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European Journal of Therapeutics (Eur J Ther) is the double-blind peer-reviewed, open access, international publication organ of the Gaziantep University School of Medicine. The journal is a quarterly publication, published on March, June, September, and December and its publication language is English.

European Journal of Therapeutics aims to contribute to the international literature by publishing original clinical and experimental research articles, case reports, review articles, technical notes, and letters to the editor in the fields of medical sciences. The journal's target audience includes researchers, physicians and healthcare professionals who are interested or working in in all medical disciplines.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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Editor: Prof. Murat Sucu
Address: Gaziantep University, School of Medicine, Journal Office, 27310 Şehitkamil, Gaziantep, Turkey
Phone: +90 342 3606060/77751
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- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: A Turkish and an English abstract should be submitted with all submissions except for Letters to the Editor. Submitting a Turkish abstract is not compulsory for international authors. The abstract of Original Articles should be structured with subheadings (Objective, Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

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subheadings. Please check Table 1 for the limitations for Original Articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Editorial Comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

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Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	30	6	7 or tatal of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Technical Note	1500	No abstract	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.
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Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the

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Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

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Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

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Editor: Prof. Murat Sucu
Address: Gaziantep University, School of Medicine, Journal Office, 27310 Şehitkamil, Gaziantep, Turkey
Phone: +90 342 3606060 / 77751
Fax: +90 342 3601617
E-mail: info@eurjther.com

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Phone: +90 212 217 17 00
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Contents

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Review / Derleme

How to Read a Meta-Analysis? A Guideline for Clinicians

Bir Meta-analizi Nasıl Okunur? Klinisyenler için Bir Kılavuz

Seval Kul

Department of Biostatistics, Gaziantep University School of Medicine, Gaziantep, Turkey

ABSTRACT

Meta-analysis is a statistical analysis that combines the results of relevant studies performed for same purpose and is used as a tool for evidence-based medicine to support clinical decision making. Because a meta-analysis includes advanced statistical analysis, the report is not easily understandable to clinicians. In this study, we aimed to write a guideline for clinicians to help them understand the statistical analysis part of a meta-analysis and interpret graphs and results of a meta-analysis.

Keywords: Forest Plot, funnel plot, meta-analysis.

ÖZ

Meta-analizi aynı amaçla gerçekleştirilen ilgili çalışmaların sonuçlarını birleştiren ve kanıta dayalı tıpta karar vermeyi desteklemek için kullanılan bir araçtır. Meta-analizleri ileri istatistiksel analizler içerdiğinden, sonuçlar klinisyenler için kolayca anlaşılabilir değildir. Bu çalışmada, klinisyenlerin bir meta-analizin istatistiksel analiz bölümünü anlamalarına, sonuçlarını ve grafiklerini yorumlamalarına yardımcı yardımcı olmak bir kılavuz yazmayı amaçladık.

Anahtar kelimeler: Forest Plot, funnel plot, meta-analizi

INTRODUCTION

Clinicians always seek for the best evidence to make a clinical decision for a specific disease, treatment, or patients. Meta-analysis is a statistical analysis that combines the results of relevant studies performed for the same purpose and achieves overall results (1). It is used as a tool for evidencebased medicine to support clinical decision making (2). Meta-analyses are considered final studies, which show the efficacy of a drug or success of an experiments (2, 3). In addition to experimental studies, meta-analyses are also performed for observational studies to determinate important risk factors, diseases, or determinants of events. The report of a meta-analysis is usually very complex and includes several statistical stages (4). Because a meta-analysis includes advanced statistical analysis, the report is not easily understandable to clinicians. In this study, we aimed to write a guideline for clinicians to facilitate understanding of the statistical analysis part of a meta-analysis. Cochrane collaboration has an extremely good reputation for the past 20 years to gather and summarize the best evidence by performing meta-analyses (5). The steps of a Cochrane review are as follows (6):

Define questions, plan eligibility criteria, plan methods, search for studies, apply eligibility criteria, collect data, assess studies for bias risk, analyze and present results, interpret results and draw conclusions, and improve and update review. The PRISMA checklist can be used to verify the quality of a meta-analysis. It was prepared for transparent reporting of systematic reviews and meta-analysis and is widely used by researchers (7). It contains 27 items; of them, 7 are for the results section, which show the importance of the result section in meta-analysis. Several papers were published to explain researchers how to perform and report meta-analysis; however, a few studies focused on understanding the statistical part, which is a big challenge for clinicians (1, 6, 8, 9). In this article, we shall only focus on the understanding of statistical analysis and interpretation of results by advising some steps.

After reading the title of the meta-analysis, researchers should view the forest plots to understand the findings of the review. Several statistical packages, such as RevMan, R, and Medcalc, are available to perform meta-analysis, but all the packages provide extremely similar forest plots.

CLINICAL AND RESEARCH CONSEQUENCES

Understanding Forest Plots

Forest plot is the most commonly used graph and is highly valuable to visualize the results of a meta-analysis. In a forest plot, the result of each included study and the total effect can be easily seen. To explain the statistical part of meta-analysis the forest

ORCID IDs of the authors: S.K. 0000-0002-4716-9554.

Corresponding Author / Sorumlu Yazar: Seva Kul **E-posta/E-mail:** sevalkul@gantep.edu.tr

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plots of the publication with the title "Effects of care pathways on the in-hospital treatment of heart failure: a systematic review" were used (10).

Example for Dichotomous (Variable with Two Categories) Outcome: For dichotomous outcomes, such as hospital mortality (yes-no), readmission (yes-no), or having a complication (yes-no), we gain risk ratios (RR) or, preferably, risk differences (RDs) and 95% confidence intervals for each study and for the overall results (2). For retrospective studies, the RR is considered odds ratio (OR); for prospective studies, the RR is considered the relative risk (11). The RD is the difference between the risk of an event in experimental and control groups (6). In addition to the overall comparison, it is also possible to show results for subgroups in the same forest plot. As it is mentioned, the aforementioned two main outcomes of "Effects of care pathways on the in-hospital treatment of heart failure: a systematic review" were used to show the interpretation of the statistical part of a meta-analysis with different outcomes (10). The aim of the study was to show the impact of care pathways (CPs) on chronic heart failure patient outcomes, such as hospital mortality, readmission rate, length of hospital stay, and hospitalization cost. Studies that compared CPs vs standard treatment were included in the meta-analysis. Standard care is used as the reference group to evaluate the effectiveness for CPs. Therefore, RRs show relative changes in the outcome interest in the CP group vs standard treatment. RRs<1 show decrease in the risk, which is demanded for mortality. Figure 1 shows forest plot to compare the rate of hospital mortality (10). For readers to understand the forest plot for hospital mortality, which is a dichotomous outcome, five steps were defined in this article. The advised steps are explained in Figure 1 using labeled arrows and boxes.

Step 1: Understanding Groups Compared in a Meta-analysis. Look at the box shown by arrow 1. In this part, one can easily see the CP compared to standard care. Because the outcome of interest is the rate of mortality, number of the event and number of the total participants were given for each included study. For example, in the first study performed by Azad et al. (Figure 1) in 2008, among 45 participants of the CP group, no one died in hospital; however, among 46 participants of the standard care group, 2 participants died. The total number of the participants was 91 for this study.

Step 2: Checking Significance for the Overall Effect. Look at the box shown by arrow 2. In this section, the p value for the combined result is given. For our example, p=0.03, which indicates that there is a significant difference between CP and standard care in terms of mortality rate. When the p value of heterogeneity is less than 0.05, researchers prefer the random effect model for effect size estimation to eliminate the variation between studies. In this example, the p values for heterogeneity are 0.005, which indicates that the included studies vary from each other.

Step 3: Understanding the Effect Size Estimation Method Used in the Meta-analysis. Look at the box shown by arrow 3. RRs and 95% confidence intervals (CIs) are given to demonstrate the effect size for each study and the overall effect. In this meta-analysis, randomized clinical trials (RCTs) and controlled clinical trials (CCTs) were included. They are both prospectively designed study types. Therefore, RRs can be interpreted as relative RRs. The random effect model was used to estimate RRs and CIs because of the heterogeneity detected in step 2.

Figure 1. Forest Plot of Comparison for the Rate of Hospital Mortality (10)

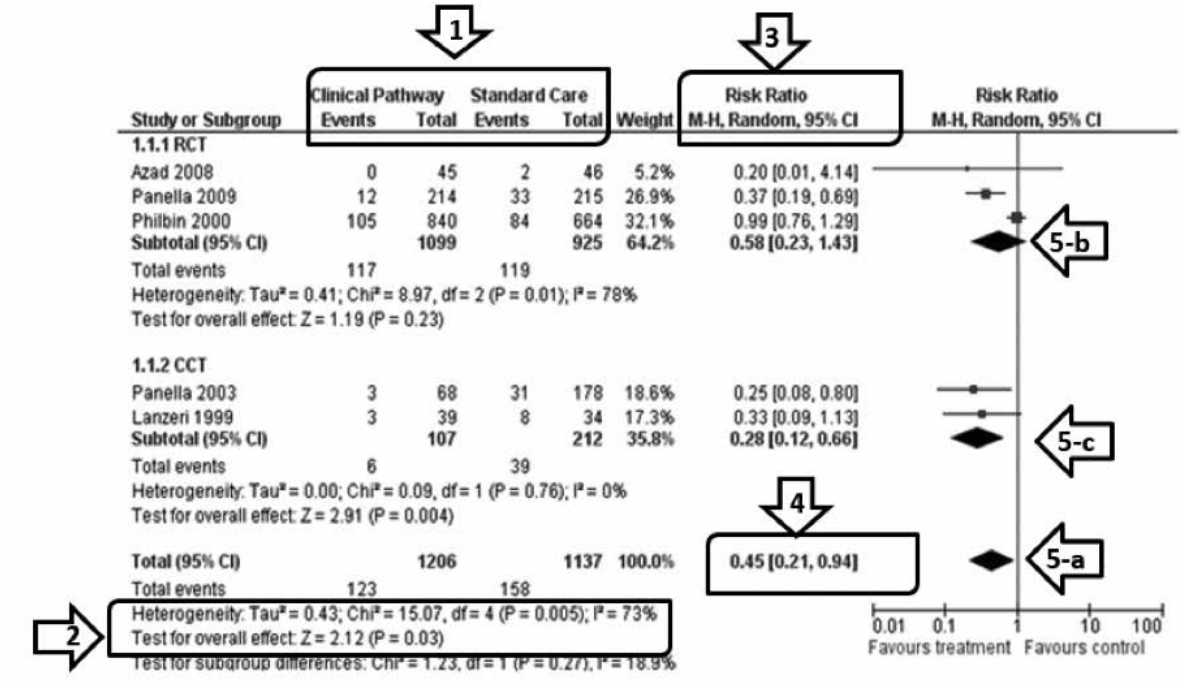
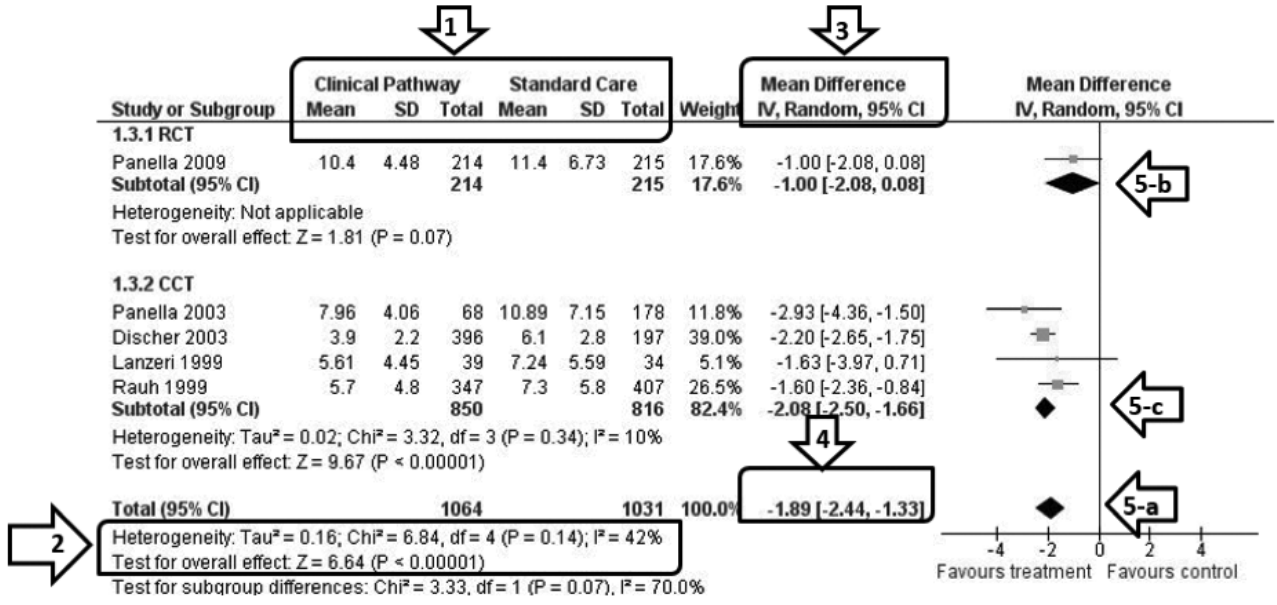


Figure 2. Forest plot of comparison for the length of hospital stay (10)



Step 4: Interpretation of the Overall Effect Size (Overall RR). Look at the box shown by arrow 4. RR>1 is interpreted as increase, RR<1 is interpreted as decrease in the risk, and RR=1 is interpreted as no significant effect (11). For this study, the RR for the total effect is estimated as 0.45, which indicates a 55% decrease of mortality rate in the CP group. In step 3, we have noted the significance of this effect, but it can be also verified by looking at the CI of RR. Because the CI of RR does not include "1," it is considered significant.

Step 5: Understanding of Diagram. Look at the boxes shown by arrow 5a, 5b, and 5c. At the right part of forest plot, a diagram is given to visualize the meta-analysis result. Because RR=1 is considered non-significant, the relative changes are given based on the vertical line located at 1 on the scale. Diamonds (▶) are used to show the overall effect size and effect size for subgroup analysis. Wider diamond demonstrates wider CI (6). There are three diamonds in Figure 1, one for the overall effect (arrow 5a), one for RCT studies (arrow 5b), and one for CCT studies (arrow 5c). When the diamond touches the vertical line, it indicates that CI includes "1," and p value is not significant for the effect (6). For example, for RCTs (arrow 5b), the diamond touches the vertical line and the p value is 0.230, which is non-significant. However, the diamond for CCT studies (arrow 5-c) does not touch the line and p=0.004.

Example for Numerical Outcome:
The mean and standard deviations are the most commonly used descriptive statistics for numerical variables, such as length of hospital stay or hospitalization cost (11). Therefore, a meta-analysis gathers the means and standard deviations of individual studies to compare the overall effect. The mean difference (MD) or standardized MD (SMD) statistics are used to measure the difference in the means in two groups (6). SMD, alternately, Cohen's d is calculated as follows.

$$SMD = \frac{\text{Difference in mean outcome between grours}}{\text{Standard deviation of outcome among participants}}$$

For interpreting the magnitude of the SMD, SMD<0.20 is interpreted as a small effect size and SMD>0.80 is interpreted as a large effect size (6).

The forest plot of comparison for the length of hospital stay is presented in Figure 2 (10). To ensure that the readers understand a forest plot, five steps are defined in this article. The advised steps are explained in Figure 2 by using labeled arrows and boxes.

Step 1: Understanding Groups Compared in the Meta-analysis. Look at the box shown by arrow 1. In this part, one can easily view the CP compared to standard care. Because the outcome of interest is the length of hospital stay, mean and standard deviations and the number of the total participants are given for each included study. For example, in the first study performed by Kul et al. (10) in 2009, the mean length of hospital stay for the CP group was 10.4 days, and 214 patients were included in the CP group; the mean is 11.4 day and 215 patients were included in the standard care group.

Step 2: Checking the Significance for the Overall Effect. Look at the box shown by arrow 2. In this section, the p value for the combined result is given. For our example, p<0.001, which means there is a highly significant difference between CP and standard care in terms of length of hospital stay.

Step 3: Understanding the Effect Size Estimation Method Used in the Meta-analysis. Look at the box shown by arrow 3. The MD and 95% CIs are given to demonstrate the effect size for each study and the overall effect. For this outcome, only one RCT reported the length of hospital stay and 4 CCTs reported the outcome.

Step 4: Interpretation of the Overall Effect Size (Overall MD). Look at the box shown by arrow 4. The MDs are calculated by extracting standard care group means from CPs. Negative MD shows a decrease in the CP group, which is desired. The MD for the overall effect is -1.89 days, which could vary between -2.44 and -1.33 days. In step 3, we have already seen the significance of this effect, but it can be also verified by noting the CI of MD. Because the CI of MD does not include "0," it is considered significant.

As mentioned above, some studies prefer to report SMD instead of MD.

Step 5: Understanding of Diagram. Look at the boxes shown by arrow 5a, 5b, and 5c. At the right part of the forest plot, a diagram is provided to visualize the result of the meta-analysis. Because MD=0 is considered non-significant, the relative changes are given based on the vertical line located at 0 on the scale. Diamonds (▶) are used to show the overall effect size and effect size for the subgroup analysis. Wider diamond demonstrates wider CI (6). There are three diamonds in Figure 2, one for the overall effect (arrow 5a), one for RCT studies (arrow 5b), and one for CCT studies (arrow 5c). When the diamond touches the vertical line, which indicates that CI includes "0," and the p value is not significant for the effect (6). For example, for RCTs (arrow 5b), the diamond touches the vertical line and the p value is 0.07, which is non-significant. Nevertheless, the diamond for CCT studies (arrow 5c) does not touch the line and $p<0.001$.

CONCLUSION

In this tutorial article, the interpretation of the meta-analysis result for numerical and dichotomous outcomes were explained in a step-by-step manner to increase the critical appraise abilities of readers for meta-analyses. We believe that the paper will be very useful for understanding and performing meta-analysis.

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Sağlıklı Erkeklerde Kinezyolojik Bantlama Uygulamasının Vücut Kitle İndeksi ile İlişkisinin Değerlendirilmesi

Evaluation the Relationship between Body Mass Index and Kinesiology Band Application to Acute Grip Strength on Healthy Men

Ender Ersin Avcı, Özlem Altındağ

Gaziantep Üniversitesi Sağlık Bilimleri Fakültesi, Fizyoterapi ve Rehabilitasyon Anabilim Dalı, Gaziantep, Türkiye

ÖZ

Amaç: Çalışma sağlıklı erkek bireylerde kinezyolojik bantlama uygulamasının kavrama kuvvetine akut etkisinin vücut kitle indeksi ile ilişkisini değerlendirme amacıyla yapılmıştır.

Yöntemler: Çalışmamıza 18-30 yaş arası doksan sağlıklı, sedanter erkek birey dahil edildi. Katılımcıların demografik bilgileri alınarak vücut kitle indeksleri (VKİ) hesaplandı. Normal kilolu, fazla kilolu ve obez olmak üzere katılımcılar otuzar kişilik 3 gruba ayrıldı. Uygulama bölgesi olarak dominant ön kol tercih edildi. Kinezyolojik bantlama (KB) uygulaması ön kol fleksör kaslarına yapıldı. Kavrama kuvvetini değerlendirmek için Jamar hidrolik el dinamometresi kullanıldı. Kinezyolojik bant uygulaması öncesi ve uygulamanın hemen sonrasında jamar hidrolik el dinamometresi ile kavrama kuvveti ölçümleri yapıldı. Tüm katılımcıların kavrama kuvveti değerinin en yüksek verisi ile vücut kitle indeksleri arasındaki ilişki istatistiksel olarak analiz edildi. Vücut kitle indeksine göre kategorize edilmiş olan alt gruplarda uygulama öncesi ve sonrasında elde edilen maksimum kuvvet değerleri istatistiksel olarak analiz edildi.

Bulgular: Tüm katılımcıların, kinezyolojik bant uygulaması sonrasında elde edilen kuvvet değerleri ile vücut kitle indeksleri arasında istatistiksel analiz yapıldı ve anlamlı sonuç elde edildi ($p<0,05$). Katılımcılar vücut kitle indekslerine göre alt gruplara ayrılarak sonuçlar analiz edildi, 30 kg/m^2 ve üzeri vücut kitle indeksine sahip bireyler dışında tüm katılımcıların kavrama kuvveti değerinde artış gözlemlendi ancak vücut kitle indekslerine göre ayrılmış alt gruplarda istatistiksel anlamlı sonuç elde edilemedi ($p>0,05$).

Sonuç: Uygulama sonrasında vücut kitle indeksi 30 kg/m^2 ve üzeri olan grupta kavrama kuvvetinde bir artış gözlenmemiştir. Vücut kitle indeksi 20-24,9 kg/m^2 ve 25-29,9 kg/m^2 aralıklarında olan gruplarda kavrama kuvvetinde artış gözlendi. Ancak bu alt grupların hiçbirinde kinezyolojik bantlama uygulamasının kavrama kuvveti üzerindeki akut etkisi ile vücut kitle indeksi değeri arasında anlamlı bir ilişki bulunmadı.

Anahtar kelimeler: Kinezyolojik bantlama, vücut kitle indeksi, kavrama kuvveti

ABSTRACT

Objective: This study aimed to evaluate the association between body mass index (BMI) and kinesio tape (KT) application in healthy men aged 18-30 years.

Methods: BMI of the participants was calculated before initiating the study. Ninety participants were equally divided into the following three groups: normal weight, overweight, and and obese. KT was applied to the flexor muscles of the dominant forearm of the participants. Using Jamar dynamometer, the grip strength of the upper extremity was measured before and immediately after applying KT. The association between average grip strength value and BMI were statistically analyzed for all participants.

Results: The categorized subgroups according to BMI of the participants. The maximum force obtained, before and after applying KT were statistically analyzed. BMI and the maximum grip strength value after applying KT were statistically analyzed for all participants. The results were statistically significant ($p<0.05$). The participants were divided into subgroups according to their BMI, and the results were then analyzed.

Conclusion: The grip strength values of all participants, except those with BMI ≥30 kg/m^2, increased after applying KT, but for each subgroups, before and after KT application values were not statistically significant ($p>0.05$). In participants with BMI ≥30 kg/m^2, there was no significant increase in the grip strength values after applying KT. In contrast, the grip strength values of the other participants with BMI 20–24.9 kg/m^2 and 25–29.9 kg/m^2 increased after applying KT.

Keywords: Kinesio tape, body mass index, grip strength

ORCID IDs of the authors: E.E.A. 0000-0002-8089-0351; Ö.A. 0000-0003-1119-2987.

Sorumlu Yazar/Corresponding Author: Ender Ersin Avcı **E-posta/E-mail:** ender.ersin.avci@gmail.com

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GİRİŞ

Kinezyolojik bantlama (KB) uygulama farkına bağlı olarak kasın gevşetilmesi ve kasın kasılmasını kolaylaştırmak amacıyla kullanılabilir. Literatürde esnek bantlamanın kasın insersiyosundan origosuna doğru uygulanması durumunda kasın kasılmasına yardımcı olduğu yönde çalışmalar mevcuttur (1).

Literatürde kinezyolojik bantlamanın etkileri üzerine yapılan çalışmaların sonuçları farklılık göstermektedir. Örneğin bir çalışmada kinezyolojik bantlamanın akut kavrama kuvvetine etkisini ölçümlenmiş ve anlamlı bir sonuç elde edilememiştir (2). Diğer yandan kinezyolojik bantlama uygulamasının kas aktivitesi ve vertikal zıplamaya etkisini gözlemleyen çalışma vertikal sıçrama ve kas aktivitesi artışı açısından anlamlı sonuçlar elde etmiştir (3).

Bu çalışmaların farklı sonuçlar açığa çıkarması katılımcıların farklı vücut kitle indekslerine sahip olmalarından kaynaklı olabilir. Bu bakış açısıyla çalışma planlayarak literatüre katkıda bulunmak, daha sonra planlanacak çalışmalara ölçümlerin doğruluğu açısından yol gösterici olacaktır.

Bu çalışmada Kinezyolojik bantlamanın akut kuvvetlendirici etkinliği ile vücut kitle indeks değeri arasında ilişki değerlendirmesi yaparak, yaygın bir kullanıma sahip olan ancak kullanım kriterleri açısından hala yeterli literatür bilgisi bulunmayan kinezyolojik bantlama uygulaması hakkında literatüre katkıda bulunmak amaç edinilmiştir.

YÖNTEMLER

Çalışma sağlıklı ve gönüllü doksan erkek bireyin katılımıyla gerçekleştirildi. Katılımcılardan çalışmaya dahil olmadan önce, çalışma için gönüllü olduklarına dair yazılı onam formu alınmıştır. Çalışma protokolü için etik komite onayı alınmıştır. Grupların homojen dağılım gösterebilmesi için katılımcılar belirlenirken bireylerin VKİ değerleri göz önünde bulunduruldu. Yaşa ve cinsiyete bağlı performans farklılıklarının etkisini azaltmak için çalışmaya alınacak olgularda belirli bir yaş aralığı belirlendi ve sadece erkek olgular çalışmaya dahil edildi. Erkek olguların tercih edilme nedeni belirlenen çalışma alanlarında daha fazla sayıda kişiye ulaşılabilme imkânının olmasıdır. Araştırma, kesitsel çalışma niteliğindedir. Çalışma Ocak 2017-Nisan 2017 tarihleri arasında 18-30 yaş aralığında sağlıklı ve gönüllü 90 erkek bireyin katılımıyla gerçekleşti. Çalışmaya katılacak bireyler vücut kitle indeksleri göz önüne alınarak normal kilolu (20-24,9 kg/m^2), fazla kilolu (25-29,9 kg/m^2) ve obez (30 ve üzeri kg/m^2) olmak üzere her biri 30 kişilik 3 ayrı grupta kategorize edilmiştir. Herhangi bir uygulama yapılmaksızın katılımcıların her birinin dominant üst ekstermitlerinin maksimum kavrama kuvvetleri jamar hidrolik el dinamometresiyle 3 kez ölçümlendi ve değerler not edildi. Ardından gönüllülerin dominant taraf ön kol fleksör kas gruplarını içine alacak şekilde kinezyolojik bantlama uygulandı. Kinezyolojik bantlama uygulaması yapıldıktan sonra tekrar jamar hidrolik el dinamometresi ile her katılımcıdan dominant üst ekstremitelerini kullanarak 3 kez maksimum kavrama yapması istenip elde edilen ölçüm değerleri kayıt edildi. Tüm kavrama ölçümleri arasında katılımcılara birer dakikalık dinlenme süreleri verildi.

Dâhil edilmeme kriterleri:

- Katılımcının son 6 ay içinde dirsek ve/veya el bileği yaralanması geçirmiş olması,
- Katılımcının 18-30 yaş aralığında olmaması
- Dominant üst ekstremitesinden herhangi bir cerrahi operasyon geçirmiş olması,
- Katılımcının düzenli olarak dominant üst ekstremitesini kuvvetlendirmeye yönelik bir spor aktivitesinin bulunması
- Katılımcıların istenilen zamanda hazır bulunmaması
- Katılımcının isteğe göre çalışmaya son vermesi

Değerlendirmeler

Kavrama kuvvetini değerlendirmek için daha önce tedarik edilmiş olan jamar hidrolik el dinamometresi kullanıldı. Ölçümler öncesinde her gönüllünün yaşı, cinsiyeti, boyu, vücut ağırlığı, dominant üst ekstremite bilgisi, ön kola yönelik spor geçmişinin olup olmadığı ve uygulama yapılacak dominant üst ekstremitesinden daha önce herhangi bir cerrahi müdahale ve/veya yaralanma geçirip geçirmediği sorgulandı ve kaydedildi. Dominant elin belirlenmesinde öncelikli olarak hangi eli ile yazı yazdığı ve günlük yaşamda top atma, bıçakla ve makasla kesme, diş fırçalama ve işaret etme gibi aktiviteleri hangi eli ile yaptığı soruldu. Aktivitelerin tümünde aynı elini kullandığını söylüyorsa belirttiği el dominant el olarak kabul edildi. Yazı yazma ve diğer aktiviteler için farklı ellerini kullandığını söyleyen olgularda ise belirtilen aktivitelerde en sık kullandığını bildirdiği eli dominant el olarak kabul edildi (4).

Olgulara genel dışlanma ölçütlerinde belirtilen sağlık problemleri ile ilgili sorgulama yapıldı. Olguların verdiği yanıtlar kayıt edildi. Herhangi bir kontraktür ve deformite mevcudiyeti, ciltte skar doku gözlemi, ödem ve dolaşım problemlerine dair belirtiler kontrol edildi. Tüm üst ekstremitede eklemler aktif olarak normal hareket açıklıkları boyunca hareket ettirilerek herhangi bir kısıtlanma olup olmadığı araştırıldı.

Vücut kitle indeksi (VKİ) kullanımı, çocuklarda, hamile kadınlarda ve kas kitlesi fazla olan sporcularda doğru sonuç vermez (5). Bu yüzden herhangi bir spor dalıyla ilgilenen ve 18 -30 yaş aralığında olmayan katılımcılar çalışmanın anlamlı sonuçlar verebilmesi için çalışma dışı bırakıldı.

Richards ve ark. (6) göre, ön kol pronasyon ve nötral pozisyonuna kıyasla en yüksek kavrama gücünü supinasyon konumundayken sağlamaktadır. Bu nedenle kavrama kuvveti ölçümü yapılaması planlanan çalışmalarda ön kolun supinasyon konumuna getirilmesini önemektedirler. Bu öneri doğrultusunda çalışmamız ölçümleri esnasında ön kol supinasyon konumu kullanımını sağlamaya çalışılmıştır. Ancak uygulamaya katılan birey tekil baz alındığı için ölçümlere başlamadan önce bireyden kendisi için en rahat olan tutuş pozisyonunu belirlemesi ve ölçümler boyunca belirlediği tutuş pozisyonunu kullanması istendi.

Jamar hidrolik el dinamometresi kavrama kuvveti ölçümlerinde en doğru ve güvenilir sonuçları veren cihaz olarak kabul görmektedir (7). Bu nedenle çalışmamızda 31109131 seri numaralı UK menşeili Jamar Hidrolik el dinamometresi kullanıldı (Jamar, Sammons Preston, Bolingbrook, Illinois, USA).

Çalışmaya dahil katılımcıların kavrama gücü katılımcı oturur konumda omuz nötralde ve dirsek 90 derece fleksiyonunda 3 kez jamar dinamometresi ile ölçüldü (8, 9). Ardından ön kol fleksör kaslarını literatürde önerildiği üzere gergin pozisyona alınıp (el bileği ekstansiyonu) kasların insersiyosundan origosuna doğru kinezyolojik bantlama uygulaması yapıldı (10). KB uygulaması yapılırken kas desteği sağlaması dolayısıyla Y tipi bantlama tekniği kullanıldı. Ardından olgulardan, bantlamasız ölçümde bahsi geçen anatomik pozisyonda jamar hidrolik el dinamometresiyle önerilen şekilde 3 defa kavrama yapmaları istendi ve elde edilen kuvvet değerleri kaydedildi (11, 12).

Yukarıda bahsi geçen tüm kavrama ölçümleri arasında, literatürde kullanılan esaslar çerçevesinde, kas yorgunluğunu elimine etmek amacıyla 1'er dakikalık dinlenme süresi uygulandı (13).

İstatistiksel Analiz

Yapılan analizler SPSS (Statistical Package for Sociel Sciences) Version 21.0 (IBM Corp.; Armonk, NY, USA) programıyla yapılmıştır. İki sayısal ölçüm arasında doğrusal bir ilişki olup olmadığını, varsa bu ilişkinin yönünü ve şiddetinin ne olduğunu belirlemek için kullanılan bir istatistiksel yöntem olması dolayısıyla Pearson Correlation analiz yöntemi kullanıldı.

BULGULAR

Klinik Araştırmalar ve Etkileri

Sağlıklı erkeklerde kinezyolojik bantlama uygulamasıyla kavrama kuvvetine akut etkinin vücut kitle indeksi ile ilişkisinin değerlendirilmesi amaçlı yaptığımız çalışmaya katılımcıların bireylerin demografik bilgileri 1. tabloda detaylı olarak sunulmuştur.

Tablo 1. Katılımcıların demografik bilgiler tablosu

	Grup-1 (20-24,9 kg/m² VKİ) ortalama±STD (30 birey)	Grup-2 (25-29,9 kg/m² VKİ) ortalama±STD (30 birey)	Grup-3 (30 ve üzeri kg/m² VKİ) ortalama±STD (30 birey)	Tüm katılımcılar ortalama±STD (90 birey)
Yaş ortalaması	22,17±0,52	22,65±0,52	24,86±0,53	23,23±0,33
En yüksek değer	30	28	30	30
En düşük değer	19	18	19	18
Boy ortalaması	178,48±1,28cm	178,00±1,13cm	174,83±1,68cm	177,10±0,81cm
En yüksek değer	190 cm	191 cm	192 cm	192 cm
En düşük değer	165 cm	162 cm	155 cm	155 cm
Kilo ortalaması	71,28±1,61 kg	85,20±1,27 kg	99,27±2,19 kg	85,25±1,58 kg
En yüksek değer	89 kg	104 kg	132 kg	132 kg
En düşük değer	54 kg	69 kg	75,4 kg	54 kg

Veriler ortalama+standart sapma şeklinde verilmiştir.
VKİ: vücut kitle indeksi; KB: kinezyolojik bantlama; STD: standart sapma

Tablo 2. Uygulama öncesi ve sonrası en yüksek ve en düşük kuvvet değerleri

	Grup-1 (20-24,9 kg/m² VKİ) ortalama±STD (30 birey)	Grup-2 (25-29,9 kg/m² VKİ) ortalama±STD (30 birey)	Grup-3 (30 ve üzeri kg/m² VKİ) ortalama±STD (30 birey)	Tüm katılımcılar ortalama±STD (90 birey)
KB Öncesi	48,62±1,60 kg	47,96±1,31 kg	46,52±1,37 kg	47,70±0,82 kg
En Yüksek Değer	80 kg	64 kg	68 kg	80 kg
En Düşük Değer	36 kg	32 kg	36 kg	32 kg
KB Sonrası	50,69±1,44 kg	51,52±1.37 kg	45,79±1,25 kg	49,33±0,82 kg
En Yüksek Değer	70 kg	66 kg	60 kg	70 kg
En Düşük Değer	38 kg	36 kg	33 kg	33 kg

VKİ: vücut kitle indeksi; KB: kinezyolojik bantlama; STD: standart sapma

Çalışmanın ölçümleri esnasında en yüksek kuvvet değeri kinezyolojik bant uygulaması öncesi 20-24,9 kg/m² VKİ (1.grup) değere sahip grup katılımcılarından elde edildi. Çalışmanın ölçümleri esnasında en düşük kavrama kuvveti değeri 25-29 ,9 kg/m² vki değerine sahip bireyler içeren 2. Grup katılımcılarından KB uygulaması öncesinde elde edildi

Katılımcıların dahil oldukları gruplara göre kinezyolojik bantlama uygulaması öncesi ve sonrasında elde edilen ortalama kavrama kuvvet değerleri Tablo 2'de ve Şekil 1'de sunulmuştur.

Tüm katılımcıların vücut kitle indeksi değerleri ile kinezyolojik bant uygulaması öncesinde elde edilen kuvvet değerleri Pearson Correlation testi ile kıyaslandı ve 0,077 değerinde negatif yönde bir korelasyon görüldü ancak bu iki değişken arasında anlamlı bir ilişki görülmedi.

Tüm katılımcılara kinezyolojik Bant uygulaması yapıldıktan sonra elde edilen kuvvet değerleri ile vücut kitle indeksi değerleri arasında 0,249 değerinde negatif yönde bir korelasyon ve uygulama yapıldıktan sonra da p<0,05'e göre iki değişken arasında anlamlı bir ilişki görüldü (Tablo 3)

Grup 1'e dahil olan katılımcıların vücut kitle indeksi değerleri ile kinezyolojik bant uygulaması öncesinde elde edilen kuvvet değerleri arasında 0,199 değerinde pozitif yönde bir korelasyon görülürken iki değişken arasında anlamlı bir ilişki görülmedi.

Grup 1'deki katılımcılara kinezyolojik bant uygulaması yapıldıktan sonra elde edilen kuvvet değeri ile vücut kitle indeksi değeri arasında 0,007 değerinde pozitif yönde bir korelasyon görülmüş ve uygulama yapıldıktan sonra da iki değişken arasında anlamlı bir ilişki görülmemiştir (Tablo 4).

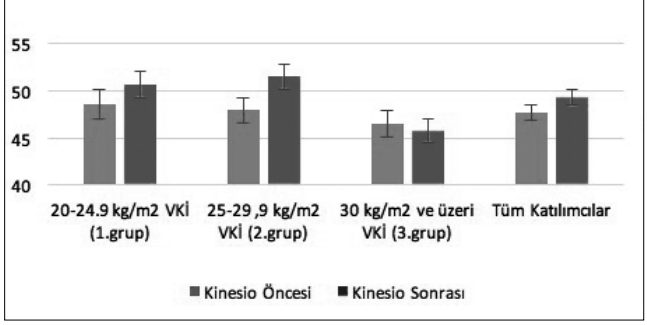
Grup 2'ye dahil olan katılımcıların vücut kitle indeksi değerleri ile kinezyolojik bant uygulaması öncesinde elde edilen kuvvet değerleri arasında 0,313 değerinde pozitif yönde bir korelasyon görülürken iki değişken arasında anlamlı bir ilişki görülmedi.

Grup 2 katılımcılarına kinezyolojik bant uygulaması yapıldıktan sonra alınan değerler ile vücut kitle indeksi değeri arasında 0.313 değerinde pozitif yönde bir korelasyon görüldü ve uygulama yapıldıktan sonra da iki değişken arasında anlamlı bir ilişki görülmedi.

Diğer gruplara göre en uygun pozitiflik değeri 25-29,9 kg/m^2 arası VKİ değerine sahip (2. grup) bireylerde olduğu görüldü (Tablo 5).

Grup 3'e dahil olan gönüllülerin vücut kitle indeksi değeri ile kinezyolojik bant uygulaması öncesinde elde edilen kuvvet değerleri arasında 0,190 değerinde negatif yönde bir korelasyon görülürken iki değişken arasında anlamlı bir ilişki görülmedi (Tablo 6).

Şekil 1. Kinesiolojik bant öncesi ve sonrası ortalama kuvvet grafiği



VKİ: vücut kitle indeksi; KB: kinezyolojik bantlama

Grup 3'te yer alan katılımcılara kinezyolojik bant uygulaması yapıldıktan sonra elde edilen kuvvet değerleri ile vücut kitle indeksi değerleri arasında 0,210 değerinde negatif yönde bir korelasyon görüldü ve uygulama yapıldıktan sonra da iki değişken arasında anlamlı bir ilişki görülmedi.

Tablo 3. Tüm katılımcıların kuvvet değeri açısından KB uygulaması öncesi ve sonrası elde edilmiş değerlerin, vki değerleri ile korelasyonu

Tüm katılımcılar (90 birey)		
KB uygulaması öncesi kuvvet değerleri	Pearson correlation	-,077
	Sig. (2-tailed)	,480
	N	90
KB uygulaması sonrası kuvvet değerleri	Pearson correlation	-,249
	Sig. (2-tailed)	,020*
	N	90

*Correlation is significant at the 0.05 level (2-tailed)
VKİ: vücut kitle indeksi; KB: kinezyolojik bantlama; Sig.: significance; N: number

Tablo 4. VKİ 20-24,9 kg/m^2 (grup1) VKİ değerine sahip katılımcıların kinezyolojik bant uygulaması öncesi ve sonrası elde edilmiş kuvvet değerlerin, vki değerleri ile korelasyonu

GRUP 1 (VKİ 20-24,9 kg/m^2)		
KB uygulaması öncesi kuvvet değerleri	Pearson correlation	,199
	Sig. (2-tailed)	,300
	N	30
KB uygulaması sonrası kuvvet değerleri	Pearson correlation	,007
	Sig. (2-tailed)	,971
	N	30

*Correlation is significant at the 0.05 level (2-tailed)
VKİ: vücut kitle indeksi; KB: kinezyolojik bantlama; Sig.: significance; N: number

Tablo 5. VKİ 20-24,9 kg/m^2 (grup1) VKİ değerine sahip katılımcıların kinezyolojik bant uygulaması öncesi ve sonrası elde edilmiş kuvvet değerlerin, vki değerleri ile korelasyonu

GRUP 2 (VKİ 25-29,9 kg/m^2)		
KB uygulaması öncesi kuvvet değerleri	Pearson correlation	,313
	Sig. (2-tailed)	,098
	N	30
KB uygulaması sonrası kuvvet değerleri	Pearson correlation	,313
	Sig. (2-tailed)	,098
	N	30

Correlation is significant at the 0.05 level (2-tailed)
VKİ: vücut kitle indeksi; KB: kinezyolojik bantlama; Sig.: significance; N: number

Tablo 6. 30 ve üzeri kg/m² VKİ değerine sahip katılımcıların kinezyolojik bant uygulaması öncesi ve sonrası elde edilmiş kuvvet değerlerin, VKİ değerleri ile korelasyonu

Grup 3 (VKİ 30 ve üzeri kg/m²)		
KB uygulaması öncesi kuvvet değerleri	Pearson Correlation	-,190
	Sig. (2-tailed)	,323
	N	30
KB uygulaması sonrası kuvvet değerleri	Pearson Correlation	-,210
	Sig. (2-tailed)	,273
	N	30

*. Correlation is significant at the 0.05 level (2-tailed)
VKİ: vücut kitle indeksi; KB: kinezyolojik bantlama; Sig.: significance; N: number

Bu veriler ışığında kinezyolojik bant uygulaması neticesinde en çok kas kuvveti artışının 25-29,9 kg/m² VKİ'ye sahip bireylerin bulunduğu 2. grupta olduğu görüldü. 20-24,9 kg/m² VKİ'ye sahip bireylerde de bu uygulamanın pozitif yönde etkileri olmuştur; fakat optimum (en uygun seviye) seviyenin 25-29,9 kg/m² arasında VKİ'ye sahip bireylerde olduğu görülmüştür. Ayrıca 30 kg/m² ve üzeri VKİ'ye sahip bireyler uygulamadan sonra uyguladıkları kuvvet negatif yönde değer almış ve olumsuz etkilenmişlerdir.

Kısaca kinezyolojik bant uygulamasının kuvvetlendirme açısından, en etkili olduğu vücut kitle indeksi 25-29,9 kg/m² arasında olan bireylerde olduğu görülmüştür ve 30 kg/m² ve üzeri vki değere sahip bireylerin uygulamadan olumsuz etkilendiği belirlendi.

TARTIŞMA

Üst ekstremitenin fonksiyonelliğini etkileyen en önemli unsurlardan bir tanesi elin işlevselliğidir. El, sınırsız kavrama ve tutma becerisine sahip iken aynı zamanda da çevreden sıcak, soğuk, sivri, künt vb. birçok duyusal uyaranlar alır. El fonksiyonlarından kavrama kabiliyeti iş hayatında ve günlük yaşam aktivitelerini gerçekleştirmede önemli bir yere sahiptir (14).

Fizyoterapist, doktor, ergoterapist vb. birçok meslek mensubu, uygulanabilirliği kolay ve ucuz bir yöntem olması dolayısıyla kavrama kuvveti ölçümünü değerlendirmelerinde sıkça kullanmaktadır (4, 15, 16). Üst ekstremite performansını değerlendirmek için kullanılan kavrama kuvveti ölçümü objektif bir ölçüm yöntemi olarak kabul görmektedir (17). Kavrama kuvvetinde herhangi bir nedenle kuvvet kaybı yaşanması durumunda, bireyin yaşam kalitesi negatif yönde etkilendiği için fizyoterapistler dahil birçok sağlık meslek grubu bu kuvvet kaybını gidermeye yönelik tedavi yöntemleri uygularlar.

Son yıllarda fizyoterapistler elastik bantlama yöntemlerini uyguladıkları tedavilere ek olarak oldukça yaygın olarak kullanmaktadırlar. Uygulamanın kas gücü artırma, vücut postürü düzeltme ve ağrı semptomunu düzenleme gibi birçok kullanım alanı mevcuttur (18, 19).

Günümüzde primer olarak kas aktivitesini değiştirmeyi hedefleyen bantlama teknikleri fizyoterapi yöntemleri içerisinde yaygın hale gelmiştir (20). Esnek bantlamanın kasın insersiyosundan origosuna doğru uygulanması durumunda kasın kasılmasına yardımcı olduğu yönde çalışmalar mevcuttur (1). Aynı zamanda bantlama yönteminin, kasın origosundan insersiyosuna doğru yapıldığı koşullarda ise kas inhibisyonu sağlandığını ve bu sayede ağrı semptomunu azaltmak amacıyla kullanılabilir bir yöntem olduğunu savunan çalışmalar vardır (20). Bizim çalışmamızda bantlama uygulaması yapılırken kas kuvveti artışı yani aktivasyonu amaçlandığı için kasın insersiyosundan origosuna doğru elastik bantlama yapılmıştır.

Literatürde kinezyolojik bantlamanın etkileri üzerine yapılan birçok çalışma bulunmakta ve bu çalışmalardan bazılarında istatistiksel açıdan olumlu sonuçlar elde edilirken bazılarında ise anlamlı sonuçlar elde edilememiştir. Bu farklılıkların hangi değişkenlerden kaynaklı olduğuna yönelik çok fazla çalışma bulunmamaktadır.

Chang ve ark. (2) 2010 yılında 21 sağlıklı üniversite öğrencisi ile gerçekleştirdiği bir çalışmada kinezyolojik bantlama yapıldıktan sonra, plasebo bantlama uygulaması ardından ve bantlama yapılmadan olmak üzere 3 farklı durumda kas kavrama kuvveti değerlendirmiş ancak istatistiksel anlamlı bir sonuç elde edilememişlerdir. Biz çalışmamızda VKİ değeri 25-29,9 kg/m² ve 20-24,9 kg/m² aralıklarında olan katılımcılarda kas kuvvet değerinde artış olduğunu belirledik. Ancak bu çalışmanın sonucuna benzer olarak, tüm katılımcıları alt gruplara ayırmadan vki değerleri ile uygulama sonrasında elde edilen kuvvet değerlerinin analizi dışında yapılan istatistiksel analizlerde anlamlı bir sonuç elde edemedik.

Diğer yandan Huang ve ark. (3) 31 sağlıklı yetişkinle planladığı ve gerçekleştirdiği kinezyolojik bantlama uygulamasının kas aktivitesi ve vertikal zıplamaya etkisini gözlemleyen çalışmada, vertikal sıçrama ve kas aktivitesi artışı açısından anlamlı sonuçlar elde etmişlerdir. Biz çalışmamızda obez bireyler dışında kinezyolojik bantlamanın kas kuvvetine olumlu etkileri olduğu sonucunu elde ettik. Spor yapan bireylerde obezite yani 30 ve üzeri vücut kitle indeksi görülme sıklığının ve buna paralel olarak vücut yağ oranının düşük olması beklenmesi dolayısıyla bu çalışmadan olumlu sonuç alınmasının bizim çalışmamızı desteklediğini düşünmekteyiz. Çünkü vücut yağ oranı düştükçe deri ile kas fasyası arasında bulunan yağ kitlesinin de bu duruma paralel olarak azalacağını ve yapılan bantlama uygulamasının kasın fasyasında daha etkili sonuçlar açığa çıkaracağını düşünmekteyiz

Kinezyolojik bantlama uygulamasının kas kuvvetine etkisini gözlemlemek amacıyla 14 sağlıklı genç sporcu üzerinde yapılan bir çalışmada ise diz ekleminde yer alan ekstansör grup kaslar izokinetik cihaz kullanılarak değerlendirilmiştir. Kas kuvveti bu kaslara KB uygulamadan önce, uyguladıktan hemen sonra ve KB uygulamasının 12 saat sonrasında olmak üzere 3 farklı durumda değerlendirmeye alınmıştır. Ancak elde edilen sonuçlar kas kuvvet değeri açısından istatistiksel olarak anlamlı bulunamamıştır (19). Biz ise çalışmamızda bu çalışmanın bölümlerinden birini oluşturan bantlamanın akut kuvvet değerlendirmesini gerçekleştirdik. 30 kg/m² ve üzeri VKİ değerine sahip katılımcıların yer aldığı grup dışındaki tüm katılımcıların kas kuvvetinde artış gözlemledik. Aynı zamanda tüm katılımcıların KB uygulaması sonrası kuvvet

değerleri ile VKİ değerleri arasında negatif yönde istatistiksel anlamlı bir ilişki olduğunu saptadık (p<0,05).

Çalışmamız neticesinde elde ettiğimiz verilere bakıldığında, kinezyolojik bant uygulamasının en uygun kuvvet artışını 25-29,9 kg/m^2 VKİ'ye sahip bireylerde sağladığı görülmüştür. 20-24,9 kg/m^2 VKİ'ye sahip bireylerde de bu uygulama pozitif yönde etkili olmuştur; fakat optimum (en uygun seviye) seviyenin 25-29,9 kg/m^2 arasında VKİ'ye sahip bireylerde olduğu görülmüştür. Ayrıca 30 kg/m^2 ve üzeri VKİ'ye sahip bireylerin uygulamadan sonra uyguladıkları kuvvet değeri negatif yönde değer almış ve bu bireyler uygulamadan olumsuz etkilenmişlerdir. Katılımcıların değerlendirmeleri yapılırken her ölçüm arasında Innes ve ark. (13) yaptıkları çalışma neticesinde önerdikleri 1'er dakikalık dinlenme süreleri uygulanmıştır. Ancak sadece 30 kg/m^2 ve üzeri VKİ değerine sahip katılımcıların bulunduğu 3. grupta kuvvet değerinin negatif yönde etkilendiği sonucu elde edilmiştir.

SONUÇ

Sağlıklı erkeklerde kinezyolojik bantlama uygulamasıyla kavrama kuvvetine akut etkinin vücut kitle indeksi ile ilişkisini değerlendirdiğimiz çalışmamızda,

1. Tüm katılımcıların, vücut kitle indeksi değerleri ile kinezyolojik bant uygulaması öncesinde yapılan ölçümler neticesinde elde edilen kuvvet değerinin istatistiksel analizi sonucunda negatif yönde bir korelasyon görülürken, p<0,05'e göre bu iki değişken arasında anlamlı bir ilişki görülmemiştir.

2. Tüm katılımcılara kinezyolojik bant uygulaması yapıldıktan sonra yapılan ölçümler neticesinde elde edilen kuvvet değerleri ile vücut kitle indeksi değerleri arasında negatif yönde bir korelasyon ve uygulama yapıldıktan sonra da p<0.05'e göre iki değişken arasında anlamlı bir ilişki görülmüştür ve istatistiksel analiz neticesi Tablo 3'te verilmiştir.

Çalışmaya katılan bireyler vücut kitle indekslerine göre otuzar kişilik 3 alt gruba ayrıldıktan sonra istatistiksel analiz yapıldığında,

1. Grupta yer alan VKİ değerleri 20-24,9 kg/m^2 arasında değişkenlik gösteren bireylere KB uygulaması yapılmadan önce ve sonra yapılan ölçümler neticesinde kg cinsinden elde edilen kuvvet değerleri ile VKİ değerleri arasında yapılan istatistiksel analiz neticesinde p<0,05'e göre anlamlı korelasyon bulunamamıştır ve Tablo 4'te istatistiksel analiz neticesi verilmiştir. Ancak KB uygulaması sonrasında kuvvet değerlerinde artış gözlemlenmiştir.

2. Grupta yer alan VKİ değerleri 25-29,9 kg/m^2 arasında değişkenlik gösteren bireylere KB uygulaması yapılmadan önce ve sonra yapılan ölçümler neticesinde kg cinsinden elde edilen kuvvet değerleri ile VKİ değerleri arasında yapılan istatistiksel analiz neticesinde p<0,05'e göre anlamlı korelasyon bulunamamıştır ve Tablo 5'te istatistiksel analiz neticesi verilmiştir. Ancak KB uygulaması sonrasında kuvvet değerlerinde artış gözlemlenmiştir ve optimum kuvvet değeri artışı bu grupta yer alan katılımcılarda görülmüştür.

3. Grupta yer alan VKİ değerleri 30 kg/m^2 ve üzeri olan bireylere KB uygulaması yapılmadan önce ve sonra yapılan ölçümler neticesinde kg cinsinden elde edilen kuvvet değerleri ile VKİ değerleri arasında yapılan istatistiksel analiz neticesinde p<0,05'e göre anlamlı korelasyon bulunamamıştır ve Tablo 6'da istatistiksel analiz neticesi vermiştir. KB uygulaması sonrasında bu grupta yer alan katılımcıların kuvvet değerlerinde azalma gözlemlenmiştir.
Kısaca kinezyolojik bant uygulamasının en etkili olduğu vücut kitle indeksi 25-29,9 kg/m^2 (2. grup) arasında olan bireylerde olduğu görülmüştür, VKİ değeri 30 kg/m^2 üzerine çıktıkça bireyin bu uygulamadan olumsuz etkilendiği belirlenmiştir.

Öneriler

Kinezyolojik bantlama uygulamasıyla kavrama kuvvetine akut etkinin vücut kitle indeksi ile ilişkisini değerlendirdiğimiz çalışmamızda, uygulamanın daha uzun etkileri değerlendirilmelidir. VKİ sınıflamasına göre obez kategorisinde değerlendirilen bireylerde kavrama kuvveti değerindeki azalmaya neden olan faktörler araştırılmalıdır. Ayrıca sağlıklı bireylerde yapılan çalışmamıza paralel olarak farklı hastalık gruplarında değerlendirmeler yapılabilir.

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Original Research / Özgün Araştırma

Effect of *Helicobacter pylori* Infection on Duodenitis in Patients with Dyspepsia

Dispepsisi Olan Hastalarda *Helicobacter pylori* Enfeksiyonunun Duodenit Üzerine Etkisi

Buğra Tolga Konduk[1], Şeniz Demiryürek[2], Abdullah Emre Yıldırım[1], Sezgin Barutçu[1], Ramazan Erdem Er[1], Ayhan Balkan[1], Yeşim Gürbüz[3], Ömer Şentürk[4]

[1]Department of Gastroenterology, Gaziantep University School of Medicine, Gaziantep, Turkey

[2]Department of Physiology, Gaziantep University School of Medicine, Gaziantep, Turkey

[3]Department of Pathology, Kocaeli University School of Medicine, Kocaeli, Turkey

[4]Department of Gastroenterology, Kocaeli University School of Medicine, Kocaeli, Turkey

ABSTRACT

Objective: *Helicobacter pylori (H. pylori)* infection is one of the principal causes of many gastroduodenal diseases, but its role in duodenitis development is not exactly known. The purpose of this study was to elucidate the role of gastric *H. pylori* infection on clinical, laboratory, and endoscopical features of duodenitis in patients with dyspepsia.

Methods: A total number of 131 patients (77 females and 54 males) were enrolled in the study. The control group was formed from *H. pylori*-negative dyspepsia patients (n=60). Clinical, biochemical, and endoscopical evaluations were performed on all subjects. Biopsies were obtained from the gastric antrum, corpus, and duodenal bulb to detect *H. pylori* and for histopathological assessments.

Results: *H. pylori* infection was positive in 71 patients (54.2%). We detected ulcer-like dyspepsia in 87 patients (66.4%) and dysmotility-like dyspepsia in 44 patients (33.6%). There were no marked differences in biochemical parameters between the groups. On the other hand, there was a marked decrease in ferritin levels in *H. pylori*-positive group (p=0.001). Endoscopical examination showed that the *H. pylori*-positive group had more frequent erosive duodenitis (p=0.039). Villous obliteration and duodenal intraepithelial lymphocytosis as histopathological features were seen more commonly in the *H. pylori*-positive group (p<0.001 for both).

Conclusion: Our data demonsrated that the presence of gastric *H. pylori* infection is one of the components that can influence the endoscopical, histopathological and laboratory features of duodenitis.

Keywords: Duodenitis, *Helicobacter pylori*, dyspepsia, endoscopy, histopathology

ÖZ

Amaç: *Helicobacter pylori* (*H. pylori*) infeksiyonu, birçok gastroduodenal hastalığın başlıca nedenlerinden biridir, fakat duodenit oluşumundaki rolü tam olarak bilinmemektedir. Bu çalışmanın amacı, dispepsili hastalarda duodenitin klinik, laboratuar ve endoskopik özellikleri üzerine gastrik *H. pylori* infeksiyonunun rolünü araştırmaktı.

Yöntemler: Bu çalışmaya toplamda 131 hasta (77 kadın ve 54 erkek) dahil edildi. Kontrol grubu *H. pylori*-negatif dispepsi hastalarından oluşturuldu (n=60). Bütün hastalarda klinik, biyokimyasal ve endoskopik değerlendirmeler yapıldı. H. pylori'yi saptamak ve histopatolojik değerlendirmeler için gastrik antrum, korpus ve duodenal bulbusdan biyopsiler alındı.

Bulgular: *H. pylori* infeksiyonu 71 hastada pozitifti (%54,2). Ülser benzeri dispepsiyi 87 hastada (%66,4) ve dismotilite benzeri dispepsiyi 44 hastada tespit ettik (%33,6). Gruplar arasında biyokimyasal parametrelerde anlamlı farklılıklar yoktu. Fakat, *H. pylori*-pozitif grupta ferritin düzeylerinde anlamlı azalma vardı (p=0,001). Endoskopik muayenede *H. pylori*-pozitif grupta daha sık erozif duodenit gözlendi (p=0,039). *H. pylori*-pozitif grupta histopatolojik özellik olarak villus obliterasyonu ve duodenal intraepiteliyal lenfositoz daha çok gözlendi (her iki grup için p<0,001).

Sonuç: Sonuçlarımız gastrik *H. pylori* infeksiyonunun varlığının duodenitin endoskopik, histopatolojik ve laboratuar özelliklerini etkileyebilen unsurlardan biri olduğunu gösterdi.

Anahtar kelimeler: Duodenit, *Helicobacter pylori*, dispepsi, endoskopi, histopatoloji

ORCID IDs of the authors: B.T.K. 0000-0002-9138-9984; Ş.D. 0000-0003-4762-4745; A.E.Y. 0000-0002-4386-9297; S.B. 0000-0003-0823-3215; R.E.E. 0000-0002-9708-1163; A.B. 0000-0002-6475-9847; Y.G. 0000-0002-4278-8241; Ö.Ş. 0000-0003-2342-9136.

Corresponding Author/Sorumlu Yazar: Buğra Tolga Konduk **E-mail/E-posta:** konduktol@yahoo.com

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INTRODUCTION

Dyspepsia is recurrent and chronic upper abdominal pain or discomfort. It affects up to 40% of the general population and is a significant cause of reduced quality of life among patients (1). Dyspeptic symptoms have been clustered into three categories as follows: ulcer-like dyspepsia in which the predominant symptom is discomfort and pain located in the upper abdomen (most troublesome); dysmotility-like dyspepsia, a bothersome or unpleasant discomfort originating in the upper abdomen associated with upper abdominal fullness, bloating, nausea, or early satiety; and nonspecific/unspecified dyspepsia characterized as the presence of symptoms that do not meet the criteria for dysmotility-like or ulcer-like dyspepsia (2). Recent studies have shown that duodenal mucosal permeability increases in patients with functional dyspepsia (3, 4). Therefore, impaired duodenal mucosal barrier function might contribute to the pathophysiology of dyspepsia.

The presence of *Helicobacter pylori* (*H. pylori*) is one of the leading causes of peptic ulcer, duodenal ulcer, duodenitis, and chronic gastritis. Additionally, *H. pylori* may be associated with various extra-gastrointestinal diseases, such as idiopathic thrombocytopenic purpura, coronary artery disease, unexplained iron deficiency anemia, and ischemic stroke (5). *H. pylori* is a small gram-negative bacillus that inhabits the human stomach and duodenum (6). Its role in producing dyspepsia symptoms is not completely understood. However, duodenitis is often associated with the presence of *H. pylori* (7, 8).

A recent systematic meta-analysis and review has demonstrated that although *H. pylori* prevalence widely varies between regions and countries, more than half the world's population is infected (9). In Turkey, *H. pylori* prevalence has been reported to be very high, estimated as 82.5% in the adult population (10). The goal of this study was to assess the presence of an association between *H. pylori* positivity and endoscopic or histological features of the duodenal mucosa in patients referred for endoscopy to investigate dyspepsia.

METHODS

Study Population

The present study group consisted of 131 adult patients with dyspepsia evaluated at a tertiary medical center. The criteria for inclusion were subjects aged >18 years who underwent endoscopy for dyspepsia. The exclusion criteria were as follows: an evidence of gastroduodenal malignancies, duodenal ulcer, gastric ulcer, or scar on gastroscopy; liver, biliary, or pancreatic diseases on ultrasound examination; the use of corticosteroids, immunosuppressives, proton pump inhibitors, oral anticoagulants, aspirin, antibiotics known to be active against *H. pylori*, or other non-steroidal anti-inflammatory drugs within the preceding 4 weeks; presence of Crohn's disease or Zollinger-Ellison syndrome involving the duodenum; pregnancy; previous upper gastrointestinal surgery; renal or hepatic failure; or other severe concomitant illnesses. Routine clinical and biochemical evaluations were performed on all subjects. Dyspepsia diagnosis was according to the Rome III criteria. The control group included patients with *H. pylori*-negative dyspepsia. The study protocol was reviewed and approved by the local Ethics Committee, and the study was conducted in accordance with the guidelines in the Declaration of Helsinki. Written informed consent was obtained from all patients and volunteers.

Endoscopy and Biopsy Sampling

All patients underwent the routine preparation for endoscopy as follows: fasting for 8 h for liquids and solids. Patients were submitted to 5-10 puffs of 10% lidocaine spray in the oropharynx just before the endoscopy. Endoscopy was performed under intravenous midazolam (0.07-0.1 mg/kg) sedation. A flexible gastroscope (Fujinon EG-250WR5, Saitama, Japan) was used. Sydney classification was employed for endoscopic findings of duodenal morphology, and the severity of endoscopic duodenitis was described as mild, moderate, or severe (11). One gastric antral, one gastric corpus, and four duodenal biopsies were taken from the duodenal bulb during each endoscopic examination. Biopsies were taken through endoscopic biopsy forceps from the mucosa of the duodenal bulb of the patients. Among these biopsies, one antral, one corpus, and one duodenal specimen were used to detect *H. pylori* by the rapid urease test, and the others were used for histological examination.

Histological Analysis

Biopsies were fixed in 10% formalin, embedded in paraffin, and cut in sequential 3-µm sections. For histological examination, sections of the tissue samples were stained with hematoxylin and eosin. Sections were stained with Alcian blue periodic acid-Schiff (AB/PAS) for assessing and identifying the extent of duodenal gastric metaplasia. Sections were also immunostained for CD3 to assess the number of intraepithelial lymphocytes present in each specimen. Histological material was examined by an experienced pathologist who was blinded to clinical and endoscopic tests. Duodenal biopsy specimens were graded according to the updated Sydney System (12). The histological severity of chronic inflammation in mucosa was assessed on a scale of four grades (normal, mild, moderate, and severe) according to the degree of mononuclear cell infiltration. Acute inflammation was characterized as the degree of stromal and epithelial neutrophil infiltration and was also graded as follows: 0, none; 1, mild; 2, moderate; 3, severe.

Data Analysis

Data were presented as percentage or mean±standard deviation. The SPSS (Statistical Package for Sociel Sciences) Version 22.0 (IBM Corp.; Armonk, NY, USA) was used for statistical analysis. Unpaired Student's t-test was used for comparisons of the differences between mean values of two groups. The Mann-Whitney U-test was used to detect significant differences between histopathological scores. Chi-squared test was used to analyze frequencies. P-values presented are two-tailed, with a significant level of 0.05.

RESULTS

The age of the patients ranged from 18-85 (mean of 46.0±16.0) years. Among all the patients, 77 (58.8%) were females and 54 (41.2%) were males. The overall *H. pylori* infection prevalence was

54.2% (n=71/131). In total, 87 patients (66.4%) presented with ulcer-like dyspepsia, whereas 44 patients (33.6%) presented with dysmotility-like dyspepsia. In total, 7 (5.3%) patients presented with celiac disease, and 4 (3.1%) presented with duodenal gastric metaplasia.

There were no differences in blood biochemical parameters of the patients with and without *H. pylori* in terms of hemoglobin, hematocrit, mean corpuscular volume, Fe^{2+}, transferrin saturation, total iron binding capacity, vitamin B12, and folic acid levels (Table 1). However, a marked decrease in ferritin levels was noted in the *H. pylori*-positive group (p=0.001).

Based on endoscopic duodenitis classification, there was a high frequency of erosive duodenitis but a low incidence of nodular duodenitis in the *H. pylori*-positive group compared with that in the *H. pylori*-negative group (p=0.039, Figure 1). Based on endoscopic duodenitis classification, there were no significant changes in the distribution of patients with ulcer-like dyspepsia or patients with dysmotility-like dyspepsia (p=0.125, Figure 2). No marked changes were noted in the severity of duodenitis in the *H. pylori*-negative and *H. pylori*-positive groups (p=0.308, Figure 3). Histopathological analysis revealed that there were marked augmentations in both duodenal intraepithelial lymphocytosis and villus obliterations in the *H. pylori*-positive group (p<0.001 for both, Figure 4).

DISCUSSION

In this study, we showed that the frequency of erosive duodenitis was high in *H. pylori*-positive patients. Moreover, augmented duodenal intraepithelial lymphocytosis, villous obliterations, and diminished ferritin levels were detected in *H. pylori*-positive patients. Our results suggest that there is an association between *H. pylori* infection and duodenitis in patients with dyspepsia. The contribution of the presence of *H. pylori* to duodenitis has been previously described in patients with duodenal ulcer (13).

Tablo 1. Characteristics of blood biochemical values of the patients with and without *H. pylori*

Parameters	Patients without *H. pylori* (n=60)	Patients with *H. pylori* (n=71)	p
Hemoglobin (g/dL)	13.3±2.0	13.1±2.1	0.580
Hematocrit (%)	38.9±5.3	38.7±5.5	0.833
MCV (fL)	83.2±8.6	82.2±12.6	0.605
Fe2+ (mg/dL)	57.5±33.1	56.9±35.7	0.921
Total iron binding capacity (mg/dL)	302.3±52.9	304.3±47.8	0.821
Transferrin saturation (%)	18.2±8.9	18.1±10.1	0.953
Ferritin (mg/dL)	84.5±12.3	76.9±13.6	0.001
Vitamin B12 (ng/dL)	305.7±37.6	292.2±41.8	0.056
Folic acid (ng/mL)	9.2±5.3	8.8±6.0	0.689

MCV: mean corpuscular volume

This previous study has indicated that biopsies with regenerative changes demonstrated a significant polymorphonuclear leukocyte infiltration regardless of the duodenal *H. pylori* status. In biopsies with no regenerative changes, *H. pylori* colonization was commonly associated with leukocyte infiltration (13). Other studies have also observed that histological duodenitis is often associated with *H. pylori* (75%-82%) (7, 14). These findings imply that *H. pylori* is another critical factor in the development of lymphocyte and leukocyte infiltration in the duodenal mucosa.

We observed an increased erosive duodenitis in *H. pylori*-positive patients. Few studies have investigated the possible role of and the association between *H. pylori* infection and the appearance of duodenitis. It has been postulated that the presence of endoscopic findings of duodenitis may appear from *H. pylori* infection or from an acid-pepsin attack and is generally associated with histopathologic abnormalities, including gastric metaplasia (15). *H. pylori* increases the production of ammonia in the gastric lumen

Figure 1. Incidences of *H. pylori*-positive and *H. pylori*-negative groups according to endoscopic duodenitis classification *p<0.05

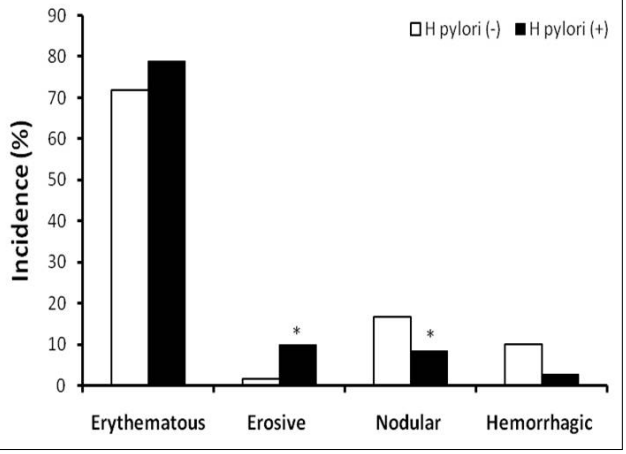
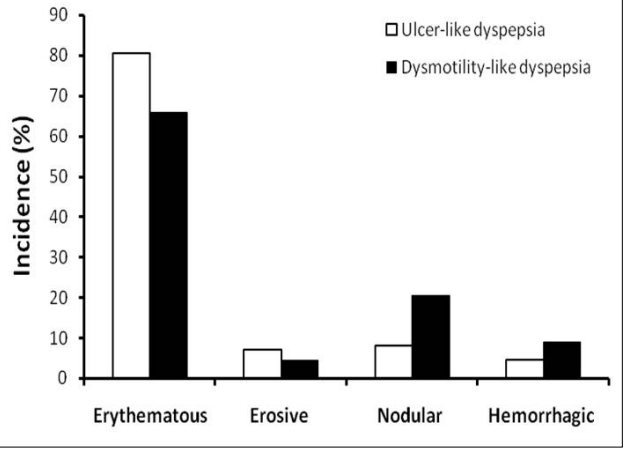


Figure 2. Incidences of patients with ulcer-like dyspepsia or patients with dysmotility-like dyspepsia according to endoscopic duodenitis classification



by its urease activity. Ammonia toxicity may cause cell destruction and the disintegration of cell permeability and active transport (6). Moreover, *H. pylori* produces factors capable of chemoattracting and activating monocytes and neutrophils that induce inflammation (16). The epithelium responds to *H. pylori* infection by mucin depletion, cellular exfoliation, the desquamation of the epithelium, and compensatory regenerative changes (17, 18). *H. pylori* is associated with cytotoxicity on mucosal cells when spread to the duodenal mucosa. *H. pylori*-induced inflammatory injury may stimulate the development of further duodenal gastric metaplasia (13, 17). In contrast, it has been demonstrated that there is an insignificant difference in the severity of endoscopic duodenitis between *H. pylori*-negative and -positive patients (19). Furthermore, effective *H. pylori* eradication has been reported to produce no marked change in endoscopic appearance (19).

Figure 3. Severity of duodenitis in *H. pylori*-positive and *H. pylori*-negative groups

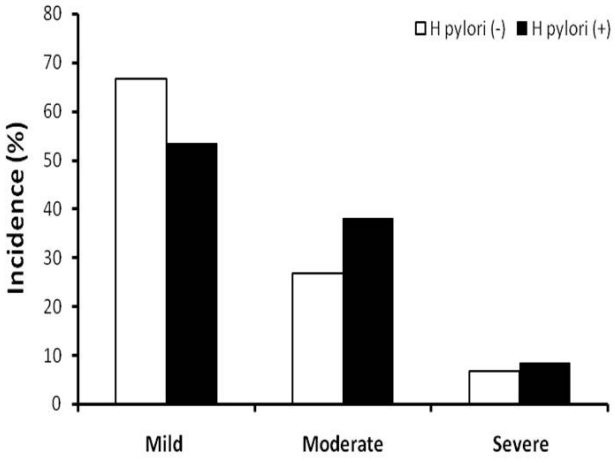
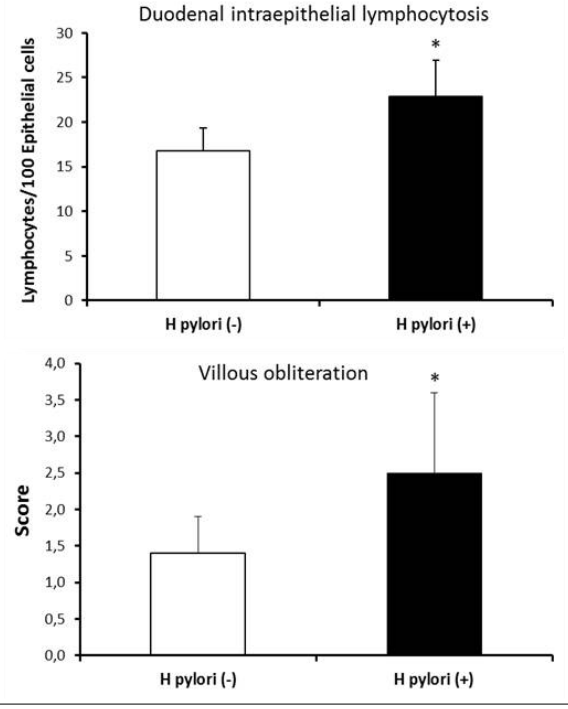


Figure 4. a, b. Duodenal intraepithelial lymphocytosis (a); and villous obliteration (b) in *H. pylori*-positive and *H. pylori*-negative groups *p<0.001 for both



Diffuse nodular duodenitis is a distinctive type of chronic duodenitis. Currently, little is known regarding the mechanism of its pathogenesis. Our data showed that there was a decrease in nodular duodenitis in *H. pylori*-positive patients. Reasons underlying this reduction are not known. Li et al. (20) have shown that neither the acid suppression treatment nor *H. pylori* eradication can significantly change the appearance of endoscopic nodular duodenitis. Therefore, the presence of *H. pylori* infection may not be associated with nodular duodenitis.

In the present study, there were increases in villus obliterations in the *H. pylori*-positive group. These data support the previous observations that reduction in villus size, increased cellular infiltrate, and mucosal architecture abnormalities are noted in biopsies from visually inflamed areas of nonspecific duodenitis (21, 22). Collectively, these findings may suggest that impaired duodenal mucosal barrier function can contribute to the pathophysiology of duodenitis and dyspepsia.

We observed that *H. pylori* infection is accompanied with diminished serum ferritin levels. Although there is significant heterogeneity among the studies, a recent meta-analysis has demonstrated that serum ferritin levels increased as a consequence of *H. pylori* eradication treatment (23).

CONCLUSION

The findings of this study provided updated information and indicated that the presence of gastric *H. pylori* infection is one of the components that can contribute to the endoscopic, histopathological, and laboratory features of duodenitis. Therefore, the determination of the degree of morphological changes associated with *H. pylori* infection in dyspepsia is valuable in the treatment and follow-up of patients. Further investigations of effects of *H. pylori* infection on duodenitis in large prospective studies would be helpful in understanding the pathogenesis of duodenitis.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kocaeli University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - B.T.K., Ö.Ş. , Ş.D., Y.G.; Design - B.T.K. , Ş.D., Y.G., Ö.Ş.; Supervision - B.T.K., Ş.D., Ö.Ş.; Resource - B.T.K., Ş.D., Ö.Ş., A.E.Y., R.E.E., S.B., A.B.; Materials - B.T.K., Y.G.; Data Collection and/or Processing - B.T.K, Ö.Ş., Ş.D., Y.G., A.E.Y., R.E.E., S.B., A.B.; Analysis and/or Interpretation - B.T.K., Ş.D., Y.G., Ö.Ş.; Literature Search - B.T.K., Ş.D.; Writing - B.T.K., Ş.D.; Critical Reviews - Ş.D.

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Original Research / Özgün Araştırma

The Efficacy of Haematologic Parameters in the Diagnosis of Missed Abortus

Hematolojik Parametrelerin Missed Abortus Tanısına Etkileri

Gülsüm Uysal[1], Fulya Çağlı[2], Eda Ülkü Karakılıç[2], Hatice Akkaya[3], Hüseyin Aksoy[2], Gökhan Açmaz[2]

[1]Department of Obstetrics and Gynecology, Adana Numune Training and Research Hospital, Adana, Turkey

[2]Department of Obstetrics and Gynecology, Kayseri Training and Research Hospital, Kayseri, Turkey

[3]Department of Obstetrics and Gynecology, Zekai Tahir Burak Womens Health, Training and Research Hospital, Ankara, Turkey

ABSTRACT

Objective: The aim of the present study was to investigate the efficacy of hematologic parameters in diagnosing missed abortus (MA). Our second aim was to elucidate the diagnostic value of maternal serum cancer antigen 125 (CA 125) levels in missed abortion.

Methods: Hemoglobin, white blood cell, neutrophil, lymphocyte, and platelet levels; mean corpuscular volume; mean platelet volume (MPV); and red cell distribution width (RDW) in complete blood count samples were obtained from all patients diagnosed with MA (group 1; n=90) and from women with healthy pregnancies (group 2; n=143).

Results: Lymphocyte, platelet, and RDW variables were significantly higher in group 1 (p=0.03, p=0.003, and p=0.005, respectively). High RDW value was independent predictors of MA (OR: 0.810, p<0.05). Mean CA 125 levels between the groups were similar. There was no significant difference in other hematologic laboratory parameters between the groups.

Conclusion: Of all hematologic inflammatory markers, higher RDW value was the only marker associated with MA. RDW might be used as an early promising predictor of MA with low cost. Second, we found that CA 125 and other hematologic inflammatory markers, such as MPV and neutrophil/lymphocyte ratio, are not good markers for predicting MA.

Keywords: Cancer antigen 125, hematologic parameters, missed abortus, red cell distribution width

ÖZ

Amaç: Missed Abortus (MA) kapalı bir serviksle maternal-fetal yapılara ait ölü dokuların günler, haftalar hatta aylarca uterin kavite içinde kalmasıdır. Fetal ölüm ve abortusun tanısı temelde klinik ve ultrason yardımı ile konulur. Gelişmiş ultrason görüntü teknikleri sonrasında MA daha sık görülmeye başlamıştır. Sağlıklı bir gebeliğin devamı ya da tespiti hakkında henüz güvenilir bir biyokimyasal marker yoktur ve etyolojisi hala net değildir. Yeni çıkan çalışmalarda bazı hematolojik parametreler ile tekrarlayan gebelik kayıpları arasında ilişki bulunmuştur. Bu çalışmada amacımız hematolojik parametrelerin MA tanısına etkisini araştırmaktır. İkincil amacımız serum Ca 125 düzeylerinin missed abortus tanısındaki rolünü değerlendirmektir.

Yöntemler: Bu çalışmaya 90'nı missed abortus, 143'ü sağlıklı kontrol olmak üzere toplamda 233 gebe dahil edilmiştir. Bu hastaların rutin hematolojik parametrelerindeki hemoglobin, beyaz küre, nötrofil, lenfosit, ortalama korpuskular hacim (MCV), ortalama platelet hacmi (MPV), eritrosit dağılım genişliği (RDW) değerleri kaydedilmiştir. Ayrıca tüm hastaların serum Ca 125 değeri de bakılıp not edilmiştir.

Bulgular: MA grubunda lenfosit, platelet ve RDW anlamlı olarak yüksek bulunmuştur. (sırasıyla; p=0,03, p=0,003, p=0,005) Gruplar arasında anlamlı çıkan bu değerler multivaryant analizde tekrar bakıldığında MA tanısında RDW'nin bağımsız faktör olduğu görülmüştür (OR: 0,810, p<0,05). Gruplar arasında Ca 125 değerleri benzer bulunmuştur (p=0,7). Gruplar arasında diğer hematolojik parametreler açısından anlamlı fark saptanamamıştır.

Sonuç: Bakılan tüm hematolojik parametreler arasında yüksek RDW missed abortusların tanısıyla ilişkili bulunmuştur. Düşük maliyetli rutin kullanılan bu testler erken tanıda ümit vaat etmektedir.

Anahtar kelimeler: Kanser antijen 125, hematolojik parametreler, missed abortus, eritrosit dağılım hacmi

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ORCID IDs of the authors: G.U. 0000-0002-9381-4892; F.Ç. 0000-0002-6492-3379; E.Ü.K. 0000-0002-6625-8544; H.A. 0000-0002-9613-1712; H.A. 0000-0003-3467-3783; G.A. 0000-0002-4215-3676.

Corresponding Author/Sorumlu Yazar: Gülsüm Uysal **E-mail/E-posta:** gulsumaykut@yahoo.com

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INTRODUCTION

Missed abortus (MA) is the term that is used to describe dead products of conception retaining for days, weeks, or even months in the uterus with a closed cervical os (1). With the development of ultrasound image techniques, the incidence of MA has become higher (3.89%-14.1%) (2). Risk factors for MA are parental chromosomal abnormalities, hereditary thrombophilia, endocrinological disorders, immunological factors, infections, apoptosis, oxidative stress, and environmental factors (3). However, the exact cause of missed abortion remains unknown.

In recent years, the role of hematologic inflammatory markers, such as neutrophil/lymphocyte ratio (NLR), red cell distribution width (RDW), and mean platelet volume (MPV) has attracted attention in recurrent pregnancy loss (4, 5).

Red cell distribution width is one of the routinely available components of total blood count tests and it is the measure of variability in the size or volume of red blood cells (4). When different red cell sizes are observed (anisocytosis) in the peripheral blood smear, RDW values are elevated and this elevation is said to be associated with recurrent pregnancy loss (4, 5). It is concluded that RDW is a low-cost, routine marker for predicting recurrent pregnancy loss in patients with a history of at least one abortus (4, 5). Moreover, it is a reliable and promising independent marker for severe pre-eclampsia (6) and is an easily available marker with no additional costs in cardiovascular risk even in young patients (7).

Cancer antigen 125 (CA 125) is a basic known marker for predicting epithelial ovarian cancer, and it is shown that CA 125 can be expressed in the fetus and on serous surfaces, such as the pericardium, pleura, and peritoneum (8). It can also be histochemically detected in the epithelium of the endocervix and endometrium. In addition, increased CA 125 levels can be found in healthy pregnant and non-pregnant women (8).

Higher CA 125 levels are detected in patients with vaginal bleeding irrespective of them having a viable pregnancy or a gestational sac at a normal location (9). On the other hand, in another study, decreased CA 125 levels were observed in a similar group of patients with vaginal bleeding (10). Therefore, the role of CA 125 in abortions and pregnancy is still controversial, and studies involving larger numbers of participants should be conducted.

Ultrasonography is mainly used for diagnosing fetal demise and abortion. There is no reliable biochemical marker for detecting a viable pregnancy or defining a biomarker for pregnancy outcome.

There is no research conducted on hematologic parameters associated with MA. We have concentrated on this issue. Therefore, in our study, we investigated the efficacy of hematologic inflammatory markers and maternal serum CA 125 levels in diagnosing MA.

METHODS

A total of 90 patients (group 1) with missed abortion between April and December 2014 were included in our study. Transvaginal ultrasound was performed in all cases, and the diagnosis was confirmed by repeated ultrasound. We used ultrasound findings and the date of the last menstrual period to determine the gestational age. An intact gestational sac without fetal cardiac activity during 6 weeks and an intrauterine gestational sac with a diameter of >10 mm but without a yolk sac were defined as first trimester missed abortion (1). Fetal demise that occurs before several weeks along with absent uterine activity to throw out the product of conception without any vaginal bleeding is usually described as a second trimester missed abortion (1). The control group (group 2) included 143 pregnant women with viable and healthy intrauterine fetus. We confirmed the gestational age and fetal cardiac activity using ultrasound. Both groups had a gestational age range of pregnancies between 6 and 16 weeks. Multiple pregnancies and pregnancies with structural fetal anomalies were excluded. Furthermore, patients with anemia, hemoglobinopathy, any systemic or chronic disease, a history of bleeding or coagulation disorder, or anticoagulant therapy were excluded. All patients were ultrasonographically examined for uterine abnormalities. We evaluated antibodies for infection, such as *Toxoplasma gondii*, rubella, cytomegalovirus, and herpes simplex virus (TORCH) and anticardiolipin and antinuclear antibodies in all patients. Our study was conducted according to the recommendations of the Declaration of Helsinki on biomedical research involving human subjects. A written informed consent was obtained from each participant.

In all cases, we collected blood samples in tripotassium Ethylene diamine tetra acetic acid (EDTA) tubes when MA was diagnosed before taking any medication. All measurements of hematologic parameters were performed using the Beckman Coulter automated blood count analyzer (Beckman Coulter Inc., CA, USA) 30 min after blood collection. CA 125 levels were determined by the electrochemiluminescence immunoassay method using the DXI 800 automatic quantitative hematology analyzer (Beckman Coulter Inc., CA, USA).

Statistical Analysis

We performed all analyses using SPSS (Statistical Package for Sociel Sciences) Version 18.0 (IBM Corp.; Armonk, NY, USA). We expressed quantitative variables as mean±standard deviation for parametric variables. We used median values as non-parametric variables and determined minimum-maximum levels. We analyzed continuous variables for normal distribution with the Kolmogorov-Smirnov test. A value of $p<0.05$ was considered to be significant. We determined differences in continuous variables between the two groups using the Student's t-test or Mann-Whitney U test. Significant parameters ($p<0.05$) were used in the multivariate analysis. We performed logistic regression analysis for multivariate analysis of independent predictors.

RESULTS

We examined a total of 233 patients, including 90 patients with MA as group 1 and 143 healthy pregnant patients as group 2. The main characteristics of the groups and mean values of hematologic laboratory parameters for each group are presented in Tables 1 and 2, respectively.

Table 1. General baseline characteristics of the groups

	Missed abortus (N=90)	Control group (N=143)	p
Age	27.2±6.7	26.7±5.7	0.5
BMI	24±3	24±4	0.8
Gravidity	2.7±1.5	2.5±1.3	0.2
Parity	2.0±0.9	1.8±1.3	0.2
Gestational age (week)	9.6±1.9	9.3±2.4	0.3

Data are presented as mean±SD
BMI: body mass index

Table 2. Investigation of hematologic laboratory parameters between the groups

	Missed abortus (N=90)	Control group (N=143)	p
Hemoglobin (g/dL)	12.9±1.0	12.8±1.1	0.2
WBC ($\times 10^3$/μL)	8.6±2.5	8.3±2.0	0.3
Neutrophil ($\times 10^3$/μL)	5.9±2.1	5.7±1.8	0.5
Lymphocyte ($\times 10^3$/μL)	2.1±0.6	1.9±0.4	0.03
Platelet ($\times 10^3$/μL)	253±73	229±46	0.003
MCV (fL)	84±6	85±7	0.9
MPV (fL)	8.8±1.3	8.8±0.9	0.9
RDW (%)	13.4±2.0	12.8±1.3	0.005
CA 125	37.2±23.4	38.1±19.7	0.7
TSH	1.4±0.7	1.3±0.8	0.4
Glucose	90±11	89±15	0.8
NLR	2.8±1.1	2.9±1.1	0.4
PLR	124±52	120±34	0.4

Data are presented as mean±SD.

WBC: white blood cell; MCV: mean corpuscular volume; MPV: mean platelet volume; RDW: red cell distribution width; CA 125: cancer antigen 125; TSH: thyroid stimulating hormone; NLR: neutrophil/lymphocyte ratio; PLR: platelet/ lymphocyte ratio

Mean values of age, gravidity, parity, and gestational age were similar in both groups. As shown in Table 2, the lymphocyte, platelet, and RDW values were significantly higher in group 1. The mean values of CA 125 between the groups were similar. There was no significant difference in other hematologic inflammatory markers between groups. Variables found to be statistically significant in univariate analysis between our groups were entered into multivariate analysis. Only RDW values were significantly higher in group 1. High RDW value was an independent predictor of MA (OR: 0.810, $p<0.05$).

DISCUSSION

To the best of our knowledge, this is the first case-control study to investigate the efficacy of hematologic inflammatory markers in diagnosing MA. Moreover, our study is one of the studies with a large number of cases of MA. The major finding of our study is that RDW might be used as an early marker of MA.

The etiology of MA remains unclear. In the literature, adenosine deaminase activity (ADA), stress factors [serum cortisol and interleukin (IL)-12], heparin-binding epidermal growth factor (HB-EGF), leptin levels, and inflammatory cytokines in maternal serum and placenta are assessed in MA (11-15). Based on these data series, low ADA, higher cortisol levels, lower IL-12 levels, increased HB-EGF expression, and lower tumor necrosis factor alpha in early pregnancy may play a role and lead to loss of pregnancy.

Early pregnancy is in a hypoxic situation that may quicken angiogenesis. Moreover, in a recent study, it has been reported that severe hypoxia and aberrant vascular endothelial growth factor signaling may cause MA (16). All studied markers are expensive and include non-routine test; in addition, the exact mechanism underlying the relationship with missed abortion are unknown.

MPV, which shows platelet activation and function, is measured in MA. MPV is a precise measure of the platelet size. Larger platelets have higher MPV values; therefore, higher MPV is more reactive and causes higher measures of the prothrombotic factors hemostatically (17). Moreover, in a group of patients with maternal thrombophilia, hypercoagulability may lead to low perfusion of the placenta, and finally, this may cause loss of the fetus (17). In the case of MA, Kosus et al. (18) compared MPV values and platelet counts of 100 patients with MA and 100 healthy controls. Both groups were between 6 and 13 weeks of gestation and had similar demographic characteristics. They found slightly increased MPV values in patients with missed abortion. They concluded that slightly increased MPV might encourage thrombosis (18). On the other hand, in a recent study, investigators suggested that MPV was significantly lower in patients with miscarriage than in the control group (19). The miscarriage group comprised biochemical and clinical abortions. The group with a miscarriage after biochemical pregnancy had the lowest MPV value. They concluded that due to inflammation and bleeding, platelets with higher activity (larger platelets) can migrate to the region in earlier gestational weeks (19). This may lead to a decrease in MPV in maternal circulation. Similarly, MPV decreases during active periods of inflammatory diseases, such as ankylosing spondylitis, systemic lupus erythematosus, and rheumatoid arthritis (20, 21).

In our study, MPV, RDW, and NLR were assessed in 90 patients with MA. These parameters were included in routine blood count measurements and did not require an additional cost. To the best of our knowledge, this was the first study in which RDW, NLR, and MPV were investigated in patients with MA. In our study, among these parameters, only RDW values were significantly different between the groups. Both elevated (18) and lower MPV values (19-21) were associated with inflammation. However, we could not deduce and show this data in our current study. Higher RDW values could be found in circumstances associated with incapability of red cell production, for example, due to B_{12} or folate inadequacy, iron deficiency, and hemoglobinopathies. Furthermore, RDW val-

ues were elevated with destruction of red cells and in hemolysis (22). Recently, Kurt et al. (6) found that RDW values were significantly higher in the severe pre-eclampsia group than in the mild pre-eclampsia group. Their study results revealed that RDW values were associated with existing pre-eclampsia and also indicated its severity (6). However, the accurate mechanism associated with hypertension and RDW has not been determined yet. Elevated inflammation is the most popular theory. It has been reported that in patients with underlying pre-eclamptic placental hypoxia, oxygen). Thus, the more the flow of immature erythrocytes increases in the vessels, the more the RDW value elevates. Dundar et al. (5) retrospectively evaluated 60 patients with recurrent pregnancy loss, 60 healthy pregnant patients in the first trimester, and 60 healthy non-pregnant multipara patients. Finally, they found a significant and positive relationship between RDW and platelet distribution width (PDW) (r=0.615, p=0.001), RDW and plateletcrit level (r=0.343, p=0.007), and PDW and plateletcrit level (r=0.340, p=0.008) in patients with recurrent pregnancy loss. They concluded that elevated PDW and RDW values were associated with recurrent pregnancy loss. They thought that inflammation and thromboembolism resulted with anisocytosis, causing elevation of RDW (5). Moreover, RDW is an available marker for myocardial infarction in young patients, but underlying mechanisms have not been clearly demonstrated (7). In our study, we found high lymphocyte, RDW, and platelet values in the MA group. Hypoxia and inflammation during abnormal pregnancy may lead to this result. In our results, there was no significant difference in MPV and NLR values between groups. Although NLR is a well-studied hematologic parameter and an independent predictor for ovarian torsion and pre-eclampsia, underlying mechanisms of inflammation in missed abortion might be different (21, 23).

RDW for red blood cells, MPV for platelets, and NLR for response to stress-related systematic inflammation are inexpensive daily parameters that are used in routine laboratory test. As mentioned above, several markers are studied to determine the etiology of MA, but it is still unclear and something different whetehr both inflammation and thrombosis might totally play a role via different mechanisms. Further studies with larger series are needed for clarifying and explaining the diagnostic potential of this situation. In addition, every laboratory has a specific normal range, but there are no generally accepted mean values. Moreover, measurements of these tests can be affected by both environmental and laboratory conditions, such as temperature, storage conditions, and time until measurement.

In addition, we measured CA 125 levels in patients with MA. There was no significant difference in CA 125 levels between groups. We have planned to study CA 125 levels both laboratory and histopathologically, but we could only investigate the laboratory part. CA 125 levels in patients with abnormal pregnancy during the first trimester were evaluated in some studies, but there was no significant difference in mean CA 125 levels among the groups (24, 25). Check (26) found a relationship between spontaneous abortion and elevated CA 125 levels, whereas other studies reported no significant difference in serum CA 125 levels (24, 25, 27). We also could not find a statistical difference, similar to the results of the previous studies. Scarpellini et al. (28) found higher CA 125 levels in the group with threatened abortion than in the controls (healthy pregnancy). Moreover, they concluded that damages in the deciduas and the fetal membrane resulted with elevation of maternal serum CA 125 levels.

In our study, preserved membranes in cases of MA may play a role in insignificant CA 125 results. Actually, there are many reasons that alter CA 125 levels in circulation, and the role and mean cut-off levels have not been clarified yet (8). Furthermore, the origin (fetal or decidual) of this CA 125 is still controversial. In a different study, the importance of diagnostic and prognostic values of repeated maternal CA 125 levels in early pregnancy was emphasized (29). They measured serum CA 125 levels of symptomatic pregnant patients with failed diagnosis of spontaneous abortion and ectopic or normal pregnancy in the first trimester. They concluded that sequential measurements of CA 125 appear to be a good sensitive prognostic marker in patients with threatened abortion (29).

There are several limitations in our study. First, we did not evaluate the pathologic materials of patients with missed abortion. Therefore, we could not compare the serum and decidual or fetal CA 125 levels. Second, repeated measurements of CA 125 levels in the MA group should be conducted after intervention. This may give an idea about the antigen origin. Further expanded and well-established studies are needed for early diagnosis and prognosis.

CONCLUSION

The aim of our study was to determine if missed abortion can be determined or recognized at the first admission using routine hematologic tests in asymptomatic pregnant women. Second, we investigated the diagnostic value of CA 125 in predicting missed abortion. We found low sensitivity of CA 125 and hematologic inflammatory markers, such as MPV and NLR, in patients with MA. Of all hematologic inflammatory markers, higher RDW was the only marker associated with MA. RDW is a low-cost, widely available marker and may be a promising prediction factor of MA.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erciyes University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Author Contributions: Concept - G.U., G.A.; Design - G.U., F.Ç.; Supervision - H.Aksoy, H.Akkaya; Resource - G.A., E.K.; Materials - E.K.; Data Collection and/or Processing - G.U., F.Ç., E.K., H.Akkaya; Analysis and/or Interpretation - G.U., H.Akkaya; Literature Search - G.U., H.Aksoy; Writing - G.U.; Critical Reviews - H.Aksoy, G.A.

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Original Research / Özgün Araştırma

The Effect of Sedative Agents on Stress Hormones and High-Sensitive Troponin in Patients Catheterized by Permanent-Tunnel Port Catheter

Kalıcı Tünelli Port Kateter Takılan Hastalarda Sedatif Ajanların Stress Hormonları ve High Sensitif Troponin Üzerine Etkileri

Yılmaz Safi[1], Cuma Yıldırım[1], Cem Şen[1], Mustafa Sabak[1], Süleyman Nogay[1], Seyithan Taysi[2], Hasan Ulusal[2], Suat Zengin[1]

[1]Department of Emergency Medicine, Gaziantep University School of Medicine, Gaziantep, Turkey

[2]Department of Biochemistry, Gaziantep University School of Medicine, Gaziantep, Turkey

ABSTRACT

Objective: To evaluate the effects of sedation and analgesia combinations on pain scales, anxiety, adrenocorticotropic hormone (ACTH), cortisol, and high-sensitive troponin in patients with a central venous catheter.

Methods: The present study was prospectively conducted in 90 patients who had been indicated for port catheterization in hematology and oncology in the emergency medicine department of Gaziantep University Medical Faculty between March 1st and September 1st, 2015. The patients were divided into three groups of 30 each. Pain levels were assessed using the Visual Analog Scale, anxiety levels using the Beck Anxiety Scale, and blood samples were collected before (0 min) and after (30 min) the procedure in order to obtain ACTH, cortisol, and high-sensitive troponin values.

Results: No statistically significant differences were observed between the groups with regard to gender and age (p=0.836 and p=0.182, respectively). Anxiety significantly decreased in all three groups. A significant decrease in level of pain was found in patients administering midazolam-fentanyl and those who received propofol; a significant decrease in systolic and diastolic blood pressure was also observed in these two groups. In all three groups, no significant cortisol change was found; however, significant high-sensitive troponin values were observed. There was no significant difference between the groups.

Conclusion: Sedative agents can be used efficiently, safely, and easily in minor surgical procedures, such as central venous catheterization. We also recommend the use of analgesic drugs, in addition to anxiolytic and sedative agents, during invasive procedures conducted in the emergency room.

Keywords: Port catheter, sedation, anxiety, troponin

ÖZ

Amaç: Santral venöz kateter takılan hastalarda sedasyon ve analjezinin ağrı sakalaları, anksiyete; adrenokortikotropik hormon (ACTH), kortizol ve High-sensitif troponin üzerine etkilerini araştırmak.

Yöntemler: Bu çalışma hematoloji ve onkoloji servisinde yatan ve acil serviste port kateterizasyon işlemi uygulanan 90 hastada yapılan prospektif bir çalışmadır. Çalışma 1 Mart- 1 Eylül 2015 tarihleri arasında Gaziantep Üniversitesi Tıp Fakültesi Acil Tıp Anabilim Dalı'nda yapıldı. Hastalar 30 kişilik gruplar halinde 3 gruba ayrıldı. Ağrı seviyeleri Visüel Anolog Skala (VAS), anksiyete seviyeleri Beck Anksiyete Skalası kullanılarak ölçüldü. İşleme başlandığı anda, işlem bittikten sonraki 30. dakikada kan alındı. ACTH, kortizol ve high sinsitif troponin seviyelerine bakıldı.

Bulgular: Gruplar arasındaki yaş ve cinsiyet farkı istatistiksel olarak anlamsızdı (p=0,836 ve p=0,182). Anksiyete her üç grupta da belirgin azalmıştı. Midazolam-fentanil grubunda ve propofol alan hastalarda ağrıda belirgin azalma oldu. Bu hastalardan aynı zamanda her iki grupta da sistolik ve diastolik kan basınçlarında belirgin azalma oldu. Her 3 grupta da high sensitive troponin düzeylerinde belirgin değişiklik olurken kortizol seviyelerinde belirgin bir değişiklik olmadı. Gruplar arası farklılıklar anlamlı değildi.

Sonuç: Özellikle santral venöz kateterizasyon olmak üzere küçük cerrahi girişimlerde sedatif ilaçların kullanımı etkili ve güvenlidir. Acil serviste yapılan invaziv işlemler sırasında anksiyolitik ve sedative ilaçların yanında analjezik ilaçların da kullanımını öneriyoruz.

Anahtar kelimeler: Port kateter, sedasyon, anksiyete, troponin

This study has been presented as a poster in the 5th Eurosian Congress on Emergency Medicine and 12th Turkish Emergency Medicine Congress November 10-13, 2016, Antalya, Turkey.

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ORCID ID of the author: C.Y. 0000-0002-3504-8771.

Corresponding Author/Sorumlu Yazar: Cuma Yıldırım **E-mail/E-posta:** yildirimca@hotmail.com

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INTRODUCTION

Port catheter is an artificial vessel with one end attached to the main vein and the other placed under the skin in the upper chest, allowing drug application. These are generally preferred in patients requiring long-course, repeated chemotherapy treatment (1).

The underlying causes of changes in serum cortisol levels were observed as unusual adrenocorticotropic hormone (ACTH) levels, clinical depression, and physiological stress sources (hypoglycemia, disease, fever, trauma, surgery, fear, pain, extreme cold or hot, and physical strain) (2).

High-sensitivity troponin testing allows for the determination of concentration levels, which cannot be detected earlier using conventional cardiac troponin tests and also allows for precise measurement and diagnosis and/or elimination of myocardial infarction without elevation of ST during admission to the hospital (3).

The present study aimed to evaluate the effect of sedative agents on stress hormones (ACTH and cortisol), high-sensitivity troponin, pain, and anxiety of patients admitted to the emergency service with requirement of port catheterization that was guided by bedside ultrasound imaging and classified according to the American society of Anesthesiologists (ASA) Physical Classification System. Simultaneously, it aims to increase patient satisfaction and the frequency of application of bedside ultrasound imaging in emergency departments.

METHODS

This prospective cohort study was conducted at the Gaziantep University Şahinbey Research and Practice Hospital Emergency Service. Approval was obtained from the Gaziantep University Faculty of Medicine Ethics Committee (ethics committee decision no: 09.03.2015/84, date: 03.09.2015). The study protocol was conducted in accordance with the Declaration of Helsinki, and was prospectively conducted at the Gaziantep University Şahinbey Research and Practice Hospital Emergency Service between March and August 2015. The patients were taken to an emergency room for port catheterization, which had been prepared earlier for the procedure. A "Patients Consent Form" was obtained from all patients.

Population and Samples

Patients who were referred to the emergency department by the hem atology and oncology departments for port catheterization were divided into three groups based on the three different sedation options planned. A total of 90 patients were included in the study. The following inclusion and exclusion criteria were followed when enrolling patients in the study:

Inclusion Criteria

- Men and women aged >18 years,
- Patients who volunteered to participate in the study,
- Those who speak Turkish or to whom the procedure can be explained to,
- Those who have stable vital findings,
- Patients to whom the port catheter was applied for the first time.

Exclusion Criteria

- Patients who did not volunteer to participate in the study,
- Male and female patients aged <18 years,
- Patients who are pregnant,
- Patients who do not speak Turkish or to whom the procedure cannot be explained to,
- Patients with unstable vital findings,
- Patients with pituitary or adrenal gland tumors affecting blood ACTH and cortisol levels,
- Patients who used drugs that affected ACTH and cortisol levels,
- Patients who previously had port catheterization,
- Patients with hormonal dysfunction,
- Patients who had been using steroids, anxiolytics, and sedative drugs,
- Patients with severe anxiety disorder, active psychosis, or dementia,
- Patients with uncontrollable hypertension,
- Patients with substance abuse,
- Patients with complications during the procedure,
- Patients with coronary artery disease,
- Patients with cerebrovascular disease,
- Patients with chronic renal failure.

The patients' ASA physical classification system values were assessed. Application of sedation analgesia to non-emergency cases in the emergency service was limited to ASA 1-2 patients.

Beck Anxiety Scale and Visual Analog Scale (VAS) were applied to the patients before and after the procedure.

The vital signs (blood pressure, pulse rate, and respiration rate) of the patients were followed and recorded (Nihon Kohden Corporation, model BSM-2351 K, 2008, Japan). ACTH, cortisol, and high-sensitive troponin levels were measured in the blood samples collected before the procedure, whereas ACTH and cortisol levels at the 30th minute and high-sensitive troponin I level at the third hour were obtained and measured in the routine biochemistry laboratory.

Blood samples were collected in biochemical tubes each time for ACTH, cortisol, and highly sensitive troponin levels. Samples collected from each patient were separated into serum by centrifugation for 10 min at 4000 rpm for comparison of ACTH, cortisol, and highly sensitive troponin levels. Serum specimens were placed in separate Eppendorf tubes, and stored at -80°C in a deep freezer at Gaziantep University Faculty of Medicine Basic Science Laboratory until use (Biotek ELx800 model, ELISA reader, USA). Patients were examined for vital signs, and the findings were recorded in the follow-up table generated by the researcher at the time of initial application, at the beginning of the procedure, and at the end of the procedure. The anxiety status of patients was assessed using the Beck Anxiety Scale when patients were first taken into the room and after the completion of the procedures. VAS was used to determine the level of pain felt by patients after the procedure was over.

The Social Sciences 18 program (IBM Ltd.; Rm 1804, 18/F, Westlands Center, Quarry Bay, Hong Kong) was used for statistical analysis. Distribution of continuous variables (ASA value, anxi-

ety value, VAS value, respiratory rate, pulse rate, diastolic blood pressure, systolic blood pressure, cortisol, and ACTH hormone level) was analyzed using Analysis of Variance tests. Independent t-test was used for comparison of independent groups showing normal distribution. Paired t-test was used for comparison of dependent variables showing normal distribution. All data were expressed as mean±standard deviation, and p<0.05 was considered statistically significant.

Table 1. Comparison of pain and anxiety levels of patients in the treatment and control groups

Parameter	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)	p*
VASPRE	0.66±1.64	1.03±1.58	1.06±2.1	0.635
VASPOST	1.20±1.9[a,b]	0.16±0.37	0.010	**0.001**
p[x]	0.122	**0.009**	**0.010**	
ANXPRE	7.43±5.89	7.43±4.84	6.50±4.07	0.706
ANXPOST	2.93±2.82[c]	1.43±4.84	1.60±2.02	0.023
px	**0.001**	**0.001**	**0.001**	
ASA	1.48±0.58	1.40±0.62	1.60±0.89	0.586

VASPRE: VAS before procedure; VASPOST: VAS after procedure; ANXPRE: anxiety value before procedure; ANXPOST: anxiety value after procedure; ASA: ASA values of patients

Group 1: Treated with midazolam and ketamine; Group 2: Treated with midazolam and fentanyl; Group 3: Treated with propofol.

p*: ANOVA test, p[x]: paired-sample t-test

[a]p=0.002, [b]p=0.000, [c]p=0.032

[a], [c]: Group 1 and Group 2; [b]: Group 1 and Group 3

Table 2. Comparison of Systolic (SBP) and Diastolic Blood Pressure Values (DBP) of patients in all the three groups

Parameter	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)	p*
SBP1	121.36±15.96[a]	132.10±16.33	124.33±18.17	**0.044**
SBP2	125.23±18.01[b]	128.23±15.00[d]	111.76±16.77	**0.001**
SBP3	121.53±17.22	125.03±14.41[e]	112.03±15.28	**0.006**
p[x]	0.958	**0.003**	**0.001**	
DBP1	73.10±12.30	78.56±12.92	71.76±9.66	0.064
DBP2	73.76±10.69c	72.13±12.12[f]	64.06±8.84	**0.001**
DBP3	69.60±10.94	67.36±9.58	64.96±11.17	0.243
p[x]	0.080	**0.001**	**0.001**	

SBP1: systolic blood pressure before procedure; SBP2: systolic blood pressure during procedure; SBP3: systolic blood pressure after procedure; DBP1: diastolic blood pressure before procedure; DBP2: diastolic blood pressure during procedure; DBP3: diastolic blood pressure after procedure

Group 1: treated with midazolam and ketamine; Group 2: treated with midazolam and fentanyl; Group 3: treated with propofol

p*: ANOVA test, p[x]: paired-sample t-test

[a]p=0.041, [b],[e]p=0.005, [c]p=0.002, [d]p=0.001, [f]p=0.012

[a]: Group 1 and Group 2; [b], [c]: Group 1 and Group 3; [d], [e], [f]: Group 2 and Group 3

RESULTS

Characteristics of gender and age of the individuals in the three sedation groups were similar to each other. No statistically significant difference in gender distribution was observed in the study. Further, no statistically significant difference in terms of age was observed in the present study.

The mean VAS before procedure (VASPRE) before treatment in the midazolam and fentanyl group was 1.03±1.58, whereas the mean VAS after procedure (VASPOST) after treatment was 0.16±0.37; this decrease in pain was found to be statistically significant (p=0.009). The mean VASPRE before treatment in the propofol group was 1.06±2.1, whereas the mean VASPOST after treatment was 0.010; this decrease in pain was found to be statistically significant (p=0.010) (Table 1, Figure 1).

The mean diastolic blood pressure 2 (DBP2) in the midazolam and ketamine group was 73.76±10.69 mm Hg, whereas the mean DBP2 in the midazolam and fentanyl group was 73.13±12.12 mm Hg. The mean DBP2 in the propofol group was 64.06±8.84 mm Hg. A statistically significant difference was observed between the DBP2 values of the midazolam with fentanyl and propofol groups (p=0.012) (Table 2, Figure 2).

Figure 1. Values of anxiety levels of patients before procedure (ANXPRE) and after procedure (ANXPOST)

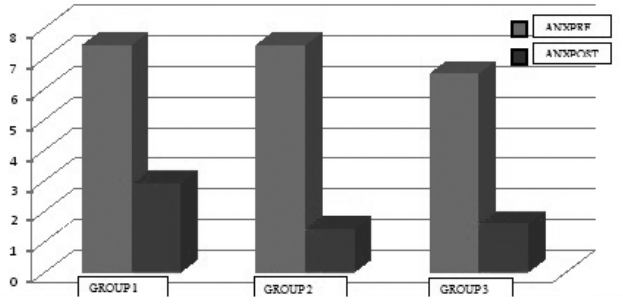


Figure 2. Comparison of systolic blood pressure (SBP) values and diastolic blood pressure (DBP) values of patients in all the three groups

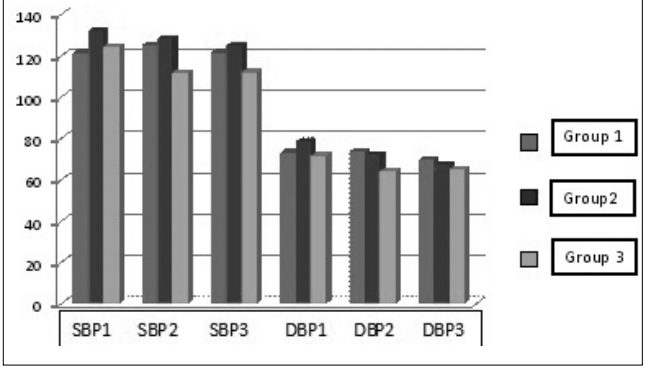


Table 3. Comparison of Pulse (PLS) and Respiratory Rate (RR) values of patients in all the three groups

Parameter	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)	p*
PLS1	95.40±19.58	94.86±16.42[d]	91.00±18.55	0.596
PLS2	100.93±19.59[a]	94.30±15.51	89.03±18.04	**0.039**
PLS3	101.26±19.89	100.30±14.65	91.40±16.85	0.056
p[x]	**0.029**	**0.003**	0.816	
RR1	18.83±6.29	17.96±6.02	17.70±4.96	0.731
RR2	20.06±8.08[b]	15.80±5.52	18.73±6.15	**0.045**
RR3	19.13±7.05	19.30±8.00	18.20±5.68	0.806
p[x]	0.710	0.453	0.629	

PLS1: pulse before procedure; PLS2: pulse during procedure; PLS3: pulse after procedure

RR1: respiratory rate before procedure; RR2: respiratory rate during procedure; RR3: respiratory rate after procedure

Group 1: treated with midazolam and ketamine; Group 2: treated with midazolam and fentanyl; Group 3: treated with propofol

p*: ANOVA test, p[x]: paired-sample test

[a]p=0.039, [b]p:=0.045

[a]: Group 1 and Group 3; [b]: Group 1 and Group 2

Table 4. Comparison of Oxygen Saturation Percentages (SPO2) of patients in the all three groups

Parameter	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)	p*
SPO2-1	97±1.77[a]	96.66±2.13d	98.40±1.61	**0.002**
SPO2-2	95.63±3.37[b]	96.53±2.58	97.73±2.40	**0.018**
SPO2-3	95.56±1.97[c]	96.66±2.55	98.00±2.33	**0.001**
p[x] pre-post	**0.001**	1.000	0.173	

SPO2-1: oxygen saturation before procedure; SPO2-2: oxygen saturation during procedure; SPO2-3: oxygen saturation after procedure.

Group 1: treated with midazolam and ketamine; Group 2: treated with midazolam and fentanyl; Group 3: treated with propofol.

p*: ANOVA test, p[x]: paired-sample test.

[a]p: 0.044 SPO2 Group 1 and Group 3; [b]p: 0.014 SPO2 Group 1 and Group 3; [c]p: 0.000 SPO2 Group 1 and Group 3; [d]p: 0.001 SPO2 Group 2 and Group 3.

Table 5. Comparison of puncture numbers of patients in all the three groups

	Number of punctures				
	1	2	3	4	Total
Group 1 (n=30)	16 (53.3%)	11 (36.6%)	2 (6.6%)	1 (3.3%)	30
Group 2 (n=30)	20 (66.6%)	7 (23.3%)	2 (6.6%)	1 (3.3%)	30
Group 3 (n=30)	18 (60%)	7 (23.3%)	5 (16.6%)	0	30
Total	54 (60%)	25 (27.7%)	9 (10%)	2 (2.2%)	90
p*	0.786				

Group 1: treated with midazolam and ketamine; Group 2: treated with midazolam and fentanyl; Group 3: treated with propofol

The mean respiratory rate 2 (RR2) in the midazolam and ketamine group was 20.06±8.08/min, whereas the mean RR2 in the midazolam and fentanyl group was 15.80±5.52/min. The mean RR2 in the propofol group was 18.73±6.15/min. A statistically significant difference was observed between the mean RR2 values of the midazolam with ketamine and propofol groups (p=0.045; Table 3).

The mean oxygen saturation (SPO) before procedure 2-3 in the midazolam and ketamine group was 95.56%±1.97%, whereas the mean SPO2-3 in the midazolam and fentanyl group was 96.66%±2.55%. The mean SPO2-3 in the propofol group was 98.00%±2.23. A statistically significant difference was observed between the mean SPO2-3 values in the midazolam with ketamine and propofol groups (p=0.001; Table 4).

Access to the vein was obtained through 1 puncture in 18 individuals (60%), 2 in 7 (23.3%), and 3 in 5 (16.6%) of the propofol group. No statistically significant difference was observed in terms of the number of punctures in the individuals in our study (p>0.05; Table 5).

In terms of diagnosis, 8 (26.6%) individuals in the midazolam and ketamine group had a hematologic diagnosis, whereas 22 (73.3%) had an oncologic diagnosis. Twelve (40%) individuals in the midazolam and fentanyl group had a hematologic diagnosis, whereas 18 (60%) had an oncologic diagnosis. Twelve (40%) individuals in the propofol group had a hematologic diagnosis, whereas 18 (60%) had an oncologic diagnosis. Oncologic diagnosis was the most common among patients.

The mean ACTH pre measured in blood samples when the patient was first received in the room and was prepared for port

Table 6. Comparison of ACTH, cortisol, and high-sensitive troponin values of patients in all the three groups

Parameter	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)	p*
ACTH Pre	13.83±7.84	17.21±12.66	13.27±10.29	0.293
ACTH Post	29.44±27.83a	17.95±7.31	19.52±7.40	0.023
p[x]	**0.007**	0.733	**0.001**	
Cort Pre	155.90±105.10	176.89±99.25	165.05±162.70	0.811
Cort Post	179.15±115.22	196±36	174.56±185.22	0.839
p[x]	0.117	0.286	0.526	
Trp Pre	1.22±0.34	1.18±0.45b	1.48±0.54	**0.026**
Trp Post	1.71±1.03	1.48±0.53	1.80±0.54	0.239
p[x]	**0.013**	**0.001**	**0.003**	

ACTH Pre: ACTH before procedure; ACTH Post: ACTH after procedure; Cort Pre: cortisol before procedure; Cort Post: cortisol after procedure; Trp Pre: troponin before procedure; Trp Post: troponin after procedure

Group 1: treated with midazolam and ketamine; Group 2: treated with midazolam and fentanyl; Group 3: treated with propofol

p*: ANOVA test; px: paired-sample test

[a]p: 0.030; [b]p: 0.034. [a]: Group 1 and Group 2, [b]: Group 2 and Group 3

catheterization procedure was 13.83±7.84 pg/mL, and the mean ACTH post-measured in blood samples after the procedure was 29.44±27.83 pg/mL in the midazolam and ketamine group. An increase in the ACTH levels of individuals in the midazolam and ketamine group was observed; this increase was found to be statistically significant (p=0.007; Figure 3).

The mean first cortisol before procedure (Cort Pre) result obtained from the blood samples in the midazolam and ketamine group was 179.15±115.22 µg/dL, whereas the mean cortisol after procedure (Cort Post) result in the midazolam and fentanyl group was 176.89±99.25 µg/dL. The mean Cort Post result in the propofol group was 165.05±162.70 µg/dL. No statistically significant difference was found between the Cort Pre results of all the three groups (p=0.811; Table 6).

The mean first Cort Pre result obtained from the blood samples in the midazolam and ketamine group was 179.15±115.22 µg/dL, whereas the mean Cort Post result in the midazolam and fentanyl group was 196±36 µg/dL. The mean Cort Post result in the propofol group was 174.56±185.22 µg/dL. No statistically significant difference was found between the Cort Pre results of all three groups (p=0.839; Figure 4).

Figure 3. Comparison of ACTH before procedure (ACTH Pre) and after procedure (ACTH Post) values of patients in all the three groups

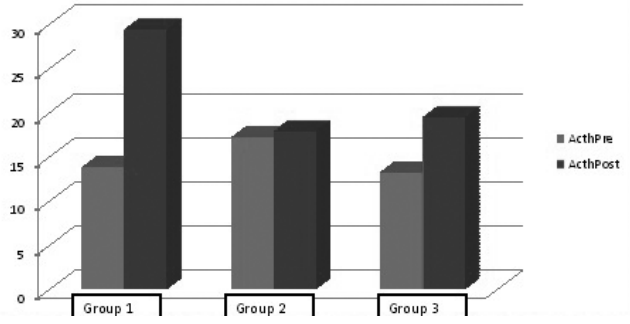
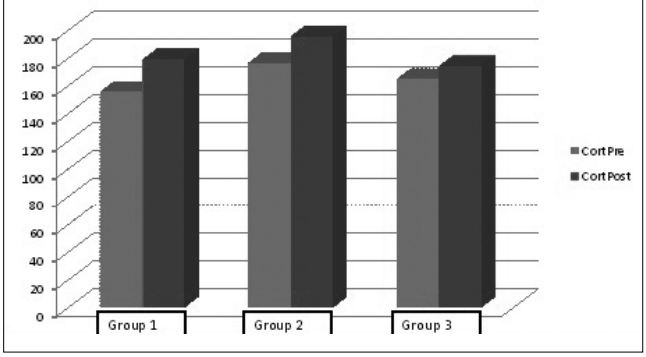


Figure 4. Comparison of cortisol before procedure (Cort Pre) and after procedure (Cort Post) values of patients in all thethree groups



The mean troponin before procedure (Trp Pre) in the midazolam and ketamine group was 1.22±0.37 ng/mL, whereas the mean Trp Pre in the midazolam and fentanyl group was 1.18±0.45 ng/mL. The mean Trp Pre in the propofol group was 1.48±0.54 ng/mL. A statistically significant difference was observed between the mean Trp Pre in the midazolam with fentanyl and propofol groups (p=0.026; Table 6).

DISCUSSION

The present study showed that sedative agents have statistically significant beneficial effects in reducing anxiety in port catheterized patients. Patients who are hospitalized or who are to be invasively treated often have anxiety. This resulting anxiety can affect the body's physiological response and pain perception (4). The body's physiological response to anxiety is a response of stress, which activates the hypothalamo-hypophyse-adrenal axis and sympathetic nervous system, resulting in stress hormone secretion (5). Anxiety is a problem that increases an individual's heart rate, blood pressure, body temperature, and respiratory rate. It decreases the pain threshold and increases postoperative analgesic requirements and the possibility of developing complications (6).

In a multicenter study assessing the effects of propofol and remifentanil with intravenous anesthesia in elective cases of 161 patients, Hogue et al. (7) reported that in addition to propofol, another opioid remifentanil infusion was added to the study and that they were able to quickly and efficiently control intraoperative stress.

In our study, the Beck Anxiety Scale was used to measure the anxiety level in patients. The results showed that midazolam with ketamine, midazolam with fentanyl, and propofol significantly reduced anxiety.

In a prospective study performed on 62 patients (31 in the ketamine/propofol group and 31 in the midazolam/fentanyl group) by Nejati et al. (8), the pain sensation in the ketamine/propofol group measured using VAS was significantly lower than that in the midazolam/fentanyl group.

In our study, VAS was also used to measure the level of pain. In conclusion, pain reduction in patients in the midazolam and ketamine group was not significant; however, pain reduction in the midazolam with fentanyl and propofol groups was significant.

Palpitation, elevation of blood pressure, and increase in respiratory rate are the physiological indicators of anxiety. Anxiety and stress can increase the number of pulsations, respiratory rate, and blood pressure by stimulating the nervous system and producing large amounts of stress hormone (5).

In a study conducted by Motov et al. (9) on 90 patients, 45 of which were in the ketamine group and 45 others in the morphine group, patients were treated with mean values of 21.8 mg ketamine or 7.7 mg morphine. No significant difference was observed between the two groups in terms of sociodemographic characteristics, basal vital findings, basal pain values, and com-

plaints. Significant reduction in pain scale value was observed in all patients at 15 and 30 minutes.

A study performed by Kramer et al. (10) aimed to compare propofol-ketamine and propofol-remifentanil infusions for sedation during the third molar tooth extraction; the intraoperative mean arterial pressure values decreased in both the groups compared with the pre-intervention values; however, this decrease was significantly different between both the groups.

In a study conducted by Funk et al. (11) on 120 pediatric patients using a combination of midazolam and ketamine, only midazolam, and only ketamine, no significant differences were observed between the vital parameters such as blood pressure, heart rate, and oxygen saturation at any stage of the study.

Chung and Evans (12) reported that fentanyl was effective in suppressing tachycardia and hypertension in an attempt to measure hemodynamic response during anesthesia induction and intubation in elderly patients.

Arslan et al. (13) performed angiographic anesthesia for a case of nesidioblastosis with insulinoma and reported that an infusion of propofol and remifentanil did not impair hemodynamic stability in their study.

In the present study, midazolam and ketamine did not cause any significant changes in the systolic and diastolic blood pressure rates of patients. Patients treated with midazolam with fentanyl and propofol showed a significant decrease in the systolic and diastolic blood pressures in the results after procedure compared with those before procedure. In comparison with the measured systolic blood pressures during and after the treatment of midazolam with fentanyl and propofol in patients, a significant decrease in blood pressure was observed in patients treated with propofol. In comparison with the measured diastolic blood pressures of midazolam with fentanyl and propofol treated patients during the procedure, a significant decrease in blood pressure was observed in patients treated with propofol. No significant difference was observed between the diastolic blood pressures measured after the procedure.

In our study, the increase in pulse rates measured in follow-ups of patients who were treated with midazolam with ketamine and with fentanyl was statistically significant. The difference in the propofol group was not found to be statistically significant. Patients treated with midazolam and ketamine had a higher pulse rate during the procedure than the propofol group, and this difference was found to be statistically significant. No significant difference was observed between the respiratory rates measured before and after the procedure in the groups. In our study, the decrease in oxygen saturation in patient follow-ups in the midazolam with ketamine group was found to be statistically significant. No statistically significant difference was observed between the oxygen saturation of midazolam with fentanyl and propofol groups. The oxygen saturation rates of the patients in the midazolam and ketamine group were lower, and the difference was statistically significant compared with the oxygen saturation results of the midazolam with ketamine and propofol treated patient groups during and after the procedure.

Port catheters are most commonly placed percutaneously in the right internal jugular vein (14). In a study by Biffi et al. (15), 403 patients were administered intravenous chemotherapy, and the placement of the single port implant was randomly chosen either as percutaneous internal jugular vein, subclavian vein with coexistence of ultrasonography or cephalic vein in the deltopectoral groove with surgical cut-down. A total of 401 patients were evaluated, and internal jugular vein access was chosen in 132 patients, subclavian vein access in 136, and cephalic vein access in 133. In our study, USG was used, and the right internal jugular vein was the commonest access location (63%) for port catheterization.

The increased pain and anxiety experienced by the patients to be invasively treated increases the release of stress hormones by intraoperative stimulation of the afferents in the surgical area. ACTH, cortisol, epinephrine, and norepinephrine are frequently used as surgical stress markers. Cortisol is a corticosteroid hormone produced in the cortical region of the adrenal gland and is associated with the body's stress response. The reasons behind the change in serum cortisol levels include unusual ACTH levels, clinical depression, and physiological stress sources such as hypoglycemia, disease, fever, trauma, surgery, fear, pain, extreme cold or hot, and physical strain.

Several studies aimed to reduce the release of preoperative stress hormones. Gruber et al. (16) compared the different uses of fentanyl to the use of midazolam in addition to fentanyl to reduce the increase in stress hormones caused by surgery in children undergoing congenital heart surgery. It has been emphasized that congenital heart surgery has a significant stress response in children, and fentanyl treatment (with or without midazolam) could not prevent this stress response as reported in the study.

In a similar group of patients, Bell et al. (17) found that serum cortisol levels did not differ between groups when a combination of remifentanil compared with fentanyl-morphine; however, serum glucose levels were higher in the remifentanil group, and consequently, there was no difference between these two methods in the prevention of stress response to surgery.

Dönmez et al. (18) compared cortisol and ACTH levels using etomidate and ketamine in the pediatric cardiac surgery population. The cortisol level was increased in the ketamine group, whereas in the etomidate group, it was decreased after induction, remained low during bypass, and was close to the control value at the end of surgery. At all stages, cortisol levels were significantly lower in the etomidate group than in the ketamine group. In the etomidate group, ACTH slightly decreased after induction, started to rise with systolic blood prossure, and reached the highest value at the end of surgery. ACTH levels in the ketamine group also tended to increase from the beginning of the induction. Plasma ACTH concentrations were not significantly different between the two groups.

Adams et al. (19) measured plasma ACTH levels in patients treated with propofol and isoflurane and found that plasma cortisol, adrenaline, and noradrenaline levels were significantly lower in the propofol group than in the isoflurane group.

In a study performed by Gülbayrak et al. (20) to investigate the comparison of monitorization of neuromuscular blockage and the depth of inhalation anesthesia and propofol anesthesia and hemodynamic and neuroendocrine responses, plasma ACTH levels were postoperatively increased at 30 minutes and lowered at 24 hours compared with preoperative control values.

In a study investigating hormonal and hemodynamic changes in percutaneous nephrolithotomy cases, Atıcı et al. (21) reported that ACTH values were increased in the postoperative period compared with preoperative measurements.

In a comparative study comparing propofol and its application as an infusion, no significant difference was observed in the cortisol and glucose levels between both the groups; however, there was a significant decrease in insulin concentrations (22).

In our study, the increase in ACTH levels of patients treated with midazolam and ketamine, midazolam and fentanyl, and propofol was statistically significant. The ACTH level of the midazolam and ketamine group was higher than that of the midazolam and fentanyl group, and this difference was statistically significant. Stress-inducing conditions such as trauma, surgical intervention, shock, heavy infection, anxiety, and hypoglycemia can increase cortisol secretion up to 10 times through neural pathways in the brain.

In a study by Aono et al. (23) involving 52 patients from the ASA I-II group that underwent laparoscopic cholecystectomy, patients underwent general anesthesia, fentanyl-assisted general anesthesia, and epidural anesthesia combined with general anesthesia. They noted that the cortisol values increased immediately before surgery and half an hour after the start of the surgery in all the three groups.

In our study, the changes in cortisol levels after treatment with midazolam and ketamine, midazolam and fentanyl, and propofol were not statistically significant.

De Hert et al. (24) investigated the effects of propofol, desflurane, and sevoflurane on cardiopulmonary function in patients with coronary surgery and found that cardiac index values of patients significantly decreased under propofol anesthesia.

A study by Lowe et al. (25) investigated gene expression to recognize expression profiles and determine the metabolic pathways affected in ketamine-treated adult mice brains. Adult male mice were intraperitoneally injected with either ketamine (80 mg/kg) or distilled water (control group). The control group showed that 50 genes were differently expressed when compared with ketamine-treated mice brains, and the expression of troponin T1 gene was 2-4 times higher in concordance.

A study by Serinken and Cenker (26) aimed to determine the relationship between 1.5 mg/kg intravenous ketamine treatment for minor procedures and myocardial injury in children with a mean age of 2 years (quartile width, 1-4 years). High-sensitive troponin levels were measured before and 3 hours after the application of ketamine. A total of 30 patients were included in the study. Two patients had elevated troponin levels after 3 hours of ketamine application. The study concluded that ketamine may be associated with elevated troponin levels in children without causing permanent cardiac dysfunction in minor procedures.

In our study, the increase in high-sensitive troponin I levels after treatment with midazolam and ketamine, midazolam and fentanyl, and propofol was found to be statistically significant. No significant difference was observed between the groups because of high-sensitive troponin I levels after the procedure.

CONCLUSION

In conclusion, since sedative agents suppress sympathetic activity, application of sedative agents is an effective, safe, and easily applicable treatment method for minor surgical procedures in emergency service. We therefore recommend the application of simultaneous sedation for invasive procedures in the emergency service, so as to be more careful in terms of cardiac events because of the negative effects of simultaneous sedation to troponin values.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethical committee of Gaziantep University (09.03.2015/84)

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Original Research / Özgün Araştırma

Assessment of Malnutrition and Nutritional Status of Hospitalized and Treated Children Aged between 12 and 60 Months

12–60 Aylık Hastanede Yatan ve Tedavi Gören Çocuklarda Malnütrisyon ve Beslenme Durumunun Değerlendirilmesi

Burcu Kumru[1], Miray Karakoyun[2]

[1]Division of Nutrition and Diet, Gaziantep Cengiz Gökçek Maternity and Children's Hospital, Gaziantep, Turkey

[2]Division of Pediatric Gastroenterology, Tepecik Training and Research Hospital, İzmir, Turkey

ABSTRACT

Objective: This study aimed to evaluate malnutrition, breastfeeding, introduction to complementary feeding, and nutritional status of hospitalized children aged between 1 and 5 years.

Methods: Along with their mothers, a total of 484 children aged between 1 and 5 years without underlying chronic diseases were included in this study. The mothers were questioned about breastfeeding, introduction to complementary feeding, and nutritional status of their children. Anthropometric measurements including body weight and height of the children were evaluated using the WHO Anthro Program. The interpretation of measurements was done by using the z-score [standard deviation (SD)] cut-points.

Results: The mean age of the patients was 2.27 years. The rate of mothers who breastfed for less than 6 m was 19.6%; among breastfed children aged between 12 and 24 m, the rate was 42.4%. The mean age to start complementary feeding was 6.8±3.01 m. The first complementary food given was yogurt in 45.6% of the babies and vegetable soup in 29.4%. The rates of acute malnutrition, chronic malnutrition, and obesity were 13.6%, 5.2%, and 7.2%, respectively.

Conclusion: Malnutrition is a major health problem. It is multifactorial and includes timing of introduction of complementary feeding, preparation techniques of food, and socioeconomic and cultural factors. To eliminate the adverse effects of nutrition on health problems, the nutritional status of individuals should be closely monitored, and necessary precautions should be taken.

Keywords: Breast milk, complementary feeding, malnutrition, obesity

ÖZ

Amaç: Bu çalışmada hastaneye yatırılan 1-5 yaş arası çocukların malnütrisyon, anne sütü alımları, tamamlayıcı beslenmeye geçiş zamanları, tamamlayıcı beslenmede verilen besinler ve beslenme durumları değerlendirildi.

Yöntemler: Bu çalışmaya altta yatan kronik hastalığı olmayan 1-5 yaş arası 484 çocuk ve anneleri alındı. Hastaların annelerine anne sütü verme, tamamlayıcı beslenmeye geçiş ve çocukların beslenme durumları ile ilgili sorular souldu. Çalışmaya alınan çocukların antropometrik ölçümleri (vücut ağırlığı ve boy uzunluğu) DSÖ Anthro Programı ile değerlendirildi. Ölçümler Z-skor (SD) kesişim noktalarına göre yorumlanmıştır.

Bulgular: Hastaların yaş ortalaması 2,27 yıl idi. Altı aydan az süreyle emziren annelerin oranı %19,6 iken, 12-24 ay arası olan çocuklarda emzirilme oranı %42,4 idi. Tamamlayıcı beslenmeye başlama zamanları ortalaması 6,8±3,01 aydı. Annelerin ilk verdikleri besinlerden %45,6'sı yoğurt olurken, %29,4'ü sebze çorbası idi. Hastalarda akut malnütrisyon %13,6, kronik malnütrisyon %5,2 ve obezite %7,2 olarak bulundu.

Sonuç: Malnütrisyon önemli bir sağlık sorunu olmakla birlikte, anne sütü alımı, tamamlayıcı besinlere başlama zamanı ve besin çeşitleri, besinleri hazırlama yöntemleri, sosyoekonomik ve kültürel faktörler gibi birçok etmen malnütrisyon gelişmesine neden olmaktadır. Beslenmenin sağlık sorunları üzerinde oluşturabileceği olumsuz etkileri ortadan kaldırmak için beslenme durumları yakından takip edilmeli ve gerekli tedbirler alınmalıdır.

Anahtar kelimeler: Anne sütü, obezite, malnütrisyon, tamamlayıcı beslenme

INTRODUCTION

The World Health Organization (WHO) recommends that infants should be exclusively breastfed for the first 6 m, with continued breastfeeding along with appropriate complementary foods up to 2 years of age. In developing countries, exclusive breastfeeding in the first 6 m of life reduces mortality and morbidity rates. Therefore, timely introduction of complementary feeding with adequate safe and appropriate foods is essential (1, 2). The appropri-

ORCID IDs of the authors: B.K. 0000-0001-5760-8218; M.K. 0000-0002-6533-6256.

Corresponding Author/Sorumlu Yazar: Burcu Kumru **E-mail/E-posta:** burcu-kumru@hotmail.com

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ate time to introduce complementary foods should be around 6 m of age, but not before 17 weeks, and should not be stopped after the 26th week we have formulated these conclusions: Exclusive or full breast-feeding for about 6 months is a desirable goal (3). Complementary feeding (ie, solid foods and liquids other than breast milk or infant formula and follow-on formula.

Malnutrition is defined as a condition in which a deficiency, excess (or imbalance) of energy, protein, and other nutrients causes measurable adverse effects on tissue/body form, function, and clinical outcomes (4). Growth and developmental delay occurs in infants and children because of inadequate and unbalanced nutrition, which also causes mortality (5). Malnutrition and its causes are associated with one third of the global disease burden, mostly in developing countries, for children aged less than 5 years (6). Anthropometric measurements are directly associated with the nutritional status of young children that affects the risk of illness and mortality. The data obtained from infants and children reflect general health status and dietary adequacy. Nutritional status affects the risk of illness and death in young children. Recently, the problem of obesity in children has considerably increased in Turkey. Several studies have demonstrated that this problem will continue to increase, unless preventive measures are taken in the near future (7, 8).

This study aimed to evaluate malnutrition, breastfeeding, introduction to complementary feeding, and nutritional status of hospitalized children aged between 1 and 5 years.

METHODS

This study was conducted at Gaziantep Cengiz Gökçek Maternity and Children's Hospital between September 2015 and March 2016 with a total of 484 hospitalized patients aged between 1 and 5 years. Patients who were hospitalized in the intensive care or the emergency unit and those with neurological or genetic disorders were excluded from the study. The mothers were questioned about breastfeeding, introduction to complementary feeding and nutritional status of their children. A total of 484 mothers provided consent to participate in the study and filled the data collection form, which was developed by the researchers. The study protocol was approved by the Gaziantep University Clinical Research Ethics Committee (Decision no. 2015/301). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Anthropometric measurements including body weight and height of the children were made by a single researcher. The obtained data were evaluated based on the age group (12-24, 25-36, 37-48, and 49-60 months). The obtained data were evaluated with the WHO Anthro Program (www.who.int/childgrowth/software/en/). The interpretation of measurements was performed using the *z*-score [standard deviation (SD)] cut-points. A weight-for-height *z*-score lower than -2 SD indicates acute malnutrition, a height-for-age *z*-score lower than -2 SD indicates chronic malnutrition, and body mass index z-score for age above +2 SD indicates those who are considered obesity.

Statistical Analysis

Statistical analyses were performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013). Continuous variables were expressed as mean±SD and median (minimum-maximum). Categorical variables were expressed as frequency (*n*) and percentage (%). p=0.05 was considered statistically significant.

RESULTS

Of the 484 patients included in the study, 208 (43%) were female and 276 (57%) were male. The mean age was 2.27 years (range, 1-5 years), and the mean birth weight was 3092 grams. Complementary feeding was introduced with a mean duration of 6.8±3.01 months (range, 1-40 months). The rates of acute malnutrition, chronic malnutrition, and obesity in the patients were 13.6%, 5.2%, and 7.2%, respectively (Table 1).

Distribution of malnutrition by age group is presented in Table 2. Acute malnutrition (40%), chronic malnutrition (44%), and obesity (48.6%) were the highest among children aged 12- 24 months. On the basis of the breastfeeding duration (never breastfed, less than 1-6 months, 1-6 months, 7-12 months, and longer than 13 months), no significant difference in the rate of acute malnutrition was observed. However, there was a significant difference

Table 1. Malnutrition status of patients

		n	%
Acute malnutrition	**No**	418	86.4
	Yes	66	13.6
Chronic malnutrition	**No**	459	94.8
	Yes	25	5.2
Obese	**No**	449	92.8
	Yes	35	7.2

Table 2. Malnutrition status according to age groups

		12–24 m	25–36 m	37–48 m	49–60 m
Acute malnutrition, n (%)	**No**	220 (54.9)	100 (24.9)	55 (13.7)	26 (6.5)
	Yes	26 (40.0)	23 (35.4)	10 (15.4)	6 (9.2)
Chronic malnutrition, n (%)	**No**	235 (53.3)	114 (25.9)	60 (13.6)	32 (7.3)
	Yes	11 (44.0)	9 (36.0)	5 (20.0)	0 (0.0)
Obese, n (%)	**No**	229 (53.1)	112 (26.0)	58 (13.5)	32 (7.4)
	Yes	17 (48.6)	11 (31.4)	7 (20.0)	0 (0.0)

m: months

in the rate of chronic malnutrition, showing the highest rate in infants who were never breastfed. No significant difference was observed in the rates of acute and chronic malnutrition between those who were breastfed for less than 6 months and those who were breastfed for longer than 7 months. In babies aged 12-24 months who were still breastfed, no significant difference was observed in the breastfeeding status of the mother and the chronic and acute malnutrition rates.

A total of 93.6% mothers breastfeed immediately after birth, whereas 88.2% of those who do not breastfeed fed sugar water. Of the children aged 12-24 m, 42.4% were still breastfed. While 9.4% children were never breastfed, 19.6% were breastfed for less than 6 m and 70.9% were breastfed for more than six months. A total of 40% mothers discontinued breastfeeding because of low milk supply and 53.2% because their babies were unable to suck milk. Additionally, 45.6% mothers fed yogurt as the first food, whereas 29.4% fed vegetable soup. Mothers used water more frequently (90.6%) while preparing the formula. Of the mothers who had picky-eating children, 45.2% force-fed their children, whereas 21.9% did not hassle. Details regarding breastfeeding and the nutritional status of children are presented in Table 3.

Table 3. Breastfeeding and nutritional status of children

		n	%
How soon after birth did you breastfeed your child?	**Immediately after birth**	412	93.6
	within 6-12 hours	2	0.5
	within 12-24 hours	0	0.0
	After a day	26	5.9
If you did not breastfeed your child	**Sugar water**	15	88.2
right after birth, what did you feed your child?	**Water**	2	11.8
Are you still breastfeeding? *(children aged 12-24 m)	**Yes**	104	42.4
	No	141	57.6
For how long did you breastfeed?	**Never breastfed**	41	9.4
	Less than 1-6 months	57	13.0
	1-6 months	29	6.6
	7-12 months	60	13.7
	13 months and more	250	57.2
Why did you cut down breastfeeding before six months?	**Lack of milk**	44	40.4
	Introduction of complementary foods	3	2.8
	Baby did not suck milk	58	53.2
	Re-pregnancy	4	3.7
What was the first complementary food you gave?	**Baby formula in jar**	53	11.0
	Yogurt	219	45.6
	Cow's milk	13	2.7
	Fruit juice	18	3.8
	Vegetable soup	141	29.4
	Pudding	36	7.5
What did you use while preparing formula at home?	**Water**	230	90.6
	Milk	16	6.3
	Water and milk	8	3.1
What do you do when your child gives you trouble while feeding?	**Force-feed**	217	45.2
	Do not hassle	105	21.9
	Give a break and try later	56	11.7
	Give appetizing syrup	2	0.4
	No eating problems	100	20.8

According to the time of introduction of complementary foods in infants, cow's milk, yogurt, and pudding were commonly fed at the age of 4-6 months. In addition, white cheese, egg, meat, rice pilaf, bulgur pilaf, pasta, lentil soup, tarhana soup (i.e., a mixture of wheat flour, yogurt, baker's yeast, salt, various vegetables, spices, and seasonings), bread, biscuit, fruit juice, fruit puree, jam-honey, and molasses were commonly fed at the age of 7-9 months. Vegetable recipes and vegetable soup were commonly fed at the age of 10-12 months (Table 4).

DISCUSSION

Malnutrition is a major health problem and is closely associated with early-stage nutrition and growth development. Healthy growth and development in the early stages of life has a great impact on the child's future. One of the most important indicators of a child's health is growth. Additionally, considering the benefits of breastfeeding on health and nutrition, the correct interpretation of the growth pattern of healthy breastfed infants is of utmost importance in terms of community health (9, 10). In a study conducted in Van province (a city in Turkey), acute malnutrition among participants was found to be 16.2% and chronic malnutrition was found to be 17.7% (11). In a study conducted by Çinar et al. (12), acute malnutrition among participants was found to be 15.2% and chronic malnutrition was found to be 4.9%. On the basis of the data of the Turkish National Nutrition and Health Survey (TBSA) 2010, these rates were shown to be 5.2% and 11.5%, respectively (7). In our study, the rate of acute and chronic malnutrition among patients was 13.6% and 5.2%, respectively. The results of previous studies conducted in various regions of Turkey have shown varied results. Malnutrition is caused by multiple factors, such as inadequacy of nutrient intake, lack of knowledge and frequent infections; however, it is mainly related to psychosocial, economic, cultural, and geographical factors.

In Turkey, obesity has been increasingly recognized as an important health issue. The rate of obese patients in our study was found to be 7.2%. According to the TBSA 2010 data, the obesity rate was 8.5% in the age group 0-5 years (7). Several factors such as inadequate breastfeeding, early start of complementary feeding and inappropriate food intake contribute to obesity. Further studies are required in this age group to reduce the risk of developing chronic illnesses in older age.

Although breastfeeding is common in Turkey, the rates fall within the first 6 months. In a study conducted by Bakiler et al. (13), the rates of mothers who breastfed for less than 6 months were 32.1%, while those who never breastfed were 4.9%. In our study, these rates were 19.6% and 9.4%, respectively. As an answer to the question "Why did you stop breastfeeding before six months?," 40.4% mothers reported insufficient breast milk, whereas 53.2% reported that their babies refused sucking milk. In another study, similar results were obtained, wherein 42.1% mothers discontinued breastfeeding because of lack of milk and 40.5% reported that their babies refused sucking milk (14). On the basis of the data of the TBSA 2010, the main reason for stopping breastfeeding was insufficiency/lack of breast milk in 47.6% mothers and refusal of sucking milk in 22.3% mothers (7). Despite consistent results, milk insufficiency is the main reason for mothers to discontinue breastfeeding. Additionally, it has been shown that, when it is about milk adequacy, mothers do not have sufficient knowledge about themselves and their babies. Therefore, mothers should be informed about proper breastfeeding techniques to ensure the continuity of the babies' breastfeeding.

On the basis of the data of the Demographic and Health Surveys (TNSA) program of Turkey in 2008, the rate to start complementary feeding before the age of 6 months was 8%; however, in 2013, this rate increased to 12%. In addition, the foods given were not appropriate for the children's age group (8). Although the time point of starting the complementary foods in our study was approximately 6 months, the nutrition that was first started generally not suitable for the sixth month of the child. As these foods add to the baby's nutrition, the rate of breastfeeding drops. Among the children aged 12-24 months, the rate of receiving breast milk was 42.4%. On the basis of the data of the TBSA 2010, this rate was 24% (7). These rates were significantly lower than that of the WHO recommendation that infants be breastfed up to 2 years of age. Timely introduction of the complementary feeding with appropriate food is important to meet the infant's needs and to ensure proper growth and development. Mothers seem to lack information regarding the introduction of complementary feeding and the continuity of breastfeeding.

The rates of starting breastfeeding after birth vary depending on regions. In a study conducted by Kutlu et al. (15), the rate of breastfeeding within the first 1-2 hours was 78.9%. In a study conducted by Akova (16), the mean time taken to initiate complementary feeding was 5.79±1.5 months, whereas in another study conducted by Telatar et al. (17), the mean time was 5.37±0.8 months. In a study conducted by Gün et al. (18), the rate of breastfeeding within the first hour was 80.5%. In another study conducted in the Mersin province of Turkey, this rate was 69.6% (19), whereas it was reported to be 59.1% in the TBSA 2010 (7). In our study, this rate was 93.6%, whereas the mean time of introduction of complementary feeding was 6.8±3.1 months. High rates of breastfeeding after birth are related to the policies of baby-friendly hospitals that are implemented in Turkey. Although this rate continues to increase over years, it is still not at the desired level.

To support the healthy growth and development of the baby in case of inadequate breastfeeding, necessary trainings should be provided to use formula milk at the right time and with appropriate preparation/techniques, rather than early introduction of complementary feeding, which is one of the incorrect and frequent practices of mothers. In our study, the rate of mothers who provided formula milk to their babies was 51.6%, and for the methods used to prepare formula milk, 90.6% mothers used water, whereas 6.3% used milk and 3.1% used milk and water. By the education programs that would be given by health care providers, misconceptions regarding the preparation of formula milk may be avoided and related nutritional problems may be prevented.

In our study, 45.2% mothers who experienced difficulties in feeding force-fed their children. In a study conducted by Sanlıer and Aytekin (20), 27.2% mothers discontinued feeding and attempted later and 13.4% force feed. Methods such as coercion, intimidation, and punishment of children without appetite have been shown to fail and to make children more irritable (21).

Complementary feeding refers to giving other foods and liquids along with breast milk to meet the nutritional requirements of infants, when breast milk alone is no longer sufficient. However, baby formulas are not included in the definition of complementary foods

(22). Complementary foods which are introduced may vary. When introducing complementary feeding, the first food to be given at 6 m of age should be yogurt, fruit juice, fruit puree, vegetable soup, and egg yolk. At 7-8 months, veal, chicken meat, fish, and cheese should be given. At 8-9 months, rice, pasta, and whole eggs should be given, and at 12 months, transition to family food is allowed (23, 24). In our study, the first complementary food given was yogurt in 45.6% and then vegetable soup in 29.4% and spoon/jar formula in 11% babies. In a study conducted by Kaya et al. (25), 28.4% mothers started complementary foods with soup, 24% with readymade yogurt, 12.4% with house yogurt, 10% with fruit, and 8.8% with ready spoon/jar formula. In a study conducted by Aydın (26), ready formula was given as a complementary food in 80.2% and yogurt and fruit puree were given in 15.2% and 4.6%, respectively. On the basis of the complementary foods according to the starting time, the introduction of cow's milk, yogurt, and milk pudding were mostly introduced at 4-6 months, whereas white cheese was started at 7-9 months. On the basis of the data of the TBSA 2010, the introduction of cow's milk, yogurt, milk pudding, and white cheese was at 8.4, 6.7, 7.6, and 8.6 months, respectively (7). However, there are some misapplications, particularly about the early start of cow's milk and milky pudding. The WHO does not recommend the use of cow's milk before 12 m of age. The reasons for this are its high protein content, which may cause renal and autoimmune diseases in the elderly. Also, the calcium/phosphorus balance is inappropriate, it has poor contents of linoleic acid and nucleotides, bad iron absorption, and also causes intestinal microbleeding and constipation besides renal solute load (24). In our study, red meat, egg, tarhana soup, and lentil soup were started predominantly at 7-9 months of age. On the basis of the TBSA 2010 data, red meat was started at 10.5 months, egg at 11 months, tarhana soup at 7.9 months, and lentil soup at 8.8 months (7). Our study results support the recommendations regarding the introduction time of these food groups. Grains such as wheat, rye, and barley contain gluten. Introducing gluten before the third and after seventh month increases the risk of celiac disease. The introduction of less amounts of gluten-containing foods between 4 and 7 months of age can be protective against celiac diseasewe have formulated these conclusions: Exclusive or full breast-feeding for about 6 months is a desirable goal (3). Complementary feeding (ie, solid foods and liquids other than breast milk or infant formula and follow-on formula. When the introduction time of grains was evaluated, rice pilaf, bulgur pilaf, pasta, bread, and biscuits were observed to be commonly started at the ages of 7-9 months. On the basis of the TBSA data, pasta/rice was started at 10 months, bread at 8.3 months, and biscuits at 8.9 months (7). According to the study results, the introduction of grains is delayed and that increases the risk of celiac disease in later stages of life. As the introduction time of vegetables and fruits, which are complementary foods that should be started in the early stages of life are evaluated; vegetable soup is mostly started at 10-12 months, whereas fruit juice is started at 7-9 months. On the basis of the TBSA 2010 data, the mean time of the introduction of these foods is 8.2 and 7.5 months, respectively (7). Early initiation of sugary tastes such as jam and honey in baby feeding increases the likelihood of these tastes in later stages of life. Additionally, honey should not be given before one year of age as it may cause infantile botulism (3) we have formulated these conclusions: Exclusive or full breast-feeding for about 6 months is a desirable goal. Complementary feeding (ie, solid foods and liquids other than breast milk or infant formula and follow-on formula. Jam-honey is mostly started at 7-9 months, and on the basis of the TBSA 2010 data, jam is started at 9.1 months and honey at 10.1 months (7). For infants to have

Table 4. Time of introduction of complementary foods

Time of introduction of complementary foods	0–3 m	4–6 m	7–9 m	10–12 m	13 m and more	Not given
Cow's milk	5 (1)	128 (26.5)	103 (21.3)	33 (6.8)	86 (17.8)	128 (26.5)
Yogurt	11 (2.3)	229 (47.4)	164 (34)	27 (5.6)	15 (3.1)	37 (7.7)
Pudding	5 (1)	145 (30)	106 (21.9)	13 (2.7)	11 (2.3)	203 (42)
White cheese	2 (0.4)	145 (30)	168 (35)	26 (5.4)	18 (3.7)	123 (25.5)
Egg	1 (0.2)	69 (14.3)	253 (52.4)	95 (19.7)	31 (6.4)	34 (7)
Meat	0	29 (6)	245 (50.8)	130 (27)	37 (7.7)	41 (8.5)
Rice pilaf	1 (0.2)	8 (1.7)	248 (51.3)	168 (34.8)	35 (7.2)	23 (4.8)
Bulgur pilaf	1 (0.2)	9 (1.9)	244 (50.5)	169 (35)	36 (7.5)	24 (5)
Pasta	1 (0.2)	9 (1.9)	229 (47.5)	171 (35.5)	39 (8.1)	33 (6.8)
Lentil soup	4 (0.8)	61 (12.6)	204 (42.2)	140 (29)	27 (5.6)	47 (9.7)
Tarhana soup	4 (0.8)	46 (9.5)	190 (39.3)	134 (27.7)	29 (6)	80 (16.6)
Vegetable soup	1 (0.2)	17 (3.5)	99 (20.5)	173 (35.8)	52 (10.8)	141 (29.2)
Bread	1 (0.2)	62 (12.8)	201 (41.6)	146 (30.2)	46 (9.5)	27 (5.4)
Biscuit	1 (0.2)	60 (12.4)	190 (39.3)	40 (30)	43 (8.9)	49 (10.1)
Fruit juice	1 (0.2)	125 (25.9)	170 (35.2)	104 (21.5)	38 (7.9)	45 (9.3)
Jam–honey	0	100 (19.9)	134 (26.5)	84 (17)	31 (6.8)	134 (29.8)

m: months

adequate energy, macronutrient and micronutrient intake and the balance between breast milk and complementary foods must be maintained (27). The wrong food choices made during the introduction of complementary foods may also cause problems with the progress of the healthy growth and development of the infants.

CONCLUSION

In conclusion, these days, excessive nutrition (overnutrition) as well as deficient nutrition (undernutrition) are major health problems. As inadequate and unbalanced nutrition may lead to many diseases and health problems also have negative effects on nutrition. To eliminate these effects, the nutritional status of individuals should be closely monitored, medical nutrition treatment should be initiated after the nutritional status is evaluated and necessary precautions should be taken. Besides training on the importance and techniques of breastfeeding, more detailed information should be given to families about when to introduce complementary feeding and the types and the right ways to prepare food. In this way, the misconceptions regarding breastfeeding and/or complementary feeding may be avoided and related malnutrition can be prevented.

Ethics Committee Approval: Ethics committee approval was received for this study from Clinical Research Ethical Committee of Gaziantep University.

Informed Consent: Written informed consent was obtained from patients who participated in this study

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Morphological and Topographical Anatomy of Nutrient Foramen in The Lower Limb Long Bones

Alt Ekstremite Uzun Kemiklerinde Foramen Nutricium'ların Morfolojik ve Topografik Anatomisi

Syeda Uzma Zahra, Piraye Kervancioğlu, İlhan Bahşi
Department of Anatomy, Gaziantep University School of Medicine, Gaziantep, Turkey

ABSTRACT

Objective: The present study aims to determine the number and position of the nutrient foramina (NF) of the human femur, tibia, and fibula and to observe the size, direction, and obliquity of the nutrient foramina.

Methods: We observed 265 adult human, lower limb long bones in the Department of Anatomy of the Gaziantep University. The nutrient foramina were identified with naked eyes, and the obliquity was determined with a hypodermic needle. Gauge 20 and 24 needles were used for size determination. Shape was observed with the naked eye and classified into oval and round types. The nutrient foramina location was determined by dividing total bone length into three segments, and the locations were validated by calculating foraminal index (FI).

Results: Results showed that 79% of the long bones had a single nutrient foramen. More than 96% of the nutrient foramina were directed away from the knees. A total of 87% of the femoral foramina were located in the middle third, 72% of the tibial foramina were located in the proximal third, and 98% of the fibular nutrient foramina were located in the middle third of the specimens. Overall, no foramina were found on the distal third of the studied bones.

Conclusion: Our study findings are in accordance to the findings from several research studies. The assessment of pathological conditions associated with the findings of foramen nutricium in our study may help clinicians and surgeons in planning treatments for applications to be performed in this region. However, it is thought that literature will be a source for basic and clinical sciences by providing reference values.

Keywords: Nutrient foramina, femur, tibia, fibula, foraminal index

ÖZ

Amaç: Bu çalışma femur, tibia ve fibula'da bulunan foramen nutricium (FN) sayısını ve pozisyonunu belirlemek ve FN büyüklüğünü, yönünü ve eğimini saptamak amacıyla yapılmıştır.

Yöntemler: Gaziantep Üniversitesi Anatomi Anabilim Dalı'nda bulunan, erişkin insana ait 265 alt ekstremite uzun kemikleri incelendi. Foramen nutricium çıplak gözle tespit edildi ve hipodermik iğne ile eğimi belirlendi. Büyüklüğünün belirlenmesi için 20 ve 24 gauge iğneler kullanıldı. Şekilleri çıplak gözle gözlemlenerek; oval ve yuvarlak tip olarak ayrıldı. Toplam kemik uzunluğunun üç segmente bölünmesiyle foramen nutricium'un yeri saptandı ve foraminal indeks (FI) hesaplanarak lokasyonlar doğrulandı.

Bulgular: Elde edilen sonuçlara göre, bu kemiklerin %79'unda tek bir FN bulunmaktaydı. Foramen nutricium'ların %96'sından fazlasının yönleri dizin ters yönüne doğru idi. Foramen nutricium, femur'ların %87'sinde orta üçte birlik kısımda, tibia'ların %72'sinde proksimal üçte birlik kısımda, fibua'ların %98'inde orta üçte birlik kısımda bulunmaktaydı. Genel olarak, incelenen kemiklerin distal üçte birlik bölümünde foramen nutricium bulunmadığı tespit edildi.

Sonuç: Çalışmamızın bulguları, literatürdeki birçok çalışmanın bulgularıyla uyumludur. Çalışmamızdaki bulgular foramen nutricium ile ilgili patolojik durumların değerlendirilmesi, bu bölgede yapılacak uygulamalar ile ilgili tedavilerin planlanması ile ilgili klinisyen ve cerrahlara yardımcı olabilecektir. Bununla birlikte literartüre referans değerler sağlayarak temel ve klinik bilimlere kaynak olacağı düşünülmektedir.

Anahtar kelimeler: Foramen nutricium, femur, tibia, fibula, foraminal indeks

INTRODUCTION

Bones are building blocks of the human skeleton and form the framework of the human body, its structure, and its mechanisms. Bones are composed of living connective tissues and are calcified in structure (1). The skeletal system comprises ligaments, cartilages, and other connective tissues, which stabilize the human skeleton and interconnect its components. Bones play several functions in the human body, including structural support to the body; protection of the organs; reservoir for storing minerals in the body; and production of different types of blood cells, such as

ORCID IDs of the authors: S.U.Z. 0000-0002-7557-4768; İ.B. 0000-0001-8078-7074.
Corresponding Author/Sorumlu Yazar: Syeda Uzma Zahra **E-mail/E-posta:** syeda_zahra15@yahoo.com
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red blood cells, white blood cells, and platelets (2). Human bones are of two types: compact and spongy. Compact bones are dense bones that form the outer shell of all bones, surround the spongy bones, and contain blood vessels and nutrient foramen (NF). Spongy bones consist of spicules of bones that enclose the marrow and do not contain blood vessels. In addition, bones are classified into different types based on their shape, including long, short, flat, irregular, sesamoid, pneumatized, and sutural or wormian bones. Long bones are tubular bones of the body, for example, humerus and femur and are relatively long and slender (1). They have two metaphyses, two epiphyses, a diaphysis, and a medullary cavity, for example, femur, tibia, fibula, and metatarsals (2, 3).

Bone is an osseous tissue and is highly vascular. The blood supply of a typical long bone is divided into four major sets of blood vessels, which are nutrient vessels, metaphyseal, epiphyseal, and periosteal (2, 4). There is usually one nutrient artery and one vein entering the diaphysis of long bone through NF. The vessel penetrates the shaft to reach the medullary cavity through the nutrient canal. The nutrient artery further divides into the ascending and descending branches approaching the epiphysis (2, 5). The nutrient artery is the main source of blood supply to the long bones and hence, is extremely important in the growth of bones during infancy, childhood, and all phases of ossification. Nutrient arteries are responsible for 70%-80% of the blood supply of the bones, and restriction of this blood supply results in the ischemia of bones (6).

Nutrient foramen is an opening in the shaft of the long bones with a distinct margin. NF provides entry to the nutrient artery and leads it to the nutrient canal. The direction and location of NF are of clinical significance. The location of NF is considered as point of initiation for longitudinal stress fractures, commonly in the tibia and less commonly in the femur, fibula, and patella bones (7). Such fractures usually result in nutrient artery rupture and peripheral vascular disruption. Apart from the importance of nutrient arteries in fracture healing, some other conditions of bones, such as developmental abnormalities and hematogenic osteomyelitis, are also dependent on the vascular system of bones (8). The study of long bone blood supply and the areas of bones supplied by the nutrient artery are important in the development of new techniques in the field of transplantation and resection (9). Given the significance of NF in clinical and morphological fields, it is of paramount importance that the characteristics of NF are studied on an ongoing basis in order to validate the findings from literature and to explore and discover new findings that can play a critical role in the field of medical science.

METHODS

Ethics Committee Approval

As the research study was conducted using the Department of Anatomy owned human bone specimens, ethical committee review was not required. The research was performed according to the World Medical Association Declaration of Helsinki (1964).

Informed Consent

The study was conducted on human lower limb long bone specimens found in the Department of Anatomy, and hence, no consent was required.

Data Collection and Analysis

A total of 265 cleaned and dry adult human bones of the lower limbs were studied. Overall, 107 femur, 91 tibia, and 67 fibula of unknown sex and age were examined in the Department of Anatomy, Faculty of Medicine.

Nutrient foramen was observed in the bones with naked eye and was identified by its elevated margin and by the presence of a distinct groove proximal to NF. Only well-defined foramina on the diaphysis were accepted (Figure 1) and foramina at the bone ends were ignored.

Observations were recorded for number of NF. In order to describe the position of NF, all bone specimens were divided into three parts. Total length of femur was measured as the distance between the proximal aspect of the head of the femur and the most distal aspect of the medial condyle (Figure 2) , and tibia full length was determined by using the distance between the proximal margin of the medial condyle and the top of the medial malleolus (Figure 3), whereas total length of fibula was recorded as the distance between the apex of the head of the fibula and the tip of the lateral malleolus (Figure 4). The foraminal index (FI) of a bone is calculated by using the formula: FI=(DiNF/TL)×100; where FI=foraminal index, DiNF=distance from the proximal end of the bone to NF, and TL=total bone length (10). All measurements were recorded using a measuring matrix chart with small squares and two metallic bars, of which one bar was adjustable and other bar was fixed. Each side of a square was equal to 5 cm (Figure 5).

Sizes of NF were measured with 24 and 20 gauge hypodermic needles (Figure 6). NF smaller or equal to the size of 24 hypodermic needles (yellow color, 0.56 mm in outer diameter) was considered as secondary nutrient foramina (SNF), whereas NF larger or equal to the size of 20 hypodermic needles (pink color, 0.908 mm in outer diameter) was considered as dominant nutrient foramina.

The results were analyzed using the SPSS (Statistical Package for the Social Sciences) 22.0 packet software (IBM Corp., Armonk, NY,

Figure 1. Nutrient foramen with distinct groove

Figure 2. Total length of femur

USA). A p value of <0.05 was considered statistically significant. The ranges, means, and averages for various parameters were determined by the left and right side bones and by the femur, tibia, and fibula separately, and were compared using Student's *t*-test.

RESULTS

Number of Nutrient Foramina

Overall, 209 (78.8%) bone specimens had a single foramina, 23 (8.7%) had double foramina, 32 (12.1%) had no foramina, and only 1 (0.4%) bone specimen had three NF. Mean number of NF in femur was 1.23±0.7 (min: 0, max: 3), in tibia was 1.03±0.23 (min: 0, max: 2), and in fibula was 0.82±0.46 (min: 0, max: 2).

Figure 3. Total length of tibia

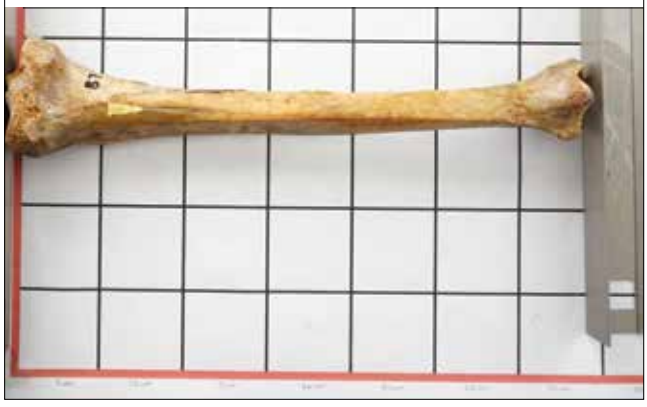

Figure 4. Total length of fibula

Figure 5. Determining location of nutrient foramina by segment

Out of 23 bones with double foramina, 20 (87%) were femur, 2 (8.65%) were tibia, and only 1 (4.35%) was fibula with a double foramina (Figure 7). The only bone with three foramina was the femur. Out of a total of 32 bones without foramen, 17 (53.13%) were femur, 14 (43.75%) were fibula, and only 1 (3.3%) tibia had no foramen (Table 1).

Direction of Nutrient Foramina

A total of 258 NF were found in 265 bone specimens. Out of all foramina, 112 (43%) were directed upwards, 143 (55%) were directed downwards, and only 3 (1%) were directed horizontally. NF in almost all examined femurs was directed upwards except the three foramina that were directed horizontally (Figure 8). A total of 91 (99%) foramina found on the tibia were directed downwards with only 1 foramen directed upwards and none directed horizontally. A total of 52 (96%) foramina found on the fibula were directed downwards, whereas only 2 (4%) were directed upwards and none was directed horizontally (Table 2, Figure 9).

Total Bone Length

Average total bone length for femur was 43.32±3.71 cm (min: 36 cm, max: 54 cm), for tibia was 35.90±2.79 cm (min: 32 cm, max: 42 cm), and for fibula was 34.65±2.31 cm (min: 30 cm, max: 41 cm) (Figure 2-4).

Distance of NF from Upper End of Long Bone

Mean distance of NF from upper end of the femur was recorded at 19.47±5.06 cm (min: 11 cm, max: 31 cm). Mean distance of NF from upper end of the tibia was recorded at 11.66±1.75 cm (min: 9 cm, max: 23 cm) and from upper end of the fibula at 16.32±3.20 cm (min: 11 cm, max: 24 cm).

Distance of NF from Lower End of Long Bone

Mean distance of NF from lower end of the femur was 23.84±5.08 cm (min: 13 cm, max: 37 cm). Mean distance of NF from lower end of the tibia was 24.23±2.28 cm (min: 18 cm, max: 30 cm) and from upper end of the fibula was 18.32±2.69 cm (min: 11 cm, max: 24 cm).

Figure 6. Determining size of nutrient foramina with hypodermic needles

Figure 7. Double nutrient foramen on linea aspera of femur

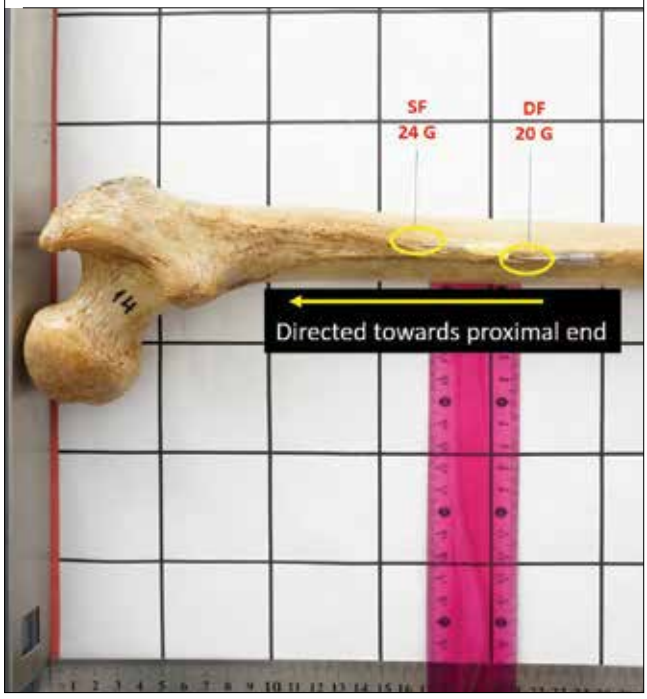

Figure 8. Nutrient foramina of femur directed upwards

Figure 9. Nutrient foramina directed towards the growing ends

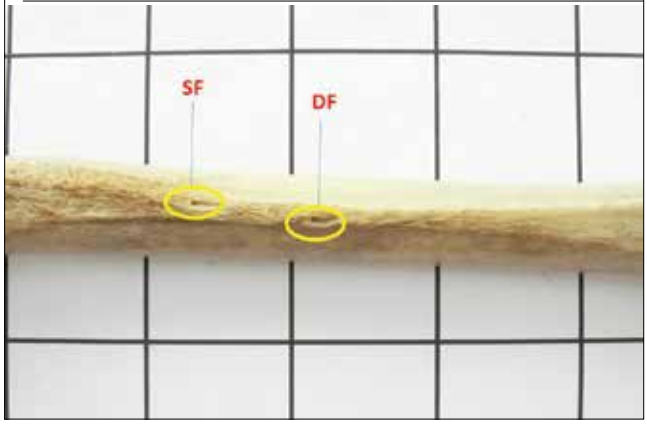

Table 1. Number of nutrient foramina observed

Long bones		No. of bones	No. of nutrient foramina 0	1	2	3
Femur	Left	54	9	32	13	0
	Right	53	8	37	7	1
	Total	107	17	69	20	1
Tibia	Left	51	1	49	1	0
	Right	40	0	39	1	0
	Total	91	1	88	2	0
Fibula	Left	23	8	15	0	0
	Right		6	37	1	0
	Total	67	14	52	1	0
Grand total (all bones)		265	32	209	23	1

Table 2. Direction of foramina (numbers and percentage)

Long bones	No. of foramina	Direction of nutrient foramina (no) Upwards	Downwards	Horizontal
Femur	112	109 (97%)	0 (0%)	3 (3%)
Tibia	92	1 (1%)	91 (99%)	0 (0%)
Fibula	54	2 (4%)	52 (96%)	0 (0%)
Total	258	112 (43%)	143 (55%)	3 (1%)

Location of NF Bby Segment of Long Bones

Out of all 258 foramina observed, 82 (32%) were present on the upper third of the long bones and had FI≤33.33. A total of 176 (68%) foramina were present on the middle third of the long bones with FI score of 33.33-66.66. No foramina were found on the lower third of the long bones. Of all foramina found on the femur, majority (87%) were on the middle segment, and of those found on the tibia, majority (72%) were on the upper segment of the long bones. Fibula showed a reverse pattern as compared with tibia as 98% of the foramina found on the fibula were located in the middle third (Table 3).

Location of NF by Surface of Long Bones

All 112 (100%) foramina found on the femur were found on the posterior surface of femur specimens with slight variation in location with relation to the lateral and medial lips of the linea aspera. A total of 3 out of 112 (2.68%) femoral foramina were found lateral to the lateral lip and 18 out of 112 (16.07%) foramina were found medial to the medial lip, whereas 39 out of 112 (34.82%) were found between the lateral and medial lips of the linea aspera. A total of 13 out of 112 (11.61%) femoral foramina were found on the lateral lip, whereas 39 out of 112 (34.82%) were found on the medial lip of the linea aspera.

Overall, 100% of the foramina present on the tibia were found on the posterior surface. A total of 19 out of 54 (35%) foramina found

on the fibula were located on the medial crest, whereas the remaining 35 (65%) were located on the posterior surface.

Size of Nutrient Foramina

A total of 172 out of 258 (67%) foramina found on the specimens were SNF. In femur specimens, approximately 63% of NF was SNF. In tibia, majority (71%) of the foramina were dominant, whereas in the case of the fibula, 100% of the foramina were SNF.

Comparison of NF Characteristics in Relation to the Left and Right Sides

Out of a total of 265 bone specimens, 128 (48%) were of the left side, whereas 137 (52%) were of the right side. A total of 54 (50.5%) femur specimens were of the left side, whereas 53 (49.5%) were of the right side. Of the 112 NF found on femur specimens, 58 (51.8%) were found on the left femur, whereas 54 (48.2%) were on the right femur. Mean number of NF for the left femur was 1.25±0.68, whereas mean number of NF for the right femur was 1.29±0.72. No significant difference was found in numbers of NF between the left and right femurs (p=0.627). Of the 109 upward facing foramina found on the femur, 57 (52.3%) were found on the left femur, whereas 52 (47.7%) were found on the right femur. Out of the total foramina found on the femur, 70 (63%) were SNF of which 37 (52.85%) were found on the left femur and 33 (47.15%) were found on the right femur. Mean FI of the left femur was 45.29±11.46, and mean FI of the right femur was 44.57±10.25.

A total of 51 out of 91 (56%) tibia were of the left side, whereas 40 (44%) were of the right limb. Of 92 NF found on the tibia, 51 (55.4%) were on the left tibia, whereas 41 (44.6%) were on the right. Mean number of NF for the left tibia was 1.01±0.24, whereas mean number of NF for the right tibia was 1.04±0.21. No significant difference was found in number of NF on the left and right tibias (p=0.543). Out of the total foramina found on the tibia, 65 (71%) were SNF of which 34 (52.3%) were found on the left tibia, and 31 (47.7%) were found on the right tibia. Average FI for foramina found on the left tibia was 32.05±4.6, whereas FI for NF found on the right tibia was 32.39±2.21.

A total of 23 out of 67 (34.3%) fibula specimens were of the left limb whereas 44 (65.7%) were of the right limb. Of 54 NF found on fibula specimens, 27.7% were found on the left fibula, whereas 72.3% of NF were found on the right fibula. Mean number of NF on the left fibula was 0.65±0.48, whereas mean number of NF on right fibula was 0.91±0.41.

Our study findings suggest that there was no significant difference between the left and right side femurs, tibias, and fibulas in terms of total size of bones and NF, distance of NF from upper and lower ends, and location of NF by FI (Table 4-6). The present study found that there is a significant difference between number of NF found on the left and right fibulas (p=0.025).

Table 3. Location of nutrient foramina by segment of long bone

		Location by segment (numbers and percentage)		
Long bones	**No. of foramina**	**Upper third**	**Middle third**	**Lower third**
Femur	112	15 (13%)	97 (87%)	0 (0%)
Tibia	92	66 (72%)	26 (28%)	0 (0%)
Fibula	54	1 (2%)	53 (98%)	0 (0%)
Total	258	82 (32%)	176 (68%)	0 (0%)

DISCUSSION

Number of Nutrient Foramina

Many research studies have reported the presence of a single foramen in most of the studied long bones (11–16). Our study findings reveal that single NF was more likely (78.8%) to be observed as compared with double and triple NF in all long bones of the lower limbs. Some studies have reported double foramina in a majority of observed femurs (9, 17–20), whereas some of the re-

Table 4. Group statistics for femur

	Group statistics for femur				
	Side	**N[1]**	**Mean**	**Standard deviation[2]**	**p[3]**
Distance from upper ends	L[4]	58	19.60	5.15	0.802
	R[5]	54	19.36	5.01	
Distance from lower ends	L	58	23.72	5.40	0.783
	R	54	23.98	4.75	
Position by foraminal index	L	58	45.29	11.46	0.729
	R	54	44.58	10.25	
Total bone length	L	58	43.32	3.63	0.994
	R	54	43.32	3.84	

[1]Sample size/number of bones
[2]Standard deviation is the dispersion or variation in a distribution of data from the mean in both directions
[3]The p–value, or calculated probability, is the probability of finding the observed results when the null hypothesis of a study question is true (www.statsdirect.com/help/basics/p_values.htm)
[4]Left side
[5]Right side

search studies suggest that a very small number of femur bones have been observed for the presence of three NF (7, 11, 18, 19). In our study, 107 femurs were studied for number of foramina, and it was observed that majority (64.5%) of femurs had only one foramen each, whereas 20 (18.7%) femurs had double foramina and only one femur bone had three foramina; a total of 17 femurs (16%) had no NF. Gumusburun et al. (18) found up to six foramina in femur, whereas Sendemir and Cimen (21) reported as high as nine foramina. However, the finding of a large number of foramina was confined to only a small fraction of the study sample Gumusburun et al. (18) found <1% of sample having six foramina and <6% of sample having four or more foramina). We were not been able to record more than three foramina on any of the studied specimen which could be the result of our definition of nutrient foramina in the present study. As described earlier, we identified NF by its elevated margin and by the presence of a distinct groove proximal to NF, and only well-defined foramina on the diaphysis were accepted. We also excluded foramina at the ends of the bones as NF is commonly located on the shaft.

Reportedly, almost 90% of the tibia had a single foramen, and double nutrient was observed in a smaller fraction of tibia (9, 17–19, 21). Majority of tibia observed in our study had only single foramina (96.7%); however, a small fraction (2.2%) had double foramina and one tibia had no foramina.

Of the 67 fibulas studied, 77.6% of bones presented a single NF, whereas 20.9% of fibula had no NF and only a small fraction (1.5%) had double foramina. Similar findings have been observed by studies reporting majority of fibula with a single foramen (11, 17,

Table 5. Group statistics for tibia

	Group statistics for tibia				
	Side	**N[6]**	**Mean**	**Standard deviation[7]**	**p[13]**
Distance from upper ends	L[9]	51	11.77	2.13	0.478
	R[10]	41	11.51	1.10	
Distance from lower ends	L	51	24.39	2.52	0.460
	R	41	24.03	1.93	
Position by foraminal index	L	51	32.50	4.60	0.884
	R	41	32.39	2.21	
Total bone length	L	51	36.17	2.96	0.285
	R	41	35.54	2.53	

[6]Sample size/number of bones

[7]Standard deviation is the dispersion or variation in a distribution of data from the mean in both directions

[8]The p–value, or calculated probability, is the probability of finding the observed results when the null hypothesis of a study question is true (www.statsdirect.com/help/basics/p_values.htm)

[9]Left side

[10]Right side

Table 6. Group statistics for fibula

	Group statistics for fibula				
	Side	**N[11]**	**Mean**	**Standard deviation[12]**	**p[13]**
Distance from upper ends	L[14]	15	16.97	3.43	0.365
	R[15]	39	16.07	3.11	
Distance from lower ends	L	15	17.20	2.85	0.056
	R	39	18.75	2.53	
Position by foraminal index	L	15	49.51	8.36	0.142
	R	39	46.02	7.46	
Total bone length	L	15	34.16	2.31	0.347
	R	39	34.83	2.31	

[11]Sample size/number of bones

[12]Standard deviation is the dispersion or variation in a distribution of data from the mean in both directions

[13]The p–value, or calculated probability, is the probability of finding the observed results when the null hypothesis of a study question is true (www.statsdirect.com/help/basics/p_values.htm)

[14]Left side

[15]Right side

19, 21, 22). Some studies also reported fibula with no NF, hence confirming the findings of our study (15, 17, 18, 21, 23). McKee reported three NF on the fibula (22).

Direction of Nutrient Foramina

It is evident from previous studies that nutrient foramina found on the femur bone are commonly directed upwards (10, 17); however, a small fraction (<1%) of the foramina on the femora are directed towards the knee (11, 12). In our study, 97% of NF found on the femora was directed upwards and away from the growing end. This finding confirms the "away from the knee and towards the elbow" theory, which claims that all the nutrient foramina in long bones are directed away from the growing ends of the long bones. This is very clearly explained by Hughes (10) suggesting that the nutrient artery enters the shaft of the long bone at an angle of 90°. As the shaft grows in length away from the growing end, the nutrient canal or artery is carried with its growth. This suggests that the course nutrient artery or canal in the long bones is directed away from the growing end. We also found 3% horizontally directed NF on femur specimens, and no foramina in femur were found to be directed towards the knee.

Collipal et al. (9) and Agarwal et al. (16) reported that most of NF found on the tibia is directed away from the knee, whereas Longia et al. (11) reported a small fraction of NF is directed towards the knee. Our study also found that 99% of NF present on the tibia was directed away from the knee, whereas only 1% of NF was directed towards the knee.

In the case of fibula, findings similar to tibia were observed, where 96% of the 54 observed NF were directed away from the knee, whereas only 4% were directed towards the knee. Literature confirms the finding of our study and reported similar variation in the direction of NF found on fibula (7, 11).

Location of Nutrient Foramina

Kizilkanat et al. (15) and Gumusburun et al. (18) reported that most of NF found on the femur is located in the middle third and a small number of NF found on the upper third of the studied femur bones. Our study also suggests that 87% of NF found on the femora was located in the middle third of the bone, and the rest was on the upper/proximal third with no foramina found on the distal third of the femora observed. Our study also suggests that 69% of NF in femur specimens was found either on or lateral to the medial lip of the linea aspera, whereas the remaining was concentrated along the linea aspera. The present study results are in accordance with previous studies suggesting that NF is concentrated along the linea aspera (11, 13, 18, 21, 24, 25).

Literature suggests that several studies have found most of NF on the proximal third and posterior surface of the tibia (9, 11, 16–18). In our study, 72% of NF found on the tibia was in the proximal third of the bone, whereas the remaining was found in the middle third and no NF was observed on the lower third. It may be for this reason that the fractures of the distal third of the tibia usually show a delayed union owing to the absence of NF and poor blood supply (26). Overall, 100% of the foramina found on the tibia were on the posterior surface. Contrary to our findings, Kizilkanat et al. (15) found most of NF in the middle third of the tibia.

Findings from our study suggest that 98% of NF found on the fibula was situated in the middle third of the bone, whereas only 2% of NF was found on the upper third. This is in accordance with the findings from previous studies suggesting high vasculature in the middle third of the fibula (9, 17–19, 21, 22, 27). Our study found that majority (65%) of NF was on the posterior surface, whereas a sizeable number (35%) was found on the medial crest. In literature, variations were observed in relation to the presence of NF on the surface of the fibula. For instance, Sendemir and Cimen (21) confer the presence of majority of NF on the medial surface of the fibula, whereas Mysorekar (17) suggests that majority of NF is found on the medial crest. Our literature review suggests that majority of NF is found on the posterior surface of the fibula (9, 15, 19, 22).

Understanding the NF location is important for surgeons especially in instances of bone grafting where the fibula is used. As our study and literature confirm that majority of studied bones suggest that the middle third of fibula is highly vascularized, this section will be ideal for use in bone grafting operations where implants with endosteal and peripheral vascularization are required (22).

Size of Nutrient Foramina

Literature suggests that two-thirds of NF found on the lower limb long bones are secondary foramina (11, 28). Our study found that almost two-thirds of the total NF of the long bones were SNF. Two-thirds (63%) of the femoral NF was secondary, whereas more than half of the foramina on the tibia were SNF, and 100% of the foramina found on the fibula were secondary. Other studies have reported that majority of the foramina observed are dominant (15), whereas Sendimir et al. (21) found that all femoral foramina are dominant.

Comparison of NF Characteristics in Relation to the Left and Right Sides

In our study, characteristics of NF found on the right and left femurs were observed to have minimal variation. Our study suggests that finding NF on the right fibula was 44% more likely as compared with that on the left fibula.

Understanding of the location and number of NF and nutrient arteries in the long bones is of utmost importance in the field of orthopedic surgery and orthopedic procedures, including femoral diaphysis transplants, fibular grafting, fracture repair, joint replacement therapy, and microsurgical procedures involving vascularized bones (15). The femoral diaphysis is provided by the nutrient arteries arising from the profunda femoris artery that can be used in the transplant surgery of femoral diaphysis. The healing of fractures, as of all wounds, is dependent upon blood supply, and hence, highly vascularized bone graft will be critical in the outcomes of such transplant surgeries. To attain better outcomes, the position and number of NF need to be determined by surgeons (29).

Literature suggests that the tibia is highly susceptible to longitudinal stress fractures; however, such fractures also occur in the femora but less commonly in fibula. The reason is that the long bones are generally weak and susceptible to fracture at the location of NF. As a result, such longitudinal stress fractures generally initiate from the position of NF on these long bones, thus understanding of the location and position of NF is critical in making correct clinical diagnosis in such fractures. Moreover, manipulating fractures of the long bones, particularly in open reduction, requires surgeons to pay careful attention to the site of NF and avoid limited areas of the long bone cortex that contain NF resulting in an improved outcome of such procedures (7).

The fibula is commonly used for grafting. The periosteum and the nutrient artery are normally transferred with a piece of fibula bone that is to be grafted so that it can remain viable and grow well at

the site where it is transplanted. In this way, it can help restore the blood supply of the bone to which it is attached. To ensure viable fibular graft, it is again important to understand the location of NF and to secure the best fibular graft (30).

CONCLUSION

Our study has attempted to compile the findings from different research studies and has used these findings to validate the outcomes of the present research. To the best of our knowledge, our study not only presents observations that are consistent with literature but also identifies the deviations found in the literature and their importance in the field of medical science. Our research will be useful not only for practicing clinicians but also for upcoming medical professionals and new graduates to understand the importance of NF in long bones.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects"(amended in October 2013).

Informed Consent: Informed consent was not received because data analysis for the study was made retrospectively.

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Hasta Onamı: Çalışmamızda retrospektif olarak veri analizi yapıldığından hasta onamı alınmamıştır.

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Original Research / Özgün Araştırma

Relationship between Serum Magnesium Level and Insulin Resistance in Obese Non-Diabetic and Diabetic Patients

Obez ve Obez Olmayan Diabetik Hastalarda İnsulin Direnci ile Serum Magnezyum Düzeyi İlişkisi

Rahma Hamid[1], Zeynel Abidin Sayiner[2], Abuzer Çelekli[1], Mustafa Araz[2]

[1]Department of Biochemistry Science and Technology, Gaziantep University School of Medicine, Gaziantep, Turkey

[2]Department of Endocrinology And Metabolism, Gaziantep University School of Medicine, Gaziantep, Turkey

ABSTRACT

Objective: Type 2 diabetes mellitus (T2DM) and obesity are multifactorial diseases that include interactions between hereditary and environmental factors. Our study aimed to evaluate the relationship between serum magnesium (Mg) level and insulin resistance (HOMA-IR) in obese non-diabetic subjects and obese patients with T2DM who were compared with healthy controls.

Methods: The present study included 120 subjects of both genders (age, 20-70 years). The subjects were divided into four groups: Group I included 30 healthy subjects as control (8 males and 22 females); group II included 30 obese non-diabetic subjects (6 males and 24 females) with the body mass index (BMI) ≥25 kg/m^2; group III included 30 (14 males and 16 females) obese patients with T2DM and disease history <1 year; and group IV included 30 (17 males and 13 females) obese patients with T2DM and disease history >5 years. Endocrinology and metabolism specialists diagnosed T2DM patients. Serum Mg, fasting glucose, fasting insulin, and fasting lipids were measured including the patients' weight and height. In addition, BMI and HOMA-IR were calculated.

Results: Serum Mg level significantly decreased in group IV (1.72±0.1 mg/dL) compared with group I (2.07±0.1 mg/dL; p<0.05). HOMA-IR significantly increased in group IV (7.9±7.0) compared with group I (1.03±0.3; p<0.05). In addition, serum fasting glucose, serum insulin, and fasting lipids were significantly higher in case groups than in the control group. The serum Mg level was inversely associated with age in all case groups. In group IV, a negative significant correlation was found between serum Mg level and age and HOMA-IR (p<0.01).

Conclusion: A low serum Mg level was found in obese patients with T2DM and obese non-diabetic subjects, whereas a high HOMA-IR level was found in obese patients with T2DM and obese non-diabetic subjects. Obese patients with T2DM show a negative correlation between the serum Mg level with HOMA-IR and age. We recommend measuring the serum Mg level regularly in obese patients with T2DM, especially in elderly patients, and patients who require supplementation.

Keywords: Type 2 diabetes mellitus, obesity, insulin resistance, magnesium

ÖZ

Amaç: Tip 2 diabetes mellitus (T2DM) ve obezite kalıtsal ve çevresel faktörler arasındaki etkileşimler de dahil olmak üzere multifaktöriyel hastalıklardır. Çalışmamızın amacı diyabetik olmayan kişilerde ve obez T2DM hastalarda serum Magnezyum (Mg) düzeyleri ile insülin direnci (HOMA-IR) arasındaki ilişkiyi değerlendirmektir.

Yöntemler: Çalışmamız her iki cinsiyetten (20-70) yaş aralığında olan 120 denekten oluşmaktadır. Denekler dört gruba ayrıldı: Grup I kontrol olarak 30 sağlıklı bireyi (8 erkek 22 kadın) içeriyordu. Grup II, BMI ≥25 kg/m^2 olan 30 obez diyabetik olmayan (6 erkek 24 kadın) denekten oluşmaktaydı. Grup III, hastalık öyküsü bir yıldan az olan 30 (14 erkek 16 kadın) obez T2DM hastasını ve beşinci yıldan fazla hastalığa sahip 30 (17 erkek ve 13 kadın) obez T2DM'yi grup IV'te gruplandırdı. T2DM hastalarının tanı endokrinoloji ve metabolizma uzmanları tarafından yapıldı. Serum Mg, açlık glikozu, açlık insülini ve açlık lipidleri ölçüldü, ağırlık, boy ölçülür. Ek olarak vücut kitle indeksi (VKI) ve HOMA-IR hesaplandı.

Bulgular: Serum Mg düzeyi grup I'de (1,72±0,1mg/dL) grup I'e (2,07±0,1mg/dL) göre anlamlı şekilde düşüktü (p<0,05). HOMA-IR, grup I'de (1,03±0,3), grup IV'te (7,9±7,0) anlamlı olarak fazla idi. (p<0,05) Ayrıca serum açlık glikozu, serum insülin ve açlık lipitleri hasta gruplarında kontrol grubuna göre anlamlı olarak daha yüksekti. Serum Mg düzeyi, tüm olgu gruplarında yaşla ters orantılı idi. Grup IV'de serum Mg düzeyleri ile yaş ve HOMA-IR arasında negatif bir korelasyon vardı (p<0,01).

Sonuç: Obez T2DM'li hastalarda ve diyabetik olmayan obezlerde serum Mg düzeylerinde düşük bulunurken, obez T2DM'li hastalarda ve diyabetik olmayan obezlerde yüksek düzeyde HOMA-IR tespit edildi. Obez T2DM hastaları serum Mg düzeyleri ile HOMA-IR ve yaş arasında negatif korelasyon göstermektedir. Özellikle yaşlı obez T2DM hastaları olmak üzere obez T2DM li hastalarda serum Mg düzeyi ölçümü yapılmasını eksiklik saptanan hastalarda replasmanın yapılmasının akılda tutulmasını önermekteyiz.

Anahtar kelimeler: Tip 2 Diabetes mellitus, obezite, insulin direnci, magnezyum

ORCID ID of the author: Z.A.S. 0000-0001-5105-0292.

Corresponding Author/Sorumlu Yazar: Zeynel Abidin Sayiner **E-mail/E-posta:** zeynelasayiner@hotmail.com

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a cause of an increasing morbidity and mortality worldwide. T2DM is characterized by hyperglycemia caused by disabled insulin activity in target tissues, such as liver, muscle, and fat tissue (insulin resistance [IR]), and impaired insulin secretion through progressive beta cell dysfunction (1). An increased incidence of obesity has taken a spotlight in the world, and recent epidemiological studies have recorded a rapid increase in its prevalence among all ages, genders, and racial/ethnic groups (2). IR is the main pathogenic factor of several metabolic disorders, including T2DM and obesity, and is a significant cause of cardiovascular disease and early death. IR is an important link between obesity and T2DM (3). Magnesium (Mg^{2+}) is a primary cofactor required for many biochemical reactions and plays an essential role in glucose metabolism. It is essential for insulin action since it is a cofactor of tyrosine kinase activity. Several studies have shown that T2DM is associated with Mg depletion. A decreased intracellular Mg concentration can lead to increased IR in diabetic patients. An increased incidence of Mg depletion was identified in T2DM patients, particularly in patients with a long history of diabetes and uncontrolled glycemic profiles. Hypomagnesaemia can be both an outcome and a reason of diabetic complications (4-6). Several studies have shown that decreased intracellular Mg leads to increased IR in diabetic patients (7). The aim of this study was to evaluate the relationship between the serum Mg level and IR in obese non-diabetic subjects and obese patients with T2DM, who were compared with healthy controls.

METHODS

Ethical Aspects

The clinical research ethics committee of Gaziantep University School of Medicine, accepted the study protocol on 08/15/2016, approval no. 2016/237. In addition, all subjects who participated in this study provided written informed consent.

Subjects And Study Design

The present study included 120 subjects of both genders and aged between 20 and 70 years. The subjects were divided into four groups. Group I included 30 (8 males and 22 females) healthy subjects as control. Group II included 30 (6 males and 24 females) obese non-diabetic subjects with a body mass index (BMI) ≥25 kg/m^2. Group III included 30 (14 males and 16 females) obese patients with T2DM and disease history <1 year, and group IV included 30 (17 males and 13 females) obese patients with T2DM and disease history >5 years. Endocrinology and metabolism specialists diagnosed the T2DM patients.

A written consent was obtained from all the participants in this study. Baseline data included basic demographics: age, gender, weight, and height were measured; BMI was calculated as kg/m^2; and hypertension, cigarette smoking, and medical and family history were recorded. In addition, all subjects in this study were clinically examined by expert doctors to determine the presence of exclusion criteria that included pregnancy, patients taking magnesium supplementation, alcohol consumption, cardiovascular disease, chronic disorders, and malignancy.

Clinical And Laboratory Evaluation

Fasting, venous blood samples were collected from all the participants. Collected samples were centrifuged, and serum was separated and then stored at -80°C.

All samples were collected for estimation and analytical measurement of biochemical parameters for serum magnesium, serum fasting glucose, total cholesterol, LDL-cholesterol, and triglycerides by the photometric enzymatic procedure using clinical chemistry laboratory instrument (Beckman Coulter, Model Au5800, Tokyo, Japan), and the lab test kits were used for each parameter. The assay of serum insulin was based on the chemiluminescent immunoassay method using the clinical laboratory instrument (Beckman Coulter, Dxİ 800 Tokyo, Japan) and lab test kits for Access Ultrasensitive Insulin. The degree of insulin resistance (IR) was determined for all study subjects by using homeostasis model of assessment (HOMA) method. The index (HOMA-IR) was calculated by the following formula: fasting serum glucose (mg/dl)×fasting serum insulin (μU/mL)/405.

Statistical Analysis

Descriptive statistical parameters were presented as mean±standard derivation (mean±SD). Demographic and clinical biochemical data among the groups were compared with one-way analysis of variance using the SPSS (Statistical Package for Sociel Sciences) Version 16.0 (SPSS Inc.; Chicago, IL, USA). Duncan's multiple range tests were used to distinguish the examined groups. The p value of <0.05 was considered as statistically significant.

RESULTS

The demographic and clinical biochemical laboratory data of the studied groups are given in Table 1.

With regard to the age of groups, a significant difference was found between the obese patients with diabetes history >5 years and healthy group ($p<0.05$). However, there was no significant difference between the obese patients with diabetes history >5 years and obese patients with diabetes history <1 year. In addition, this study found a negative statically significant association between the serum Mg level and age ($r=-0.88$, $p<0.01$) in obese patients with diabetes history >5 years, as shown in Table 2.

HOMA-IR had a negative correlation with serum Mg levels in obese patients with disease history >5 years, but the association was not significant (Table 3).

DISCUSSION

Mg^{2+} is a primary cofactor required for many biochemical reactions. Mg^{2+} is an important factor in glucose metabolism, and it is necessary for glucose transportation between the membranes, glucose oxidation, reactions involving phosphorylation, and energy exchange. It is essential for insulin action since it is a cofactor of tyrosine kinase activity (8).

The present study revealed that the serum Mg level in obese non-diabetic subjects was lower (1.98 mg/dL) than in the healthy control group (2.02 mg/dL). These results are in agreement with

Table 1. Demographic and clinical biochemical data of studied groups. Group I is control, group II is obese non-diabetic, group III is obese T2DM with disease history <1 year, and group IV is obese T2DM with disease history >5 years. N indicates the number of subjects

		Healthy	Obese Non-DM	Obese DM <1y	Obese DM >5y
N		30	30	30	30
Male/Female		8/22	6/24	14/16	17/13
Parameters	Unit	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Age	year	36.0±10.6[a]	44.4±9.7[b]	52.7±9.9[c]	55.7±8.3[c]
Height	cm	164.5±5.4[a]	161.7±6.0[a]	163.5±6.2[a]	169.4±3.7[b]
Weight	kg	63.56±5.4[a]	87.03±7.8[b]	88.66±9.5[b]	97.03±8.8[c]
BMI	kg/m^2	19.06±1.6[a]	27.28±3.1[b]	26.95±3.2[b]	28.7±2.3[c]
Mg	mg/dL	2.07±0.1[c]	1.98±0.2[b]	1.98±0.2[b]	1.72±0.1[a]
FG	mg/dL	91±4.4[a]	101.8±8.2[a]	140.86±44.5[b]	202.8±42.4[c]
Insulin	µU/mL	7.9±3.1[a]	11.39±9.0[a,b]	14.81±9.2[b,c]	16.7±7.0[c]
HOMA-IR		1.03±0.3[a]	2.82±2.3[b]	4.99±4.1[c]	7.9±3.7[d]
TC	mg/dL	169.0±34.2[a]	204.8±48.5[b]	198.8±33.3[b]	195.7±27.0[b]
TG	mg/dL	144.1±43.8[a]	179.1±69.5[b]	170.7±63.4[a,b]	201.6±74.9[b]
LDL-C	mg/dL	90.2±21.7[a]	111.4±44.4[b]	105.6±24.2[a,b]	102.1±23.7[a,b]

*BMI: Body mass index; Mg: Magnesium; FG: Fasting glucose; TC: Total cholesterol; TG: Triglyceride; LDL-C: Low-density lipoprotein-cholesterol; HOMA-IR: Homeostasis model assessment of insulin resistance

**Different lowercase letters indicate statistical difference at α=0.05 level among the groups. Values with the same letters in the same parameters indicate that the values did not differ by the Duncan test at 0.95 confidence interval

Table 2. Correlation between the serum Mg level with anthropometric measurement and biochemistry parameters in all groups

		Healthy		Obese Non-DM		Obese DM 1-5 years		Obese DM >5 years	
Parameters		**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**
Age	year	-0.057	0.764	-0.033	0.862	-0.673	0.000	-0.886	0.000
Height	cm	-0.150	0.430	0.002	0.991	0.118	0.534	0.120	0.528
Weight	kg	-0.16	0.382	0.039	0.836	0.003	0.987	-0.084	0.657
BMI	kg/m^2	-0.071	0.713	0.055	0.772	-0.169	0.369	-0.057	0.765
Glucose	mg/dL	-0.097	0.612	-0.190	0.315	-0.055	0.770	-0.317	0.088
Insulin	µU/mL	-0.190	0.314	0.128	0.500	0.104	0.581	0.128	0.499
HOMA-IR	mg/dL	-0.192	0.310	0.121	0.524	0.149	0.429	-0.099	0.604
Cholesterol	mg/dL	0.128	0.499	0.107	0.575	-0.112	0.552	-0.169	0.373
Triglyceride	mg/dL	0.016	0.943	-0.157	0.406	-0.027	0.884	-0.200	0.290
LDL	mg/dL	-0.290	0.120	0.080	0.673	-0.031	0.870	-0.235	0.210

*r: Pearson correlation coefficient; p<0.05 is significant

**BMI: Body mass index; Mg: Magnesium; FG: fasting glucose; TC: Total cholesterol; TG: Triglyceride; LDL-C: Low-density lipoprotein-cholesterol; HOMA-IR: Homeostasis model assessment of ınsulin resistance

previous studies (9, 10). Additionally, another study found a low serum Mg level in overweight or obese patients (11). Moreover, as the present study revealed, the serum Mg level was decreased in obese patients with T2DM, especially in obese patients having T2DM >5 years. Previous studies also reported that serum Mg decreased in T2DM (12, 13). This indicates the association of hypomagnesaemia with T2DM. In addition, the present study indicates that the serum Mg level in obese patients (1.72 mg/dL) with diabetes history >5 years was significantly lower than in obese patients (1.98 mg/dL) with diabetes history <1 year. This

Table 3. Correlation between calculated HOMA-IR with anthropometric measurement and biochemistry parameters in all groups

		Healthy		Obese Non-DM		Obese DM 1-5 years		Obese DM >5 years	
Parameters		**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**
Age	year	-0.126	0.504	-0.147	0.437	-0.133	0.48	0.188	0.319
Height	cm	0.191	0.310	-0.19	0.302	-0.097	0.608	-0.250	0.182
Weight	kg	0.351	0.056	-0.124	0.513	-0.035	0.853	-0.086	0.650
BMI	kg/m^2	0.151	0.424	0.138	0.464	-0.015	0.936	-0.128	0.499
Glucose	mg/dL	0.364	0.040	0.195	0.301	0.355	0.053	0.412	0.020
Insulin	µU/mL	0.990	0.000	0.991	0.000	0.881	0.000	0.818	0.000
Mg	mg/dL	-0.191	0.309	0.121	0.523	0.149	0.429	-0.098	0.604
Cholesterol	mg/dL	0.082	0.665	0.432	0.017	0.024	0.897	0.194	0.303
Triglyceride	mg/dL	0.449	0.012	0.539	0.002	0.007	0.966	-0.097	0.609
LDL-C	mg/dL	0.047	0.804	0.561	0.001	-0.235	0.209	-0.085	0.653

*r: pearson correlation coefficient, $p<0.05$ is significant

**BMI: Body mass index; Mg: Magnesium; FG: Fasting glucose; TC: Total cholesterol; TG: Triglyceride; LDL-C: Low-density lipoprotein-cholesterol; HOMA-IR: Homeostasis model assessment of ınsulin resistance

was in compliance with several other studies that reported an elevated Mg deficiency in T2DM patients with longer duration of diabetes and uncontrolled glycemic profiles (14-15).

Hypomagnesaemia can be both a consequence and a cause of diabetic complications. The causes of hypomagnesaemia in patients with T2DM are not clear, but they may consist of poorer dietary consumption of Mg, decreased intestinal Mg absorption, increased urinary loss of Mg, or decreased Mg uptake into cells compared with that in healthy individuals.

In addition, with respect to age, a significant difference was found between obese patients with diabetes history >5 years and the healthy group ($p<0.05$). However, there was no significant difference between obese patients with diabetes history >5 years and those with diabetes history <1 year. As this study found, in obese patients having T2DM for >5 years, there was a negative statically significant association between the serum Mg level and age ($r=-0.88$, $p<0.01$). The elderly may be susceptible to having a low serum Mg level because aging is related with decreased intracellular Mg levels. In addition, the elderly are unable to profit from Mg-rich foods because of their hard texture and unsuitable physical properties.

A negative correlation between serum Mg levels and serum fasting lipids was found in patients with T2DM for >5 years, but the association was not significant. This finding was in agreement with a study by Elementol et al. (16), which reported no statistically significant effect of Mg concentration on the content of lipids analyzed in blood serum. Noticeably, obesity may increase the cardiovascular risk and the mortality rate related to low Mg levels.

Moreover, in the present study, HOMA-IR had a negative correlation with serum Mg levels in patients with T2DM for >5 years, but the association was not significant. This finding was in agreement with Lima et al. (17), who found a negative association between HOMA-IR and serum Mg level in patients with T2DM, although it was not statistically significant.

The present study reported low serum Mg levels in obese patients with T2DM and obese non-diabetic subjects, while a high level of HOMA-IR was found in obese patients with T2DM and obese non-diabetic subjects. Obese patients with T2DM showed a negative correlation between the serum Mg level with HOMA-IR and age. The association between serum Mg level and IR may be another risk factor for uncontrolled diabetes and diabetic complications. Preservation of the normal levels of serum Mg may prove to be useful in the prevention of diabetic complications.

CONCLUSION

Consequently, we recommend weight loss in obese patients and regular measurement of serum Mg levels in obese patients with T2DM, especially in elderly patients and patients who require supplementation should be considered.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University School of Medicine (Decision date: 08.15.2016/Decision no: 2016/237).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Original Research / Orijinal Araştırma

Paced Corrected QT İnterval is Associated with Lv Diastolic Dysfunction in Patients With Permanent Pacemakers and Preserved Left Ventricular Ejection Fraction

Paced Düzeltilmiş QT İntervali Kalıcı Kalp Pili Olan Sol Ventrikül Ejeksiyon Fraksiyonu Korunmuş Hastalarda Sol Ventrikül Diyastolik Disfonksiyonu ile İlişkilidir

Onur Kaypaklı

Department of Cardiology, Mustafa Kemal University School of Medicine, Hatay, Turkey

ABSTRACT

Objective: Although chronic right ventricular apex (RVA) pacing is usually well tolerated in patients with normal cardiac function, recent studies report that not only left ventricular (LV) systolic function but also diastolic function is adversely affected. The aim of the present study was to detect the relationship between paced QRS, paced corrected QT (pQTc) duration, and echocardiographic parameters of LV diastolic dysfunction to examine the effects of RVA pacing in patients with preserved LV ejection fraction (LVEF).

Methods: We included 74 patients with LVEF>50% and DDD(R) pacemakers implanted for atrioventricular block (45 men and 29 women; mean age 64.9±11.6 years). Patients were included to the study at least 6 months after battery implantation. Patients with RVA pacing rate <70% were excluded from the study. Patients were classified into two groups according to the left atrial (LA) volume index.

Results: pQTc was associated with LA volume index, LA volume, LA end-diastolic diameter, E-wave deceleration time, septal annular e' velocity, and mitral E/e' ratio in bivariate analysis. The cut-off value of pQTc obtained by receiver operating characteristic curve analysis was 512 ms for prediction of increased (>34 mL/m^2) LA volume index (sensitivity: 88.0% and specificity: 79.6%). The area under the curve was 0.848 (p<0.001).

Conclusion: pQTc duration was found to be significantly associated with the echocardiographic parameters of LV diastolic dysfunction. We suggest that pQTc be used as a marker to predict the risk of diastolic dysfunction after permanent pacemaker implantation in patients with preserved LVEF. It can also be used to optimize the RV pacing area with intraoperative measurements.

Keywords: Paced QT interval, cardiac pacing, paced qrs width

ÖZ

Amaç: Kronik sağ ventrikül apikal pacing, normal kardiyak fonksiyonlu hastalarda genellikle iyi tolere edilse de, son çalışmalarda sadece sol ventrikül sistolik fonksiyonunda değil diastolik fonksiyonda da olumsuz etkilenme saptanmıştır. Ejeksiyon fraksiyonu korunmuş hastalarda sağ ventrikül pacingin etkilerini incelemek için paced QRS, paced QTc süresi ve sol ventrikül diyastolik disfonksiyonunun ekokardiyografik parametreleri arasındaki ilişkiyi saptamayı amaçladık.

Yöntemler: Sol ventrikül EF>%50 olan ve AV blok nedeniyle DDD(R) kardayak pacemaker implante edilmiş olan 74 hasta (45 erkek, 29 kadın; ortalama yaş 64,9±11,6 yıl) çalışmaya dahil edildi. Hastalar, pacemaker implantasyonundan en az 6 ay sonra çalışmaya dahil edildi. Sağ ventrikül apikal pacing oranı <%70 olan hastalar çalışma dışı bırakıldı. Hastalar sol atriyum hacim endeksine göre iki gruba ayrıldı.

Bulgular: Paced QTc, bivariate analizde sol atriyum hacim endeksi, sol atriyum hacmi, sol atriyum diyastolik son çapı, E dalga deselerasyon zamanı, septal anüler e' hızı ve mitral E/e' oranı ile ilişkiliydi. ROC eğrisi analizi ile elde edilen artmış (>34 mL/m^2) sol atriyum hacim endeksi için pQTc'nin cut-off değeri 512 ms olarak bulundu (duyarlılık: %88,0, özgüllük: %79,6). Eğri altındaki alan 0,848 idi (p<0.001).

Sonuç: Paced QTc süresinin, sol ventrikül diyastolik disfonksiyonunun ekokardiyografik parametreleri ile anlamlı derecede ilişkili olduğu bulundu. Sol ventrikül EF korunmuş hastalarda kalıcı pacemaker implantasyonundan sonra diyastolik disfonksiyon riskini öngörmek için pQTc'nin bir belirteç olarak kullanılabileceğini öneriyoruz. Ayrıca intraoperatif ölçümlerle sağ ventrikül pacing alanını optimize etmek için de kullanılabileceği düşünülmektedir.

Anahtar kelimeler: Paced QT interval, kardiyak pacemaker, paced QRS genişliği

ORCID IDs of the authors: O.K. 0000-0002-5065-3283.

Corresponding Author / Sorumlu Yazar: Onur Kaypaklı **E-posta/E-mail:** onurkaypakli@hotmail.com

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INTRODUCTION

Right ventricular (RV) pacing has been demonstrated to have detrimental effects on cardiac hemodynamics and is associated with a reduction in left ventricular (LV) function (1). It is thought that approximately 25% of patients receiving RV pacing for sick sinus syndrome and complete heart block experience "pacemaker syndrome" with symptoms of shortness of breath, dizziness, palpitations, abnormal pulsations, or chest pain (2). Chronic RV apex (RVA) pacing is usually well tolerated in patients with normal cardiac function; however, recent studies report that not only LV systolic function but also diastolic function is adversely affected (3, 4). These adverse effects may cause deterioration on the left atrial (LA) structure and function and trigger new-onset atrial arrhythmias.

The aim of the present study was to detect the relationship between paced QRS (pQRS), paced corrected QT (pQTc) duration, and echocardiographic parameters of LV diastolic dysfunction to examine the effects of RVA pacing in patients with preserved LV ejection fraction (LVEF).

METHODS

Study Protocol and Study Population

We included 74 patients with LVEF>50% and DDD(R) pacemakers implanted for atrioventricular (AV) block (45 men and 29 women; mean age 64.9±11.6 years). Patients were included to the study at least 6 months after battery implantation. Patients with RVA pacing rate <70% were excluded from the study. To eliminate the negative effects on LV diastolic function in patients with permanent atrial fibrillation, congenital heart disease, history of coronary artery disease, primary pulmonary hypertension, hypertension, diabetes, renal insufficiency (serum creatinine level>1.5 mg/dl), respiratory diseases (pulmonary embolism and chronic obstructive pulmonary disease), isolated right heart failure (HF), and moderate and severe aortic and mitral valve diseases were excluded from the study. Complete blood count, N-terminal pro-B-type natriuretic peptide, uric acid, serum lipids, serum electrolytes, and renal function tests were performed. Patients were classified into two groups according to the LA volume index. All statistical analyses were made between the two groups. The local ethics committee approved the study protocol. Written informed consent was obtained from each participant.

Echocardiographic and Electrocardiographic Parameters of the Study Population

Echocardiography was performed using a 2.5-3.5 MHz transducer (Philips HD11 Ultrasound System; Bothell, USA). LV transverse axis dimensions from M-mode recordings were measured according to the recommendations of the American Society of Echocardiography (5). Simpson's equation was used to compute LVEF. Peak E-wave velocity, peak A-wave velocity, mitral valve (MV) E/A ratio, MV deceleration time, and isovolumetric relaxation time were calculated with PW Doppler. Lateral annular e' velocity, septal annular e' velocity, and mitral E/e' ratio were determined with PW and color tissue Doppler. Indices of LA volumes for body surface area were also calculated. The AV delay of DDD(R) pacemakers was at factory setting (130-170 ms). The pQRS duration was measured in the lead with the widest QRS complex. The interval between the earliest onset of the QRS complex and the end of the T-wave was determined as the QT interval. The corrected QT was calculated using Bazett's formula (6).

Statistical Analysis

Variables were divided into two groups as categorical and continuous. Categorical data were expressed as numbers and percentages and compared with the chi-square test. Continuous variables were expressed as mean±SD. Normal distribution of continuous variables was calculated by the Shapiro-Wilk test. Normally distributed continuous variables were compared with independent sample t-test. Non-normally distributed variables were compared using Mann-Whitney U test. Multivariate logistic regression analysis was performed with variables that are found to be significant in univariate analysis. Results were expressed as the p-value and odds ratio in 95% confidence interval. Receiver operating characteristic (ROC) curve analysis was made to determine the cut-off value of pQTc to detect increased LA volume index. Statistical analysis were conducted using SPSS (Statistical Package for Sociel Sciences) Version 20.0 (IBM Corp.; Armonk, NY, USA). A $p<0.05$ was considered statistically significant.

RESULTS

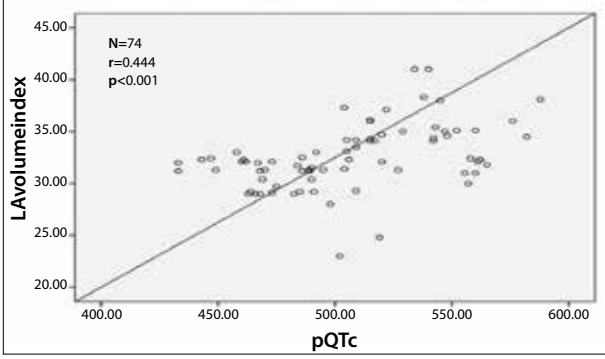
Comparison of Baseline Clinical and Laboratory Parameters in Patients with and without Increased (>34 mL/m^2) LA Volume Index

Table 1 shows a comparison of the baseline clinical and laboratory parameters. There were no significant differences between the two groups ($p>0.05$, for all).

Comparison of Electrocardiographic and Echocardiographic Parameters in Patients with and without Increased (>34 mL/m^2) LA Volume Index

LA end-diastolic diameter, LA volume, LA volume index, diastolic filing, and pQTc were significantly higher; lateral and septal annular e' velocity was significantly lower ($p<0.05$, for all) in patients with increased (>34 mL/m^2) LA volume index (Table 2). pQRS width was higher in patients with increased (>34 mL/m^2) LA volume index, but there was no statistically significant difference ($p = 0.092$).

Figure 1. Scatter plot diagram of the relationship between pQTc and LA volume index. LA, left atrial



Bivariate Relationships of pqtc and pqrs Duration

pQTc was associated with LA volume index (r=0.444, p<0.001), LA volume (r=0.350, p=0.002), LA end-diastolic diameter (r=0.373, p=0.001), E-wave deceleration time (r=0.293, p=0.011), septal annular e' velocity (r=0.267, p=0.022), and mitral E/e'ratio (r=0.260, p=0.025) in bivariate analysis. Figure 1 shows a scatter plot diagram of the relationship between pQTc and LA volume index. pQRS duration was not found to be associated with LA volume index (p=0.67), LA volume (p=0.70), LA end-diastolic diameter (p=0.90), E-wave deceleration time (p=0.88), septal annular e'velocity (p=0.30), lateral annular e'velocity (p=0.30), and mitral E/e'ratio (p=0.16).

Figure 2. ROC curve analysis to determine the predictive value of pQTc for increased (>34 mL/m^2) LA volume index. ROC, receiver operating characteristic; LA, left atrial

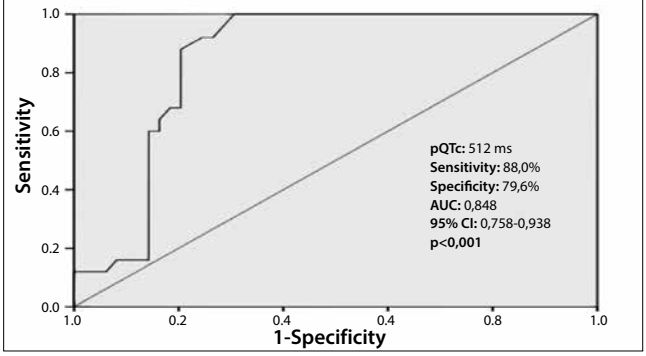


Table 1. Comparison of baseline clinical and laboratory parameters in patients with and without increased (>34 mL/m2) LA volume index

	Normal LA volume index (≤34 mL/m^2)	Increased LA volume index (>34 mL/m^2)	
	n=49	n=25	p
Age (years)	65.9±12.0	62.9±10.8	0.319
Gender (male, %)	31 (63)	14 (56)	0.545
Smoking status (n, %)	20 (41)	7 (28)	0.279
Baseline NYHA (I/II)	12/37	2/22	0.206
Hemoglobin (g/dL)	11.7±1.6	11.1±1.5	0.189
BUN (mg/dL)	45.3±72	43.5±7.6	0.324
Creatinine (mg/dL)	0.94±0.23	0.98±0.28	0.528
LDL cholesterol (mg/dL)	124.3±31.4	127.1±30.0	0.717
HDL cholesterol (mg/dL)	48.8±7.9	48.2±7.6	0.591
Triglycerides (mg/dL)	136.5±31.1	129.5±32.1	0.369
NT-proBNP (pg/mL)	319±84	349±99	0.225
Uric acid (mg/dL)	6.0±1.5	5.9±1.6	0.790

LA: left atrial, NYHA: New York Heart Association, BUN: blood urea nitrogen, LDL: low-density lipoprotein, HDL: high-density lipoprotein, NT-proBNP: N-terminal pro-B-type natriuretic peptide

ROC Curve Analysis to Determine Predictive Value of pqtc for Increased (>34 mL/m^2) LA Volume Index

The cut-off value of pQTc obtained by ROC curve analysis was 512 ms for prediction of increased (>34 mL/m^2) LA volume index (sensitivity: 88.0% and specificity: 79.6%). The area under the curve was 0.848 (p<0.001) (Figure 2).

DISCUSSION

To the best of our knowledge, the present study was the first to reveal a significant association between pQTc interval and LV diastolic functions in patients with preserved LV systolic function and permanent pacemakers. The main findings of the present study were that (1) pQTc>512 ms predicted increased (>34 mL/m^2) LA volume index with 88.0% sensitivity and 79.6% specificity and (2) pQTc was associated with echocardiographic parameters of LV diastolic function such as LA volume index, LA volume, LA end-diastolic diameter, E-wave deceleration time, septal annular e'velocity, and mitral E/e'ratio in bivariate analysis.

Patients with permanent cardiac pacemakers are rising every day with increased life expectancy. In general practice, among different ventricular pacing sites, RVA pacing is most commonly

Table 2. Comparison of the baseline electrocardiographic and echocardiographic features of the study population

	Normal LA volume index (≤34 mL/m^2)	Increased LA volume index (>34 mL/m^2)	
	n=49	n=25	p
Paced QRS width (ms)	164.3±21.1	173.0±19.0	0.092
Paced QTc (ms)	491.4±35.3	536.1±23.3	**<0.001**
LV end-diastolic diameter (mm)	50.1±5.4	51.8±6.8	0.254
LV end-systolic diameter (mm)	34.7±4.4	35.4±4.4	0.511
LVEF (%)	56.9±4.9	55.5±4.5	0.225
LVEDV (mL)	109.0±23.4	108.9±26.3	0.992
LVESV (mL)	46.3±8.8	48.0±11.0	0.467
Peak E-wave velocity (cm/s)	53.5±17.9	48.2±16.3	0.219
Peak A-wave velocity (cm/s)	41.1±11.4	41.8±15.0	0.832
MV E/A ratio	1.31±0.25	1.18±0.33	0.066
Lateral annular e'velocity (cm/s)	11.9±2.0	10.0±2.8	**0.004**
Septal annular e'velocity (cm/s)	9.1±1.4	7.4±2.4	**0.003**
Mitral E/e'ratio	5.1±1.5	6.0±3.0	0.094
MV deceleration time (ms)	183.0±33.6	203.4±39.4	**0.033**
IVRT (ms)	80.0±9.8	74.2±13.6	0.066
LA end-diastolic diameter (mm)	34.7±2.6	39.1±3.1	**<0.001**
LA volume (mL)	44.6±4.8	53.4±7.7	**<0.001**
LA volume index (mL/m^2)	30.8±1.9	35.9±2.0	**<0.001**

LA: left atrial, LV: left ventricular, LVEF: left ventricular ejection fraction, LVESV: left ventricular end-systolic volume, LVEDV: left ventricular end-diastolic volume, IVRT: isovolumetric relaxation time, MV: mitral valve

used owing to its stability for lead positioning, safety, easy accessibility, and cost-effectiveness (7, 8). However, RVA pacing was shown to be associated with cardiac dysfunction and an increased rate of rehospitalizations in previous studies (9-13). Negative effects of chronic RVA pacing are more significant in certain populations such as patients with a high rate of RVA pacing. Thus, there is a need for parameters to predict possible deterioration in LV systolic and diastolic functions to evaluate the early risks posed to patients who are expected to have high rate of RVA pacing in order to optimize the pacing strategy.

A longer pQRS duration indicates more myocardium tissue to be activated by muscle to muscle conduction before the pacing activation front enters the normal conduction system, whereas a relatively shorter pQRS duration indicates earlier entry of pacing activation front to His-Purkinje system and a more physiological conduction. Previous studies showed that prolonged pQRS duration is associated with LV systolic function (14, 15). In a study conducted by Miyoshi et al. (14), prolonged pQRS duration is found to be associated with impaired LV systolic function in patients with AV block. Pan et al. (15) also demonstrated that pQRS duration is correlated with the structure and systolic function of the left ventricle. However, LV systolic function of most of the patients with preserved EF did not decrease after permanent pacemaker implantation. Nevertheless, HF symptoms can develop in these patients due to diastolic dysfunction, not systolic dysfunction. To our knowledge, there are no studies that investigated the association of pQRS duration with LV diastolic function. In our study, we found pQRS duration to be associated with none of the echocardiographic parameters of LV diastolic function.

There have been many data about the clinical implications of intrinsic QTc interval in the general population and populations such as hypertrophic cardiomyopathy, coronary artery disease, and HF. These studies investigated the association of QTc with the risk of ventricular tachyarrhythmia or sudden cardiac (16-19). In the study by Lee et al. (20), patients with more pQTc prolongation were found to have higher mortality rate than those with less pQTc prolongation. In their study, Cho et al. (21) revealed a significant association between the development of new LV systolic dysfunction and cardiac death and the degree of pQTc interval after permanent cardiac pacemaker implantation in patients with preserved LVEF. In our study, we found pQTc interval to be associated with echocardiographic parameters of LV diastolic function such as LA volume index, LA volume, LA end-diastolic diameter, E-wave deceleration time, septal annular e'velocity, and mitral E/e'ratio.

The present study has some limitations. The sample size is relatively small, and our results need to be confirmed in future large multicenter prospective trials. Owing to the observational nature of our study, we did not make modifications on pacemakers of patients such as AV delay optimization. Therefore, we did not have the chance to evaluate the effects of pacemaker modifications on LV diastolic function. Since our study was not a follow-up study, we could not determine the change of LV systolic and diastolic functions in time and its association with pQTc. We did not use long-term Holter electrocardiogram monitoring to detect atrial arrhythmias; thus, we did not have the chance to detect the association of pQTc with atrial arrhythmias such as atrial fibrillation.

CONCLUSION

Paced corrected QT duration was found to be significantly associated with the echocardiographic parameters of LV diastolic function. We suggest that pQTc be used as a marker to predict the risk of diastolic dysfunction after permanent pacemaker implantation in patients with preserved LVEF. It can also be used to optimize the RV pacing area with intraoperative measurements. Larger and long-term studies are needed to determine the relationship between pQTc and prognostic parameters after permanent pacemaker implantation.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Çukuruva University (Decision Date: 2017).

Informed Consent: Informed consent was obtained from all patients who participated in this study.

Peer-review: Externally peer-reviewed.

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

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Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

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Original Research / Orijinal Araştırma

Effect of Modified Global Risk Classification on Prognosis at Patients Undergoing Bypass Surgery and Percutaneous Coronary Intervention with Multi-vessel Disease

Çoklu Damar Hastalığı Olan Baypas Cerrahisi ve Perkütan Koroner Girişim Yapılan Hastalarda Modifiye Global Risk Skorunun Prognoz Üzerindeki Etkisi

Onur Kaypaklı[1], Durmuş Yıldıray Şahin[3], Ali Deniz[2], Halil Aktaş[2], Rabia Eker Akıllı[2], Yahya Kemal İçen[3], Çağlar Emre Çağlayan[2], Mustafa Demirtaş[2]

[1]Department of Cardiology, Mustafa Kemal University School of Medicine, Hatay, Turkey

[2]Department of Cardiology, Çukurova University School of Medicine, Adana, Turkey

[3]Department of Cardiology, Health Sciences University, Adana Health Practices and Research Center, Adana, Turkey

ABSTRACT

Objective: The aim of this study was to compare mortality and myocardial infarction in patients with multi-vessel disease using "Modified Global Risk Classification" (mGRC).

Methods: We divided 579 patients into low, intermediate risk with a high EuroSCORE (IE), intermediate risk with a high SYNTAX score (IS), and high Modified Global Risk groups. Patients were evaluated for death, myocardial infarction, cerebrovascular events, need for re intervention, and a primary endpoint, which denotes the occurrence of any one of the four events.

Results: Comparing the bypass surgery and percutaneous coronary intervention groups using mGRC showed significantly better prognostic results in the bypass surgery patients for the rate of the occurrence of the myocardial infarction for the IS group (p=0.047). In terms of the primary endpoint, the EuroSCORE, SYNTAX score, and Global Risk Classification (GRC) were found to be independent risk factors in logistic regression analysis. The ability of GRC to discriminate for the 1-year mortality was found to be better than that of the EuroSCORE and SYNTAX score.

Conclusion: With the evaluation of the EuroSCORE and SYNTAX score together, the modified GRC, which includes both anatomical and clinical risk factors, provides an additional benefit for predicting the prognosis and decision of treatment in patients with multi-vessel disease.

Keywords: Modified global risk score, coronary artery bypass surgery, percutaneous transluminal coronary angioplasty

ÖZ

Amaç: Bu çalışmanın amacı, "Modifiye Global Risk Sınıflaması" kullanarak çok damar hastalığı olan hastalarda mortalite ve miyokard enfarktüsünü karşılaştırmaktır.

Yöntemler: EuroSCORE ve SYNTAX Skoru değerleri göz önüne alınarak 579 hasta; düşük, yüksek EuroSCORE'lu orta, yüksek SYNTAX Skorlu orta ve yüksek modifiye Global Risk gruplarına ayrıldı. Hastalar ölüm, miyokard enfarktüsü, serebrovasküler olay gelişimi, tekrar girişim ihtiyacı ve bu dördünden herhangi birinin gelişmesi anlamına gelen bileşke sonlanım noktası açısından taburculuk öncesi, 1. ay, 6. ay ve 12. ayda değerlendirildi.

Bulgular: Modifiye Global Risk skorlamasına göre bypass cerrahisi ve perkutan koroner girişim yapılan hasta grupları karşılaştırıldığında yüksek SYNTAX skorlu orta risk grubunda miyokard enfarktüsü gelişimi oranında (p=0,047) bypass cerrahisi yapılan hastalarda daha iyi prognostik sonuçlar elde edildi. Logistik regresyon analizinde bileşke sonlanım noktasına ulaşma için EuroSCORE, SYNTAX Skoru ve Global Risk Skoru bağımsız risk faktörü olarak saptanmıştır. mGRC'nin 1 yıllık mortalite için diskriminasyon yeteneğinin EuroSCORE ve SYNTAX skorundan daha iyi olduğu bulunmuştur.

Sonuç: Çoklu damar hastalığına sahip hastalarda EuroSCORE ve SYNTAX skorunun beraber değerlendirilmesiyle oluşturulan, anatomik ve klinik risk faktörlerine birleştiren bir risk skorlaması olan modifiye Global Risk Skoru prognozun öngörülmesinde ve tedavi seçiminde ek fayda sağlamaktadır.

Anahtar kelimeler: Modifiye global risk skoru, koroner arter bypass cerrahisi, perkütan translüminal koroner anjiyoplasti

ORCID IDs of the authors: O.K. 0000-0002-5065-3283;D.Y.Ş. 0000-0002-3519-0962;A.D. 0000-0003-1068-4277;H.A. 0000-0001-7229-1474;R.A.E. 0000-0003-4922-6556;Y.K.İ. 0000-0003-0070-5281;Ç.E.Ç. 0000-0003-1114-9014;M.D. 0000-0003-3560-7489.

Corresponding Author / Sorumlu Yazar: Onur Kaypaklı **E-posta/E-mail:** onurkaypakli@hotmail.com

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INTRODUCTION

Historically, coronary artery bypass grafting (CABG) has been the preferred method of revascularization in patients with complex coronary artery disease (CAD); however, recent evidence indicates that percutaneous coronary intervention (PCI) can offer a safe and suitable alternative in specific groups of patients (1). With the increasing use of PCI, a systematic approach is needed to stratify these complex patients for choosing the appropriate revascularization option for each patient.

Various risk scores with various risk factors have been developed to decide the choice of treatment and to predict the short- and long-term prognosis in CAD.

The EuroSCORE is the most widely used clinical risk score. It is a prognostic scoring system developed for patients undergoing cardiac surgery and has gained wide popularity over time because its performance has been validated in several local populations (2, 3). The EuroSCORE can also reasonably stratify PCI population into risk categories because most of its variables are derived from the clinical status of the patient (4). However, one common concern of using clinical risk scores in the setting of PCI is that they do not incorporate any comprehensive information regarding the anatomy and extent of CAD.

The SYNTAX score is the most widely used anatomic risk score. It has been developed as a combination of several previously validated angiographic classifications aiming to grade the coronary anatomy with respect to the number of lesions and their functional impact, location, and complexity (5). Higher SYNTAX scores, indicative of a more complex condition, are likely to represent a bigger therapeutic challenge and to have a potentially worse prognosis in patients undergoing contemporary revascularization with PCI.

In order to improve its performance to determine the procedural risk and to detect the appropriate treatment for patients who had multi-vessel CAD, the parallel use of a clinical score, such as the EuroSCORE that determines the procedural risks, was thought to be a better option than the use of the SYNTAX score alone. A new tool called Global Risk Classification (GRC), which includes both angiographic and clinical information contained in the SYNTAX score and EuroSCORE, respectively, was developed as a combined risk model.

For better identification of patients who would benefit greatly from CABG treatment, we developed the "Modified Global Risk Classification" (mGRC) with a slight change in GRC. The aim of this study was to compare mortality, myocardial infarction, and a primary endpoint in patients undergoing CABG and PCI with multi-vessel disease using mGRC, which includes both anatomical and clinical risk factors.

METHODS

Patient Population

We included 579 patients who underwent coronary angiography at the coronary angiography units of t he Çukurova University Hospital and Adana Numune Training and Research Hospital in this retrospective cohort study. Patients with stable angina pectoris, unstable angina, non-ST segment elevation myocardial infarction, and those undergoing bypass surgery and PCI were included in this study. The local ethics committee approved the study protocol, and written informed consent obtained from each participant.

Patients with left main coronary artery (LMCA) lesion (>50%), three-vessel disease (3VD) (>50%), left anterior descending artery diagonal I, diagonal II bifurcation lesion (>50%), proximal left anterior descending, and circumflex or right coronary artery 2-vessel disease (>50%) were included. Patients with ST-elevation myocardial infarction, a history of severe liver disease, neutropenia, thrombocytopenia with contraindications or intolerance to aspirin and clopidogrel, a history of previous CABG, non-cardiac disease limiting the life expectancy, severe valvular disease requiring surgical treatment, and those requiring non-cardiac surgery in a short time were excluded from the study.

The treatment strategy (CABG or PCI) was determined by the responsible clinician independently from the study.

Definition of scoring systems

Each coronary lesion with a diameter stenosis ≥50% in vessels ≥1.5 mm was scored with the SYNTAX score as originally described (6). The EuroSCORE was calculated based on the original methodology (2). GRC was created by a combination of the SYNTAX score and EuroSCORE strata (7).

A low mGRC risk is defined as a EuroSCORE of 0-5 and SYNTAX score of ≤32, an intermediate mGRC risk with a high EuroSCORE (IE) is defined as a EuroSCORE of ≥6 and SYNTAX score of ≤32, an intermediate mGRC risk with a high SYNTAX score (IS) is defined as a EuroSCORE of 0-5 and SYNTAX score of ≥33, and high mGRC risk is defined as a EuroSCORE of ≥6 and SYNTAX score of ≥33. In our study, the intermediate risk group is divided into two groups for the first time. The reason of this implementation is to separate the patient population with high SYNTAX score and low EuroSCORE, and this could benefit more from CABG treatment (Figure 1).

Echocardiography

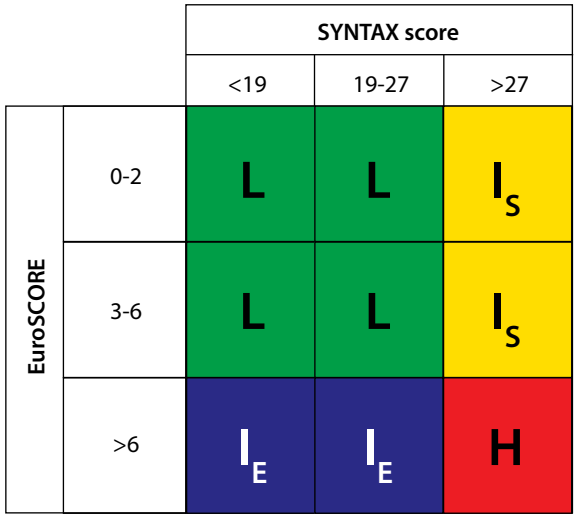
The standard 2-dimensional and Doppler echocardiography were performed for all patients. Left ventricle (LV) end-diastolic diameters (LVDd), end-diastolic interventricular septal thickness, and end-diastolic left ventricular posterior wall thickness were measured at end-diastole according to the established standards of the American Society of Echocardiography. LV ejection fraction (EF) was determined using the biplane Simpson's method.

Follow-up of patients

Patients were evaluated before discharge and at 1, 6, and 12 months for death, myocardial infarction, cerebrovascular accident, need for re-intervention, and a primary endpoint, which denotes the occurrence of any one of the four events. The primary endpoint of the study was the occurrence of mortality. Patients were followed up through phone calls.

Figure 1. Nomogram of mGRC

-Low mGRC Risk (L): EuroSCORE 0-5, SYNTAX score ≤32
-Intermediate mGRC Risk with high EuroSCORE (IE): EuroSCORE ≥6, SYNTAX score ≤32
-Intermediate mGRC Risk with high SYNTAX score (IS): EuroSCORE 0-5, SYNTAX score ≥33
-High mGRC Risk (H): EuroSCORE ≥6, SYNTAX score ≥33



Statistical Analysis

The Statistical Package for Social Sciences (SPSS) 17.0 (SPSS Inc.; Chicago, IL, USA) program was used for statistical analysis. Continuous variables were presented as mean±standard deviation (SD) or as median and interquartile range; categorical variables were presented as number and percentage.

The chi-square test or Fisher's exact test was used to compare categorical variables. Continuous variables with normal distribution were compared using ANOVA and Student's unpaired *t* test. Continuous variables without normal distribution were compared using the Kruskal-Wallis or Mann-Whitney rank sum test. The normality assumption for continuous variables was evaluated using the Kolmogorov-Smirnov test.

A logistic regression analysis was used to find independent predictors of mortality, myocardial infarction, and the primary endpoint. The discrimination of GRC, SYNTAX score, and EuroSCORE was first assessed using the areas under the receiving operator characteristic curves (AUROC). The level of statistical significance was set at 0.05 for all tests.

RESULTS

Baseline Characteristics

The percentage of male patients was significantly higher in the PCI group (p<0.05). The percentage of peripheral artery disease history and presence of a LMCA lesion were found to be significantly higher in the CABG group (p<0.05, for all). There were no significant differences in other demographic data (Table 1).

Table 1. Baseline and procedural characteristics of patients

Variable	PCI (n=282)	CABG (n=297)	Total (n=579)	p value
Age, years±SD	63.6±9.9	62.5±8.9	63.1±9.4	0.193
Male sex n (%)	200 (86.2)	180 (66.7)	380 (75.7)	<0.001
Diabetes n (%)	88 (37.9)	112 (41.5)	200 (39.8)	0.655
Smoking history n (%)	135 (58.2)	140 (51.9)	275 (54.8)	0.177
Hypercholesterolemia n (%)	46 (19.8)	70 (25.9)	116 (23.1)	0.112
Family history n (%)	50 (21.6)	78 (28.9)	128 (25.5)	0.065
Hypertension n (%)	87 (37.5)	108 (40.0)	195 (38.8)	0.583
Previous MI n (%)	55 (23.7)	72 (26.7)	127 (25.3)	0.472
Previous PCI n (%)	34 (14.7)	55 (20.4)	89 (17.7)	0.102
Previous CVA n (%)	1 (0.4)	4 (1.5)	5 (1.0)	0.380
Previous PAD n (%)	2 (0.9)	31 (11.4)	33 (6.6)	<0.001
LMCA lesion n (%)	23 (9.9)	44 (16.3)	67 (13.3)	0.048
EF (%)±SD	48.7±23.2	51.8±8.6	50.4±17.1	0.037
Creatinine (mg/dL) ±SD	1.0±0.3	1.1±0.7	1.1±0.6	0.010
LDL (mg/dL)±SD	108.2±36.5	117.6±40.2	113.2±38.7	0.007
HDL (mg/dL)±SD	37.9±28.3	36.2±21.8	37.0±25.1	0.446
EuroSCORE	3.23±2.47	3.45±2.35	3.34±2.41	0.70
SYNTAX score±SD	25.1±6.9	25.5±6.9	26.6±7.5	0.441

MI=myocardial infarction, CVA=cerebrovascular event; LMCA=left main coronary artery; PAD=peripheral arterial disease, SD=standard deviation, PCI=percutaneous coronary intervention, EF=ejection fraction. LDL=low-density cholesterol, HDL=high-density cholesterol

Compared with the PCI group, EF, creatinine, and low-density cholesterol levels were found to be significantly higher in the CABG group (p<0.05, for all). There were no significant differences in other laboratory data (Table 1). Baseline characteristics of the patients with and without mortality are shown in Table 2.

Independent Predictors of Mortality, Myocardial Infarction, and the Primary Endpoint

Age (odds ratio [OR]=1.19, p=0.001), presence of a LMCA lesion (OR=11.90, p=0.001), smoking history (OR=20.34, p<0.001), family history of CAD (OR=29.80, p=0.017), EuroSCORE (OR=1.55, p=0.049), SYNTAX score (OR=1.21, p=0.002), and intermediate- (OR=5.42, p=0.048) and high-risk mGRC (OR=18.28, p=0.033) were found to be independent predictors of mortality in the logistic regression analysis (Table 3).

The EuroSCORE (OR=1.18, p=0.040), SYNTAX score (OR=1.186, p<0.001), and intermediate- (OR=8.08, p=0.006) and high-risk mGRC (OR=18.69, p=0.004) were found to be independently associated with the occurrence of new myocardial infarction in the logistic regression analysis. EF (OR=0.93, p=0.006) was found to be inversely associated with the occurrence of myocardial infarction.

Table 2. Baseline characteristics of patients with and without mortality

Variable	Patients without mortality (n=547)	Patients with mortality (n=32)	p value
Age, years±SD	70.9±7.1	62.8±9.2	<0.001
Male sex n (%)	417 (76.2)	27 (84.4)	0.290
Diabetes n (%)	227 (41.5)	18 (56.2)	0.112
Smoking history n (%)	296 (54.1)	25 (78.1)	0.008
Hypercholesterolemia n (%)	131 (23.9)	7 (21.9)	0.789
Family history n (%)	138 (25.2)	1 (3.1)	0.004
Hypertension n (%)	209 (38.2)	13 (40.6)	0.785
Previous MI n (%)	137 (25.0)	12 (37.5)	0.117
Previous PCI n (%)	89 (16.3)	7 (21.9)	0.407
Previous CVA n (%)	5 (0.9)	0 (0)	0.380
LMCA lesion n (%)	73 (13.3)	10 (31.3)	0.005
EF (%)±SD	50.4±16.4	42.4±13.4	0.007
Creatinine (mg/dL)±SD	1.0±0.5	1.3±0.4	0.007
LDL (mg/dL)±SD	114.3±38.1	118.2±48.3	0.581
HDL (mg/dL)±SD	36.8±23.9	32.0±9.3	0.251
EuroSCORE	3.23±2.37	5.25±2.39	<0.001
SYNTAX score±SD	26.3±7.5	32.3±4.6	<0.001
Revascularization type PCI n (%)	265 (48.4)	17 (53.1)	0.607

MI=myocardial infarction, CVA=cerebrovascular event, SD=standard deviation, PCI=percutaneous coronary intervention, EF=ejection fraction. LDL=low–density cholesterol, HDL=high–density cholesterol

The EuroSCORE (OR=1.38, p=0.018), SYNTAX score (OR=1.13, p=0.001), and high-risk mGRC (OR=8.01, p=0.008) were found to be independent risk factors to reach the primary endpoint in the logistic regression analysis (Table 3).

Comparison of Mortality, Myocardial Infarction, and the Primary Endpoint Rates for All Patients with GRC

The mortality rates were 1.9%, 7.7%, and 14% for the low-, medium-, and high-risk mGRC groups, respectively. There were statistically significant differences between the low-to-moderate (p=0.016) and low-to-high (p=0.001) risk groups.

The rates of the occurrence of new myocardial infarction were 3.9%, 9.3%, and 14% at the low-, medium-, and high-risk mGRC groups, respectively. There were statistically significant differences between the low-to-moderate (p=0.041) and low-to-high (p=0.004) risk groups.

The primary endpoint rate was 7.7%, 14.2%, and 25.6% at low, medium-, and high-risk groups, respectively. There were statistically significant differences between the low-to-moderate (p=0.034), low-to-high (p=0.001), and medium-to-high (p=0.027) risk groups.

Comparison of Mortality, Myocardial Infarction, and the Primary Endpoint Rates According to mGRC in Patients Undergoing CABG and PCI

With regard to the mortality rates of CABG and PCI groups with mGRC, the prognostic results were better with CABG in the IS group and with PCI in the IE group. However, there was no statistically significance (p>0.05, for all). The prognostic results were better with CABG in the IS group and with PCI in the IE group for primary endpoint rates. However, there was no statistically significance (p>0.05, for all). The prognostic results for the rate of occurrence of myocardial infarction in the IS group were significantly better in CABG patients (p=0.047; Table 4).

Discrimination Analysis

The ability of GRC to discriminate for 1-year mortality was found to be better than that of the EuroSCORE and SYNTAX score. The AUROC was 0.712 (95% confidence interval [CI]: 0.62-0.80, p<0.001) with mGRC, 0.705 (95% CI: 0.62-0.78, p<0.001) with the SYNTAX score, and 0.690 (95% CI: 0.60-0.77, p<0.001) with the EuroSCORE (Table 5).

DISCUSSION

To the best of our knowledge, this is the first description of mGRC that represents a risk score combining both clinical and angiographic variables. The main findings from this study are that mGRC has an ability superior to either the SYNTAX score or EuroSCORE alone for predicting the 1-year mortality in patients with multi-vessel disease undergoing PCI and CABG. Furthermore, mGRC is found to have the ability to isolate patients with a high SYNTAX score and with low or intermediate EuroSCORE (IS group), who can potentially benefit greatly from surgical treatment.

The SYNTAX score is a reliable risk score for predicting the cardiac mortality in CAD, and it was created using angiographic risk factors (6-9). The EuroSCORE, Mayo Clinic score, Personnet score, ACEF score, and NCDR CathPCI score can be considered as clinical risk scores. There was a need to create a new diagnostic tool that combines the angiographic and clinical risk factors for a more precise prediction of cardiac mortality and for better guidance in deciding treatment modalities.

One of the studies with a combined risk classification approach was the Clinical SYNTAX Score (CSS) (10). CSS was calculated retrospectively for each of the 512 patients undergoing PCI with complex CAD using the formula CSS=[SYNTAX Score]×[modified ACEF score]. The modified ACEF score (ACEF creatinine clearance [CrCl]) was calculated retrospectively using the formula age/EF+1 point for every 10 mL/min reduction in CrCl below 60 mL/min per 1.73 m^2 (up to a maximum of 6 points). The clinical outcomes in terms of major adverse cardiac and cerebrovascular events (MACCE) and mortality at 1- and 5-year follow-ups were stratified according to the CSS tertiles: CSSLOW≤15.6 (n=170), 15.6<CSSMID<27.5 (n=171), and CSSHIGH≥27.5 (n=171). At

Table 3. Predictors of mortality and primary endpoint in the logistic regression analysis

	Mortality		Primary endpoint	
Variable	**OR**	**p**	**OR**	**p**
Age, years	1.19 (1.07–1.32)	0.001	1.01 (0.97–1.06)	0.456
Male sex	1.78 (0.26–12.02)	0.550	1.14 (0.47–2.75)	0.763
Diabetes	0.85 (0.20–3.47)	0.823	1.30 (0.61–2.74)	0.485
Smoking history	20.34 (4.30–96.21)	0.001	1.85 (0.93–3.68)	0.078
Family history	29.80 (1.84–482.66)	0.017	1.06 (0.46–2.45)	0.880
Hypercholesterolemia	2.62 (0.50–13.69)	0.254	0.88 (0.40–1.93)	0.756
Hypertension	1.02 (0.29–3.51)	0.970	1.38 (0.72–2.63)	0.319
Previous MI	4.635 (0.82–26.19)	0.083	1.31 (0.49–3.48)	0.589
Previous PCI	3.539 (0.50–24.95)	0.205	1.01 (0.32–3.15)	0.983
EF	1.01 (0.95–1.07)	0.761	0.99 (0.96–1.02)	0.663
Creatinine	2.09 (0.89–4.88)	0.086	1.25 (0.72–2.16)	0.422
LMCA lesion	11.90 (2.71–52.27)	0.001	1.91 (0.87–4.17)	0.105
Revasc. type (CABG)	1.00 (0.39–2.55)	0.985	1.53 (0.84–2.79)	0.159
EuroSCORE	1.55 (0.99–2.42)	0.049	1.38 (1.05–1.80)	0.018
SYNTAX score	1.21 (1.07–1.37)	0.002	1.13 (1.06–1.21)	0.001
GRC (Int. Risk)	5.425 (0.82–35.61)	0.048	2.60 (0.89–7.52)	0.078
GRC (High Risk)	18.289 (1.25–266.47)	0.033	8.01 (1.71–37.38)	0.008

MI=myocardial infarction, LMCA=left main coronary artery, OR=odds ratio, EF=ejection fraction, CABG=coronary artery bypass graft, GRC=Global Risk Classification, Revasc=revascularization, PCI=percutaneous coronary intervention

Table 4. Comparison of mortality, myocardial infarction, and the primary endpoint rates according to mGRC in patients undergoing CABG and PCI

		IE (n=79)	IS (n=104)	p
Mortality (%)	PCI (n=93)	5.4	10.7	0.48
	CABG (n=90)	9.5	4.2	0.28
	p	*0.43*	*0.26*	
MI (%)	PCI (n=93)	8.1	16.1	0.10
	CABG (n=90)	7.1	4.2	0.77
	p	*0.40*	*0.047*	
Primary	PCI (n=93)	13.5	16.1	0.19
endpoint (%)	CABG (n=90)	16.7	10.4	0.34
	p	*0.35*	*0.46*	

MI=myocardial infarction, IE=Intermediate mGRC Risk with a high EuroSCORE, IS=Intermediate mGRC Risk with a high SYNTAX score, CABG=coronary artery bypass graft, mGRC=modified Global Risk Classification

Table 5. Discriminatory measures of mGRC, EuroSCORE, and SYNTAX score for 1-year mortality

Risk measure	1-year mortality AUROC
mGRC	0.712
SYNTAX score	0.705
EuroSCORE	0.690

mGRC=modified Global Risk Classification, AUROC=area under the receiver operator characteristic curved

the 1-year follow-up, the rates of repeat revascularization and MACCE were significantly higher in the CSSHIGH group. CSSHIGH had significantly higher rates of repeat revascularization and overall MACCE compared with patients in the lower 2 tertiles at the 5-year follow-up. The c-statistics for the CSS, SYNTAX score, and ACEF score for the 5-year mortality were 0.69, 0.62, and 0.65 and for the 5-year MACCE were 0.62, 0.59, and 0.57, respectively. As different from our study, only PCI patients were enrolled in the study. The modified ACEF score has limited clinical data (age, EF, and GFR) because it does not contain enough clinical data about the prognosis of a surgical procedure. For this reason, CSS may not be appropriate for the risk classification of CABG patients. For same reason, it may have a limited capacity to help in deciding treatment modalities.

The GRC was first used in a study published by Capodanno et al. (11). In this study, the EuroSCORE and SYNTAX score were used together to estimate the procedural and long-term risks for 255 patients undergoing PCI with a LMCA lesion. When the Euro-

SCORE was added into the SYNTAX score model, the c-statistic increased from 0.681 to 0.732 for the prediction of cardiac mortality. The likelihood ratio test for the significance of adding the EuroSCORE term to the model was $\chi 2=4.109$ (p=0.043) with a net re-classification improvement of 26% (p=0.002). GRC was found to have the best prediction and discriminative ability in terms of the 2-year cardiac mortality (hazard ratio [HR]: 3.40, p=0.001; c-statistic: 0.756) compared with the SYNTAX score (HR:2.87, p=0.006; c-statistic: 0.747) and the EuroSCORE (HR:3.04, p=0.005; c-statistic: 0.708) alone. In this study, GRC was compared with the EuroSCORE and SYNTAX score for predicting the cardiac mortality for the first time. It has been shown to result in a significant increase in the power to predict mortality. This study had only included LMCA lesion patients treated using PCI. LMCA lesions and their treatment have a different nature because of technical differences. Furthermore, this study had no data about patients with LMCA lesions treated surgically. Therefore, it may not be appropriate to generalize these results to all the multi-vessel disease population.

The Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) trial results at 3 years were published recently (12). In this study, at the 36-month period, the all-cause mortality and MACCE were compared using GRC in patients undergoing CABG and PCI treatment with LMCA lesion and 3VD. In this study, the clinical variables (EuroSCORE) were found to be more predictive of the clinical outcomes (all-cause death and MACCE) compared with anatomical variables (SYNTAX score) in the PCI population. In the LMCA lesion PCI population, the Global Risk was found to have greater predictive ability compared with the SYNTAX score or EuroSCORE alone. In the low-risk GRC patient population with LMCA lesion (n=701), mortality was significantly lower in the PCI group compared with CABG patients (CABG: 7.5%, PCI: 1.2%, HR: 0.16, p=0.0054). Likewise, in the low-risk GRC patient population with LMCA lesion, the MACCE incidence was found to be lower in the PCI group than in the CABG group even if there was no statistical significance (CABG: 23.1%, PCI: 15.8%, HR: 0.64, p=0.088). In the low-risk GRC patient population with 3VD (n=1,088), there was no significant difference in mortality between CABG and PCI patients (CABG: 5.2%, PCI: 5.8%, HR: 1.14, p=0.71). Likewise, in the low-risk GRC patient population with 3VD, there was no significant difference in the MACCE incidence between CABG and PCI patients (CABG: 19.0%, PCI: 24.7%, p=0.10). In the 3VD PCI population, the Global Risk improved the risk stratification of patients compared with the SYNTAX score alone by proving that low SYNTAX score patients with a high EuroSCORE had a mortality benefit in undergoing CABG over PCI.

The main strengths of the Global Risk are that it can be applied across the entire spectrum of the surgical and percutaneous-treated patients and that the addition of the EuroSCORE to the SYNTAX score is a simple non-invasive calculation. Furthermore, it is the first and maybe the best-combined assistance for deciding between CABG and PCI.

In the low-risk mGRC patient population of our study, similar to the 3-year results of the SYNTAX study, there was no statistical significance in mortality (CABG: 1.8%, PCI: 2.1%, p=0.56). In the low-risk mGRC patient population, different from the 3-year results of the SYNTAX study, the rate of reaching the primary endpoint was significantly lower in the CABG group and PCI group (CABG: 6.1%, PCI: 9.7%, p=0.005). Patients with a LMCA lesion have not been separated from the complete multi-vessel disease population in the present study because of the small number of patients with pure LMCA lesion.

In the IE mGRC patient population, mortality was higher in patients undergoing CABG compared with PCI but the difference was not statistically significant (CABG: 9.5%, PCI: 5.4%, p=0.43). In the IE mGRC patient population, there was no statistically significant difference in the rate of reaching the primary endpoint (CABG: 16.7%, PCI: 13.5%, p=0.35). However, in the 3-year results of the SYNTAX study, patient with a low SYNTAX score and a high EuroSCORE have been found to get a mortality benefit in undergoing CABG over PCI.

In the IS mGRC patient population, mortality was higher in the PCI group, though there was no statistically significant difference (CABG: 4.2%, PCI: 10.7%, p=0.26). The incidence of myocardial infarction was found to be significantly lower in the CABG group (CABG: 4.2%, PCI: 16.1%, p=0.047). The rate of reaching the primary endpoint was significantly lower in the CABG group, although there was no statistically significant difference (CABG: 10.4%, PCI: 16.1%, p=0.46). As expected, in the IS patient population, the incidence of myocardial infarction was significantly lower in the CABG group. CABG seems to be more advantageous than PCI in terms of mortality and primary endpoint in this population as expected, but statistical significance was not provided because of the relatively low number of patients in these groups. A greater stent burden and higher complication rates with PCI in patients with a high SYNTAX score can be considered as the reason for this prognostic advantage with CABG in the IS patient population. Furthermore, complete revascularization rates with CABG are likely to be higher than PCI in patients with a high SYNTAX score.

In the high-risk mGRC patient population, there was no statistical significance in mortality (CABG: 14.3%, PCI: 13.6%, p=0.93). The rate of reaching the primary endpoint was lower in the CABG group than in the PCI group, although there was no statistically significant difference (CABG: 21.4% PCI: 29.5%, p=0.38). These results were similar to those of previous studies.

Intermediate and high GRC were found to be independent predictors of mortality, myocardial infarction, and the primary endpoint in the logistic regression analysis. The ability of GRC to discriminate for the 1-year mortality was found to be better than the EuroSCORE and SYNTAX score. The ability may be improved by converting it to a scoring system with quantitative values.

Limitations

The current study is limited by its post hoc nature. Patients within the PCI and CABG groups have not been randomized because the present study was observational. Thus, the distribution of some of the demographic data was not equal between the groups. In total, 579 patients were included in the study. Although the total

number of patients seems to be sufficient, particularly, the number of patients in the intermediate- and high global risk groups was relatively low. Therefore, a statistical significance could not been obtained, even though there were proportional differences at some parameters.

CONCLUSION

mGRC, which can be applied across the whole spectrum of CABG and PCI patients, improved the risk classification in multi-vessel disease patients with a greater prediction power for cardiac adverse events. More importantly, mGRC should be considered for treatment decisions between CABG and PCI in multi-vessel disease.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Çukurova University. (2012)

Informed Consent: Informed Consent was obtained from patients who participated in this study.

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Case Report / Olgu Sunumu

Unilateral *Brucella* Dacryoadenitis

Unilateral *Brusella* Dakriyoadeniti

Alper Mete[1], Ayşe Özlem Mete[2], Sabit Kimyon[1], İbrahim Edhem Yılmaz[1], Necdet A Bekir[1]

[1]Department of Opthalmology, Gaziantep University School of Medicine, Gaziantep, Turkey
[2]Clinic of Infectious Diseases, Gaziantep 25 Aralık Public Hospital, Gaziantep, Turkey

ABSTRACT
Brucellosis is a multi-systemic disease with the involvement of several organs and tissues. Ocular brucellosis is a rare type of the disease and manifests most commonly with uveitis, choroiditis, keratitis, and optic neuropathy. Here we report a 49-year-old female, who presented with unilateral dacryoadenitis. Ocular examination, magnetic resonance imaging of the orbits, serology, and blood culture confirmed the diagnosis of brucellosis. Rifampicin and ciprofloxacin were given to the patient for 6 weeks. At the first month control examination, patient's ocular findings was completely resolved. Therefore we suggest that brucellosis should be considered in the differential diagnosis of patients with dacryoadenitis, paticularly in endemic regions.
Keywords: Brucellosis, dacryoadenitis, ocular brucellosis

ÖZ
Bruselloz, birçok organ ve dokuyu tutabilen multisistemik bir hastalıktır. Oküler bruselloz nadir görülmekle birlikte sıklıkla üveit, koroidit, keratit ve optik nöropati şeklinde ortaya çıkmaktadır. Bu olgu sunumunda, manyetik rezonans görüntüleme ile tek taraflı lakrimal gland büyümesi gösterilen, 49 yaşında kadın hastadan bahsedilmiştir. Klinik bulgular, tüp aglütinasyon testi ve kan kültürü ile bruselloz tanısı konulmuştur. Hastaya 6 hafta süre ile oral siprofloksasin 1500mg/gün ve rifampisin 600mg/gün tedavisi verildi. Birinci ay sonunda kontrol muayenesinde hastanın şikayetlerinin sekelsiz tamamen iyileştiği izlendi. Bu olguda "dakriyoadenit ayırıcı tanısı yaparken özellikle endemik bölglerde brusellozun akılda tutulması gerektiği" vurgulanmıştır.
Anahtar kelimeler: Bruselloz, dakriyoadenit, oküler bruselloz

INTRODUCTION

Brucellosis is a zoonotic diseaseand is a serious health care problem in some regions, such as the Middle East, Mediterranean, and Central and South American regions. In most developed countries, it has been eradicated or is under control (1). Fourspeciesare found to infect humans: *Brucella melitensis, B. abortus, B. canis, and B. suis.*The most commonly isolated pathogen is *B. melitensis,* which isknown to be the most virulent species (2). Turkey is also an endemic country, especially in its middle and southeastern regions (3). Usually, the microorganisms are transmitted to humans via the gastrointestinal tract from unpasteurized dairy products. Individuals belong to some occupations, such as farmers and veterinarians, can be directly infected by contact of the skin, blood, or conjunctiva (4).

Brucellosis is a multi-systemic disease with many organ and tissue involvement, which makes it a diagnostic challenge (5). Ocular brucellosis is a rare type of the disease and manifests most commonly with uveitis, choroiditis, keratitis, optic neuritis, and optic neuropathy (5-9).

Here we report a case of unilateral dacryoadenitis caused by brucellosis, which was confirmed by serology. To the best of our knowledge, only a few brucellosis-related dacryoadenitis cases have been reported in existing literature.

CASE PRESENTATION

A 49-year-old female Caucasian presented to the Ophthalmology Department of Gaziantep University School of Medicine with complains of slight pain and swelling in the superotemporal region of the right eye for a month. She also had a history of fever, malaise, generalized arthralgia, sweating, and lower back pain lasting for 6 months. She had been treated for 2 months due to brucellosis. However, it was not properly controlled because of inappropriate use of drugs on account of socioeconomic problems.

Complete ocular examination was performed. Her right eyelid was displaced temporally with mild proptosis, and the left eyelid was normal (Figure 1). Visual acuity was 20/20 in both eyes. Intraocular pressure was 18 and 16 mmHg in right and left eye, respectively. Slit-

ORCID IDs of the authors: A.M. 0000-0002-1712-5163;A.Ö.M. 0000-0003-0994-4465;N.B. 0000-0002-6755-2550;S.K. 0000-0001-91949841;İ.E.Y. 0000-0003-1154-425X.
Corresponding Author/Sorumlu Yazar: Ayşe Özlem Mete **E-mail/E-posta:** ayseozlem_ornek@hotmail.com
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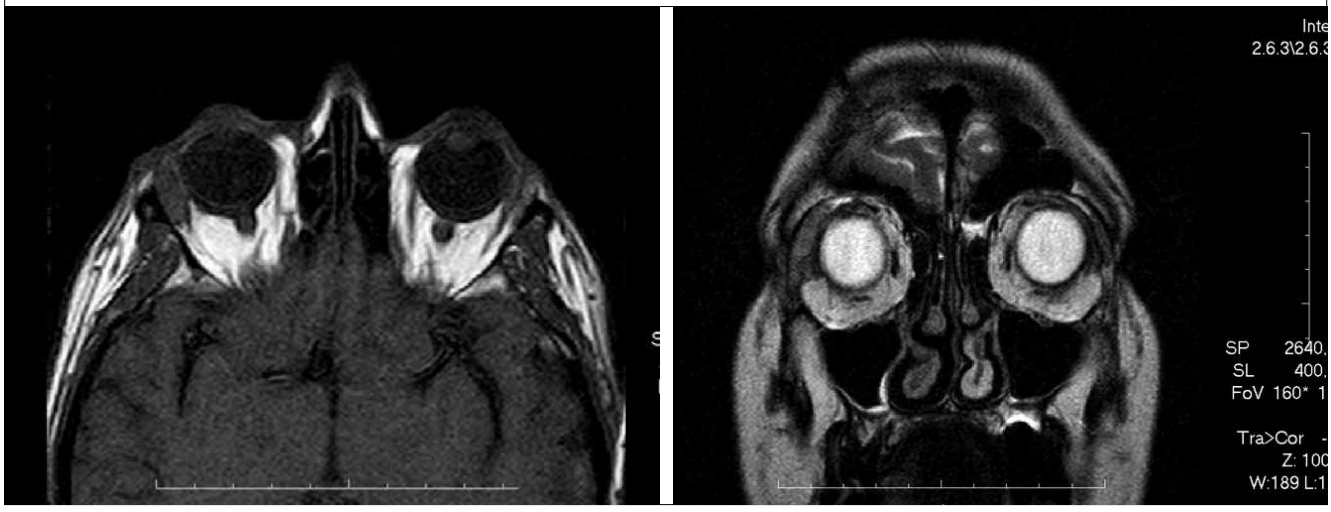
Figure 1. a-c. Temporally displaced right eyelid with mild proptosis

Figure 2. a, b. Axial and coronal magnetic resonance imaging shows unilateral right lacrimal gland enlargement



lamp examination and fundoscopy findings were normal bilaterally. Direct and indirect pupillary light reflexes were normal. The Hertel exophthalmometry measurement was 19 mm in the right eye and 17 mm in the left eye. There was no restriction in the movement of either eyes, but lateral gaze with the right eye was painful. Laboratory examination results were hemoglobin (Hgb), 15.2 g/dL (13.6-17.2); C-reactive protein, 13.42 mg/L (0-5); erythrocyte sedimentation rate, 24 mm/h (1-20);white blood cell, 8.99×10^3/µL (3.98-10.04) [neutrophil: 41.6% (34-71), lymphocyte: 48.3% (19.3-51.7)]; brucella immune capture agglutination test (Vircell Microbiologists, Granada, İspanya), positivetiter of 1/320; toxoplasma IgM, negative; cytomegalovirus IgM, negative; Epstein-Barr virus viral capsid antigen (EBV VCA) IgM, negative; and Gruber-Widal (Salmonella agglutination) test, negative. There was no growth on blood culture (BacT/Alert 3D, bioMerieux, Fransa). Magnetic resonance imaging showed marked contrast enhancement lateral to the lateral rectus muscle including the surrounding tissue, which was interpreted as an accompanying myositis of the lateral rectus muscle (Figure 2).

Oral rifampicin (600 mg/day), ciprofloxacin (1,500 mg/day), and lansaprazole (30 mg/day) were given to the patient for 6 weeks. At the first month control examination, patient's findings were resolved without any sequelae and ophthalmic examination finding was normal.

Informed consent was obtained from the patient for the publication of this case report and images.

DISCUSSION

Brucellosis is a frequent disease in the southeastern region of Turkey. Although ocular involvements are uncommon, itmay cause morbidity if left undiagnosed. Ocular brucellosis cases are mostly reported from endemic regions. In two different studies,Rolando (2) and Sungur (1) showed that the most frequent ocular manifestation is uveitis. Tabbara and Al-Kassimi (10) reported a patient with uveitis. The patient was not responsive to steroid treatment and the attacks were recurrent. They found that she had a paravertebral brucellar abscess, and she responded to systemic antibiotics and recovered. Although lacrimal gland infectionwith*B. melitensis* is infrequent, there are brucellosis cases that support exocrine gland involvement, such as mastitis and pancreatitis (11, 12). To the best of our knowledge, this case is the third case of *B. melitensis* infection after two dacryoadenitis cases reported by Bekir et al. (13, 14).

Diagnosis of ocular involvement of brucellosis is based on clinical ophthalmic examinations, microbiological culture of the associated ocular structure, and serology. Al Faran reported that *B. melitensis* is a causative organism of endophthalmitis bystandard tube agglutination and cultureof aqueous humor and vitreous (15). In our case, we confirmed the diagnosisbased on serology and clinical findings.

Eye involvement of brucellosis can exist in both chronic and acute phases of the disease, but mostly occur in the chronic phase (2, 7). Patients not seeking medical care until the disease has progressed to the chronic phase, late diagnosis because of the diagnostic challenge, or like in our case, patient noncompliance to the treatment are the reasons why the brucellosis complicates.

Standard treatment of brucellosis is rifampin and doxycycline for 6-8 weeks. In case of ocular involvement, a combination of local and systemic corticosteroids for 2-4 weeks with antibiotherapy leads to considerable improvement (2, 8). We treated our patient with rifampcin and ciprofloxacin combination without corticosteroids for 6 weeks. The patient completely recovered.

Therefore, in this case, we conclude that the lacrimal gland is one of the glands that can be affected in brucellosis.

CONCLUSION

In conclusion, particularly in endemic regions, eye involvement of brucellosis should be considered. Through routine ophthalmic examination of brucellosis patients, the risk of blindness may be decreased.

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Hakem Değerlendirmesi: Dış Bağımsız.

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Case Report / Olgu Sunumu

Anesthetic Management with Total İntravenous Anesthesia in Hereditary Spherocytosis

Herediter Sferositoz'da Total İntravenöz Anestezi ile Anestezi Yönetimi

Betül Kocamer Şimşek[1], Yunus Baydilek[1], Ahmet Ziya Şahin[2], Hakan Darıcı[3]

[1]Department of Anesthesiology and Reanimation, Sanko University School of Medicine, Gaziantep, Turkey

[2]Department of Internal Medicine, Adana Aşkın Tüfekçi Public Hospital, Adana, Turkey

[3]Sanko University School of Medicine, Department of Histology and Embryology, Gaziantep, Turkey

ABSTRACT

Hereditary spherocytosis (HS) is a type of hemolytic anemia. Anesthetic management of any surgery with HS requires close monitoring of hypothermia, hypoxia, acidosis, and postoperative pain.

We report a case of a 14-year-old male patient with HS scheduled for laparoscopic cholecystectomy. He was operated for splenectomy 5 years prior to admission. Hemoglobin (Hb) was 11.5 g/dL, platelets were 2,97,000 /mL, and total bilirubin was 4.50 mg/dL with direct bilirubin being 0.41 mg/dl. In peripheral blood smear (PBS) before surgery, spherocytosis percentage was 19%. He was premedicated with midazolam. After induction with propofol, fentanyl, and atracurium, anesthesia was maintained with air and O2 and total intravenous anesthesia (TIVA) was maintained with propofol and remifentanil. Electrocardiography, non-invasive blood pressure, peripheral oxygen saturation, and end-tidal carbon dioxide were monitored. We used an air warmer blanket to avoid hypothermia. Intraoperative arterial blood gas (ABG) values were evaluated at pH 7.37 (PCO_2 = 38.1 mm Hg, PO_2 = 177 mm Hg, Hb = 11.5 g/dL, and glucose = 109 mg/dL). Furthermore, intraoperative PBS was repeated, and spherocyte percentage was 11%. In post-anesthesia care unit, ABG values at pH 7.36 for PCO2, PO_2, and Hb were 37.4 mm Hg, 210 mm Hg, and 11.4 g/dL, respectively. PBS was repeated on the next day, and spherocyte percentage was 16%. Multimodal analgesia was provided with tramadol, paracetamol, and local infiltration of the surgical site. Paracetamol infusion was given postoperatively three times a day for pain control.

Intraoperative spherocyte percentage was less than that observed in preoperative PBS (11% and 19%, respectively). We consider that TIVA decreased spherocytes owing to appropriate anesthetic management, ABG stabilization, and normothermia each, either alone or together. On the next day, the spherocyte percentage was increased (16%) but still remained below the first spherocyte count. We consider that this is due to good pain control and well-balanced hydration. In conclusion, TIVA provided a safe anesthetic management.

Keywords: Hereditary spherocytosis, anesthesia management, TIVA, propofol

ÖZ

Herediter sferositoz (HS) bir hemolitik anemi türüdür. HS hastasında her tür cerrahide anestezi yönetiminde hipotermi, hipoksi, asidoz ve postoperatif ağrı açısından yakından izlenmelidir.

Beş yıl önce splenektomi operasyonu olan laparoskopik kolesistektomi planlanan 14 yaşındaki erkek HS hasta olgusunu sunduk. Ameliyattan önce hemoglobin (Hb) 11,5g/dL, total bilirubin 4,50 mg/dL direkt bilirubin 0,41mg/dL, trombositler 297K/mL, periferik kan yaymasında (PKY) sferositoz yüzdesi %19 idi. Midazolam ile premedikasyon yapıldı. Propofol, fentanil ve atrakuryum ile anestezi indüksiyon sağlandı, propofol ve remifentanil ile Total İntravenöz Anestezi (TİVA) ve hava, O2 ile idame sağlandı. Nabız, tansiyon arteryel, oksijen saturasyonu, end-tidal karbondioksit (EtCO2) izlendi. Üflemeli ve alt gövde battaniyesi ile hasta ısıtıldı. Ameliyatta arteryel kan gazı (AKG) değerleri PH 7,37, PCO_2 38,1 mmHg, PO_2 177 mmHg, Hb 11,5 g/dL glukoz 109 mg/dL olarak değerlendirildi. Ayrıca ameliyat sırasında PKY tekrarlandı ve sferosit yüzdesi %11 olarak belirlendi. Postoperatif AKG'da pH 7,36, PCO_2 37,4 mmHg, PO_2 210 mmHg, Hb 11,4 g/dL olarak belirlendi. PKY ertesi gün tekrarlandı ve sferosit yüzdesi % 16 olarak belirlendi. Multimodal analjezi tramadol, parasetamol ve insizyon yerlerine lokal anestezikinfiltrasyonu ile sağlandı. Ameliyat sonrası ağrı kontrolü günde üç kez parasetamol infüzyon ile sağlandı.

Operasyon sırasında sferositoz yüzdesi önceki PKY oranla (%11 /%19) daha düşük bulundu. TİVA'nın tek başına veya birlikte iyi anestezi yönetimi, iyi AKG stabilizasyonu, normotermi sağladığı için sferosit sayısında azalma sağladığını düşünüyoruz. Ertesi gün artış görülmüş (%16) ancak yine de ilk PKY değerinin altında kalmıştır. Biz bunu iyi ağrı kontrolü ve iyi dengelenmiş hidrasyon nedeniyle olduğunu düşünmekteyiz Sonuç olarak, TİVA güvenli bir anestezi yönetimini sağlamıştır.

Anahtar kelimeler: Herediter sferositoz, tıtal intravenöz anestezi, propofol, anestezi yönetimi

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ORCID IDs of the authors: B.K.Ş. 0000-0001-8220-9542

Corresponding Author/Sorumlu Yazar: Betül Kocamer Şimşek **E-mail/E-posta:** btlkcmr@gmail.com

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INTRODUCTION

Hereditary spherocytosis (HS) is an inherited hemolytic disorder with clinical features ranging from an asymptomatic condition to a fulminant hemolytic anemia requiring erythrocyte transfusion; incidence of HS is 1:5000. The primary lesion is reduced deformability of erythrocytes due to defects in the membrane protein ankyrin, spectrin, or protein 4.2 (1). The patient was admitted for laparoscopic cholecystectomy under general anesthesia with total intravenous anesthesia (TIVA). Hypothermia, hypoxia, and acidosis were considered and monitored with arterial blood gas (ABG) values, and an air warmer blanket was used to avoid hypothermia. In addition, TIVA was chosen for a good recovery to avoid hypoxia during the extubation period.

CASE PRESENTATION

We report a case of a 14-year-old male patient (weight, 39.9 kg; height, 161 cm) with HS scheduled for laparoscopic cholecystectomy after his parents provided written consent. Another approval was obtained from his parents for the case presentation. He presented with repeated episodes of jaundice, loss of appetite, easy fatigability, and pain in the right hypochondria. Hemoglobin (Hb) was 11.5 g/dL, and vitamin B12 level was 114 pg/ml. Ultrasonography of the abdomen showed no spleen and echogenic sludge in the gallbladder. He was operated for splenectomy 5 years ago. Platelets (2,97,000 /mL), prothrombin time (16.1 s), INR (1.30), total bilirubin (4.50 mg/dL) with direct bilirubin (0.41 mg/dL), and liver enzymes were normal. Other routine investigations were unremarkable. Peripheral blood smear (PBS) was performed in another institution, and spherocytosis percentage was 19% 4 days before the surgery. Reticulocyte percentage was 2.5%.

In the operation theater, two wide-bore cannulae were secured. The patient was premedicated with midazolam 1 mg (Dalizom; Generica, İstanbul, Türkiye). After induction with propofol (2 mg/kg; Propofol; Fresenius Kabi, Graz, Austria) and fentanyl (1 µg/kg; Talinat; Vem İlaç, Ankara, Türkiye) and intubation facilitated by atracurium (Tracrium; GSK, S.p.A, Italia), anesthesia was maintained with air and O_2 and TIVA with propofol and remifentanil (Ultiva; GSK, S.p.A, Italia).

Intraoperative care was ensured to avoid hypoxia, hypothermia, and acidosis. Electrocardiography, non-invasive blood pressure, peripheral oxygen saturation, end-tidal carbon dioxide, and esophageal temperature probe were monitored throughout the surgery. Temperature was maintained between 36.3°C and 36.7°C.

Intraoperative ABG values evaluated at pH 7.37 for PCO_2, PO_2, Hb, glucose, and HCO_3 were 38.1 mm Hg, 177 mm, 11.5 g/dL, 109 mg/dl, and 22.0 mmol/l, respectively. In addition, intraoperative PBS was repeated, and spherocyte percentage was found to be 11% (Figure 1). In post-anesthesia care unit (PACU), ABG values evaluated at pH 7.36 for PCO_2, PO_2, Hb, and HCO_3 were 37.4 mm Hg, 210 mm Hg, 11.4 g/dL, and 21.6 mmol/L, respectively. PBS was repeated on the next day, and spherocyte percentage was 16% (Figure 2).

Surgery continued for 45 min and was uneventful. Multimodal analgesia was provided using tramadol, paracetamol, and local infiltration of the surgical site with bupivacaine 0.25% and lidocaine 2% mixture. Patient was extubated after surgery, had a good recovery, and was shifted to PACU for observation. Postoperatively, 1 mg/kg paracetamol infusion was given three times a day for pain control. There was no need for pain medicine. He was discharged on the third day.

DISCUSSION

Patients with HS typically present with anemia, jaundice, gallstones, and splenomegaly. There may be a similar family history. Many patients have compensated hemolysis and a normal Hb level with reticulocytosis. Complications of HS include cholelithiasis, a consequence of chronic hemolysis; aplastic crisis, most commonly after parvovirus B19 infection; hemolytic crisis during intercurrent infection; and megaloblastic crisis in the presence of folic acid deficiency (1). Acute chest syndrome, onset of new lobar infiltration on chest X-ray (excluding atelectasis) associated with fever, respiratory distress, or chest pain has been reported (2).

If gallstones are present, cholecystectomy may be performed simultaneously with splenectomy or at a later date (3). In our case,

Figure 1. Intraoperative peripheral blood smear

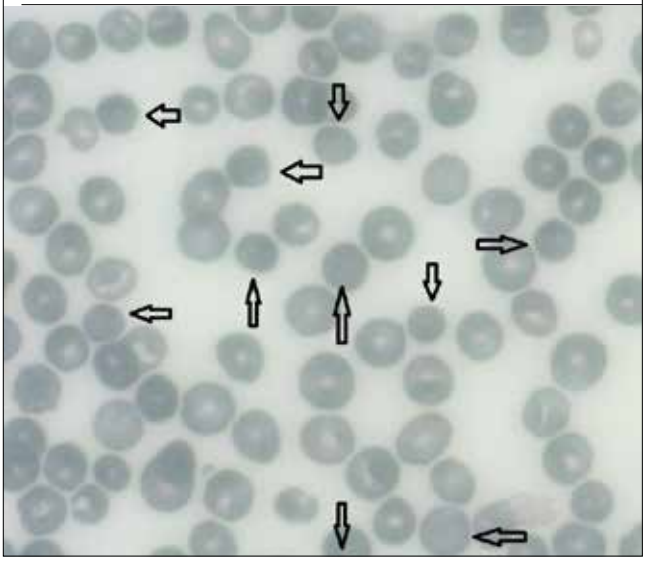
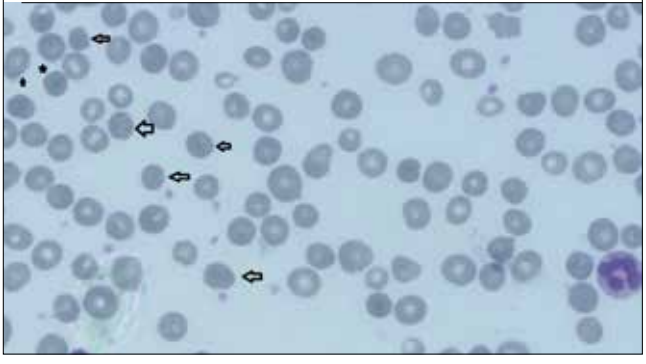


Figure 2. Postoperative peripheral blood smear



cholecystectomy operation was preferred later. Anesthetic management of HS involves hydration and avoidance of hypoxia, hypothermia, and acidosis and a good pain management.

Intraoperatively, avoidance of hypoxemia is the key. Sedatives and opioid analgesics should be used with extreme caution to prevent respiratory depression, hypoxia, and sickling. Blood loss should be replaced whenever necessary. Normothermia should be maintained to minimize vasoconstriction and associated circulatory stasis (4).

In our case, ABG values and temperature were normal. Furthermore, spherocyte percentage was 11% in intraoperative PBS less than preoperative smear percentage (19%). Recovery was well enough after surgery. We consider that TIVA with propofol and remifentanil did not increase spherocyte percentage. This could be due to appropriate anesthetic management, normothermia, and appropriate ABG stabilization each, either alone or together.

However, on the next day, spherocyte percentage increased (16%) but still remained below the first spherocyte value. We consider that this is because of good pain control and well-balanced hydration.

CONCLUSION

Perioperative management of HS largely depends on the severity of anemia and the degree of hemolysis. Anesthetic goals include avoidance of hypoxia, acidosis, and hypothermia and good pain management postoperatively. Patients with HS are at an increased risk of developing perioperative complications, such as aplastic crisis and hemolytic episodes, for which awareness and vigilance are important. TIVA with propofol and remifentanil decreased spherocytosis percentage and provided an appropriate anesthetic management. We concluded that TIVA is safe for patients with HS.

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