/acem.468057 Araştırma makalesi / Research article

Can the quick Sequential Organ Failure Assessment (qSOFA) score, combined with plasma lactate concentration, predict the mortality for patients with infections in the emergency department?

Hızlı Sofa skorunun plazma laktat konsantrasyonu ile birlikte kullanımı acil serviste enfeksiyon hastalarındaki mortaliteyi öngörebilir mi?

Mustafa Korkut [1], Cihan Bedel [1]

Abstract

Aim: Few studies have looked at the predictive role of plasma lactate measure combined with the score of quick sequential organ failure assessment (qSOFA) on hospital mortality. The aim of the study was to investigate whether the score of qSOFA combined with plasma lactate is independently associated with in-hospital mortality among patients with infections in the emergency department (ED).
Methods: Scores of qSOFA and plasma lactate measurements of 60 patients in ED were collected prospectively from May 2017 to March 2018. We used the area under receiver operating characteristic curve (AUC) and sensitivity analysis to compare the applicability of qSOFA score alone and qSOFA score combined with lactate level for patient mortality.
Results: Thirteen patients (21.6%) died in the hospitalization period. According to the qSOFA alone, qSOFA score combined with lactate measurement was more successful (AUC = 0.798 vs. 0.885 p<0.001, respectively). When qSOFA was used alone, sensitivity and specificity were 92% and 54%, otherwise those of the combined with lactate measurement were 100% and 43%, respectively (p<0.001).
Conclusion: Combining the qSOFA with lactate has higher sensitivity for patient mortality than that seen with qSOFA alone.

Keywords: qSOFA, lactate, mortality

Öz

Amaç: Hızlı SOFA skorunun plazma laktat düzeyi ile birlikte kullanımının hastane içi mortaliteyi öngörmedeki rolü ile ilgili çok az çalışma vardır. Bu çalışmamızın amacı plazma laktat düzeyi ile kombine bir hızlı SOFA skorunun, acil serviste enfeksiyonlu hastalarda hastane içi mortalite için ilişkili olup olmadığını araştırmaktı.
Yöntemler: Mayıs 2017- Mart 2018 tarihleri arasında acil servise başvuran 60 hastanın qSOFA ve plazma laktat ölçümleri prospektif olarak toplandı. Olguların qSOFA skorunun tek başına ve laktat ile birlikte kullanımının mortaliteyi öngörmedeki analizi yapıldı.
Bulgular: On üç hasta (%21,6) hastaneye yatış süresinde öldü. Laktat ölçümü ile kombine edilmiş qSOFA, qSOFA skoru tek başına kullanımına göre daha başarılı bulunmuştur (sırasıyla AUC = 0,798 ve 0,885, sırasıyla p<0,001). qSOFA için tek başına duyarlılık ve özgüllük %92 ve %54 iken, laktat ile kombine edilmesiyle sırasıyla %100 ve %43 olduğu saptandı (p<0,001).
Sonuç: qSOFA'nın laktat ile kombine edilmesi, qSOFA'nın tek başına kullanılmasına göre mortalite üzerinde daha yüksek hassasiyete sahiptir.

Anahtar kelimeler: qSOFA, laktat, mortalite

[1] **Health Science University Antalya Training and Research Hospital, Department of Emergency Medicine, Antalya, Turkey.**

Ethics Committee Approval: The study wass approved by the local ethical authority.
Etik Kurul Onayı: Çalışma lokal etik komite tarafından onaylanmıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Geliş Tarihi / Received: 07.10.2018
Kabul Tarihi / Accepted: 13.02.2019
Yayın Tarihi / Published: 15.03.2019

Sorumlu yazar / Corresponding author:
Cihan Bedel
Health Science University Antalya Training And Research Hospital, Kazım Karabekir Street postal zip code: 07100, Muratpaşa, Antalya, Turkey.
e-posta: cihanbedel@hotmail.com
Tel/Phone: +905075641254

Introduction

Recently, the description of sepsis changed and qSOFA is recommended as a new classification system [1]. The qSOFA criteria for sepsis include an altered mental status (AMS), systolic blood pressure (SBP) less than or equal to 100 mm/ Hg and respiratory rate (RR) greater than or equal to 22 per minute (calculated by assigning 1 point each to yield a score value between 0 and 3). In the original study, the qSOFA score was useful to predict mortality and it was superior than that of the more complicated SOFA score [2]. Lactate is known as an independent indicator of mortality in septic shock and as an available marker of cellular and metabolic stress [3].

Higher serum plasma lactate measurements are correlated with enhancement morbidity and mortality in various patient samples, including [4, 5]. When lactate level ≥ 2 mmol / L was combined with the score of qSOFA, the mortality raised but serum lactate measurement did not supply statistics verges [2]. Otherwise, only limited number of studies investigated the predictive role of qSOFA in combination with plasma lactate levels in hospital mortality (Lactate ≥2mmol/L adds qSOFA enhances efficacy over qSOFA alone in the ED patients with suspected sepsis). Our purpose for this study was to investigate whether combining qSOFA with plasma lactate concentration is independently correlated with in-hospital mortality among patients who were admitted to the ED with infections.

Material and methods

The present research was a single center study and the samples were observed prospectively. Our population was the patients with clinically suspected or diagnosed infection at the ED from May 2017 to March 2018. Our hospital is a 2000-bed education and research hospital with about 360 000 ED visitors per year. This study was approved by the ethics committee of our institution. Informed consent documents were taken from all the patients. The study was performed following the Helsinki Declaration.

Our inclusion criteria for this study were being ≥18 years, with infection diagnosed or suspected by an emergency physician, and admitted to the ED. Pneumonia was diagnosed through chest radiography with two or more symptoms of dyspnea, fever, cough, sputum, breathlessness and/or pleuritic chest pain. Inflammatory markers such as C-reactive protein and leukocyte count were used for the diagnosis of infection [6]. Intra-abdominal infections were defined within any abdominal organ or cavity, containing radiographic or imaging indication of infection and one or more of such symptoms as fever, nausea, vomiting, abdominal pain or jaundice. Other infections contained skin and soft tissue infections, cerebral infection, and pyelonephritis. A qSOFA score ≥ 1 was included in this study. During the study period, 96 adults were admitted with suspected infection, 60 patients (62.5%) who met the inclusion criteria were included in the final analysis. A total of 36 patients were excluded from the study; 12 of these patients were missing data and 24 patients were excluded from the study with exclusion criteria (Figure 1).

The exclusion criteria were respectively: age <18 years (n=2), a qSOFA score< 1 (n=3), trauma (n=2), cardiac arrest (n=2), aortic dissection (n=1), acute pulmonary thromboembolism (n=1), acute cardiac failure (n=2), end stage malignant diseases (n=3), burns (n=1), human immunodeficiency virus positivity (n=1), intubated patients (n=1), use of immunosuppressant drugs (n=1).Those admitted for palliative therapies (n=2), and patients who refused to participate (n=2) in the study were also excluded.

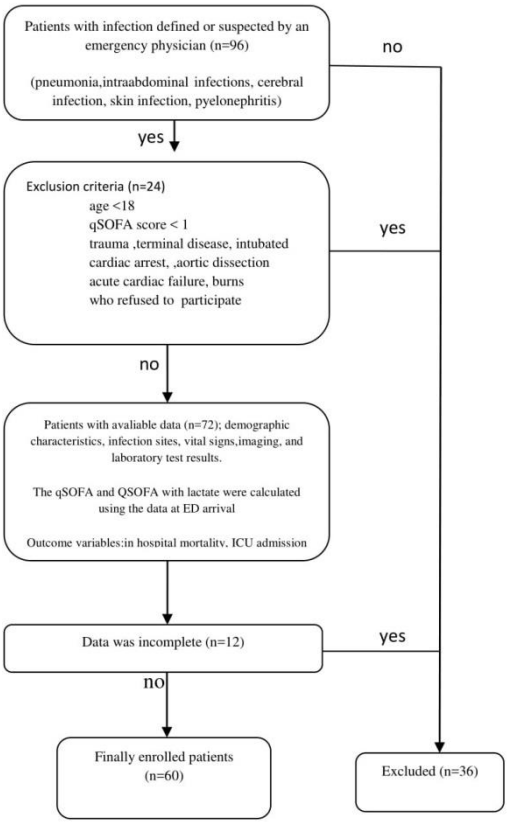

Figure 1: Flowchart of patient enrollment.

After application to triage in ED, we collected demographic status, focus of infection, vital signs, radiographic imaging and laboratory test results of registered patients. We first calculated the qSOFA score (within 2 minutes or less) within a range of 0 to 3. This score was calculated according to values of systolic blood pressure (SBP) less than or equal to 100 mm/ Hg and respiratory rate (RR) greater than or equal to 22 per minute and any alteration of mental status (calculated by assigning 1 point each to yield a score value between 0 and 3). The emergency physician assessed the state of consciousness of the patient, where patients with Glasgow coma score <15 were accepted as altered mental status (AMS). AMS also included any altered mentation such as somnolence and disorientation. Plasma lactate levels stabilized during the patient's first hour in the ED We measured lactate levels of patients after the first hour. For the patients whose plasma lactate levels were≥ 2 mmol/L, one additional point was added to the score of patient's qSOFA. qSOFA+lactate (qSOFA score with plasma lactate score) scores were calculated within the range of 0 to 4. We compared the effect of these measurements on mortality. In our study, the primary outcome was about hospital mortality. Secondary outcomes were about hospital admission, ICU admission, and total length of stay at the hospital, from ED triage to discharge from the hospital.

Statistical analysis

We used SPSS software version 20.0 (SPSS, Inc, Chicago, IL) for all statistical analyses. Normally distributed data were given as means± standard deviations. We compared normally distributed variables using the independent-samples t test. Data with does not have normal distribution were presented

as median and quartiles, which we analyzed by using Mann-Whitney U test. We compared categorical variables using $\chi 2$ statistics. The independent variables of outcomes that statistical significance evaluated by logistic regression analysis. We tested all variables with statistical difference in a binary logistic analysis together with qSOFA. We formed receiver operating characteristic (ROC) curves and evaluated the AUC to define predictive values. We also calculated prognostic parameters (sensitivity and specificity). All statistical tests were two-tailed, and $p<0.05$ was considered significant.

Results

Ninety-six patients were asked to fill in the study data forms for the study. Thirty six patients who fulfill one or more of the exclusion criteria were excluded from the study (Figure 1). Of the 60 patients included in the study, 41 (68.3%) were female and 19 (63%) were male. The mean age of the patients was 67.23±16.75 years. Of the patients, 47 patients (78.4%) survived and 13 patients (21.6%) died during hospitalization. Cardiovascular disease was the most common cause of comorbidities of the patients in 18 (30%) followed by chronic obstructive lung disease in 16 (26.7%), diabetes mellitus and immunosuppression diseases in 11 (18.3%). Baseline population characteristics are shown in Table 1.

A SBP ≤ 100 mmHg and a RR ≥ 22 breaths/min were founded at 29 (48.33%) and 53 (88.33%) of the patients, respectively. 14 (23.33) of the patients were AMS cases. Higher lactate measurements, qSOFA and qSOFA combined lactate scores were statistically significant in the dead patients (Table 2).

Table1. Demographic Status of Patients.

Variable	Overall (n=60)	Alive (n=47)	Dead (n=13)	p
Sex (Female/male)	41/19	30/17	11/2	0.194
Age (year) #	67.23±16.75	66.36±18.05	70.38±10.38	0.443
Comorbidities				
Diabetes mellitus¥	11 (18.3)	7 (14.8)	4 (30.7)	0.231
Chronic obstructive lung disease¥	16 (26.7)	15 (31.9)	1 (7.7)	0.153
Chronic renal disease¥	9 (15)	6 (12.7)	3 (23.1)	0.392
Chronic liver disease¥	4 (6.7)	2 (4.2)	2 (15.4)	0.202
Cardiovascular disease¥	18 (30)	12 (25.5)	6 (46.2)	0.181
Immunosuppression¥	11 (18.3)	4 (8.5)	7 (53.8)	0.001
Life style changes in the urban¥	44 (73.3)	35 (79.6)	9 (20.4)	0.560
Infection focus				
Pneumonia¥	28 (46.7)	23 (48.9)	5 (38.4)	0.547
Intraabdominal infection¥	10 (16.7)	5 (50)	5 (50)	0.017
Urinary tract infection¥	11 (18.3)	9 (19.2)	2 (15.4)	0.557
Others¥	11 (18.3)	9 (19.2)	2 (15.4)	0.557
Blood culture positive¥	10 (16.6)	8 (17)	2 (15.4)	0.384
Urine culture positive	5 (8.4)	4 (8.5)	1 (7.6)	0.716
Sputum culture positive¥	3 (5)	2 (4.2)	1 (7.6)	0.394
ICU admission¥	20 (33.3)	10 (21.2)	10 (76.9)	<0.001
LOS in hospital median, ≤10 days¥	40 (66.7)	28 (70)	12 (30)	0.027
Discharge from emergency department¥	11 (18.3)	11(100)	0 (0)	0.054

ICU: Intensive care unit, LOS: Length of stay, #: mean±SD, ¥: n (%)

This study investigated the effectiveness of the qSOFA, lactate and the combining score (qSOFA with lactate) for the prediction of the mortality using ROC analysis. It was found that the area under curve (AUC) values of these variables were statistically significant to predict mortality (Table 3; Figure 2). qSOFA with lactate had the highest AUC (0.885; p<<.001) followed by qSOFA and lactate (AUC=0.798; p=0.790, respectively). Moreover, the combining score had a higher sensitivity with a little alteration in specificity compared with that of the qSOFA score alone. In our study, when the qSOFA score was compared with lactate levels for the prediction of the mortality; qSOFA had the lower specificity (54%), though it had the higher sensitivity (92%) with a AUC value of 0.798 (Table 3).

Table 2. Distribution of lactate levels and qSOFA, qSOFA + lactate scores.

Variable	Overall (n=60)	Alive (n=47)	Dead (n=13)	p
Lactate, mmol/L#	2.15±2.3	1.55±1.28	4.32±3.65	<0.001
Lactate ≥ 2.0 mmol/L¥	17 (28.3)	9 (19.1)	8 (61.5)	<0.001
qSOFA Score	1.65±0.63	1.49±0.54	2.23±0.59	<0.001
qSOFA¥				<0.001
1	26 (43.3)	25 (53.2)	1 (7.7)	
2	29 (48.4)	21 (44.7)	8 (61.5)	
3	5 (8.3)	1 (2.1)	4 (30.8)	
qSOFA + lactate score¥				<0.001
1	20 (33.3)	20 (42.6)	0 (0)	
2	25 (41.7)	22 (46.8)	3 (23.1)	
3	14 (23.3)	5 (10.6)	9 (69.2)	
4	1(1.7)	0 (0)	1 (7.7)	

#: mean±SD, ¥: n (%).

Table 3. Receiver operating characteristics analysis of each parameter for the prediction of mortality.

Variable	Sensitivityμ	Specificityμ	AUCμ	p
Lactate	61 (32-86)	81 (67-91)	0.790 (0.650-0.925)	<0.001
qSOFA	92 (64-99)	54 (38-68)	0.798 (0.654-0.945)	<0.001
qSOFA +lactate	100 (76-100)	43 (28-58)	0.885 (0.789-0.980)	<0.001

qSOFA: quick sequential organ failure assessment, AUC: area under curve, μ: mean (range).

Figure 2. Receiver operation characteristic curve for patient mortality using qSOFA alone and QSOFA with lactate score. The combined qSOFA and lactate level score has a higher AUC than qSOFA alone (AUC=0.885 vs. 0.798, p<0.001, respectively). AUC = area under curve, qSOFA = quick Sequential Organ Failure Assessment

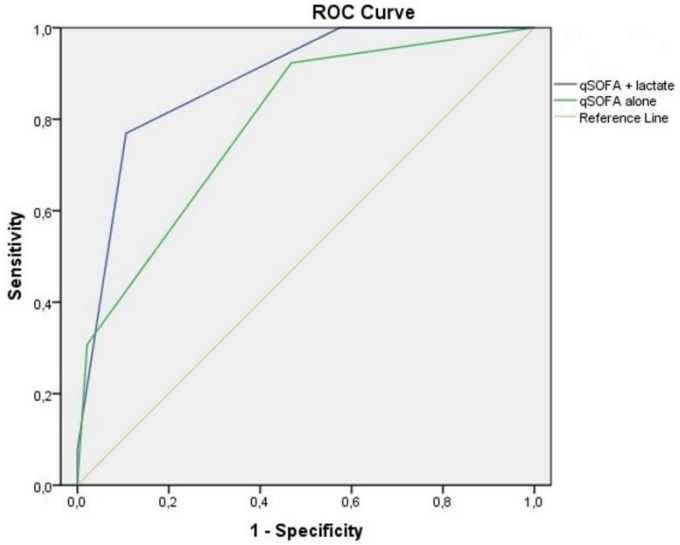

Figure 2. Receiver operation characteristic curve for patient mortality using qSOFA alone and QSOFA with lactate score. The combined qSOFA and lactate level score has a higher AUC than qSOFA alone (AUC=0.885 vs. 0.798, p=0.001, respectively). AUC = area under curve, qSOFA = quick Sequential Organ Failure Assessment.

Discussion

Our findings proved that only the qSOFA has higher sensitivity. It was a mild predictive performance. In contrast to our study, the literature found poor sensitivity with qSOFA scores, which created a growing concern. The risk of in-hospital mortality increases if resuscitation delays in the ED [7]. qSOFA with lactate resulted in enhanced sensitivity with a vaguely decreased specificity. In a study presented in ED structured by Williams et al. 26.8% had a SBP ≤ 100 mmHg, 21.1% of patients had a RR ≥ 22 breaths/min and only 5.1% of patients had AMS [8]. This study also showed that only 14 patients (% 23.3) in this study sample (60 patients) had AMS. Among patients applied to the ED with AMS, only 13 (92.85%) of our patients had a qSOFA score ≥2, which makes it complicated to investigate. Thus, identifying patient's mortality risk increased. In our study group, one patient had a qSOFA score < 2 and died.

Other studies presented that qSOFA had poor sensitivity, so that it was not useful for the screening test for sepsis [8, 9].

We found that qSOFA and qSOFA with lactate scores were significantly correlated with all measured outcomes, including in hospital mortality, intensive care unit (ICU) admission and hospitalization. In this study, the qSOFA score performed well in showing mortality for the patients with suspected infection. Therefore, the qSOFA score, easily calculated in consent with vital signs, can be used as a generic scale to predict clinically important outcomes for ED patients. ED patients covered in the study are likely to be admitted regardless of whether mortality is suspected. qSOFA score of 2 or greater had higher sensitivity. Besides this, a qSOFA score of <2 had perfect negative predictive value, with high sensitivity and specificity. The performance of the qSOFA in our study was similar to that of more complex scores such as the mortality in ED sepsis score originally derived by Shapiro et al. [10]. In this study, the AUC for the score was 0.82 and more advanced prediction scores were declared to have even greater accuracy [11]. The superiority of the qSOFA score is its simplicity and the fact that it can be calculated without any laboratory tests.

We analyzed combination scores containing qSOFA and plasma lactate measurement. As recommended in many studies, plasma lactate level is a significant predictor of mortality in seriously critical patients [12, 13]. In contrast to the literature, only plasma lactate level with a cutoff value of 2 mmol/L showed a well predictive performance, but when combined with qSOFA, its efficacy of predictive value in-hospital mortality was lower in our study population.

The rapid point-of-care (POC) measurement blood lactate level is practical, feasible, and reliable. Singer et al. [14] recorded that bedside POC lactate measurement in adult ED patients decrease time to administration of septic patients, leading to a decrease of in hospital mortality for these patients. Combined lactate levels with qSOFA score increases qSOFA's discriminating power and can be used as a rapid and simple method. Recently Seymour et al. [2] have reported the predictive value of qSOFA for inpatient mortality within ICU encounters was 0.66 (95% CI 0.64 to 0.68). The predictive value within non-ICU encounters was 0.81 (95% CI 0.80 to 0.82). This was statistically significant unlike the results for SOFA or systemic inflammatory response syndrome criteria [2]. In contrast to the literature, our finding qSOFA with lactate had the highest AUC (0.885) followed by qSOFA and lactate (AUC=0.798). But, qSOFA with lactate had a higher sensitivity with a lower specificity compared with lactate or qSOFA score alone.

Our study has some limitations. First, our study sample was from a single center with an early quantitative resuscitation program for sepsis patients who were presented to the ED. Thus, our findings may not be widely generalizable to other centers at which resuscitation programs are not applicable for sepsis management. Second, lactate was not simultaneously measured in all patients valid for the study. Third, due to the small population, there may have been inadequate statistical power to identify some of the significant findings.

As a result, in the ED using only the qSOFA score has poor sensitivity for screening patients with high risk of mortality. Combining the qSOFA with lactate has higher sensitivity for patient mortality than that seen with qSOFA alone.

References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock. JAMA. 2016;315:801-10.
2. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of clinical criteria for sepsis: for the Third International Consensus Definitions for Sepsis and Septic Shock. JAMA. 2016;315:762-74.
3. Casserly B, Phillips GS, Schorr C, Dellinger RP, Townsend SR, Osborn TM, et al. Lactate measurements in sepsis-induced tissue hypoperfusion: results from the Surviving Sepsis Campaign database. Crit Care Med. 2015;43:567-73.
4. Mikkelsen ME, Miltiades AN, Gaieski DF, Goyal M, Fuchs BD, Shah CV, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. Crit Care Med. 2009;37:1670-7.
5. Del Portal DA, Shofer F, Mikkelsen ME, Dorsey Jr PJ, Gaieski DF, Goyal M, et al. Emergency department lactate is associated with mortality in older adults admitted with and without infections. Acad Emerg Med. 2010;17:260-8.
6. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Crit Care Med. 2007;44:27-72.
7. Sartelli M, Kluger Y, Ansaloni L, Hardcastle TC, Rello J, Watkins RR, et al. Raising concerns about the Sepsis-3 definitions. World J Emerg Surg. 2018;13:6.
8. Williams JM, Greenslade JH, McKenzie JV, Chu K, Brown AF, Lipman J. Systemic inflammatory response syndrome, quick sequential organ function assessment, and organ dysfunction: insights from a prospective database of ED patients with infection. Chest. 2017;151:586-96.
9. Dorsett M, Kroll M, Smith CS, Asaro P, Liang SY, Moy HP. qSOFA has poor sensitivity for prehospital identification of severe sepsis and septic shock. Prehosp Emerg Care. 2017;21:489-97.
10. Shapiro NI, Wolfe RE, Moore RB, Smith E, Burdick E, Bates DW. Mortality in Emergency Department Sepsis (MEDS) score: a prospectively derived and validated clinical prediction rule. Crit Care Med. 2003;31:670-5.
11. Singer AJ, Ng J, Thode Jr HC, Spiegel R, Weingart S. Quick SOFA scores predict mortality in adult emergency department patients with and without suspected infection. Ann Emerg Med. 2017;69:475-9.
12. Chebl RB, El Khuri C, Shami A, Rajha E, Faris N, Bachir R, et al. Serum lactate is an independent predictor of hospital mortality in critically ill patients in the emergency department: a retrospective study. Scand J Trauma Resusc Emerg Med. 2017;25:69.
13. Lokhandwala S, Andersen LW, Nair S, Patel P, Cocchi MN, Donnino MW. Absolute lactate value vs relative reduction as a predictor of mortality in severe sepsis and septic shock. J Crit Care. 2017;37:179-84.
14. Shapiro NI, Fisher C, Donnino M, Cataldo L, Tang A, Trzeciak S, et al. The feasibility and accuracy of point-of-care lactate measurement in emergency department patients with suspected infection. J Emerg Med. 2010;39:89-94.

Arch Clin Exp Med 2019;4(1):14-16. e-ISSN: 2564-6567

DOI:10.25000/acem.486816 Araştırma makalesi / Research article

Dorsal approach for excision of Morton's interdigital neuroma: A mid-term follow-up study

Dorsal yaklaşım ile Morton nöroma eksizyonu cerrahisi orta dönem sonuçları

Haluk Çelik [1], Metin Uzun [2]

Abstract

Aim: Morton's neuroma is a paroxysmal neuralgia of forefoot and when nonsurgical treatment is unsuccessful, neuroma excision is indicated. The purpose of the present study was to evaluate the outcomes, complications and existing symptoms following an excision of the neuroma using dorsal approach.

Methods: The study evaluated 27 patients (21 women) with an average age of 49 years (range, 24-74) and an average follow-up of 52 months (range, 24-96). The clinical diagnosis was confirmed by history and clinical evaluation. Clinical outcomes were assessed using the interdigital neuroma score and the patients were asked in terms of the level of pain, shoe modification, and sensorial problems.

Results: Average interdigital neuroma score improved from 20 to 62 points following the surgery ($p<0.05$). An excellent interdigital neuroma score was reported in 11 cases (41%), well in 13 (48%) and fair in one patient (4%); and two patients (7%) had a poor result with a similar pain prior to surgery. Numbness was reported in 16 patients (59%) without a restriction in daily life. Seven patients (26%) reported mild limitation with fashionable shoes and one patient (4%) reported severe intolerance in footwear. 19 patients (70%) were completely pain-free.

Conclusion: Surgical excision via dorsal approach is an effective method for the treatment of Morton's neuroma. In spite of the fact that mild degree shoe modification and numbness were the most common existing symptoms after the surgery, clinical scores were not related to ongoing symptoms.

Keywords: Morton, interdigital neuroma, metatarsalgia

Öz

Amaç: Morton's nöroma ön ayağın ilerleyici ve ağrılı bir hastalığı olup, cerrahi dışı yöntemler başarısız olduğunda nöroma eksizyonu tedavi seçenekleri arasındadır. Bu çalışmada dorsal yaklaşım ile nöroma eksizyonu yapılan olgularda fonksiyonel sonuçlar, komplikasyonlar ve devam eden şikayetler araştırılmıştır.

Yöntemler: Morton's nöroma tanısı ile dorsal nöroma eksizyonu yapılan 27 hasta (21 kadın) çalışmaya dahil edildi. Ortalama yaş 49 yıl (Yaş aralığı 24-74 yıl) ortalama takip süresi 52 ay idi (Yaş aralığı 24-96 yıl). Klinik skorlar interdigital nöroma skorlama sistemine göre değerlendirildi. Hastalar son takiplerinde ağrı şiddeti, ayakkabı değişiklikleri ve duyu problemleri açısından sorgulandı.

Bulgular: Cerrahi öncesi 20 puan olan ortalama interdigital nöroma skorlaması, son takipte ortalama 62 puan olarak saptandı ($p<0.05$). Onbir olguda (%41) mükemmel, 13 olguda (%48) iyi, bir olguda (%4) orta ve iki olguda (%7) kötü sonuç elde edildi. Onaltı olguda (%59) günlük hayatı etkilemeyen his kaybı saptandı. Yedi hasta (%26) zaman zaman ayakkabı değişikliği yapmaları gerektiğini bildirirken, bir hasta (%4) özel ayakkabı dışında ayakkabı kullanamadığını ifade etti. 19 hastada (%70) hiç ağrı saptanmadı.

Sonuç: Dorsal yaklaşım ile nöroma eksizyonu, Morton nöroma tedavisinde etkili bir tedavi yöntemidir. Hafif dereceli ayakkabı intoleransı ve his kaybı sık devam eden şikayetler arasında olup klinik skorları ile ilişki saptanmamıştır.

Anahtar sözcükler: Morton, interdigital nöroma, metatarsalji

[1] University of Health Sciences, Umraniye Training and Research Hospital, Department of Orthopedics and Traumatology, Istanbul, Turkey.

[2] Maslak Acibadem Hospital, Department of Orthopedics and Traumatology, Istanbul, Turkey.

Ethics Committee Approval: The study was approved by the local ethical authority.
Etik Kurul Onayı: Çalışma lokal etik komite tarafından onaylanmıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Geliş Tarihi / Received: 26.11.2018
Kabul Tarihi / Accepted: 25.02.2019
Yayın Tarihi / Published: 15.03.2019

Sorumlu yazar / Corresponding author:
Haluk Çelik
Adres/Address: Ümraniye Eğitim ve Araştırma Hastanesi, Ortopedi ve Travmatoloji Kliniği, Elmalıkent Mahallesi, Adem Yavuz Cd. 34764 Ümraniye, İstanbul
e-posta: drhalukcelik@gmail.com
Tel/Phone: 05326443375

Introduction

An interdigital neuroma is among the causes of the forefoot pain and a controversy still exists for the etiology and treatment [1, 2]. It was first reported by Civinini [3] in 1835 and later by Morton in 1876.[4] Ischemia of the nerve and the entrapment of the common digital nerve by the deep transverse ligament has been considered as the possible etiologies [2, 5, 6]. Fibrosis of the soft tissue, demyelination and endoneurial fibrosis of the nerve are the main histopathological findings [7, 8]. The golden standard method for diagnosis is a clinical examination and the imaging modalities are usually used to exclude other causes of forefoot pain [9, 10]. The pain is aggravated by walking while rest and removal of shoes bring relief [8]. An acute pain is induced with palpable clicking sensation when pressure is applied to intermetatarsal space (Mulder's sign) [8]. The third and second web spaces were the most commonly affected regions [11, 12]. Various conservative methods such as orthosis, shoe modifications, metatarsal unloading, and local steroid infiltrations are the initial treatment. Surgical excision of Morton's neuroma via dorsal or palmar approach is the most common techniques in case of the failure of the conservative treatment with a high success rate [2]. In spite of the fact that the case series related to the surgical treatment of Morton's neuroma indicate successful outcomes, the number of studies are limited [1]. We aimed to report the functional results of our patients after surgical neuroma excision via a dorsal approach and evaluated the possible factors affecting the clinical outcomes.

Material and methods

The present study was approved by the local ethics committee of Umraniye Training and Research Hospital. Between 2010 and 2016, 35 consecutive patients underwent a dorsal neuroma excision for Morton's neuroma were reviewed retrospectively. Inclusion criteria were pain with activities, positive Mulder clunk sign, local tenderness, loss of sensory and unresponsiveness to the conservative management. Three patients were excluded due to association of another anatomical forefoot patologies and 5 patients could not be reached for a final follow-up. Magnetic resonance imaging (MRI) was used to confirm the neuromas and to exclude the other possible causes. Informed consent was obtained for each patient prior to the surgery. All surgeries were performed by the senior author.

Surgical technique

All operations were performed using spinal anesthesia or continuous epidural anesthesia combined with spinal anesthesia. Patients were placed in the supine position on the operating table, and the lower limb tourniquet was inflated. A 5-6 cm dorsal longitudinal incision was made on the affected interdigital space. Dissection was carried down to the transverse intermetatarsal ligament and a lamina spreader was utilized to have enough space between metatarsal heads. Once transverse ligament was released, the common digital nerve was identified just below the ligament. The neuroma was resected such that 1 cm distal and 3 cm proximally to the bulking tissue (Figure). All tissues were prepared for pathological examination. Once bleeding control was made skin closed with nonabsorbable multi-ligament sutures and a compressive bandage was utilized. After ten days sutures were removed and weight-bearing was allowed. The patients were not undergo any rehabilitation protocol.

The histopathological evaluation indicated interdigital neuroma in all patients. At the final follow-up, all patients were asked to complete an interdigital neuroma clinical evaluation score [9]. The neuroma score includes the assessment of pain, walking distance, sensitivity, and footwear choices into a numerical scale from zero to 80 points (Table). The patients were also asked related to their pain level, restrictions in their life, and sensorial changes on the distal part of the surgical incision and the distance of walking. Clinical scores were compared in terms of gender and location of the neuroma. In addition, the patients were asked whether they had another operation related to this issue and their satisfaction with the surgery.

Statistical analysis was performed using SPSS version 12 (SPSS Inc, Chicago, IL). Means and frequencies were calculated to summarize the study data. Normal distribution was investigated using the Shapiro-Wilk test. A paired Student t-test and a qi-square test were used to detect significant differences. The threshold for significance was set at $p<0.05$.

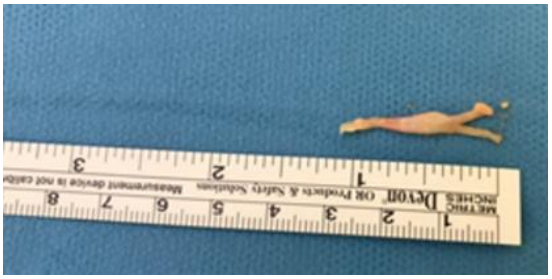

Figure: Excised bulky interdigital neuroma tissue.

Table. Interdigital neuroma clinical evaluation score

Parameter		Score
Pain		
	None	20
	Mild	10
	Severe	0
Maximum walking distance		
	Without limitation (>6 blocks)	20
	Some limitation (2-6 blocks)	10
	Severe limitation (<2 blocks)	0
Sensitivity		
	Normal	20
	Numbness	10
	Dysesthesia	0
Footwear requirement		
	Fashionable conventional shoes	20
	Comfort footwear or shoe insert	10
	Diffficulty with any shoewear	0

Results

The study evaluated 27 patients (21 women) with an average age of 49 years (range 24-74 year) and an average follow-up of 52 months (range 24-96 months). Sixteen neuroma pathologies were located at the left side. In eight patients, neuromas were detected in the second web space, 18 had in the third web space and one patient had in both. No patients had postoperative superficial or deep infection or soft tissue problem.

Prior to surgical treatment, the interdigital neuroma score was an average of 20 points (range 10 to 30). 21 patients (78%) reported severe limitation in walking and all the patients had a restriction on footwear. The numbness was recorded in 9 patients (33 %) and no patient had dysesthesia.

At the final follow-up, average interdigital neuroma score was found 62 points (range 20 to 70) with a statistically significant improvement compared to prior to surgery. ($p<0.05$) An excellent interdigital neuroma score was reported in 11 cases

(41%), good in 13 cases (48%), fair in one patient (4%) and two patients (7%) had a poor result with a similar pain prior to surgery. One of the patients who had poor result was recommended to undergo a revision neuroma excision surgery due to the persistent pain however, the patient did not accept the surgery. The other patient had radiofrequency treatment for polyneuropathy and satisfied after the treatment.

There was no significant difference in outcomes related to gender or location of the neuroma ($p>0.05$). Numbness was reported in 16 patients (59%) without a restriction in daily life. 19 patients (70%) had no restriction in wearing any style of shoes. Seven patients (26%) reported mild limitation with fashionable shoes and one patient reported severe intolerance in footwear. Nineteen patients (70%) were completely pain-free whereas the other patients described a residual discomfort of the situation.

Discussion

Despite its histological nature, no study has provided a gold standard treatment method and significant risk factors regarding the failure in Morton's neuroma. Neuroma excision using either a dorsal or plantar approach has been the most common surgical method for the treatment of the disease. Giannini et al. [9] described a functional scoring system for interdigital neuroma and reported 85% good and excellent results with neuroma excision using dorsal approach. In similar, Coughlin et al. [13] and Kasparek et al. [2] reported 85% and 78% good and excellent results, respectively. Contrary to the aforementioned studies Womack et al. [14] determined poor results in 40% of patients and the authors stated that the higher rate of numbness in their series might cause poor results [14]. We obtained a high rate of good to excellent results in our series similar to literature. Only two patients had poor clinical scores and one of them satisfied after the additional treatment.

Pain after the interdigital neuroma surgery has been reported in 25%- 64% of the patients. In a study a quarter of the cohort was reported an interspace tenderness after surgery with no effect on patients' satisfaction [2]. In our cohort, 30 % of the patients determined a low-level pain without a restriction in their daily life. One of our patients had a severe pain due to possible amputation neuroma below the metatarsal head or scar tissue formation. The patient did not accept the further treatment even though we had recommended an additional surgery.

Shoe modification is a common existing symptom has been reported commonly [8]. Schroven et al. determined that even after a successful surgery, a part of patients had problems with wearing normal shoes [15]. We observed shoe modification in 8 patients (30%) Patients reported that although that situation does not affect their daily life, they choose comfortable shoes. No patient used a special orthosis after surgery. As similar the previous studies, we think that shoe modification does not affect the patient satisfaction.

Numbness in the distal part of the incision is a well-described complication after interdigital neuroma surgery and reported between %51- 72 of the patients [2, 13]. In our cohort, 16 patient had numbness in the last follow up. We also assessed the influence of the sensory deficit on clinical scores, however, we did not find a significant difference between the patients had a sensory deficit or not.

The location of neuroma was mostly reported in third intermetatarsal space. Womack et al. [14] reported lower functional scores with the neuromas located in second web space however in another study the location was not seen as a predictor for lower results [16]. In our study, the most interdigital neuromas were located in the third web space; however, we did not find any statistical difference in outcome between the patients had neuromas in the second or the third web space.

Number of the neuromas might affect the clinical scores and multiple neuromas associated worse outcomes [2]. However, Coughlin et al. [13] reported that patients who had undergone excision of multiple neuromas had a slightly lower of satisfaction without a statistical difference. In our patients, one patient had neuromas in adjacent interspaces and reported good result at the final follow-up.

The second most common procedure for excision of the neuroma is plantar approach. Even though neuroma excision can be performed succesfully via plantar approach, scar related problems, delayed wound healing, inclusion cysts were higher than dorsal approach [1].

Limitations of the present study are possible recall bias due to its retrospective design and the lack of comparison with a different surgical technique. In addition lack of a power analysis was another limitation for the present study.

In conclusion, surgical excision via a dorsal approach is an effective method for the treatment of Morton's neuroma. In spite of the fact that mild degree shoe modification and numbness are the most common existing symptoms after the surgery, clinical scores are not affected due to ongoing symptoms.

References

1. Di Caprio F, Meringolo R, Shehab Eddine M, Ponziani L. Morton's interdigital neuroma of the foot: A literature review. Foot Ankle Surg. 2018;24: 92-8.
2. Kasparek M, Schneider W. Surgical treatment of Morton's neuroma: clinical results after open excision. Int Orthop. 2013;37: 1857-61.
3. Civinini F. Su d'un nervoso gangliare rigonfiamento alla pianta del piede. Lettera anatomica al Dr. Salomone Lampronti, Pistoia, Tip. Bracali, 1835.
4. Morscher E, Ulrich J, Dick W. Morton's intermetatarsal neuroma: morphology and histological substrate. Foot Ankle Int. 2000;21: 558-62.
5. Bennett GL, Graham CE, Mauldin DM. Morton's interdigital neuroma: a comprehensive treatment protocol. Foot Ankle Int. 1995;16: 760-3.
6. Graham CE, Graham DM. Morton's neuroma: a microscopic evaluation. Foot Ankle. 1984;5: 150-3.
7. Zanetti M, Strehle JK, Kundert HP, Zollinger H, Hodler J. Morton neuroma: effect of MR imaging findings on diagnostic thinking and therapeutic decisions. Radiology. 1999;213: 583-8.
8. Pace A, Scammell B, Dhar S. The outcome of Morton's neurectomy in the treatment of metatarsalgia. Int Orthop. 2010;34: 511-5.
9. Giannini S, Bacchini P, Ceccarelli F, Vannini F. Interdigital neuroma: clinical examination and histopathologic results in 63 cases treated with excision. Foot Ankle Int. 2004;25: 79-84.
10. Coughlin MJ. Common causes of pain in the forefoot in adults. J Bone Joint Surg Br. 2000;82: 781-90.
11. Nery C, Raduan F, Del Buono A, Asaumi ID, Maffulli N. Plantar approach for excision of a Morton neuroma: a long-term follow-up study. J Bone Joint Surg Am. 2012;94: 654-8.
12. Dereymaeker G, Schroven I, Steenwerckx A, Stuer P. Results of excision of the interdigital nerve in the treatment of Morton's metatarsalgia. Acta Orthop Belg. 1996;62: 22-5.
13. Coughlin MJ, Pinsonneault T. Operative treatment of interdigital neuroma. A long-term follow-up study. J Bone Joint Surg Am. 2001;83-A: 1321-8.
14. Womack JW, Richardson DR, Murphy GA, Richardson EG, Ishikawa SN. Long-term evaluation of interdigital neuroma treated by surgical excision. Foot Ankle Int. 2008;29: 574-7.
15. Schroven I, Geutjens G. Results of excision of the interdigital nerve in the treatment of morton's metatarsalgia. The Foot. 1995;5: 196-8.
16. Mann RA, Reynolds JC. Interdigital neuroma--a critical clinical analysis. Foot Ankle. 1983;3: 238-43.

Arch Clin Exp Med 2019;4(1):17-20. e-ISSN: 2564-6567

DOI:10.25000/acem.475094 Araştırma makalesi / Research article

Thymosin beta-4 A/T polymorphism and acute coronary syndrome risk

Timozin beta-4 A/T polimorfizmi ve akut koroner sendrom riski

Melike Gezen [1], Ümit Yılmaz [1, 2], Osman Fazlıoğulları [3], Nesibe Yılmaz [1, 4], Cem Horozoğlu [1], Arzu Ergen [1], Ümit Zeybek [1]

Abstract

Aim: Acute coronary syndrome (ACS) describes all the clinical conditions due to myocardial infarction that is caused by decreased blood flow in the coronary artery. Thymosin beta-4 (Tβ4) plays a significant role in the recovery of damaged tissues and promoting the survival of cardiomyocytes in ACS. In this study, it was aimed to determine the Tβ4 A/T (rs75112573) variation in ACS and its effects on the disease.

Methods: This was a prospective case-control study. Forty-eight patients with ACS and 45 healthy controls were recruited for this study. Genetic analysis was performed using polymerase chain reaction/restriction fragment length polymorphism (PCR/RFLP).

Results: The AT genotype (p<0.001, X2:12.40, OR:5.42, 95% CI:2.02-14.53) and the A allele (p<0.001, X2:17.22, OR:6.66, 95% CI:2.61-16.98) frequency was found significantly higher in the patient group, while in the control group the TT genotype was statistically higher (p<0.001, X2:17.22, OR:2.13, 95% CI:1.44-3.16). LDL-cholesterol levels in the patient group (p<0.001, 95% CI:30.12-55.90), and HDL-cholesterol levels in the control group (p<0.001, 95% CI:5.30-15.34) were significantly higher. In the patient group, total cholesterol and HDL-cholesterol levels were found significantly higher in AT genotype carriers compared to the AA genotype carriers (p=0.036, 95% CI:0.59-17.25), while VLDL-cholesterol levels were higher in the AA genotype carriers compared to the AT (p=0.011, 95% CI:6.73-49.86), and TT (p=0.018, 95% CI:4.95-49.49) genotype carriers.

Conclusion: It can be concluded that carrying the Tβ4 A/T (rs75112573) gene polymorphism AT genotype and the A allele may increase risk of ACS.

Keywords: Thymosin beta-4 A/T, polymorphism, acute coronary syndrome, PCR-RFLP

Öz

Amaç: Akut koroner sendrom (ACS), koroner arter kan akımının azalması sonucu miyokard iskemisinin neden olduğu klinik tabloların tamamını ifade eder. Thymosin beta-4 geni (Tβ4) hasarlı dokuların iyileşmesinde ve ACS'de kardiyomiyositlerin canlı kalmasında önemli rol oynamaktadır. Bu çalışmada ACS'li hastaların Tβ4 genindeki A/T (rs75112573) varyasyonunun tespit edilmesi ve akut koroner hastalığına olan etkilerinin belirlenmesi amaçlanmıştır.

Yöntemler: Bu prospektif bir vaka kontrol çalışmasıdır. Çalışmaya ACS'li 48 hasta ve 45 sağlıklı kontrol birey dahil edildi. Genetik analiz, polimeraz zincir reaksiyonu/restriksiyon parça uzunluk polimorfizmi (PCR / RFLP) yöntemleri kullanılarak yapıldı.

Bulgular: Kontrol grubu ile karşılaştırıldığında hasta grubunda AT genotipi (p<0.001, X2:12.40, OR:5.42, %95 CI:2.02-14.53) ve A alleli (p<0.001, X2:17.22, OR:6.66, %95 CI:2.61-16.98) taşıma sıklığı anlamlı olarak yükselmiştir. Kontrol grubunda ise TT genotip sıklığının hasta grubuna göre istatistiksel olarak yüksek olduğu gözlemlenmiştir (p<0.001, X2:17.22, OR:2.13, %95 CI:1.44-3.16). Hasta grubumuzun LDL-kolesterol seviyesi (p<0.001, %95 CI:30.12-55.90), kontrol grubumuzun ise HDL-kolesterol seviyesi yüksek bulunmuştur (p<0.001, %95 CI:5.30-15.34). Hasta grubunda AT genotipi taşıyanlarda AA genotipi taşıyanlara göre kolesterol ve HDL-kolestrol düzeyleri anlamlı derecede yüksek olarak bulunmuştur (p=0.036, %95 CI:0.59-17.25). VLDL-kolestreol düzeyleri ise hasta grubunda AA genotipi taşıyanlarda, AT (p=0.011, %95 CI:6.73-49.86) ve TT (p=0.018, %95 CI:4.95-49.49) genotipi taşıyanlara göre anlamlı şekilde yükselmiştir.

Sonuç: Tβ4 A/T (rs75112573) gene polymorphism için AT genotipi ve A alleli taşımanın ACS riskini artırabileceği sonucuna ulaşılabilir.

Anahtar kelimeler: Timozin beta-4 (Tβ4) A/T, polimorfizm, akut koroner sendrom, PCR-RFLP

[1] Istanbul University, Aziz Sancar Institute of Experimental Medicine, Department of Molecular Medicine, Istanbul, Turkey.
[2] Inonu University, Faculty of Medicine, Department of Physiology, Malatya, Turkey.
[3] Avicenna Hospital, Department of Cardiovascular Surgery, Istanbul, Turkey.
[4] Inonu University, Faculty of Medicine, Department of Anatomy, Malatya, Turkey.

Ethics Committee Approval: The study wass approved by the local ethical authority.
Etik Kurul Onayı: Çalışma lokal etik komite tarafından onaylanmıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The present work was supported by the Research Fund of Istanbul University. Project No: 30910.
Finansal Destek: Bu çalışma İstanbul Üniversitesi Bilimsel Araştırmalar Proje Birimi tarafından desteklenmiştir. Proje No: 30910.

Geliş Tarihi / Received: 26.10.2018
Kabul Tarihi / Accepted: 23.01.2019
Yayın Tarihi / Published: 15.03.2019

Sorumlu yazar / Corresponding author:
Ümit Zeybek
Adress/Adres: Istanbul University, Aziz Sancar Institute of Experimental Medicine, Department of Molecular Medicine, Vakif Gureba Cad., Sehremini-Fatih 34093 Istanbul, Turkey.
e-posta: umz67@yahoo.com
Tel/Phone: +90 532 405 87 40

Introduction

Cardiovascular diseases are the most significant reason of general morbidity and mortality in industrialized and developing countries [1]. Acute coronary syndrome (ACS) is the leading case of cardiovascular diseases, the most common reason of administration to emergency response service or hospitals, especially the coronary care units, and death in both Turkey and worldwide, although many innovations and advances have been made in the diagnosis and treatment lately [2-4]. ACS comprises all clinical conditions that cause myocardial ischemia, which is identified as reduced blood flow in the coronary artery, including unstable angina, ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction [5, 6].

Thymosin beta-4 (Tβ4) is an actin binding protein, containing 43 amino acids and weighing 5kDa, coded by the TMSB4X gene. Tβ4, which has a preventive effect against many pathological conditions, play important roles in repair of damaged tissues and perpetuating cardiomyocytes in acute coronary syndrome [7, 8]. Moreover, it also shows functions as enabling endothelial cell migration, acceleration of angiogenesis, slowing down the inflammatory response, and avoiding apoptosis and oxidative damage [9]. Some studies suggested that Tβ4 might be a significant factor in regulation of myocardial infarction since it is found in high concentrations in platelets and wound fluids [10]. Recently, it has been shown that Tβ4 is expressed in developing hearts, induces cardiomyocytes and migration of endothelial cells, and ultimately play an important role in cardiac vessel development [11, 12].

To date, there have been no studies present conducted on the genetic variants of Tβ4. In this study, it was aimed to determine the Tβ4 gene A/T (rs75112573) variant in ACS patients and its effects on the disease.

Material and methods

Subject Selection

This research has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the Istanbul Medical Faculty Ethical Committee, Istanbul University (#2012/1669-1263). The sample size to be used in the study was determined with power analysis. According to the results of this analysis, the minimum sample size required to detect a significance difference using this test should be at least 40 individuals in each group (in total 80 individuals), considering type I error (α) of 0.05, power (1-β) of 0.8 and effect size of 0.9.

The Tβ4 A/T (rs75112573) gene polymorphism was investigated in 45 healthy subjects (28 women, 17 men) who did not have any heart disease and 48 patients (22 women, 26 men) diagnosed with ACS admitted to the Department of Cardiovascular Surgery, Medicana Bahcelievler Hospital, Istanbul, Turkey, between January 2013 and January 2014.

The patient group was randomly selected patients who were diagnosed with ACS in the hospital which the samples were collected. ST segment elevated q positive or non ST segment elevated but enzyme positive patients are included into the group. Unstable angina pectoris (USAP) patients were excluded. All patients who are diagnosed with acute coronary syndrome had at least one vessel disease detected angiographically. The mentioned control group was created by the people who are working at the same hospital via a survey. Especially the lack of family history was the main criteria to maintain the survey. While creating the control group, the age range was held constant with the patient group.

The biochemical values of individuals with ACS included in the study were obtained from routine laboratory tests and are shown in Table 1.

Table 1. Clinical details of the patient and control groups.

Parameters	Patient Group (n=48)	Control Group (n=45)	P
LDL-cholesterol (mg/dL)	130.10±32.7	87.09±29.9	<0.001
Blood urea nitrogen (mg/dL)	21.25±14.2	-	-
HDL-cholesterol (mg/dL)	39.90±9.4	50.22±14.6	<0.001
Cholesterol (mg/dL)	213.12±40.0	167.96±35.4	<0.001
VLDL-cholesterol (mg/dL)	43.15±24.8	30.17±18.6	<0.001
Triglyceride (mg/dL)	153.29±93.1	27.85±22.1	<0.001
Creatinine (mg/dL)	1.20±1.2	-	-
Urea (mg/dL)	42.97±27.8	-	-
Presence of diabetes Mellitus (%)	58.3	-	-
Presence of hypertension (%)	81.2	-	-
Glucose (mg/dL)	155.98±85.4	-	-

LDL: Low density lipoprotein, HDL: High density lipoprotein, VLDL: Verl low density lipoprotein.

DNA Isolation and Analysis of Polymorphism

In EDTA containing tubes, 10ml of venous blood samples were obtained from the participants. Samples were stored at -20°C until the genomic DNA isolation was performed using the salting out method [13]. Primers used for the polymerase chain reaction (PCR) amplifications of the regions of the Tβ4 A/T polymorphism are given in Table 2. Reaction volumes were set for a total of 25 µl as 16.5 µl apyrogenic water, 2.5 µl MgCl2 free (10X) buffer, 1.7 µl MgCl2 (25mM), 1.5 µl dNTP (10 mM), 1.5 µl mix of forward (10 pmol) and reverse primers (10 pmol), 0.3 µl Taq polimerase (5U/µl) and 1 µl 200 ng/µl genomic DNA sample. PCR mixes were prepared on ice and in a sterile cabin.

For the Tβ4 A/T polymorphism, the PCR reaction conditions were set as following the initial denaturation of 95ºC for 5 minutes, 94 ºC for 45 sec, 65 ºC for 45 sec and 72 ºC 45 sec for 35 cycles and a final elongation duration of 5 min at 75 ºC. PCR yields were controlled on 3% agarose gel electrophoresis.

In order to determine the Tβ4 A/T polymorphism, obtained PCR yields were digested with the Tsp45I restriction enzyme. Digested yields were separated on 3% agarose gel electrophoresis and genotyped after being viewed under UV light. The obtained PCR and restriction yields and genotyping of the polymorphisms are shown in Table 2.

Table 2. PCR–RFLP-based evaluation of the Tβ4 A/T (rs75112573) polymorphism.

Primers	Restriction enzymes	Interpretation (bp)
F: 5'-GTCACAGGAATCGTACCCCT-3' R: 5'-ATTTTTGCAACAGCAGCGCA-3'	Tsp45I	TT: 113+79 TA: 193+113+79 AA: 193

(F: Forward primer, R: Reverse primer)

Evaluation of the Tsp45I Restriction Enzyme Digestion Results

Following digestion, fragments of 193, 113 and 79bp were observed. A single band of 193bp was evaluated as AA (homozygote variant), 113 and 79bp TT (homozygote wildtype) and all three as (heterozygote variant).

Statistical Analysis

The statistical analysis was performed using SPSS version 16.0 (SPSS inc. Chicago, USA). Values of $p<0.05$ were considered as statistically significant. Distributions of the genotype and allele frequencies between patient and control

groups were evaluated using the Chi-square and Fisher's exact test. Demographic data between the patient and control groups were compared using the Student's T and Anova tests. Allele frequencies were calculated according to the gene counting method.

Results

Clinical parameters of the patient group are given in Table 2. In the patient group, total cholesterol (p<0.001, 95% CI:29.62-60.71), LDL-cholesterol (p<0.001, 95% CI:30.12-55.90), VLDL-cholesterol (p<0.001, 95% CI:3.88-21.87) and triglyceride (p<0.001, 95%CI:97.96-152.90) levels were statistically higher than the control group. On the other hand, HDL- cholesterol (p<0.001, 95%C I: 5.30-15.34) levels were higher in the control group than the patient group.

When the patient and control groups were evaluated in terms of the Tβ4 A/T polymorphism genotype and allele distributions, the TT genotype frequency was statistically higher in the control group (p<0.001, X2:17.22, OR:2.13, 95% CI:1.44-3.16). In the patient group, the AT genotype (p<0.001, X2:12.40, OR:5.42, 95% CI:2.02-14.53) and A allele presence (p<0.001, X2:17.22, OR:6.66, 95% CI:2.61-16.98) were significantly higher (Table 3).

Table 3.The Tβ4 A/T (rs75112573) genotype/allele distributions in the patient and control groups.

		Patient Group (n=48) (n (%))	Control Group (n=45) (n (%))	P
Genotype	TT	18 (37.5)	36 (80)	<0.001
	AT	24 (50)	7 (15.6)	<0.001
	AA	6 (12.5)	2 (4.4)	-
Allele	T	60 (62.5)	79 (87.7)	-
	A	36 (37.5)	11 (12.3)	<0.001

In the patient group, the AT genotype carriers had significantly higher HDL- cholesterol levels compared to the AA carriers (p=0.036, 95% CI:0.59-17.25). Total cholesterol levels, however, were higher in the AA genotype carriers than AT carriers (p=0.038, 95% CI:2.15-73.68). Moreover, VLDL-cholesterol levels were significantly higher in the AA carriers than AT (p=0.011, 95% CI:6.73-49.86) and TT (p=0.018, 95% CI:4.95-49.49) carriers. When we compared according to the alleles, total cholesterol (p=0.048, 95% CI:0.41-72.82) and VLDL (p=0,009, 95% CI:7.44-48.21) levels were significantly lower in T allele carriers (Table 4) and in the control group, total cholesterol levels were lower in A allele carriers (p=0.048, 95% CI:0.18-51.64) (Table 5).

Table 4. Relationship between the Tβ4 A/T (rs75112573) polymorphism and plasma lipid levels in the patient group (n=48).

		Cholesterol (mg/dL)	HDL-cholesterol (mg/dL)	LDL-cholesterol (mg/dL)	VLDL-cholesterol (mg/dL)	Triglyceride (mg/dL)	p
Genotype	TT (n=18)	210.28±43.9	38.67±9.5	131.39±36.3	40.28±19.0	19.83±9.6	-
	AT (n=24)	207.25±35.8	42.42±9.4	125.62±30.7	39.21±18.3	32.54±27.0	<0.05
	AA (n=6)	245.17±34.5	33.50±5.2	144.17±29.3	67.50±46.7	33.17±23.4	<0.05
Allele	T (n=42)	208.55±39.0	40.81±9.5	128.10±32.9	39.67±18.9	27.10±22.1	<0.05
	A (n=30)	214.83±38.2	40.63±9.4	129.33±30.9	44.87±27.8	32.67±26.0	-

Discussion

Cardiovascular diseases are the leading cause of mortality in Turkey and worldwide. In Europe, cardiovascular diseases are responsible for 45% of female deaths under the age of 75 and it is 38% for men [14, 15]. The term ACS describes all the clinical syndromes from unstable angina pectoris to ST – segment elevation and non-ST- segment elevation myocardial infarction [16]. Tβ4 is excessively expressed during fetal development and in cardiovascular systems following injury such as myocardial infarction, and induces endogenous stem cell arrival to the site of injury by increasing neovasculogenesis and paracrine signals to support wound healing. Therefore, recently, many studies have been published on the fact that Tβ4 decreases the infarct area and preserves cardiac function [17, 18]. In these studies, it has been shown that Tβ4 prevents damage to the heart muscle and coronary arteries by providing cardiac protection following heart diseases [19], induces angiogenesis in cardiovascular sites [20], prepares the ischemic and epicardium-derived progenitor cells to differentiate to cardiomyocytes [21], promotes cardiac cell migration [11] and also prevents inflammation in ACS with its anti-inflammatory effects [22].

Table 5. Relationship between the Tβ4 A/T (rs75112573) polymorphism and plasma lipid levels in the control group (n=45).

		Cholesterol (mg/dL)	HDL-cholesterol (mg/dL)	LDL-cholesterol (mg/dL)	VLDL-cholesterol (mg/dL)	Triglyceride (mg/dL)	p
Genotype	TT (n=36)	173.14±37.2	49.92±15.2	90.86±32.0	32.06±19.0	162.17±95.3	-
	AT (n=7)	144.86±17.4	56.00±9.7	70.71±12.1	17.43±7.9	89.43±38.5	-
	AA (n=2)	155.50±5.0	35.50±10.6	76.50±9.2	43.00±24.0	217.0±121.6	-
Allele	T (n=43)	168.53±36.2	50.91±14.5	87.58±30.5	29.67±18.5	150.3±121.6	-
	A (n=9)	147.22±15.9	51.44±12.9	72.00±11.3	23.11±15.7	117.78±78.3	<0.05

There was only a single study investigating Tβ4 in ACS that was conducted on the Turkish population. However, this study was not a genetic study and authors evaluated the endogenous Tβ4 levels before and after primary percutaneous coronary intervention (PCI) in patients administered with ST-segment elevation acute myocardial infarction. They reported that Tβ4 levels were elevated to the point similar to the control group after PCI [9].

To this date, there have been no studies conducted on Tβ4 genetic variants to our knowledge, which makes the presented study the first. Our results indicate that since the TT genotype frequency was statistically higher in the control group, the TT genotype may decrease the risk of ACS. Moreover, the AT genotype and the A allele frequencies being higher in the patient group suggest that the AT genotype and the A allele may disrupt the function of Tβ4, promoting the survival of cardiomyocytes in ACS, therefore increase the risk of ACS.

Consequently, we believe that the low number of individuals in our study affected our results, and further studies with larger sample groups are needed to exactly clarify the role of the Tβ4 polymorphism in the pathogenesis of ACS. But even so there were a limited number of participants included in the study; we think that our findings will contribute to the understanding of the molecular mechanisms of ACS.

References

1. Moodie DS. The Global Burden of Cardiovascular Disease. Congenit Heart Dis. 2016; 11:213.
2. American College of Cardiology/American Heart Association Task Force on Practice G. ACC/AHA guidelines for the management of patients with unstable angina and non-ST segment elevation myocardial infarction: executive summary and recommendations. Catheter Cardiovasc Interv. 2000; 51:505-21.
3. Coskun A, Eren SH, Korkmaz I, Guven FMK. The epidemiological and prognostic importance of the aVR lead among patients with and without ST segment elevation. Turk Gogus Kalp Damar Cerrahisi Dergisi-Turkish J Thorac Cardiovasc Surg. 2011;19:570-5.
4. Van de Werf F, Ardissino D, Betriu A, Cokkinos DV, Falk E, Fox KA, et al. Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J. 2003;24:28-66.
5. Kumar A, Cannon CP. Acute coronary syndromes: diagnosis and management, part I. Mayo Clin Proc. 2009;84:917-38.

6. Smith JN, Negrelli JM, Manek MB, Hawes EM, Viera AJ. Diagnosis and management of acute coronary syndrome: an evidence-based update. J Am Board Fam Med. 2015;28:283-93.
7. Shrivastava S, Srivastava D, Olson EN, DiMaio JM, Bock-Marquette I. Thymosin beta4 and cardiac repair. Ann N Y Acad Sci. 2010;1194:87-96.
8. Goldstein AL, Hannappel E, Kleinman HK. Thymosin beta4: actin-sequestering protein moonlights to repair injured tissues. Trends Mol Med. 2005;11:421-9.
9. Yesilay AB, Karakurt O, Akdemir R, Erden G, Kilic H, Acikel S, et al. Thymosin beta4 levels after successful primary percutaneous coronary intervention for acute myocardial infarction. Turk Kardiyol Dern Ars. 2011;39:654-60.
10. Sosne G, Qiu P, Kurpakus-Wheater M. Thymosin beta 4: A novel corneal wound healing and anti-inflammatory agent. Clin Ophthalmol. 2007;1:201-7.
11. Bock-Marquette I, Saxena A, White MD, Dimaio JM, Srivastava D. Thymosin beta4 activates integrin-linked kinase and promotes cardiac cell migration, survival and cardiac repair. Nature. 2004;432:466-72.
12. Crockford D. Development of thymosin beta4 for treatment of patients with ischemic heart disease. Ann N Y Acad Sci. 2007;1112:385-95.
13. Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res. 1988;16:1215.
14. Kilic S, Simsek E, Soner Kemal H, Yuce EI, Turkoglu C, Kayikcioglu M. The role of specialized prevention clinics for the short term follow-up of acute coronary syndromes. Turk Kardiyol Dern Ars. 2017;45:498-505.
15. Ozkan AA. [Acute coronary syndromes: epidemiology]. Turk Kardiyol Dern Ars. 2013;41:1-3.
16. Achar SA, Kundu S, Norcross WA. Diagnosis of acute coronary syndrome. Am Fam Physician. 2005;72:119-26.
17. Marks ED, Kumar A. Thymosin beta4: Roles in Development, Repair, and Engineering of the Cardiovascular System. Vitam Horm. 2016;102:227-49.
18. Pipes GT, Yang J. Cardioprotection by Thymosin Beta 4. Vitam Horm. 2016;102:209-26.
19. Srivastava D, Saxena A, Michael Dimaio J, Bock-Marquette I. Thymosin beta4 is cardioprotective after myocardial infarction. Ann N Y Acad Sci. 2007;1112:161-70.
20. Bock-Marquette I, Shrivastava S, Pipes GC, Thatcher JE, Blystone A, Shelton JM, et al. Thymosin beta4 mediated PKC activation is essential to initiate the embryonic coronary developmental program and epicardial progenitor cell activation in adult mice in vivo. J Mol Cell Cardiol. 2009;46:728-38.
21. Smart N, Bollini S, Dube KN, Vieira JM, Zhou B, Davidson S, et al. De novo cardiomyocytes from within the activated adult heart after injury. Nature. 2011;474:640-4.
22. Libby P. Molecular bases of the acute coronary syndromes. Circulation. 1995;91:2844-50.

Arch Clin Exp Med 2019;4(1):21-24. e-ISSN: 2564-6567

DOI:10.25000/acem.454426 Araştırma makalesi / Research article

Changes in incidence and age distribution of scabies: A retrospective cohort study in a tertiary hospital

Uyuz insidansı ve yaş dağılımındaki değişiklikler: Bir üçüncü basamak hastanede retrospektif bir kohort çalışması

Habibullah Aktaş [1], Aybala Cebecik [2]

Abstract

Aim: Scabies is a pruritic skin disease caused by an ectoparasite named sarcoptes scabies var hominis. It sometimes makes endemics depending on lifestyles of communities. In this study, we point out that patients with scabies have increased in recent years.

Methods: A retrospective review was carried out in the patients with scabies diagnosis between 2013January and 2018 July at the dermatology outpatient clinic of Karabuk Research and Training Hospital. The age and gender of the patients, and the season of diagnosis were recorded from the hospital database.

Results: In this study, we found that the incidence of scabies increased from 0.4 % to 1% in the last 5 years in the dermatology outpatient clinic of our hospital (r=0,886 p=0.000). The mean age of scabies patients decreased from 49.7 to 31.4 within 5 years (r=-0,753 p=0,006). The female patients were much more than male patients (56% vs 44%), and their mean age was older than males (44 vs 37) (p=0,000).

Conclusion: Scabies cases are increasing in number and the mean age of the patients is decreasing gradually at recent years.

Keywords: Gender, scabies, young population

Öz

Amaç:Uyuz, sarkoptes scabies var hominis adlı bir ektoparazitin neden olduğu kaşıntılı bir deri hastalığıdır.Değişen hayat tarzlarına bağlı olarak endemiler yapmaktadır.Bu çalışmada uyuz tanısı alan hastaların son yıllarda arttığına dikkat çektik.

Yöntemler: Karabük Eğitim ve Araştırma Hastanesi Dermatoloji polikliniğinde 2013 Ocak -2018 Temmuz arasında, uyuz tanısı alan hastalar retrospektif olarak incelendi.Hastane kayıtları kullanılarak yapılan çalışmada,uyuz tanılı hastaların yaş ve cinsiyetleri alındı.Uyuz tanısının konulduğu mevsim not edildi.

Bulgular:Çalışmamızda, son beş yıl içinde , hastanemiz dermatoloji polikliniğinde uyuz görülme sıklığının % 0.4 den %1'e kadar yükseldiğini saptadık (r=0,886 p=0,000). Uyuz tanısı alan hastaların yaş ortalamasının da, bu 5 yıl içinde 49.7'den 31.4 'e düştüğünü gözledik (r=-0,753 p=0,006) . Uyuz tanılı kadın hastalar daha fazlaydı (%56 vs %44) ve uyuzlu kadın hastaların yaş ortalaması erkek hastaların yaş ortalamasına göre daha büyüktü (44 'e 37) (p=0,000).

Sonuç: Son yıllarda,uyuz tanısı konulan olgular artıyor ve uyuz görülme yaşı da düşüyor.

Anahtar kelimeler: Cinsiyet,genç nüfus,uyuz

[1] Karabuk University Faculty of Medicine, Department of Dermatology, Karabük, Turkey.
[2] Karabuk University Faculty of Medicine, Department of Family Medicine, Karabük, Turkey.

Ethics Committee Approval: The study wass approved by the local ethical authority.
Etik Kurul Onayı: Çalışma lokal etik komite tarafından onaylanmıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Geliş Tarihi / Received: 17.08.2018
Kabul Tarihi / Accepted: 06.12.2018
Yayın Tarihi / Published: 15.03.2019

Sorumlu yazar / Corresponding author:
Habibullah Aktas
Adres/Address: Karabuk Training and Research Hospital Department of Dermatology Karabuk/Turkey
e-posta: aktashabib@hotmail.com
Tel/Phone: 05324084611

Introduction

Scabies is an itchy skin disease caused by an ectoparasite, sarcoptes scabies var hominis. It has been known for 2500 years and affects 300 million people a year worldwide. It is more common in people with low income. This parasite has a life cycle of human compulsory; it can live up to only 2-3 days outside of human skin. The most prominent clinical manifestation of scabies is severe itching, especially localized in abdominal circumference, hand and foot ankles and genital area. Face and interscapular area are not involved, but may be widespread involvement in immunosuppressant or elderly patients including those areas as well. Although the history and clinical appearance often predispose to the diagnosis of the disease, direct microscopy, dermatoscopy, reflexive confocal microscopy and even biopsy help in difficult cases [1-3].

Scabies is a disease, especially of developing countries. Chronic renal and rheumatic heart diseases which can be seen as a complication of streptococcal skin infections that develop secondary to infections in young patients are remarkable social health problems [4].

Scabies has been reported more frequently in the pediatric age group, and in terms of sex, some studies have found male patients to be more frequent in contrast to some others [5, 6]. Female patients were found more frequently in studies conducted in our country [7].

We hypothesised that there is an increase in scabies cases in our city at recent years. Therefore, we aimed to evaluate incidence and demographic data of of scabies in recent years.

Material and methods

The study included patients diagnosed as scabies at the dermatology outpatient department in Karabuk Training and Research Hospital between January 2013 and July 2018. Ethical approval of was taken from Karabuk University local ethics committee (6-19/18.6.2018). Written consent could not be taken due to the retrospective design of the study. The study was performed in accordance with Declaration of Helsinki.

Data containing age and sex of the patients, and the season that scabies diagnosis was put were obtained from the hospital records. Scabies was diagnosed clinically by a dermatologist. Patients with scabies recorded in other departments such as pediatrics were not included in this study.

Since all patients diagnosed with scabies in the dermatology database were evaluated, no exclusion criteria were defined.

Patients with scabies were evaluated according to the years and the seasons. They were also categorized based on age and sex, and analysed for patients whose age was >40 years.

Statistical analysis

All statistics were performed using SPSS version 20.0 for Windows. Normally distributed continuous and categorical variables were expressed as mean±standard deviation and frequencies and percentages, respectively. Student's t - test, ANOVA and Spearman's rank correlation coefficient were used as statistical methods to interprete outcomes. The statistical results were presented with a 95% confidence interval. The differences were accepted statistically significant in case of p value <0.05.

Results

Within the specified period (2013 January - 2018 July), 1947 patients were diagnosed as scabies. They were 1090 women (56%) and 857 men (44%). The mean age of the patients was 41,1 years. The mean age of male patients was 37±22.43 years, while the mean age of female patients was 44.5±21.97 years (p=0.001). The details of total number of the patients and their mean ages according to the years are shown at Table 1.

Table 1: Number of patients with scabies according to years

Year	Total number and age of cases §	Scabies per 1000 cases$^{\beta}$	Total number and age of male patients§	Total number and age of female patients§
2013	165 (49.7)	4	73 (46.3)	92 (52.2)
2014	262 (48.7)	5	97 (46.3)	165 (50.2)
2015	341 (46.4)	5	152 (40.8)	189 (51.5)
2016	364 (41.7)	6	155 (38.7)	209 (43.8)
2017	439 (37.3)	7	216 (31.8)	223 (42.6)
2018 ¥	377 (31.4)	10	165 (29.2)	212 (33.2)
Total	1947 (41.1)		857 (37)	1090 (44)

§: number (mean age)
$^{\beta}$: number of scabies patients per 1000 dermatological patients
¥: the first 6.5 months.

Figure 1 shows the distribution of the cases throughout the years. There was a clear and significant increase in the number of the cases starting from 0.4 % in 2013 to 1% in 2018 (r=0.886, p=0.001). Number of the patients with scabies was much higher in both 2017 and 2018 compared to 2013 (r=0.886, p=0.001) (Table 1).

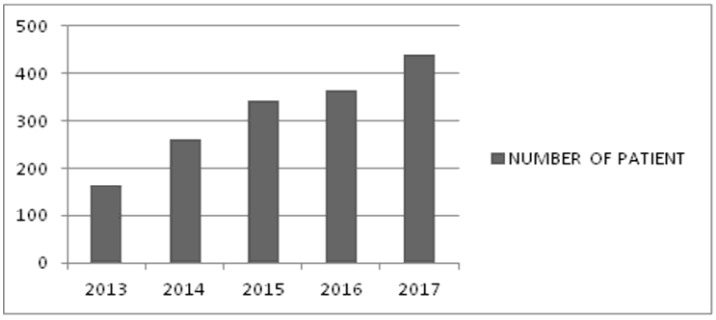

Figure 1. Number of patients with scabies according to the years.

The mean age of the patients with scabies was also found to decrease in both males and females from 49.7 years in 2013 to 31.4 years in 2018 (r=-0.753, p=0.006) (Figure 2).

Figure 3 points the number of scabies cases seen at different seasons throughout the years. Winter was the most common season in which scabies was seen (p=0.001).

Proportion of female patients over 40 years of age was higher than males (p=0.005) (Table 2).

Table 2. Proportion of the patients over 40 years old according to sex.

Year	% of all patients	% of male patients	% of female patients
2013	68.4	63.0	72.8
2014	66.0	53.6	73.3
2015	58.6	44.7	69.8
2016	50.2	41.9	56.4
2017	41.2	28.2	53.8
2018¥	32.0	24.2	38.2
Total	49.8	38.7	58.6

¥: The first 6.5 months.

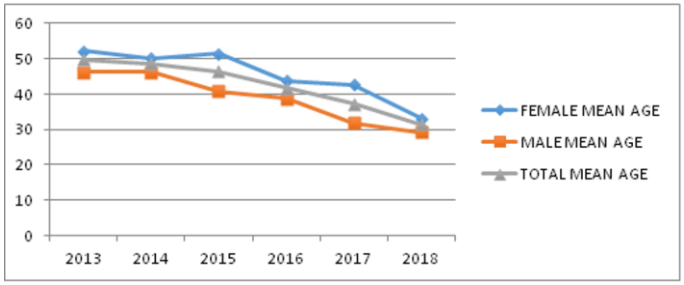

Figure 2. Mean age of all patients categorized according to sex.

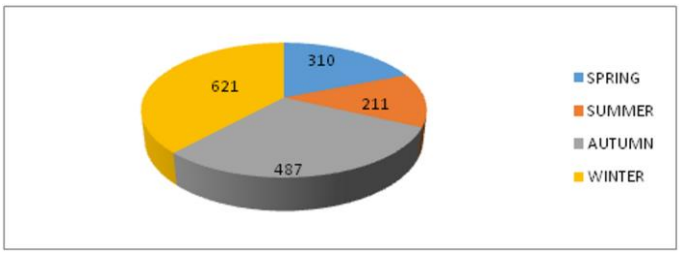

Figure 3. Number of scabies cases according to season.

Discussion

Scabies continues to be a social health problem despite urbanization and effective hygienic methods. It seems to be increased at recent years due to crowded lifestyles in developing countries just like we detected in this study. Scabies is a condition that should not be neglected in children, especially since it affects frequency of septic bacterial infections and indirectly incidence of glomerulonephritis and rheumatic heart diseases, as well as impairment of life comfort caused by intense pruritus [4, 8, 9].Control of scabies endemics can also reduce incidence of glomerulonephritis and rheumatic heart disease in the community. Fortunately, we did not see any patient presenting with these findings or being exposed to these complications during the follow-up.

Scabies is known to be a problem of developing countries. It is most commonly seen in the tropical geography of the world. Its frequency varies from 2.7 cases per 1000 to 46% among the dermatology patients in the literature. This high rate might be attributed to an endemic outbreak [10]. Our study found that the diagnosis of scabies increased from 4 to 10 for 1000 dermatology patients between 2013 and 2018.

Although scabies is thought to be a problem of hot climates [11], our results shows that scabies is seen more frequently in the cold seasons in our geography. In the present study, scabies was identified mostly in winter season, then, autumn, spring and summer seasons respectively, as confirmed in some other studies [12-14].

In a study conducted between 1994 and 1996, Karaoğlu et al. [14] found the rate of scabies to be 3.25%, equally observed in both sexes, and most frequently in childhood. These findings do not coincide with our results. We observed scabies mostly in middle-aged people and women.

In the study of Çetinkaya et al. [7], female patients and middle age group constituted the most frequent group of patients. Our findings also show similarity as to those results. In our study, the most frequent age group of scabies is the middle and advanced age group, but there was a significant increase in the number of young patients over the years. So, the mean age of patients with scabies has decreased. Probably, the reason for this was the crowded lifestyle of university students which increase in number, and immigrants placed in the city. In the epidemiological study conducted by Tüzün and his colleagues [15] in 1980, scabies was reported more commonly in males and in ages between 15-44 years. A finding of this study was that, as we observed, it peaked in the winter months. Predominance of female patients in our study may be the result of change in life conditions as women may be more involved in social life than in 1980.

Karaman et al. [16] reported that scabies were more frequent in female patients as in our results. Gender distrubition of scabies varies based on study and country [17].

Pannell et al. [6] reported that the most common age group was between 15 and 24 years of age. This observation is similar to our observations of the past few years. Although it has been reported that scabies is more frequent in young people [6], this is not compatible with our findings. One reason for this is that a significant proportion of childhood scabies cases may be referred to pediatric outpatient clinics.

It is known that the incidence of scabies epidemics coincides with the increase in the use of common clothes and the culture of crowded living [18]. The fact that the scabies cases of the recent five years have been increasing and the mean age has also been falling constantly implies the marked change in the sociocultural structure of the city in which we studied.

When we look at the data given 5 years ago, 63% of male cases and 72% of male cases were over 40 years old. This would need an explanation for the reason at that time. When compared to the prevalence study conducted by Çetinkaya et al. [7] in Kayseri province, our results showed a regular increase, unlike the results of Çetinkaya et al. [7]. It is difficult to explain the difference when we think that Kayseri province is also a busy student city. It is likely that the young population of our city suddenly increased. Therefore, there may not be sufficient experience in the hygiene of common living areas such as dormitories,aparts etc.

The main limitation of our study was that the study is retrospective. The fact that the diagnoses were confirmed in response to the treatment would strengthen the data. In additon, data of pediatrics department and primary care health centers were not included. This would probably change the total number and the mean age of scabies cases .

In conclusion, our study clearly showed that scabies is much more seen as to the past years, and the number of young patients also increases.

References

1. Khalil S, Abbas O, Kibbi AG, Kurban M. Scabies in the age of increasing drug resistance. PLoS Negl Trop Dis.2017;30:11.
2. Falay T, Gurel MS.Uyuz.Turkiye Klinikleri J Dermatol-Special Topics. 2017;10:143-53.
3. Thomas J, Peterson GM, Walton SF, Carson CF, Naunton M, Baby KE. Scabies: an ancient global disease with a need for new therapies. BMC Infect Dis.2015;15:250.
4. Hay RJ,Steer AC, Engelman D, Walton S. Scabies in the developing world--its prevalence, complications, and management. Clin Microbiol Infect. 2012;18:313-23.
5. Anderson KL, Strowd LC. Epidemiology, Diagnosis, and Treatment of Scabies in a Dermatology Office.J Am Board Fam Med. 2017;30:78-84.
6. Pannell RS, Fleming DM, Cross KW. The incidence of molluscum contagiosum, scabies and lichen planus. Epidemiol Infect. 2005;133:985-91.
7. Çetinkaya Ü, Şahin S, Ulutabanca RÖ. The Epidemiology of Scabies and Pediculosis in Kayseri. Turkiye Parazitol Derg. 2018;42:134-7.
8. Marks M, Taotao-Wini B, Satorara L, Engelman D, Nasi T,Mabey DC, et al. Long Term Control of Scabies Fifteen Years after an Intensive Treatment Programme. PLoS Negl Trop Dis. 2015;9:e0004246.
9. Thornley S, Marshall R, Jarrett P, Sundborn G, Reynolds E, Schofield G. Scabies is strongly associated with acute rheumatic fever in a cohort study of Auckland children. J Paediatr Child Health. 2018;54:625-32.

10. Fuller LC. Epidemiology of scabies. Curr Opin Infect Dis. 2013;26:123-6.
11. Figueroa JI, Fuller LC, Abraha A, Hay RJ. Skin disease in south western Ethiopia: rationale for a community approach. Int J Dermatol.1998;37:752-8.
12. Savin JA. Scabies in Edinburgh from 1815 to 2000. J R Soc Med. 2005;98:124-9.
13. Mimouni D, Ankol OE, Davidovitch N, Gdalevich M, Zangvil E, Grotto I. Seasonality trends of scabies in a young adult population: a 20-year follow-up. Br J Dermatol. 2003;149:157-9.
14. Karaoğlu S. Amasya'da 1994-96 Yılları Arasında Uyuzun Durumu. T Klin J Dermatol. 1997;7:10-12.
15. Tüzün Y, Kotoğyan A, Cenesizoğlu E, Baransü O, Ozarmağan G, Ural A, et al. The epidemiology of scabies in Turkey. Int J Dermatol.1980;19:41-4.
16. Karaman Ü, Enginyurt Ö, Dündar Y, Baykal MK, Gür S. Infestation of Sarcoptes Scabiei and Pediculus Capitis in Terms of Socio-Economical Status.ODU J Med. 2014;2:23-9.
17. Lapeere H, Naeyaert JM, De Weert J, De Maeseneer J, Brochez L. Incidence of scabies in Belgium. Epidemiol Infect. 2008;136:395-8.
18. Sara J, Haji Y, Gebretsadik A. Scabies Outbreak Investigation and Risk Factors in East Badewacho District, Southern Ethiopia: Unmatched Case Control Study. Dermatol Res Pract. 2018;2018:7276938.

Arch Clin Exp Med 2019;4(1):25-28. e-ISSN: 2564-6567

DOI:10.25000/acem.477680 Araştırma makalesi / Research article

Intragastric balloon therapy for obesity: Is it safe and effective?

Obezite tedavisinde intragastrik balon yöntemi güvenli ve etkili mi?

Onur Bayraktar [1], Abdullah Alp Özçelik [2], Ahmet Ragıp Öktemgil [3], Barış Bayraktar [4]

Abstract

Aim: Bariatric surgery is a costly and invasive method with permanent effects and medications for treatment of obesity is less costly but may cause systemic side effects. Intragastric balloon (IGB) therapy is a minimal invasive and temporary option between medical therapy and bariatric surgery. The aim of this study is to evaluate the safety and efficiency of intragastric balloon application and present our results.

Methods: 39 patients who underwent IGB therapy between 2015 and 2017 were included in the study. IGB was advanced into the stomach, and then the balloon was filled with saline and methylene blue solution. The patients were assessed by a nutritionist during the follow-up period and after balloon removal they were evaluated for results.

Results: Of 39 patients, 33 were female and the median body mass index (BMI) was 33.2 kg/m^2 before the procedure. Three patients (7.6%) could not tolerate the balloon; therefore balloon extraction was performed on the day 1, 5 and 25. Median duration of therapy was 8 months (1 day-17 months). While excessive weight loss (EWL) ratio was 22.8% in patients whose balloon was removed in 6 months, EWL ratio was 41.6% in patients whose balloon remained more than 6 months. The median BMI after balloon removal was 28.3 kg/m^2. The only complication was spontaneous IGB deflation and excretion transanally.

Conclusion: Intragastric balloon therapy may be recommended as a safe and effective option for the patients who have had failed attempts of diet and exercise and will not undergo bariatric surgery.

Key words: obesity, gastric, balloon, colonization, bariatric

Öz

Amaç: Obezite tedavi yöntemlerinden bariatrik cerrahi, invazif ve maliyetli bir yaklaşım olup kalıcı yan etkilere sahipken, göreceli daha az maliyetli medikal tedavinin sistemik yan etkileri söz konusu olabilir. İntragastrik balon (IGB) uygulaması ise medikal tedavi ve bariatrik cerrahi arasında minimal invazif ve geçici bir yöntemdir. Bu çalışmanın amacı, IGB uygulamasının etkinliğini ve güvenliğini değerlendirmektir.

Yöntemler: Çalışmaya 2015 – 2017 yılları arasında IGB tedavisi uygulanan 39 hasta dahil edildi. İşlem öncesi ve sonrası vücut kitle indeksi (VKİ), fazla kilonun kayıp oranı, balonun hastalar tafından tolere edilebilmesi ve gelişen komplikasyonlar değerlendirildi.

Bulgular: İşlem öncesi ortanca vücut kitle indeksi (VKİ) değeri 33.2 kg/m^2 olan 39 hastanın 33'ü (%84,6) kadındı. İşlemi tolere edemeyen 3 hastanın (%7,6) balonu 1., 5. ve 25. günlerde çıkarıldı. Tedavinin ortanca süresi 8 aydı (1 gün-17 ay). Balonları ilk 6 ayda çıkarılan hastalarda fazla kilonun kayıp oranı %22,8 iken, 6 aydan uzun kalanlarda bu oran %41,6 idi. Balon çıkarılması sonrası VKİ ortanca değeri 28.3 kg/m^2 olarak bulundu. Sadece bir hastada (%2,5) spontan IGB rüptürü ve balonun defekasyonla atılması görüldü.

Sonuç: IGB uygulaması başarısız diyet ve egzersiz denemeleri olan ve bariatrik cerrahi yapılmayacak hastalara güvenli ve etkili bir yöntem olarak önerilebilir.

Anahtar Kelimeler: obezite, mide, balon, üreme, bariatrik

[1] Istanbul Bilim University, School of Medicine Department of General Surgery, Istanbul, Turkey.

[2] Yalova Hospital, Department of General Surgery, Yalova, Turkey.

[3] Bursa Yüksek İhtisas Education and Research Hospital, Department of Microbiology and Clinical Microbiology, Bursa, Turkey.

[4]Konak Hospital, Department of General Surgery, Kocaeli, Turkey.

Ethics Committee Approval: The study wass approved by the local ethical authority.
Etik Kurul Onayı: Çalışma lokal etik komite tarafından onaylanmıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Geliş Tarihi / Received: 02.11.2018
Kabul Tarihi / Accepted: 23.01.2019
Yayın Tarihi / Published: 15.03.2019

Sorumlu yazar / Corresponding author:

Onur Bayraktar
Adres/Address: Şişli Florence Nightingale Hospital Abide-i Hurriyet caddesi No: 164 Şişli/İstanbul, Turkey
e-posta: dronurbayraktar@gmail.com
Tel/Phone: (+90) 05336406624

Introduction

Over 1.4 billion adults worldwide are overweight or obese [1]. Obesity may cause some health problems such as diabetes, hypertension, and heart disease. It has been shown that losing weight of about 10% may be adequate to postpone or prevent the onset of diabetes and other obesity-related illnesses [2-5].

While bariatric surgery has established effectiveness in treating morbidly obese patients, it is not generally used in patients whose BMI is between 30 to 34.9 kg/m^2, due to its costs, invasiveness and possibly permanent side effects [6]. Medications for treatment of obesity are non-invasive and less costly, but they result in restricted loss of weight and may have major side effects [7].

Intragastric balloon (IGB) therapy is a minimal invasive and temporary option between medical treatment of obesity and bariatric surgery. IGB works by decreasing preprandial hunger, maintaining postprandial satiety, and promoting weight loss in the short term [8]. This method may be feasible in patients who are not yet candidates for surgery, who have failed previous attempts at weight loss with diet and exercise, those who refuse or who are unable to access to surgery, and hoping to lose a significant amount of weight without the invasiveness of surgery or the systemic side effects of drugs. Besides, severely obese patients (BMI > 50 kg/m^2) are at risk of having operative technical difficulties due to massive amounts of intra-abdominal fat and hepatomegaly or anesthesia-related complications. Preoperative weight loss may decrease the complexity and risks following bariatric procedure [9-11]. IGB therapy may be used as a bridge to bariatric surgery of these patients.

The aim of this study was to evaluate the safety and efficiency of IGB application.

Material and methods

Patients

After the ethics committee approval (Bezmialem Vakif University-54022451-050.05.04-17/12/2018-7410), a total of 39 patients who have undergone IGB therapy due to obesity in our endoscopy unit between April 2015 and June 2017 were retrospectively evaluated. The investigation conformed to the principles outlined in the Declaration of Helsinki. The patients comprised of 33 female (84.6%) and 6 male (15.3%), with a median age of 37 years (range, 20-62 years). Before the procedure, informed consent was obtained from all patients and median BMI was calculated as 33.2 kg/m2 (range, 28-63 kg/m2).

Procedure

Under endoscopic view and propofol sedation, an upper gastrointestinal endoscopy was performed before the procedure to exclude other pathologies. The balloon (MedSil® Intragastric Balloon, Russia) was advanced blindly into the stomach, then the endoscope was reinserted and the balloon was positioned in the stomach and filled with saline (600 mL) and methylene blue solution (10 mL). After 2 hours of observation, the patients were given a liquid diet and were discharged when they tolerated the diet. Proton pump inhibitors (during treatment) and antiemetics (1-2 weeks) were prescribed. They were recommended to have a liquid diet for 4 weeks and thereafter a soft diet with calorie restriction. Follow-up controls were performed weekly in the first month, then on the third and sixth months. All patients were informed that the duration of IGB therapy was 6 months. During the follow-up controls with a nutritionist, the nutrition plan and weight control were assessed, and nutritional education was reinforced. IGBs were extracted endoscopically using the IGB removal kit and microbiological examination was performed on all the balloons. Patients were evaluated in terms of weight loss (WL) (kg), excessive weight loss (EWL) (%), body mass index (BMI) (kg/m2) changes, time of balloon removal, microbiological examination of the removed balloons, procedure-related side effects, symptoms and complications.

Statistical Analysis

Data were evaluated using SPSS for windows 21.0 software (SPSS Inc., Chicago, IL). Descriptive statistics were calculated as frequency and percentage for categorical variables and as mean, standard deviation and median for numerical variables.

Table 1. Characteristics of the patients.

Feature	n (%)
Sex	
Female	33 (84.6%)
Male	6 (15.3%)
Age (years)	37 (20-62)
BMI (before treatment, kg/m^2)	33.2 (28-63)
Median excessive weight (kg)	34 (17-105)

Table 2. Outcomes of IGB application.

Feature	n
Duration (months) (n(range))	8 (1-17)
BMI (After balloon removal, kg/m^2)(n(range))	28.3 (19.7-61.9)
Median weight loss (kg)(n(range))	10 (0-42)
Median EWL (%)(n(range))	33.3 (0-110)
IGB therapy duration <6 months, median EWL (%)	22.8 (0-67.6)
IGB therapy duration >6 months, median EWL (%)	41.6 (0-110.5)
Median balloon extraction time (months)	8
Early balloon removal (n (%))	3 (7.6)
Patients with positive balloon culture (n (%))	9 (23)

Results

IGB was placed successfully in all patients with a success rate of 100%. Characteristics of the patients are presented in Table 1. The median BMI before treatment was 33.2 kg/m^2 (range 28-63) and median duration of the therapy was 8 months. While the median weight loss was 10 kg, EWL ratio was 33% and median BMI was 28.3 kg/m^2 (range 19.7-61.9) after the treatment (Table 2).

More than 60% of the patients have continued to experience mild and intermittent gastrointestinal symptoms after the second week of therapy, but the symptoms were severe enough to necessitate balloon removal only in 3 patients (7,6%). The symptoms that caused early removal were significant nausea and vomiting (n= 1), abdominal pain (n=1), and reflux and burping (n=1) on the 1st , 5th and 25th day of the balloon application, respectively. In the other patients, the IGB's remained between 2 and 17 months (Table 3).

There was spontaneous IGB deflation and excretion of the balloon transanally in one patient (2.5%). In 9 patients (23%), microbiologic examination of the removed balloon revealed positive culture results (Table 4).

While the median duration of IGB therapy was 8 months in all patients, this period was 5 months in the patients with fungal or bacterial contamination of the balloon. In addition, the median rate of patients complaining of at least one symptom was 66%, while this rate was 23% in patients with positive culture results.

Table 3. Side effects of IGB therapy.

Symptoms	n (%)
Abdominal pain	25 (64)
Lasting longer than 2 weeks, mild and intermittant	7(17.9)
Nausea and vomiting	25 (64)
Dyspepsia and burping	27 (69)
Reflux and burning	18 (48)

Table 4. Culture results of the removed balloons.

Microbial Growth	n
Fungi	6
Candida Albicans	3
Crytococcus Laurentii	1
Stephanoascus Ciferrii	1
Candida SPP	1
Bacteria	3
Burkholderia Cepacia	1
Enterobacter Cloacae	1
Serratia Marcescens	1

Discussion

The mean reason of struggle for weight loss in obese patients is that obesity is associated with a noteworthy raise in mortality and comorbidities such as type 2 diabetes mellitus, coronary heart disease, hypertension, dyslipidemia [12, 13].

The efficiency of IGBs on weight loss has been reported in many randomized studies [14]. Losing weight induces a reduction in energy consumption which makes it challenging to succeed and preserve weight loss. Regaining of lost weight is a common problem in treating obesity [1]. The amount of weight loss may vary depending on the type of balloon used, and is about 30% of excessive body weight [14]. Similar to the literature, the median excess weight loss rate was determined as 33% in this study.

Approximately 50% of the weight loss which succeed during IGB therapy can be maintained for one year after balloon removal with diet and exercise [1, 15]. In a study consisting of approximately 400 patients who lost ≥20% of EWL with IGB therapy, it has been declared that the same amount of EWL could be preserved in 23% of the patients at five-year follow up [15].

Therefore behavior modification strategies are advised to minimize subsequent weight gain [16-18]. The duration of IGB therapy can be modified according to endoscopist's preference, type of the balloon and the patient's need. Repeated therapies are shown to be as effective as the initial treatment. IGBs may be re-applied in patients who request further weight loss after a compulsory one-month interval [19, 20]. Remaining the balloons in the stomach longer than the planned period may cause risk of rupturing and migrating into the intestine. While usually migrated balloons are excreted uneventfully, some may cause intestinal obstruction [1, 21, 22]. The patients were informed about the balloon removal time and the possible complications of therapy. But some of the patients have disrupted the follow-up procedure and delayed the balloon removal time. The reasons were declared as satisfaction of losing weight and avoiding to increase the cost by repeating process. The median EWL of the patients whose balloons were removed within 6 months after the procedure was 22.8%, and this rate was 41.6% in patients whose balloons were removed after the 6th month. No complications were observed in these patients except one who excreted the balloon transanally uneventfully.

In the early days of the IGB therapy, most of the patients have some gastrointestinal symptoms due to gastric accommodation of the balloon. These symptoms include abdominal pain, nausea, vomiting, burping, dyspepsia, acid reflux and constipation [23, 24] and usually resolved with proton pump inhibitors, antiemetics and anticholinergics. However, early balloon removal may be necessary if severe symptoms persist [25, 26]. And three patients (7.6%) of this study had persisting symptoms which caused early removal.

The stomach is usually sterile or colonized by small amounts of bacteria or yeasts. But overgrowth may not occur in the existence of a normal healthy microbiota [27, 28]. Delayed gastric emptying and gastric stasis which are the effects of IGB's may be initiative factors causing opportunistic organisms to colonize readily [29]. Hypochlorhydric gastric medium formed by proton pump inhibitors is condisered to be an other predisposing factor for opportunistic infections [30, 31]. Microorganisms that colonize the stomach consist of streptococci and lactobacilli as well as Veillonella and Clostridium subspecies, and Candida albicans as a common cause of colonization of medical devices [32].

Microbiological examination was performed to determine if the symptoms of the patients were related to the colonization of the balloons. Microbial growth was detected in the balloon of 23.7% (n=9) of patients. All were opportunistic microorganisms and the majority (n= 5) was Candida albicans. No antimicrobial treatment was given to the patients with positive culture results. Because the infection defined on the balloon was just local colonization, there were no signs of systemic infection. But, the presence of microbial contamination did not influence the duration of the balloon therapy and the frequency of symptoms and side effects.

Like other therapeutic endoscopic procedures, balloon removal can also be associated with gastrointestinal bleeding, esophageal tear or perforation and the other complications. No serious complication was observed in our analysis.

Mortality rates were reported as 0 – 0,005% in a systematic review published in 2016 [33]. And the only study that presented its results on IGBs remained in the stomach over six months declared greater results than that up to 6 months without complications [34].

This retrospective study has some limitations. Low number of patients, lack of long-term results and evaluating the effectiveness of the procedure only with weight loss and BMI were the major limitations.

In conclusion, IGB therapy is a minimal invasive and temporary option between medical treatment and bariatric surgery and may be recommended as a safe and effective option as an interval approach.

References

1. Gaur S, Levy S, Mathus-Vliegen L, Chuttani R. Balancing risk and reward: a critical review of the intragastric balloon for weight loss. Gastrointest Endosc. 2015;81:1330–6.
2. Lau DC, Teoh H. Benefits of modest weight loss on the management of type 2 diabetes mellitus. Can J Diabetes. 2013;37:128–34.
3. Obesity: The Prevention, Identification, Assessment and Management of Overweight and Obesity in Adults and Children [Internet].
Centre for Public Health Excellence at NICE (UK); National Collaborating Centre for Primary Care (UK). London: National Institute for Health and

ClinicalExcellence(UK);2006. https://www.ncbi.nlm.nih.gov/pubmed/22497033
4. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894: i-xii, 1-253.
5. Dastis NS, François E, Deviere J, Hittelet A, Ilah Mehdi A, Barea M, et al. Intragastric balloon for weight loss: results in 100 individuals followed for at least 2.5 years. Endoscopy. 2009;41:575-80.
6. Mathus-Vliegen EM. Endoscopic treatment: the past, the present and the future. Best Pract Res Clin Gastroenterol. 2014;28:685-702.
7. Ling H, Lenz TL, Burns TL, Hilleman DE. Reducing the risk of obesity: defining the role of weight loss drugs. Pharmacotherapy. 2013;33:1308-21.
8. Mathus-Vliegen EM, Tytgat GN. Intragastric balloon for treatment-resistant obesity: safety, tolerance, and efficacy of 1-year balloon treatment followed by a 1-year balloon-free follow-up. Gastrointest Endosc. 2005;61:19-27.
9. Martins Fernandes FA Jr, Carvalho GL, Lima DL, Rao P, Shadduck PP, Montandon ID, et al. Intragastric Balloon for Overweight Patients. JSLS. 2016;20:pii: e2015.00107.
10. Stanford FC, Kyle TK, Claridy MD, Nadglowski JF, Apovian CM. The influence of an individual's weight perception on the acceptance of bariatric surgery. Obesity. 2015;23:277-81.
11. Göttig S, Weiner RA, Daskalakis M. Preoperative weight reduction using the intragastric balloon. Obes Facts. 2009;2:20-3.
12. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al. Body-mass index and cause-specific mortality in 900,000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009;373:1083-96.
13. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation. 2014;129:102-38.
14. Moura D, Oliveira J, De Moura EG, Bernardo W, Galvão Neto M, Campos J, et al. Effectiveness of intragastric balloon for obesity: A systematic review and meta-analysis based on randomized control trials. Surg Obes Relat Dis. 2016;12:420-9.
15. Kotzampassi K, Grosomanidis V, Papakostas P, Penna S, Eleftheriadis E. 500 intragastric balloons: what happens 5 years thereafter? Obes Surg. 2012;22:896-903.
16. Wing RR. Behavioral approaches to the treatment of obesity. In: Handbook of Obesity: Clinical Applications, 2nd Ed, Bray GA, Bouchard C [Eds], Marcel Dekker, New York, 2004.
17. Hartmann-Boyce J, Johns DJ, Jebb SA, Aveyard P. Effect of behavioural techniques and delivery mode on effectiveness of weight management: systematic review, meta-analysis and meta-regression. Obes Rev. 2014;15:598-609.
18. Butryn ML, Webb V, Wadden TA. Behavioral treatment of obesity. Psychiatr Clin North Am. 2011;34:841-59.
19. Alfredo G, Roberta M, Massimiliano C, Michele L, Nicola B, Adriano R. Long-term multiple intragastric balloon treatment--a new strategy to treat morbid obese patients refusing surgery: prospective 6-year follow-up study. Surg Obes Relat Dis. 2014;10:307-11.
20. Genco A, Cipriano M, Bacci V, Maselli R, Paone E, Lorenzo M, et al. Intragastric balloon followed by diet vs intragastric balloon followed by another balloon: a prospective study on 100 patients. Obes Surg. 2010;20:1496-500.
21. Yap Kannan R, Nutt MR. Are intra-gastric adjustable balloon systems safe? A case series. Int J Surg Case Rep. 2013;4:936-8.
22. Roman S, Napoléon B, Mion F, Bory RM, Guyot P, D'Orazio H, et al. Intragastric balloon for "non-morbid" obesity: a retrospective evaluation of tolerance and efficacy. Obes Surg. 2004;14:539-44.
23. PMA P140008: FDA Summary of Safety and Effectiveness Data. http://www.accessdata.fda.gov/cdrh_docs/pdf14/P140008b.pdf [Accessed on January 25, 2016].
24. PMA P140012: FDA Summary of Safety and Effectiveness Data. http://www.accessdata.fda.gov/cdrh_docs/pdf14/P140012b.pdf [Accessed on January 25, 2016].
25. Dumonceau JM. Evidence-based review of the Bioenterics intragastric balloon for weight loss. Obes Surg. 2008;18:1611-7.
26. Imaz I, Martínez-Cervell C, García-Alvarez EE, Sendra-Gutiérrez JM, González-Enríquez J. Safety and effectiveness of the intragastric balloon for obesity. A meta-analysis. Obes Surg. 2008;18:841-6.
27. Marshall JC. Gastrointestinal flora and its alterations in critical illness. Curr Opin Clin Nutr Metab Care. 1999;2:405-11.
28. Zilberstein B, Quintanilha AG, Santos MA, Pajecki D, Moura EG, Alves PR, et al. Digestive tract microbiota in healthy volunteers. Clinics. 2007;62:47-54.
29. Rajablou M, Ganz RA, Batts KP. Candida infection presenting as multiple ulcerated masses. Gastrointest Endosc. 2007;65:164-6.
30. Pasqualotto AC, Nedel WL, Machado TS, Severo LC. A comparative study of risk factors and outcome amongout patient-acquired and nosocomial candidaemia. J Hosp Infect. 2005;60:129-34.
31. Wang K, Lin HJ, Perng CL, Tseng GY, Yu KW, Chang FY, Lee SD. The effect of H2-receptor antagonist and proton pump inhibitor on microbial proliferation in the stomach. Hepatogastroenterology. 2004;51:1540-3.
32. Kotzampassi K, Vasilaki O, Stefanidou C, Grosomanidis V. Candida albicanscolonization on an intragastric balloon. Asian J Endosc Surg. 2013;6:214-6.
33. Yorke E, Switzer NJ, Reso A, Shi X, de Gara C, Birch D, et al. Intragastric Balloon for Management of Severe Obesity: a Systematic Review. Obes Surg. 2016;26:2248-54.
34. Genco A, Maselli R, Frangella F, Cipriano M, Forestieri P, Delle Piane D, et al. Intragastric balloon for obesity treatment: results of a multicentric evaluation for balloons left in place for more than 6 months. Surg Endosc. 2015;29:2339-43.

Arch Clin Exp Med 2019;4(1):29-32. e-ISSN: 2564-6567

DOI:10.25000/acem.491222 Araştırma makalesi / Research article

Is gestational diabetes a risk factor for neonatal hearing loss?

Gestasyonel diyabet yenidoğan işitme kaybında bir risk faktörü müdür?

Fatih Mehmet Hanege [1], Burcu Yılmaz Hanege [2], Serdal Çelik [1], Ahmet Göçmen [2], M. Tayyar Kalcıoğlu [1]

Abstract

Aim: Newborn hearing screening is important for early detection of hearing loss in newborns. Gestational diabetes is a metabolic disease that can occur in pregnancy and cause complications such as those in the other diabetes mellitus patients. As uncomplicated gestational diabetes has not been described as a cause for prenatal complications in the literature, this study aimed to determine whether gestational diabetes is a risk factor for hearing impairment among newborns.

Methods: This retrospective study included infants born between 2015 and 2017. The infants were divided into two groups: Control group consisted of 100 randomly selected children of healthy mothers. Study group consisted of 79 infants whose mothers had gestational diabetes mellitus. Exclusion criteria included other risk factors and 8 infants were excluded from the study due to risk factors other than gestational diabetes mellitus. The results of transient evoked otoacoustic emissions in infants of mothers with gestational diabetes were compared with those of infants of healthy mothers.

Results: In this study, we compared transient evoked otoacoustic emission results of 71 infants of gestational diabetic mothers with 100 infants of healthy mothers. All the infants of healthy mothers, as well as the infants of mothers with gestational diabetes without risk factors, passed the transient evoked otoacoustic emission test.

Conclusions: There was no difference detected in the hearing screening results between infants of mothers with gestational diabetes and infants of healthy mothers.

Keywords: Gestational diabetes, neonatal hearing loss, hearing screening, otoacoustic emission

Öz

Amaç: İşitme kaybı, yenidoğanlar arasında en sık görülen konjenital anomalilerden biridir. Yenidoğan işitme tarama programı işitme kaybı olan yenidoğanlarda erken tanı için önem arz etmektedir Gestasyonel diyabet ise gebelikte ortaya çıkan ve diğer diyabetes mellitus tanısı alan hastalardaki gibi komplikasyonlara neden olabilen metabolik bir hastalıktır. Komplike olmamış gestasyonel diyabeti işitme kaybı riski oluşturan prenatal bir komplikasyon olarak tanımlayan bir çalışma literatürde bulunmamaktadır. Bu çalışmada gestasyonel diyabetin yenidoğanlarda işitme bozukluğu için bir risk faktörü olup olmadığını belirlemeyi amaçladık.

Metod: Bu retrospektif çalışmaya 2015-2017 yılları arasında doğan bebekler dahil edildi. Bebekler iki gruba ayrıldı; Kontrol grubu: Rastgele seçilen sağlıklı 100 annenin çocuğundan oluşuyordu. Çalışma grubu: 8 tanesi en az bir risk faktörüne sahip olup çalışma dışında bırakılan, gestasyonel diyabeti olan annelerden doğan 79 bebekten oluşan grup idi. Gestasyonel diyabeti olan annelerden doğan bebeklerin transient otoakustik emisyon sonuçlarının sağlıklı annelerden doğanların sonuçları ile karşılaştırdık.

Bulgular: Bu çalışmada 71 gestasyonel diyabeti olan anne bebeği ile 100 sağlıklı anne bebeğinin transient otoakustik emisyon sonuçları ile karşılaştırıldı. Sağlıklı annelerin bebeklerinin yanı sıra risk faktörü olmayan gestasyonel diyabeti olan anne bebeklerinin tümü transient otoakustik emisyon testini geçti.

Sonuç: Annesinde gestasyonel diyabeti olan bebeklerin işitme tarama sonuçları ile annesi sağlıklı olan bebeklerin işitme tarama sonuçları arasında bir fark tespit edilememiştir.

Anahtar Kelimeler: Gestasyonel diyabet , yenidoğan işitme kaybı, işitme taraması, otoakustik emisyon

[1] Istanbul Medeniyet University Faculty of Medicine, Department of Otorhinolaryngology, Istanbul, Turkey.

[2] Istanbul Medeniyet University Faculty of Medicine, Department of Obstetrics and Gynecology, Istanbul, Turkey.

Ethics Committee Approval: The study wass approved by the local ethical authority.
Etik Kurul Onayı: Çalışma lokal etik komite tarafından onaylanmıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Geliş Tarihi / Received: 02.12.2018
Kabul Tarihi / Accepted: 13.02.2019
Yayın Tarihi / Published: 15.03.2019

This study was presented at the 40th Turkish National Otorhinolaryngology-Head and Neck Surgery Congress, 7-11 November, 2018, Antalya, Turkey.
Bu çalışma 7-11 Kasım 2018'de Antalya, Türkiye'de düzenlenen 40. Ulusal Otorinolaringoloji-Baş ve Boyun Cerrahisi Kongresi'nde sunulmuştur.

Sorumlu yazar / Corresponding author:
Fatih Mehmet Hanege
Adres/Address:
Dr. Erkin Cad. Goztepe, Kadikoy, Istanbul, Turkey.
e-posta: hanege@hotmail.com
Tel/Phone: (+90) 216 5664000

Introduction

Hearing loss is one of the most common congenital anomalies among newborns. The incidence of impairment of bilateral congenital hearing is 1.4 per 1000 births [1]. Early diagnosis and treatment is important for the development of hearing systems and for the preservation of the cognitive functions in newborns. Normal hearing capacity in early infancy is very important for social, emotional and mental development as well as speech and language development in children.

The Joint Committee on Infant Hearing has been focusing on the importance of newborn hearing screening (NHS) for a long time [2]. In 1978, Kemp applied transient evoked otoacoustic emissions (TEOAE) to assess the hearing status of newborns [3]. After some preliminary studies on neonatal hearing screening, it was suggested that these tests could be used for diagnosing premature hearing loss in newborns [4]. NHS is highly functional in early diagnosis and was approved as a national program originally in the United Kingdom and the United States and subsequently in Europe, and was starting to be performed on all newborns in some countries [5-9].

Early diagnosis and treatment can prevent the negative consequences of hearing loss. TEOAE and auditory brainstem response (ABR) are known to be suitable and usable basic tools for NHS [10]. If a newborn does not have a risk factor such as prenatal and neonatal infection, immaturity, asphyxia, ototoxic drug use, and hyperbilirubinemia, the first choice for NHS is TEOAE. The above mentioned factors are defined as risk factors for neonatal hearing impairment [11]. Newborns with one of these risk factors and those who failed the TEOAE in one or two ears directly refer to ABR test.

Gestational diabetes is a pathological condition that occurs in the second and third trimesters in mothers who have no previous history of diabetes. Diabetes mellitus is a metabolic disorder that also has a genetic predisposition to complete or partial impairment of insulin function. Metabolic changes manifest clinically with vascular or neuropathic complications. Gestational diabetes is a metabolic disease that can occur during pregnancy and cause complications such as those in other diabetes mellitus patients. The main aim of the treatment of gestational diabetes mellitus is prevention of complications. Although diabetes mellitus often results in hearing impairment, there is little data showing whether gestational diabetes is an antenatal risk factor for cochlear damage and hearing loss [12].

In this study, we aimed to determine whether there is a risk factor for hearing impairment in neonates from mothers with gestational diabetes. We compared the TEOAE outcomes of infants from mothers with gestational diabetes with those from healthy mothers.

Material and methods

This study began after receiving permission from the local ethics committee (# 11th February, 2014; 2014/0031). This study was conducted in accordance with the principles of the Declaration of Helsinki.

This retrospective case-control study involved infants born between January 2015 and January 2017 in Istanbul Medeniyet University Goztepe training and research hospital. The infants were divided into two groups. The control group consisted of 100 randomly selected children from healthy mothers. These mothers were those who did not have diseases such as gestational hypertension, gestational diabetes, preeclampsia, threatened preterm labor and those who did not have a history of additional drug use. 100 term newborns who have not experienced any complications during and after birth were included in the study as the control group. Study group consist of 79 infants whose mothers had gestational diabetes mellitus .Exclusion criteria included other risk factors such as craniofacial anomalies, low birth weight (<1500gr), meningitis, ototoxic drug use, hyperbilirubinemia, low Apgar score, intrauterine infections, family history of hearing loss, presence of any syndrome related to congenital hearing loss and 8 infants were excluded from the study due to risk factors other than gestational diabetes mellitus. The study was performed with the remaining 71 patients. In this study, screening tests (TEOAE) were performed using a Madsen Accuscreen otoacustic emission scanner (Madsen Accuscreen Pro handheld, GN Otometrics, Denmark), which emits a series of clicks ranging from 35 dB to 65 dB. In cases when the infant fails the test, the scan is repeated at 15 and 30 days. Infants, who did not pass the test on 30th day, were evaluated with ABR. Infants with risk factors were screened directly with ABR. All screening tests were performed by the same audiometrist with the infants sleeping in a quiet room.

Informed Consent: Written informed consent was obtained from the patients' parents.

Statistical analysis

To describe categorical variables frequencies and percentages was used. First, the 15th day and the 30th day TEOAE rates between neonates of healthy mothers and neonates of gestational diabetic mothers were evaluated by using Fisher Exact test. The critical value for statistical significance was set at 0.05. Statistical calculations were performed by IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp

Results

The mean age of the mothers in control and study groups was 30.29 years (range: 19-47) and 29.30 years (range: 19-45), respectively. Four of 71 infants could not pass the first TEOAE test on day 5. Two of these were administered the test on the 15th day; two infants who did not pass the first two tests passed the screening on the 30th day. Five out of 100 infants from randomly selected healthy mothers were not able to pass the 5th day TEOAE. Of the remaining five infants, three went through the 15th day scan and two were administered TEOAE on the 30th day and two infants who did not pass the first two tests passed the screening on the 30th day. ABR test was performed to four babies in total who failed TEOAE from both groups. All those babies passed the ABR test.

There was no significant difference in the rate of failure on the 5th day TEOAE test between infants from gestational diabetic mothers (5.6%) and infants from healthy mothers (5%) ($p=1.000$, $p>0.05$).

There was no significant difference in the rate of failure on the 15th day TEOAE test between infants from gestational diabetic mothers (50%) and of those from healthy mothers (40%) ($p=1.000$, $p>0.05$).

There was no significant difference in the rate of failure on the 30th day TEOAE between infants from gestational diabetic mothers who failed on second TEOAE test (100%) and infants from healthy mothers who failed on 30th day TEOAE test (100%) ($p=1.000$, $p>0.05$) (Table).

Discussion

The inner ear is very sensitive to ischemic and immunological damage, and vascular occlusion can cause hearing loss [13,14]. Therefore, gestational diabetes can theoretically damage the inner ear and cause sensorineural hearing loss in both mother and newborn due to microcirculation and the effects on possible immunological pathogenesis. If the mother is affected, it is reasonable to think that the fetus, the newborn, is also affected.

Table. TEOAE results of neonates born from healthy and diabetic mothers.

	Neonates of healthy mothers		Neonates of diabetic mothers		P
N (%)	Failed	Total	Failed	Total	
TEOAE on 5th day after the birth	5 (5)	100 (100)	4 (5.6)	71 (100)	1.00
TEOAE on 15th day after the birth	2 (40)	5 (100)	2 (50)	4 (100)	1.00
TEOAE on 30th day after the birth	2 (100)	2 (100)	2 (100)	2 (100)	1.00

TEOAE: Transient evoked otoacoustic emissions

There are limited studies on hearing loss in newborns from gestational diabetic mothers. In addition, the results of current studies are contradictory. When we focus on studies of hearing loss from mothers with gestational diabetes, we notice different results. In a study by Ewart-Toland et al. [15], nine of 27 children from diabetic mothers with craniofacial anomalies were found to have hearing loss. Mixed or sensorineural hearing loss was detected in 4 of these infants, while transmission type hearing loss was detected in 2 and unrecognized hearing loss in the remaining 3 infants [15]. In our study, no hearing loss was detected in any of the 71 babies born from the diabetic mothers.

Gratz et al. [16] reported two cases of gestational diabetes mellitus presenting with hypoplasia ipsilateral facial paralysis and ipsilateral deafness. Kelemen evaluated the results of histopathological analysis of specimens collected from a woman with severe gestational diabetes whose pregnancy was terminated during the second trimester. In this evaluation, it was determined that temporal bone development was normal, but there were bleeding spots on the cochlea and vestibulocochlear nerve [17]. None of the babies born from the mothers having gestational diabetes who were included in the study had any additional complication.

The most important complications of gestational diabetes are prematurity and abnormal birth weight. Many studies in the literature have found that gestational diabetes was a risk factor for premature labor, and macrosomia (> 4000 g) rates were high despite premature labor [18-20]. There is no study in the literature about neonatal hearing evaluation of diabetic pregnant women who had delivered without any complication. When we evaluated the results, we found no significant difference between screening tests of infants of mothers with gestational diabetes born after 35th week and infants from healthy mothers.

However, several limitations exist in our study. As our study was conducted retrospectively, ABR test results were not used in our study because the newborn hearing screening was performed by using TOAE before 2017. According to the national newborn hearing screening program, ABR test was performed to all newborns either having a risk factor or not since 2017. Currently, the usage of ABR test in studies that will be performed will give a clearer insight about the effect of gestational diabetes on neonatal hearing.

As an overall conclusion, gestational diabetes mellitus was not found to be a risk factor for congenital hearing loss in infants born to mothers with gestational diabetes without any complication.

References

1. Turchetta R, Conti G, Marsella P, Orlando MP, Picciotti PM, Frezza S, et al. Universal newborn hearing screening in the Lazio region, Italy. Ital J Pediatr. 2018;44:104.
2. Committee on Fetus and Newborn. Joint statement on neonatal screening for hearing impairment.Pediatrics. 1971;47:1085.
3. Kemp DT. Stimulated acoustic emissions from within the human auditory system. J Acoust Soc Am. 1978;64:1386-91.
4. National Institutes of Health Consensus Development Conference Statement. Early identification of hearing impairment in infants and young children. Int J Pediatr Otorhinolaryngol. 1993;27:215-27.
5. Wood SA, Sutton GJ, Davis AC. Performance and characteristics of the Newborn Hearing Screening Programme in England: The first seven years. Int J Audiol. 2015;54:353-8.
6. Chung W, Beauchaine KL, Grimes A, O'Hollearn T, Mason C, Ringwalt S. Reporting Newborn Audiologic Results to State EHDI Programs. Ear Hear. 2017;38:638-42.
7. Grandori F. European Consensus Statement on Neonatal Hearing Screening. J Laryngol Otol. 1998;112:1219.,
8. Kemaloglu YK, Gokdogan C, Gunduz B, Onal EE, Turkyilmaz C, Atalay Y. Newborn Newborn hearing screening outcomes during the first decade of the program in a reference hospital from Turkey. Eur Arch Otorhinolaryngol. 2016;273:1143-49.
9. Jakubíková J, Kabátová Z, Pavlovcinová G, Profant M. Newborn hearing screening and strategy for early detection of hearing loss in infants. Int J Pediatr Otorhinolaryngol. 2009;73:607-12.
10. Arslan S, Işik AU, Imamoglu M, Topbas M, Aslan Y, Ural A. Universal newborn hearing screening; automated transient evoked otoacoustic emissions. B-ENT. 2013;9:122-31.
11. Meyer C, Witte J, Hildmann A , Hennecke KH, Schunck KU, Maul K. Neonatal screening for hearing disorders in infants at risk: incidence, risk factors, and follow-up. Pediatrics. 1999;104:900-4.
12. Selcuk A, Terzi H, Turkay U, Kale A, Genc S. Does gestational diabetes result in cochlear damage? J Laryngol Otol. 2014;128:961-5.
13. Woolf NK, Harris JP. Cochlear pathophysiology associated with inner ear immune responses. Acta Otolaryngol. 1986;102:353-64.
14. Hanege BY, Hanege FM, Kalcioglu MT, Gocmen A. Is maternal preeclampsia risk factor for neonatal hearing loss? B-ENT. 2017;13:219-23.
15. Ewart-Toland A, Yankowitz J, Winder A, Imagire R, Cox VA, Aylsworth AS. Oculoauriculovertebral abnormalities in children of diabetic mothers. Am J Med Genet. 2000;90:303-9.
16. Gratz ES, Pollack MA, Zimmerman RD. Congenital facial palsy and ipsilateral deafness: association with maternal diabetes mellitus. Int J Pediatr Otorhinolaryngol. 1981;3:335-41.
17. Kelemen G. Aural changes in the embryo of diabetic mother. AMA Arch Otolaryngol. 1955;62:357-69.
18. Sudasinghe BH, Wijeyaratne CN, Ginige PS. Long and short-term outcomes of Gestational Diabetes Mellitus (GDM) among South Asian women - A community-based study. Diabetes Res Clin Pract. 2018;145:93-101.
19. Schwartz R, Teramo KA. Effects of diabetic pregnancy on the fetus and newborn. Semin Perinatol. 2000;24:120-35.

20. Weintrob N, Karp M, Hod M. Short- and long-range complications in offspring of diabetic mothers. J Diabetes Complications. 1996;10:294-301.

Arch Clin Exp Med 2019;4(1):33-36. e-ISSN: 2564-6567

DOI:10.25000/acem.489634 Araştırma makalesi / Research article

Comparing Efficacy of Surgicel ® Application with Nasal Packing in Epistaxis

Surgicel ® kullanımının epistaksis kontrolünde nazal tampon ile karşılaştırılması

Tevfik Sözen [1], Övsen Önay [1], Seyit Mehmet Ceylan [2]

Abstract

Aim: To evaluate the efficacy and tolerability of Surgicel ® application with transseptal suturing in epistaxis.

Methods: Thirty-four patients who underwent therapy for epistaxis from Kiesselbach's area, between January 2015 and August 2016, were retrospectively analyzed. As a treatment modality, anterior nasal packing (Merocel® tampon with airway) was inserted to 18 patients, and transseptal suturing combined with the Surgicel ® application was performed in 16 patients. The pain experienced during the procedure and compliance of the patients was evaluated using the NRS-11 morbidity scale that was administered during the control visits.

Results: No significant difference was identified between the two groups regarding the efficacy of bleeding control. Transseptal suturing combined with the Surgicel ® application was tolerated better and had lower morbidity compared to nasal packing.

Conclusion: This study showed that transseptal suturing with the Surgicel ® application is an effective and well-tolerated procedure in the treatment of anterior epistaxis.

Keywords: Nasal packing, epistaxis, nasal bleeding.

Öz

Amaç: Transseptal sütürasyon ile Surgicel ® tatbikinin burun kanamasındaki etkinliğinin ve tolere edilebilirliğinin belirlenmesi.

Metod: Ocak 2015 ile Ağustos 2016 tarihleri arasında Kiesselbach bölgesinden kanaması tespit edilen ve tedavi edilen hastalar retrospektif olarak tarandı. Tedavide anterior nazal tampon (Merocel®) uygulanmış 18 hasta, transseptal sütürasyon ile Surgicel ® tatbiki yapılmış olan 16 hasta çalışmaya dahil edildi. Hastaların kontrol vizitlerinde NRS-11 morbidite skalası kullanılarak elde edilmiş olan veriler, kişinin tecrübe ettiği ağrı ve yapılan işleme gösterdiği uyumu kıyaslamada kullanıldı.

Bulgular: İki grup arasında kanama rekürrensi açısından istatiksel olarak anlamlı fark bulunmadı. Transseptal sütürasyon ile Surgicel ® tatbikinin nazal tampona kıyasla daha iyi tolere edildiği ve düşük morbiditeye sahip olduğu görüldü.

Sonuç: Anterior epistaksiste transseptal sütürasyon ile Surgicel ® tatbikinin etkili ve iyi tolere edilebilir alternatif bir prosedür olduğu görüldü.

Anahtar kelimeler: Nazal tampon, epistaksis, burun kanaması.

[1] Hacettepe University Medical School, Department of ENT, Ankara, Turkey.

[2] SANKO University Medical School, Department of ENT, Gaziantep,Turkey.

Ethics Committee Approval: The study wass approved by the local ethical authority.

Etik Kurul Onayı: Çalışma lokal etik komite tarafından onaylanmıştır.

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

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Geliş Tarihi / Received: 03.12.2018

Kabul Tarihi / Accepted: 04.01.2019

Yayın Tarihi / Published: 15.03.2019

This study was presented at the 13th International Otorhinolaryngology-Head and Neck Surgery Congress, 5-7 April, 2018, Ankara, Turkey.

Bu çalışma 5-7 Nisan 2018'de Ankara, Türkiye'de düzenlenen 13. Uluslararası Kulak Burun Boğaz ve Baş-Boyun Cerrahisi Kongresi'nde sunulmuştur.

Sorumlu yazar / Corresponding author:

Övsen Önay

Adres/Address: Department of Otolaryngology, Hacettepe University Hospital, Sıhhiye, Ankara, Turkey

e-posta: ovsenonay8@gmail.com

Tel/Phone: (+90) 5057338340

Introduction

Epistaxis is one of the most common otolaryngologic emergencies. Epistaxis affects up to 60% of the population in their lifetime, and 6% of these cases require additional therapies [1-5]. The optimal treatment option for epistaxis should provide bleeding control with minimal pain. The patient should be allowed to return to their daily routine in a short time and the treatment should be well tolerated [5]. Localization of the bleeding focus and cauterization is normally sufficient in most cases with anterior nasal bleeding [6-12]. In clinical practice, anterior nasal packing is indicated in cases when heavy bleeding interferes with the localization of the bleeding focus, or where chemical cauterization fails to achieve control, as well as in cases with traumatic anterior epistaxis [13-15].

Currently, various advanced local hemostatic agents are used in addition to conventional surgical bleeding control methods, including oxidized cellulose (Surgicel ®). Surgicel ® is applied in one or two layers, absorbing water from the application site and expanding to produce an artificial clot from forming cellulosic acid. It forms a gel upon contact with blood. Although the action mechanism has not yet completely understood, it produces a plug-like layer that stops the bleeding when it becomes hydrated on the surface of hemorrhagic vascular structures. Histological studies have shown that Surgicel ® produces no inflammatory response other than connective tissue proliferation [16-19].

Transseptal suturing is commonly performed during septoplasty procedures to achieve hemostasis, and while some surgeons prefer to combine Surgicel ® application with transseptal suturing in septoplasty procedures, there are limited studies into the combined use of these two methods in the treatment of anterior epistaxis [20-22]. It is known that Surgicel ® application has been combined with transseptal suturing to control epistaxis, similar to that seen in septoplasty procedures. There are insufficient numbers of studies that compare the technique used in the present study, in which transseptal suturing and the Surgicel ® application was combined with anterior nasal packing.

We perform this study to identify the efficacy and tolerability of Surgicel ® application with transseptal suturing, and compare it with anterior nasal packing treatment.

Material and methods

This was a retrospectively designed observational study. The study was approved by the local ethics committee (Hacettepe University, GO17/127-37), and the study protocol adhered to the tenets of the Declaration at Helsinki. Written consent could not be taken due to the retrospective design of the study.

Fifty-eight patients who were admitted to the Department of Otorhinolaryngology at Hacettepe University between January 2015 and August 2016 with epistaxis (patients presenting to the department after the admission to the emergency room, and applied to the outpatient clinics directly) were evaluated. The medical charts of the patients were reviewed retrospectively, based on which, 49 patients with localized bleeding from the Kiesselbach's area on initial examination with anterior rhinoscopy. However, patients with postoperative bleeding, epistaxis related to a tumor, patients below the age of 18, pregnant women, patients with hereditary hemorrhagic telangiectasia, patients with nasal bleeding secondary to anticoagulant use, and patients with inaccessible medical data were excluded. Therefore, a total of 34 patients that met these criteria were evaluated in this study.

Thirty-four patients were treated with nasal packing only (Group A) and Surgicel ® application with transseptal suturing (Group B) were included in this study. Patients with nasal bleeding secondary to hypertension, and posttraumatic epistaxis were included also.

The control visit records (3, 5 and 14 days) of the patients that underwent treatment for epistaxis were reviewed to evaluate the recurrence status/efficacy of treatment, any complaints related to the treatment, and possible morbidities. In the control visits, if recurrent bleeding occurred recurrent bipolar cauterization and/or chemical cauterizations with silver nitrate sticks was performed to make coagulation and to control bleeding. In addition, a morbidity test (a numerical rating scale to assess self-reported pain intensity [NRS-11]) performed during the control visits was evaluated in the scope of this study [4].

Techniques used in anterior nasal packing (Group A)

One ml adrenalin and 1ml 10% lidocaine-impregnated swabs were placed in each patient's nasal cavity to achieve analgesia and decongestion for 5 minutes. A standard 8 cm-long Merocel nasal pack ® (Medtronic, Turkey) was used for anterior nasal packing and the length of Merocel nasal pack ® was reduced in some cases when required i.e. patients with posterior deviation. Anterior nasal pack was inserted via anterior rhinoscopy in the epistaxis side. Prophylactic antibiotics (amoxicillin/clavulanate 1000/125mg twice daily) were prescribed to all patients treated with nasal packing. The patients were asked to attend routine control visits to remove the nasal packing at 72 hours after the initial intervention. A second control visit was made five days after the initial intervention. Morbidity was evaluated using a patient-reported questionnaire about the level of pain during treatment on a scale of 0 to 10 (NRS-11), and the severity of most common complaints in the first two weeks rated on a scale of 0 to 5.

Techniques used in Surgicel ® application with transseptal sturing (Group B)

1ml adrenalin, and 1ml 10% lidocaine-impregnated swabs, as topical anesthesia, were placed in each patient's nasal cavity to achieve analgesia and decongestion for 5 minutes. Then, 4 mL of lidocaine HCl 20 mg/ml and epinephrin 0.0125 mg/mL (Jetokain®) was injected bilaterally into the septal mucosa using a 27 G needle, in addition to topical anesthesia. After the placement of two layers of Surgicel ® (Ethicon, Somerville, USA) into the anterior nasal mucosa, 4-0 coated VICRYL rapide suture ® (Ethicon, Somerville, USA) were placed around the bleeding focus via primary suturation, 3 times passing through the Surgicel ® and septum. Bilateral Surgicel ® was applied simultaneously to the patients with bilateral epistaxis. No antibiotics were administered for prophylaxis. The patients were asked to attend routine control visits for evaluations of the early outcomes of Surgicel ® application with transseptal suturing at 72 hours after the initial intervention. A second control visit was made five days after the initial intervention. Morbidity was evaluated using a patient-reported questionnaire about the level of pain during treatment on a scale of 0 to 10 (NRS-11), and the severity of most common complaints in the first two weeks rated on a scale of 0 to 5.

Statistical Analysis

Major outcome was regarded as comparison of Surgicel® application with transseptal suturing with nasal packing regarding epistaxis recurrence rates (efficacy of

treatment), and the resulting morbidities including pain, headache, respiratory distress, epiphora, nasal congestion, and minor bleeding.

Statistical analysis was carried out using SPSS version 22.0 (SPSS Inc. Chicago, IL, USA) software. For the comparison of normally distributed numeric variable's independent groups Student-T test was used, to compare not normally distributed variables we used Man Whitney U- test and for the comparison of categorical data Chi Square test was used.

Table 1. Demographic features of the patients.

Variable	Group A (n=18)	Group B (n=16)	P
Male[¥]	14 (77.8%)	11 (68.8%)	0.700
Age (year)[£]	60.5 (26-76)	64 (16-79)	0.640
Hypertension[¥]	11 (61.1%)	10 (62.5%)	0.930

[¥]: n (%), [β]: mean ± standard deviation, [£]: median (min-max)

Table 2. Pain scores and recurrent bleeding comparison between both treatment options.

	STS	ANP	p
Number of patients	16	18	
Mean NRS-11 score at initial treatment	3.06 ± 1.28	5.01±1.02	0.001
Percentage of major recurrent nasal bleeding (n)	0%	22.2% (3)	0.105
Percentage of minor recurrent nasal bleeding (n)	38.9% (7)	50% (8)	0.510

(STS: Surgicel ® application with transseptal suture, ANP: anterior nasal packing)

Results

Thirty four patients were included in the study; 25 male patients, 9 female patients were evaluated, mean age was 58±14 years, and the incidence of hypertension was 62%. Eighteen patients were treated with anterior nasal packing (Group A), 16 patients were treated by Surgicel ® application with transseptal suturing (Group B). Patient demographics in these two groups are shown in Table 1.

In this follow up period, no recurrent bleeding occurred within the patients treated by Surgicel® application with transseptal suturing, although eight patients experienced minor bleeding that resolved itself spontaneously (50%). Of the 18 patients who were treated with anterior nasal packing, seven of them (39%) experienced minor bleeding that resolved spontaneously, and four patients (22.2%) experienced recurrent nasal bleeding (Table 2). Four patients were admitted to the emergency outpatient clinic due to recurrent nasal bleeding within 24 hours of the removal of the anterior nasal tampon, and bipolar cauterization (one patient) and chemical cauterizations with silver nitrate sticks (three patients) was performed on this patient. This intervention needed recurrent bleedings were admitted as major bleedings (Table 2). The recurrence rate for epistaxis was slightly higher in patients who were treated with anterior nasal packing when compared to the patients treated with Surgicel® application with transseptal suturing.

According to the NRS-11 scale evaluation performed at patients' first control visit, all the patients in both procedure groups had pain complaint. According to NRS-11, the mean level of pain during the procedure was significantly higher in the anterior nasal tampon group and this difference was statistically significant (p=0.001) (Table 2). When the morbidities of each procedure in the first three days after treatment were compared, the anterior nasal tampon was significantly more discomforting, while Surgicel ® application with transseptal suturing was tolerated better regarding nasal congestion, epiphora, breathing difficulty, headache/pain, and these were statistically significant (p=0.001) (Table 3).

Table 3. Level of discomfort, according to treatment options was measured with NRS-11 at control visits after 72 hours of treatment.

Median score at NRS-11	Group A[£]	Group B[£]	p
Pain/headache	3 (2-5)	0 (0-2)	0.001
Respiratory distress	2 (0-5)	0 (0-0)	0.002
Epiphora	2 (0-4)	0 (0-0)	0.002
Nasal congestion	3 (1-5)	0 (0-0)	0.003

[£]: median (min-max)

Discussion

Most patients with anterior epistaxis are treated successfully with silver nitrate cauterization or anterior nasal packing. In most instances, the focus of bleeding is detectable in an anterior rhinoscopy and allows cauterization via silver nitrate application [23]. There are studies supporting the success of silver nitrate cauterization when the bleeding focus is detected [2, 8-10, 24], although silver nitrate application cannot be recommended in all cases with anterior nasal bleeding [23]. Heavy nasal bleeding and bleeding from an extensive area may not allow silver nitrate cauterization, and so other treatment options should be considered. Nasal packing is commonly used in the treatment of nasal bleeding, as a considerably effective and simple treatment method. Its ready availability and short application time have rendered this option the first file therapy; however, nasal packing could be uncomfortable and may lead to various complications and side effects [25, 26]. Some complications, such as Eustachian tube dysfunction during application, epiphora, pain and vasovagal reactions are mild and self-limiting, whereas devastating complications may also occur, such as sinusitis, orbital infections, toxic shock syndrome, infective endocarditis, septal abscess, inferior concha and nasal alar necrosis. More importantly, nasal packing has been shown to impair cardiovascular functions and may cause hypoxia, hypercapnia and bradycardia [27]. No complications occurred related to anterior nasal packing in our study patients, although the level of discomfort was higher in the nasal packing group, and the difference was statistically significant. The reported failure rates for nasal packing are as high as 52%, and recurrent nasal bleeding reaches a rate of 70% in patients with bleeding disorders [25]. In the patients in the present study, the rate of recurrent nasal bleeding with anterior nasal packing was 22.2 percent within a two-week follow-up period, and this low rate of recurrence can be attributed to the short follow-up period and bias in the patient randomization. No recurrence was observed in patients who were treated with transseptal suturing combined with the Surgicel ® application. It can be assumed that; addititonal to transseptal suturing, the efficacy of Surgicel® is an additive affect for maintaining the hemostasis and as discussed previously in the literature due to this cumulative affect [28], no recurrent bleeding was observed in this group.

In recent years, various hemostatic agents have been used in the treatment of nasal bleeding. For example, Surgicel ® (oxidized regenerated cellulose) and FloSeal have seen success in promoting clot stabilization [19, 29, 30]. Hemostatic agents alone are effective in only 65% patients with epistaxis [12]. The present study evaluated transseptal suturing combined with the Surgicel ® application as an alternative to nasal packing in the treatment of anterior epistaxis, and this study noted a success rate of 85% and no recurrence during the follow-up. Even though these results are found statistically insignificant, this may be due

to our low number of patients. Further studies conducted with larger patient groups may give more reliable results regarding this subject. The use of sutures in the Little's area and the use of a transseptal suturing technique have been covered in two previous studies [22, 31], and in both, a suturing technique was used in cases where nasal packing and/or bipolar cauterization failed to achieve control. This technique can be used in patients with bilateral epistaxis, as bilateral cauterization is associated with the risk of septal perforation.

In our study, we combined transseptal sutures with the application of Surgicel ®. Therefore, it is impossible to evaluate the individual contributions of these techniques to hemostasis. Further studies regarding this subject may be designed to compare these techniques, where some patients are treated with transseptal suturing or Surgicel ® application only, making the comparison possible.

The procedural pain was significantly less common in the transseptal suturing group, which may be attributed to the administration of infiltration anesthesia in addition to topical anesthesia before suturing. Patients' complaints related to the therapy were significantly lower when compared to the nasal packing group. On the other hand, we should highlight that, this method has some notable disadvantages, being more time consuming and the requirement for local anesthetic infiltration and expertise.

One of the biggest limitations of this study is patient numbers that are involved in the study. Our study can be improved with bigger patient numbers in treatment groups. Also, we have used the NRS-11 scale to determine the pain levels, but more effective visual analog scales are described in the literature, and these can be used to get more reliable results for evaluating the morbidity of the procedures.

In conclusion, the optimal treatment option for epistaxis should provide bleeding control with minimal morbidity. Surgicel ® application with transseptal suturing could be considered an alternative treatment for nasal packing, in cases of anterior septal epistaxis. Transseptal suturing combined with the Surgicel ® application was tolerated better and had lower morbidity compared to nasal packing We recommend the use of this technique in patients with bleeding from a wide area, patients with bilateral anterior septal nasal bleeding, those with traumatic anterior bleeding and in cases in which chemical cauterization has failed to achieve success.

References

1. Pallin D, Chng Y, McKay M, Emond J, Pelletier A, Camargo C. Epidemiology of epistaxis in US emergency departments 1992 to 2001. Ann Emerg Med. 2005;46:77–81.
2. Vhichweg T, Roberson J, Hudson J. Epistaxis: diagnosis and treatment. J Oral Maxillofac Surg. 2006; 64:511–8.
3. Ha J, Hodge J, Lewis R. Comparison of nasendoscopic-assisted cautery versus packing for the treatment of epistaxis. ANZ J Surg. 2011;81:336-9.
4. Bahreini M, Jalili M, Morafi-Lakeh M. A comparison of three self-reported pain scales in adults with acute pain. J Pain. 2013;14:1653-62.
5. Duncan I, Fourie P, Ic Grange C, Van der Walt H. Endovascular treatment of intractable epistaxis results of a 4 year local audit. S Afr Med J. 2004;94:373-8.
6. McGarry G, Moulton C. The first aid management of epistaxis by accident and emergency department staff. Arc of Emerg Med.1993;10:290-300.
7. Farneti P, Pasquini E, Sciarretta V, Macrì G, Gramellini G, Pirodda A. Comparison of Local Sclerotherapy With Lauromacrogol Versus Nasal Packing in the Treatment of Anterior Epistaxis. Clin Exp Otorhinolaryngol. 2016; 9:131-5.
8. Kucik CJ, Clenney T. Management of epistaxis. Am Fam Physician. 2005;71:305–11.
9. Morgan DJ, Kellerman R. Epistaxis: evaluation and treatment. Prim Care. 2014;41:63–73.
10. Toner JG, Walby AP. Comparison of electro and chemical cautery in the treatment of anterior epistaxis. J Laryngol Otol. 1990;104:617–8.
11. Stangerup SE, Dommerby H, Lau T. Hot water irrigation as a treatment of posterior epistaxis? Rhinology. 1996;34:18-20.
12. Meric A, Korkut AY, Kahya V, Gedikli O. Prospective, randomized, controlled clinical trial of Ankaferd Blood Stopper in patients with acute anterior epistaxis. Eur Arch Otorhinolaryngol. 2010; 267:1377–81.
13. Certal V, Silva H, Santos T, Correia A, Carvalho C. Trans-septal suturing technique in septoplasty: a systematic review and meta-analysis. Rhinology. 2012;50:236-45.
14. Zayyan E, Bajin MD, Aytemir K, Yılmaz T. The effects on cardiac functions and arterial blood gases of totally occluding nasal packs and nasal packs with airway. Laryngoscope. 2010;120:2325-30.
15. Dubin MR, Pletcher SD. Postoperative packing after septoplasty: is it necessary? Otolaryngol Clin North Am. 2009;42:279-85.
16. Al-Shaikh S, Muddaiah A, Lee RJ, Bhutta MF. Oxidised cellulose powder for haemostasis following sinus surgery: a pilot randomised trial. J Laryngol Otol. 2014;128:709-13.
17. Valentine R, Wormald PJ, Sindwani R. Advances in absorbable biomaterials and nasal packing. Otolaryngol Clin North Am. 2009;42:813-28.
18. Lewis KM, Spazierer D, Urban MD, Lin L, Redl H, Goppelt A. Comparison of regenerated and non-regenerated oxidized cellulose hemostatic agents. Eur Surg. 2013;45:213-20.
19. Bhatnagar RK, Berry S. Selective Surgicel ® packing for the treatment of posterior epistaxis. Ear Nose Throat J. 2004;83:633-4.
20. Günaydın RÖ, Aygenc E, Karakullukcu S, Fidan F, Celikkanat S. Nasal packing and transseptal suturing techniques: surgical and anaesthetic perspectives. Eur Arch Otorhinolaryngol. 2011;268:1151-6.
21. Certal V, Silva H, Santos T, Correia A, Carvalho C. Trans-septal suturing technique in septoplasty: a systematic review and meta-analysis. Rhinology. 2012;50:236-45.
22. Wysocki J, Niszczota CS. Use of trans-septal mattress suture of Little's area for anterior epistaxis. J Laryngol Otol. 2011;125:399-401.
23. Newton E, Lasso A, Petrcich W, Kilty S.J. An outcomes analysis of anterior epistaxis management in the emergency department. J Otolaryngol Head Neck Surg. 2016;45:24.
24. Gallo A, Moi R, Minni A, Simonelli M, DeVincentiis M. Otorhinolaryngology emergency unitcare: the experience of a large university hospital in Italy. ENT J. 2000;79: 155–60.
25. Traboulsi H, Alam E, Hadi U. Changing Trends in the Management of Epistaxis. Int J Otolaryngol. 2015; 2015:263987.
26. Hady MR, Kodeira KZ, Nasef AH. The effect of nasal packing on arterial blood gases and acid-base balance and its clinical importance. J Laryngol Otol. 1983;97:599-604.
27. Schaitkin B, Strauss M, Houck J R. Epistaxis: medical versus surgical therapy: a comparison of efficacy, complications, and economic considerations. Laryngoscope. 1987;97:1392–96.
28. Aslan G, Güvenç MG, Sapçi T, Candan S. Use of nasal bivalve septal teflon splint for the treatment of recurrent epistaxis in patients undergoing anticoagulant therapy. Rhinology. 2009;47:141-3.
29. Huggins S. Control of hemorrhage in otorhinolaryngologic surgery with oxidized regenerated cellulose. Eye Ear Nose Throat Mon. 1969;48:420-3.
30. Mathiasen RA, Cruz RM. Prospective, randomized, controlled clinical trial of a novel matrix hemostatic sealant in patients with acute anterior epistaxis. Laryngoscope. 2005;115: 899-902.
31. ZhengHua Z , Gang F, BingWei Z, JiaWen C. Suturing of Little's area of the nasal septum for epistaxis. J Laryngol Otol. 2009;123:787-8.

Arch Clin Exp Med 2019;4(1):37-40. e-ISSN: 2564-6567

DOI:10.25000/acem.494415 Araştırma makalesi / Research article

Evaluation of inflammatory markers in patients with migraine

Migren hastalarında enflamatuvar belirteçlerin değerlendirilmesi

Aysel Tekeşin [1], Abdülkadir Tunç [2]

Abstract

Aim: The aim of this study was to evaluate erythrocyte sedimentation rate (ESR), high sensitivity C-reactive protein (hsCRP), neutrophil-to-lymphocyte ratio (NLR), monocyte to HDL-C ratio (MHR), and bilirubin levels in patients with migraine and compare with levels measured in healthy subjects.
Methods: This retrospective case-control study included 136 migraine patients and 80 healthy controls who were admitted to our neurology outpatient clinic or emergency between June 2017 and June 2018. Laboratory examinations, disease characteristics, presence of aura, and the presence of white matter hyperintensities (WMHs) were recorded and demographic features and laboratory data were compared between two groups.
Results: The mean age of the case group was 36.9 ± 10.6 years and the control group was 37 ± 12 years. In the patient group, total bilirubin, direct bilirubin, indirect bilirubin, and lymphocyte values were significantly lower than the control group. NLR, hsCRP, and ESR levels were significantly higher in the patient group than the control group. The patient and control groups did not show a significant difference according to the presence of WMHs. In the group with aura, monocyte and MHR values were higher than those without aura. The hsCRP values in the group with aura were significantly lower than the group without aura.
Conclusion: This study showed that low bilirubin and high NLR, MHR, hsCRP, and ESR values might be potential inflammatory markers in migraine patients. These markers may contribute to our understanding of the pathophysiology of migraine. Since the cost of these tests is cheap and they are widely used, it is possible to believe that they may be useful for protecting migraine patients against long-term comorbidities.
Keywords: Migraine, inflammation, laboratories, biomarker

Öz

Amaç: Bu çalışmanın amacı migren hastalarında eritrosit sedimentasyon hızı (ESR), yüksek duyarlılıklı C-reaktif protein (hsCRP), nötrofil-lenfosit oranı (NLO), monosit-HDL-C oranı (MHO) ve bilirubin düzeylerinin değerlendirilmesi ve sağlıklı bireylerde ölçülen seviyelerle karşılaştırılmasıdır.
Yöntemler: Bu retrospektif vaka-kontrol çalışmasına Haziran 2017-Haziran 2018 tarihleri arasında hastanemiz nöroloji polikliniğine veya acil servisine başvuran 136 migren hastası ve 80 sağlıklı kontrol dahil edildi. Tüm katılımcıların laboratuvar tetkikleri, hastalık özellikleri, aura varlığı ve beyaz cevher lezyonlarının varlığı kaydedildi ve demografik özellikler ve laboratuvar verileri iki grup arasında karşılaştırıldı.
Bulgular: Vaka grubunun yaş ortalaması 36.9 ±10.6 yıl ve kontrol grubunun 37±12 yıl idi. Hasta ve kontrol grupları arasında yaş ve cinsiyet açısından anlamlı fark saptanmadı. Vaka grubunda total bilirubin, direkt bilirubin, indirekt bilirubin, lenfosit değerleri kontrol grubuna göre anlamlı derecede düşüktü. Hasta grubunda NLO, hsCRP, ESR düzeyleri kontrol grubuna göre anlamlı yüksekti. Vaka ve kontrol grupları beyaz cevher lezyonları varlığı açısından anlamlı farklılık göstermedi. Aurası olan ve olmayan migren hastalarında yaş, cinsiyet, total bilirubin, direkt bilirubin ve indirekt bilirubin değerleri, NLO, ürik asit, lenfosit ve ESR düzeyleri açısından anlamlı fark saptanmadı. Auralı grupta monosit ve MHO değerleri aurasız gruba göre yüksekti. Auralı grupta hsCRP değeri aurasız gruba göre istatistiksel olarak anlamlı düşüktü.
Sonuç: Bu çalışma, migren hastalarında düşük bilirubin ve yüksek NLO, CRP ve ESR değerlerinin potansiyel enflamatuvar marker olabileceğini göstermiştir. Bu markerlar hastalığın patofizyolojisini anlamamıza katkıda bulunabilir. Ayrıca söz konusu testlerin maliyeti ucuz ve yaygın kullanılan tetkikler olduğundan özellikle migren hastalarını olası uzun dönem komorbiditelerden korumak açısından faydalı olabileceği görüşündeyiz.
Anahtar Kelimeler: Migren, enflamasyon, laboratuvar, biyomarker

[1] **Health Sciences University, Istanbul Training and Research Hospital, Clinic of Neurology, Istanbul, Turkey.**
[2] **Sakarya University, Sakarya Training and Research Hospital, Clinic of Neurology, Sakarya, Turkey.**

Ethics Committee Approval: The study wass approved by the local ethical authority.
Etik Kurul Onayı: Çalışma lokal etik komite tarafından onaylanmıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Geliş Tarihi / Received: 10.12.2018
Kabul Tarihi / Accepted: 25.02.2019
Yayın Tarihi / Published: 15.03.2019

Sorumlu yazar / Corresponding author:
Abdulkadir TUNÇ
Adres/Address: Sakarya University, Sakarya Training and Research Hospital, Clinic of Neurology, Sakarya, Turkey
e-posta: drkadirtunc@hotmail.com
Tel/Phone: (+90) 5545144524

Introduction

Migraine is a common, multifactorial primary headache disorder. It is characterized by recurrent throbbing headache, nausea, and sensitivity to stimulants such as sound, light, and movement [1]. The prevalence ranges from 5% to 20% in the general population [2]. Although the pathophysiology is still debatable, it's thought that some peptides (e.g., substance P, calcitonin gene-related peptide, and neurokinin A) are released from the perivascular trigeminal regions after the activation of the brain tissue; that caused inflammation and dilation of the extraparenchymal vessels [3].

Erythrocyte sedimentation rate (ESR) and high sensitivity C-reactive protein (hsCRP) are the most widely used inflammatory markers in current clinical practice [4, 5]. The neutrophil-to-lymphocyte ratio (NLR) was reported to be novel inflammatory biomarkers in patients with Guillain-Barré syndrome and venous thrombosis [6, 7]. Increased monocyte counts and decreased HDL-cholesterol (HDL-C) levels were also found to be associated with inflammation, and monocyte to HDL-C ratio (MHR) was suggested to be used as a potential inflammatory biomarker [8, 9]. A significant relationship was shown between high bilirubin levels and antiinflammation in various diseases [10].

Therefore, in this study we aimed to evaluate ESR, hsCRP, NLR, MHR, and bilirubin levels in patients with migraine and compare with levels measured in healthy subjects. Secondly, their relationship with the presence of aura and cranial magnetic resonance imaging (MRI) findings were evaluated.

Material and methods

This retrospective case-control study included 136 migraine patients and 80 healthy controls aged between 16 and 66 years, who were admitted to our neurology outpatient clinic or emergency between June 2017 and June 2018.

It was approved by our local ethics committee. An informed written consent was taken from all the participants. 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. The inclusion criterion for migraine patients was the diagnosis of migraine according to the International Classification of Headache Disorders III (beta version) (ICHD-III) [11]. Exclusion criterion were as follows: other ICHD-III diagnosis (e.g., tension type headache, cluster headache etc.); pregnancy/puerperium, any systemic diseases, neurological disorders, inflammatory diseases or any other condition that can affect the inflammatory biomarkers, and the patients under medical treatment with any antiinflammatory medications.

The control group was selected among the relatives of the migraine patients, hospital employees, or the general population. Written informed consent was obtained from them for voluntary participation in the study. The inclusion criteria for the control group were as follows: absence of migraine, the maximum frequency of any headache less than 1 episode per month (e.g., tension type headache, or any other type of chronic headache). Exclusion criteria for the healthy controls were the same as those for the migraine patients.

The blood samples were obtained by careful venipuncture during emergency or outpatient clinic admission before medical treatments. Samples for hematological tests were collected in EDTA tubes, and in dry tubes for biochemical tests. The laboratory investigations included serum hemogram, full biochemistry profiles including HDL, bilirubins, hsCRP, and ESR, which were measured using automated standard laboratory methods. Automated hematology analyzer XE–1200 (Sysmex, Kobe, Japan) was used for complete blood count's measurements. A molecular analyzer (Roche Diagnostics, Manheim, Germany) was used for the biochemical measurements. Hs-CRP measurement was done using an automatized analyser (Beckman Coulterw IMMAGE) using nephelometric measurement.

Demographic features, laboratory examinations, disease characteristics, presence of aura, brain MRI findings were recorded. A computerized database was used to collect the laboratory data. NLR and MHR ratios were calculated and compared between the patients and healthy subjects.

Statistical Analysis

The data were transferred into the IBM SPSS Statistics 22.0 program and the analyses were completed. Mean, standard deviation, median, lowest- highest, frequency and ratio were included in the descriptive statistics of the data. The distribution of the variables was measured by the Kolmogorov-Smirnov test. Independent sample t test, and Mann-Whitney U test were used in the analysis of quantitative independent data. A chi-square test was applied to analyze the significance of the multiple comparison of relative frequencies among the groups, and Fischer test was used when chi-square test did not meet the conditions. Spearman correlation analysis was used for correlation analysis. The limit for statistical significance was accepted as $p<0.05$.

Results

The mean age of the case group was 36.9±10.6 years and the control group was 37±12 years. No significant difference was found between the patient and control groups in terms of age and gender. In the patient group, total bilirubin (TB), direct bilirubin (DB), indirect bilirubin (IB) and lymphocyte values were significantly lower than the control group ($p= 0.001$, $p= 0.005$, $p= 0.001$, and $p=0.001$, respectively). NLR, hsCRP, and ESR levels were significantly higher in the patient group ($p= 0.001$, $p= 0.001$, and $p=0.001$, respectively).

The patient and control groups did not show a significant difference according to the presence of white matter hyperintensities (WMHs) ($p= 0.320$) (Table 1). There was no significant difference in terms of age, gender, total bilirubin, direct bilirubin, and indirect bilirubin values, NLR, uric acid, lymphocyte, and ESR levels in patients with and without aura ($p>0.05$). In group with aura (MwA), monocyte and MHR values were higher than those migraine patients without aura (MwoA) ($p= 0.002$, $p= 0.013$). The hsCRP values in the MwA group were significantly lower than the MwoA group ($p= 0.026$) (Table 2).

Discussion

Our study revealed that inflammation may be connected with the pathogenesis of migraine. ESR, hsCRP, and NLR values were significantly higher and bilirubin, and lymphocyte values were significantly lower in migraine patients compared with the healthy subjects in this study. Monocyte and MHR values were higher in MwA patients.

It has been revealed that migraine pathogenesis is strongly related to the neurogenic inflammation [12]. In the literature, it has also been demonstrated that a significant association is detected between migraine and cardiovascular

Table 1. Evaluation of demographic and laboratory findings in migraine patients and healthy controls.

	Controls (n=80)	Patients(n=136)	P
Age (year)[β]	37±12	36.9±10.6	0.823
Gender[¥]			0.140
Female	70 (87.5)	127 (93.4)	
Male	10 (12.5)	9 (6.6)	
Smoking[¥]			0.453
No	69 (86.3)	112 (82.4)	
Yes	11 (13.8)	24 (17.6)	
Alcohol[¥]			0.531
No	80 (100)	134 (98.5)	
Yes	0 (0)	2 (1.5)	
Presence of WMHs[¥]			0.320
No	73 (91.3)	118 (86.8)	
Yes	7 (8.8)	18 (13.2)	
Lesion count (n)[β]	5.86±5.08	4.39±3.93	0.409
Uric Acid (mg/dL)[β]	3.87±0.79	4.05±1.15	0.151
Total Bilirubin (mg/dL)[β]	0.89±0.36	0.60±0.34	0.001
Direct Bilirubin (mg/dL)[β]	0.16±0.07	0.14±0.09	0.005
Indirect Bilirubin (mg/dL)[β]	0.74±0.31	0.46±0.27	0.001
Neutrophil count ($\times10^3/\mu l$)[β]	4.12±1.30	4.27±1.46	0.697
Lymphocyte count ($\times10^3/\mu l$)[β]	2.66±0.71	2.26±0.67	0.001
Monocyte count ($\times10^3/\mu l$)[β]	0.52±0.16	0.50±0.18	0.252
Neutrophil/Lymphocyte[β]	0.61±0.69	2.16±2.15	0.001
Monocyte/HDL[β]	0.011±0.004	0.01±0.004	0.080
hsCRP (mg/L)[β]	0.34±0.23	0.58±0.41	0.001
HDL(mg/L)[β]	50.5±12.7	53.1±11.6	0.072
ESR (mm/h)[β]	14.0±8.2	20.5±10.2	0.001

[¥]: n (%), [β:] Mean±standard deviation
ESR: Erythrocyte sedimentation rate; HDL: High density lipoprotein; hsCRP: High sensitivity C-reactive protein; WMHs: White matter hyperintensities.

disease, stroke, and atherosclerosis, and a causal link has been put forward between migraine attacks and inflammatory arteriopathy of the brain vessels [13, 14]. Emerging evidences about the migraine pathogenesis showed that several cytokines mainly IL-6, TNF, and IL-10 are involved, wherein sensitization of nerve endings can be promoted by these inflammatory cytokines during recurrent migraine attacks [15, 16]. Moreover, increased CRP values have been demonstrated to be related to migraine, and have been considered to be an inflammatory marker in migraine patients [17]. Consistent with these studies, our study revealed an increased serum concentration of ESR and hsCRP levels in patients with migraine compared with healthy individuals.

Interestingly, lower levels of TB, DB, and IB were found in migraine patients, and a negative correlation between CRP and bilirubin levels was detected in a study of Peng et al [18]. In another earlier trial, serum bilirubin was exhibited an antiinflammatory property and was shown to be stronger than other antioxidants [19]. In support of this, our study observed lower bilirubin levels in migraine patients. An overconsumption of bilirubin by neurogenic inflammation may be responsible from these physiological phenomenon.

The NLR is a simply calculated biomarker from the lymphocyte and neutrophil counts in the venous blood samples. It was investigated in several studies and elevated levels were shown to be important biomarker in coronary artery diseases [20, 21]. The role of MHR in predicting inflammation has been demonstrated by limited number of studies [22, 23]. It has been shown to be an independent predictor of cardiovascular events in chronic renal failure patients and poor prognosis for cardiovascular mortality [9]. Our study showed higher levels of NLR in migraine patients. On the other hand, monocyte and MHR values were significantly higher in MwA patients. In the literature, some inflammatory biomarkers such as high leptin, Soluble urokinase plasminogen activator receptor, apolipoprotein E, and CRP levels were found to be increased in MwA patients supporting the inflammatory hypothesis [24-27]. Further studies with serum markers and inflammatory citokines are needed to evaluate the possible relationship.

Table 2. Evaluation of demographic and laboratory findings of the MwA and MwoA patients.

	Aura (-) (n=95)	Aura (+) (n=41)	P
Age(mean±sd)	36.4±10.2	38.1±11.5	0.413
Gender[¥]			0.198
Female	87 (91.6)	40 (97.6)	
Male	8 (8.4)	1 (2.4)	
Smoking[¥]			0.908
No	78 (82.1)	34 (82.9)	
Yes	17 (17.9)	7 (17.1)	
Alcohol[¥]			1.000
No	93 (97.9)	41 (100)	
Yes	2 (2.1)	0 (0)	
Presence of WMHs[¥]			0.356
No	84 (88.4)	34 (82.9)	
Yes	11 (11.6)	7 (17.1)	
Lesion count[β]	4.45±4.13	4.29±3.90	0.963
Right Localisation[¥]	32 (33.7)	16 (39)	
Left localisation[¥]	21 (22.1)	7 (17.1)	0.747
Bilateral localisation[¥]	42 (44.2)	18 (43.9)	
Migraine duration, (year)[β]	7.3±4.8	6.8±6.6	0.161
Attack frequency, (month)[β]	3.6±2.5	4.1±3.4	0.814
Attack duration, (hour)[β]	14.6±15.3	28.0±22.6	0.002
Uric Acid (mg/dL)[β]	4.00±1.04	4.15±1.36	0.699
Total Bilirubin (mg/dL)[β]	0.60±0.34	0.58±0.33	0.368
Direct Bilirubin (mg/dL)[β]	0.15±0.10	0.12±0.06	0.089
Indirect Bilirubin (mg/dL)[β]	0.46±0.27	0.46±0.27	0.608
Neutrophil count ($\times10^3/\mu l$)[β]	4.19±1.52	4.46±1.30	0.111
Lymphocyte count ($\times10^3/\mu l$)[β]	2.22±0.68	2.36±0.62	0.279
Monocyte count ($\times10^3/\mu l$)[β]	0.47±0.14	0.58±0.21	0.002
Neutrophil/Lymphocyte[β]	2.21±2.51	2.03±0.88	0.676
Monocyte/HDL[β]	0.009±0.004	0.012±0.005	0.013
hsCRP (mg/L)[β]	0.63±0.41	0.48±0.40	0.026
HDL (mg/L)[β]	53.0±11.2	53.4±12.7	0.917
ESR (mm/h)[β]	21.6±10.6	18.0±9.0	0.064

[¥]: n (%), [β:] Mean±standard deviation
ESR: Erythrocyte sedimentation rate; HDL: High density lipoprotein; hsCRP: High sensitivity C-reactive protein; WMHs: White matter hyperintensities.

An association between MwA and WMHs was shown in most of the previous studies [28, 29]. Contrary, there was no significant differences in terms of presence and number of WMHs between migraine patients and healthy controls. That might be due to low number of patients in our study.

Our study had some limitations. First, the number of patients were relatively low. Second, the correlation between evaluated serum markers and inflammatory cytokines such as IL-6, IL-10, and TNF were not analyzed. It was unclear whether these biomarkers and systemic inflammation had a causative relationship. Third, body mass index and disease duration were not evaluated, and finally, evaluation of oxidative stress biomarkers would be more precious.

This study showed that low bilirubin and high NLR, MHR, hsCRP, and ESR values might be potential inflammatory markers in migraine patients. These markers may contribute to our understanding of the pathophysiology of migraine. In addition, since the cost of these tests is cheap and they are widely used, it is possible to believe that they may be useful for protecting migraine patients against long-term comorbidities.

References

1. Burstein R, Noseda R, Borsook D. Migraine: multiple processes, complex pathophysiology. J Neurosci. 2015;35:6619-29.
2. Lipton RB, Bigal ME. Migraine: epidemiology, impact, and risk factors for progression. Headache. 2005;45:3-13.
3. Sinclair AJ, Matharu M. Migraine, cerebrovascular disease and the metabolic syndrome. Ann Indian Acad Neurol. 2012;15:72-7.
4. Nagai M, Terao S, Yilmaz G, Yilmaz CE, Esmon CT, Watanabe E, et al. Roles of inflammation and the activated protein C pathway in the brain edema associated with cerebral venous sinus thrombosis. Stroke. 2010;41:147-52.

5. Ammirati E, Moroni F, Norata GD, Magnoni M, Camici PG. Markers of inflammation associated with plaque progression and instability in patients with carotid atherosclerosis. Mediators Inflamm. 2015;2015:718329.
6. Ozdemir HH. Analysis of the albumin level, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio in Guillain-Barré syndrome. Arq Neuropsiquiatr. 2016;74:718-22.
7. Artoni A, Abbattista M, Bucciarelli P, Gianniello F, Scalambrino E, Pappalardo E, et al. Platelet to Lymphocyte Ratio and Neutrophil to Lymphocyte Ratio as Risk Factors for Venous Thrombosis. Clin Appl Thromb Hemost. 2018;24:808-14.
8. Çiçek G, Kundi H, Bozbay M, Yayla C, Uyarel H. The relationship between admission monocyte HDL-C ratio with short-term and long-term mortality among STEMI patients treated with successful primary PCI. Coron Artery Dis. 2016;27:176-84.
9. Kanbay M, Solak Y, Unal HU, Kurt YG, Gok M, Cetinkaya H, et al. Monocyte count/HDL cholesterol ratio and cardiovascular events in patients with chronic kidney disease. Int Urol Nephrol. 2014;46:1619-25.
10. Kapitulnik J. Bilirubin: An endogenous product of heme degradation with both cytotoxic and cytoprotective properties. Mol Pharmacol. 2004;66:773–9.
11. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders: 3rd edition (beta version). Cephalalgia. 2013;33:629-808.
12. Spierings EL. Pathogenesis of the migraine attack. Clin J Pain 2003;19:255-62.
13. Yetkin E, Ozisik H, Ozcan C, Aksoy Y, Turhan H. Decreased endothelium-dependent vasodilatation in patients with migraine: A new aspect to vascular pathophysiology of migraine. Coron Artery Dis 2006;17:29-33.
14. Avci AY, Lakadamyali H, Arikan S, Benli US, Kilinc M. High sensitivity C-reactive protein and cerebral white matter hyperintensities on magnetic resonance imaging in migraine patients. J Headache Pain. 2015;16:9.
15. Wang F, He Q, Ren Z, Li F, Chen W, Lin X, et al.Association of serum levels of intercellular adhesion molecule-1 and interleukin-6 with migraine. Neurol Sci. 2015;36:535-40.
16. Liu R, Ma M, Cui M, Dong Z, Wang X, Zhang W, et al. Effects of tumor necrosis factor-β (TNF-β) 252A>G polymorphism on the development of migraine: a meta-analysis. PLoS One. 2014;9:e100189.
17. Lippi G, Mattiuzzi C, Cervellin G. C- reactive protein and migraine. Facts or speculations? Clin Chem Lab Med. 2014;52:1265-72.
18. Peng YF, Xie LQ, Xiang Y, Xu GD. Serum Bilirubin and Their Association With C-Reactive Protein in Patients With Migraine. J Clin Lab Anal. 2016;30:982-5.
19. Stocker R, Yamamoto Y, McDonagh AF, Glazer AN, Ames BN. Bilirubin is an antioxidant of possible physiological importance. Science. 1987;235:1043-6.
20. Nunez J, Nunez E, Bodi V, Sanchis J, Miñana G, Mainar L, et al. Usefulness of the neutrophil to lymphocyte ratio in predicting long-term mortality in ST segment elevation myocardial infarction. Am J Cardiol. 2008;101:747–52.
21. Yuksel M, Yildiz A, Oylumlu M, Akyüz A, Aydın M, Kaya H, et al. The association between platelet/lymphocyte ratio and coronary artery disease severity. Anatol J Cardiol. 2015;15:640-7.
22. Rezende SM, Lijfering WM, Rosendaal FR, Cannegieter SC. Hematologic variables and venous thrombosis: red cell distribution width and blood monocyte count are associated with an increased risk. Haematologica. 2014;99:194-200.
23. Efe TH, Arslan ED, Ertem AG, Yayla Ç, Felekoğlu MA, İnci S, et al. The prognostic value of the monocyte/hdl ratio in predicting short-term mortality in patients with acute pulmonary embolism. Koşuyolu Heart Journal. 2016;19:149-53.
24. Pisanu C, Preisig M, Castelao E, Glaus J, Cunningham JL, Del Zompo M, et al. High leptin levels are associated with migraine with aura. Cephalalgia. 2017;37:435-41.
25. Yılmaz N, Yılmaz M, Sirin B, Yılmaztekin S, Kutlu G. The relationship between levels of plasma-soluble urokinase plasminogen activator receptor (suPAR) and presence of migraine attack and aura. J Recept Signal Transduct Res. 2017;37:447-52.
26. Yuasa N, Nagata E, Fujii N, Ito M, Tsukamoto H, Takizawa S. Serum apolipoprotein E may be a novel biomarker of migraine. PLoS One. 2018;13:e0190620.
27. Lippi G, Mattiuzzi C, Cervellin G. C-reactive protein and migraine. Facts or speculations? Clin Chem Lab Med. 2014;52:1265-72.
28. Tunç A, Tekeşin AK, Güngen BD, Arda E. Cognitive performance in young and middle-aged adults with migraine: Investigating the correlation with white matter hyperintensities and psychological symptoms. Neurol Neurochir Pol. 2018;52:470-6.
29. Bashir A, Lipton RB, Ashina S, Ashina M. Migraine and structural changes in the brain: a systematic review and meta-analysis. Neurology. 2013;81:1260-8.

Arch Clin Exp Med 2019;4(1):41-44. e-ISSN: 2564-6567

DOI:10.25000/acem.494922 Araştırma makalesi / Research article

Investigation of the effect of hearing aid on hearing disability in elderly people with presbycusis

İşitme cihazının presbiakuzili yaşlılarda işitme engelliliğine olan etkisinin araştırılması

Süha Ertuğrul [1], Emre Söylemez [2]

Abstract

Aim: To determine the effect of hearing aid on the level of hearing disability in elderly patients with presbycusis.

Methods: A hearing handicap inventory scale (HHI) was applied to 43 patients with presbycusis over the age of 65 years (mean age: 73.44 ± 7.03 years, range: 65-89 years, male: 26, female: 17) six months before using the hearing aid and 6 months after starting to use the hearing aid. HHI scores were compared before and after hearing aid.

Results: HHI scores (22.51 ± 14.81) after hearing aid use were significantly lower compared to HHI scores before hearing aid (68.97 ± 16.97) (p=0.000). There was no significant difference between HHI score gains obtained after hearing aids according to gender (p=0.737). There was no significant difference between HHI score gains obtained after hearing aids in patients with profound and severe hearing loss and the scores of the patients with moderate and moderate to severe hearing loss (p=0.521).

Conclusion: The hearing aid significantly reduces the level of auditory disability in elderly individuals.

Keywords: Hearing handicap inventory scale, hearing aid, hearing loss, presbycusis, sensorineural, elderly.

Öz

Amaç: Presbiakuzili yaşlı hastalarda işitme cihazının işitsel engellilik seviyesine olan etkisini saptamaktır.

Yöntemler: 65 yaş üstü presbiakuzili 43 hastaya (ortalama yaş: 73.44 ± 7.03 yıl (aralık 65-89 yıl), erkek:26, kadın:17) işitme cihazı kullanmadan önce ve işitme cihazı kullanmaya başladıktan 6 ay sonra işitme engeli envanteri ölçeği (hearing handicap inventory scale-HHI) uygulandı. İşitme cihazı öncesi ve sonrası HHI skorları karşılaştırıldı.

Bulgular: İşitme cihazı kullanımı sonrası HHI skorları (22.51 ± 14.81), işitme cihazı öncesi HHI skorlarına (68.97 ± 16.97) göre anlamlı derecede düşüktü (p=0.000). Cinsiyetlere göre, hastaların işitme cihazı sonrası elde edilen HHI skor kazançları arasında anlamlı fark yoktu (p=0.737). Derin ve ileri işitme kaybı ile orta ve orta ileri işitme kayıpları bulunan hastaların, işitme cihazı sonrası elde edilen HHI skor kazançları arasında anlamlı bir fark yoktu (p=0.521).

Sonuç: İşitme cihazı, yaşlı bireylerde işitsel engellilik düzeyini önemli derece düşürmektedir.

Anahtar Kelimeler: İşitsel engellilik envanter skalası, işitme cihazı, işitme kaybı, presbiakuzi, sensorionöral, yaşlı.

[1] Karabuk University, Faculty of Medicine, Department of Otorhinolaryngology, Karabuk, Turkey.

[2] Karabuk University, Faculty of Medicine, Department of Audiology, Karabuk, Turkey.

Ethics Committee Approval: The study wass approved by the local ethical authority.

Etik Kurul Onayı: Çalışma lokal etik komite tarafından onaylanmıştır.

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

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Geliş Tarihi / Received: 11.12.2018

Kabul Tarihi / Accepted: 26.02.2019

Yayın Tarihi / Published: 15.03.2019

Sorumlu yazar / Corresponding author:

Süha Ertuğrul

Adres/Address: Sirinevler mahallesi, Alpaslan caddesi, no:1, Postal code: 78200. Merkez, Karabuk, Turkey

e-posta: drsuhaertugrul@hotmail.com

Tel/Phone: (+90) 03704125628

Introduction

Sensorineural hearing loss (SNHL) may occur in many conditions such as maternal diseases and drugs used in the intrauterine period, genetic factors, premature birth, ototoxicity, exposure to high-intensity noise and aging. Having so many risk factors for SNHL makes it one of the most common health problems. SNHL can cause many problems such as tinnitus, anxiety, depression and decrease in quality of life in addition to communication problems [1].

Aging is continuous and irreversible changes emerge in tissues and organs with aging. The increase in average life expectancy and the increase in the elderly population also increased the number of individuals with hearing loss [2]. The elderly hearing loss is called presbycusis [3]. In presbycusis, hearing loss is bilateral, symmetrical, progressive and sensorineural. Hearing loss usually occurs at high frequencies and other frequencies get affected over time [4, 5]. Genetic factors and environmental conditions are effective in the emergence and progression of presbycusis [6]. In addition to presbycusis, elderly people may have conductive and mixed type hearing loss [3]. In this case, the treatment modalities of hearing loss may also change. There is no medical or surgical treatment of presbycusis. The only treatment is a suitable hearing aid (HA). The use of hearing aids in individuals with presbycusis in the early stage may stop the progression of SNHL. In addition, early use of hearing aids can also prevent cognitive impairment and psychological problems [7]. Approximately, 40% of the individuals, on whom HA applied, stop using HA due to psychological problems or cognitive impairment by thinking that they do not benefit from it [8, 9]. Therefore, it is recommended that patients with presbycusis be diagnosed in the early stage and start using hearing aid early. However, there is resistance and prejudice against the early use of hearing aids in our country. For this reason, many patients in our country prefer to use hearing aids when they have a severe hearing loss.

In this study, we aimed to determine whether the hearing aid had an effect on hearing disability level in the elderly patients with presbycusis.

Material and methods

Patient selection

In this prospective study, patients admitted to the otorhinolaryngology outpatient clinic with complaints of hearing loss between February 2018 and April 2018 were evaluated. After the detailed history of all patients, ear-nose-throat examinations were performed. Patients aged 65 years and over, whose otoscopy examination was evaluated as normal, who had no acute or chronic infectious disease, have not undergone any ear surgery, have never previously used hearing aids, were diagnosed with presbycusis and in who have SNHL as bilateral 35 dB or more, were included in the study. The patients who have previously used hearing aids, patients who had ear surgery, patients under 65 years old, patients with unilateral SNHL, patients with conductive or mixed type hearing loss were excluded from the study. Patients who did not have Tip A tympanograms were also excluded from the study. Sixty patients who met the inclusion and exclusion criteria were recommended a digital programmable postauricular hearing aid. It has been planned to apply hearing handicap inventory scale (HHI) (Table 1) to the patients before the hearing aid and six months after the patient started to use the device. Although hearing aid was recommended, patients who did not use hearing aids and patients who did not come for follow-up at the sixth month were excluded from the study. As a result, the study was completed with 43 patients.

The working protocol was prepared in accordance with the principles set out in the Helsinki Declaration. An approval was received from the clinical research ethics committee within our university (2018-6/8). Written informed consent was obtained from all patients.

Table 1. Hearing Handicap Inventory Scale.

Question		Yes	Sometimes	No
1S	Does your difficulty in hearing bring you problems when using the telephone?			
2E	Does a hearing problem cause you to feel embarrassed when meeting new people?			
3S	Does a hearing problem cause you to avoid groups of people?			
4E	Does a hearing problem make you irritable?			
5E	Does a hearing problem cause you to feel frustrated when talking to members of your family?			
6S	Does a hearing problem cause you difficulty when attending a party?			
7S	Does a hearing problem cause you to feel frustrated when talking to co-workers, clients, or customers?			
8E	Does a hearing problem cause you difficulty when going to the cinema or theater?			
9S	Do you feel handicapped by a hearing problem?			
10E	Does a hearing problem cause you difficulty when visiting friends, relatives, or neighbors?			
11S	Does a hearing problem cause you tdifficulty to listen/understand co-workers?			
12E	Does a hearing problem cause you to be nervous?			
13S	Does a hearing problem cause you to visit friends, relatives, or neighbors less often than you would like?			
14E	Does a hearing problem cause you to have arguments with family members?			
15S	Does a hearing problem cause you difficulty when listening to TV or radio Does a hearing problem cause you difficulty when listening to TV or radio?			
16S	Does a hearing problem cause you to go shopping less often than you would like?			
17E	Does any problem or difficulty with your hearing upset you at all?			
18E	Does a hearing problem cause you to want to be by yourself?			
19S	Does a hearing problem cause you to talk to family members less often than you would like?			
20E	Do you feel that any difficulty with your hearing limits or hampers your personal or social life?			
21S	Does a hearing problem cause you difficulty when in a restaurant with relatives or friends?			
22E	Does a hearing problem cause you to feel depressed?			
23S	Does a hearing problem cause you to listen to TV or radio less often than you would like?			
24E	Does a hearing problem cause you to feel uncomfortable when talking to friends?			
25E	Does a hearing problem cause you to feel left out when you are with a group of people?			

Total score:_____ E Score:_____ S score:_____

Assessment of hearing

All audiological tests were performed by the authors. Clinical audiometry device (AC 40, DK-500; Interacoustics, Middelfart, Denmark) was used to evaluate the hearing levels. Pure-tone air conduction hearing threshold values of patients were measured at frequencies of 125 Hz, 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, 6000 Hz, and 8000 Hz. Pure-tone bone conduction hearing threshold values of the patients were measured at frequencies of 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz. Speech recognition threshold (SRT) and speech recognition

score (SRS) tests were performed. The pure tone average (PTA) was calculated by taking the average of hearing thresholds at frequencies of 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz. According to PTA results, the degree of hearing loss was considered to be mild (26 dB to 40 dB), moderate (41 dB to 55 dB), moderate to severe (56 dB to 70 dB), severe (71 dB to 90 dB) and profound (91 dB and above). Tympanometry measurement was performed with the impedance audiometer (AZ 26; Interacoustics, Middelfart, Denmark) in 226 Hz octave band by using 86 dB SPL probe tone stimulation. Type A tympanogram was accepted as normal.

Hearing Handicap Inventory Scale

HHI consists of 25 questions. 12 of these questions contain information about the social situation and 13 of them contain about emotional status [10]. Every question includes three options as yes (4 points), sometimes (2 points) and no (0 points) and the total score is evaluated over 100 points. Total score; 0-16 points were considered as no handicap, 18-42 points as a mild to moderate handicap and 44-100 points as a significant handicap.

Social, emotional and total HHI scores were compared before the use of hearing aid and at the sixth month of use. HHI score gains obtained by patients after HA were compared according to gender. HHI score gains were compared between the patients with severe and profound hearing loss and the patients with moderate and moderate to severe hearing loss.

Statistical Analysis

As a statistical method, SPSS version 21 (SPSS software, SPSS Inc., Chicago, IL, USA) was used. Percent, mean, standard deviation (SD), median, minimum and maximum values were presented for descriptive statistics. A Paired t-test was used to evaluate the difference between HHI scores before the using HA and the HHI scores that were applied at the sixth month of the HA use. Student's T-test was used to compare the HHI score gains obtained by the patients after HA according to the test. Student's T-test was used to compare HHI score gains that severe and profound hearing loss patients and patients with moderate and moderate to severe hearing loss obtained after HA. P value as <0.05 was considered statistically significant.

Results

Of the 43 patients included in the study, 17 (39.5%) were female and 26 (60.5%) were male. The mean age was 73.44 ± 7.03 years (range, 65-89 years). HA was provided to the left ear of 23 patients (53.4%) and the right ear of 20 patients (56.6%). The results of PTA, SRT, and SRS before using the hearing aids on the right and left ears of the patients are given in Table 2. Fourteen of the patients (32.5%) had moderate hearing loss, 16 (37.2%) had moderate to severe, 11 (25.5%) were severe and two (4.6%) had profound hearing loss. Forty-one patients (95.3%) had a significant handicap and two patients (4.7%) had mild to moderate handicap according to HHI scores before using HA. According to the HHI scores applied at the six months after the use of HA, the auditory disability was completely disappeared in 17 patients (39.5%), 22 patients (51.2%) had a mild to moderate handicap and four patients (9.3%) had a significant handicap. After using hearing aids, the emotional, social and total HHI scores of women and men were significantly decreased (p=0.001) (Table 3). There was no significant difference between the gains in HHI score of the patients according to gender (p=0.737). There was no significant difference between the HHI score gains obtained after HA in patients with the profound and severe hearing loss and the scores of the patients with moderate and moderate to severe hearing loss (p=0.521).

Table 2. Pure tone averages, speech receiving threshold values and speech discrimination rates of the patients before use of the hearing aid in the right and the left ear.

Variable	Right ear		Left ear	
	Mean ± SD	Min-Max	Mean ± SD	Min-Max
PTA (dB nHL)	64.65 ± 17.14	30-113	65.58 ± 15.92	45-112
SRT (dB nHL)	61.04 ± 16.53	30-100	60.69 ± 14.62	40-100
SRS (%)	59.58 ± 23.59	0-96	58.55 ± 24.84	0-96

PTA: pure tone averages, SRT: speech recognition threshold, SRS: speech recognition scores, SD: standart deviation, Min: minimum, Max: maximum.

Table 3. HHI scores of the patients before using the hearing aid and 6 months after.

Variable	Before HA		After HA		P
	Mean ± SD	Min-Max	Mean ± SD	Min-Max	
Total HHI Score	68.97 ± 16.97	20-96	22.51 ± 14.81	0-60	0.001
Male	69.07 ± 18.26	20-96	23.00 ± 16.33	0-60	
Female	68.82 ± 15.34	38-88	21.76 ± 12.56	6-52	
Total emotional score	33.90 ± 12.54	12-54	10.72 ± 6.94	0-24	0.001
Male	34.00 ± 9.74	12-48	11.07 ± 8.06	0-24	
Female	33.76 ± 11.02	18-54	10.23 ± 4.94	4-20	
Total social score	35.06 ± 9.32	8-52	11.76 ± 8.92	0-40	0.001
Male	35.07 ± 10.26	8-52	11.92 ± 9.55	0-40	
Female	35.05 ± 7.97	20-44	11.52 ± 8.14	0-32	

HHI: hearing handicap inventory scale, HA: hearing aid, SD: standart deviation, Min: minimum, Max: maximum.

Discussion

As it affects the whole body, aging also affects the Corti organ, the auditory nerve, and the auditory cortex. Cell aging in the auditory pathway leads to SNHL, which is defined as presbycusis. Presbycusis causes difficulty in understanding the conversations, decreasing verbal communication skills, negatively affecting social lives and decreasing quality of life [3, 6, 11]. There are many questionnaires evaluating health quality and satisfaction level of patients using hearing aids. Glasgow Hearing Aid Benefit Profile, The Speech, Spatial and Qualities of Hearing Scale, Hearing Aid Performance Questionnaire, Satisfaction with Amplification in Daily Life, Abbreviated Profile of Hearing Aid Benefit and International Outcome Inventory for Hearing Aids are some of those. In our study, we wanted to investigate the effect of hearing aid on auditory disability rather than its effect on patient satisfaction. For this reason, we chose the HHI scale, which contains easy to understandable questions for the Turkish people.

In our study, we have found that the use of HA significantly decreases the level of social and emotional disability in elderly individuals with presbycusis. However, there was no difference in terms of the benefit that men and women with presbycusis gained from HA. In some studies, it has been reported that there is no relationship between gender and hearing aid satisfaction [12-15]. According to the studies evaluating the relationship between age and hearing aid satisfaction, different results are obtained in the literature. Many studies have found that age does not affect hearing aid satisfaction [12, 15-17]. In some studies, young elderly people were found to be more satisfied with hearing aids than older ones [18, 19]. Korkmaz et al. [20] found that the satisfaction of hearing devices decreased in advanced ages. They also stated that there is an overall

decrease in general life satisfaction due to activity limitations and increased systemic problems with advanced ages [20].

In the literature, there are many studies suggesting that the HA improves quality of life and reduces hearing disability rates [3, 21]. In the study conducted on Iranian people, Lotfi et al. [3] reported that HA improved quality of life. In their study, they applied HHI scale before and 3 months after the use of HA and found that the total HHI score decreased from 65 to 22. Vuorialho et al. [21], in their study in Finland, applied the HHI scale before the use of the hearing aid and 6 months after the use of the device and found that HHI scores decreased from 28.7 to 12.7. In our study, we also performed HHI 6 months after the patients started to use HA for the realization of auditory adaptation similar to Vuorialho et al. [21]. In our study, HHI scores performed before HA were high as in the study Lotfi et al. [3] conducted. However, in the study conducted in Finland [21], the pre-HA HHI scores were significantly lower compared to the scores both in our study and the study by Lotfi et al. [3] conducted. The reasons for such a difference between societies according to HHI scores are due to the socio-cultural differences and economic reasons. These results may be indicative of the fact that patients in advanced western countries, such as Finland, have begun to use hearing aids without increasing the level of hearing disability.

In some studies, it has been reported that hearing loss does not only affect individuals with presbycusis, but also adversely affects families and close friends [6, 21]. In our study question, #14 (Does your hearing loss cause you to argue with your family members?) was one of the questions receiving the highest scoring (not shown data). Elderly individuals with having arguments with the families or close environment can cause them to be more withdrawn and lead to social isolation. In addition, one of the biggest problems experienced by the patients in our study was to listen to the radio or television which was questioned on the HHI scale by #15 question (not shown data). Elderly people may be more directed towards television and radio, but because they do not fully understand the television and radio, dissatisfaction and unhappiness may be increasing.

HA is an important and effective rehabilitation method for moderate and moderate to severe hearing loss, and it can be recommended as a preventive method for patients with mild hearing loss [22, 23]. It has been stated that the fitting setting of the hearing aid changes the use and effect of the device [21]. Magni et al. [24] investigated the effectiveness of analog and digital hearing aids. They stated that devices with different features had differed from the benefits provided to the individuals, however, the patients benefited from both devices. In our study, all individuals were using digital and postauricular programmable HA. In addition, although HA is an effective rehabilitation method for moderate and moderate to severe hearing loss, in our study, it was found that individuals with severe and profound hearing loss also benefited from HA. With the developing HA technology and HA fitting experience, we think that hearing aids may be recommended for more severe and profound hearing loss in the future.

The limitations of our study were low patient population and lack of speech recognition scores with hearing aids.

As a conclusion, HA is an effective treatment for the rehabilitation of elderly individuals with presbycusis. HA reduces auditory disability in patients with moderate, moderate to severe, severe and profound hearing loss and significantly increase these individuals' social and emotional life quality emerging due to hearing loss.

References

1. Dalton DS, Cruickshanks KJ, Klein BE, Klein R, Wiley TL, Nondahl DM. The impact of hearing loss on quality of life in older adults. Gerontologist. 2003;43:661-8.
2. Byun YS, Kim SS, Park SH, Park EB, Kim HJ, Kim SH, et al. Characteristics of patients with hearing aids according to the degree and pattern of hearing loss. J Audiol Otol. 2016;20:146-52.
3. Lotfi Y, Mehrkian S, Moossavi A, Faghih-Zadeh S. Quality of life improvement in hearing-impaired elderly people after wearing a hearing aid, Arch Iran Med. 2009;12:365-70.
4. Crispim KGM, Ferreira AP. Prevalence of self-reported hearing loss and associated risk factors among the elderly in Manaus: a population-based study. Rev CEFAC. 2015;17:1946-56.
5. Paiva KM, Cesar CL, Alves MC, Barros MB, Carandina L, Goldbaum M. Aging and self-reported hearing loss: a population-based study. Cad Saude Publica. 2011;27:1292-300.
6. Fischer N, Weber B, Riechelmann H. Presbycusis - age related hearing loss. Laryngorhinootologie. 2016;95:497-510.
7. Carniel CZ, Sousa JCF, Silva CDD, Fortunato-Queiroz CAU, Hyppolito MÂ, Santos PLD. Implications of using the hearing aids on quality of life of elderly. Codas. 2017;29:e20160241.
8. Smeeth L, Fletcher AE, Ng ES, Stirling S, Nunes M, Breeze E, et al. Reduced hearing, ownership, and use of hearing aids in elderly people in the UK – the MRC trial of the assessment and management of older people in the community: a cross-sectional survey. Lancet. 2002;359:1466-70.
9. Rutman D, Boisseau B. Acquired hearing loss: social and psychological issues and adjustment processes. Int J Rehabil Res. 1995;18:313-23.
10. Weinstein BE, Ventry IM. Audiometric correlations of the Hearing Handicap Inventory for the elderly. J Speech Hear Disord. 1983;48:379-84.
11. Veras RP, Mattos LC. Audiology and aging: literature review and current. Braz J Otorhinolaryngol. 2007;73:122-8.
12. Uriarte M, Denzin L, Dunstan A, Sellars J, Hickson L. Measuring hearing aid outcomes using the Satisfaction with Amplification in Daily Life (SADL) questionnaire: Australian data. J Am Acad Audiol. 2015;16:383-402.
13. Wong LL, Hickson L, McPherson B. Hearing aid satisfaction: what does research from the past 20 years say? Trends Amplif. 2003;7:117-61.
14. Knudsen LV, Oberg M, Nielsen C, Naylor G, Kramer SE. Factors influencing help seeking, hearing aid uptake, hearing aid use and satisfaction with hearing aids: a review of the literature. Trends Amplif. 2010;14:127-54.
15. Jerram JCK, Purdy SC. Technology, expectations, and adjustment to hearing loss: predictors of hearing aid outcome. J Am Acad Audiol. 2001;12:64-79.
16. Chang WH, Tseng HC, Chao TK, Hsu CJ, Liu TC. Measurement of hearing aid outcome in the elderly: comparison between young and old elderly. Otolaryngol Head Neck Surg. 2008;138:730-34.
17. Brooks DN, Hallam RS. Attitudes to hearing difficulty and hearing aids and the outcome of audiological rehabilitation. Br J Audiol. 1998;32:217-26.
18. Mulrow CD, Tuley MR, Aguilar C. Correlates of successful hearing aid use in older adults. Ear Hear.1992; 13:108-13.
19. Hosford-Dunn H, Halpern J. Clinical application of the SADL scale in private practice II: predictive validity of fitting variables. Satisfaction with amplification in daily life. J Am Acad Audiol. 2001;12:15-36.
20. Korkmaz MH, Bayır O, Er S, Isık E, Saylam G, Tatar EC, et al. Satisfaction and compliance of adult patients using hearing aid and evaluation of factors affecting them. Eur Arch Otorhinolaryngol. 2016;273:3723-32.
21. Vuorialho A, Karinen P, Sorri M. Effect of hearing aids on hearing disability and quality of life in the elderly. Int J Audiol. 2006;45:400-5.
22. Choi J, Chung WH. Age-related hearing loss and the effects of hearing aids. J Korean Med Assoc. 2011;54:918-24.
23. Chang YS, Choi J, Park GY, Youm HY, Byun HY, Cho YS. Evaluation of satisfaction with hearing aids using a questionnaire based on markeTrak survey. Korean J Otorhinolaryngol-Head Neck Surg. 2014;57:304-13.
24. Magni C, Freiberger F, Tonn K. Evaluation of satisfaction measures of analog and digital hearing aid users. Braz J Otorhinolaryngol. 2005;71:650-7.

Arch Clin Exp Med 2019;4(1):45-48. e-ISSN: 2564-6567

DOI:10.25000/acem.531385 Araştırma makalesi / Research article

Retrospective analysis of risk factors for development of biliary fistula after liver cyst hydatid surgery

Karaciğer hidatik kist cerrahisi sonrası oluşan safra fistülünün gelişimindeki risk faktörlerinin retrospektif analizi

Emin Köse[1], Nilay Tuğba Baz[1], Deniz Tazeoğlu[1], Mehmet Emin Gürbüz[1], Hasan Tok[1], Ayhan Özsoy[1], Servet Rüştü Karahan[1]

Abstract

Aim: Hepatic hydatidosis is common parasitosis in Turkey and caused by Echinococcus granulosus. Biliary fistula is the most common complication after liver hydatid cyst surgery. The aim of this study was to investigate an appropriate treatment strategy for patients whose biliary fistula might develop, by revealing variables that affect biliary fistula.

Methods: A total of 118 patients who underwent liver hydatid cyst surgery were included in this study. The following variables were analyzed between patients with biliary fistula (group 2) and without fistula (group 1): Age, gender, hematologic and liver function tests, and features of the cysts (type, cyst size, number, and localization).

Results: Cystobiliary fistula was detected in 19 (16%) of 118 patients. In-group 2, cyst size, white blood cell, alkaline phosphatase and g-Glutamyl transpeptidase levels were higher than group 1 on univariate analysis (p=0.03, p=0.008, p=0.04 and p=0.001, respectively). In the multivariate model, only cyst diameter remained as an independent predictor (odds ratio 0.03, 95% confidence interval 0.002 to 0.06; p=0.03) On the receiver operating characteristic curve, the 100% sensitive, 100% specific, and optimal cutoffs of the cyst diameter were 7.5 cm, 4.0 cm and14.6 cm, respectively (The area under the receiver operator characteristic curve was 0.67).

Conclusion: Preoperative cyst size is a valuable parameter for predicting biliary fistula. Our study suggests that cyst size greater than 7.5 cm is a risk factor for biliary fistula.

Key words: Hydatid liver disease, cystobiliary fistula, Echinococcus granulosus

Öz

Amaç: Karaciğer hidatik kist hastalığı Echinococcus granulosus'un neden olduğu, Türkiye'de yaygın görülen bir parazitozdur. Karaciğer kist hidatik cerrahisi sonrası en sık gelişen komplikasyon safra fistülüdür. Bu çalışmadaki amacımız safra fistülü gelişimini etkileyen değişkenleri ortaya koymak ve uygun tedavi seçeneklerini incelemektir.

Yöntemler: Bu çalışmaya karaciğer kist hidatik cerrahisi uygulanmış olan 118 hasta dahil edildi. Hastalar safra fistülü gelişen (grup2) ve gelişmeyen (grup1) olarak iki gruba ayrıldı ve değişkenler analiz edildi: yaş, hematolojik ve karaciğer fonksiyon testleri ve kistin özellikleri (tip, kist boyutu, sayısı ve yerleşim yeri).

Bulgular: 118 hastanın 19 (%16)'unda safra fistülü saptandı. Grup 2'de kist boyutu, lökosit, alkalin fosfataz ve g-Glutamin transpeptidaz değerleri tek değişkenli analiz sonucuna göre grup 1'den daha yüksekti (p=0,03, p=0,008, p=0,04, p=0,001). Çok değişkenli analiz sonucuna göre; safra fistülü gelişimine etki eden tek bağımsız değişken yalnızca kist boyutu olarak saptandı (olasılık oranı 0.03, 95% güven aralığı 0,002-0,06; p=0,03). İşlem karakteristik eğrisine göre, kist boyutlarının 100% duyarlılık, 100% özgüllük ve eşik değeri, sırasıyla 7,5 cm, 4,0 cm ve 14,6 cm olarak bulundu. (Eğrinin altındaki alan 0,67).

Sonuç: Safra fistülünün tahmininde preoperatif kist boyutu önemli bir parametredir. Bizim çalışmamıza göre; kist boyutunun 7,5 cm'den büyük olması safra fistülü gelişimi için bir risk faktörüdür.

Anahtar Kelimeler: Karaciğer kist hidatik hastalığı, safra fistülü, Echinococcus granulosus

[1] **Health Sciences University, Okmeydani Education and Research Hospital, Department of General Surgery, Istanbul, Turkey.**

Ethics Committee Approval: The study wass approved by the local ethical authority.
Etik Kurul Onayı: Çalışma lokal etik komite tarafından onaylanmıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Geliş Tarihi / Received: 23.02.2019
Kabul Tarihi / Accepted: 27.02.2019
Yayın Tarihi / Published: 15.03.2019

Sorumlu yazar / Corresponding author:
Emin Kose
Adres/Address: Kaptan Paşa Mahallesi, Darülaceze Cad. No:25, 34384 Şişli, İstanbul, Turkey
e-posta: dreminkose@yahoo.com
Tel/Phone: (+90) 02123145555

Introduction

Hepatic hydatidosis is an endemic disease in South America, Middle East, East Mediterranean, African countries and Turkey. Liver hydatid cyst (LHC) is most common caused by Echinococcus granulosa. LHC can be symptomatic due to its size, location, and involvement of the biliary tree and infectious [1, 2].

Previous studies have reported that 5-25% of cases with LHC are associated with biliary tracts and can be complicated by 40-60% [3]. LHC can cause cystobiliary fistula (CBF) in 1-17% of patients with cyst-biliary communication after surgery or minimally invasive treatments [4, 5]. The treatment strategy varies depending on time of the realizing cyst-biliary communication, however the gold standard method is not determined for diagnosis of cyst-biliary communication [6]. There are some studies on scoring systems that are about CBF after hydatid cyst surgery; but still couldn't determine a standard approach for clinical practice [7].

Previous studies have shown that the cyst size, cyst location, and the compression on biliary tract may cause CBF [8, 9]. Even though there are many studies about evaluating cyst-biliary communication with preoperative imaging techniques, there are so less studies on relation between preoperative biochemical tests and biliary fistula [10, 11]

The aim of this study was to investigate appropriate treatment strategy for patients whose biliary fistula might develop, by revealing variables that affect biliary fistula.

Material and methods

The records of all patients who underwent surgery for LHC at Okmeydani Research and Educational Hospital during the period from April 2014 to May 2017 were retrospectively analyzed. This was a retrospective analysis of prospectively collected data and approved by the local ethical committee at Okmeydani Research and Educational Hospital (date: May 9th, 2017; decision no: 653). All of the procedures were in accordance with the World Medical Association Helsinki Declaration of 1964 and later versions. Written consent could not be obtained from all participants for being included in this retrospective study.

A total of 132 patients were included in the study considering these inclusion criteria (1) Patients underwent open or laparoscopic liver surgery for LHC from April 2014 to May 2017 (2) Patient has a preoperative computerized tomography in a month.

Exclusion criteria were as follows: (1) Liver diseases such as benign and malignant liver tumors, and hepatic abscess in addition to LHC; (2) Radical liver surgery such as hepatectomy for LHC (3) Biliary diseases such as bile duct stones and structure in addition to LHC.

In addition, because of high preoperative serum bilirubin and liver function test levels, ten patients who were performed preoperative ERCP and four patients with lack of data were also excluded from the study. At the end, a total of 118 patients were included in this study (Figure 1).

The data of the remaining 118 patients, including age, sex, laboratory data (alanine transaminase (ALT) (U/l), aspartate transaminase (AST) (U/l), alkaline phosphatase (ALP) (U/L), g-Glutamyl transpeptidase (GGT) (U/L), total and direct bilirubin (mg/dl) and hematologic tests), cyst type, cyst size and location, presence of intraoperative bile leakage and type of the procedure if bile leakage was present, type of surgery, presence of a postoperative biliary fistula, and length of hospital stay were recorded. The stage of each cyst was determined according to Gharbi classification [12]. All patients have pre-operative and post-operative laboratory tests and preoperative CT scan in a month.

Surgical Technique

As a surgical technique, in addition to partial cystectomy; unroofing, omentoplasty and drainage were done by surgeon decision and cyst properties. Hypertonic saline was used as the scolicidal agent. After cyst was aspirated, hypertonic saline was injected into the cyst cavity and 10 minutes later the cyst cavity was opened. After evacuating the cystic membranes and vesicles, the cyst cavity was explored for biliary leakage, and these patients were recorded. Based on the individual surgeon' decision and location of the cyst (near the gall bladder), cholecystectomy was performed on the patients that had biliary leakage in the cyst cavity and tried to find the communication with biliary tree by injected serum saline or methylene blue through the cystic duct. The localizations of the biliary leakage were then sutured. T-tube drainage was performed in patients whom location of biliary leakage was not detected. The drain was inserted into the cyst cavity in all patients. Postoperatively, if bile leakage was detected in drains, defined as Group1 and if not detected, defined as Group 2, postoperatively.

All patients were treated with albendazole 10 mg/kg after surgery. The patients with T-tube drainage were performed cholangiography at the first week. T-tube was clamped and removed after 4 weeks when there was no leakage on the first week' cholangiography.

Statistical Analysis

Data analyses were performed using JMP version 13.1 (SAS, Cary, NC). Quantitative values were represented as mean ± standard deviation, while independent categories were represented as number (%). In-group comparisons, the Student t test was used to evaluate the differences between continuous variables and the chi-square test was used for categorical variables. Parameters with a P value of less than or equal to 0.05 on univariate analysis were included in the Cox Proportional Hazards Model to identify independent predictors of bile leakage. A P value of less than 0.05 was considered significant. Receiver operating characteristic (ROC) curves was used to evaluate optimal cut-off values of cyst diameter in relation to bile leakage.

Figure 1. Flow chart for included patients in this study

Results

There were 118 patients, 74 (63%) female and 44 (37%) male patients with a mean age of 42±16.6 years. There was 1 cyst in 89 patients (76%); there were multiple cysts in 29 patients (26%). The mean cyst diameter was 6.3±1.9 cm. Of the 191 dominant cysts, 140 (92%) underwent partial cystectomy-drainage, 13 (8%) underwent partial cystectomy-drainage and T tube, 8 (6%) underwent partial cystectomy-drainage and

omentoplasty and 30 (25%) underwent partial cystectomy-drainage and cholecystectomy.

In the cyst size analysis between CBF present (group 2, n=19) and absent (group 1, n=99); in the present group the cyst size was bigger than the absent group (7.5±2.4 cm vs 6.1±1.8 cm p=0.003). On the receiver operating characteristic curve, the 100% sensitive, 100% specific, and optimal cutoffs of cyst diameter were 7.5 cm, 4.0 cm and 14.6 cm, respectively. The area under the ROC curve was 0.67 (Figure 2). According to Gharbi classification; in the CBF present group, there were type 2 in eight patients, type 3 in six patients and type 4 in four patients. There was no significant difference between two groups (p=0.13) (Table 1).

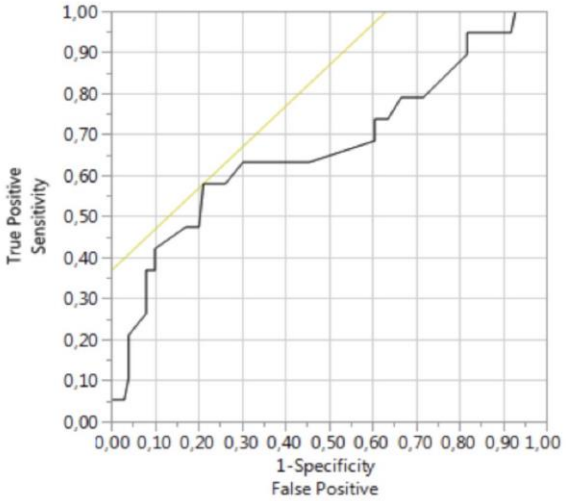

Figure 2. ROC curve analysis for cyst diameter. Area under curve: 0.67

Laboratory results are summarized on the table 2 and in the CBF present group cyst size, WBC, ALP, and GGT levels were higher than group 1 on univariate analysis (p=0.03, p=0.008, p=0.04 and p=0.001, respectively) (Table 2). All of the variables (size, WBC, ALP and GGT levels) that could be assessed before operation were included in multivariate model. In the multivariate model, only cyst diameter remained as an independent predictor (odds ratio 0.03, 95% confidence interval 0.002 to 0.06; p=0.03; Table 3).

Table 1. Demographic and cyst characteristics of patients with or without a cystobiliary fistula.

Parameters	Overall	Cystobiliary fistula present (n = 19)	Cystobiliary fistula absent (n = 99)	p value
Age (mean±sd)	41.9 ±16.6	39.7±15,5	42.4±16.9	0.51
Gender, n (%)				0.11
Female	74 (63)	15	59	
Male	44 (37)	4	40	
Cyst number, n (%)				0.86
Single	85 (72)	14	71	
Multiple	33 (28)	5	28	
Cyst location, n (%)				0.95
Right	84 (71)	14	70	
Left	8 (7)	1	7	
Right and left	26 (22)	4	22	
Cyst size (cm)	6.3 ±1.9	7.5±2.4	6.1±1.8	0.03
Cyst type				0.13
1	5	1	4	
2	26	8	18	
3	65	6	59	
4	20	4	16	
5	2	0	2	

SD: standard deviation

Table 2. The relation of the preoperative laboratory results and cystobiliary fistula present or absent.

Parameters	Cystobiliary fistula present (n=19)	Cystobiliary fistula absent (n=99)	p value
White blood cell count (per mm3) (mean±SD)	9.93±2.9	7.83±2.8	0.008
Hemoglobin (g/dl)	11.7±1.7	12.3±1.8	0.22
Mean liver function test levels (mean±SD)			
Total bilirubin (mg/dL)	0.88±0.5	0.75±0.6	0.34
Direct bilirubin (mg/dL)	0.52±0.4	0.41±0.5	0.29
Aspartate aminotransferase (U/L)	43.4±30.4	40.1±75.4	0.75
Alanine aminotransferase (U/L)	46.2±35.9	42.8±78.6	0.77
Alkaline phosphatase (U/L)	124.7±46.0	82.1±36.0	0.001
g-Glutamyl transpeptidase (U/L)	104.9±70.3	47.1±48.2	0.001

SD: standard deviation

Intraoperative, 19 patients with biliary leakage in the cyst cavity were performed primarily sutured; three patients with not localized biliary leakage were performed T-tube drainage.

Postoperative, the biliary fistula occurred in 19 patients (16.1%). Spontaneous closure occurred in two of them, and performed ERCP and sphincterotomy were performed in the remaining 17 patients. The mean time to fistula closure was 15.3 days (range 11-21). We didn't experienced anaphylactic reaction and mortality in our patients.

Table 3: Multivariate analysis model for predictors of the biliary fistula.

Variables	OR	CI	p value
Cyst size (cm)	0.03	0.002-0.06	0.03
White blood cell count (per mm^3)	0.07	0.14-0.27	0.51
Alkaline phosphatase (U/L)	0.018	0.001-0.037	0.07
g-Glutamyl transpeptidase (U/L)	0.004	0.009-0.018	0.50

OR: Odd ratio, CI: Confidence interval

Discussion

Hepatic hydatidosis is rare public health problem in the world but is still a common cause of morbidity and mortality in East countries, including Turkey. The aims of surgery are evacuate the cyst content and wall, restrict cavity of cyst; in some cases cyst excision and/or minor/major hepatectomy can be required, according the cyst localization [13]. Biliary fistula is the main reason of morbidity associated with LHC [14]. Some theories have been proposed about the pathophysiology of CBC.

The cyst may compress and destruct the biliary tract, the other theory is small biliary branches in the cyst wall generate high intracystic pressure, resulting in atrophy followed by the rupture of the biliary tract [8, 9]. The incidence of biliary communication in patients with hepatic hydatidosis varies in different studies, from 1% to 17% [5]. Preoperative or perioperative revealing of CBF are critical factors in the treatment of LHC. The current series represent a sample of 118 patients who had surgery for LHC at a research and educational hospital. We identified the factors associated with the incidence of CBF in this study. We found no differences in age, gender, number, location, types of cyst, Hb, AST, ALT, total/direct bilirubin and CRP count between patients with or without CBF and the biliary fistula rate is 16.1%. These results are reliable with those of other studies of LHC [15, 16].

LHC can be symptomatic according to size and location of cyst [17]. Although the growth rate of cyst shows several variations, about 20% of cyst grows 1 cm per year [18] The liver is most common organ (60-70%) involved with hydatid disease; approximately 20% of cyst can affect the lung, the brain, muscles, the kidney, bones, the heart and the pancreas [13,

18]. LHC involves the right lobe in liver 60-85% and it is usually asymptomatic up to 10 cm in size [18]. In this study 71% of cysts were in the right lobe of the liver, 22% of cysts were in the right and the left in live; but no significant difference was found between the location of the cyst and development of CBF. Alan and colleagues [8] have shown that there is a relation between the cysts in the right lobe and development of CBF; no significant difference was found in the central cysts.

The most common postoperative complication is biliary fistula, if there is communication between the cyst and the biliary tree. Endoscopic or surgical intervention may be necessary in persistent cases with fistula after surgery [19]. Intraoperative diagnosis of cyst-biliary communication can be difficult but preoperative predictive factors assessment of a biliary fistula might help in patients with LHC.

The size of the cyst was found in our series as a significant predictor of biliary fistula; other authors found that a cyst size of >10.5 cm is a significant predictor of cyst-biliary fistula had increased morbidity rates after surgery [13, 20]. Demircan et al. [15] reported that a cyst diameter of >8.5 cm, Atli et al. [21] found that cyst diameter of >14.5 cm was an independent predictor factor. We found that the diameter of the cyst was an independent predictor of CBF. The mean cyst diameter was 7.5 ± 2.4 cm in patients with biliary fistula versus 6.1 ± 1.8 cm in patients without fistula. On the receiver operating characteristic curve, the 100% sensitive, 100% specific, and optimal cutoffs of cyst diameter were 7.5 cm, 4.0 cm and 14.6 cm, respectively. The area under the ROC curve was 0.67. This result suggested that changes in cyst diameter might have a direct relationship with cyst-biliary communication. Our results support those of Kilic et al. [19] who stated that a cyst diameter of >7.5 cm was a risk factor for biliary fistula.

Increased serum ALP, GGT, direct bilirubin levels were reported to be markers for the biliary fistula between hydatid cysts and biliary tree [4, 21, 22]. Additionally Unalp et al. [23] stated that increased WBC levels might related to be for the biliary fistula. Our findings support that increased risk of biliary fistula in patients with increased WBC, ALP and GGT levels.

The main limitation of this study was its retrospective design. It should be stated that the limitation of patient selection might have influenced by the meaning of a selection bias (e.g. underwent liver resection due to cyst location). Therefore the other limitation was the relatively small size of the study group.

In conclusion, preoperative cyst diameter is a valuable parameter for predicting biliary fistula. However, larger prospective studies are needed in this purpose. Our study suggests that cyst size greater than 7.5 cm is a risk factor for biliary fistula. ERCP might be considered before surgical treatment in selective patients.

References

1. Jenkins DJ, Romig T, Thompson RC. Emergence/re-emergence of Echinococcus spp.—a global update. Int J Parasitol. 2005;35:1205-19.
2. Romig T, Dinkel A, Mackenstedt U. The present situation of echinococcosis in Europe. Parasitol Int. 2006;55:187.
3. Alper A, Arioglu O, Emre A, Uras A, Okten A. Choledochoduodenostomy for intrabiliary rupture of hydatid cyst of liver. Br J Surg. 1987;74:243–5.
4. Atahan K, Kupeli H, Deniz M, Gur S, Cokmez A, Tarcan E. Can occult cystobiliary fistulas in hepatic hydatid disease be predicted before surgery? Int J Med Sci. 2011;8:315-20.
5. Vicente E, Meneu JC, Hervas PL, Nuno J, Quijano Y, Devesa M, et al. Management of biliary duct confluence injuries produced by hepatic hydatidosis. World J Surg. 2001;25:1264-9.
6. Karabay Ö, Bostancı Ö. Biliary fistula after liver hydatid cyst surgery: Is it a predictable complication? Arch Clin Exp Med. 2018;3:186-9.
7. Saylam B, Coşkun F, Demiriz B, Vural V, Çomçalı B, Tez M. A new and simple score for predicting cystobiliary fistula in patients with hepatic hydatid cysts. Surgery, 2013;153:699-704.
8. Alan B, Kapan M, Teke M, Hattapoğlu S, Arıkanoglu Z. Value of cyst localization to predict cystobiliary communication in patients undergoing conservative surgery with hydatid cyst. Ther Clin Risk Manag. 2016;12:995-1001.
9. Manouras A, Genetzakis M, Antonakis PT, Lagoudianakis E, Pattas M, Papadima A, et al. Endoscopic management of a relapsing hepatic hydatid cyst with intrabiliary rupture: a case report and review of the literature. Can J Gastroenterol. 2007;21:249-53.
10. Erden A, Ormeci N, Fitoz S, Erden I, Tanju S, Genç Y. Intrabiliary rupture of hepatic hydatid cysts: diagnostic accuracy of MR cholangiopancreatography. AJR Am J Roentgenol. 2007;189:W84-9.
11. Chautems R, Buehler LH, Gold B, Chilcott MJ, Morel P, Mentha G. Long term results after complete or incomplete surgical resection of liver hydatid disease. Swiss Med Wkly. 2003;133:258-62.
12. Gharbi HA, Hassine W, Brauner MW, Dupuch K. Ultrasound examination of the hydatic liver. Radiology. 1981;139:459-63.
13. Daradkeh S, Husam EM, Farah G, Sroujieh AS, Abu-Khalaf M. Predictors of morbidity and mortality in the surgical management of hydatid cyst of the liver. Langenbeck's Arch Surg. 2007;392:35-9.
14. Valle-Sanz Yd Y, Lorente-Ramos RM. Sonographic and computed tomographic demonstration of hydatid cysts communicating with the biliary tree. J Clin Ultrasound. 2004;32:144–8.
15. Demircan O, Baymus M, Seydaoglu G, Akinoglu A, Sakman G. Occult cystobiliary communication presenting as postop- erative biliary leakage after hydatid liver surgery: are there significant preoperative clinical predictors? Can J Surg. 2006;49:177-84.
16. Yildirgan MI, Başoğlu M, Atamanalp SS, Aydinli B, Balik AA, Celebi F, Ören D. Intrabiliary rupture in liver hydatid cysts: results of 20 years' experience. Acta Chir Belg. 2003;103:621-5.
17. Frider B, Larrieu E, Odriozola M. Long-term outcome of asymptomatic liver hydatidosis. J Hepatol. 1999;30:228-31.
18. Moro PL, Lopera L, Bonifacio N, Gonzales A, Gilman RH, Moro MH. Risk factors for canine echinococcosis in an endemic area of Peru. Vet Parasitol. 2005:130:99-104.
19. Kilic M, Yoldas O, Koc M, Keskek M, Karakose N, Ertan T, Tez M. Can biliary-cyst communication be predicted before surgery for hepatic hydatid disease: does size matter? The Am J Surg. 2008;196:732-5.
20. Agarwal S, Sikora SS, Kumar A, Saxena R, Kapoor VK. Bile leaks following surgery for hepatic hydatid disease. Indian J Gastroenterol. 2005;24:55–8.
21. Atli M, Kama NA, Yuksek YN, Doganay M, Gozalan U, Kologlu M, et al. Intrabiliary rupture of a hepatic hydatid cyst: associated clinical factors and proper management. Arch Surg. 2001;136:1249-55.
22. Kayaalp C, Bzeizi K, Demirbag AE, Akoglu M. Biliary com- plications after hydatid liver surgery: incidence and risk fac- tors. J Gastrointest Surg. 2002;6:706-12.
23. Unalp HR, Baydar B, Kamer E, Yilmaz Y, Issever H, Tarcan E. Asymptomatic occult cysto-biliary communication with- out bile into cavity of the liver hydatid cyst: a pitfall in conservative surgery. Int J Surg. 2009;7:387-91.

Arch Clin Exp Med 2019;4(1):49-53. e-ISSN: 2564-6567

DOI:10.25000/acem.451820 Araştırma makalesi / Research article

Cervical blood flow velocity values in patients with unilateral intracranial aneurysm: Preliminary results

Tek taraflı intrakranial anevrizmalı hastalarda servikal kan akış hızı değerleri: Ön sonuçlar

Engin Tekin [1], Murat Pehlivan [2], Ömer Kitiş [3]

Abstract

Aim: Brain aneurysm is a balloon shaped dilatation of brain vessels as a result of attenuation of the vessel walls. The aim of this study was to evaluate the relationship between blood flow velocities in the right and left arterial vessels in an unruptured aneurysm and healthy group, and to investigate whether this analysis can help early diagnosis of aneurysm.

Methods: Four aneurysm patients (four female, mean age 57.25 ± 0.75 years) and four healthy subjects (two female, 2 male male, mean age 36.35 ± 6.19 years) were included in the study. Blood flow velocity values of right and left internal carotid arteries, vertebral artery and right and left internal jugular veins were obtained during a cardiac cycle with phase contrast technique. Spearman's correlation analysis was applied to flow velocity values. Statistically significant blood flow similarities between right and left brain were investigated.

Results: In the aneurysm group, there was a significant difference between right and left cervical arterial blood flow velocity values (p=0.001). Spearman correlation coefficient values between right and left arterial blood flow velocity values and right and left side arteriovenous blood flow velocity values were lower in the aneurysm group compared to the control group however, there was no statistical significance (p≥0.05 for all).

Conclusion: The difference between the right and left arterial blood flow velocities obtained in the aneurysm group and the low correlation values may be useful in early diagnosis of aneurysm.

Key words: Cerebral aneurysm, Spearman's correlation analysis, blood flow velocity, phase contrast MR.

Öz

Amaç: Beyin anevrizması damar çeperlerindeki zayıflama sonucu beyin damarlarında oluşan balon şeklinde genişlemedir. Bu araştırmanın amacı, kanamasız anevrizmalı ve sağlıklı grupta sağ ve sol arteriyel damarlardaki kan akış hızlarını değerlendirmek ve bu analizin anevrizma ön tanısına yardımcı olup olamayacağını araştırmaktır.

Yöntemler: Araştırmaya dört anevrizma hastası (dört kadın, ortalama yaş 57,25 ± 0,75) ve dört sağlıklı denek (iki kadın, iki erkek, ortalama yaş 36,35 ± 6,19) dahil edildi. Sağ ve sol iç karotis arter, vertebral arter ve sağ ve sol iç jugular ven kan akış hızı değerleri faz kontrast tekniği ile bir kardiyak döngü boyunca elde edildi. Spearman'ın ilişki analizi akış hızı değerlerine uygulandı. Beyinin sağı ve solu arasındaki istatistiksel olarak anlamlı kan akış benzerlikleri araştırıldı.

Bulgular: Anevrizma grubunda, sağ ve sol taraf servikal arteriyel kan akış hızı değerleri arasında anlamlı fark bulundu (p=0,001). Sağ ve sol arteriyel kan akış hızı değerleri arasındaki ve sağ ve sol taraf arteriyovenöz kan akış hızı değerleri arasındaki Spearman ilişki katsayı değerleri anevrizma grubunda kontrol grubuna göre düşüktü, ancak istatistiksel anlamlılık yoktu (hepsi için p≥0,05).

Sonuç: Bu ön araştırmanın sonuçları, anevrizma grubunda elde edilen sağ ve sol arteriyel kan akış hızları arasındaki belirgin farkın ve düşük ilişki değerlerinin anevrizma tanısında faydalı olabileceğini düşündürdü.

Anahtar kelimeler: Beyin anevrizması, Spearman ilişki analizi, kan akış hızı, faz kontrast MR.

[1] Usak University School of Health Sciences, Medical Imaging, Usak, Turkey.
[2] Ege University Faculty of Medicine, Dept of Biophysics, Izmir, Turkey.
[3] Ege University Faculty of Medicine, Dept of Radiodiagnostics, Izmir, Turkey.

Ethics Committee Approval: The study was approved by the local ethical authority.
Etik Kurul Onayı: Çalışma lokal etik komite tarafından onaylanmıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Geliş Tarihi / Received: 07.08.2018
Kabul Tarihi / Accepted: 13.02.2019
Yayın Tarihi / Published: 15.03.2019

This study was presented at the 1st International Health Sciences Congress, 02-05 May, 2018, Mehmet Akif University, Burdur, Istanbul.
Bu çalışma, 02—05 Mayıs 2018'de düzenlenen Burdur Mehmet Akif Üniversitesi 1. Uluslararası Sağlık Bilimleri Kongresi'nde sunulmuştur.

Sorumlu yazar / Corresponding author:
Engin Tekin
Adres/Address: 1 Eylül Kampüsü, MA3 Blok, Kat1, İzmir Yolu 8. Km. 64200, Uşak, Turkey
e-posta: engin.tekin@usak.edu.tr
Tel/Phone: (+90) 5053971636

Introduction

Intracranial aneurysms are balloon-like pathologic dilations of the cerebral blood vessel walls. An estimated 2%-5% of the general population is affected bye intracranial aneurysms. Rupture of intracranial aneurysms is an event associated with high mortality and disability rates [1]. Due to the high mortality rate predetermining of the probality of an aneurysm is very precious for public health.

Aneurysms frequently encountered unilaterally, and also 'Mirror-like' aneurysm, which are located bilaterally on corresponding arteries, has been reported to constitute less than 5 % of overall aneurysm [2, 3].

The flow dynamics of cerebral aneurysms have been studied in numerous experimental models and clinical studies to investigate the role of aneurysmal hemodynamics in their initiation, growth and rupture [4-6]. However, flow velocity changes of the vessels that supplying brain has never been used before for early diagnosis of aneurysm.

Besides it was reported that the velocity-time waveforms would be key to knowing the effect of aneurysm on flow. Just considering the geometric changes in the artery caused by an aneurysm would seem to suggest that there must be some disruption in flow [7]. So it is expected that the hemodynamic change that occurs with the formation of the aneurysm in intracranial arteries will also affect the hemodynamics of blood in the arteries supplying brain. It is suggested that there may be a difference in the flow velocity of right and left cervical arteries in aneurysm cases. This statistically correlation between blood flow velocity values of the right and the left side arteries may be important for suspicion of aneurysm. As far as we know, this hypothesis has not been found in the literature so far. Therefore, in this preliminary study, we evaluated the blood flow velocity of the right and the left carotid and the vertebral arteries and the internal jugular vein to examine the changes in blood flow velocity of the vessels supplying brain in cerebral aneurysm cases.

Material and methods

The research was approved by the local ethics comittee (Ege University Ethical Committe of Clinical Studies; 13-2.1/14) and the study protocol adhered to the tenets of the Declaration at Helsinki. Written consent could not be taken due to the retrospective design of the study.

Four aneurysm patients (four female, mean, 56.25 ± 0.75 years) and four control subjects (two female, two male, mean, 36.5 ± 6.2 years) between the ages of 21 to 73 years were included in the study. All patients with unruptured-unilateral aneurysms were retrospectively selected. There was no history of subarachnoid hemorrhage and other neurological diseases. Aneurysms were at the level of the right middle cerebral artery, the left anterior cerebral artery, the right posterior communicating artery, the left posterior communicating artery and saccular type. Aneurysm diameters were between 3.5 and 8 mm. Controls had no history of cerebral aneurysm, stroke and other cerebrovascular diseases.

All Magnetic resonance examinations were performed with 1.5 Tesla Magnetic Resonance (MR) unit (Siemens Symphony, Erlangen, Germany). The quantitative evaluation of arterial and venous blood velocities were performed with two dimensional (2D) phase contrast technique. Phase images were obtained by perpendicular to the foramen magnum on axial plane. For the internal carotid artery, C1 cervical segment was measured. For the vertebral artery, V2 vertebral segment was measured. The measurement parameters were as follows: TR, 33 ms; TE, 7 ms; slice thickness, 5 mm; Flip Angle, 15°; matrix, 256×256; FOV, 160 mm. The number of images varied depending on the heart rate. The total acquisition times ranged between 25 min and 30 min depending on the patient's individual heart rate (18–25 acquired cardiac phases). Cardiac gating was performed prospectively with electrocardiogram. Velocity encoding (Venc) was set at 100 cm/s for arterial blood flow velocity and 20 cm/s for internal jugular vein velocity.

The acquired phase images were transferred to ARGUS (ARGUS flow analysis tool, QoSient, LLC. New York, USA) post-processing program. Region of interest (ROI) was placed on each phase images (Figure 1), and, then, velocity-time curves of the right and the left internal carotid artery, the vertebral artery and the internal jugular vein were obtained by phase contrast technique throughout one cardiac cycle. Data were interpolated to the maximum number of points (cardiac phases) allowed per cardiac cycle (n=32) to equal the number of data for arteriovenous analysis.

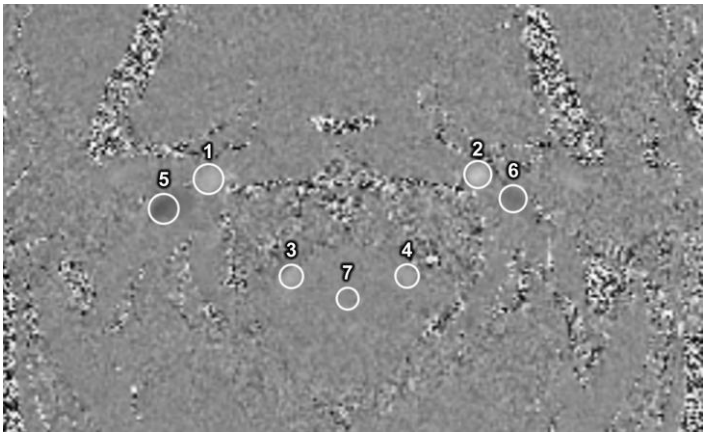

Figure 1. Region of interest (ROI) in phase images: 1, 2: Right and left internal carotid artery; 3, 4: Right and left vertebral artery; 5, 6: Right and left internal jugular vein; 7: Brain stem (using as a reference).

Spearman's correlation analysis was applied to flow velocity values (Table 1) including the correlation between blood flow velocity values of the right and the left internal carotid arteries in each subject (Correlation1-corr1), the correlation between total arterial blood flow velocities on the right and left side of brain (Correlation 2-corr2) and the correlation between right arteriovenous flow and left arteriovenous flow rates in each subject (Correlation 3-corr3).

Table 1. Descriptions of Spearman's correlation analysis groups.

Group	Description
Correlation1	Between the right and the left internal carotid arteries.
Correlation2	Between sum of the internal carotid artery and the vertebral artery for the right side and sum of the internal carotid artery and the vertebral artery for the left side of brain.
Correlation3	Between arteriovenous flow at the right and left sides.

Arteriovenous flow was found by subtracting venous flow (the jugular vein) from total arterial flow (total carotid and vertebral artery flows) [8]. In the study, arteriovenous flow was calculated by subtracting the jugular vein blood flow velocity value from the sum of blood flow rates of the carotid and vertebral arteries separately for the right and left sides of brain.

Statistical Analysis

SPSS 11.0 statistical software program (SPSS Inc., Chicago, IL) was used for statistical tests. Mann-Whitney U test was used to determine whether there was a difference between the right and the left internal carotid, the vertebral artery and the

internal jugular vein blood flow velocity values of each subject and if the Spearman's correlation coefficient values were significantly different between the aneurysm and the control group. P values less than or equal to 0.05 were considered as statistically significant.

Results

An example of right and left internal carotid and vertebral artery and internal jugular vein velocity-time curves obtained from the aneurysm and control group subjects are shown in Figures 2, 3 and 4. As the flow rate was measured over a cardiac cycle, the time axis in the graphs varied according to the heart rate.

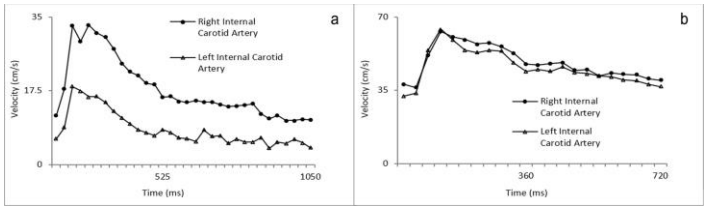

Figure 2. Velocity-time curves of internal carotid arteries. A) right and left internal carotid arteries of aneurysm subject B) right and left internal carotid arteries of healthy subject.

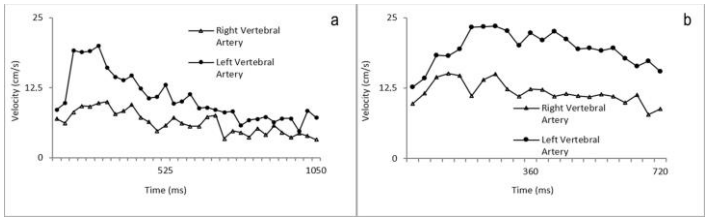

Figure 3. Velocity-time curves of vertebral arteries. A) right and left vertebral arteries of aneurysm subject B) right and left vertebral arteries of healthy subject.

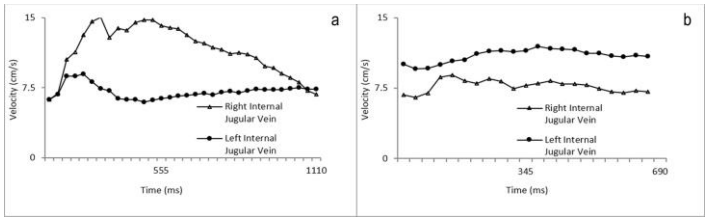

Figure 4. Velocity-time curves of internal jugular veins. A) right and left internal jugular veins of aneurysm subject B) right and left internal jugular veins of healthy subject.

The mean and peak velocities of the aneurysm group were smaller than control group in terms of flow velocity (p=0.001).The mean and peak blood velocities of arteries for right and left side of brain were significantly different in the aneurysm group as compared to control group (Table 2, 3). All blood velocity values are given as mean ± std error.

Table 2. Values of the mean and peak velocities of the internal carotid artery for the aneurysm and control groups.

	Mean velocity (cm/s) ¥		Peak velocity (cm/s) ¥	
Subject	Right	Left	Right	Left
Aneurysm (n=2) *	12.0±2.7	23.6±4	32.7±6.3	46.6±4.1
Aneurysm (n=2) **	31.0±0.8	17.3±0.7	64.9±5.5	50.3±4.5
Control (n=4)	33.3±3.3	33.4±2.5	58.7±5.0	61.7±4.4

*Aneurysm on the right side. ** Aneurysm on the left side.
¥:mean±standart deviation.

Table 3. Values of the mean and peak velocities of the vertebral artery for the aneurysm and control groups.

	Mean velocity (cm/s) ¥		Peak velocity (cm/s) ¥	
Subject	Right	Left	Right	Left
Aneurysm (n=2) *	4.4±1.0	8.8±1.0	25.4±8.5	29.7±4.6
Aneurysm (n=2) **	6±1.6	12.9±1.8	12.4±3.9	29.7±1.0
Control (n=4)	12.7±0.6	14.0±0.5	23.2±0.5	26.4±0.9

*Aneurysm on the right side. ** Aneurysm on the left side.
¥:mean±error.

There was no significant difference with regard to the mean and peak blood velocities of the jugular vein for the right and the left side of brain in two groups (p=0.196) (Table 4).

Table 4. Values of the mean and peak velocities of the jugular vein for the aneurysm and control groups.

	Aneurysm group (n=4)		Control Group (n=4)	
Veins	Mean Velocity (cm/s) ¥	Peak Velocity (cm/s) ¥	Mean Velocity (cm/s) ¥	Peak Velocity (cm/s) ¥
Right internal jugular	8.9±0.9	16.4±1	8.8±1.4	19.3±0.1
Left internal jugular	8.1±0.3	14.4±0.8	7.6±1.2	17±0.5

¥:mean±error.

Spearman's correlation coefficient values were lower in the aneurysm group compared to the control group for Corr1, Corr2 and Corr3 analysis, but there was no statistical significance (Table 5) (p=0.265).

Table 5. Spearman's correlation values of the aneurysm and control groups.

Age	Gender	Group	Correlation1	Correlation2	Correlation3
57	Female	Aneurysm	0.768	0.787	0.559
55	Female	Aneurysm	0.856	0.775	0.774
58	Female	Aneurysm	0.728	0.746	0.712
55	Female	Aneurysm	0.493	0.433	*0.359
21	Male	Control	0.949	0.891	0.982
21	Male	Control	0.980	0.982	0.978
73	Female	Control	0.967	0.988	*0.880
31	Female	Control	0.944	0.940	0.920

*There was aliasing in the right and the left jugular veins.

For each correlation analysis, the mean values of correlation analysis in aneurysm and control group are listed in Table 6.

Table 6. Correlation values of the aneurysm and control groups.

Group	Correlation1¥	Correlation2¥	Correlation3¥
Aneurysm	0.7113 ± 0.0387	0.6852± 0.0422	0.6010 ± 0.0462
Control	0.9600 ± 0.0041	0.9502 ± 0.0112	0.9400 ± 0.0122

¥:mean±error.

Discussion

We found a difference between the right and left mean and peak blood velocity of the carotid and the vertebral arteries in aneurysm group. This result suggests that there is an asymmetry between the right and the left side of brain in the aneurysm group. Similarly, there are studies reporting that there is asymmetric blood flow in aneurysm cases. In patients with aneurysm in the basilar artery, the mean value of the right vertebral artery was 2.1 ml/s and the mean value of the left vertebral artery was 0.7 ml/s. [9]. In another study, a flow rate of 54 ml/min on the right side and 93 ml/min on the left side of the patient with 2.5 mm aneurysm in the right anterior communicating artery was reported [10].

In addition, a study in the literature reported that the relationship between cerebral aneurysm size and risk of rupture was well documented but the effect of aneurysms on distal intracranial hemodynamics was not known [11]. The aneurysm

cases (unruptured and unilateral) included in our study were similar to this study in the literature. Aneurysms in the carotid segments and they found that mean pulsatility index in the ipsilateral ICA was 0.38 and mean pulsatility index in contralateral ICA was 0.35. Although aneurysms occured in the carotid artery, they could not find any difference between right and left carotid flow. However, this result was not similar to our results. We have found a significant asymmetry between the ipsilateral and contralateral sides in aneurysm group regard hemodynamic carotid flow. As far as we know, a study that evaluating preliminary diagnosis of intracranial aneurysms by using the blood flow dynamics of the arteries supplying the brain has not been found in the literature so far.

Besides this blood flow velocities in ipsilateral (on the obstructed side) internal carotid artery were lower compared with the contralateral (on the unobstructed side). This may be due to autoregulation. Blood flow velocities of ipsilateral vertebral artery were lower in comparison to contralateral in two patients, the other two patients had the opposite. It is thought that the reason for not getting meaningful difference is due to the vascular structures. It should be also investigated that in which side of brain (the aneurysm side or contralateral) the cervical artery velocities will be higher. Morover, more study on aneurysm cases is needed to understand if an asymmetry occurs because of an aneurysm formation or if an aneurysm cause an asymmetry.

An asymmetry between the right and left jugular vein blood flow velocities could not be obtained. In aneurysm groups, it should be investigated in more cases whether there is a blood flow asymmetry for jugular vein.

Corr1 and corr2 analysis values were lower in the aneurysm group compared to the control group. These results show that aneurysm impairs blood flow dynamics in one side of brain. In the aneurysm group, low correlation values also suggest that there is an asymmetry between the right and the left side of brain in terms of total arterial blood flow velocity. It is thought that the cranial cerebral aneurysm has caused velocity change in the veins supplying the brain unilaterally and this change is compensated by the arterial elasticity.

It was reported that the net arterial flow into the skull over an average cardiac cycle must be equal the net outflow of venous blood plus possible net outflow of CSF through the Foramen Magnum and this is affected by the intracranial compliance and pressure [12]. So impact of aneurysm formation on the compliance was investigated in Corr3 analysis. The low Corr3 values found in the aneurysm group due to arteriovenous flow difference between the right and left sides. Compliance in the cervical veins has changed by the effect of autoregulation.

Skull is a rigid body that has apertures with vessels and Foramen Magnum. Any difference in compliance caused by pulsatile blood pressure may have revealed some delay in any fluid flow rate if there was an existing aneurysm. For this reason, Corr3 values may be a measure to show this flow rate delay as asymmetry. Further study with a large number of cases is needed to test this hypothesis.

There was no significant difference between right and left arterial blood flow velocities in the control group. The correlation coefficients were also higher in control group as compared to aneurysm group. These values indicate that there is no asymmetry between the right and left of brain. This result is also consistent with the literature. Since the aneurysm group consists of older subjects compared to the control group in this research, it may be thought that asymmetry have occurred because of age. Although there was a decrease in blood flow with age, no flow difference between right and left arteries supplying the brain was reported. [13-15].

Other conditions and diseases that may cause asymmetry should also be examined. This hemodynamic difference between the right and left sides and asymmetry may also be caused by other conditions and diseases such as stenosis and stroke. In the literature, increased blood flow velocity on the ipsilateral side was reported for carotid artery stenosis [16]. However, if an asymmetry in the cervical arteries is proved in aneurysms cases, an awareness will be created in clinicians for diagnosis of aneurysm.

Obtaining carotid and vertebral arteries blood flow values with doppler ultrasound are more practical than phase contrast MR technique. To take the advantage of doppler ultrasound, we propose to use ultrasound as a initial method for fast screening of aneurysm, as we have found correlation values of carotid artery flow (Corr1) smaller in aneurysm group in our study. If any suspicious flow velocities were found, then we propose to use phase contrast MR to get the detailed information for early diagnosis.

This study contains some limitations. Firstly, a small number of aneurysm patients cannot statistically indicate a powerful conclusion. The reason small number of patients is that data acquisition time is very long. In addition, the MR technique is sensitive to movement and heart beat.

The second limitation of the study is that a low Velocity Encoding (Venc) value was prefered while jugular vein blood flow velocity was being measured. As a result, Aliasing was observed. Venc value is an important measure to be set during phase contrast technique in MRI. If this value is set lower than the actual flow rate, aliasing occurs and unaccurate flow rate can be obtained. Higher Venc value should be selected in future studies.

In addition, further study is necessary to improve accuracy of cine MR imaging and to confirm its accuracy with that obtained by doppler ultrasound.

The use of a unilateral aneurysm group is a limitation in the study. It will not be possible to determine the velocity difference and the correlation between right and left sides in the bilateral aneurysm cases on the two sides of brain. To determine the the usefullness or accuracy of correlation analysis in bilateral aneurysms, unruptured bilateral aneurysm groups should be studied in comparison to control groups.

Vasculitis, stenosis and atherosclerosis were not seen in the image sections. In the origin of the vessels whose blood flow velocities were measured, any vascular disease that could lead to asymmetric blood flow have not been detected. However, the origin of the common carotid artery (CCA) could not be evaluated because it was not in the MRI image area. Another limitation of this study is that we don't know whether the asymmetric blood flow derived from a CCA-induced factor (but it is known that aneurysm patients do not have a history of cardiovascular disease).

As a result, in this preliminary study, asymmetry between the arteries supplying the right and left brain and low correlation coefficients were found in the aneurysm group. The use of this asymmetric flow in clinical routine practice may be important for early diagnosis of aneurysm. Therefore, more further studies should be performed in larger groups by using the doppler ultrasonography method.

References

1. Doddasomayajula R, Chung B, Hamzei-Sichani F, Putman CM, Cebral JR. Differences in Hemodynamics and Rupture Rate of Aneurysms at the Bifurcation of the Basilar and Internal Carotid Arteries. AJNR Am J Neuroradiol. 2017;38:570-6.

2. Zhao L, Zhang L, Zhang X, Li Z, Tian L, Wang Y-XJ. An Analysis of 1256 Cases of Sporadic Ruptured Cerebral Aneurysm in a Single Chinese Institution. PLoS One. 2014;19:e85668.
3. Wang R, Zhang D, Zhao J, Wang S, Zhao Y, Niu H. A comparative study of 43 patients with mirror-like intracranial aneurysms: risk factors, treatment, and prognosis. Neuropsychiatr Dis Treat. 2014;10:2231-7.
4. Hu P, Qian Y, Lee CJ, Zhang HQ, Ling F. The energy loss may predict rupture risks of anterior communicating aneurysms: a preliminary result. Int J Clin Exp Med. 2015;8:4128-33.
5. Berg P, Beuing O. Multiple intracranial aneurysms: a direct hemodynamic comparison between ruptured and unruptured vessel malformations. Int J Comput Assist Radiol Surg. 2018;13:83-93.
6. Liu J, Fan J, Xiang J, Zhang Y, Yang X. Hemodynamic characteristics of large unruptured internal carotid artery aneurysms prior to rupture: a case control study. J Neurointerv Surg. 2016;8:367-72.
7. Gwilliam MN, Hoggard N, Capener D, Singh P, Marzo A, Verma PK et al. MR derived volumetric flow rate waveforms at locations within the common carotid, internal carotid, and basilar arteries. J Cereb Blood Flow Metab. 2009;29:1975-82.
8. El Sankari S G-JC, Fichten A, Godefroy O, Serot JM, Deramond H, Meyer ME, et al. Cerebrospinal fluid and blood flow in mild cognitive impairment and Alzheimer's disease: a differential diagnosis from idiopathic normal pressure hydrocephalus. Fluids Barriers CNS. 2011;8:12.
9. Boussel L, Rayz V, Martin A, Acevedo-Bolton G, Lawton MT, Higashida R et al. Phase-Contrast Magnetic Resonance Imaging Measurements in Intracranial Aneurysms In Vivo of Flow Patterns, Velocity Fields, and Wall Shear Stress: Comparison with Computational Fluid Dynamics. Magn Reson Med. 2009;61:409-17.
10. Karmonik C, Yen C, Grossman RG, Klucznik R, Benndorf G. Intra-aneurysmal flow patterns and wall shear stresses calculated with computational flow dynamics in an anterior communicating artery aneurysm depend on knowledge of patient-specific inflow rates. Acta Neurochir (Wien). 2009;151:479-85.
11. Hussein AE, Brunozzi D, Shakur SF, Ismail R, Charbel FT, Alaraj A. Cerebral Aneurysm Size and Distal Intracranial Hemodynamics: An Assessment of Flow and Pulsatility Index Using Quantitative Magnetic Resonance Angiography. Neurosurgery. 2018;83:660-5.
12. Alperin N, Vikingstad EM, GomezAnson B, Levin DN. Hemodynamically independent analysis of cerebrospinal fluid and brain motion observed with dynamic phase contrast MRI. Magn Reson Med. 1996;35:741-54.
13. Filatova OV, Sidorenko AA, Skorobogatov YY. Age and Sex Dependence of Hemodynamic Parameters of Human Internal Carotid Arteries. Hum Physiol. 2014;40:554-62.
14. Salk İ, Yıldız G, Eğilmez H, Atalar MH, Candan F, Çetin A. Carotid artery Doppler ultrasonography in patients with chronic kidney disease. Med Sci Monit. 2014;20:11-7.
15. Al-Eqabi DAM, Al-Sıaıdy WF, Al-Sabbagh AAJ, Al-Kırwi IN. Internal Carotid Peak-Systolic and End-Diastolic Velocities are the Sensitive Parameters in Predicting Conditions in Type 2 Diabetes. J Biomed Bioeng. 2013;4:90-2.
16. Hope TA, Hope MD, Purell DD, von Morze C, Vigneron DB, Alley MT et al. Evaluation of intracranial stenoses and aneurysms with accelerated 4D flow. Magn Reson Imaging. 2010;28:41-6.

Arch Clin Exp Med 2019;4(1):54-56. e-ISSN: 2564-6567

DOI: 10.25000/acem.460782 Olgu Sunumu / Case Report

The right coronary artery originating from the left anterior descending artery: A variant of single coronary artery anomaly

Sol ön inen koroner arterden kaynaklanan sağ koroner arter: Tek koroner arter anomalisinin farklı bir tipi

Yakup Alsancak [1], Sina Ali [2]

Abstract

Although coronary artery anomalies have been accepted as benign conditions, clinical presentations have a large spectrum including chest pain, dyspnea, palpitations, malign arrhythmias, myocardial infarction, syncope and sudden death. An atypical anomalous form of single coronary artery in which the right coronary artery originates from the left anterior descending (LAD) coronary artery is an extremely rare situaiton.

In this report, we presented a case of 63 years old woman who was taken to the coronary angiography due to recurrent chest pain and acute coronary syndrome. Coronary angiography revealed an atypical form of single coronary artery anomaly that the right coronary artery originates from LAD coronary artery. The treatment strategy was discussed with heart team and patient. Percutaneous coronary intervention (PCI) was performed because of her recurrent chest pain and isolated LAD lesion and preference of the patient.

In conclusion, this case is important for demonstrating the feasibility of PCI in patients with single coronary artery anomaly.

Keywords: Anomaly, percutaneous intervention, single coronary artery

Öz

Benign bir durum olarak kabul edilmelerine rağmen, koroner arter anomalilerinin klinik görünümü göğüs ağrısı, nefes darlığı, çarpıntı, malign aritmiler, miyokard enfarktüsü, senkop ve ani ölüm gibi geniş bir spektruma sahiptir. Sağ koroner arterin sol ön inen koroner arterden köken aldığı tek koroner arterin atipik formu son derece nadir bir koroner anomalidir.

Bu yazıda, tekrarlayan göğüs ağrısı ve akut koroner sendrom nedeniyle koroner anjiyografiye alınan 63 yaşında bir kadın olgu sunuldu. Koroner anjiyografide, sağ koroner arterin sol ön inen koroner arterden köken aldığı atipik bir tek koroner arter anomalisi saptandı. Tedavi stratejisi kalp takımı ve hasta ile tartışıldı. Tekrarlayan göğüs ağrısı, izole sol ön inen koroner arter lezyonu ve hastanın tercihi nedeniyle perkütan koroner girişim (PKG) yapıldı.

Sonuç olarak, bu olgu, tek koroner arter anomalisi olan hastalarda PKG'in uygulanabilirliğini göstermesi bakımından önemlidir.

Anahtar kelimeler: Anomali, perkütan girişim, tek koroner arter

[1] Necmettin Erbakan University, Meram Faculty of Medicine, Department of Cardiology, Meram, Konya, Türkiye.

[2] Etimed Hospital, Department of Cardiology, Etimesgut, Ankara, Türkiye.

Informed Consent: The written consent was received from the patient who was presented in this study.
Hasta Onamı: Çalışmada sunulan hastadan yazılı onam alınmıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this case has received no financial support.
Finansal Destek: Yazarlar bu olgu için finansal destek almadıklarını beyan etmişlerdir.

Geliş Tarihi / Received: 17.09.2018
Kabul Tarihi / Accepted: 28.12.2018
Yayın Tarihi / Published: 15.03.2019

Sorumlu yazar / Corresponding author
Yakup Alsancak
Adres/Address: Necmettin Erbakan University, Meram Faculty of Medicine, Department of Cardiology, Meram, Konya, Türkiye. Postal code: 42090.
e-mail: dryakupalsancak@gmail.com
Tel/Phone: +90 0332 223 65 00

Introduction

Most of the coronary artery anomalies (CAA) are detected incidentally during coronary angiography and are usually asymptomatic. Altough they have been accepted as a benign condition, clinical presentation of CAA has a large spectrum including chest pain, dyspnea, palpitations, malign arrhythmias, myocardial infarction, syncope and sudden death [1, 2]. An isolated single CAA is defined as a solitary coronary artery arising from the sinus valsalva, giving rise to the major coronary branches such the left anterior descending coronary artery (LAD), the circumflex artery and the right coronary artery (RCA). In other words, both the left main coronary artery and the RCA arise from a single aortic sinus. The prevelance of single CAA have been reported as a range of 0.031% to 0.066% [3, 4]. The atypical form of single coronary artery that RCA originates from LAD is an extremely rare coronary anomaly [1].

Herein, we present a case of atypical form of single CAA that presented with acute coronary syndrome and successfully managed with percutaneous coronary intervention (PCI).

Case report

A 61-year-old female patient was admitted to our emergency department with chest pain that had lasted one hour. Except from diabetes mellitus and chronic renal failure, there was no reported history of cardiac risk factor. On admission, her electrocardiography revealed normal sinus rythm with 95/min heart rate and ST depression on anterior derivations without ST elevations. The echocardiographical examination revealed left ventricular hypertrophy with normal systolic function. After that day, she was transferred to catheter laboratuary due to recurrent chest pain and elevated troponin levels. Her coronary angiography revealed an anomalous RCA originating from the middle portion of LAD which had severe thrombotic stenosis at the above of RCA ostium (Figure 1 A-D). This patient was accepted as a two-vessel disease because of both LAD and RCA being affected by thrombotic stenosis. We discussed the option of surgical treatment or PCI with the patient. Because of her recurrent chest pain and isolated LAD lesion and preference of the patient, we decided to perform PCI. A floppy guidewire was advanced into the RCA and a second wire was reach down to the LAD. 3.0x18 mm drug eluting stent was directly implanted with a high pressure, and postdilatation was performed with a 3.5x15 mm non-compliant balloon. Coronary angiography demonstrated the successful outcome after stent implantation without any stenosis or obstruction of RCA ostium. (Figure 2 A-D). Computed tomographic angiography (CTA) could not been performed to show the course of the coronary arteries because of the patient's chronic renal failure. Patient was discharged after two days without any complication.

Written consent was taken from the patient.

Discussion

The incidence of CAA is 1.3% and RCA is known as the most commonly affected coronary artery [5]. It is well known that many of anomalous origin of the RCA are asymptomatic, but Taylor et al. [6] has demonstrated a 25% rate of sudden death with this situation. Moreover, it has been reported that congenital anomalies such as coronary arteriovenous fistula, transposition of the great vessels or bicuspid aortic valve may be related with single coronary anomaly [7]. Single CAA may also be detected as a cause of sudden cardiac death with a range of 4% to 15% in younger populations [8]. Single CAA may have benign or malignant prognosis due to its location, but generally accepted as a hemodynamically benign form of CAA's. Single CAA arising from the left sinus valsalva has a more benign prognosis than arising from the right sinus valsalva. And, that arising from the left sinus valsalva may be associated with sudden cardiac death after vigorous exertion before age of 20 [9]. Although the majority of CAAs were detected during conventional coronary angiography, it is not always a sufficient method to assess the prognosis of the disease. CTA may have a more beneficial role to identify the course of the coronary arteries and their associations with structural tissues [9]. Ghadri JR et al. [10] have demonstrated that the confirming of CAA's is higher with CTA than standard coronary angiography. And they also supported that standard coronary angiography is not enough technique to identify the CAA's.

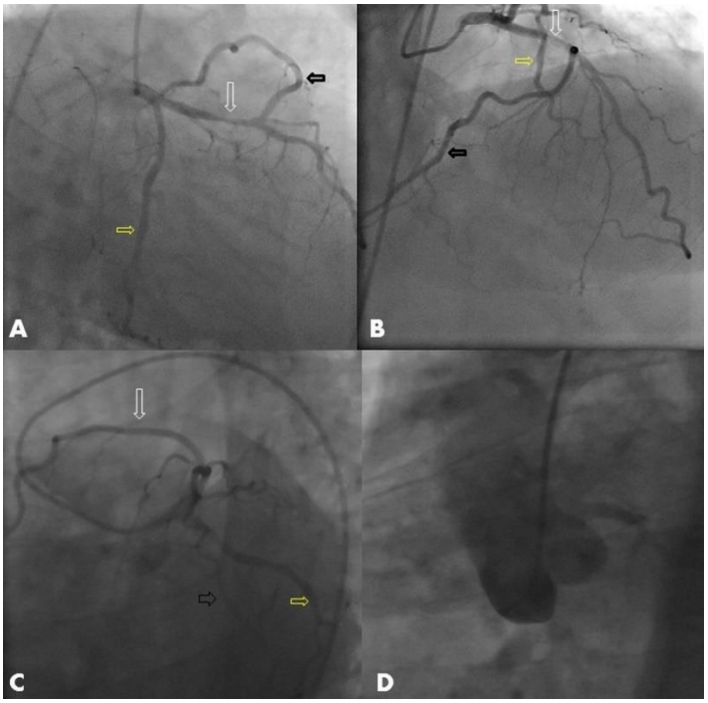

Figure 1. The left anterior descending coronary artery with severe thrombotic stenosis (white arrows), the circumflex coronary artery (yellow arrows) and anomalous right coronary artery from mid portion of the left anterior descending coronary artery (black arrows) (A-C) Aortography demonstrated the left main coronary artery without the right coronary ostium in the right sinus valsalva (D).

The run of the coronary arteries is the one of the main determinants for the patient's prognosis. It may cause myocardial ischemia or sudden cardiac death during exercise, if it is located between the aorta and the surrounding tissues such as the pulmonary trunk [11]. Moreover, acute coronary syndromes, in these patients, have an increased risk for cardiovascular death compared with the patients who have normal coronary anatomy because of the excessive ischemic burden. Even in patients with single-vessel disease that need revascularization, treatment should be well considered. Medical, surgical or PCI may be a choice for treatment and such methods should be well discussed with patients.

Several case reports were published about percutaneous revascularization to single CAA [2, 12]. Percutaneous coronary interventions may be lethal as a result of complications during procedure due to wide ischemic area and complex coronary anatomy. Comparing with normal population, PCI in patients with CAA has considerable technical difficulties [13]. Mishra TK and colleagues [12] have been well summarized the risks involved in the process during percutaneous interventions. At

first, they mentioned that procedure has a similar risk with intervention of unprotected the left main coronary artery disease due to the large size of the threatened myocardial area. Any coronary dissection that occurs during catheter manipulation or percutaneous interventions (guidewire induced or balloon dilatation or edge dissection after stent implantation) may result in death. In addition, prolonged dilation of coronary balloons may cause of development of malignant arrhythmias. Stent thrombosis can lead to fatal consequences for patients in short and long term follow up [12]. Finally, drug eluting stents must be chosen because of that the use of drug eluting stents versus bare metal stents are associated with significant reductions in major adverse cardiovascular events, all-cause mortality, myocardial infarction, target-lesion revascularization, and target-vessel revascularization in patients with chronic kidney disease [14].

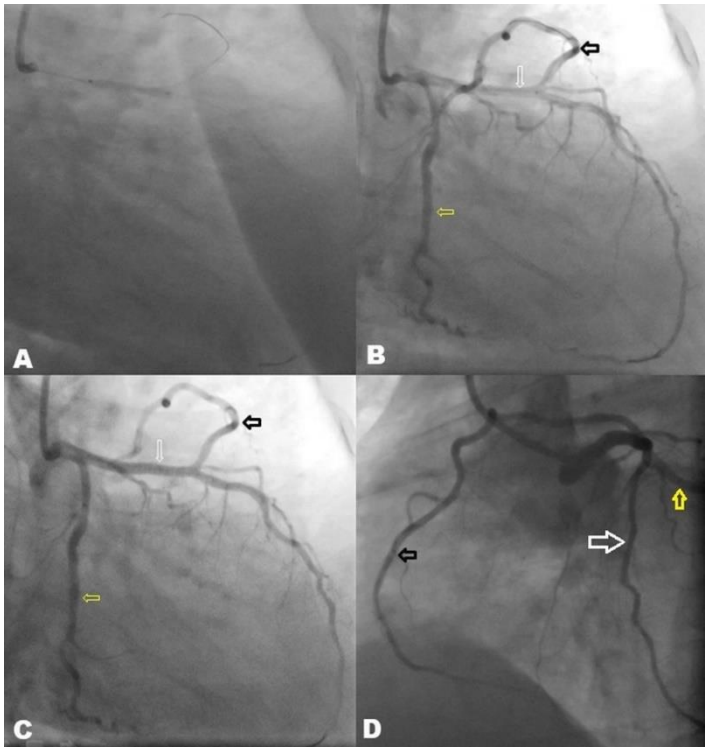

Figure 2. Stages of percutaneous coronary intervention (black arrows: the right coronary artery, white arrows: the left anterior descending coronary artery, yellow arrows: the circumflex coronary artery (A-C). The course of the right coronary artery in right anterior oblique view (D).

In this case, we preferred PCI due to comorbid conditions of the patient. Because of the excessive ischemic burden, PCI might be performed with mechanical assisted device with support of cardiovascular surgery. This case is important for demonstrating the feasibility of PCI in patients with single coronary artery anomaly.

References

1. Yurtdas M, Gulen O. Anomalous origin of the right coronary artery from the left anterior descending artery: review of the literature. Cardiol J. 2012;19:122–9.
2. Alsancak Y, Sezenöz B, Duran M, Unlu S, Turkoglu S, Yalcın R. Acute Anterior Myocardial Infarction Accompanied by Acute Inferior Myocardial Infarction: A Very Rare Coronary Artery Anomaly. Case Rep Cardiol. 2015;2015:347126-3.
3. Desmet W, Vanhaecke J, Vrolix M, Van de Werf F, Piessens J, Willems J, et al. Isolated single coronary artery: a review of 50,000 consecutive coronary angiographies. Eur Heart J. 1992;13:1637-40.
4. Turkmen S, Yolcu M, Sertcelik A, Ipek E, Dokumaci B, Batyraliev T. Single coronary artery incidence in 215,140 patients undergoing coronary angiography. Folia Morphol (Warsz). 2014;73:469-74.
5. Yamanaka O, Hobbs RE. Coronary artery anomalies in 126,595 patients undergoing coronary arteriography. Cathet Cardiovasc Diagn. 1990;21:28–40.
6. Taylor AJ, Rogan KM, Virmani R. Sudden cardiac death associated with isolated congenital coronary artery anomalies. J Am Coll Cardiol. 1992;20:640–7.
7. Ogden JA, Goodyer AV. Patterns of distribution of the single coronary artery. Yale J Biol Med. 1970;43:11-21.
8. Alexander RW, Griggith GC. Anomalies of the coronary arteries and their clinical significance. Circulation. 1956;14:800-5.
9. Villa AD, Sammut E, Nair A, Rajani R, Bonamini R, Chiribiri A. Coronary artery anomalies overview: The normal and the abnormal. World J Radiol. 2016;8:537-55.
10. Ghadri JR, Kazakauskaite E, Braunschweig S, Burger IA, Frank M, Fiechter M, et al. Congenital coronary anomalies detected by coronary computed tomography compared to invasive coronary angiography. BMC Cardiovascular Disorders. 2014;14:1.
11. Wańha W, Roleder T, Kowalówka A, Wojakowski W. Acute coronary syndrome in a patient with an anomaly of the right coronary artery, which originated from the medial part of the left anterior descending artery. Kardiol Pol. 2015;73:375.
12. Mishra TK, Mishra CK, Das B. Percutaneous coronary intervention in a patient with single coronary artery. Indian Heart J. 2014;66:382-5.
13. Lanzieri M, Khabbaz K, Salomon RN, Kimmelstiel C. Pri¬mary angioplasty of an anomalous left main coronary artery: diagnostic and technical considerations. Catheter Cardiovasc Interv. 2003;58:185-8.
14. Lu R, Tang F, Zhang Y, Zhu X, Zhu S, Wang G, et al. Comparison of Drug-Eluting and Bare Metal Stents in Patients With Chronic Kidney Disease: An Updated Systematic Review and Meta-Analysis. J Am Heart Assoc. 2016;5:e003990.Alergol. 2018;35:225-6.

Arch Clin Exp Med 2019;4(1):57-59. e-ISSN: 2564-6567

DOI: 10.25000/acem.479332 Olgu Sunumu / Case Report

Successful management of late coronary aneurysm after bare metal stent implantation: An insidious threat

Çıplak metal stent implantasyonu sonrası geç koroner arter anevrizmasının başarılı yönetimi: Bir sinsi bir düşman

Emre Özdemir [1]

Abstract

Development of coronary arterial aneurysm (CAA) is a rare complication after stent implantation, and even more uncommon after bare metal stents (BMS) compared with drug eluting stents. The case is here presented of a 55-year-old male with in-stent CAA, which developed 9 months after BMS implantation. The patient was treated with percutaneous re-implantation of BMS and at the clinical follow-up examination, 10 months after this treatment, there were no problems on the coronary angiography and the patient had no complaints. The treatment strategy is not clear for CAAs, so it must be decided after consultation between the cardiologist and cardiac surgeon. BMS re-implantation can be a successful treatment.

Key words: bare metal stent, coronary aneurysm, coronary stent, percutaneous coronary intervention

Öz

Koroner arter anevrizmaları (KAA) gelişimi, stent implantasyonu sonrası nadir görülen bir komplikasyondur, özellikle de ilaç salınımlı stentlerle karşılaştırıldığında çıplak metal stentlerden (ÇMS) sonra çok nadir görülür. 55 yaşında bir hastanın ÇMS implantasyonundan 9 aylık bir süre sonra gelişen in-stent KAA ait bir vaka sunulmuştur. Bu KAA perkütan olarak tedavi edilmiş olup, bu tedaviden 10 ay sonra yapılan kontrol koroner anjiyografi ve klinik takiplerde her hangi bir sorun ya da şikayet kalmadığı görülmüştür. KAA için tedavi yöntemi net değildir; bu nedenle kardiyolog ve kalp cerrahı arasındaki konsültasyondan sonra kararlaştırılmalıdır. ÇMS'in yeniden implantasyonu başarılı bir tedavi yöntemi olabilir.

Anahtar Kelimeler: çıplak metal stent, koroner anevrizma, koroner stent, perkütan koroner girişim

[1] Katip Celebi University, Ataturk Education and Research Hospital, Cardiology Clinic, Izmir, Turkey.

Informed Consent: The written consent was received from the patient who was presented in this study.
Hasta Onamı: Çalışmada sunulan hastadan yazılı onam alınmıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this case has received no financial support.
Finansal Destek: Yazarlar bu olgu için finansal destek almadıklarını beyan etmişlerdir.

Geliş Tarihi / Received: 06.11.2018
Kabul Tarihi / Accepted: 06.03.2019
Yayın Tarihi / Published: 15.03.2019

Sorumlu yazar / Corresponding author
Emre Ozdemir
Adres/Address: Izmir Katip Celebi University Ataturk Education and Research Hospital, Cardiology, Basin Sitesi/Karabaglar-Izmir, Turkey, Post Code:35360.
e-mail: emreozdemir27@yahoo.com.tr
Tel/Phone: +90 (232) 244 44 44

Introduction

Coronary arterial aneurysms (CAAs) are defined as dilatation of the coronary artery exceeding 50% of the reference vessel diameter [1] The known incidence of CAAs is 0.3%–5.3% with angiography and 1.4% with autopsy [2]. The incidence of CAAs after percutaneous transluminal coronary angioplasty is approximately 5% [3].

Drug-eluting stent (DES) implantation is associated with altered vascular healing and delayed endothelialization due to inhibition of intimal healing [4]. This is the main reason for ~1% risk of CAAs after DES implantation [4]. CAAs may also develop after bare metal stent (BMS) implantation due to wall-stretching, stent fracture and intimal-dissection [5].

Other reasons for aneurysm development include Kawasaki disease, polyarteritis nodosa, systemic lupus erythematosus, infection, traumatic injury, endocarditis, rheumatic fever, and congenital malformation and de novo atherosclerosis [6].

The case is here presented of a patient who developed CAA within 9 months of BMS implantation in the left anterior descending (LAD) artery applied as primary coronary intervention for an acute anterior myocardial infarction.

Case report

A 55-year-old male patient with no comorbid disease was admitted to the Emergency Department(ED) with chest pain. Acute anterior myocardial infarction was detected on ECG. Coronary angiography (CAG) revealed a lesion with 99% thrombosis in the proximal LAD, circumflex artery (Cx) plaque, optus marginalis (OM) 80% stenosis (diameter < 2 mm) and a 70% mid lesion in the right coronary artery (RCA). The LAD lesion was treated with a 4.5 x 24 mm Ephesus BMS (Alvimedica, Istanbul, Turkey) after 2.0 x 20 mm balloon pre-dilation during primary percutaneous coronary intervention (PCI) (Figure-1a, b, c). When left ventricular ejection fraction (LVEF) was detected as 50%, the patient was discharged successfully after clinical follow-up with medical treatment included acetylsalicylic acid, clopidogrel, metoprolol and statin.

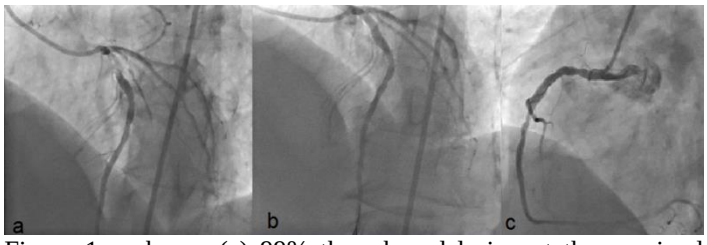

Figure 1. a, b, c : (a) 99% thrombosed lesion at the proximal LAD, (b) successful implantation of BMS in the LAD lesion, (c) 70% thrombosed lesion at the middle of RCA(c).

At approximately one month after the primary PCI, the patient was re-admitted to ED with recently developed chest pain. CAG was performed, and the LAD stent was observed to be patent but PCI was applied again to the RCA mid 70% lesion with direct implantation of a 3.5x15 Ephesus BMS (Alvimedica, Istanbul, Turkey) (Figure-2a, b).

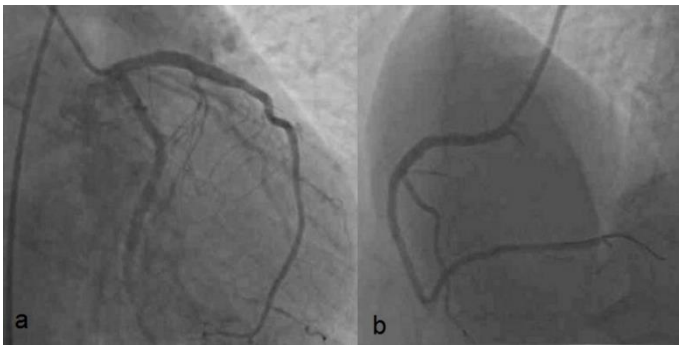

Figure 2. a, b: (a) Patent LAD stent without aneurysm, (b) Image of RCA after BMS implantation.

During follow-up, anterior-wall myocardial ischemia was detected on myocardial perfusion scintigraphy (MPS) at 8 months after the RCA PCI. CAG was applied again, which revealed a LAD in-stent 90% lesion and in-stent coronary aneurysm after the lesion, but the RCA stent was patent and there was non-obstructive plaque in Cx. Intravascular ultrasound (IVUS) or optical coherence tomography (OCT) could not be applied. Therefore, the treatment strategy had to be decided only based on the CAG findings. Following an in-clinic consultation, it was decided to continue with PCI. Pre-dilatation was performed with a 4.0 x 16 mm balloon and a 4.5 x 20 mm Liberte BMS (Boston Scientific, MA, USA) was then implanted in the stent, to close the in-stent aneurysmal segment. There was no significant residual aneurysm or occlusion on CAG after PCI. The patient was discharged successfully one day after PCI. Clopidogrel treatment was changed to ticagrelor.

At the follow-up examination 10 months after this procedure, no symptoms were observed on CAG. There was no aneurysm on the LAD stent position, the RCA stent was patent but LAD in-stent re-stenosis (50%) was detected but was confirmed as non-critical via fractional flow reserve measurement (Figure-3a, b, c). At the 2-month clinical follow-up examination after the last CAG, the patient had no complaints. The left ventricular ejection fraction was still 55% and he continued to take acetylsalicylic acid, ticagrelor, metoprolol and statin.

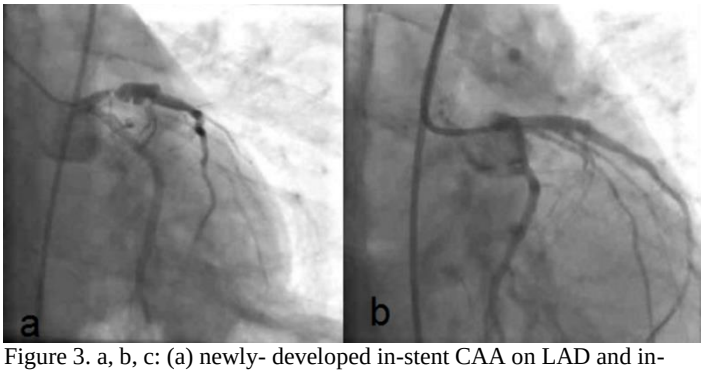

Figure 3. a, b, c: (a) newly- developed in-stent CAA on LAD and in-stent critical restenosis, (b) CAA successfully treated with a new BMS implantation in the old stent to cover the aneurysm, (c) no aneurysm on the final follow-up CAG.

Written informed consent was obtained from the patient for all procedures.

Discussion

CAAs can be asymptomatic or may be complicated by angina pectoris, myocardial infarction or sudden death [7]. CAAs can be classified in three pathological groups: atherosclerotic, inflammatory, and non-inflammatory. Non-inflammatory CAAs

also include iatrogenic aneurysms. These iatrogenic aneurysms can be associated with injuries of the vessel wall with a focal tear secondary to intravascular intervention [8].

CAA due to DES implantation is a rare complication, seen in approximately 1% of cases [9]. Interventional procedures, hypersensitivity reactions associated with the stent platform (metal), drug carrier polymer, DES drugs or infectious (mycotic) processes are the factors responsible for the development of CAAs after DES implantation [4]. Coronary dissection, stent fracture associated with high-pressure balloon inflation or coronary atherectomy, may also lead to the development of CAA after BMS implantation [11]. Furthermore, a hypersensitive reaction to molybdenum, nickel and chromium has been reported in ~ 10% of the patients with BMS implantation [12].

CAAs due to stent implantation can be categorized as three types. Type I develops in the first 4 weeks after PCI, and Type II develops more than 6 months after PCI. These two types can be asymptomatic or can present with angina. Type III is associated with superinfection (mycotic aneurysm), and may present with systemic signs such as fever [4].

The current patient had non-specific symptoms, so was applied with CAG after evaluation with MPS. In this case, there was in-stent CAA at approximately 9 months after BMS implantation, but at 1 months after LAD PCI a control CAG was performed and the LAD stent was patent and there was no aneurysm at that time. Therefore, this case can be classified as Type-II CAA.

There are no documented guidelines for the management of post-stent CAAs. The optimal management method remains unclear due to conflicting data from individual case reports. Treatment strategies can be classified as medical therapy including antiplatelet or anticoagulant therapy [13], PCI therapy encompassing stent implantation, coil embolization, and BMS implantation [14-15] or surgical therapy [16].

Previous reports include the presentation by Yasuaki Hada et al. [14] of CAA that developed after DES implantation and was treated successfully with BMS, and Ioannis Iakovou et al. [15] presented 3 CAA cases successfully treated with BMS.

In accordance with this information, it was decided, after consultation, to treat the current patient with BMS implantation therapy instead of covered stent or surgery. After pre-dilatation with a 4.0 x 16 mm balloon, a 4.5 x 20 mm Liberty BMS was successfully implanted into the old-stent, to close the in-stent aneurysmal segment. The patient was thus successfully treated with PCI. Clopidogrel treatment was changed to ticagrelor. The patient was discharged with high-dose statin (atorvastatin 80 mg) + acetylsalicylic acid + ticagrelor + metoprolol regime. Ten months later, follow-up CAG and LAD FFR showed no aneurysm or critical lesion in the LAD stent. The patient has remained free of complaints with clinical follow-up visits.

We didn't use advanced techniques like, intravascular ultrasound or optical coherence tomography, so we couldn't explain the etiology. This issue can be regarded as the main limitation of the paper. However, treatment of in-stent aneurysm with a simple and inexpensive method is the strength of the case.

The case was here reported of a patient with CAA 9 months after BMS implantation, which developed in a 1-month period. A hypersensitivity reaction against the BMS metal, stent fracture or dissection under the stent due to over-dilatation can be reasons for CAA after BMS implantation. Due to problems with reimbursement agency payments, intravascular ultrasound or optical coherence tomography could not be applied. Therefore, the treatment strategy had to be decided only based on the CAG findings. The use of intravascular ultrasound can prevent over-dilation of the stent and/or the selection of an over-sized stent, thereby avoiding stretching of the coronary wall. The treatment strategy must be decided after consultation between the cardiologist and the cardiac surgeon and BMS re-implantation can be a successful treatment.

References

1. Syed M, Lesch M. Coronary artery aneurysm: a review. Prog Cardiovasc Dis. 1997;40:77-84.
2. Warisawa T, Naganuma T, Tomizawa N, Fujino Y, Ishiguro H, Tahara S, et al. High prevalence of coronary artery events and non-coronary events in patients with coronary artery aneurysm in the observational group. Int J Cardiol Heart Vasc. 2016;10: 29–31 .
3. Bal ET, Plokker HWT, Van de Berg EMJ, Ernst SMPG, Mast EG, Gin RMTJ, et al. Predictability and prognosis of PTCA-induced coronary artery aneurysms. Cathet Cardiovasc Diagn. 1991;22:85–8.
4. Aoki J, Kirtane A, Leon MB, Dangas G. Coronary artery aneurysm after drug-eluting stent implantation. J Am Coll Cardiol Intv. 2008;1:14-21.
5. Nichols L, Lagana S, Parwani A: Coronary artery aneurysm: A review and hypothesis regarding etiology. Arch Pathol Lab Med. 2008;132:823–8.
6. Chrissoheris MP, Donohue TJ, Young RS, Ghantous A. Coronary artery aneurysms. Cardiology in review. 2008;16:116-23.
7. Pappy R, Wayangankar S, Kalapura T, Abu-Fadel MS. Rapidly evolving coronary aneurysm in a patient with rheumatoid arthritis. Cardiol Res Pract. 2011;2011:659439.
8. Cabarrus M, Yang B, Schiller N, Miller DC, Ordovas K. Iatrogenic giant coronary artery pseudoaneurysm with "daughter aneurysm" formation: serial imaging findings and natural history. J Thorac Imaging. 2012;27:185-7.
9. Ahn CM, Hong BK, Kim JY, Min PK, Yoon YW, Lee BK, et al. Incidence and natural history of coronary artery aneurysm developing after drug-eluting stent implantation. Am Heart J. 2010;160:987-94.
10. Nonin S, Hasegawa T, Hirai H, Suehiro S, Yoshiyama M. Gi¬ant mycotic coronary aneurysm associated with late stent infection. Eur Heart J Cardiovasc Imaging. 2014;15: 630.
11. Crawley PD, Mahlow WJ, Huntsinger DR, Afiniwala S,Wortham DC. Giant coronary artery aneurysms: Review and update. Tex Heart Inst J. 2014;41:603-8 .
12. Köster R, Vieluf D, Kiehn M, Sommerauer M, Kähler J, Baldus S. et al. Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. Lancet. 2010;356:1895-7.
13. LaMotte LC, Mathur VS. Atherosclerotic coronary artery aneurysms: 8-year angiographic follow-up. Tex Heart Inst J. 2000;27: 72-3.
14. Hada Y, Fujii H, Shimizu M, Yamawake N, Nishizaki M. Effectiveness of Bare Metal Stent Implantation for the Treatment of Coronary Artery Aneurysm: A Multimodality Imaging Evaluation. Intern Med. 2017;56:3305-9.
15. Iakovou I, Dimopoulos A, Dangas G. Normal to normal: a method of treatment of coronary aneurysms with deployment of bare-metal stents. J Invasive Cardiol. 2011;23:121-5.
16. Ghanta RK, Subroto Paul, Gregory SC. Successful revascularization of multiple coronary artery aneurysms using a combination of surgical strategies. Ann Thorac Surg. 2007;84:10-1.