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AIMS AND SCOPE

İstanbul Medical Journal is the scientific, peer reviewed, open access publication of İstanbul Training and Research Hospital. The journal is printed six times in a year; on January, March, May, July, September, November and its publication language is Turkish and English.

The aim of the journal is to publish high level clinical and experimental studies conducted in all fields of medicine. Reviews comprising the latest research findings, reports on rare and educative cases and letters to the editor are also published.

The target population of the journal includes specialists in all fields of medicine, academicians and relevant health care professionals.

The İstanbul Medical Journal is indexed in Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, EBSCO and GALE.

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Originality, high scientific quality, and citation potential are the most important criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts that have been submitted to another journal for evaluation and rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts that have been presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

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- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, and highest academic degree(s) of the author(s),
- 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.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Methods, Results, Discussion, and Conclusion 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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Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Report, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

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
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.

Figures and Figure Legends

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 product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

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

References

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Journal Article: Rankovic A, Rancic N, Jovanovic M, Ivanović M, Gajović O, Lazić Z, et al. Impact of imaging diagnostics on the budget – Are we spending too much? Vojnosanit Pregl 2013; 70: 709-11.

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.

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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.

REVISIONS

When submitting a revised version of a paper, the author must submit a detailed “Response to the reviewers” that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer’s comment, followed by the author’s reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

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Case Report

UZM. DR. AHMET CÜNEYT MÜDERRİSOĞLU'NA VEDA

AHMET CÜNEYT MÜDERRİSOĞLU, M.D.

İstanbul Medical Journal was first published in 1994 under the name of "İstanbul Medical Journal" and Müderrisoğlu M.D. was the founding father and Editor-in-Chief for 11 years. İstanbul Medical Journal has gained widespread recognition throughout our country, and he made great efforts to make it searchable in a large number of national and international indexes. Müderrisoğlu M.D. passed away unexpectedly.

Müderrisoğlu M.D. was Chief of 1st Internal Medicine Clinic in İstanbul Training and Research Hospital and he graduated from Hacettepe Faculty of Medicine in second place in 1977. Between 1977-1981, he completed his residency training in Hacettepe University Medical Faculty, Department of Internal Medicine. He completed his military service in Ankara GATA Cardiology Clinic. In April 1983, he started to work in İstanbul Training and Research Hospital as the Chief Intern of the Internal Medicine Clinic. In 1989, he became Assistant Chief and in 1992, he became Chief of Clinic. During his 27 years of teaching, he played an active role in the training of many internal medicine specialists and healed thousands of patients. He achieved many innovations in our hospital. Together with the Infectious Diseases Clinic, he established the Hepatitis outpatient clinic for the first time and served in the Hepatitis Council for many years. He established the Internal Medicine Clinic seminar room, and worked and updated the infrastructure so that regular trainings were held here. He was the coordinator of Family Physicians and also trained a number of family medicine specialists. He took part in numerous scientific and administrative boards. He conducted many national and international studies. With his mastery of computer use and statistics, he solved the problems of the whole clinic, fulfilled the literature needs and contributed to scientific studies. He has always worked hard and provided unforgettable services for both public health and the scientific world.

He was fatherly to his assistants, affectionate towards his patients, extremely respectful and ethical to his colleagues. With his calm, restrained and firm personality, he has never been offensive. He exhibited a living example of being a good physician and a good person. He was in love with his profession and was attached to his hospital, so that he could continue working after a cardiac treatment. Müderrisoğlu M.D., who was married and had one child, left us unexpectedly on 22 April 2019 while he was continuing his duty. The entire family of İstanbul Training and Research Hospital will always commemorate Müderrisoğlu M.D. with gratitude, love, respect and mercy. Rest in peace.

Editorial Board

UZM. DR. AHMET CÜNEYT MÜDERRİSOĞLU

1994 yılında yayın hayatına başlayan önce İstanbul Tıp Dergisi adıyla, 2013 yılından itibaren İstanbul Medical Journal adıyla yayın hayatına devam eden İstanbul Eğitim ve Araştırma Hastane'mizin kurucu editörü ve 11 yıl boyunca dergimizin baş editörlüğünü yapmış olan Cüneyt hocamız beklenmedik bir şekilde aramızdan ayrıldı.

İstanbul Medical Journal'ın ülkemiz genelinde yaygın tanınırlık kazanması, ayrıca ulusal ve uluslar arası çok sayıda indekste taranır hale gelmesinde büyük emekleri olan değerli hocamız, İstanbul Eğitim ve Araştırma Hastanesi, İç Hastalıkları Kliniği, 1. Dahiliye Klinik Şefi Uzm. Dr. Ahmet Cüneyt Müderrisoğlu 1977'de Hacettepe Tıp Fakültesi'ni ikincilikle bitirdi. 1977-1981 arasında Hacettepe Tıp Fakültesi, İç Hastalıkları Anabilim Dalı'nda uzmanlık eğitimini tamamladı. Askerlik görevini Ankara GATA Kardiyoloji Kliniğinde yaptı, Nisan 1983'te İstanbul Eğitim ve Araştırma Hastanesi, İç Hastalıkları Kliniği Başasistanı olarak hastanemizde göreve başladı. 1989'da klinik şef yardımcısı, 1992'de klinik şefi oldu. Yirmi-yedi yıllık hocalık döneminde çok sayıda iç hastalıkları uzmanın yetiştirilmesinde aktif rol oynadı. Binlerce hastaya şifa verdi. Hastanemizde pek çok yeniliğe imza attı. Enfeksiyon hastalıkları kliniğiyle birlikte ilk kez hepatit polikliniğini kurdu ve uzun yıllar hepatit konseyinde görev aldı. İç hastalıkları kliniği seminer salonunu kurdu ve altyapısını işler ve güncel hale getirerek düzenli olarak eğitimlerin burada yapılmasını sağladı. Aile hekimleri koordinatörlüğünü yürüttü ve yine çok sayıda aile hekimliği uzmanı yetiştirdi. Çok sayıda bilimsel ve idari kurulda yer aldı. Ulusal ve uluslararası çalışmalara, bildirilere imza attı. Bilgisayar kullanımı ve istatistik konusunda ustalığıyla tüm kliniğin sorunlarını çözdü, literatür ihtiyaçlarını giderdi ve bilimsel çalışmalara katkı sağladı. Her zaman çok çalıştı, hem toplum sağlığı, hem bilim dünyası için unutulmaz hizmetler verdi.

Asistanlarına karşı babacan, hastalarına karşı şefkatli, meslektaşlarına karşı son derece saygılı ve etikti. Sakin, ölçülü ve sağlam kişiliğiyle hiçbir zaman kırıcı olmadı. İyi hekim ve iyi insan olmanın canlı örneğini sergiledi. Kalp rahatsızlığının ardından tedavi sonrası çalışmaya devem etmeyi isteyecek kadar mesleğine aşık ve hastanesine bağlıydı. Evli ve bir çocuk babası olan Cüneyt Müderrisoğlu, görevine devam ederken 22 Nisan 2019'da beklenmedik bir şekilde aramızda ayrıldı. Cüneyt Hoca'mızı tüm İstanbul Eğitim ve Araştırma Hastane'si ailesi her zaman minnetle, sevgiyle, saygıyla ve rahmetle anacaktır. Ruhu şad, mekanı cennet olsun.

Editöryel Kurul

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Assessment of Knowledge Levels of Elementary and High School Teachers on Childhood Asthma

İlköğretim ve Lise Öğretmenlerinin Çocukluk Çağı Astımı ile İlgili Bilgi Düzeylerinin Değerlendirilmesi

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ABSTRACT

Introduction: Asthma is a major cause of absenteeism in school-age children. Studies have shown that teachers' knowledge of asthma reduces school attendance rates. Collaboration between patients, physicians, family and teachers is an important factor in the success of treatment and decrease in the frequency of attacks in asthma patients. In order for teachers to take a more active role in this cooperation, their knowledge levels should be increased by providing trainings on childhood asthma. The aim of this study was to evaluate the knowledge levels of elementary (primary and secondary) and high school teachers working in İstanbul regarding childhood asthma.

Methods: This questionnaire was conducted between June and December 2012 with the participation of 825 teachers working in 22 randomly selected schools. The questionnaire was given to the teachers participating in the study, which questioned the general information, symptoms, triggering factors of asthma crisis, emergency intervention and treatment information about childhood asthma.

Results: In our study, the level of general knowledge about childhood asthma was found to be the highest and the level of knowledge about asthma triggering factors was the lowest. Regarding gender, the mean scores of the female teachers about asthma were significantly higher than male teachers. The total asthma awareness scores of the teachers working in public schools were found to be significantly lower than the teachers working in private schools (p=0.001). Having asthma experience was found to cause a significant increase in childhood asthma knowledge scores of teachers (p=0.001). When the comparison was made according to the expertise in teaching, experienced teachers had more knowledge about asthma triggering factors, whereas the teachers with less professional experience were more knowledgeable about the emergency intervention in asthma attack (p=0.016).

Conclusion: Our study will contribute to the national asthma control program. We believe that informing teachers about asthma is important in asthma control and will contribute to the guidelines for training programs.

Keywords: Asthma, childhood, teacher, school, knowledge level

ÖZ

Amaç: Astım okul çağı çocuklarında devamsızlığın başta gelen nedenlerindendir. Yapılan çalışmalar öğretmenlerin astım hakkında bilgi sahibi olmasının okula devamsızlık oranlarını azalttığını göstermektedir. Astım hastalarında tedavi başarısı ve atak sıklığının azalması için hasta, doktor, aile ve öğretmen arasındaki iş birliği önemli bir unsurdur. Bu iş birliğinde öğretmenlerin daha etkin rol alabilmeleri için çocukluk çağı astımı hakkında eğitimler verilerek bilgi düzeyleri artırılmalıdır. Çalışmanın amacı; İstanbul ilinde görev yapan ilköğretim ve lise öğretmenlerinin çocukluk çağı astımı ile ilgili bilgi düzeylerinin değerlendirilmesidir.

Yöntemler: Bu anket çalışması randomize olarak seçilen toplam 22 okulda görev yapan 825 öğretmenin katılımı ile Haziran-Aralık 2012 tarihleri arasında yapıldı. Çalışmaya katılan öğretmenlere çocukluk çağı astımı hakkında genel bilgileri, belirtileri, astım krizini tetikleyen faktörleri, ilk müdahale ve tedaviyle ilgili bilgileri sorgulayan bir anket formu dağıtıldı.

Bulgular: Çalışmamızda; çocukluk çağı astımı genel bilgisine ilişkin bilgi düzeyi puanı en yüksek, astım tetikleyici faktörlere ilişkin bilgi düzeyi puanı en düşük bulundu. Cinsiyete göre değerlendirmede kadın öğretmenlerin astımla ilgili verdikleri cevapların puanlarının ortalaması erkek öğretmenlerden anlamlı şekilde yüksek bulundu. Okul türlerine göre devlet okulunda görev yapan öğretmenlerin astım bilinci total puanları, özel okulda görev yapan öğretmenlere göre anlamlı şekilde düşük bulundu. Astım ile ilgili yaşanmış deneyimi olmasının öğretmenlerin çocukluk çağı astımı bilgi puanlarında anlamlı oranda yükselmeye neden olduğu bulundu. Öğretmenlik süresine yani mesleki deneyime göre karşılaştırma yapıldığında astım tetikleyici faktörler konusunda deneyimli öğretmenler daha fazla bilgiye sahipken, astım atağında ilk müdahaleye ilişkin ise mesleki deneyimi az olan öğretmenlerin daha bilgili olduğu görüldü.

Sonuç: Bu çalışma öğretmenler için gerçekleştirilecek eğitim programları ve seminerler için ulusal bir rehber hazırlanmasına yardımcı olması açısından önemlidir.

Anahtar Kelimeler: Astım, çocukluk çağı, öğretmen, okul, bilgi düzeyi

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Introduction

Asthma is one of the most common chronic diseases in childhood and is one of the main reasons for absenteeism and low participation in school activities such as gymnastics (1-11). One study showed that 7% of the students could not go to school on average seven days a year due to wheezing, and another study showed that 67% of the students did not attend school at least once a year due to wheezing or asthma (8,9).

Children spend an important part of their day at school separately from their families, which causes anxiety in families of children with chronic diseases such as asthma. Studies have shown that teachers' knowledge about asthma reduces family anxiety and child absenteeism rates. It is important for teachers to recognize the symptoms of asthma at the beginning of the attack and to know how to use the drugs to prevent the development of severe attacks. If the factors that trigger the development of asthma attacks are known by the teacher, inappropriate environmental conditions in the school will be corrected, thus preventing attack development. Since there are no nurses or health personnel in most of the primary schools in our country, it is very important that teachers are made aware of this issue. In some developed countries, projects such as "asthma friendly school" have been developed for the care of children with asthma at school (12-14).

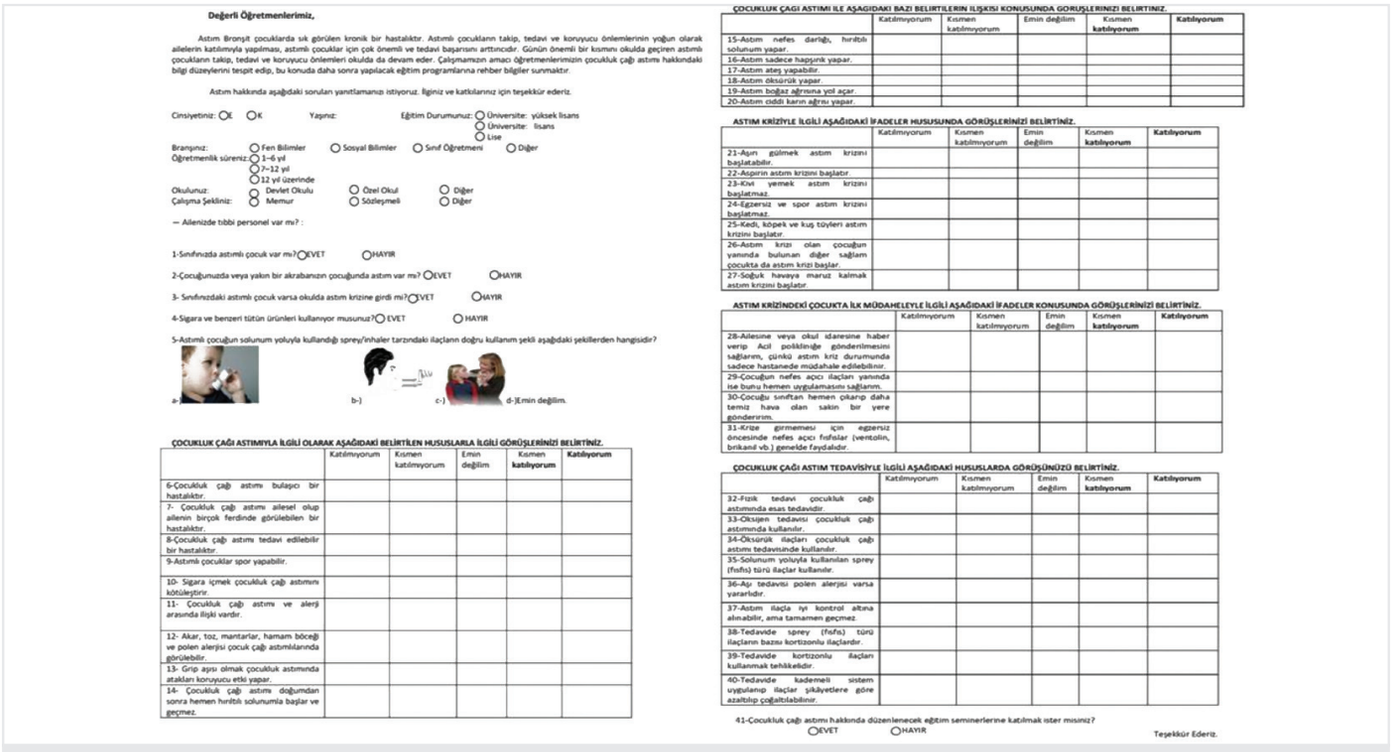
In this study, a questionnaire consisting of general information, symptoms, triggering factors, first intervention and treatment during the attack in childhood asthma was distributed to the teachers and their level of knowledge was tried to be determined, and it was aimed to provide information that could guide future trainings and national programs to be developed.

Methods

This study was conducted between June and December 2012 with the aim of measuring the level of knowledge of primary and high school teachers about childhood asthma in various public and private schools in İstanbul under the responsibility of a Training and Research Hospital Pediatric Clinic.

In this study, 20 elementary schools (primary and secondary schools) and 2 high schools were visited and questionnaires were distributed to approximately 1000 teachers. Nine hundred teachers agreed to participate in the study and completed the questionnaire appropriately (rate of answering the questionnaire: 90%). Of the 900 questionnaires, 825 were included in the study and the remaining 75 were excluded from the study due to inadequate answering.

In the questionnaire used in this study, there are questions regarding general demographic information (age, gender, expertise in teaching, education level, school type etc.) about the teachers. The questionnaire consists of three questions about the asthma experience asking whether there is a child with asthma in the family/school, one question about smoking and one illustrated question about the use of spray/inhaler-type medications used by the asthmatic child. In the next part of the questionnaire, there are a total of 41 questions including nine questions on general information about asthma, six questions questioning the relationship of some symptoms with asthma, seven questions about factors triggering asthma crisis, four questions about emergency intervention in asthma crisis, nine questions about asthma treatment and one question related to the training seminar (Figure 1).



Değerli Öğretmenleriniz,

Astım Bronşit çocuklarda sık görülen kronik bir hastalıktır. Astımlı çocukların takip, tedavi ve koruyucu önlemlerinin yoğun olarak ailelerin katılımıyla yapılması, astımlı çocuklar için çok önemli ve tedavi başarısını arttırıcıdır. Günün önemli bir kısmını okulda geçiren astımlı çocukların takip, tedavi ve koruyucu önlemleri okulda da devam eder. Çalışmamızın amacı öğretmenlerimizin çocukluk çağı astımı hakkındaki bilgi düzeylerini tespit edip, bu konuda daha sonra yapılacak eğitim programlarına rehber bilgiler sunmaktır.

Astım hakkında aşağıdaki soruları yanıtlamanızı istiyoruz. İlginiz ve katkılarınız için teşekkür ederiz.

Cinsiyetiniz: ○E ○K Yaşınız: Eğitim Durumunuz: ○ Üniversite: yüksek lisans ○ Üniversite: lisans ○ Lise

Branşınız: ○ Fen Bilimler ○ Sosyal Bilimler ○ Sınıf Öğretmeni ○ Diğer
Öğretmenlik süreniz: ○ 1-6 yıl ○ 7-12 yıl ○ 12 yıl üzerinde

Okulunuz: ○ Devlet Okulu ○ Özel Okul ○ Diğer
Çalışma Şekliniz: ○ Memur ○ Sözleşmeli ○ Diğer

– Ailenizde tıbbi personel var mı? :

1-Sınıfınızda astımlı çocuk var mı? ○EVET ○HAYIR

2-Çocuğunuzda veya yakın bir akrabanızın çocuğunda astım var mı? ○EVET ○HAYIR

3- Sınıfınızdaki astımlı çocuk varsa okulda astım krizine girdi mi? ○EVET ○HAYIR

4-Sigara ve benzeri tütün ürünleri kullanıyor musunuz? ○EVET ○HAYIR

5-Astımlı çocuğun solunum yoluyla kullandığı sprey/inhaler tarzındaki ilaçların doğru kullanım şekli aşağıdaki şekillerden hangisidir?

a-) b-) c-) d-)Emin değilim.

ÇOCUKLUK ÇAĞI ASTIMIYLA İLGİLİ OLARAK AŞAĞIDAKİ BELİRTİLEN HUSUSLARLA İLGİLİ GÖRÜŞLERİNİZİ BELİRTİNİZ.

	Katılmıyorum	Kısmen katılmıyorum	Emin değilim	Kısmen katılıyorum	Katılıyorum
6-Çocukluk çağı astımı bulaşıcı bir hastalıktır.					
7- Çocukluk çağı astımı ailesel olup ailenin birçok ferdinde görülebilen bir hastalıktır.					
8-Çocukluk çağı astımı tedavi edilebilir bir hastalıktır.					
9-Astımlı çocuklar spor yapabilir.					
10- Sigara içmek çocukluk çağı astımını kötüleştirir.					
11- Çocukluk çağı astımı ve alerji arasında ilişki vardır.					
12- Akar, toz, mantarlar, hamam böceği ve polen alerjisi çocuk çağı astımlılarında görülebilir.					
13- Grip aşısı olmak çocukluk astımında atakları koruyucu etki yapar.					
14- Çocukluk çağı astımı doğumdan sonra hemen hırıltılı solunumla başlar ve geçmez.					

ÇOCUKLUK ÇAĞI ASTIMI İLE AŞAĞIDAKİ BAZI BELİRTİLERİN İLİŞKİSİ KONUSUNDA GÖRÜŞLERİNİZİ BELİRTİNİZ.

	Katılmıyorum	Kısmen katılmıyorum	Emin değilim	Kısmen katılıyorum	Katılıyorum
15-Astım nefes darlığı, hırıltılı solunum yapar.					
16-Astım sadece hapşırık yapar.					
17-Astım ateş yapabilir.					
18-Astım öksürük yapar.					
19-Astım boğaz ağrısına yol açar.					
20-Astım ciddi karın ağrısı yapar.					

ASTIM KRİZİYLE İLGİLİ AŞAĞIDAKİ İFADELER HUSUSUNDA GÖRÜŞLERİNİZİ BELİRTİNİZ.

	Katılmıyorum	Kısmen katılmıyorum	Emin değilim	Kısmen katılıyorum	Katılıyorum
21-Aşırı gülmek astım krizini başlatabilir.					
22-Aspirin astım krizini başlatır.					
23-Kivi yemek astım krizini başlatmaz.					
24-Egzersiz ve spor astım krizini başlatmaz.					
25-Kedi, köpek ve kuş tüyleri astım krizini başlatır.					
26-Astım krizi olan çocuğun yanında bulunan diğer sağlam çocukta da astım krizi başlar.					
27-Soğuk havaya maruz kalmak astım krizini başlatır.					

ASTIM KRİZİNDEKİ ÇOCUKTA İLK MÜDAHELEYLE İLGİLİ AŞAĞIDAKİ İFADELER KONUSUNDA GÖRÜŞLERİNİZİ BELİRTİNİZ.

	Katılmıyorum	Kısmen katılmıyorum	Emin değilim	Kısmen katılıyorum	Katılıyorum
28-Ailesine veya okul idaresine haber verip Acil polikliniğe gönderilmesini sağlarım, çünkü astım kriz durumunda sadece hastanede müdahale edilebilinir.					
29-Çocuğun nefes açıcı ilaçları yanında ise bunu hemen uygulamasını sağlarım.					
30-Çocuğu sınıftan hemen çıkarıp daha temiz hava olan sakin bir yere gönderirim.					
31-Krize girmemesi için egzersiz öncesinde nefes açıcı fısfıslar (ventolin, brikanil vb.) genelde faydalıdır.					

ÇOCUKLUK ÇAĞI ASTIM TEDAVİSİYLE İLGİLİ AŞAĞIDAKİ HUSUSLARDA GÖRÜŞÜNÜZÜ BELİRTİNİZ.

	Katılmıyorum	Kısmen katılmıyorum	Emin değilim	Kısmen katılıyorum	Katılıyorum
32-Fizik tedavi çocukluk çağı astımında esas tedavidir.					
33-Oksijen tedavisi çocukluk çağı astımında kullanılır.					
34-Öksürük ilaçları çocukluk çağı astımı tedavisinde kullanılır.					
35-Solunum yoluyla kullanılan sprey (fısfıs) türü ilaçlar kullanılır.					
36-Aşı tedavisi polen alerjisi varsa yararlıdır.					
37-Astım ilaçla iyi kontrol altına alınabilir, ama tamamen geçmez.					
38-Tedavide sprey (fısfıs) türü ilaçların bazısı kortizonlu ilaçlardır.					
39-Tedavide kortizonlu ilaçları kullanmak tehlikelidir.					
40-Tedavide kademeli sistem uygulanıp ilaçlar şikâyetlere göre azaltılıp çoğaltılabilinir.					

41-Çocukluk çağı astımı hakkında düzenlenecek eğitim seminerlerine katılmak ister misiniz?
○EVET ○HAYIR

Teşekkür Ederiz.

Figure 1. The questionnaire

In the evaluation of the questionnaire, a 5-point Likert scale, including "strongly agree", "agree", "neither agree nor disagree", "disagree" and "strongly disagree" choices, was used. The correct answer was given "5 points" and the other answers were scored as "4, 3, 2, 1" points according to the closeness to the correct answer. After calculating the scores of the parts, 100-point conversion was applied to the total points obtained, thus the highest score being 100 and the lowest score being 0.

Questionnaire results were evaluated separately for five main parts and under asthma awareness total score title for the total score of 35 questions. In addition, the answers were evaluated separately according to gender, education level (university/bachelor's degree and master's degree), teacher's field of study, smoking status, expertise in teaching (professional experience), type of school (public, private) and asthma experience (the presence of asthmatic individuals in the family or school).

Informed verbal and written informed consent was obtained from the teachers. Ethics committee approval was obtained for the study (İstanbul University Training and Research Hospital Ethics Committee (decision no: 16/J, date: 25/10/2011).

Statistical Analysis

Statistical analysis was performed using Number Cruncher Statistical System 2007&PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA). In the evaluation of the study data, descriptive statistical methods (mean, standard deviation, median, frequency, percentage) were used. One-way ANOVA with post-hoc Tukey HSD was used for the comparison of quantitative data with normal distribution and determining the source of the difference. Student's t-test was used in pairwise comparisons. Significance was evaluated at $p<0.05$.

Results

The study was conducted with 825 teachers (500 females, 325 males) between June 2012 and December 2012. The mean age of the teachers was 32.6±7.2 years (range: 23-62 years). While 24.2% of the teachers were smokers, 75.5% did not smoke. Fourteen point five percent of the teachers (n=120) had master's degree and 84.5% (n=705) had bachelor's degree. Fourteen point five percent of the teachers were in the field of science, 12.5% were in the social sciences, 33% were in other fields and 40% were classroom teachers. Forty-three point seven percent of the teachers were working for 1-6 years, 31.1% for 7-12 years and 25.1% for more than 12 years. Eighty-two point eight percent of the teachers (n=684) were working in public schools and 17.2% (n=141) were in private schools. While 38.7% of the teachers (n=320) had children with asthma in their classes, 61.3% (n=505) did not have any children with asthma in their classes. While 37.5% of the teachers had asthma in their kids or close relative's kids, 62.5% did not have any asthma in their kids or close relative's kids.

While 5.1% of the teachers had children with asthma attacks in their classes, 94.9% did not have children with asthma attacks in their classes. Regarding the illustrated question about the correct use of spray/inhaler drugs used by asthmatic children, 47.3% of the teachers chose the picture in "a" as the correct answer, 16.6% in "b" and 12.3% in "c". Twenty-three point four percent of the teachers answered as "I am not sure". Accordingly, only 12% know the correct use of the inhaler type medication used by the asthmatic child. While 64.2% of the teachers (n=530) wanted a training seminar on childhood asthma, 35.8% (n=295) did not want to attend the training seminar. While 26% of the teachers had medical staff in their families, 74% did not have any medical staff in their families.

Regarding gender, there was a statistically significant difference between the scores of teachers' general knowledge about asthma, symptoms and triggering factors of childhood asthma, and the mean scores of female teachers' answers to childhood asthma were significantly higher than male teachers (p=0.001). However, there was no statistically significant difference between female and male teachers in terms of emergency intervention, treatment evaluation and total asthma awareness scores.

There was no statistically significant difference between asthma knowledge, symptoms, triggering factors, emergency intervention, treatment and asthma awareness total scores according to the education level of the teachers.

There was no statistically significant difference between asthma knowledge, symptoms, treatment and total asthma awareness scores according to the expertise in teaching (professional experience). Knowledge scores of asthma triggering factors were found to be statistically significantly lower in teachers whose expertise in teaching was between 1-6 years compared to those between 7-12 years and over 12 years. It was found that there was no significant difference in the scores of the emergency intervention in the asthma crisis between teachers with an expertise in teaching between 1-6 years and between 7-12 years. The mean scores of emergency intervention in children with asthma crisis were found to be significantly lower in patients with an expertise in teaching for 12 years or more (Table 1).

Table 1. Evaluation of asthma awareness according to expertise in teaching (professional experience)

	Expertise in teaching			p
	1-6 years (n=362)	7-12 years (n=257)	>12 years (n=207)	(One-way ANOVA)
Asthma knowledge scores	70.93±12.08	72.65±12.23	73.01±12.37	0.088
Asthma symptom score	68.47±14.55	67.85±13.03	67.66±14.90	0.774
Triggering factors knowledge score	53.99±14.75	57.36±16.40	56.62±14.68	0.016
Emergency intervention knowledge score	72.83±14.23	72.98±15.62	69.72±15.75	0.033
Treatment knowledge score	61.39±11.06	60.96±9.55	60.10±8.86	0.340
Asthma awareness total score	65.05±8.10	65.21±7.93	65.13±7.92	0.970

Teachers who had asthma in their kids, classes or relatives, or experienced an asthma attack in their classes, were considered to have experience with childhood asthma. The mean scores of the answers given by the experienced teachers to the questions about childhood asthma were found to be significantly higher than those without experience. Regarding asthma experience, there was a statistically significant difference between teachers in terms of asthma knowledge and triggering factors knowledge scores (p=0.001 and p=0.024; respectively). However, there was no statistically significant difference in terms of asthma symptoms, emergency intervention, treatment scores and total asthma awareness scores (Table 2).

No statistically significant difference was found between the teachers in terms of asthma knowledge, symptoms, triggering factors and emergency intervention scores according to school types. A statistically significant difference was found between asthma treatment and total asthma awareness scores according to school types (p=0.022 and p=0.001, respectively). The total scores of treatment and asthma awareness of the teachers working in public schools regarding childhood asthma were significantly lower than the teachers working in private schools (Table 3).

There was no statistically significant difference between asthma knowledge, symptoms, triggering factors, treatment and asthma awareness scores of the teachers in terms of field of study. The mean scores of emergency intervention of classroom teachers were significantly lower than those of science and social sciences. There was no statistically significant difference between the other fields (Table 4).

There was no statistically significant difference between general knowledge, triggering factors, emergency intervention, treatment and asthma awareness total scores according to smoking status. A statistically significant difference was found between childhood asthma symptom scores according to smoking status (p=0.021).

Discussion

Many studies conducted on the level of knowledge of childhood asthma showed that teachers' level of knowledge is limited (12-20). In the study

Table 2. Evaluation of asthma awareness according to asthma experience

	Asthma experience		p (Student's t-test)
	Experienced (n=474)	Inexperienced (n=352)	
Asthma knowledge scores	73.75±11.63	69.66±12.61	**0.001**
Asthma symptom score	68.63±14.38	67.25±13.92	**0.165**
Triggering factors knowledge score	56.75±15.69	54.32±14.72	**0.024**
Emergency intervention knowledge score	71.66±14.24	72.67±16.17	**0.351**
Treatment knowledge score	60.94±10.26	60.97±9.87	**0.967**
Asthma awareness total score	65.06±7.83	65.24±8.05	**0.756**

Table 3. Evaluation of asthma awareness according to school type

	School type		p (Student's t-test)
	Public (n=684)	Private (n=142)	
Asthma knowledge scores	72.35±11.91	70.34±13.53	**0.076**
Asthma symptom score	67.91±14.04	68.69±14.96	**0.549**
Triggering factors knowledge score	55.84±15.31	55.08±15.38	**0.589**
Emergency intervention knowledge score	71.84±15.18	73.33±14.70	**0.285**
Treatment knowledge score	60.58±10.27	62.71±8.98	**0.022**
Asthma awareness total score	64.62±8.14	67.61±6.19	**0.001**

Table 4. Evaluation of asthma awareness according to field of study

	Field of study				p (One-way ANOVA)
	Science (n=106)	Social sciences (n=105)	Class teacher (n=331)	Other (n=284)	
Asthma knowledge scores	71.09±13.04	72.27±12.55	72.92±11.30	71.05±12.92	**0.243**
Asthma symptom score	61.17±16.10	68.92±12.82	67.05±14.27	69.05±13.82	**0.280**
Triggering factors knowledge score	55.82±15.50	55.54±16.61	55.79±14.61	55.59±15.59	**0.998**
Emergency intervention knowledge score	75.41±14.36	75.59±16.50	69.99±15.65	71.85±13.78	**0.001**
Treatment knowledge score	62.23±10.69	61.61±9.83	60.40±9.85	60.78±10.22	**0.361**
Asthma awareness total score	65.58±7.74	65.99±7.87	64.95±7.40	65.07±7.82	**0.609**

All numerical values are given as mean ± standard deviation
n: number of teachers participating in the survey, p: statistical significance between means

conducted by Ones et al. (21), asthma awareness total score was found to be 74% and the answers given to the questions including the symptoms and general knowledge about asthma were found to be satisfactory. Among the symptoms of asthma, shortness of breath was known accurately at a rate of 71%, wheezing at a rate of 50% and cough at a rate of 29%. In our study, asthma awareness total score was found to be 65% and the answers given to the questions including the symptoms and general knowledge of childhood asthma were consistent with the other study, while the answers to the questions about the triggering factors had the lowest score with 55.7±15.3. Among the symptoms of asthma, shortness of breath and wheezing were known accurately at a rate of 89.6% and cough at a rate of 81.4%, and the rates were significantly higher than in the other study. This shows that, unlike the previous study, our teachers' level of knowledge about the most common and important symptoms of childhood asthma was satisfactory, but their asthma awareness total scores were lower.

In a study conducted with 792 elementary school teachers in 2006, asthma knowledge levels of women were found to be significantly better than men (p=0.003). In our study, the mean scores of female teachers were also significantly higher than male teachers (p=0.001). This difference was thought to be due to female teachers' interest in children's disease more than male teachers. Consistent with the literature data, there was no significant difference in asthma knowledge levels according to the educational status of the teachers.

In the study conducted with 199 teachers in 46 schools in Dublin City, teachers' level of knowledge about asthma symptoms and factors triggering attacks was found sufficient, however, knowledge about asthma treatment and emergency intervention was considered insufficient (22). In our study, teachers' knowledge of asthma treatment and emergency intervention was also evaluated as inadequate. Unlike the study in Dublin City, the answers to the questions about the factors triggering an asthma attack had the lowest mean score of 55.7±15.3. This situation can be explained by the difference in social education and culture. These studies indicate that teachers should be educated on these issues and that schools need to develop an action plan especially in intervention in acute asthma attack.

In the studies evaluating the knowledge level of teachers about childhood asthma, it was found that teachers' age, gender and education levels did not affect their knowledge level about childhood asthma (23). Aydın Güçlü et al. (24) found that young age and female gender had a significant relationship with the number of correct answers in the questionnaire. In our study, it was found that the knowledge levels of the teachers who had master's degree were higher and there was a significant difference between the asthma knowledge levels of the teachers according to their education level. While there was no statistically significant relationship between professional experience and asthma knowledge level in our study, Canitez et al. (25) found that the knowledge level of teachers with 10 years or more professional experience on asthma was significantly higher.

In our study, similar to the studies conducted in the literature, having an experience of asthma caused a general knowledge level about asthma knowledge and triggering factors but did not affect having sufficient knowledge about treatment and emergency intervention requiring more specific information.

In a study conducted with 76 teachers in 11 primary schools, including eight public and three private schools, in Southampton, teachers were asked about the symptoms of childhood asthma, triggering factors, treatment and emergency intervention, and teachers' level of knowledge about asthma was found to be very low. It was found that there was no significant difference in asthma knowledge levels of teachers working in public and private schools. Eighty-six percent of the teachers requested to be informed about asthma (26). In our study, it was found that asthma knowledge levels of teachers working in public schools were significantly lower. In private schools, it was found out that the parents met with the teachers more often and shared the information about their children frequently and that this situation affects the development of teachers' knowledge about the diseases of the children. In addition, teachers are given frequent trainings on child health issues. Therefore, it is thought that teachers working in private schools have better knowledge about childhood asthma.

In childhood asthma, it is very important to regulate appropriate treatment in order to control the disease and to prevent irreversible damage to the respiratory tract and patient adherence to treatment is also very important. In patients with difficult pediatric asthma where control cannot be achieved with effective treatment, it is necessary to question the differential diagnosis and whether the treatment is applied correctly and regularly (27). In a study conducted by De Boeck et al. (28) in 51 patients with the diagnosis of difficult pediatric asthma, it was shown that all of them had symptom control, that four of them had no asthma and that only five of them had a slightly worse symptom control. In school-aged asthmatic children, the role of teachers as well as family and patient is important in terms of treatment compliance. It may be necessary to check whether the children who spend most of their time at school receive their treatment in a timely and correct manner or not, and emergency intervention methods, asthma symptoms and attack triggering factors should be known by the teacher and some applications should be performed. Therefore, the correct use of inhaler-type medications used in the treatment of asthma should be known by teachers. Similar to the studies conducted in Europe and the USA, in our study, only 12% of the teachers correctly answered the illustrated question asking about the use of inhaler medications used in asthma treatment, while 23% stated that they were not sure (29,30). It is very important in terms of demonstrating the necessity to provide training on the use of inhaler drugs.

Study Limitations

If the teachers were informed with seminars or trainings and evaluated before and after the training, we would have the opportunity to have information about the necessity and effectiveness of the training.

Conclusion

In order to control asthma and prevent the development of attacks, it is very important to know the triggering factors and to create suitable living spaces in the school. The continuation of prophylactic treatment without interruption in school time will be ensured by raising the

awareness of teachers. Action plans for asthma attacks (asthma friendly school, etc.) should be prepared in each school. Information can be provided effectively by health personnel by seminars and brochures. Collaboration between student, family, teacher and doctor is essential for treatment success and decreasing the frequency of attacks in asthma. In order for teachers to take a more active role in this cooperation, their knowledge levels should be increased by providing trainings on childhood asthma. Our research will contribute to the preparation of guidelines that include training programs for teachers as well as the development of a country-specific strategy in our national asthma control program.

Ethics Committee Approval: Ethics committee approval was obtained for the study (İstanbul University Training and Research Hospital Ethics Committee (decision no: 16/J, date: 25/10/2011).

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Comparison of Fluorometric İmmunoassay and Tandem Mass Spectrometry Methods Used in the Diagnosis of Phenylalanine Metabolism Disorders in Turkish Children

Türk Çocuklarında Fenilalanin Metabolizma Bozukluklarının Tanısında Kullanılan Florometrik İmmünolojik Test ve Tandem Kütle Spektrometresi Yöntemlerinin Karşılaştırılması

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ABSTRACT

Introduction: Phenylketonuria is one of the common causes of preventable mental retardation. Therefore, dietary and/or cofactor therapy initiated by early detection of the disease is of great clinical importance. In this study, the specificity and sensitivity of fluorescence immunoassay (FIA), tandem mass spectrometry (MS/MS) and plasma amino acid analysis methods used in the diagnosis of phenylalanine metabolism disorder (PMD) were compared.

Methods: Patients who were referred to our clinic with a prediagnosis of PMD disorder (n=163) from primary health care institutions were included in the study.

Results: The median age of the patients on admission was 3 months (range: 0-25 months). It was observed that the samples were resent to the newborn screening program at a rate of 68.1%. The sensitivity and specificity of FIA for phenylalanine (Phe) with a cut-off value of 2.95 mg/dL were 73.3% and 78.6%, respectively. The sensitivity and specificity of MS/MS for Phe with a cut-off value of ≥94.94 µmol/L were 93.3% and 92.2%, respectively.

Conclusion: A clinical delay was detected in the diagnosis of the cases. Because of this clinical delay, it is considered that the samples in the screening program are repeated frequently and that families do not have enough information about the disease. In our study, it was shown that MS/MS was more effective than FIA. The use of MS/MS instead of FIA for the detection of phenylalanine metabolism disorder in the neonatal screening program may be effective in preventing the diagnostic delay.

Keywords: Phenylketonuria, fluorescence, immunoassay, liquid chromatography, neonatal screening

ÖZ

Amaç: Fenilketonüri (FKU), önlenebilir zihinsel geriliğin yaygın nedenlerinden biridir. Bu nedenle, hastalığın erken tespiti ile başlatılan diyet ve/veya kofaktör tedavisi, klinik açıdan çok önemlidir. Bu çalışmada, fenilalanin metabolizma bozukluğu (FMB) tanısında kullanılan floresans immünolojik testi (FIA), tandem kütle spektrometrisi (MS/MS) ve plazma amino asit analiz (AAA) yöntemlerinin özgüllüğü ve duyarlılığı karşılaştırıldı.

Yöntemler: Birinci basamak sağlık kurumlarından FMB (n=163) ön tanısıyla kliniğimize yönlendirilen hastalar çalışmaya dahil edildi.

Bulgular: Kliniğimize başvuran hastaların medyan yaşı 3 aydı (minimum-maksimum: 0-25). Numunelerin yenidoğan tarama programında %68,1 oranında tekrar gönderildiği görüldü. FIA ile belirlenen 2,95 mg/dL fenilalanin (Phe) cut-off değerinde, %73,3 duyarlılık ve %78,6 özgüllük saptandı. MS/MS ile belirlenen Phe ≥94,94 µmol/L kesme değeri için %93,3 duyarlılık ve %92,2 özgüllük saptandı.

Sonuç: Olguların tanısında klinik bir gecikme tespit edildi. Klinik gecikmeye sebep olarak, tarama programındaki örneklerin sık tekrarlanması ve ailelerin hastalık hakkında yeterli bilgiye sahip olmaması düşünülmektedir. Çalışmamızda MS/MS'nin FIA'dan daha etkili bir yöntem olduğu gösterilmiştir. Yenidoğan tarama programında FMB tespitinde FIA yerine MS/MS kullanımının tanısal gecikmenin önlenmesinde etkili olabileceği düşünülmektedir.

Anahtar Kelimeler: Fenilketonüri, floresans, immünolojik test, sıvı kromatografi, yenidoğan taraması

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Introduction

Phenylketonuria (PKU) is a hereditary, autosomal recessive (AR) phenylalanine metabolism disorder (PMD) resulting from a variety of mutations in genes encoding phenylalanine hydroxylase (PAH). In the presence of cofactor tetrahydrobiopterin, molecular oxygen and iron PAH normally convert phenylalanine (Phe) to tyrosine (Tyr) (1). The enzyme deficiency causes a significant increase in Phe concentration in the blood and brain, and this can lead to a variety of neurocognitive and neuromotor disorders, including attention deficit symptoms and serious intellectual impairments if left untreated in the neonatal period (2-5). PMD may appear in a wide variety of clinical situations ranging from mild hyperphenylalaninemia (HPA) to classic PKU (5). Considering data from newborn screening programs (NSP), it is observed that the prevalence of PAH deficiency varies in different regions (for example, it is 1 in 1.000.000 births in Finland, it is 1 in 4200 births in Turkey) (5,6).

While patients consume normal protein, PMD can be classified according to Phe concentrations (5,7). According to this classification, the groups were defined as classical PKU (Phe ≥1200 µmol/L, residual PAH activity less than 1%), mild PKU or HPA (Phe=600-1200 µmol/L, residual PAH activity between 1-5%), non-PKU-HPA and moderate HPA (Phe=600-120 µmol/L; more than 5% residual PAH activity) (2,5,7).

In the 1960s, with the development of a simple test by Guthrie and Susi (8) based on a bacterial inhibition assay to detect HPA, PKU became the first disease to be diagnosed and treated early in NSP. Detection of newborns with PKU using this screening test has led to a reduction in the incidence of PKU-associated cognitive deficits when combined with early treatment (9). Over time, the use of fluorometric immunoassay (FIA) and tandem mass spectrometry (MS/MS) methods in screening programs has allowed for more precise and sensitive measurements (10,11). While Guthrie method could only detect positive or negative results, Phe level in heel blood became measurable by FIA method when integrated into NSP (11). Today, Phe levels in heel prick blood are measured more precisely by MS/MS method compared to FIA method and it also provides information about Tyr level simultaneously (12). However, since many different diseases can be detected concurrently with MS/MS method, it is now used as a more cost-effective method in NSP in many developed countries (13-16).

Methods

This study was conducted in Turkey between 07.05.2018-31.12.2018. Before the study, written informed consent was obtained from the parents of the patients who participated in this study. This study conformed to the principles of the 2008 Declaration of Helsinki and was approved by the Local Ethics Committee of Harran University Faculty of Medicine, Turkey (decision no: Session 5, 19747, date: 03.05.2018).

Out of 216 patients, a total of 163 patients, who were referred to the pediatric metabolic disease clinic after suspicion of PMD by primary health care institutions, were included in the study. Samples for FIA and MS/MS analysis were taken on a filter paper from heel prick blood (FIA: Whatman 903, MS/MS: Whatman 10538018). In all primary health care institutions in Şanlıurfa, samples for NSP were taken on a filter paper in accordance with the manufacturer's instructions. Samples were stored in a refrigerator at 4 ºC for the period from drying at room temperature to laboratory analysis. Samples were moved to central laboratories, which are under the authority of Turkish Public Health Institution, at room temperature conditions twice a week. All Phe levels obtained in NSP were quantitatively determined by FIA (ODAK Neonatal Phenylalanine Assay, ISLAB, İstanbul, Turkey) method in mg/dL. Sampling on the filter paper for MS/MS analysis was performed simultaneously with plasma amino acid analysis (AAA). Heel prick blood MS/MS analysis results were obtained by liquid chromatography (LC)-MS/MS method (Shimadzu LCMS-8040, Kyoto, Japan). Venous blood samples (2 mL) for plasma AAA were taken into a heparinized tube. The levels of all amino acids detected by plasma AAA were obtained by LC-MS/MS method (Shimadzu LCMS-8045, Kyoto, Japan).

Inclusion and Exclusion Criteria

According to NSP applied in Turkey, Phe ≤2 mg/dL (≤120 mmol/L) in the heel prick blood sample taken between the 48th hours and seventh day of life is considered negative, patients with Phe values between 2.1-3.9 mg/dL are requested to give samples again, and patients with Phe ≥4 mg/dL are directly referred to the pediatric nutrition and metabolic disease clinic (17,18). Also, samples taken during the first 48 hours of life (duplicate) and samples found to be inconvenient in terms of the sampling technique, storage and transportation conditions are taken again (17). In case of repeated heel prick blood sampling, the patient's last sample result was evaluated within the scope of the study. Among the patients who applied to our clinic, those who could not be fed orally for any reason within the first 48 hours of life and who underwent intravenous blood transfusion were excluded from the study. Currently, MS/MS method is recommended in NSPs and Phe >120 µmol/L value in blood is considered to be significant for moderate HPA (2). Among the patients who were referred from the primary health care institutions, those having Phe >120 µmol/L with at least one of the plasma AAA or heel prick blood MS/MS methods were evaluated as positive group and followed up. In order to exclude laboratory errors in patients included in the study, a control test was performed at the earliest month in patients who did not receive Phe restricted diet and patients with Phe >120 µmol/L in plasma AAA were included in the study. Patients with Phe ≤120 µmol/L in both heel prick blood MS/MS and plasma AAA were considered as the negative group. In our study, Phe/Tyr ratio was also taken into account (5). In addition, the Phe/Tyr ratio of cases, who was confirmed by only one method (heel prick blood MS/MS or plasma AAA) in the positive group, was more than 3 as assessed by both plasma AAA and heel prick blood MS/MS methods, whereas the Phe/Tyr ratio of all the cases in the negative group was less than 3 as determined by both methods.

Statistical Analysis

Statistical analysis was performed using SPSS 24.0 version (SPSS Inc., Chicago, IL). Descriptive statistics were expressed as number, percentage, mean, median and standard deviation. The suitability of the variables to the normal distribution was investigated using visual (histogram and probability charts) and analytical methods (Kolmogorov-Smirnov test). Continuous variables were analyzed by either Student's t-test or Mann-Whitney U test depending on distribution and homogeneity of the

data. In the correlation analysis, the relationship between sequential variables and numerical variables was performed by Kendall's Tau B test. Specificity and sensitivity analyzes were performed using receiver operator characteristic curve (ROC) analysis method. In the ROC analysis, the area under the curve (AUC) values were studied. Pearson chi-square analysis was used to compare ordinal data. Statistical significance level was accepted as $p<0.05$ in all statistical analyses.

Results

Among all patients referred to our clinic from primary health care institutions with suspicion of PMD, 163 patients were included in the study. Of the patients, 53.4% were male and 46.6% were female. Phe levels of 163 patients were examined with heel prick blood MS/MS and plasma AAA methods, and it was found that eight patients (4.9%) had classical PKU (Phe ≥1200 µmol/L), one patient (0.6%) had mild PKU (Phe 600-1200 µmol/L), 51 patients (31.3%) had moderate HPA (Phe 600-120 µmol/L), and 103 patients (63.2%) were PKU negative (Phe <120 µmol/L). Sixty patients with PMD (classical-mild PKU and moderate HPA) were evaluated as positive. Accordingly, the percentage of consanguineous marriage among the parents in the positive group was 78.3% and 36.9% in the negative group (Table 1). The rate of siblings with PKU was 15% in the positive group and 2.9% in the negative group. In the positive group, unexplained sibling death at birth was present in three cases, with one classic PKU and two HPA. There was no unexplained sibling death in the negative group.

The median age at diagnosis was 2 months (range: 0-13 months) in the positive group and it was (range: 0-25 months) in the negative group. The median age at diagnosis in the positive group was statistically significantly lower than the negative group (Table 2). In 68.1% of the cases, heel prick blood samples taken in NSP were resent due to various reasons (Table 2). In the positive group, NSP replicate samples were sent in 41.7% of the cases and this rate was significantly higher in the negative group (83.5%) (Table 2). In the positive group, the number of sample repeats in NSP was statistically significantly lower than the negative group (Table 2). In Kendall's Tau B analysis, there was a positive correlation between the reference age of the patients and the number of repeat heel prick blood screening tests ($r=0.686$, $p<0.0001$). Again, there was a negative correlation between the Phe level measured by FIA method and the number of repeat heel prick blood screening test in Kendall's Tau B analysis ($r=-0.368$, $p<0.0001$). When 193 samples that were resent for various reasons in NSP were examined, it was found that 112 samples (57.7%) were resent because they had a Phe value between 2.1-3.9 mg/dL, 51 samples (26.6%) were taken within the first 24-48 hours of life, and 30 samples (15.7%) were resent due to inappropriate sampling or transfer (Table 2).

While the mean Phe level of the positive group considered as having PMD was 6.06±6.26 mg/dL, the mean Phe level measured by FIA was 2.78±1.13 mg/dL in the negative group without PMD. The mean Phe level measured by FIA method was significantly higher in the positive group than in the negative group. In the MS/MS analysis, the mean Phe level of the positive group was 394.15±561.44 µmol/L and the median Phe/Tyr ratio was 2.67. On the other hand, the mean Phe level in the negative group was 64.10±21.45 µmol/L and the median Phe/Tyr ratio was 0.84. The mean Phe level and median Phe/Tyr ratio in the MS/MS analysis were significantly higher in the positive group than in the negative group (Table 2). Finally, the mean Phe level measured by plasma AAA method in the positive group was 396.62±546.81 µmol/L and the median Phe/Tyr ratio was 2.70. On the other hand, the mean Phe level in the negative group was 61.39±23.59 µmol/L and the median Phe/Tyr ratio was 0.73. The mean Phe level and median Phe/Tyr ratio measured by plasma AAA method were significantly higher in the positive group than in the negative group (Table 2).

ROC curves were plotted to compare FIA, MS/MS and plasma AAA methods used in the diagnosis of 163 patients with suspected PMD (Figure 1). In the FIA method, AUC was 0.814 ($p<0.0001$). Accordingly, sensitivity was 73.3% and specificity was 78.6% for a Phe cut-off value of ≥2.95 mg/dL determined by FIA method, while sensitivity was 46.7% and specificity was 89.3% for a Phe cut-off value of ≥4 mg/dL (Table 3). In the MS/MS method, AUC was 0.964 ($p<0.0001$). Sensitivity and specificity of MS/MS method were 93.3% and 92.2%, respectively, for a

Table 1. Socio-demographic and clinical evaluation of cases

	Positive group (Phe >120 µmol/L), (n=60)			Negative group (Phe <120 µmol/L), (n=103)	[a]p
	Classical PKU, (n=8)	Mild PKU, (n=1)	Moderate HPA (n=51)		
Gender					
Male/Female	6/2	1/-	24/27	56/47	0.739
Age, months					
Mean ± SD (min-max)	4±4.87 (0-13)	1	3.27±3.66 (0-13)	5.40±4.87 (0-18)	-
Consanguineous marriage among the parents, Yes/No	8/-	0/1	39/12	38/65	<0.001
PKU history in sibling, Yes/No	3/5	0/1	6/45	3/100	0.009
Unexplained dead sibling at birth, Yes/No	2/6	0/1	1/49	0/103	-
Plasma AAA Phe level mean ± SD (µmol/L)	1741.06±248.16	713.4	179.52±70.14	61.39±23.59	-
Plasma AAA Phe/Tyr ratio	35.79±14.86	15.51	2.58±1.31	0.77±0.32	-

Phe: phenylalanine, PKU: phenylketonuria, HPA: hyperphenylalaninemia, [a]: the Pearson chi-square test was carried out between the positive and negative groups as 2x2, SD: standard deviation, AAA: amino acid analysis, min: minimum, max: maximum

Phe cut-off value of ≥94.94 µmol/L (Table 3). Finally, when the AUC was 0.987 (p<0.0001), the sensitivity and specificity of plasma AAA method were 95% and 92.2%, respectively, for a Phe cut-off value of ≥101.42 µmol/L (Table 3). While 46 of the 60 patients in the positive group were identified as Phe >120 µmol/L by both heel prick blood MS/MS and plasma AAA method, Phe >120 µmol/L was determined and considered as positive in eight patients by plasma AAA method. It was seen that 14 patients considered to be positive by a single method had Phe/Tyr ratio >3 both in heel prick blood MS/MS analysis and in plasma AAA.

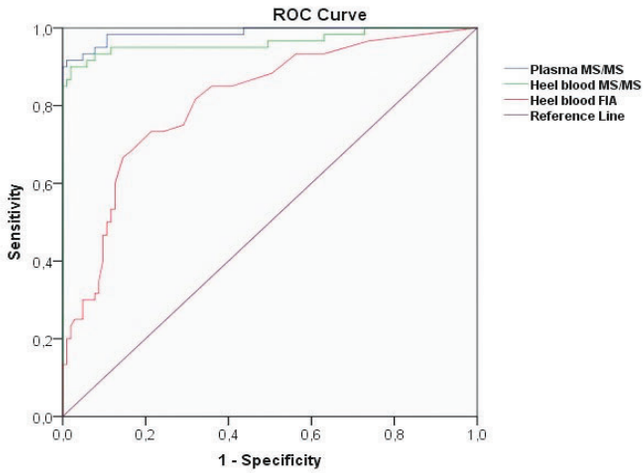

Figure 1. Comparison of ROC analysis results of phenylalanine level measurement methods

ROC: receiver operator characteristic curve, MS/MS: tandem mass spectrometry, FIA: fluorometric immunoassay

Discussion

PKU is one of the common causes of preventable motor and mental retardation, and diet and/or cofactor therapy starting with early diagnosis of PKU has great clinical importance (2). Today, NSPs are performed in USA, Canada and most European countries by MS/MS method (14). The traditional FIA method can also be successfully performed in some eastern European countries, such as Slovenia (15,16). NSPs are applied with various methods in many developing Middle Eastern and Latin American countries as MS/MS method is less used (14). However, in some African and Latin American countries, it is still not possible to carry out an effective NSP nowadays (14). NSP for PKU in Turkey is accomplished with FIA method (17). In our study, eight classic PKU cases and one mild PKU case were detected in Şanlıurfa in 2018. Considering the birth rate of Şanlıurfa province in Turkey in 2018, PKU incidence in our study was found to be 1/7214. As PKU is an AR disease, it is more commonly seen in geographical regions with frequent consanguineous marriages, as in Turkey (2,5,18,19). In our study, it was seen that the consanguineous marriages and PKU histories in siblings were more frequent in positive cases with positive PMD compared to the negative group.

Table 2. Repeat sample reasons and comparison of laboratory results of groups

	Positive group, (Phe >120 µmol/L) (n=60)	Negative group, (Phe <120 µmol/L) (n=103)	p
Age, month			
Median (min-max)	2 (0-13)	4 (0-25)	[a]0.001
Heel prick blood screening repeat count			
Median (min-max)	1 (1-4)	2 (1-4)	[a]<0.0001
Sample again, yes/no	25/35	86/17	[b]<0.0001
Number of samples, n (%)			
- 1st sampling	35 (58.3)	17 (16.5)	-
- 2nd sampling	14 (23.3)	36 (35)	
- 3rd sampling	7 (11.7)	33 (32)	
- 4th sampling	4 (6.7)	17 (16.5)	
The reason for repeat sample n (%) (n=193)			-
- Taken within the first 48 hours of life (duplicated)	21 (11)	30 (15.6)	
- Inappropriate sample	12 (6.3)	18 (9.4)	
- Phe level is between 2.1 and 3.9 mg/dL	9 (4.7)	102 (53)	
FIA Phe (mean ± SD) (mg/dL)	6.06±6.26	2.78±1.13	[c]<0.0001
Heel prick blood MS/MS Phe (mean ± SD) (µmol/L)	394.15±561.44	64.10±21.45	[c]<0.0001
Plasma AAA Phe (µmol/L)	396.62±546.81	61.39±23.59	[c]<0.0001
Heel prick blood MS/MS Phe/Tyr ratio Median (min-max)	2.67 (0.27-52.68)	0.84 (0.14-2.37)	[a]<0.0001
Plasma AAA Phe/Tyr ratio Median (min-max)	2.70 (0.81-64.79)	0.73 (0.14-1.92)	[a]<0.0001

[a]: analyzed by Mann-Whitney U test, [b]: pearson chi-square, [c]: student's t-test, duplicated sample: sample taken within the first 24-48 hours of life, FIA: fluorometric immunoassay, MS: mass spectrometry, Phe: phenylalanine, Plasma AAA: amino acid analysis measurement from venous blood by mass spectrometry method, SD: standard deviation, Tyr: tyrosine, min: minimum, max: maximum

Table 3. Comparison of test methods used for phenylalanine metabolism disorders

	AUC	Cut-off value	Sensitivity (%)	Specificity (%)	p
Heel prick blood FIA Phe (mg/dL)	0.814	2.95 4	73.3 46.7	78.6 89.3	<0.0001
Heel prick blood MS/MS Phe, (µmol / L)	0.964	94.94	93.3	92.2	<0.0001
Plasma AAA Phe, (µmol / L)	0.987	101.42	95	92.2	<0.0001

AAA: amino acid analysis, AUC: area under the ROC Curve, MS/MS: tandem mass spectrometry, Phe: phenylalanine, Tyr: tyrosine

Because delays in PKU can lead to serious mental problems, early diagnosis of the disease is extremely important (2,20). As a matter of fact, when the reasons for delay in NSPs are examined in the past, the most common reason is stated as "not having an effective NSP" (21). In our study, the median age at diagnosis was 2 months in the positive group and 4 months in the negative group. The cases in the positive group were admitted to our clinic at a significantly earlier age than the negative group, but delayed admission was determined in both groups. When the possible causes of clinical delay were examined, considering the flowchart of NSP applied for PMD in Turkey, it was seen that the sample could be obtained from the infant after the fourth time due to repeated and/or inappropriate sampling and/or because Phe levels were detected between 2.1-3.9 mg/dL. In our study, only 31.9% of the cases were referred to our clinic after the first sampling in NSP. Kendall Tau-B correlation analysis showed a positive correlation between age at admission to our clinic and the number of NSP sample repeats. Repeat sample rate was 83.5% in the negative group with lower mean Phe values and 41.7% in the positive group with higher mean Phe values. In the negative group, repeat sample rate was found to be significantly higher than the positive group. As a matter of fact, in Kendall Tau-B correlation analysis, there was a negative correlation between FIA Phe level and number of NSP repeat sample. In our study, it was emphasized that every repeat sample may contribute to delayed diagnosis since the parents should be reached again.

Since clinically late diagnosis of PKU cases can cause serious mental problems, it is thought that it would be useful to investigate the presence and causes of diagnostic delay together with the studies to be performed in different clinical centers. In a study carried out by Heidari et al. (22) in Iran, attention has been drawn to the difficulty faced by physicians to reach the families and to raise awareness in NSP for PKU, inability to implement the screening program entirely in the country as well as the social and financial problems of the families. Despite the effective implementation of NSP in Turkey, problems in reaching families on time and raising awareness are considered to be likely. As a matter of fact, the mean age of the patients with classic PKU who were referred to our clinic after the first screening test was 4±4.87 (range: 0-13) months. While five patients were treated within the first two months, it was seen that the families had low educational and socio-economic status and did not have enough awareness about the importance of the disease in three cases with diagnostic delay. Therefore, it is thought that there may be a delay in the diagnosis due to the socio-economic and educational level of the parents even if the sampling is not repeated.

In our study, it was determined that a total of 193 repeat samples were sent by primary health care institutions in NSP. When the reasons of repeat samples were examined, the most frequent reason was Phe levels being in the range of 2.1-3.9 mg/dL and duplicate sampling. It is thought that both causes may be directly related to the specificity and sensitivity of the FIA method used in the screening. In fact, blood Phe levels were also measured by simultaneous plasma AAA and heel prick blood MS/MS methods in all cases directed to our clinic. As a result of the ROC analysis performed for the FIA method, although the FIA method used in NSP had a certain specificity and sensitivity, it was found to be inadequate (AUC=0.814). The MS/MS method was found to be more specific and sensitive than the FIA method (AUC=0.964) (Figure 1). Today, heel prick blood MS/MS method is used together with plasma AAA in the clinical follow-up of patients with PKU (2). Although the most specific and sensitive test was plasma AAA as expected in our study, heel prick blood MS/MS method was also found to be able to perform highly effective analysis (Table 2).

Conclusion

Despite the fact that the first screening tests of the cases were performed with FIA method at the appropriate time in NSP in Turkey, patients with suspected PMD as a result of screening were found to referred late to the pediatric metabolic disease clinic. Moreover, it was thought that socio-economic and educational status of the families could contribute to the clinical delay in cases where repeat samples were not sent. Depending on the socio-economic status and educational level, the presence of family-related diagnostic delay may be considered as a limitation of our study. Further studies in various centers are needed. In our study, MS/MS has been shown to be a more effective method than FIA. It is thought that the use of MS/MS instead of FIA in the NSP for the PMD may be effective in avoiding the diagnostic delay.

Ethics Committee Approval: This study conformed to the principles of the 2008 Declaration of Helsinki and was approved by the Local Ethics Committee of Harran University Faculty of Medicine, Turkey (decision no: Session 5, 19747, date: 03.05.2018).

Informed Consent: Before the study, written informed consent was obtained from the parents of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

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The Relationship Between Disease Activity, Vegf, E-selectin Levels and Arterial Stiffness in Patients with Rheumatic Diseases

Romatizmal Hastalığı Bulunan Hastalarda Arteriyel Sertlik, Vegf ve E-selektin Düzeyi ile Hastalık Aktivitesi Arasındaki İlişki

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ABSTRACT

Introduction: The endothelial damage, changes in vascular permeability and plaque formation are caused by the effects of cytokines and chemokines that plays role in chronic inflammation in rheumatoid arthritis (RA) and ankylosing spondylitis (AS). It has been reported that arterial stiffness and the level of cell adhesion molecules are affected by inflammation. In this study, we aimed to determine the relationship between vascular endothelial growth factor (VEGF), E-selectin, arterial stiffness and disease activity in patients with rheumatic diseases.

Methods: Thirteen patients diagnosed with AS, 28 patients diagnosed with RA and 30 healthy controls were included in the study. Arterial stiffness, VEGF, E-selectin, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were evaluated in all patients and healthy controls. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Disease Activity Score-28 (DAS-28) were calculated in patients with rheumatic diseases. The level of serum VEGF and E-selectin were determined by ELISA, and arterial stiffness was measured by oscillometric method. The data were statistically evaluated by using Student t-test, Mann-Whitney U Test and Wilcoxon test.

Results: DAS-28, BASDAI, ESR and CRP levels were significantly decreased on the 3rd month of treatment in all patients ($p<0.001$). VEGF and E-selectin levels increased, and pulse wave velocity (PWV) and augmentation index (Alx) parameters decreased with treatment. While the level of PWV did not change, Alx decreased on the 3rd month of non- tumor necrosis factor treatment in RA patients.

Conclusion: DAS, ESR and CRP were decreased with the reduction of inflammation in RA and AS patients with treatment. PWV and Alx of arterial stiffness parameters decreased after 3 months of treatment, but it did not reach statistical significance. Arterial stiffness and cardiovascular risk are expected to reduce significantly with ongoing treatment process.

Keywords: Rheumatoid arthritis, ankylosing spondylitis, arterial stiffness, vascular endothelial growth factor, E-selectin, disease activity

ÖZ

Amaç: Romatoid artrit (RA) ve anklozan spondilitte (AS) endotel hasarı, damar geçirgenliğinde değişim, plak oluşumu kronik enflamasyonda rolleri olan sitokin ve kemokinlerin etkisi ile olmaktadır. Yapılan çalışmalarda enflamasyon düzeyi ile arteryel sertlik ve hücre adezyon molekül miktarında değişim olduğu bildirilmiştir. Bu çalışmada, romatizmal hastalığı olan hastalarda vasküler endotel büyüme faktörü (VEGF), E-selectin, arteriyel sertlik ve hastalık aktivitesi arasındaki ilişkiyi belirlemeyi amaçladık.

Yöntemler: Çalışmamıza AS tanılı 13 hasta, RA tanılı 28 hasta ve 30 sağlıklı kontrol dahil edildi. Tüm hasta ve sağlıklı kontrol grubunda arteriyel sertlik, VEGF ve E-selektin, eritrosit sedimentasyon hızı (ESH) ve CRP düzeylerine bakıldı. Romatizmal hastalığı bulunan grupta hastalık aktivite göstergeleri olan Banyo Ankilozan Spondilit Hastalığı Aktivite İndeksi (BASDAİ) ve DAS-28 skorları hesaplandı. Serum VEGF ve E-selektin ölçümü ELISA yöntemi ile, arteriyel sertlik ölçümü ise osilometrik metotla bakıldı. Elde edilen veriler Student t-testi, Mann-Whitney U testi ve Wilcoxon testi ile istatistiksel olarak karşılaştırıldı.

Bulgular: Tüm hasta gruplarında tedavi sonrasında 3. ayda DAS-28, BASDAİ skorları, ESH ve CRP düzeylerinde anlamlı bir azalma olduğu gözlenmiştir ($p<0,001$). Tedavi ile birlikte VEGF ve E-selektin düzeylerinde artış, nabız dalga hızı (NDH) ve artırma indeksi (Alx) parametrelerinde ise azalma olduğu gözlenmiştir. Non-tümör nekroz faktörü tedavisi alan RA hastalarında NDH düzeyi değişmezken, Alx düzeyi tedavinin 3. ayında azalmıştır.

Sonuç: RA ve AS hastalarında tedavi ile birlikte inflamasyonun azalması hastalık aktivite skorunda, ESH, CRP değerlerini azaltmaktadır. Arteryel sertlik parametrelerinden NDH ve Alx'i tedavinin 3. ayında azalma ile birlikte anlamlı düzeye ulaşmamıştır. Devam eden tedavi sürecinde arteryel sertliğin ve kardiovasküler riskin anlamlı düzeyde azalacağı düşünülmektedir.

Anahtar Kelimeler: Romatoid artrit, ankilozan spondilit, arteriyel sertlik, vasküler endotelyal growth faktör, e-selektin, hastalık aktivitesi

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Introduction

Rheumatic diseases such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS) can cause morbidity with extra-articular involvement. Various cytokines involved in RA pathogenesis lead to synovial cell proliferation, expression of endothelial adhesion molecules and collagen production. Rapid atherosclerosis and increased risk of cardiovascular disease are also mentioned in AS and RA patients, and inflammatory processes have an important role (1-3). Atherosclerosis is more common in RA patients than in the general population (1,2). Arterial stiffness is a condition that leads to decreased expansion capacity of the vessels in response to pressure changes. Arterial stiffness is an independent risk factor for cardiovascular disease and can be used as an indicator of subclinical cardiac injury (4,5).

It is known that angiogenesis and angiogenetic factors play a role in the development of rheumatic diseases. Vascular endothelial growth factor (VEGF) is a potent angiogenic factor and oversecretion can lead to the development of many pathological conditions such as atherosclerosis, age-related macular degeneration, RA and diabetic retinopathy (6,7). E-selectin (CD62E), a cell adhesion molecule expressed in endothelial cells, plays a mediator role in the interaction between vascular endothelium and circulating leukocytes in many pathophysiological conditions such as inflammation, infection and cancer metastasis. This interaction is an important part of various pathophysiological processes such as inflammation and atherosclerosis (8).

In this study, we aimed to present the relationship between disease activation, arterial stiffness and changes in the level of cell adhesion molecules in patients diagnosed with RA and AS.

Methods

Forty-one patients (28 RA and 13 AS) (BASDAI>5 and DAS28>5.1) with rheumatic disease and 30 healthy controls were included in the study. AS was diagnosed according to the axial spondyloarthritis classification criteria and RA was diagnosed using 2010 ACR/EULAR 2010 classification criteria (9,10). Regarding healthy controls, subjects with rheumatologic or other concomitant conditions (hypertension, diabetes mellitus, chronic renal failure, liver disease, hypo-hyperthyroidism, chronic obstructive pulmonary disease, peripheral arterial disease, coronary artery disease, malignancy) were excluded from the study. Demographic and laboratory features of the patients were recorded. Informed consent form was signed by all participants. Adnan Menderes University Faculty of Medicine, Non-invasive Clinical Research Ethics Committee (decision no: 2015/739, date: 25.12.2015).

VEGF and E-selectin were measured with human ELISA kit (SunRed Biological Technology, Shanghai, China). Standard solutions of 75, 150, 300, 600, 1200 ng/L were prepared using the stock standard solution in the kit. 50 µL control, standard and samples were placed in antibody-coated wells in the plate, respectively. 50 µL chromogen/substrate solution was placed in all wells and kept at 37 °C for 10 minutes without light. ELISA (DAR 800, Diagnostic Automation, California, USA) was automatically calculated at 450 nm with the help of standard solutions prepared using a microplate reader.

Arterial stiffness was measured by using a single cuffed oscillometric "arteriograph device". Patients were rested for at least 5 minutes before measurement and were asked not to smoke or drink caffeinated beverages at least 30 minutes before. The cuff of the device was adjusted to fit in the position and at the heart level, and 3 consecutive measurements were taken automatically for 30 seconds. The augmentation index (Alx) and pulse wave velocity (PWV) levels were measured by a computer.

Statistical Analysis

The data were evaluated using SPSS version 22 statistical program. Descriptive data were expressed as mean, standard deviation, median, minimum, maximum and percentage. The obtained data were statistically compared with Student's t-test, Mann-Whitney U test and Wilcoxon test. A p value less than 0.05 was considered statistically significant.

Results

Forty-one patients and 30 healthy controls were included in this study. There were 28 patients (68.3%) diagnosed with RA and 13 patients (31.7%) diagnosed with AS. Fourteen patients (34.1%) were male and 27 (65.9%) were female. The mean age was 51.0±12.1 years (range: 27-74 years). In the control group, 10 subjects (33.3%) were male and 20 (66.7%) were female. The mean age was 51.9±10.8 (range: 29-71 years). The mean body mass index (BMI) of the patients was 30.7±6.5, while the mean BMI of the control group was 29.5±3.9. There was no statistically significant difference between patients and control groups in terms of age and BMI (p>0.05). Twenty-eight patients were using anti-tumor necrosis factor (anti-TNF) and the remaining 13 patients were using non-TNF biological agents.

A statistically significant decrease in DAS-28, BASDAI, erythrocyte sedimentation rate (ESR) and C-Reaktif Protein (CRP) levels were observed in all patients after 3 months of treatment. The pre- and post-treatment median levels of E-selectin (359.5 ng/L vs 386.5 ng/L, p=0.311) and VEGF (956.5 ng/L vs 1093.5 ng/L, p=0.046) in RA patients are shown in Table 1. The post-treatment median levels of E-selectin (414.0 ng/L vs 393.0 ng/L, p=0.724) and VEGF (1035.0 ng/L vs 1028.0 ng/L, p=0.422) were increased in the AS patients (Table 1). Despite a slight decrease in E-selectin levels and a slight increase in VEGF levels after treatment, there was no

Table 1. Serum E-selectin and vascular endothelial growth factor levels in rheumatoid arthritis and ankylosing spondylitis patients

	Rheumatoid arthritis			Ankylosing spondylitis		
	Pre-treatment (ng/L)	Post-treatment 3rd month (ng/L)	p-value	Pre-treatment (ng/L)	Post-treatment 3rd month (ng/L)	p-value
E-selectin	359.5	386.5	0.311	393.0	414.0	0.724
VEGF	956.5	1093.5	0.046	1028.0	1035.0	0.422

VEGF: vascular endothelial growth factor

Table 2. Arterial stiffness parameters in rheumatoid arthritis and ankylosing spondylitis patients

	Rheumatoid arthritis			Ankylosing spondylitis		
	Pre-treatment (ng/L)	Post-treatment 3rd month (ng/L)	p-value	Pre-treatment (ng/L)	Post-treatment 3rd month (ng/L)	p-value
Alx	28.8±9.0	26.7±10.7	0.217	27.4±8.2	27.7±10.9	0.927
PWV	8.0±1.5	7.9±1.6	0.553	6.4±0.9	6.3±0.8	0.679

Alx: augmentation index, PWV: pulse wave velocity

statistically significant difference in E-selectin and VEGF levels between anti-TNF or non-TNF treatment in both AS and RA patients. A statistically significant difference was not detected in the parameters of Alx and PWV before and after 3 months of treatment in RA and AS patients (Table 2).

Discussion

VEGF is an angiogenic cytokine that plays a role in angiogenesis, and also stimulates the migration and proliferation of endothelial cells (6). Serum and synovial fluid VEGF levels in RA patients were found to be higher than patients with osteoarthritis systemic lupus erythematosus and scleroderma, and healthy subjects (11,12). Serum VEGF levels were found to be higher in AS patients compared to healthy controls (13). In our study, we did not find any significant difference between AS and healthy control group in terms of serum VEGF level. In our study, VEGF levels were significantly lower in the patient groups than in the control group, whereas there was no statistically significant difference between AS and RA patients.

Serum VEGF levels have been reported to decrease in patients with AS treated with infliximab (14). Selaas et al. (15) found a decrease in VEGF levels on the 3rd, 6th and 12th months in RA patients treated with infliximab. In our study, VEGF levels were increased on the 3rd month of treatment, but there was no statistically significant difference compared to baseline. Positive correlation between VEGF levels, CRP and BASDAI was reported in 201 AS patients treated with infliximab (14). In our study, AS patients showed a significant decrease in BASDAI, CRP, and ESR values 3 months after treatment. On the other hand, there was no significant difference in VEGF levels compared to pre-treatment levels.

E-selectin is a cell adhesion molecule expressed on the endothelial surface in response to proinflammatory cytokines (8). E-selectin levels were investigated and no significant differences were found between the control group and AS patients (16). In a study by Baeten et al. (17), 21 patients with spondyloarthropathy were treated with anti-TNF therapy and it was reported that E-selectin levels remained unchanged in synovial examination 12 weeks after treatment. It was reported that there was no change in E-selectin and VEGF levels at the end of 14 weeks in RA patients receiving TNF-alpha (α) blockade (18). In our study, E-selectin levels did not differ significantly in both AS and RA patients compared with control group. The cause of subclinical atherosclerosis may be due to platelet parameters, which are another important component in the atherosclerotic process because AS patients have normal endothelial function (19). We also found no significant difference in E-Selectin levels between all patients with rheumatic disease and control group.

Arterial stiffness is a structural change in the arterial wall caused by increase in PWV. PWV is widely accepted as an accurate and non-invasive method for assessing arterial stiffness. Even though PWV is a direct measurement of arterial flexibility, Alx is a more complex parameter of vascular elasticity and peripheral resistance. PWV and AIx are considered independent predictors of major cardiovascular events and all-cause mortality (20). Studies have shown that arterial stiffness is increased in RA patients compared to the control group; this may contribute to increased cardiovascular risk by accelerating the atherosclerotic process (21,22). In our study, there was no significant difference in PWV and Alx parameters between RA patients and control group. Even though we observed a decrease in PWV and Alx parameters in all patient groups on the 3rd month of treatment. This decrease was not significant compared to the baseline.

We found no significant difference in the levels of Alx and PWV in RA patients treated with infliximab compared to control group. In another study comparing etanercept with methotrexate, Alx was measured on the 2nd and 4th month. It was found that Alx improved in the etanercept group and remained unchanged in the methotrexate group (23). Different results obtained from different studies suggest that these may be related to the lack of direct measurement of arterial stiffness, differences in the reflectance of peripheral in RA patients and also other poorly understood concomitant factors (22).

There are inconsistent results in the literature regarding arterial stiffness in AS patients compared with the control group. In one study, no significant difference was found in arterial stiffness between AS patients and the control group. Avram et al. (24) compared 24 AS patients with 24 controls and found that Alx and PWV levels were significantly higher in the patient group. In our study, PWV levels were significantly lower in patients with AS than in the control group. On the other hand, there was no significant difference in Alx levels between the control group and AS patient group. In AS patients, Alx value increased from 27.4±8.2 to 27.7±10.9 on the 3rd month of treatment. However, this increase was not statistically significant.

Although systemic inflammation is the primary cause of increased atherosclerosis in AS patients, the role of inflammation in stiffness of arteries is still unclear (24). When we compared Alx and PWV levels in all patient groups with the control group, we did not find any significant difference. In all patient groups, there was a significant decrease in disease activity score, sedimentation and CRP values at 3-month values after biological agent treatment. Despite the difference in Alx and PWV levels with biochemical treatment, it was not statistically significant. The main limitation of this study is that we have no information about the long-term effect of anti-TNF agents on these parameters. Another limitation is the small sample size.

Conclusion

In our study, there were no significant difference in the levels of E-selectin and VEGF, AIx and PWV parameters in AS patients treated with biological agents compared with pre-treatment levels. The comparison between RA and AS patients showed no significant difference in terms of VEGF, E-selectin, and also PWV and Alx. It was shown that both PWV and Alx values decreased insignificantly in RA patients who received biological treatment. PWV levels remained unchanged in RA patients receiving non-TNF-α biotherapy, but Alx levels decreased in the 3rd month of treatment. Reduction of the inflammatory process with treatment is thought to cause a decrease in the arterial stiffness, which is an important risk factor for cardiovascular diseases.

Ethics Committee Approval: Adnan Menderes University Faculty of Medicine, Non-interventional Clinical Research Ethics Committee (decision no: 2015/739).

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Investigation of the Relationship between Blood Gas Parameters and Thirty-day Mortality in Elderly Patients Diagnosed with Sepsis

Sepsis Ön Tanılı Yaşlı Hastalarda Kan Gazı Parametreleri ve Otuz Günlük Mortalite Arasındaki Ilişkinin Araştırılması

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ABSTRACT

Introduction: Although sepsis is one of the most important causes of death in hospitalized patients, information on early predictive factors for predicting mortality and morbidity is limited. The aim of this study was to determine the relationship between defined arterial blood gas parameters and 30-day mortality in adult patients aged 65 years and older who were admitted to the emergency department and diagnosed with sepsis.

Methods: Arterial blood gas parameters of patients older than 65 years who were diagnosed with sepsis in the emergency department during the 5-month period between March and August 2017 were analyzed retrospectively. The relationship between pH, lactate, anion gap, bicarbonate and base-excess and 30-day mortality was analyzed.

Results: A total of 103 elderly patients with sepsis were included in the study. Fifty-eight patients (56.3%) were female and the mean age was 77.74±8.45 years (range: 65-99 years). Twenty-two patients (21.4%) died within 30 days. The admission "Quick Sepsis-related Organ Failure Assessment" values were found to be 2 or more in 32 patients (31.1%). Bicarbonate (p=0.001), lactate (p<0.001), anion gap (p=0.007) and base-excess (p=0.001) values were found to be significantly associated with 30-day mortality.

Conclusion: In our study, we found that the levels of lactate, bicarbonate, anion gap and base-excess in arterial blood gas were associated with 30-day mortality in elderly patients diagnosed with sepsis. These parameters should be closely monitored in septic patients. Monitoring of these parameters may help early clinical decision-making in emergency department patients with sepsis and may affect the outcome of sepsis.

Keywords: Blood gas analysis, mortality, sepsis, elderly patient

ÖZ

Amaç: Sepsis hastanede yatan hastalarda en önemli ölüm nedenlerinden biri olsa da mortalite ve morbiditeyi öngörmeye yönelik erken prediktif faktörlerle ilgili bilgiler sınırlıdır. Bu çalışmada acil servise başvuran ve sepsis ön tanılı 65 yaş ve üzeri erişkin hastalarda tanımlanmış arteriyel kan gazı parametreleriyle 30 günlük mortalite arasındaki ilişkinin belirlenmesi amaçlandı.

Yöntemler: Mart-Ağustos 2017 tarihleri arasındaki 5 aylık süreçte acil serviste sepsis ön tanısı konulmuş 65 yaş üzeri hastaların arteriyel kan gazı parametreleri retrospektif olarak incelendi. Kan gazı parametrelerinden pH, laktat, anyon açığı, bikarbonat ve baz açığı ile 30 günlük mortalite arasındaki ilişki analiz edildi.

Bulgular: Sepsis tanılı 103 yaşlı hasta çalışmaya dahil edildi. Hastaların 58'i (%56,3) kadındı ve yaş ortalaması 77,74±8,45 yıl (aralık: 65-99) olarak saptandı. Hastaların 22 (%21,4) tanesi 30 gün içerisinde öldü. Başvuru "Hızlı Sepsisle İlgili Organ Yetmezliği Değerlendirmesi" değerleri 32 (%31,1) hastada 2 veya daha üzeri olarak saptandı. Parametrelerden bikarbonat (p=0,001), laktat (p<0,001), anyon açığı (p=0,007) ve baz açığı (p=0,001) değerlerinin 30 günlük mortalite ile anlamlı olarak ilişkili olduğu bulundu.

Sonuç: Çalışmamızda 65 yaş ve üzeri sepsis ön tanılı hastalarda arteriyel kan gazında saptanan laktat, bikarbonat, anyon açığı ve baz fazlalığı düzeylerinin 30 günlük mortalite ile ilişkili olduğunu saptadık. Septik hastalarda bu parametreler yakından izlenmelidir. Bu parametrelerin izlenmesi, sepsis ön tanılı acil servis hastalarında erken klinik karar almaya yardımcı olabilir ve sepsis sonucunu etkileyebilir.

Anahtar Kelimeler: Kan gazı analizi, mortalite, sepsis, yaşlı hasta

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Introduction

Sepsis is a life-threatening organ dysfunction syndrome resulting from an inappropriate host response to infection (1-3). Sepsis and septic shock, which affects millions of people around the world every year and cause the death of one in four people, is an important health problem (4,5). Early diagnosis and initiation of appropriate treatment in the first hours after sepsis improve outcomes. Especially in the last guidelines, dynamic measurements instead of static are recommended for evaluation of response to fluid treatment and determination of subsequent fluid treatment. Sepsis-induced hypoperfusion is manifested by acute organ dysfunction and/or ± a decrease in blood pressure and an increase in serum lactate levels. Although serum lactate level is not an indicator of direct tissue perfusion, increased lactate levels have been reported to be associated with poor outcome regardless of source (6,7). When the studies evaluating lactate-guided resuscitation in septic shock patients are examined, it is also known that there is a significant decrease in mortality in lactate-guided resuscitation compared to resuscitation without lactate monitoring (8,9). The use of lactate is also recommended in the follow-up of patients' response to treatment in sepsis. Blood lactate levels can be evaluated in arterial or venous blood gas examinations in many health facilities and blood gas examinations are used almost routinely in sepsis patients.

Population over 65 years of age is increasing day by day in developing and developed countries and in parallel with this; the number of emergency service admissions is increasing in this age group. Elderly patients have the highest hospitalization rate, the longest hospital stay, and the highest resource utilization rate compared to other age groups (10). Due to the high frequency of atypical presentations, weakened physiological responses, complex medical backgrounds and the presence of chronic diseases, these patients have higher mortality during hospitalizations compared to all other age groups (11).

Although sepsis is one of the most important causes of death in hospitalized patients, information on early predictive factors for predicting mortality and morbidity is limited. The aim of this study was to determine the relationship between 30-day mortality and defined arterial blood gas parameters in adult patients aged 65 years and older who were admitted to the emergency department with the diagnosis of sepsis.

Methods

This study was planned as retrospective, cross-sectional and observation-based in our emergency department. After the approval of the İstanbul Training and Research Hospital Local Ethics Committee (decision no: 2011-KAEK-50), five-month data between March 1, 2017 and August 1, 2017 were retrospectively reviewed. Patients who were 65 years or older and were admitted to the emergency department within this date range and who underwent blood gas analysis in the emergency room were detected using the laboratory computer system. The medical files of these patients were examined using the infection-related ICD diagnostic codes and the patients with a prediagnosis of sepsis constituted the study cohort. According to the Third International Consensus, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (1). In our study, patients diagnosed with sepsis by clinician were confirmed in each case using Third International Consensus definitions. Quick Sepsis-related Organ Failure Assessment (qSOFA) score was calculated retrospectively for patients with registered respiratory rate, systolic blood pressure (SBP), and consciousness on admission to the emergency department. Patients with a score of 2 or more were evaluated as sepsis at the emergency department and patients with a score of less than 2 were included in the study if their qSOFA score increase to 2 or more within 24 hours after verifying with respiratory rate, SBP and consciousness. Among the patients who were clinically thought to have sepsis, patients who were 65 years or older and who had arterial blood gas analysis within the first 4 hours in the emergency department with available results in the laboratory software system were selected for the study. Patients under the age of 65 years, patients with qSOFA score less than two in the first 24 hours, patients without arterial blood gas analysis within the first 4 hours or patients with no blood gas analysis due to technical reasons were excluded from the study. Considering these criteria, 103 patients were included in the study. The demographic, laboratory and clinical data of the patients were retrospectively reviewed and recorded from the hospital software system. The patients were asked whether they were alive on the 30th day either by screening from the population registry system or by telephone. The relationship between pH, bicarbonate, lactate, anion gap and base-excess and 30-day mortality was investigated. The study was carried out in accordance with the Helsinki Declaration with the data obtained from the patient file and laboratory software system.

SPSS 16.0 was used for statistical analysis (SPSS Inc., Chicago, IL, USA). The normality of continuous variables was evaluated by Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as number and percentage. Chi-square test was used for comparisons between categorical variables. Student's t-test was used for comparison of the normally distributed parameters and Mann-Whitney U test was used for the comparison of non-normally distributed parameters. The receiver operating characteristic (ROC) curve was plotted to calculate the probability of predicting mortality and the area under the curve was calculated. Statistical significance was accepted as $p<0.05$.

Results

The mean age of 103 patients included in the study was 77.74±8.45 years (range: 65-99 years). Fifty-eight patients (56.3%) were female and 45 (43.7%) were male. Thirty-two patients (31.1%) had a qSOFA score of 2 or more on admission to the emergency department and the remaining 71 patients (68.9%) had a qSOFA score of 2 or more within 24 hours although they had a score less than 2 on admission. On admission to the emergency department, 41 patients (39.8%) had a Glasgow Coma scale score of 13 or less, 23 (22.3%) had SBP of 100 mmHg and less, and 20 (19.4%) had respiratory rate of 22 and above per minute. Of the 103 patients included in the study, 22 (21.4%) died within 30 days. On admission, median respiratory rate was 15/min, mean SBP was 131.6±30.7 mmHg, mean diastolic blood pressure was 70.6±14.0 mmHg, and mean arterial pressure 90.9±18.2 mmHg, mean heart rate was 88.7±17.5 beats/minute, mean body temperature was 36.8±1.0 °C and mean peripheral oxygen saturation was 94.0±4.7 (Table 1). When the sources of infection were examined, it was found that 49 (47.6%)

were due to respiratory system, 23 (22.3%) were due to urinary system and the remaining 31 (30.1%) were due to other infections.

In all patients, the mean lactate was 2.2±1.6 mmol/L (range: 0.1-7.7), base-excess was 1.5±4.9 mmol/L (range: -17.3-23.4), anion gap was 1.9±4.8 mmol/L (range: -20.4-17.1), bicarbonate was 25.8±5.0 mmol/L (range: 9.5-48.2), ionized calcium was 1.12±0.08 mmol/L (range: 0.62-1.33) and pH was 7.41±0.68 (range: 7.18-7.61). Lactate ($p<0.001$) and anion gap ($p=0.007$) values were higher, and base-excess ($p=0.001$) and bicarbonate ($p=0.001$) values were lower in the mortality group and these differences were statistically significant. Ionized calcium values were found to be significantly higher in the mortality group, but this value had no clinical significance. There was no significant correlation between pH and mortality ($p=0.913$) (Table 2).

Regarding ROC curve and areas under the curve, lactate (0.825), bicarbonate (0.742), base-excess (0.733) and anion gap (0.687) were found to predict mortality. The ROC curves of the parameters are shown in Figure 1.

Discussion

Sepsis is defined as a life-threatening organ dysfunction caused by an abnormal host response to infection and is one of the leading causes of death. The prevalence of sepsis is increasing in the whole world. Although there are many factors contributing to this increase, the increase in the proportion of the elderly population plays an important role in this and mortality is higher in this age group. Blood gas assessment is almost routinely used in the management of patients with sepsis. The aim of this study was to determine the relationship between defined arterial blood gas parameters and 30-day mortality.

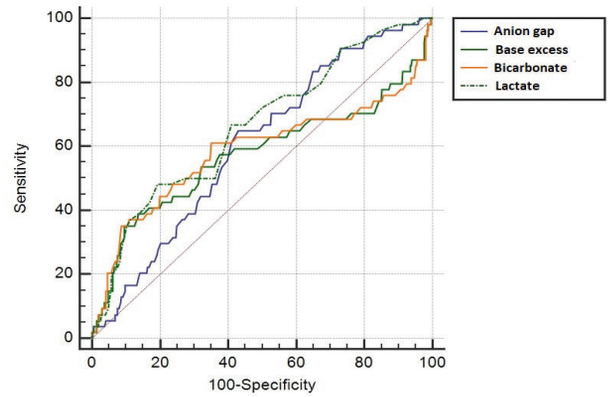

Figure 1. ROC analysis of defined parameters for predicting 30-day mortality
ROC: receiver operating characteristic

Table 1. Comparison of the cases included in the study with all variables according to mortality

Variable	Study cohort (n=103)	30-day mortality		p
		Yes (n=22)	No (n=81)	
Age, Mean ± SD	77.74±8.45	79.86±1.44	77.16±0.98	0.147
Female, n (%)	58 (56.3%)	12 (20.7%)	46 (79.3%)	0.519
Male, n (%)	45 (43.7%)	10 (22.2%)	35 (77.8%)	
Admission qSOFA ≥2, n (%)	32 (31.1%)	8 (25%)	24 (75%)	0.220
24th hour qSOFA ≥2, n (%)	71 (68.9%)	14 (19.7%)	57 (80.3%)	
GCS score ≤13, n (%)	41 (39.8%)	12 (29.3%)	29 (70.7%)	0.090
SBP mmHg, Mean ± SD	131.6±30.7	127.1±6.4	132.9±3.4	0.267
DBP mmHg, Mean ± SD	70.6±14.0	70.6±3.3	70.5±1.5	0.587
MAP mmHg, Mean ± SD	90.9±18.2	89.6±4.0	91.3±2.0	0.385
Heart rate/min, Mean ± SD	88.7±17.5	89.9±3.9	88.4±1.9	0.834
Respiratory rate/min, median (IQR)	15 (13-17)	14.5 (12-19)	15 (13-16.5)	0.874
Body temperature °C, Mean ± SD	36.8±1.0	36.6±0.2	36.9±0.1	0.301
SpO2 %, Mean ± SD	94.0±4.7	93.4±1.2	94.2±0.5	0.926

SD: standard deviation, qSOFA: Quick Sepsis-related Organ Failure Assessment, GCS: Glasgow Coma scale, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, IQR: interquartile range, SpO2: peripheral oxygen saturation

Table 2. Relationship between blood gas parameters and 30-day mortality

Variable, Mean ± SD	Study cohort (n=103)	30-day mortality		p
		Yes (n=22)	No (n=81)	
Lactate, mmol/L	2.2±1.6	4.0±0.4	1.8±0.1	<0.001
Base-excess, mmol/L	1.5±4.9	-1.1±0.8	2.2±0.6	0.001
Anion gap, mmol/L	1.9±4.8	4.0±0.9	1.3±0.5	0.007
Bicarbonate, mmol/L	25.8±5.0	22.8±0.8	26.6±0.6	0.001
Ionized calcium, mmol/L	1.12±0.08	1.13±0.02	1.12±0.01	0.001
pH	7.41±0.68	7.42±0.02	7.41±0.01	0.913

SD: Standard Deviation

Respiratory and genitourinary tract infections are the most common sepsis foci in the elderly (12). In our study, respiratory tract infections were found to be the most common (47.6%) etiologic cause in accordance with the literature. Increased awareness of sepsis and significant improvements in diagnosis and management have led to improvements in outcomes in all age groups. However, despite all developments, the overall mortality rate remains high in elderly adults. In-hospital mortality rate in patients 65 years and older is reported to be 30-60% in the literature and this rate increases to 40-80% in patients 80 years and older (4,13,14). In our study, 30-day mortality was 21.4%. This result may be due to the fact that sepsis cases with less severe clinical severity were retrospectively included in our study. When our cohort was examined, it was seen that the number of cases with a qSOFA score of 2 or more on admission was 32 (31.1%).

Sepsis may cause respiratory failure, acute kidney damage, organ dysfunction and metabolic acidosis associated with shock and multiple organ failure. Therefore, assessment and careful management of acid-base status is often necessary (4,15). Blood gas analysis is not only used for this, but also it has the advantages of performing analyzes such as sodium, potassium, glucose, hemoglobin, lactate, ionized calcium and ionized magnesium on the sample taken. It has been well defined that serum lactate levels are predictors of mortality in trauma and sepsis (16-18), and the importance of lactate in the treatment of sepsis is often emphasized and it has been also stated that some treatment approaches have to be made dependent on lactate levels (19). In our study, higher serum lactate levels were found in patients who died due to sepsis. Although it has been proved that serum lactate levels may help to manage septic shock treatment and the necessity of routine study is recommended, lactate level may not be evaluated routinely in all centers due to lack of technical infrastructure. In these cases, anion gap has traditionally been used as an indicator for lactate levels. Bakker et al. (20) reported that high anion gap is a good but not perfect indicator for high lactate levels in emergency department patients at risk of sepsis. In our study, higher anion gap levels were found in patients with sepsis who died on the 30th day compared to the survivors.

Shock is best described as organ dysfunction resulting from inadequate tissue perfusion due to inadequate oxygen delivery. Inadequate oxygen supply to tissues often causes metabolic acidosis, and therefore metabolic acidosis is a common finding in patients with septic shock. In many studies, it has been reported that metabolic acidosis evaluations in the first days of hospitalization in patients with septic shock are associated with good clinical outcomes (21). Carrara et al. (22) reported that there was a significant association between decreased blood pH and oxygenation and mortality in patients with severe sepsis and septic shock (22). There are also studies reporting that neither bicarbonate, lactate and base deficit nor regional perfusion endpoints are superior to each other in the diagnosis of shock (23). In our study, low bicarbonate level was found to be significantly associated with mortality, but we found no significant relationship between blood pH and mortality.

Base-excess represents the additional base amount that should be added to one liter of blood to normalize the pH. It has been reported that base-excess is a predictor of morbidity and mortality in critically ill and trauma patients (24,25). Similarly, in our study, the base-excess level was found to be lower in patients who died.

We had some limitations in the study. It was a single-center, retrospective study and the sample size was relatively small. Intensive care treatment processes (inotropic initiation, antibiotherapy, interventions, etc.) in some sepsis patients could not be monitored and recorded due to referral to other centers for intensive care unit stay. When we examined the reports in the literature in our age group, our mortality values were lower. This may be due to diagnosis-related deficiencies, or to the fact that the selected patients were clinically better patients with sepsis.

Conclusion

Regardless of clinical severity, the majority of sepsis patients are first examined in the emergency department. Therefore, it is important for emergency physicians to accurately evaluate disease severity and mortality risk when confronted with these patients. In our study, we demonstrated that the levels of lactate, bicarbonate, ionized calcium, anion gap, and base-excess in the arterial blood gas were associated with 30-day mortality in patients aged 65 years and older. These parameters should be closely monitored in septic patients. Monitoring of these parameters may help early clinical decision-making in emergency department patients with sepsis and may affect the outcome of sepsis.

Ethics Committee Approval: After the approval of the İstanbul Training and Research Hospital Local Ethics Committee (decision no: 2011-KAEK-50), five-month data between March 1, 2017 and August 1, 2017 were retrospectively reviewed.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

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Overview of Patients with Multiple Primary Tumors During Eighty-four Months Follow-up: A Single Center Experience

Seksen-dört Aylık İzlemde Çoklu Primer Tümör Tanılı Hastalarımıza Bakış: Tek Merkez Deneyimi

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ABSTRACT

Introduction: Advances in oncological diagnosis and treatment increase survival and remission of the disease. However, prolonged survival also increases the likelihood of developing second primary malignancies. The aim of this article was to evaluate whether the second primary tumor is associated with the first primary tumor and to determine the survival time in patients diagnosed with cancer, treated, and followed-up, and to make recommendations about the follow-up of these patients.

Methods: Patients who were admitted to the İstanbul Training and Research Hospital, Clinic of Radiation Oncology and Medical Oncology, between January 2011 and December 2017, and who had a follow-up of more than 6 months were retrospectively reviewed. Of 9892 patients, multiple primary tumors (MPT) were detected in 121 patients. The origin of tumor, occurrence time, gender, age, metastasis and survival rates of the patients were investigated. Data were collected using Excel and transferred to SPSS 22.0 program.

Results: There were 56 (46%) female and 65 (54%) male patients. The mean age of the female patients was 58 years and the mean age of the male patients were 64 years. The median age for both sexes was 63 (range: 37-82). The second primary tumor was found to be metachronous in 89 patients (74%) and synchronous in 32 patients (26%). The incidence of MPT was 1.22%. Breast-breast cancer pair in women and larynx-lung cancer pair in men were in the foreground. Eighty-one patients (67%) had a history of smoking and 18 patients (15%) had a history of alcohol use. In synchronous and metachronous tumors, the most common metastasis was observed in the skeletal system. Median overall survival was 51 months in synchronous tumors and 72 months in metachronous tumors.

Conclusion: The development of a second primary cancer in a patient diagnosed with cancer is higher than in those who have not been diagnosed with cancer. Early diagnosis of patients and prolongation of survival may increase the incidence of second primary tumors. For this reason, new complaints emerging

ÖZ

Amaç: Onkolojik tanı ve tedavilerdeki gelişmeler sağkalımı artırmakta ve hastalığın remisyonunu sağlamaktadır. Bununla birlikte uzamış sağkalım ikincil primer malignitelerin gelişmesi olasılığını da artırmaktadır. Bu makalenin amacı kanser tanısı konulmuş, tedavi almış ve takip edilen hastalarda ikinci tümörün birinci tümörle ilişkili olup olmadığını ve sağkalım sürelerini değerlendirmek, bu hastaların takibinde neler yapılabileceği konusunda önerilerde bulunmaktır.

Yöntemler: Ocak 2011 ile Aralık 2017 tarihleri arasında, İstanbul Eğitim ve Araştırma Hastanesi Radyasyon Onkolojisi ve Tıbbi Onkoloji polikliniklerine başvuran, 6 aydan uzun süreli takipleri olan, 9892 hasta dosyası retrospektif olarak incelendi. Yüz yirmi bir hastada multiple primer tümör (MPT) olduğu saptandı. Tümörün hangi organlarda oluştuğu, ne zaman geliştiği, hastaların cinsiyeti, yaşı, metastaz, sağkalım oranları araştırıldı. Veriler Excel'de toplanarak SPSS 22.0 programına aktarıldı.

Bulgular: 56 (%46) kadın, 65 (%54) erkek hasta vardı. Kadın hastaların yaş ortalaması 58, erkek hastaların ise 64 olarak bulundu. Her iki cins için ortanca yaş 63 (37-82) olarak tespit edildi. Hastaların 89'unda (%74) ikinci tümör metakron, 32'sinde (%26) senkron olarak saptandı. Çoklu MPT görülme oranımız %1,22 idi. Kadınlarda meme-meme kanseri; erkelerde larenks-akciğer kanseri çiftleri ön planda gözlendi. 81 (%67) hastada sigara içme öyküsü; 18 (%15) hastada alkol kullanma alışkanlığı öyküsü vardı. Senkron ve metakron tümörlerde en sık metastaz iskelet sisteminde gözlendi. Senkron tümörlerde medyan genel sağkalım 51 ay, metakron tümörlerde 72 ay olarak saptandı.

Sonuç: Kanser tanısı almış bir hastada ikinci bir kanser gelişimi, kanser tanısı almamış kimselere göre daha fazladır. Hastaların erken teşhis edilmesi ve sağkalımın uzaması ile ikincil tümöre yakalanma sıklığı artabilmektedir. Bu nedenle kanser tanısı almış hastaların takipleri sırasında ortaya çıkan

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during the follow-up of patients diagnosed with cancer should be considered and second primary tumors should be suspected. We think that long-term follow-up, especially for detecting early metachronous tumors, will contribute to survival in patients with cancer.

Keywords: Multiple primary tumors, synchronous, metachronous

yeni yakınmalar önemsenmeli ve ikincil tümörler göz önünde bulundurulmalıdır. Özelikle metakron tümörleri erken saptamak için kanserli hastalarda uzun süreli takibin sağkalıma katkısı olacağını düşünüyoruz.

Anahtar Kelimeler: Çoklu primer tümör, senkron, metakron

Introduction

Advances in oncologic diagnosis and treatment increase survival and remission of the disease. However, prolonged survival increases the likelihood of developing second primary malignancies. The term "multiple primary malignant tumors" was first used by Billroth in 1889, and the first paper describing multiple primary tumors (MPT) was published by Warren and Gates in 1932 (1,2). According to today's definition, the features that should be available in MTPs are: 1) Each tumor should be diagnosed as malignant histopathologically, 2) each tumor should be histopathologically different tumors, and 3) each tumor should not be recurrence or metastasis of other tumor. While synchronous tumors are defined as tumors seen within 6 months after primary tumor diagnosis, metachronous tumors are tumors diagnosed after 6 months of primary tumor diagnosis (2). Although the mechanism of occurrence cannot be determined exactly, genetic mutations, chemotherapy and/or radiotherapy applications and prolonged survival of cancer patients are known to increase the risk of second primary tumor development (3-6).

The aim of this article was to evaluate whether the second primary tumor is associated with the primary tumor in patients who were treated and followed-up with cancer diagnosis, to evaluate the survival time and to make recommendations about the follow-up of these patients.

Methods

The files of 9892 patients who were followed for more than 6 months in Radiation Oncology and Medical Oncology clinics between January 2011 and December 2017 were examined. One hundred and twenty-one patients with primary tumors diagnosed as having synchronous or metachronous tumors were included in the study. The incidence of MPT was 1.22%. Patients with ≥ primary tumors and those who had been diagnosed with cancer for the first time in more than 7 years were excluded from the study. Overall survival (OS) was defined as the time from diagnosis to last follow-up or death. The data about whether the patients were alive or not were obtained from the computer system of our hospital. Patient case report forms and consent are included in each patient's file. Approval was obtained from the İstanbul Training and Research Ethics Committee of our hospital (decision no: 1628, date: 04.01.2019).

Statistical Analysis

Data were collected in Excel and transferred to SPSS 22.0 program. Mean, standard deviation, median, minimum, maximum, frequency and percentage values were used in statistical analysis. The definition of the variables was measured by the Kolmogorov Smirnov test. The chi-square test was used for the analysis of qualitative independent data, and Fisher's Exact test was used when the chi-square conditions were not met. Independent sample t-test was used for the analysis of quantitative independent data. Kaplan-Meier log-rank test was used for survival analysis.

Results

Of 121 patients, 56 (46%) were female and 65 (54%) were male. The mean age of the female patients was 58±10.37 years and the mean age of the male patients was 64±8.62 years. The median age for both sexes was 63 (37-82) years. The second primary tumor was found to be metachronous in 89 patients (74%) and synchronous in 32 patients (26%). The time between the detection of the first and second primary tumors was 1.1 months (range: 0-6) in synchronous tumors and 30.8 months (range: 7-78) in metachronous tumors. Eighty-one patients (67%) had a history of smoking and 18 patients (15%) had a history of alcohol use.

In 32 patients with synchronous tumors, breast cancer/breast cancer pair was the most common tumor pair (38%), followed by breast cancer/colorectal cancer pair (13%). Among 89 patients with metachronous tumor, laryngeal cancer/lung cancer was the most common tumor pair (13%), followed by prostate cancer/lung cancer (8%). When MPTs were evaluated histopathologically, invasive ductal carcinoma/invasive lobular carcinoma was most common in synchronous tumors, whereas adenocarcinoma was the most common carcinoma in metachronous tumors, followed by epidermoid carcinoma.

The metastasis was observed after a mean period of 15 (4.78±11.29) months in synchronous tumors and 29 (9.07±18.24) months in metachronous tumors. The most common site of metastasis was observed as skeletal system in four (40%) patients with synchronous tumor and in nine (36%) patients with metachronous tumor (p=0.126). Demographic characteristics of patients with synchronous and metachronous tumors are shown in Table 1.

In our study, the most common tumor in women was found to be breast cancer (64%) and the second most common tumor was colorectal cancer (14%). In men, laryngeal cancer (25%) was the most common cancer, followed by prostate cancer (17%). Tumor pairs were breast-breast and breast-colorectal in women, and larynx-lung and prostate-lung in men. The distribution of tumors by gender is shown in Table 2.

In our study, surgery for synchronous tumors was performed in 25 patients (78%). Then, the curative treatment of the patients was determined starting from the tumor, whichever of the diseases would determine the survey. The curative treatment was performed to primary tumor in 82 patients (92%) with metachronous tumors. Median OS was 51 (95% confidence interval (CI): 43.69-58.30) months for synchronous

tumors and 72 (95% CI: 59.44-84.55) months for metachronous tumors (log rank: 0.145). General survival graphs of synchronous and metachronous tumors are shown in Figure 1.

Table 1. Demographic distribution of synchronous and metachronous tumors

	Synchronous tumor, n=32 (26%)	Metachronous tumor, n=89 (74%)	p
Gender			
Female	24 (75)	32 (36)	<0.001
Male	8 (25)	57 (64)	
Smoking			
Smoker	19 (59)	62 (70)	0.289
Non-smoker	13 (41)	27 (30)	
Alcohol use			
Yes	1 (3)	17 (19)	0.029
No	31 (97)	72 (81)	
Metastasis			
Present	10 (31)	26 (29)	0.829
Absent	22 (69)	63 (71)	
1. Primary			
Localization[1]			
Breast	18 (56)	21 (24)	0.002
Colorectal	5 (16)	12 (14)	
Larynx	-	16 (18)	
Other	9 (28)	40 (45)	
Histopathology[1]			
Adenocarcinoma	11 (34)	29 (33)	0.003
IDC/ILC	17 (53)	21 (24)	
SCC	1 (3)	24 (27)	
Other	3 (9)	15 (17)	
Stage[1]			
Stage 1-2	21 (66)	61 (69)	0.762
Stage 3-4	11 (34)	28 (31)	
2. Primer			
Localization[2]			
Breast	16 (50)	15 (17)	0.001
Lung	2 (6)	29 (33)	
Colorectal	3 (9)	7 (8)	
Other	11 (34)	38 (43)	
Histopathology[2]			
Adenocarcinoma	8 (25)	27 (30)	0.001
IDC/ILC	16 (50)	15 (27)	
SCC	2 (6)	24 (27)	
Other	6 (19)	23 (26)	
Stage[2]			
Stage 1-2	21 (66)	54 (61)	0.621
Stage 3-4	11 (34)	35 (39)	

[1]first primary tumor, [2]Second primary tumor, IDC/ILC: invasive ductal carcinoma/ invasive lobular carcinoma, SCC: squamous cell carcinoma

Table 2. Gender distribution of most common tumor, histopathology and stage

	Female, n=56 (46%)	Male, n=65 (54%)	p
Localization[1]			
Breast	36 (64)	3 (5)	<0.001
Colorectal	8 (14)	9 (14)	
Larynx	-	16 (25)	
Gynecological	4 (7)	-	
Prostate/bladder	0/2 (0/4)	11/6 (17/9)	
Other	6 (11)	20 (30)	
Histopathology[1]			0.004
Adenocarcinoma	14 (25)	26 (40)	
IDC/ILC	34 (60)	4 (6)	
SCC	2 (4)	23 (35)	
Other	6 (11)	12 (19)	
Stage[1]			
Stage 1-2	40 (71)	42 (65)	0.426
Stage 3-4	16 (29)	23 (35)	
Localization[2]			
Breast	30 (54)	1 (2)	<0.001
Lung	4 (7)	27 (42)	
Colorectal	5 (9)	5 (8)	
Prostate/bladder	-	8/2 (12/3)	
Other	17 (30)	22 (33)	
Histopathology[2]			
Adenocarcinoma	13 (23)	22 (34)	0.065
IDC/ILC	30 (54)	1 (2)	
SCC	3 (5)	23 (35)	
Other	10 (18)	19 (29)	
Stage[2]			
Stage 1-2	39 (70)	36 (55)	0.109
Stage 3-4	17 (30)	29 (45)	

[1]first primary tumor, [2]second primary tumor, IDC/ILC: invasive ductal carcinoma/invasive lobular carcinoma, SCC: squamous cell carcinoma

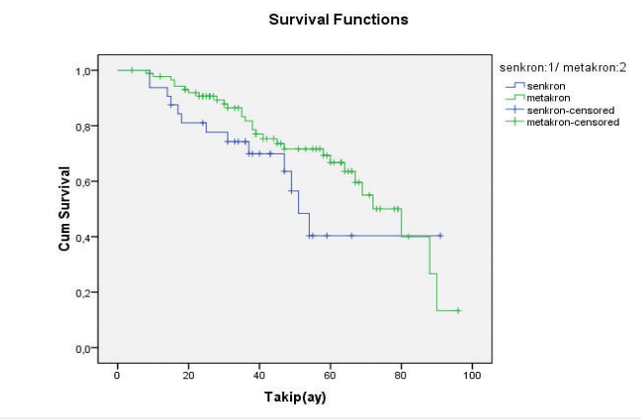

Figure 1. Overall survival in synchronous and metachronous tumors

Discussion

We see that the number of patients diagnosed with cancer at an early stage has increased with the increased use of screening programs and that the survival of patients has been prolonged with new treatments developed. With long survival times, the probability of developing a second primary tumor increases. Metachronous tumors often develop as a result of previous cancer treatments such as chemotherapy and radiotherapy, whereas synchronous tumors are associated with organ-specific carcinogens such as cigarettes and alcohol (3). The development of a second cancer in a patient diagnosed with cancer is 1.29 times higher than in patients with no diagnosed cancer (4). This is due to cancer development in different organs as a result of exposure to the same carcinogens in the primary tumor site (such as smoking, alcohol use) or genetic changes (7,8). Smoking and alcohol use can also trigger a second cancer in the lung, esophagus, pancreas, cervix and bladder. This condition is called "field cancerization effect" (9-11). Thirty-three patients (27.2%) in our study had the first tumor diagnosis in these organs.

MPTs can occur at any age, but they are reported to be more common after the age of 50 (12-14). The median age of our patients was 63 (37-82) and was consistent with the literature. We can attribute the incidence of MPT in advanced age to weakening of immunity with aging, prolongation of exposure to carcinogens, and sensitization to carcinogens with aging.

According to surveillance, epidemiology, end results program data, in which annual cancer statistics are published, prostate-respiratory system cancer is the most common tumor pair in men, followed by prostate-colon cancer (primary tumor-second tumor). Breast cancer-breast cancer pair is the most common and breast cancer-colorectal cancer pair is the second most common pair in women (15). In this study, similar to the above data, the most common MPT pair in female patients was breast-breast and breast-colorectal cancer pairs. However, the situation was slightly different in male patients. In men, larynx-lung and prostate-lung cancer were the most common cancer pairs. We think that the difference in male patients is mainly due to the fact that we have more head and neck cancer patients and small number of cases diagnosed with lung cancer. This difference can be explained by the high smoking and alcohol use in male patients.

The male/female ratio in patients with MPTs varies between 0.9 and 3.5 in various publications (15,16). The male/female ratio was 1.1 in our patients and this was consistent with the literature. MPTs are mostly seen as metachronous (16,17). Eighty-nine patients (73.6%) in our study had metachronous tumors.

In the literature, the incidence of MPT in genitourinary tumors is reported as 13.5% (17). In our study, there were 17 patients with genitourinary cancer and this rate was found to be 14%. In a study evaluating the success of Positron-emission tomography/ Computed Tomography (PET/CT) in the detection of synchronous primary tumor, 9.5% of patients had synchronous primary tumor, PET/CT detected 84% of them and treatment changed in 80% of patients (18). Similar to the other studies, metachronous tumors (76%) were observed more in our study. However, in contrast to the above study, the incidence of synchronous tumors was higher (36%). In our study, the contribution of PET/CT in detecting synchronous and metachronous tumors, in the initial staging and in follow-up was significant. Almost all cases were diagnosed in this way.

In terms of prognosis, it is seen that there is a worse survival time in MPT cases especially in synchronous tumors. The reason for this is to fight two cancers in the same period in the synchronous tumor group, whereas the primary tumor is treated in metachronous tumors and the time to development of a second cancer was shown to be longer (19). In our study, the median OS was 51 months in synchronous tumors and 72 months in metachronous tumors.

In the literature, the incidence of MPT varies between 0.4% and 21% (19,20). This rate was 1.22% in our patients. Adenocarcinoma was the most common histological type in one series (21). Similar to the literature, the histology of adenocarcinoma was prominent in 37 patients (31%) in our study.

While synchronous tumors are caused by exposure to similar carcinogens, the negative effects of the treatments for first tumor can be mentioned on the development of metachronous tumors. The etiology may include the causes of the primary tumor or treatments applied to the primary tumor (22). In our study, 81 patients (67%) had a history of smoking and 18 (15%) had a history of alcohol use. Regarding the relationship between synchronous and metachronous tumors with alcohol use and smoking in our study, no difference was found between smoking and development of both tumors, while alcohol use was higher in metachronous tumors. As mentioned above, we could expect more cigarette and alcohol use in synchronous tumors, but this was not observed in this group because synchronous tumor pairs had more breast meme breast carcinomas. We know that smoking and alcohol use are not as intensely related to the etiology of breast tumors, as in head and neck and lung cancers. Laryngeal-lung carcinoma pair was more common in metachronous tumors. The association of this tumor pair is generally associated with smoking and alcohol use. As a result, alcohol use in metachronous tumors was statistically higher in our study.

Conclusion

Early detection of cancer and prolonged survival may increase the incidence of second primary tumors. For this reason, new complaints emerging during the follow-up of patients diagnosed with cancer should be considered and second primary tumors should be suspected. When metachronous tumor is diagnosed, multidisciplinary approaches may prolong survival in these patients. In addition, patients should be given increased awareness by giving up smoking and alcohol, paying attention to their weight, doing sports, and participating in screening test programs (fecal occult blood test, smear examination, mammography etc.). We think that long-term follow-up will contribute to the survival of patients who have survived more than 5 years, especially for cancers that may develop metachronously.

Ethics Committee Approval: Approval was obtained from the İstanbul Training and Research Ethics Committee of our hospital (decision no: 1628, date: 04.01.2019).

Informed Consent: Patient case report forms and consent are included in each patient's file.

Peer-review: Externally and internally peer-reviewed.

Author Contributions: Data Collection and/or Processing - Ö.M.; Analysis and/or Interpretation - Ö.M., R.U.G.; Literature Search - Ö.M.; Writing Manuscript - Ö.M.

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Attitudes and Behaviors of Anesthesia Workers in Turkey Towards Drug Labeling: A Questionnaire Study

Türkiye'de Anestezi Çalışanlarının İlaç Etiketleme ile İlgili Tutumları ve Davranışları: Anket Çalışması

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ABSTRACT

Introduction: Standard drug syringe labels can reduce drug errors. In this study, it was aimed to report the attitudes of anesthesia workers (AW) towards labeling, to emphasize the importance of drug labeling in drug errors and to contribute to safe anesthesia practices by raising awareness about standardization.

Methods: The study was initiated after obtaining permission from the Zonguldak Bülent Ecevit University Clinical Research Ethics Committee. A confidential, self-reporting questionnaire was sent to each member of Turkish Anesthesiology and Reanimation Society and to technicians whose e-mail addresses were known.

Results: A total of 189 people participated. Of all participants, 49.2% were aware of standard syringe label (SSL). While 67.3% of these participants stated that they used color-coded self-adhesive labels, 47% stated that they did not know which standards these labels met. AWs suggested that color-coded self-adhesive labels (92.9%), SSL for vials (97.3%) and pre-prepared syringes (87.8%) were effective in reducing drug administration errors (DAE). Of all participants, 89.9% stated that they did not know DAE and 84.7% stated that they read the label each time before administration. AWs stated that DAE could be prevented through standard labeling procedures (47%), attention (23%), education (21%) and producing the vials in different sizes and colors (9%).

Conclusion: AWs stated that developing and standardizing the vial labels, scheduling trainings, paying care and attention were important in prevention of labeling-related errors.

Keywords: Anesthesia workers, labeling, drug error, standardization

ÖZ

Amaç: Standart ilaç enjektör etiketleri ilaç hatalarını azaltabilir. Çalışmamızda, ülkemizde anestezi çalışanının (AÇ) ilaç etiketleme konusundaki tutumlarını, ilaç hatalarında etiketlemenin önemini vurgulamak ve standardizasyon bilincinin artmasına yönelik bir farkındalık yaratarak güvenli anestezi uygulamalarına katkı sağlanması amaçlanmıştır.

Yöntemler: Bu çalışma Zonguldak Bülent Ecevit Üniversitesi Klinik Araştırma Etik Kurulu'ndan izin alındıktan sonra tamamlandı. Türk Anesteziyoloji ve Reanimasyon Derneği'nin her üyesine ve posta adresleri bilinen teknisyenlere gizli, kendi kendini raporlama anketi gönderildi.

Bulgular: Toplam 189 kişi katıldı. Katılımcıların %49,2'si standart enjektör etiketinin (SEE) farkındaydı. Bu katılımcıların %67,3'ü renk kodlu kendinden yapışkanlı etiket kullandıklarını belirtirken, %47'si bu etiketlerin hangi standartları karşıladığını bilmediklerini belirtmiştir. AÇ'ler ilaç uygulama hatalarını (İUH) azaltmak için; renk kodlu kendinden yapışkanlı etiketlerin %92,9, flakonların %97,3 ve önceden hazırlanmış SSE'nin %87,8 oranında etkili olacağını belirtti. Katılımcıların %89,9'u İUH bildirmediğini, %84,7'si, uygulama öncesi her defasında etiketi okuduğunu belirtti. AÇ'ler, İUH'yi önlemede SEE'nin (%47), dikkat (%23), eğitim (%21) ve flakon-ampullerin farklı renk ve boyutlarda yapılması (%9) gerektiğini belirtmişlerdir.

Sonuç: AÇ'ler, etiketleme ile ilgili hataların önlenmesi için; flakon etiketlerinin geliştirilmesinin ve standartlaştırılmasının, eğitimlerin planlanmasının, özen ve dikkatin önemini belirtmiştir.

Anahtar Kelimeler: Anestezi çalışanları, etiketleme, ilaç hatası, standardizasyon

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Introduction

Errors in drug selection and drug use are among the common adverse events in hospitals (1,2). The European Board of Anesthesiology and the European Society of Anesthesiology have stated that drug errors reduce patient safety, but that they can be prevented (3,4). Most anesthesia workers (AW), who are responsible for completing all steps of drug administration, encounter drug errors in the complex and rapidly changing environment of the operating theater (1,5). Each drug should be used at the right time, in the right dose and right order during the perioperative period. It is very easy to confuse the drugs. Color labels used for specific drugs reduce drug administration errors (DAE) and the standard syringe label (SSL) improves patient safety (6,7). Most anesthesiologists suggest that the color of the label is an important factor for identifying a drug (8,9).

The use of handwritten labels is a problem because it is easy to make mistakes either in writing or reading them. Therefore, the current drug syringe label situation has been documented as one of the primary causes of error. The International Organization for Standardization (ISO) and anesthesiology societies have guidelines focused on the development of prepared syringe labels for dosage, volume, dilution and color coding, and recommend standardization of syringe labeling (10,11).

In our study, it was aimed to report the attitudes of AW (resident, specialist, lecturer, technician) towards labeling, to emphasize the importance of drug labeling in drug errors and to contribute to safe anesthesia practices by raising awareness about standardization.

Methods

This cross-sectional study was conducted between September 2016 and January 2017 with the permission of the Zonguldak Bülent Ecevit University Local Ethics Committee (decision no: 2016/10, date: 24.08.2016). Informed consent wasn't obtained because it was a survey study.

Data Collection Methods: AW in our country were contacted through the Turkish Anesthesiology and Reanimation Society (TARD), which have approximately 4000 members. The questionnaire form was created by reviewing the studies in the literature (Appendix). The questionnaire was sent with a text providing information about the subject. The data were obtained from the participants through a web-based questionnaire data form. The questionnaire was sent twice in 4-week intervals to each member of TARD and to technicians whose email addresses were known, and those who had participated previously were reminded not to participate again. The identities of the participants were kept confidential.

Questionnaire Form: The questionnaire consisted of four sections. The first section contained data on the demographic characteristics, duties, institutions and working years of the workers. The second section inquired about the experiences of drug errors, potential causes, and one or more factors for each event. The clinical outcomes of drug errors were reported. The third section included the ideas of AW on label and package characteristics, SSL awareness, the rate of color-coded self-adhesive label use, and data on standardization of labels. The last section inquired about the rate of notifying drug errors and informing the patients about the event, the reasons for not notifying errors, whether AW were punished for the errors or not, whether they notified the errors to a national reporting program, and whether or not they asked the protocol from TARD for labeling and recommendations for prevention of drug errors. Except for the first section, multiple-choice questions in the other sections can be marked with multiple choices.

Statistical Analysis

Frequency (%) of the answers of the volunteering participants was determined.

Results

A total of 189 questionnaires were evaluated. Demographic characteristics of the participants are presented in Table 1. A total of 325 DAEs were described and are shown in Table 2. Fifty-two point nine percent (n=100) of the participants stated that they administered the incorrect drug during anesthesia induction at least once. Table 2 also displays the frequency of DAE observation. Results of DAE are explained in Table 3. When participants were asked to state the importance of some of the features they used to identify the syringe or the label, the label

Table 1. Demographic characteristics of the participants (n=189)

		n (%)
Gender	Female	108 (57.1)
	Male	81 (42.9)
Duty	Anesthesia technician	63 (33.4)
	Anesthesia specialist	60 (31.7)
	Lecturer	38 (20.1)
	Anesthesia resident	28 (14.8)
Institution	State hospital	72 (38.1)
	University hospital	64 (33.9)
	Training and Research Hospital	34 (18.0)
	Private hospital	19 (10.0)
Working years	<5 years	51 (27.0)
	6-10 years	41 (21.7)
	11-15 years	39 (20.6)
	16-20 years	26 (13.8)
	>21 years	32 (17.4)

Table 2. Frequency of observation of Drug Administration Errors (n=325)

Causes	n (%)
Injection of the drug in the incorrect dose	53 (16.3)
Using the incorrect syringe	45 (13.8)
Not reading the label	42 (12.9)
Incorrect definition of the vial	40 (12.3)
Incorrect labeling of the syringe	36 (11.0)
Filling the syringe with incorrect drug	35 (10.7)
Incorrect injection site	25 (25.0)
Others	49 (15.0)

*Percentages do not sum to 100% because responders often reported multiple factors

Table 3. Results of medication errors (n=127)	
Effect of drug errors on outcomes	**n (%)**
No clinical importance	69(54.3)
Minor morbidity (requiring immediate intervention for prevention of permanent damage)	48(37.7)
Major morbidity (i.e. cardiac arrest, stroke or permanent damage)	4(3.1)
Death (may lead or contribute to death)	4(3.1)
Others	2(1.5)
*Percentages do not sum to 100% because responders often reported multiple factors	

Table 4. Reasons for not reporting drug errors (n=114)	
Reasons	**n (%)**
The error was insignificant	76 (66.6)
Not correctly knowing to where or whom to report	19 (16.6)
Medico-legal concerns	12 (10.5)
Concerns about the opinions of the colleagues	5 (4.38)
Others	2 (1.75)
*Percentages do not sum to 100% because responders often reported multiple factors	

color of the vial and the color of the vial were found to be "extremely important" at rates of 42.3% and 32.8%, and the font size for prepared syringes was found to be "extremely important" at a rate of 44.4%. Of the participants, 49.2% (n=93) were aware of SSL. While 66.7% of these participants stated that they used color-coded self-adhesive labels, 46.2% stated that they did not know which standards these labels met. Color-coded self-adhesive labels (92.9%), standardized labeling system for vials (97.3%) and the prepared syringes (87.8%) were suggested by AW to be effective in reducing DAE. Of the participants, 89.9% (n=170) stated that they did not know DAE. Of the participants who notified DAE, 56.2% (n=16) stated that they reported the error to the chief of the clinic, but they did not report it to the official website of an institution, and three participants were found not to respond to this question. The reasons for not reporting DAE are presented in Table 4. The errors were not reported to the patients at a rate of 94.7% (n=179), and the rate of being not punished was 99.4% (n=182). Of the responders, 90.5% (n=171) stated that they would notify the DAE if there were a single notification center and 95.8% stated that they wanted TARD to develop a protocol for labeling. AW (n=100) stated that DAE could be prevented through standard labeling procedures (47%), attention and care (23%), training (21%) and producing the vials in different sizes and colors (9%).

Discussion

Our study revealed that most AW had at least one or more DAE experience, and that 54.3% of the errors were clinically insignificant. Most of the participants stated that color was the most important feature in the identification of drugs. We determined the rate of SSL awareness as 49.2% and the use of color-coded self-adhesive labels as 66.7%; however, 46.2% of the participants did not know the standards required for the labels.

AW can make mistakes with loss of concentration despite problem solving, decision-making and application skills. DAEs may arise at any stage of the therapeutic procedure, and its incidence has been reported to be between 1-10%, and this rate has been reported not to significantly change over a period of more than 15 years (8,12-18). In two questionnaire studies, the rate of observation of one or more DAEs by AW was %61.7 and %91.8 (8,19). We determined that 52.9% of the participants experienced at least one DAE during anesthesia applications. We consider that AW may be reluctant to report all errors, and that the number of the reported errors is small given the large number of drugs used in anesthesia. Prospective studies are required to determine the prevalence of DAE, and our findings may lead to awareness of AW.

There are many reasons for DAEs in anesthesia applications. The most common causes of perioperative DAE include injection of the incorrect drug, administration of an excessive dose, incorrect route of administration and negligence. Inadequate follow-up of treatment or side effects, inadequate standardization of labels and protocols, carelessness, excessive workload, inappropriate working hours, poor communication, impetuousness, fatigue, medical and paramedical staff-related problems were also reported to contribute to DAE (4,8,14,17-24). In addition, incorrect or missing drug labels, interchange of syringe labels and vials, unlabeled syringes, and failure to estimate the dose of the drug were also reported (5,7,8,12,22). There are studies reporting that errors arise from interchange of the syringe (44.4%-70.4%) and incorrect definition of the label (46.8%) (5,8,18,22). In our study, consistent with the literature, we found that errors were caused by many reasons such as incorrect drug and dose.

There are various measures for the prevention of DAEs in anesthesia as they are preventable and may be potentially fatal (24,25). Regarding the recommendations for preventing DAEs, Russel W. (26) recommended different color codes for the syringes according to the drug types. The Japanese Society of Anesthesiology reported that outcomes of the series of preventive measures in preventing DAE were not satisfactory despite the current measures; and that the current syringe labels are among the main causes of DAE (27). The recommendations also include the use of international color codes for labeling and color syringes, and production of different looking drugs by drug companies (17,22,28).

Considering the safety, designing labels is a step toward developing a safer system. Canada developed the first standardization for labeling vials and prepared syringes (14). Many countries use a standard color code for anesthetic drug syringes. Many studies have reported that the rate of SSL use is between 19% and 96%, while some authors report that they have developed their standards, and some others report that they use the color codes of ISO standards (3,8,9,17,28-30). Orser et al. (8) reported the rate of awareness of anesthetists regarding self-adhesive color-coded labels as 86.5% in their questionnaire study, and 84% of the participants in this study stated that drug label standards would reduce the incidence of DAE. In our study, consistent with the literature, we determined that the standard labeling procedure was an important factor in the prevention of DAE. We also determined that the rate of awareness and use of SSL in our study was lower than European data. No mandatory regulations are available for labeling standardization in our country, and our study revealed that AW supported labeling standards. We also determined that AW did not know the standards from which the color-coded labels were prepared and they suggested that TARD should

participate in the protocol selection. We believe that AW should demand from hospital pharmacists and Ministry of Health that drug labels be prepared in accordance with the international standards.

It has been reported that specific protocols should be developed for prevention of DAE, trainings should be scheduled, routines for equipment care and control should be improved, and that more manpower and communication should be provided (22). We think that DAE may be reduced with similar measures.

Some DAE may lead to severe morbidity and even mortality, although most of them are not significant (12,21). The reason for minor morbidities caused by DAE in anesthesia include early recognition of the error, rapid physiological changes caused by drugs and special follow-up methods in critical events. There are also studies reporting mortality (5,8,12,14,21,22). We detected that the adverse events in our study were consistent with the literature and most of them resulted in minor morbidities, with only four deaths with unknown origin.

Orser et al. (8) reported that 60.1% of DAEs in anesthesia applications were not reported due to being considered as insignificant. The participants also reported that they did not know where to and whom to report the errors. In the same study, almost half of the participants reported that they would report the errors to a national notifying program. It is also known that DAEs are not reported individually or by the department (2,17). In our questionnaire, we observed that 89.9% of the errors were not reported and, if reported, they were mostly reported to the chief of the department. A Safety Notifying System (www.kalite.saglik.gov.tr) is available in our country; however, most AW are unaware of this website and we consider that critical errors should be reported in accordance with the relevant rules.

One limitation of our study is that our study was a web-based questionnaire study and the number of responders was less than similar studies in the literature. Therefore, the results may not reflect the attitudes of all AW. Besides, the prevalence cannot be determined, as the details of the errors experienced years ago could have been forgotten.

The results of the present study may in general present the preliminary data for the development of quality standards in our country. We observed that most AW participating in the study did not use SSL, and that more than half experienced at least one DAE, and that these were caused by mislabeling.

Conclusion

In our study, AW stated that developing and standardizing the vial labels, scheduling trainings, paying care and attention were important for the prevention of labeling-related errors. In addition, DAEs were not frequently reported. Anesthetists and managers should be aware of this problem. Notification mechanisms should be utilized for the prevention of potential events and future events, and determination of the measures. Prospective randomized studies are required for investigating strategies to reduce DAEs. The use of error notification systems would develop a safer patient culture.

Ethics Committee Approval: This cross-sectional study was conducted between September 2016 and January 2017 with the permission of the Zonguldak Bülent Ecevit University Local Ethics Committee (decision no: 2016/10, date: 24.08.2016).

Informed Consent: Informed consent wasn't obtained because it was a survey study.

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Conflict of Interest: The authors have no conflict of interest to declare.

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Attitude and Behavior of Anesthesia Workers about Labelling in Anesthetic Drug Administration

Dear colleagues,

The following questions were prepared with the aim of determining attitudes and behaviors about labeling in anesthetic drug administration. Answering the questions is optional. You will not be prompted to enter your first name or last name on the forms. Confidentiality will be ensured by researchers. After reading the statements, please mark the appropriate choice. The survey should take approximately 10 minutes. If you have already answered this survey, please do not complete it again. Thank you in advance for answering our survey.

(Asst. Prof. Dr. Gamze Küçükosman, Bülent Ecevit University, Dept. of Anesthesiology and Reanimation, Zonguldak)

Note: *Mandatory questions

SECTION 1

1. Your job*:

1. Anesthesia assistant

2. Anesthesia specialist

3. Teaching staff

4. Anesthesia technician (vocational school of higher education)

5. Anesthesia technician (vocational high school)

2. Your gender*:

1. Female

2. Male

3. How long have you been in the anesthesia profession? (Including your education)*

1. 0-5 years

2. 6-10 years

3. 11-15 years

4. 16-20 years

5. 21-25 years

6. >25 years

4. Hospital of employment*:

1. State hospital

2. Training and Research hospital

3. Private hospital

4. University hospital

SECTION 2

5. Have you ever experienced giving the incorrect drug to any patient during anesthesia administration?*

1. Yes (go to the 6th question)

2. No (go to the 9th question)

6. Did any of the following factors affect this drug error? If your answer is yes, please state the error number, you may mark multiple choices.

1. Misidentification of ampoule or vial……

2. Mislabeling of syringe…….

3. Incorrect injector used……

4. Illegibility of label……

5. Incorrect drug in the syringe……..

6. Incorrect administration site…….

7. Incorrect dose of drug injected……..

8. Other (please give details)……..

7. If you answered the 6th question, please state any other reason or reasons that you think caused drug errors

8. What was the outcome of the event(s) related to drug administration error you were involved in? (You may mark multiple choices)

1. No clinical importance

2. Minor morbidity (requiring rapid intervention to prevent permanent injury)

3. Major morbidity (e.g., heart attack, paralysis or permanent injury)

4. Death (caused or contributed to death)

5. Other (please give details).....

SECTION 3

9. What is the importance of labeling that helps in the identification of anesthetic drugs?*

(Mark one box in each row).

0=not important **2**=moderately important

1=slightly important **3**=very important

Ampoules	**0**	**1**	**2**	**3**
Ampoule color	-	-	-	-
Label colors	-	-	-	-
Font size	-	-	-	-
Font type	-	-	-	-
Ampoule size	-	-	-	-
Color band at ampoule break point	-	-	-	-

Vial	**0**	**1**	**2**	**3**
Vial color	-	-	-	-
Vial lid color	-	-	-	-
Font color	-	-	-	-
Font size	-	-	-	-
Font type	-	-	-	-
Vial size	-	-	-	-
Vial shape	-	-	-	-

Previously filled syringes	**0**	**1**	**2**	**3**
Font color	-	-	-	-
Font size	-	-	-	-
Font type	-	-	-	-
Syringe size	-	-	-	-

10. Are you aware of the usefulness of standardized color-coded labels for anesthetic drug syringes?*

1. Yes (go to the 11th question)

2. No (go to the 13th question)

11. If yes, do you use these color-coded self-adhesive labels?

1. Yes (go to the 12th question)

2. No (go to the 13th question)

12. If yes, what standards do these color-coded self-adhesive labels meet?

1. Canadian Anesthesiologists' Society

2. FDA (Food and Drug Administration)

3. ASA American Society of Anesthesiologists

4. Ministry of Health Pharmacy and Pharmacology Unit

5. I don't know

6. Other (please give details)……

13. Please state the degree of agreement/disagreement with the following statements*

(Mark one box for each row)

0=Definitely disagree

1=Partly agree

2=Mostly agree

3=Definitely agree

	0	1	2	3
1. Color-coded self-adhesive labels will reduce the incidence of drug errors in anesthesia	-	-	-	-
2. Standardized systems for medication ampoule and vial labeling will reduce the incidence of drug errors	-	-	-	-
3. Previously prepared injectors for anesthesia will reduce drug errors	-	-	-	-
4. If all anesthetic medications have the same appearance the incidence of drug errors will reduce	-	-	-	-

SECTION 4

14. Have you reported any drug error?*

1. Yes

2. No

15. If yes, to whom and where did you report the drug error?

16. If you have not reported an error (errors), why?* (You may mark multiple choices)

1. No errors

2. The error was insignificant

3. Concerns about my colleagues' opinions

4. Uncertainty about whom or where to report

5. Concerns related to medico-legal risks

6. Other (please give details)……..

17. Did you tell the patient about the drug errors?

1. Yes

2. No

18. Were you punished due to drug administration error?

1. Yes (go to the 19th question)

2. No (go to the 20th question)

19. If yes, please state the type of punishment and who gave it.

20. If there was a single reporting center for anesthetic medication errors, would you report error(s) to this unit?*

1. Yes

2. No

21. Would you like our association to issue protocols to prevent drug errors?*

1. Yes

2. No

22. What precautions do you think should be taken to prevent drug errors in relation to labeling?*

Comment: _____

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Corticosteroid-induced Knee Osteonecrosis and Accompanying Femoral Head Osteonecrosis

Kortikosteroid Kaynaklı Diz Osteonekrozu ve Eşlik Eden Femur Başı Osteonekrozu

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ABSTRACT

Introduction: The aim of this study was to investigate the prevalence and magnetic resonance imaging (MRI) findings of knee osteonecrosis (ON) in patients with arthralgia who received corticosteroid therapy. We also aimed to demonstrate the diagnostic performance of plain radiography in knee ON when MRI is accepted as the gold standard and to investigate the prevalence of accompanying femoral head ON in patients who underwent hip MRI.

Methods: One hundred and sixty-two knee X-rays and MRI examinations of 136 patients with knee pain and a history of corticosteroid intake were retrospectively evaluated for the presence of ON. Localization, maximum size of dominant lesion, multiplicity of lesions, presence of bone edema, double-line sign and subchondral extension were evaluated in patients with ON. Accompanying femoral head ON was also investigated in patients who underwent hip MRI.

Results: MRI revealed ON in 37 knees of 28 patients. The sensitivity and specificity of plain radiography in the diagnosis of knee joint ON was 29.73% and 98.40%, respectively. There were multiple lesions in 31 knees and subchondral space was affected in 24 knees. The double-line sign and bone marrow edema were present in most of the lesions. Of the 28 patients with knee ON, only 16 had hip joint MRI and five of these patients (31.3%) had femoral head ON.

Conclusion: Plain radiography has low sensitivity but high specificity for the diagnosis of knee ON. Corticosteroid-induced ON tends to be multifocal, and a significant proportion of patients with knee ON during corticosteroid therapy have ON of the hip joint.

Keywords: Magnetic resonance imaging, plain radiography, osteonecrosis, corticosteroid, knee, hip

ÖZ

Amaç: Bu çalışmadaki amacımız kortikosteroid tedavisi alan ve artralji şikayeti olan hastalarda diz ON'nin (ON) manyetik rezonans görüntüleme (MRG) ile prevalansını ve görüntüleme bulgularını araştırmaktır. Ayrıca MRG altın standart olarak kabul edildiğinde diz ON'de düz radyografinin tanısal performansını göstermeyi ve bu hastalarda eşlik eden femur başı ON'nin prevalansını araştırmayı amaçladık.

Yöntemler: Kortikosteroid alımı öyküsü ve diz ağrısı olan 136 hastaya ait 162 diz grafisi ve MRG tetkiki ON varlığı açısından retrospektif olarak değerlendirildi. ON'si olan hastalarda lokalizasyon, maksimum dominant lezyon boyutu, lezyonun çokluğu, kemik ödemi varlığı, çift hat işareti ve subkondral tutulum değerlendirildi. Kalça MRG uygulanan hastalarda eşlik eden femur başı ON'si de araştırıldı.

Bulgular: MRG'de 28 hastaya ait 37 dizde ON vardı. Diz eklemi ON tanısında düz grafinin duyarlılık ve özgüllüğü sırasıyla %29,73 ve %98,40 idi. Otuz bir dizde çok sayıda lezyon vardı ve 24 dizde subkondral boşluk etkilenmekteydi. Lezyonların çoğunda çift çizgi işareti ve kemik iliği ödemi mevcuttu. Diz ON'si olan 28 hastanın sadece 16'sında kalça eklemi MRG yapılmıştı ve bu hastaların 5'inde (%31,3) femur başı ON'si vardı.

Sonuç: Düz radyografi diz ON tanısı için düşük duyarlılığa ve yüksek özgüllüğe sahiptir. Kortikosteroid kaynaklı ON çok odaklı olma eğilimindedir ve kortikosteroid tedavisi sırasında diz ON'si olan hastaların önemli bir kısmında kalça eklemi ON'si vardır.

Anahtar Kelimeler: Manyetik rezonans görüntüleme, düz radyografi, osteonekroz, kortikosteroid, diz, kalça

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Introduction

Osteonecrosis (ON), also known as avascular necrosis of bone, is a disease with unexplained pathogenesis that disrupts joint structure and causes progressive dysfunction (1). Early recognition of ON is very important in terms of protection of joints (2). The most common symptom of ON is pain that is exacerbated by exercise. ON has many causes and corticosteroid (CS) intake is one of the most important causes (1-3). The relationship between CS dose and ON is contradictory. Although many authors claim that the cumulative CS dose is the most important factor (4-6), others have shown that ON may develop independently of dose (7,8). Vreden et al. (7) showed that even patients receiving CSs at physiological doses for adrenal insufficiency might develop ON. CS-induced ON is most commonly seen in the femoral head and it may also be seen around the knee, shoulder, elbow, hand and ankle joints. Magnetic resonance imaging (MRI) is the most sensitive and useful method for the early diagnosis of ON (1,5,9). However, there is no consensus on whether asymptomatic patients who are on CS therapy should be screened for ON.

Our aim in this study was to investigate the prevalence and imaging findings of knee ON by MRI in patients who were on CS therapy and complaining of arthralgia. We also aimed to demonstrate the diagnostic performance of plain radiography when the MRI is accepted as the gold standard for detection of knee ON and to investigate the prevalence of accompanying femoral head ON in patients who underwent hip MRI.

Methods

This study was approved by institutional Pamukkale Universtiy Ethics Committee (decision no: 60116787-020/8340). Informed consent was waived due to retrospective nature of the study. Patients with a history of knee joint surgery were excluded from the study because they could cause misinterpretation of imaging findings. One hundred and sixty-two knee MRI examinations and X-rays of 136 patients (102 females, mean age: 39.5±14.5 years, range: 16-78 years) with knee pain and history of CS intake due to various chronic diseases were retrospectively evaluated by two radiologists (with an experience of 3 and 20 years) in consensus for the presence of ON. Anteroposterior and lateral X-rays of all patients were obtained. MR images were obtained using a 1.5 Tesla superconducting magnet (GE Signa Excite HD, GE Medical Systems, Milwaukee, Wisconsin, USA) and a dedicated quad knee coil. Knee joint MRI examinations consisted of a sagittal T1-weighted (T1W) spin echo (SE), sagittal proton density-W fast spin-echo (FSE) with fat suppression (FS), axial proton density-W FSE with FS and coronal T2W FSE with FS. Other MRI parameters are shown in Table 1.

Knee joint X-rays were investigated for the presence of ON and findings such as sclerotic lesions, focal osteopenia, cortical collapses and subchondral radiolucency consistent with ON were recorded. The observers were blinded to the clinical information and MRI findings of patients. Then, at least 30 days later, knee joint MRI examinations of the patients were evaluated for the presence of ON according to predefined MRI findings (10). Localization, maximum size of the dominant lesion, multiplicity of lesions, presence of bone edema, double-line sign and subchondral extension were evaluated in these patients. Accompanying femoral head ON was also investigated in patients who underwent hip MRI.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows (Version 24.0, SPSS Inc. IBM Corp, Chicago, IL). Continuous variables were expressed as mean ± standard deviation and range (minimum-maximum), and categorical variables as number and percentage. Comparison of groups

Table 1. Magnetic resonance imaging parameters

	FOV (cm)	Matrix/NEX	Slice thickness/ gap (mm)	TR (msn)	TE (msn)	ETL	BW
Sagittal T1-W SE	16	256x192/1	3/0.5	600	30	-	16
Sagittal PD-FSE	16	196x256/1	4/0.5	4000	40	8	16
Axial PD-FSE	16	196x256/1	3/0.5	4000	40	8	16
Coronal T2-W FSE	16	196x256/1	3/0.5	4300	40	8	16

FOV: field of view, NEX: number of excitations, TR: time-to-repetition, TE: time-to-echo, ETL: echo train length, BW: bandwidth, T1-W: T1-weighted, SE: spin-echo, PD: proton density weighted, FSE: fast spin-echo

Table 2. Diagnostic performance of plain radiography in the diagnosis of knee joint osteonecrosis (magnetic resonance imaging is accepted as gold standard)

	Value	95% CI
Sensitivity	29.73%	15.87% to 46.98%
Specificity	98.40%	94.34% to 99.81%
Positive likelihood ratio	18.58	4.31 to 80.12
Negative likelihood ratio	0.71	0.58 to 0.88
Positive predictive value	84.62%	56.06% to 95.95%
Negative predictive value	82.55 %	79.30% to 85.38%
Accuracy	82.72%	76.00% to 88.20%

CI: confidence interval

with non-normal distribution was performed using Mann-Whitney U test. Independent samples t-test was used for comparisons in normally distributed data. P<0.05 was considered statistically significant.

Results

Only 13 (9.6%) knee joint X-rays showed a lesion compatible with ON. However, in a total of 162 knee joint MRI examinations, 37 knees (22.8%) (21 left and 16 right knees) of 28 patients (20.6%) (18 female, mean age: 42.8±13.4 years, range: 16-75 years) had ON. Accepting MRI as gold standard, diagnostic performance of plain radiography for diagnosis of knee ON is shown in Table 2.

MRI revealed multiple lesions in 31 knees (n=162, 19.1%) and single lesion was found in six knees (n=162, 3.7%) with ON. Dominant lesions in each knee were evaluated by MRI, and 28 of 37 lesions (75.7%) had a double-line sign, 33 of 37 knees (89.2%) had bone marrow edema and the size of dominant lesions ranged from 9 to 98 mm (mean: 37.7±19.8 mm, median: 37 mm) (Figure 1-3). The lesions were found to extend to the subchondral space in 24 knees (64.9%). There was no significant

Figure 1 a-e. A 36-year-old female patient with Behçet's disease treated with corticosteroid for 6 years. Anteroposterior (a) and lateral (b) plain X-rays show sclerotic changes (arrows) in both proximal tibia and distal femur without collapse. Sagittal proton density weighted (W)-fast spin-echo (FSE) (c), sagittal T1-W) spin-echo (d) and coronal T2-W FSE (e) images show multifocal serpiginous areas suggesting osteonecrosis around both knees (arrows). The areas have inner hypointense and outer hyperintense rim on T2-W images (double-line sign). Overall features are suggestive of osteonecrosis that also involves the subarticular regionA 32-year-old male patient with retroperitoneal fibrosis treated with corticosteroid for 3 years.

Table 3. Involved sites of osteonecrosis in patients with single lesion and multiple lesions

	Single lesion (n=6)	Multiple lesions (n=31)
Distal femoral diaphysis	2 (33.3%)	20 (64.5%)
Lateral femoral condyle	2 (33.3%)	27 (87.1%)
Medial femoral condyle	1 (16.7%)	24 (77.4%)
Medial tibial plateau	1 (16.7%)	10 (32.3%)
Lateral tibial plateau	-	8 (25.8%)
Proximal tibial diaphysis	-	4 (12.9%)
All compartments	-	11 (35.5%)

relationship between the number of lesions and the distribution sites (p=0.452). The distribution sites of knee ON in patients with single and multiple lesions are shown in Table 3.

The duration of CS intake was between 1 and 13 years (median: 7 years). The CS doses taken during the course of the disease varied and unfortunately these doses could not be determined. Clinical indications for CS therapy in patients with knee ON are shown in Table 4.

Only 16 out of 28 patients with knee ON had hip joint MRI (57.1%) who had hip pain. Five of 16 patients (31.3%) had femoral head ON and four of these five patients (80%) had ON of both femoral heads.

Discussion

Our results showed that approximately one third of patients suffering from arthralgia who had knee ON during CS therapy had femoral head ON. CS-induced knee ON was present in approximately one of the five patients with long-term CS intake. Double-line sign and bone marrow edema were the most common MRI findings in CS-induced knee ON. Plain radiography has low sensitivity, but high specificity for the diagnosis of knee joint ON in patients suffering from arthralgia and receiving CS therapy.

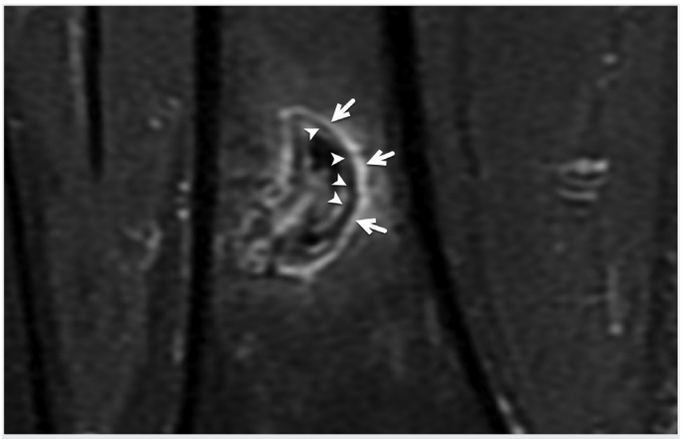

Figure 2. The coronal T2-Weighted fast spin-echo image shows serpiginous area in the distal femoral diaphysis with inner hypointense (arrowheads) and outer hyperintense rim (arrows) (double-line sign)

Following hip joint, the knee joint is the second most frequent joint affected by ON. Knee joint involvement will occur in 10% of patients with hip joint ON (1). Gladman et al. (2) showed that bilateral femoral head ON in 54.7% of systemic lupus erythematosus (SLE) patients treated with CS, and knee ON in 18.9% of these patients. However, our study showed that 31.3% of patients suffering from arthralgia with knee joint ON on CS therapy had hip joint ON. When the results of this study are evaluated together with the findings in the literature, our results support that the femoral head is affected more frequently than the knee in patients on CS therapy.

MRI is considered the gold standard for the diagnosis of ON and it has a very high diagnostic performance (1,5,9,11). Other imaging modalities such as plain radiography, bone scanning, positron-emission tomography and computed tomography for the diagnosis of femoral head ON have been previously studied extensively (11-14). Prompt diagnosis and early treatment of ON is critical because it is associated with a more favorable prognosis (13,15). Previous studies have shown that plain radiography has very low sensitivity for the early period of femoral head ON (10-13). Conklin et al. (16) and Deutsch et al. (17) described that plain radiography has a sensitivity of 41% and 44%, respectively, for the detection of CS-induced femoral head ON. To the best of our knowledge, there are no studies evaluating the performance of plain radiography in the diagnosis of knee joint ON. We found that the sensitivity of plain radiography for the diagnosis of knee joint ON was only 29.7% in patients receiving CS therapy with complaints of arthralgia. However, because of its high specificity (98.4%), and being cheap and easily accessible, we suggest that plain radiography should be the first choice in knee joint in patients receiving CS therapy, as well as in the hip joint.

CS-induced ON tends to be multifocal lesions at multiple joints, as illustrated by studies of patients with SLE who are on long-term CS therapy (2,18,19). Similarly, we found that five of 16 (31.3%) patients with knee joint ON had femoral head ON who were complaining of hip joint pain. In the presence of multiple joint pains in patients receiving CS therapy, clinicians should be aware of ON. We suggest that knee joint MRI should be performed to exclude the presence of ON if plain radiography is unremarkable and patient still complains of knee joint pain.

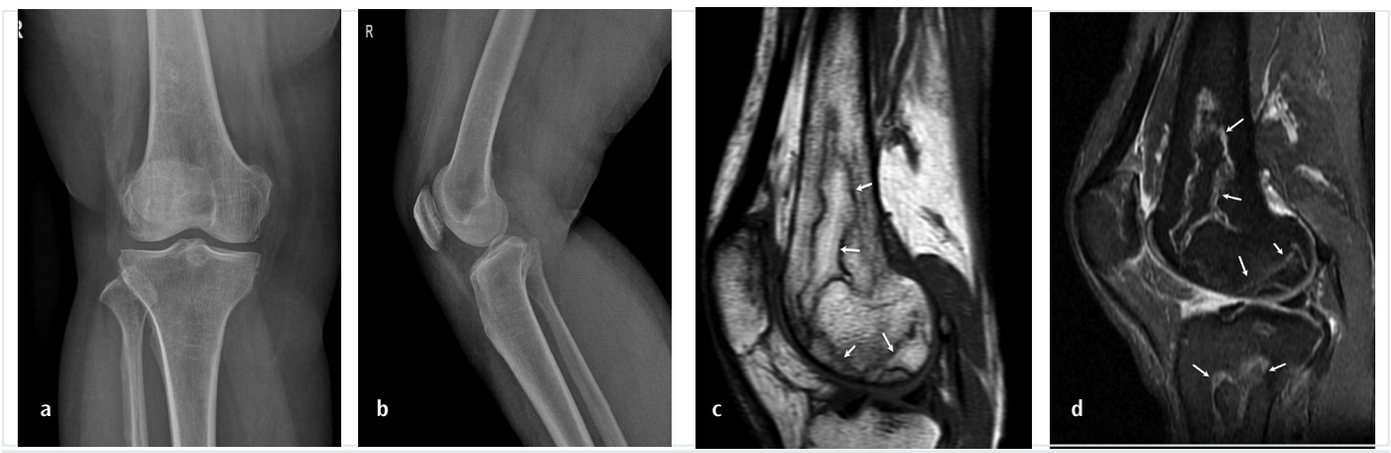

Figure 3. a-d. A 28-year-old female patient with systemic lupus erythematosus treated with corticosteroid for 7 years. Anteroposterior (a) and lateral (b) X-rays are unremarkable. Sagittal T1-Weighted (T1-W) spin-echo (c) and sagittal proton density weighted-fast spin-echo (d) images show multifocal serpiginous areas consistent with osteonecrosis that also involves the subarticular region (arrows)

Table 4. The clinical indications for corticosteroid therapy in patients

Indications for corticosteroid therapy	Number of patients (patients with knee osteonecrosis)
Lymphoma	21 (4)
History of renal transplantation	20 (4)
Rheumatoid arthritis	21 (3)
Systemic lupus erythematosus	10 (3)
Behçet's disease	8 (3)
Dermatomyositis	6 (2)
Retroperitoneal fibrosis	5 (2)
Sarcoidosis	11 (2)
Ulcerative colitis	11 (1)
Ankylosing spondylitis	11 (1)
Giant cell arthritis	9 (1)
Sjögren's syndrome	8 (1)
Pemphigus vulgaris	4 (1)

Spontaneous ON of the knee, described by Ahlbäck et al. (20), is a disorder of unknown etiology and usually affects a single location in older patients. However, CS-induced knee joint ON usually affects younger patients and presents with multiple simultaneous lesions in the femur or tibia (21). Similarly, we found multiple lesions in 31 of 37 knee joints (83.8%) with ON.

A circumscribed subchondral "band-like" hypointense lesion on T1W images and "double-line sign" on T2W images were considered pathognomonic for femoral head ON (22). The "double-line sign" consists of a hypointense outer rim (represents the reactive bone) and a hyperintense inner rim (represents granulation tissue) on T2W images. Double-line sign was found to be present in 80% of the lesions. Similarly, we found that 75.7% of dominant lesions had double-line sign on T2W images. The presence of bone marrow edema in MRI is controversial because it has two main causes: ON and bone marrow edema syndrome. The distinction between these entities is very important because treatment is different. ON is a progressive disease requiring early diagnosis and treatment, whereas bone marrow edema syndrome resolves spontaneously and surgery is not recommended. In MRI, presence of diffuse pattern in the absence of subchondral lesions seems to almost always correspond to transient bone marrow edema syndrome, which is a self-limiting disorder (23,24). In addition, the presence of bone marrow edema in patients with ON has been shown to be correlate with pain (23). In our cohort, all patients with knee joint MRI complained of pain and we found that 89.1% of knee joints with ON showed bone marrow edema. We also found that subchondral spaces were involved in 64.9% of knee joints with ON.

Study Limitations

One limitation of our study was the lack of histopathological diagnosis of the lesions. However, this did not significantly affect our results because MRI is the gold standard for the diagnosis of ON with a very high sensitivity and specificity. Second, due to the retrospective nature of our study, we could not determine the doses of CS taken by patients. However, many authors claim that the cumulative CS dose is the most important factor for the development of ON (4-6). Third, the number of patients is limited in our study. Therefore, there is a need for prospective studies with larger number of patients. Finally, all patients in our study had complaints of joint pain, thus there was a lack of pain-free patients receiving CS therapy.

Conclusion

Thirty-one point three percent of patients with knee joint ON with arthralgia who were receiving CS therapy had ON of the hip joint. Regarding its high specificity and easy accessibility, plain radiography should be the first choice in knee joint pain in patients on CS therapy. Despite a normal plain radiography, MRI should be performed in patients whose complaints are not resolved. There were multiple lesions in MRI in most of the patients who had CS-induced knee joint ON. Double-line sign and bone marrow edema were the most common MRI findings in CS-induced ON of the knee.

Ethics Committee Approval: This study was approved by institutional Pamukkale Universtiy Ethics Committee (decision no: 60116787-020/8340).

Informed Consent: Informed consent was waived due to retrospective nature of the study.

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Comparison of Early Results Between Single and Quadruple Injection of Corticosteroid-local Anesthetic in Patients with Subacromial Impingement

Subakromial Sıkışma Hastalarında Tekli Kortikosteroid-lokal Anestetik Enjeksiyonu ile Dörtlü Enjeksiyonun Erken Dönem Sonuçlarının Karşılaştırılması

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ABSTRACT

Introduction: Subacromial impingement syndrome (SAS) is a painful condition of the shoulder that affects daily activities. The objective of this study was to compare the results of single and quadruple injection (with addition of three other possible trigger points) in patients with SAS.

Methods: Sixty-eight patients with the diagnosis of SAS were randomized into two groups. The first group received a single posterior subacromial injection of 1 mL 3 mg Betamethasone (BM) + 9 mL 5 mg 0.5% Bupivacaine (BC). The second group received three extra injections in addition to the posterior subacromial injection; 1 mL BM + 9 mL BC around suprascapular nerve, 1 mL BM + 4 mL BC into the glenohumeral joint and 1 mL BM + 4 mL BC around the bicipital groove. Visual analog scale (VAS) scores, American Shoulder and Elbow Society (ASES) scores and range of motion of the patients were recorded just before the injection and at 3rd, 12th and 24th weeks. Independent samples t-test was used to compare the results of the two groups statistically.

Results: Range of motion and ASES scores were found to be higher in the quadruple injection group at all follow-up intervals ($p<0.05$). VAS scores were statistically better at the third and twelfth week for the quadruple injection group, however the difference between the two groups was statistically insignificant at the sixth month ($p=0.42$).

Conclusion: Quadruple injection resulted in increased range of motion and better functional scores at follow-up intervals up to six months in patients with subacromial impingement.

Keywords: Quadruple injection, subacromial impingement, conservative

ÖZ

Amaç: Subakromial sıkışma sendromu (SSS), omuz ağrısı ile seyreden ve günlük aktiviteleri etkileyen klinik bir tablodur. Bu çalışmanın amacı, SSS olan hastalarda tek enjeksiyonla dörtlü enjeksiyonun (muhtemel 3 tane tetik noktasının eklenerek) sonuçlarının karşılaştırılmasıdır.

Yöntemler: SSS tanısı konan 68 hasta randomize olarak iki gruba ayrılmıştır. İlk gruba posteriordan tek bir 1 mL 3 mg Bethamethasone (BM) + 9 mL 5 mg %0,5 Bupivacaine (BC) enjeksiyonu yapılırken, ikinci gruba 4'lü enjeksiyon yapılmıştır: Posterior enjeksiyona ek olarak, supraskapular sinir komşuluğuna 1 mL BM + 9 mL BC, glenohumeral ekleme 1 mL BM + 4 mL BC, bisipital oluk etrafına 1 mL BM + 4 mL BC. Enjeksiyon öncesi ve 3., 12. ve 24. haftadaki VAS skorları, hareket açıklıkları ve ASES skorlamaları kaydedilmiştir. İstatiksel hesaplamalarda, independent t-test kullanılmıştır.

Bulgular: Öne fleksiyon dışındaki tüm hareket açıklıkları ve ASES skorları, dörtlü enjeksiyon grubunda tüm kontrol aralıklarında daha yüksek bulunmuştur ($p<0.05$). Altıncı ayda ikinci gruptaki hastalar öne fleksiyon açısından daha memnun iken istatistiksel fark gözlenmemiştir ($p=0.36$). VAS skorları üçüncü ve on ikinci haftada ikinci grupta daha iyiyken altıncı ayda gruplar arasında anlamlı fark saptanmamıştır ($p=0.33$).

Sonuç: Dörtlü enjeksiyon subakromial sıkışma hastalarında altıncı aya kadar olan kontrol aralıklarında, hareket açıklığının artmasını ve fonksiyonal sonuçların daha iyi olmasını sağlamıştır.

Anahtar Kelimeler: Dörtlü enjeksiyon, subakromial sıkışma, konservatif

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Introduction

Subacromial impingement syndrome (SAS) is a wide spectrum of diseases that range from tendinitis to partial or full-thickness rotator cuff tears (1). This common disorder affects daily activities, especially during overhead activities or sleep. The concept of subacromial impingement was first described by Neer (2). The initial management of SAS includes rest or activity modification and shoulder exercises (3,4). Local injections and physiotherapy may also aid in healing of the patients (3,5-8). Although the pharmacologic mechanism of action is not similar, both corticosteroids and local anesthetics produce similar effects with regard to pain and subsequent improvement in strength and upper limb function (9). Combination of corticosteroids and local anesthetics is widely used in orthopedics and general practice in a variety of conditions including SAS. In routine practice, a single injection of corticosteroids and local anesthetics is performed into the subacromial space via posterior or anteromedial route for SAS. There are some studies reporting that the posterior route is more accurate for subacromial injections where as the results were shown to be comparable for either route in another study (10-12). There is sufficient evidence that proves subacromial injection will yield good results since the process of subacromial impingement involves subacromial bursitis and supraspinatus tendinitis.

The aim of this study was to compare the results of a single posterior subacromial injection and quadruple injection (around suprascapular nerve, into glenohumeral joint space and around biceps tendon in addition to the classical subacromial injection). The hypothesis was that the injection of four trigger points could yield better results since it involved the possible areas that could help pain relief.

Methods

Sixty-eight patients who were admitted to the orthopedics and traumatology clinic with the diagnosis of subacromial impingement between 2017 and 2018 were included in the study. The inclusion criteria were as follows: a) between ages 30 and 70 years, b) the presence of painful arc of motion, c) the presence of impingement and/or Hawkins sign, and d) the absence of pathologies on plain radiographs besides osteopenia (like osteoarthritis or mesoacromion). The exclusion criteria were as follows: a) the presence of loss of passive motion more than 25% in at least two directions (forward flexion, internal rotation, external rotation and abduction) compared to the other shoulder, b) the presence of rotator cuff tear in magnetic resonance imaging (MRI) and/or presence of a positive Jobe supraspinatus test during physical examination, c) previous shoulder surgery on the affected side, and d) the presence of systemic diseases that may be related to shoulder disorders, including diabetes mellitus or thyroid disorders. Informed consent was obtained from all participants included in the study. The ethics committee approval for this study was obtained from İstanbul Medeniyet University, Göztepe Training and Research (decision no: 2018/0256, date: 18.07.2018). The patients were divided into two groups by simple randomization using n, n+1 principle. The first group received a single posterior subacromial injection of 1 mL 3 mg Betamethasone (BM) + 9 mL 5 mg 0.5% Bupivacaine (BC). The subacromial injections were performed 2 cm distal and 2 cm medial to the posterolateral edge of the acromion. The second group received four injections: 1 mL BM + 9 mL BC around suprascapular nerve, 1 mL BM + 4 mL BC into the glenohumeral joint and 1 mL BM + 4 mL BC around the bicipital groove in addition to the posterior subacromial injection. The suprascapular nerve injection was performed according to the indirect technique described by Dangoisse (13) and the entry point was 2 cm cephalad to the middle of the spine of the scapula. The glenohumeral injection was performed 1 cm lateral to coracoid process which can easily be palpated. The long head of biceps can easily be palpated while flexing the elbow. The bicipital injection was performed just next to the tendon after feeling the rubbery consistency of the tendon. As the injections were performed, physiotherapy was started the following day and was administered to all patients for 12 weeks. Visual analog scale (VAS) scores, range of motion (measured with a goniometer) and [(American Shoulder and Elbow Society (ASES)] scores of the patients were recorded immediately before injection. The same parameters were recorded at 3rd, 12th and 24th weeks.

Table 1. Comparison of visual analogue scale, American shoulder and elbow society scores and forward flexion, abduction, internal rotation, external rotation between two groups during follow-up intervals

Time Point	Group	VAS scores (Mean ± SD)	ASES scores (Mean ± SD)	FF (Mean ± SD)	ABD (Mean ± SD)	IR (Mean ± SD)	ER (Mean ± SD)
Baseline*	Group I	7.2±0.81	44.4±2.27	119.4±5.52	88.13±4.23	44.1±3.52	68.2±3.31
	Group II	6.69±0.86	47.5±3.09	118.34±3.82	95.09±4.04	46.16±1.55	65.09±2.63
3rd Week**	Group I	6.67±0.61	51.77±2.37	137.3±4.38	107.8±4.98	51.4±3.46	71.03±3.99
	Group II	5.69±0.86	58.28±2.5	139.44±4.1	125.5±2.44	54.78±1.56	73.47±3.44
3rd Month***	Group I	4.3±0.65	59.93±2.43	153.17±3.42	110.8±4.77	52.5±3.39	73.5±4.03
	Group II	3.19±0.64	67.03±2.78	153.38±4.65	125.81±2.56	57.5±1.05	79.56±1.29
6th Month****	Group I	2±0.53	72.53±2.32	158.1±3.03	116.17±5.19	54.3±3.05	75.43±3.56
	Group II	1.88±0.66	83.28±3.38	155.53±4.38	189.19±2.21	61.5±2.42	81.22±1.13
p+	-	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001

*Baseline: p=0.02; p<0.001; p=0.39; p<0.001; p<0.01; p<0.001 (independent t-tests for baseline scores), **3rd week: p<0.001; p<0.001; p=0.05; p<0.001; p<0.001; p=0.01 (independent t-tests for 3rd week scores), ***3rd month: p<0.001; p<0.001; p=0.84; p<0.001; p<0.001; p<0.001 (independent t-tests for 3rd month scores), ****6th month: p=0.42; p<0.001; p=0.01; p<0.001; p<0.001; p<0.001 (independent t-tests for 6th month scores).

VAS: visual analogue scale, ASES: American shoulder and elbow society, FF: forward flexion, ABD: abduction, IR: internal rotation, ER: external rotation, SD: standard deviation, Group I: experimental group, Group II: control group, +: Results of one-way ANOVA with repeated measures

Statistical Analysis

SPSS version 24.0 (IBM Corp., Armonk, NY, USA) was used for analysis. Mean and standard deviation was reported for each measurement period and each group. Kurtosis and skewness were calculated for normality, and Independent t-test was used to determine differences between groups. One-way ANOVA with repeated measures was performed to define overall effect of measurements at different time points. $P<0.05$ was considered significant.

Results

Four patients in the experimental group and two patients in the control group were lost during follow up. The experimental group consisted of 30 patients (11 men, 19 women; mean age: 53.9±6.6 years) and the control group consisted of 32 patients (9 men, 23 women; mean age: 55.4±5.2 years).

For all scores, time has a significant effect on each group as a result of repeated ANOVA measures ($p<0.001$ for all scores and groups). Independent samples t-test was performed for each time point between each group to indicate which differences were significant between the groups. At baseline, 3rd week and 3rd month time points, the results were statistically significantly better for controls regarding all scores except for forward flexion. All scores were significantly better for controls at 6th month compared to Table 1 experimental group.

Discussion

The diagnosis of subacromial impingement is usually simple and can be made after several clinical tests. The most reliable diagnostic tests are Hawkins sign and the presence of a painful arc. Conservative treatment should be the initial choice of treatment. Local injection and shoulder exercise therapy should be specific and of low intensity and high frequency (8). The prognostic factors related to conservative treatment along the natural course of subacromial impingement were investigated in a study, and younger age, lower body mass index, higher functional capacity, shorter symptomatic period, reversible changes on MRI, and higher Constant and ASES scores at initial evaluation were reported as good prognostic factors (14). Increased thoracic flexion and a posture with head ahead of trunk, posterior capsule tightness and less passive internal rotation were shown to be related to symptoms when asymptomatic population and subacromial impingement patients were compared (15). Physical therapy may include interventions to increase thoracic extension. One hundred and fifty-seven British Elbow and Shoulder Society member surgeons were asked to complete a questionnaire, and the responses revealed that 97% of surgeons performed subacromial injection, 87% repeated the injection if the previous injection was performed by a general practitioner and 94% recommended physical therapy (40% for three months) (5).

Corticosteroids are used for their anti-inflammatory and direct analgesic effects. They reduce proinflammatory mediators and have effect on the cells involved in inflammatory responses (16). Other possible mechanisms include local hyperemia, reflex muscle relaxation and enhancing local tissue metabolism (17). Corticosteroid injections may lead to complications such as skin atrophy and discoloration, septic arthritis, as well as deleterious effects on intraarticular cartilage or tendon degeneration and even spontaneous tendon ruptures (18). The onset of action of corticosteroids takes place within 24-48 hours, and its effect enhances for approximately 2-3 weeks (19). Local anesthetics such as lidocaine act by membrane stabilization with a preferential block to small fibers that carry pain and autonomic impulses (20). Some studies suggest that the combination of local anesthetics with corticosteroids is effective, however, some authors state that the results of injection of local anesthetic alone and combination with corticosteroid are comparable (7,21). A prospective, randomized controlled double-blind study involved a lidocaine injection group of 19 patients which was compared with a control group of 20 patients who received lidocaine + triamcinolone injection. During a follow up period of six months, forward flexion and external rotation were significantly increased in the control group (increase forward flexion: 24 °C vs 11 °C external rotation: 10 °C vs 5 °C, respectively) (7). There are also studies against the efficacy of corticosteroids. In another study involving 58 patients with a 6-month follow-up period, xylocaine and xylocaine + betamethasone injection yielded comparable results for all follow-up intervals (21). A meta-analysis of 11 studies and 726 patients reported that corticosteroid injections had no significant effect at three-month follow up (22). In clinical practice, physicians often use a combination of corticosteroid suspension with local anesthetics for local intra-articular injections. The optimal dosage, concentration and volume in the subacromial space are still controversial (9). There are several studies on the combinations of corticosteroid suspension with either high-volume (23,24) or low-volume (25). A study involving two groups of 26 patients reported that 3 cc lidocaine + 1 cc triamcinolone and 9 cc lidocaine + 1 cc triamcinolone yielded comparable results during a follow-up of 8 weeks (9).

Neer's three-stage classification is commonly used in the literature to evaluate patients with subacromial impingement (26). In our study, only patients with Neer type 1 and 2 impingement that did not have a partial or full tear of the rotator cuff were included to provide homogenous sample groups. The three additional trigger points that are highly possible to play a major role in pain were targeted for local injection. The first one is around the suprascapular nerve. Infiltration of suprascapular nerve by injection contributes tremendously in pain relief, so the suprascapular nerve block is commonly used for the treatment of chronic painful shoulder, especially in adhesive capsulitis (27). The relationship between subacromial impingement, posterior capsule tightness and loss of internal rotation has been clearly defined (27). The second injection into the glenohumeral joint space through the rotator interval is likely to yield better range of motion, especially in terms of internal rotation, and it may also help alleviate symptoms related to synovitis in the glenohumeral joint. Our results have shown that patients with restricted internal rotation had better range of motion after the fourth injection. The third point is near the long head of biceps, since it has been already shown that the biceps tendon is commonly involved in subacromial impingement and that it plays a leading role in shoulder pain (28,29). Pain relief in the short term is crucial for patients with shoulder pain. Shoulder disorders frequently lead to depression secondary to chronic pain, which interferes with daily activities, and sleep quality is almost always negatively affected. A recent study has shown that shoulder pain affecting the patients for more than three months resulted in depression, anxiety and sleep disorders (30).

Conclusion

The results in this study were better with the fourth injection during six months follow-up in terms of range of motion (excluding forward flexion) and ASES scores. VAS scores improved significantly until the third month, as the scores were indifferent at six months. The range of motion was increased, especially in terms of internal-external rotation and abduction with multiple injection technique. The main target in the treatment of subacromial impingement is strengthening the rotator cuff muscles. Reaching this target is easier when the patient is painless with a greater range of motion. Further studies may be necessary for the long-term results of multiple injections.

Ethics Committee Approval: The ethics committee approval for this study was obtained from İstanbul Medeniyet University, Göztepe Training and Research (decision no: 2018/0256, date: 18.07.2018).

Informed Consent: Informed consent was obtained from all participants included in the study.

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Cerebral Venous Thrombosis in Pregnancy

Gebelikte Serebral Venöz Tromboz

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ABSTRACT

Introduction: Although not a prevalent disease, cerebral venous thrombosis (CVT) has been considered relatively morbid. There is little research about CVT in Iran, but it is more likely during pregnancy and puerperium. Therefore, we conducted this study to determine the incidence and risk factors during pregnancy.

Methods: Twenty-eight patients were selected from the hospital archives. The files of pregnant patients who were diagnosed as CVT and who were admitted to the hospital between April 2015 and March 2018 were studied for demographic and gestational information. Statistical methods and software were utilized.

Results: The incidence of CVT was 14.52 cases per 100.000 pregnancies. Less than one third of the cases occurred in the postpartum period with a mean disease age higher than the pregnancy period. Immobility, primiparity, 0 Rh+ blood type or consanguineous marriage was found in most of the cases. Past medical histories were positive in 11 cases. Caesarean delivery or onset in the first postpartum week was found in most of the postpartum cases. magnetic resonance imaging managed to diagnose all cases, while computed tomography scan failed to do so. CVT was in the transverse sinus in most of the cases.

Conclusion: The study reveals some risk factors for CVT, such as immobilization, chronic hypertension, preeclampsia and caesarean section.

Keywords: Venous thrombosis, pregnancy, postpartum period

ÖZ

Amaç: Sık görülen bir hastalık olmasa da, serebral venöz tromboz (SVT) nispeten morbid olarak kabul edilmiştir. İran'da SVT hakkında çok az araştırma vardır, ancak hamilelik ve lohusalıkta daha olasıdır. Bu nedenle gebelikte insidans ve risk faktörlerini belirlemek için bu çalışmayı yaptık.

Yöntemler: Yirmi sekiz olgu hastane arşivinden seçildi. Nisan 2015-Mart 2018 tarihleri arasında hastaneye başvuran ve SVT tanısı almış gebelerin dosyaları demografik ve gebelik bilgileri açısından incelendi. İstatistiksel yöntemler ve yazılım kullanıldı.

Bulgular: SVT insidansı, 100,000 gebelikte 14,52 idi. Olguların üçte birinden daha azı doğum sonrası dönemde görülürken, bu hastaların ortalama hastalık yaşı gebelik dönemindeki hastalardan daha yüksekti. Olguların çoğunda immobilite, primiparite, 0 Rh+ kan grubu veya akraba evliliği tespit edildi. Geçmiş tıbbi öykü 11 olguda pozitifti.

Postpartum olguların çoğunda sezaryen doğum veya doğum sonrası birinci haftada hastalık başlangıcı bulundu. Manyetik rezonans görüntüleme tüm olguları teşhis etmeyi başarırken, bilgisayarlı tomografi taraması bunu yapamadı. SVT, olguların çoğunda transvers sinüslerde idi.

Sonuç: Bu çalışma, SVT için hareketsizlik, kronik hipertansiyon, preeklampsi ve sezaryen gibi bazı risk faktörlerini ortaya koymaktadır.

Anahtar Kelimeler: Venöz tromboz, gebelik, doğum sonrası dönem

Introduction

In a study conducted in 2012, the annual incidence of cerebral venous thrombosis (CVT) was 1.32 per 100.000 persons (1). Sasannejad et al. (2) reported that CVT was more frequent during the fasting months, accompanied by the consumption of oral contraceptives (OCPs). CVT is three times more likely in women due to gender-related risk factors, e.g. consumption of OCPs and hormone replacement therapy (3). Pregnancy and postpartum period are also known risk factors for CVT (4).

The most frequent symptoms include headache, seizures and focal neurological deficits (5,6). CVT is believed to be a significant cause of stroke, thus a high-mortality disease (7). The major predictors of outcome are a parenchymal lesion size >6 cm, bilateral Babinski signs, male gender, parenchymal hemorrhage and level of consciousness (8). Mortality has decreased in the recent years (9) and this may be due to a progress in diagnostic methods and earlier detections.

There is scarce reliable data about the medical histories and prognosis of patients with CVT, and they are generally based on the findings

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obtained by studying one facility or area with small samples (10). There is not enough recorded data about CVT in Iran. Due to the severe complications of CVT, this study was conducted in order to determine the incidence in pregnant women, to list the risk factors, including demographic and gestational factors, and to suggest an interventional approach for quick and proper management to be used in curative and palliative scheduling and decision making about these patients.

Methods

Procedure

This was a descriptive study on the files of pregnant patients admitted to the emergency department with a diagnosis of CVT between April 2015 and March 2018. Following authorization, we visited the hospital archives and obtained the list of pregnant patients diagnosed with "CVT" within the specified 3-year period.

First, a checklist of information gathering including demographics [age, gestational age, occupation, education, body mass index (BMI), etc.] and gestational factors (gravidity, number of abortions, family history of preeclampsia, history of preeclampsia in previous pregnancies, blood type, the mother's hemoglobin level, contraception method, complications of pregnancy, drugs used, history of hormone therapy, etc.) was assembled. Then, we visited the archives and filled out each checklist by carefully examining the corresponding file.

The acquired cases were evaluated according to inclusion and exclusion criteria, and a total of 28 patients and their data were evaluated. Total statistics of pregnancies submitted within the three years were extracted from the reports of the provincial health center.

Target Population and Sample

Due to the low number of pregnant patients with this diagnosis, the sample size was considered as all the pregnant patients visiting from April 2015 to March 2018 with the mentioned diagnosis, having acquired it during pregnancy or postpartum period. The sampling method was a headcount until completion.

Inclusion Criteria

- Pregnant patients with CVT confirmed by magnetic resonance imaging (MRI), CT scan or cerebral MR venography,

- Complete clinical and radiological data.

Exclusion criterion

- Coagulopathy before pregnancy.

Statistical Analysis

Data were analyzed using IBM SPSS v20 (IBM Corporation, Armonk, New York, US). The findings were analyzed using descriptive statistical methods [including tables, charts and calculation of mean and standard deviation (SD)], and chi-square test and Fisher's exact test were used for comparison of categorical variables. In all cases, the results were considered statistically significant if they had a p value <0.05.

Ethical Considerations

- A warrant was obtained from the Office of the Vice Chancellor of Research (decision no: 54-12167, date: 28.09.2014). Written consent was obtained.

- The data collected from the files of the patients were kept completely confidential. For further assurance, the names of patients were removed from the checklists and patients were given ID numbers.

- The findings and results of the research were presented to the beneficiaries and published in coordination with them.

Results

According to the statistics obtained from the provincial health center, a total of 192.773 pregnant women were registered in three years; and since the hospital under study is a facility of referral for patients with this diagnosis, the incidence of CVT in this study was calculated as 14.52 cases per 100.000 pregnancies.

Of the 28 patients studied, 20 cases (71.4%) were affected during pregnancy and eight cases (28.6%) were affected in the postpartum period.

The status of the patients for each year they were referred to the center is stated in Table 1. The highest number of patients was from April 2017 to March 2018, followed by April 2015 to March 2016 and then April 2016 to March 2017. The mean number of patients diagnosed with CVT was 9.33 per year.

The mean age of the patients was 31.85±8.08 years. The oldest age was 55 years and the youngest age was 20 years. In addition, the mean age was 30.9±7.12 years in the group affected during pregnancy and was 34.25±10.25 years in the group affected in the postpartum period.

Regarding education, patients were classified into 3 groups: illiterate, primary and secondary education, and higher education. Two cases were illiterate, 19 cases had primary or secondary education, and seven cases had higher education. Regarding occupational status, patients were classified into two groups. Twenty-four patients (85.7%) were housewives and four patients (14.3%) were employed.

Height, weight and BMI of the patients were also recorded. Mean, SD, minimum and maximum values for each case are stated in Table 2.

Table 1. Pregnancy status of patients according to years

Time of referral	Pregnancy	Postpartum	Sum
April 2015 to March 2016	5	4	9
April 2016 to March 2017	5	1	6
April 2017 to March 2018	10	3	13
Total	20	8	28

Table 2. Mean height, weight and body-mass index of the patients

	Minimum	Maximum	Mean	Standard deviation
Height	154	176	162.28	5.46
Weight	50	86	69.82	8.31
BMI	21.06	32.76	26.50	3.10

BMI: body mass index

The patients were investigated in terms of obstetrical history, gravidity, abortions and labors. Mean, SD, minimum and maximum values for each case are stated in Table 3. There was no history of abortions in 17 patients, while 11 cases mentioned at least one abortion. The percentages of these histories with the number of abortions are illustrated in Figure 1. Based on parity, the patients were divided into three groups: nulliparous, primiparous and multiparous. The frequencies of each are illustrated in Figure 2.

The patients were also investigated for history of OCP use. While 16 cases (57.14%) did not mention any history of OCP use, 12 cases (42.86) mentioned it. In addition to OCP use, drug history of the patients was recorded separately. There was no history of drug use in 18 cases (64.3%), while 10 cases (35.7%) had a history of routine drug use. One patient had a history of multiple drug use (warfarin and fluoxetine). There were two patients with a history of warfarin use, one due to a CVT in the previous pregnancy and the other due to a CVT unrelated to pregnancy.

Smoking history, alcohol consumption and substance abuse were investigated. Twenty-five patients had a negative history, one case had a history of smoking and two cases had a history of infrequent alcohol consumption.

The patients were also examined based on blood type and 0 Rh+ was the most common blood type. The full results are stated in Figure 3.

The past medical history of the patients was also studied. Seventeen cases had no history. Two patients reported a history of chronic hypertension (HTN) and two cases had a history of treated CVT. Other recorded histories are stated in Figure 4.

Platelet and hemoglobin levels of the patients were recorded and stated in Table 4. Two patients (7.14%) had hemoglobin levels below 10 g/dL and 26 patients (92.86%) had hemoglobin levels between 10 and 14 g/dL. In addition, five patients (17.86%) had platelet levels below 150.000/µL, 22 patients (78.57%) had platelet levels between 150.000 and 450.000 and one patient (3.57%) platelet levels above 450.000.

Seventeen patients (60.71%) did not have coagulopathy, while seven patients (39.29%) had coagulopathy. Familial history of thrombosis was investigated in the first-degree relatives of the patients. The results

Table 3. Number of pregnancies, abortions and labors

	Minimum	Maximum	Mean	Standard deviation
Gravidity	1	4	2.35	1.02
Abortion	0	3	0.5	0.74
Labor	0	3	1.17	0.81

Table 4. Platelet and hemoglobin levels of the patients

	Minimum	Maximum	Mean	Standard deviation
Platelet	22000	520000	223928.57	110141.29
Hemoglobin	8.5	13.6	11.59	1.18

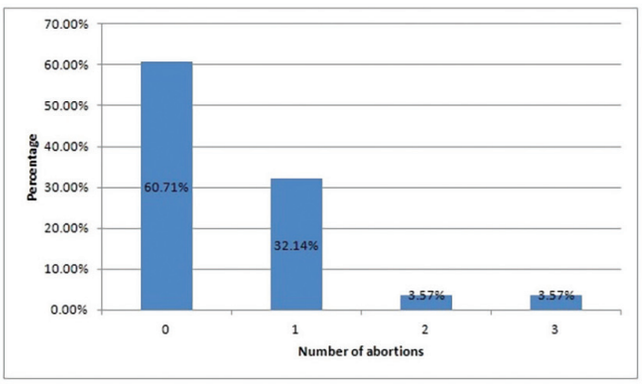

Figure 1. Number of abortions and percentages

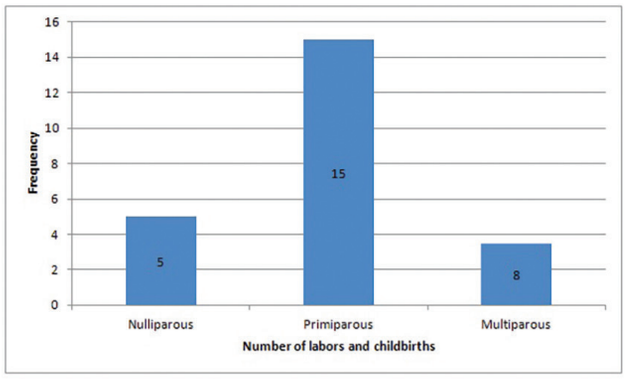

Figure 2. Number of labors and percentages

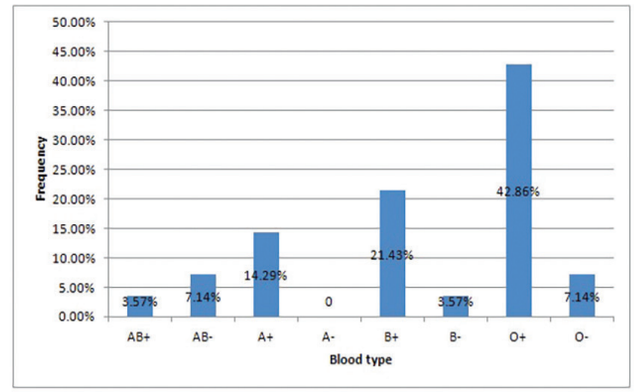

Figure 3. Blood types of patients and percentages

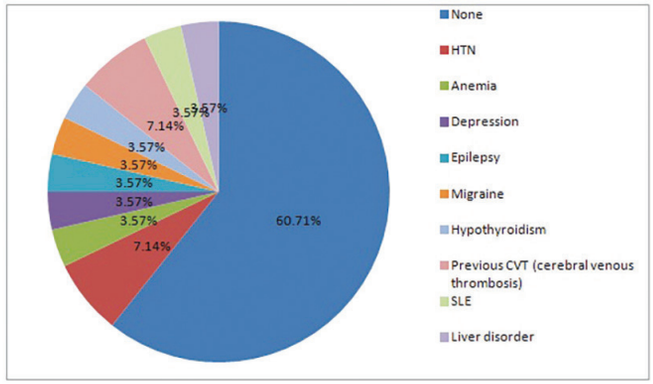

Figure 4. Past medical history of the patients

were positive in five cases (17.86%) and negative in 23 cases (82.14%). Regarding consanguineous marriage, sixteen cases (57.14%) had such marriage, while 12 cases (42.86%) did not.

The seasons of referral were also recorded. Eight patients were referred in spring, six cases in summer, eight cases in fall and six cases in winter.

The diagnostic procedures requested for the patients were studied. MRI was used in 25 cases, all of which resulted in diagnosis. CT scans were performed in 16 patients, of which only one failed to diagnose. Some of these procedures revealed the veins with thrombosis, as illustrated in Figure 5. In one case, the patient refused MRI, leading to a CT scan that failed to find the specific area.

The outcomes of therapeutic measures taken until the patient was discharged were investigated. Twenty-four patients were discharged with general wellbeing. Two patients were discharged with personal consents and two patients died at hospital due to this condition. The outcomes according to pregnancy status at the time of referral are stated in Table 5. There was no significant difference in outcomes between the two groups (p=0.76).

The following findings were obtained when eight postnatal patients were examined: Three cases were affected after vaginal delivery, while the other five were affected after caesarean delivery. The mean time from delivery to referral to the facility and diagnosis was equal to 6.87±1.80 days, with a minimum of 4 and maximum of 10 days. This period was also divided into two sets, first week after delivery (six cases) and second week (two cases). One patient suffered from preeclampsia. One case had a history of CVT in her previous pregnancy. One case managed to become pregnant by IVF. Two cases mentioned history of abortions in their previous pregnancies. Three patients did not specify any conditions in their current pregnancy or previous pregnancies.

Table 5. Final outcomes of the patients according the pregnancy status

	Well during discharge	Dead	Not defined	Total
Pregnant	17	1	2	20
Postpartum	7	1	0	8

Table 6. Gestational ages by weeks and days

	Minimum	Maximum	Mean
Days	42	259	106.05
Weeks	6	37	15 weeks and 1 day

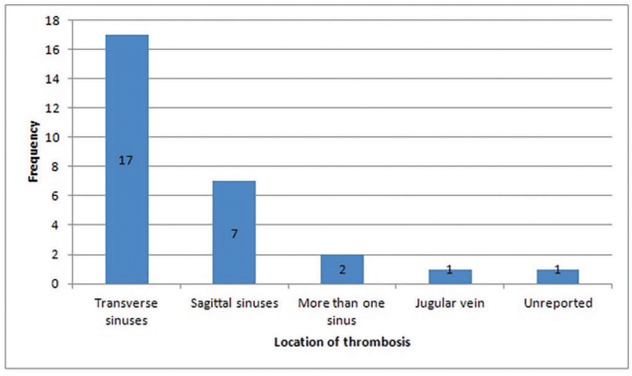

Figure 5. Involved veins and percentages

Regarding 20 patients who were affected before delivery, the following findings were achieved: The gestational age by days and weeks was calculated and is stated in Table 6. Ten patients were affected in the first trimester, seven cases in the second trimester and three cases in the third trimester. There was no statistically significant difference in outcomes among patients with different trimesters (p=1.00). The patients were also examined for pregnancy complication risks. Twelve cases had safe pregnancy. Five cases had risky pregnancies due to a history of abortion, one case due to stillbirth in a previous pregnancy, one case due to IVF and one case due to a diagnosis of HELLP syndrome.

Discussion

The incidence of CVT in our study was 14.52 cases per 100.000 pregnancies. In a study by Coutinho et al. (1) in 2012, the incidence was 1.32 per 100.000 person-years, while it was 2.78 among women between the ages of 31 and 50 years.

Liang et al. (11) reported that 60.47% of CVT cases in pregnancy occurred in the postpartum period. We found a lower rate of postpartum cases, which was 28.57%. However, our cohort had a smaller size compared to the aforementioned study.

The mean age was 31.85±8.08 years, close to what was observed in a study on stroke (12). However, the minimum and maximum values were higher in our study.

Most of the patients were housewives. Although there is not enough data to support immobilization as an independent risk factor for CVT, the high prevalence could indicate a role, even temporary. Engbers et al. (13) studied a larger sample and found immobility as a risk factor for venous thrombosis. However, our patients had lower ages compared to the minimum age of inclusion in the mentioned study (70 years), therefore not covering pregnant women.

In a study, it was proposed that obesity was a risk factor of CVT, apparently stronger when accompanied with OCP use (14). However, our study subjects had a normal mean BMI. Another study demonstrated short-term use of OCPs as a risk factor (10), but the association was not very strong in our study.

Most of the cases in our study were primiparous. Al-Hayali et al. (15) conducted a case-series study on 30 peripartum women with acute neurological emergencies received in the critical care unit and found most cases of CVT were multiparous compared to eclampsia, which was more common in the primiparous cases.

In a study, non-0 blood types were associated with venous thromboembolism (16), while the cases in our study were mostly 0 Rh+. Regardless of the Rh type, the 0 type was still dominant.

Miller et al. (17) conducted a study on the risk factors of stroke in pregnancy and found that infection, chronic HTN, prothrombotic state, coagulopathy and severe preeclampsia or eclampsia as the most common factors. Most of the patients in our study did not have any past

medical history, while two cases had chronic HTN and two had previous CVT.

While a study by Liu et al. (18) showed an inverse relationship between lower hemoglobin levels and CVT prognosis, most of our cases had normal hemoglobin levels. However, the minimal normal level in our study was 10 g/dL, whereas the minimal level was 11 g/dL in the mentioned study. It should be noticed that our mean level was close to the lower threshold in the mentioned study. In another study, anemia was also shown as a risk factor for CVT (19).

MRI had a 100% diagnostic value in our study, whereas CT scan missed one patient. A review by Lee et al. (20) showed that CT scan was not specific. The transverse and sigmoid sinuses were presented as the most common site of thrombosis in a cross-sectional study by Coutinho et al. (1) investigating the most common areas of CVT (1). In our study, the majority of CVT cases were in the transverse sinuses, followed by sagittal sinuses.

Most of the cases in our study were generally well at discharge. In a review by Luo et al. (4), most of the participants had good prognosis after discharge, but unable to return to previous work.

Similar to the results of a report by Ehler et al. (21), most of the postpartum cases in our study occurred following caesarean section. While most of our postpartum cases had occurred in the first week, another study showed a majority of cases in the second and third weeks following delivery (22). Mean gestational age of the cases during pregnancy was 106.05 days or 15 weeks and 1 day. Fifty percent of the cases in our study were in the first trimester. However, no statistically significant relationship was found between the outcome and the trimester of occurrence in our study (p=1.00).

This study was conducted with the patients in only one referral center. The data could not be generalized well. Due to the low prevalence of CVT, the sample had a small size. We suggest further studies with more hospitals and facilities and thus larger samples. Systematic reviews are also recommended.

Conclusion

CVT could afflict pregnant women with similar odds before or after delivery, though postpartum cases usually occur at slightly higher ages. Immobility could at least have a temporary role. Obesity does not have any association with CVT; the same could be said for OCP use. Gravidity is irrelevant to the risk of CVT. Blood type does not have any association either. Chronic HTN, anemia and preeclampsia are partially strong risk factors for CVT. Coagulopathy does not have any role either. CT scan is not an appropriate diagnostic method in CVT, as opposed to MRI. The transverse sinuses are common areas of occurrence. CVT has a generally well prognosis. Caesarean section is associated with a higher risk of CVT. The disease is likely in all three weeks after delivery. The same could be said for all trimesters during pregnancy. It is suggested to notice signs and symptoms of CVT in patients admitted 1 to 3 weeks after delivery, especially in those with a caesarean section. In addition, the pregnant patients should be educated about the symptoms and risk factors.

Ethics Committee Approval: A warrant was obtained from the Office of the Vice Chancellor of Research (decision no: 54-12167, date: 28.09.2014).

Informed Consent: Written consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - A.A., S.K., S.S.V.; Concept - S.K.; Design - S.S.V.; Data Collection and/or Processing - A.A., S.K.; Analysis and/or Interpretation - H.H., S.S.V; Literature Search - A.A., H.H.; Writing Manuscript - H.H.

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

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Negative Impact of Postoperative Early Surgical Incision Dressing: A Prospective Observational Study

Postoperatif Erken Cerrahi İnsizyon Pansumanının Negatif Etkisi: Prospektif Gözlemsel Bir Çalışma

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ABSTRACT

Introduction: Povidone-iodine (Betadine®) is a commonly used solution to prevent surgical site infection in the postoperative period. In this study, time of first dressing after surgery was investigated. Early (second day) povidone-iodine dressing was compared with late (fifth day) dressing in terms of wound healing or inflammation.

Methods: The study was conducted in a gynecology clinic between June 2017 and June 2018. The patients who underwent surgery were divided into two groups as early and late dressing. The two groups were compared in terms of wound healing or inflammation. Inflammation was defined as the presence of redness, swelling and serous discharge (non-purulent) at the wound site.

Results: The study included 49 women with median incision. Inflammation was observed in 11 patients (22.4%). Mean age (45.7±11.3 vs 49.3±9.5), Body mass index (29.02±5.6 vs 30.89±4.0), rate of diabetic patients (21% vs 36%), rate of hypertensive patients (34% vs 36%), rate of smoking (13% vs 34%), operative time >4 hours (32% vs 63%), and operation category (malign or benign) were not statistically different between patients with normal wound healing and patients with inflammation. Twenty-two patients were dressed with povidone-iodine on postoperative day 2 (early group) and 27 patients were on postoperative day 5 (late group). The incidence of wound inflammation was significantly higher in the early group (11% vs 36%, p=0.035).

Conclusion: According to this study, early dressing had no advantage compared to late dressing. In addition, the rate of inflammation in the incision line was higher in the early dressing group. Before epithelialization of the surgical wound is completed, contact of povidone-iodine with the surgical incision wound and subcutaneous penetration of povidone-iodine may adversely affect the wound healing process.

Keywords: Povidone-iodine, inflammation, epithelialization, surgical site infection

ÖZ

Amaç: Povidone-iodine (Betadine®), ameliyat sonrası dönemde cerrahi alan enfeksiyonunu önlemek için yaygın olarak kullanılan bir solüsyondur. Bu çalışmada cerrahi sonrası ilk pansuman zamanı araştırıldı. Erken (ikinci gün) povidion iyot pansumanı, yara iyileşmesi veya enflamasyonu açısından geç (beşinci gün) pansumanla karşılaştırıldı.

Yöntemler: Çalışma Haziran 2017-Haziran 2018 tarihleri arasında bir kadın hastalıkları ve doğum kliniğinde yapıldı. Cerrahi uygulanan hastalar erken ve geç pansuman olarak iki gruba ayrıldı. İki grup, yara iyileşmesi veya enflamasyonu açısından karşılaştırıldı. Enflamasyon, yara bölgesinde kızarıklık, şişme ve seröz akıntı (pürülan olmayan) varlığı olarak tanımlandı.

Bulgular: Çalışmaya medyan batın insizyonu olan 49 kadın alındı. Enflamasyon 11 hastada gözlendi (%22,4). Ortalama yaş (45,7±11,3 ve 49,3±9,5), vücut kitle indeksi (29,02±5,6 ve 30,89±4,0), diyabetik hasta oranı (%21 ve %36), hipertansif hasta oranı (%34 ve %36), sigara içme oranı (%13 ve %34), uzun ameliyat süresi (>4 saat) (%32 ve %63) ve ameliyat kategorisi (malign veya bening) enflamatuvar grupta istatistiksel olarak anlamlı değildi. Yirmi iki hastaya ameliyat sonrası ikinci günde (erken grup) povidon-iyot ile pansuman yapılmış, 27 hastaya beşinci günde (geç grup) yapılmıştı. Yara enflamasyonu insidansı erken grupta anlamlı olarak yüksekti (%11'e karşılık %36, p=0,035).

Sonuç: Bu çalışmada, erken pansumanın geç pansumanla karşılaştırıldığında avantajı gözlenmedi. Erken pansuman yapılan grupta, insizyon hattındaki enflamasyon oranı daha yüksek gözlendi. Cerrahi yaranın epitelizasyonu tamamlanmadan önce, povidon iyodinin cerrahi yara ile teması ve povidon iyodinin subkütan penetrasyonu yara iyileşmesi sürecini olumsuz etkileyebilir.

Anahtar Kelimeler: Povidon iyot, enflamasyon, epitelizasyon, cerrahi alan enfeksiyonu

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Introduction

Povidone-iodine irrigation is a commonly used solution to prevent surgical site infection. The most commonly used commercial form is a 10% solution in water yielding 1% available iodine (1). The effects of povidone-iodine on wound healing are not clear. Some studies have shown that wound healing is adversely affected by povidone-iodine (2,3).

Povidone-iodine solution is usually used for postoperative wound dressing in clinics. In our clinic, the incision dressing is opened on the second postoperative day. The incision is closed back after wiping with povidone iodine solution. In this study, we investigated whether wound healing was affected if the first dressing was postponed to the fifth day. We have chosen the fifth day because granulation tissue in an incision line begins to form approximately four days after the lesion (4-6). Our aim was to investigate whether dressing after epithelialization and granulation tissue formation would be more advantageous.

Methods

The study was conducted between June 2017 and June 2018 in Gynecology and Obstetrics Clinic of İstanbul Training and Research Hospital. Informed consent forms were obtained from the patients. In this study, patients with median abdominal incisions were included in the analysis, as patients with Pfannenstiel incisions were not hospitalized long enough to be evaluated on the fifth day.

Incision dressing is routinely opened on the second postoperative day in our clinic. Dressing with povidone-iodine solution is done and then the incision is closed back. For this study, the first dressing days of some patients with median incisions were postponed to the fifth day. The patients who underwent surgery were randomly divided into two groups as early and late dressing. The two groups were compared in terms of wound healing or inflammation. Inflammation was defined as the presence of redness, swelling and serous discharge (non-purulent) at surgical incision site. In this study, the evidence for the presence of infection was not investigated. In fact, none of the patients had purulent discharge to support the presence of infection. This study was an observational clinical study and ethics committee approval was not required.

Statistical Analysis

Statistical analysis was performed using SPSS software. Data were expressed as median and interval for continuous variables. Binary variables were reported as numbers and percentages. Categorical variables were evaluated according to group size using the $\chi 2$ test or Fisher's exact test. $P<0.05$ was accepted to indicate statistical significance. This study was an observational clinical study and ethics committee approval was not required.

Results

The study included 49 women with median incisions (Table 1). Inflammation was observed in 11 patients (22.4%). Mean age (45.7±11.3 vs 49.3±9.5), body mass index (29.02±5.6 vs 30.89±4.0), rate of diabetic patients (21% vs 36%), rate of hypertensive patients (34% vs 36%), rate of smoking (13% vs 34%), operative time >4 hours (32% vs 63%), and operation category (malign or benign) were not statistically different between patients with normal wound healing and patients with inflammation. Twenty-two patients were dressed with povidone-iodine on postoperative day 2 (early group) and 27 patients were on postoperative day 5 (late group). The incidence of wound inflammation was significantly higher in the early group (11% vs 36%, p=0.035) (Table 2).

Table 1. General characteristics of 49 patients with median abdominal incision

Age, median (min-max)	46 (18-70)
BMI, mean ± SD (min-max)	29.4+5.2 (19-39)
Diabetes, % (n)	24.5% (12)
Hypertension, % (n)	34.7% (17)
Smoking, % (n)	18.4% (9)
Operation category	
Benign	46.9% (23)
Malign	53.1% (26)
Operative time	
<2 hours	20.4% (10)
2-4	40.8% (20)
<4	38.8% (19)
Inflammation, (presence of redness, swelling and serous discharge)	22.4% (11)

BMI: body mass index; min: minimum; max: maximum; SD: standard deviation

Table 2. Comparison of patients with normal wound healing and patients with inflammation

Feature	Normal wound healing	Patients with inflammation	p
Number of patients	38	11	-
Age, mean ± SD	45.7±11.3	49.3±9.5	0.335
BMI, mean ± SD	29.02±5.6	30.89±4.0	0.316
Diabetes			
Yes	8 (66%)	4 (33%)	0.427
No	30 (81%)	7 (19%)	
Hypertension			
Yes	13 (77%)	4 (23%)	1.000
No	25 (78%)	7 (22%)	
Smoking			
Yes	5	4	0.506
No	33	7	
Operative time			
<2 hours	9	1	0.150
2-4 hours	17	3	
>4 hours	12 (32%)	7 (63%)	
Day			
2	14	8	0.035
5	24	3	

Inflammation was accepted as presence of redness, swelling and serous discharge
BMI: body mass index, SD: standard deviation

Discussion

In this observational prospective study, the effects of early and late dressing with povidone-iodine on wound healing were compared. The absence of redness, swelling or discharge at the wound site was considered normal wound healing. According to the results of the study, wound healing was better in late dressing.

Povidone-iodine is a topical antimicrobial that has been shown to be effective against bacteria, fungi, several viruses, spores, protozoa and amoebic cysts (7-9). *In vitro* studies on this subject reported different results. Some *in vitro* studies have suggested that even dilute solutions of povidone-iodine are toxic to human fibroblasts (2,3). These authors stated that caution should be used when povidone-iodine is placed on an open wound, and that prolonged contact with viable uncontaminated tissue should be avoided. On the other hand, in vitro studies or meta-analysis of povidone-iodine in wound healing demonstrated that concentrations less than 10% generally do not inhibit the granulation and epithelialization processes (10,11). Several animal studies investigating the effect of povidone-iodine on wound microcirculation have shown inconsistent findings (1,12,13).

The stages of wound healing proceed in an organized way and follow four processes: hemostasis, inflammation, proliferation and maturation. The purpose of the proliferative stage is to form a viable epithelial barrier to activate keratinocytes (5). The closure of the lesion itself, which includes angiogenesis, fibroplasia, and re-epithelialization, occurs at this stage. These processes begin in the lesion within the first 48 hours and may continue up to the 14th day (6). Granulation tissue begins to form approximately four days after the lesion (5).

Conclusion

In our opinion, contact with povidone-iodine before epithelialization and granulation may adversely affect wound healing steps. Early opening of a surgical wound that has been closed in the operating room under sterile conditions does not provide an advantage. This observational prospective study may help clinicians in planning postoperative surgical incision dressing.

Ethics Committee Approval: This study was an observational clinical study and ethics committee approval was not required.

Informed Consent: Informed consent forms were obtained from the patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.K., O.S., K.O., I.K., F.F.V.; Design - A.K., O.S., K.O., I.K., F.F.V.; Data Collection and/or Processing - O.S., K.O.; Analysis and/or Interpretation - A.K., O.S.; Literature Search - A.K., I.K.; Writing Manuscript - A.K., I.K.

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

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The Values of First-trimester Maternal Serum Markers in Predicting Poor Obstetric Outcomes

İlk Trimester Maternal Serum Belirteçlerinin Kötü Obstetrik Sonuçları Öngörmede Değeri

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ABSTRACT

Introduction: The effects of pregnancy-associated plasma protein A (PAPP-A) and maternal serum free beta-human chorionic gonadotropin (β-hCG), which are first trimester maternal serum markers, on assisting in the diagnosis of chromosomal abnormalities and perinatal outcome are discussed. The aim of the presented study was to investigate the predictive value of first-trimester PAPP-A and β-hCG) levels in predicting poor obstetric outcomes.

Methods: A total of 549 patients who underwent first trimester screening in Perinatalogy Outpatient Clinic of our hospital between January 2016 and March 2018 were included in this study. Patients with crown-rump length (CRL) measurements in the range of 45-84 mm, patients with singleton pregnancy and patients who delivered at 24 weeks or later were included in the study. CRL, nuchal translucency, mean uterine artery pulsatility index, PAPP-A and free β-hCG levels were recorded. The 5th and 10th percentile values of PAPP-A and free β-hCG levels were designated according to the literature.

Results: There was no difference between PAPP-A percentile groups in terms of mean birth weight or gestational age at delivery. However, mean gestational age at delivery was lower in patients with free β-hCG levels below 10th percentile. Preterm delivery was significantly higher in the group with PAPP-A levels below 5th percentile (p=0.049). Also, preeclampsia (PE) was higher in the group with free β-hCG below 10th percentile (p=0.003).

Conclusion: The risk poor obstetric outcome such as preterm delivery, low birth weight and PE may be associated with low PAPP-A and free β-hCG levels. However, further studies are needed to explain the relationship between first trimester screening markers and neonatal outcomes.

Keywords: Pregnancy-associated plasma protein A, beta HCG, preeclampsia, preterm delivery

ÖZ

Amaç: İlk trimester maternal serum belirteçlerinden olan Gebelikle ilişkili plazma proteini-A (PAPP-A) ve maternal serum free beta-insan koryonik gonadotropin (sβ-hCG) düzeylerinin kromozomal anomalilerin tanısına yardımcı olmanın dışında perinatal sonuçlar üzerine etkileri üzerinde durulmaktadır. Çalışmamızın amacı ilk trimester PAPP-A ve sβ-hCG düzeylerinin kötü obstetrik sonuçları öngörebilmedeki değerini incelemektir.

Yöntemler: Çalışmamıza, ilk trimester taramasını Ocak 2016-Mart 2018 yılları arasında hastanemiz Perinataloji Polikliniği'nde yaptırmış 549 hasta dahil edilmiştir. Ultrasonografik taramada fetüs baş-pop uzunluğu (CRL) ölçümü 45-84 mm aralığında olan, tekil, 24 hafta ve üzerinde doğum yapmış olan hastalar çalışmaya alınmıştır. CRL, nukal kalınlık, ortalama uterin arter pulsatilite indeks ölçümleri ve PAPP-A, sβ-hCG değerleri kaydedilmiştir. Literatüre göre PAPP-A ve sβ-hCG'nin 5. ve 10. persentil değerleri düzenlenmiştir.

Bulgular: PAPP-A persentil grupları ile ortalama doğum kilosu veya ortalama doğum haftası arasında bir ilişki bulunmamıştır. Bunun yanında sβ-hCG'nin 10. persentil altı düzeylerinde ortalama doğum haftasının daha düşük olduğu izlenmiştir. PAPP-A'nın 5. persentil altı düzeylerinde preterm doğum oranı daha sık (p=0,049) ve sβ-hCG'nin 10. persentil altı düzeylerinde preeklampsinin belirgin olarak yüksek oranda görüldüğü izlenmiştir (p=0,003).

Sonuç: Preterm doğum, düşük doğum ağırlığı ve preeklampsi gibi kötü obstetrik sonuç gelişme riski düşük PAPP-A ve sβ-hCG düzeyleri ile ilişkili olabilir. Yine de, ilk trimester tarama belirteçleri ile obstetrik sonuçlar arasındaki ilişkiyi açıklayabilmek için çok sayıda çalışmaya ihtiyaç duyulmaktadır.

Anahtar Kelimeler: PAPP-A, beta HCG, preeklampsi, preterm doğum

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Introduction

First trimester screening has a paramount importance to reveal anomalies in the fetus. The combination of maternal age, nuchal translucency (NT), maternal serum free beta-human chorionic gonadotropin (free β-hCG) and pregnancy-associated plasma protein A (PAPP-A) identifies trisomy-21 with an 85% detection rate with a 5% false positivity (1,2). Also, some studies have shown a relationship between low PAPP-A and free β-hCG levels in the 11-13th weeks of gestation with poor obstetric outcomes such as stillbirth, fetal growth restriction (FGR), preterm delivery and preeclampsia (PE) (3-7).

PAPP-A is an insulin-like growth factor binding protein-4 (IGFBP-4) protease, which is secreted by trophoblasts and decidual cells. Low PAPP-A levels decrease the IGF levels by increasing the IGFBP-4 level. IGF is a stimulant molecule for fetal growth and maturity (8). Meanwhile, free β-hCG is secreted by syncytiotrophoblasts of the placenta in addition to the corpus luteum of the ovary in early pregnancy and it promotes angiogenesis, and its secretion increases under different conditions such as uteroplacental insufficiency (9).

The aim of the presented study was to investigate the predictive value of first trimester PAPP-A and free β-hCG levels for poor obstetric outcomes. Although different cut-off values have been proposed in the literature, we took the 5th and 10th percentile ranks of FASTER study to detect the effect of PAPP-A and free β-hCG levels on obstetric outcomes (5).

Methods

The study cohort consisted of pregnant women who underwent first trimester screening in our Perinatology Clinic between January 2016 and March 2018. The medical records were evaluated retrospectively and 549 patients were included in the study. Patients with crown-rump length (CRL) measurement between 45 and 84 mm, patients with singleton pregnancy and patients who delivered at 24 weeks or later were included.

A single operator performed all ultrasonographic evaluations with a 5-8 MHz 3D transducer ultrasound system (General Electric Voluson E8™, GE Healthcare, Chicago, Illinois, United States) via transabdominal route. All maternal variables such as age, height, weight, body mass index, gravidity and parity were recorded. Also, CRL measurements with the concordant gestational week, NT, mean uterine artery pulsatility index, PAPP-A and free β-hCG levels were noted.

PAPP-A and free β-hCG levels were measured by chemiluminescent immunometric assay from blood samples of pregnant women using Immulite 2000 XP device (Siemens A6 Healthcare Sector, Erlangen, Germany). These indicators were converted into multiples of the expected median (MoM) value with PRISCA 5.0 software considering the maternal age, medical history and patient-specific factors. The 5th and 10th percentile ranks of PAPP-A and free β-hCG values were determined according to FASTER study and groups were constructed amongst these values to compare the possible differences of preterm delivery, low birth weight (LBW) and PE between groups (5).

According to the World Health Organization, preterm delivery is accepted as labor before 37th weeks of pregnancy. According to the American College of Gynecologists, LBW is accepted as <2500 gr live birth. PE criteria were as follows: hypertension (systolic pressure ≥140 mmHg/diastolic pressure ≥90 mmHg) starting after 20th gestational week and accompanied by proteinuria (≥300 mg proteinuria in 24 hours or rate of protein/creatinine >0.3) or end organ dysfunction (platelet count <100000/mL or serum creatinine level ≥1.1mg/dL or two-fold increase in serum transaminase levels). Adana Dr. Turgut Noyan University, Non-interventional Clinical Research Ethics Committee (decision no: KA18/187).

Statistical Analysis

All recorded values such as maternal characteristics, correlation between birth weight and gestational age at delivery between pregnancy groups according to 5th and 10th percentile values of PAPP-A (0.42 MoM/0.52 MoM) and free β-hCG (0.35 MoM/0.44MoM) were analyzed with SPSS version 21 software package. Categorical variables were expressed as number and percentage, and constant variables were expressed mean and standard deviation (median and range, where necessary). Student's t-test for constant variables and Fisher's Exact test for categorical variables were used to compare baseline characteristics and perinatal outcomes. Spearman correlation analysis was used to describe the relationship between gestational age at delivery, birth weight and PAPP-A and free β-hCG levels. Presence of PE was evaluated with Mann-Whitney U test between groups. A p value of <0.05 was accepted as significant in all statistical analysis.

Results

A total of 736 records were evaluated and it was realized that 170 patients were lost during follow-up. Also, five pregnancies were terminated due to congenital anomalies, nine patients had stillbirth before 20th gestational week and one patient delivered at 23rd gestational week, so these patients were excluded. All patients excluded from the analysis had a PAPP-A and free β-hCG levels above 10th percentile, but one intrauterine ex fetus (14th gestational week) had a low PAPPA level (0.26 MoM). Consequently, a total of 549 patients were included in the study. The maternal characteristics and evaluated variables are presented in Table 1. Table 2 shows the patients having PAPP-A or free β-hCG below 5th and 10th percentiles.

The indications for preterm delivery were PE, preterm premature rupture of membrane, spontaneous preterm birth, acute fetal distress, chorioamnionitis, abruptio placenta, fetal cardiac anomaly and maternal decompensated cardiac failure.

According to our retrospective calculations, PAPP-A had a power of %95 for preterm delivery/PE comparison and free β-hCG had a power of 100% for PE comparison.

We did not find any significant difference between PAPP-A percentile groups in terms of mean birth weight (5th and 10th percentile, p=0.243 and p=0.139, respectively) or gestational age at delivery (5th and 10th percentile, p=0.229 and p=0.523 respectively). However, there was a statistically significant difference between free β-hCG percentile groups regarding mean gestational age at delivery (5th percentile p=0.013 and 10th percentile p=0.037). There was no difference in birth weights

according to free β-hCG levels (5th percentile p=0.232 and 10th percentile p=0.778).

The rate of LBW, preterm delivery and PE were 5.5% (n=30), 6.9% (n=38) and 7.8% (n=43) in entire cohort, respectively. Only preterm delivery was significantly higher in PAPP-A below 5th percentile group (p=0.049). However, no significant cut-off value was obtained by ROC analysis. Also, PE was higher in free β-hCG groups below the 5th and 10th percentiles (p=0.032 and p=0.003, respectively). ROC analysis for relationship between free β-hCG levels and PE revealed an AUC of 0.6 (0.5-0.7, 95% CI). A cut-off value of 0.765 MoM for free β-hCG (64% sensitivity, 53.5% specificity, 11.2 % negative predictive value and 63.2% positive predictive value) was determined for the prediction of PE (p=0.03).

SGA and PE were detected at a rate of 50% (n=19) and 29% (n=11) in all preterm deliveries (n=38), respectively. The relationship between maternal serum PAPP-A and free β-hCG values above and below 5th and10th percentiles with mean gestational age at delivery, weight and adverse perinatal outcomes are presented in Table 3.

Discussion

According to our results, the rate of preterm delivery was higher in lower percentiles of PAPP-A and the rate of PE was higher in the lower percentiles of free β-hCG. Preterm delivery is considered as a result of the suboptimal intrauterine environment, which causes FGR. The higher prevalence of preterm deliveries with low PAPP-A in our cohort might be affected by the presence of LBW babies in this group (10).

There is a controversy in the literature about the use of first trimester NT, PAPP-A and free β-hCG measurements, alone or in a combination, to estimate birth weight, gestational age at delivery and perinatal outcomes

Table 1. The maternal characteristics, first trimester screening variables and mean gestational age at delivery/weight

	n	mean (±SD)	minimum-maximum
Maternal age	549	30.4 (±4.7)	18-45
Gravidity/parity	549	2/1	1-9/0-4
BMI (kg/m^2)	509	24.2 (±4.2)	15.5-46
Gestational age	549	12^{+3}w (±0.5)	11^{+2}-14w
CRL (mm)	549	60 (±7.35)	45-82
NT (mm)	547	1.6 (±0.33)	1-2.6
Mean uterine artery PI	462	1.90 (±0.6)	0.71-5.27
PAPP-A (MoM)	549	1.07 (±0.6)	0.17-3.53
Free β-hCG (MoM)	549	1.18 (±0.96)	0.15-14.5
Gestational age at delivery	549	38^{+4}w (±1.4)	28^{+3}-41^{+1}w
Birth weight (g)	549	3306 (±500)	1050-5000

SD: standard deviation; BMI: body mass index; CRL: crown-rump length; NT: nuchal translucency; PI: pulsatility index; PAPP-A: pregnancy-associated plasma protein A, MoM: multiples of median, β-hCG: beta-human chorionic gonadotropin

Table 2. The evaluation of the patient groups in the <5th percentile and <10th percentile groups of PAPP-A and free β-hCG

	PAPP-A (MoM)	n (%)	Free β-hCG (MoM)	n (%)
<5th centile	0.42	40 (7.3%)	0.35	24 (4.4%)
<10th centile	0.52	75 (13.6%)	0.44	67 (12.2%)

PAPP-A: pregnancy-associated plasma protein A, MoM: multiples of median, β-hCG: beta-human chorionic gonadotropin

Table 3. The relationship between maternal serum PAPP-A and free β-hCG values with mean gestational age at delivery, weight and adverse perinatal outcomes in groups according to 5th and 10th percentiles

	Mean birth weight, (g)	p	Mean gestational age at delivery	p	LBW, n (%)	p	Preterm delivery n (%)	p	Preeclampsia, n (%)	p
PAPP-A<5th	3213	0.243	37w6d	0.229	1 (2.5%)	0.715	6 (15%)	0.049	5 (12.5%)	0.228
PAPP-A≥5th	3313		38w2d		29 (5.7%)		32 (6.3%)		38 (7.5%)	
PAPP-A<10th	3244	0.139	38w2d	0.523	2 (2.7%)	0.409	7 (9.3%)	0.336	9 (12%)	0.164
PAPP-A≥10th	3315		38w4d		28 (5.9%)		31 (6.5%)		34 (7.2%)	
Free β-hCG <5th	3208	0.232	37w6d	0.013	1 (4.2%)	1	3 (12.5%)	0.227	5 (20.8%)	0.032
Free β-hCG≥ 5th	3310		38w3d		29 (5.5%)		35 (6.7%)		38 (7.2%)	
Free β-hCG <10th	3267	0.778	38w0d	0.037	4 (6%)	0.776	6 (9%)	0.445	12 (17.9%)	0.003
Free β-hCG ≥10th	3311		38w4d		26 (5.4%)		32 (6.6%)		31 (6.4%)	

PAPP-A: pregnancy-associated plasma protein A; β-hCG: beta-human chorionic gonadotropin; LBW: low birth weight

(1,11-13). Poon and Nicolaides stated that PAPP-A, placental growth factor and uterine artery Doppler measurements, in combination with first trimester maternal risk factors, predict early onset PE with a rate of 95% (14). Dugoff et al, in their multicenter FASTER study, defined the percentile ranks of MoM values with the combination of first trimester NT, PAPP-A, and free β-hCG measurements in a cohort of 33.395 pregnant women. Their results showed that a level of PAPP-A ≤10th percentile indicated almost 2.5-fold higher risk for LBW and correlation with poor obstetric outcomes. For free β-hCG levels, they identified a relationship with spontaneous loss below 24th weeks of gestation in ≤1st percentile group (5). Covans and Spencer supported the results of the FASTER study in their study, which confirmed the relationship between low PAPP-A levels and LBW (15). Also, Kaijomaa et al. compared groups with PAPP-A <0.3 MoM and PAPP-A ≥0.3 MoM, and they stated that low PAPP-A values indicated poor obstetric outcomes (16). Our results did not demonstrate any association with mean gestational age at delivery, weight, LBW and PE at low values of PAPP-A, yet we only found that the preterm delivery rate increased with PAPP-A levels below 5th percentile (<0.42 MoM).

Similarly, conflicting results have been published about the relationship between low levels of free β-hCG in the first trimester and poor pregnancy outcomes. Sirikunalai et al. reviewed 13.620 singleton pregnancies and summarized in their study that free β-hCG <0.5 MoM value was associated with FGR, preterm delivery, LBW and low APGAR scores (17). Nevertheless, another study did not show a similar relationship between β-hCG at first or second trimester and FGR and PE, but reported that second trimester intact hCG >3 MoM might predict FGR. The authors concluded that the placental dysfunction might lead to pregnancy complications such as FGR or PE (18). In our cohort, the rate of PE was higher in the lower percentiles of free β-hCG. Extreme levels of free β-hCG may be considered as a marker for prenatal surveillance of pregnancies.

Two studies from our country showed contradictory results. In the first study with 318 singleton pregnancies, no significant relationship was found between low PAPP-A levels and incidence of subsequent pregnancy outcomes (19). In the other study, there was a correlation between low PAPP-A levels (≤0.35 MoM) and preterm delivery, low mean birth weight and low gestational age at delivery. However, low free β-hCG levels were not associated with measured variables (20). In our study, the lower percentiles of free β-hCG were associated with lower gestational age at delivery. On the contrary, such a correlation could not be demonstrated between lower PAPP-A percentiles and birth weight or gestational age at delivery.

Sonek et al. stated that first trimester markers in combination with maternal characteristics predicted early or late onset PE with a high detection rate and a low false positive rate (21). Similarly, we found a relationship between low free β-hCG levels and PE.

On the other hand, there are many studies in the literature stating that PAPP-A levels were not helpful in predicting poor obstetric outcomes (22-24). In our study, however, there was an increase in preterm delivery in low PAPP-A group and the difference was statistically significant. We did not reach any conclusions to accept the null hypothesis since the effect seemed limited. On the other hand, considering literature and our results, pregnancies with a level of PAPP-A below 5th percentile and free β-hCG do not require exceptional monitoring (25).

Our study has some limitations, including (i) retrospective nature, (ii) lack of interpretation of possible covariates, and (iii) lack of evaluation of comprehensive obstetric outcomes (diabetes mellitus, placental pathologies, etc.).

The main difficulty in making a definitive conclusion on this topic is the heterogeneity of the cohorts and methodological differences between the studies in the literature. In addition, different measurement techniques, experiences, thresholds and analysis methods lead to inconsistent outcomes (11,12, 21, 26-28). Considering the literature, more studies with larger cohorts are needed to establish nomograms in the pregnant population.

Conclusion

Early pregnancy markers such as NT, PAPP-A or free β-hCG, alone or in combination, seem unsatisfactory to predict adverse pregnancy outcomes. The clinical implication of these markers should have better positive predictive values and coherent understanding of the mechanisms of the pathophysiological process of the poor obstetric outcomes. Further studies are needed to explain the relationship between first trimester screening markers and neonatal outcomes while considering possible covariates.

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Attitudes of Married Women Towards Induced Abortion in Manisa

Manisa'daki Evli Kadınların İsteyerek Düşüğe Karşı Tutumları

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ABSTRACT

Introduction: This study was aimed at revealing attitudes of married women towards induced abortion.

Methods: This study was descriptive and the study population included 64.382 married women aged 15-49 years in the city of Manisa. Three hundred and eighty-three women were selected from 11 "family health care centers" by proportional stratified sampling. The data were collected using "Socio-demographic Information Form", "Attitude Inventory of Induced Abortion" and "Knowledge of Induced Abortion Form".

Results: The participants had the highest rates of agreement with the items "induced abortion is a sin" and "induced abortion is a murder". Multivariate analyses showed that women at an older age, women with higher education, women having a nuclear family, women with fewer living children, women with a previous induced abortion, women using a modern family planning method, women defining themselves as nullifidians or who did not fulfil religious rituals, and women having higher scores for knowledge of induced abortion had a more positive attitude towards induced abortion.

Conclusion: The results of the study showed that the attitudes of women towards induced abortion were affected by religion, but that they had the enough flexibility to have a positive attitude when a medical or social necessity arose.

Keywords: Abortion, medical abortion, women

ÖZ

Amaç: Bu araştırma evli kadınların isteyerek düşük konusundaki tutumlarının incelenmesi amacıyla planlanmıştır.

Yöntemler: Araştırma tanımlayıcı tiptedir ve araştırmanın evrenini Manisa kent merkezindeki 15-49 yaş evli 64,382 kadın oluşturmaktadır. Manisa kent merkezinde hizmet veren 11 adet aile sağlığı merkezinden orantılı tabakalama yöntemi ile 383 evli kadına ulaşılmıştır. Araştırmanın verileri "Sosyo-demografik Bilgi Formu", "İsteyerek Düşüğe Yönelik Tutum Envanteri" ve "İsteyerek Düşüğe Yönelik Bilgi Formu" ile toplanmıştır.

Bulgular: Araştırmada kadınların isteyerek düşüğe yönelik tutum ifadelerinden en yüksek katılımı; "isteyerek düşük yaptırmak günahtır" "isteyerek düşük bir cinayettir" ifadelerine göstermişlerdir. Yapılan çok değişkenli analizlerde; yaşı büyük, daha uzun süreli eğitim almış, çekirdek aile yapısına sahip, yaşayan çocuk sayısı az olan, daha önce isteyerek düşük yapan, modern aile planlaması yöntemi kullanan, kendini inançsız ya da dini inançları yerine getirmeyen biri olarak tanımlayan ve isteyerek düşük konusunda bilgi puanı yüksek olan kadınların isteyerek düşüğe yönelik tutumlarının daha olumlu olduğu görülmüştür.

Sonuç: Araştırma sonucunda kadınların isteyerek düşüğe yönelik tutumlarının dinden etkilendiği, fakat tıbbi ve toplumsal bir gereklilik ortaya çıktığında ise isteyerek düşüğe olumlu bakabilecek esnekliğe sahip oldukları düşünülmektedir

Anahtar Kelimeler: Düşük, medikal düşük, kadın

Introduction

Induced abortion is an important problem associated with reproductive health in all countries, especially in developing countries. According to the World Health Organization, 210 million women become pregnant each year and 42 million of these pregnancies are terminated with abortion (1). Induced abortion is an indicator of the fact that family planning needs cannot be fulfilled in developing countries (2). Turkey Demographic and Health Survey (2013) revealed that 5% of married women had induced abortion (3). That is, the rate of unfulfilled family planning needs is 5% in Turkey. Induced abortion is one of the most important and debatable issues related to reproductive health. Regulations made under the influence of religious and social values usually cause familial, religious and social pressure on women (4). Using family planning methods and having induced abortion are regulated by laws around the world. While

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induced abortion is legal in some countries, it is only permitted for medical, psychological and social reasons in other countries (5). With the adoption of the law in 1983, induced abortion was taken under state control and the number of induced abortions has considerably decreased in Turkey (6). Since induced abortion is performed under safe conditions after the law came into force, the maternal mortality rate due to induced abortion has decreased from 50% to 2% (7). Although many people are in favour of the idea that induced abortion is necessary in some occasions, religious and political approaches contradict individual tendencies, and moral and religious debates over induced abortion even overshadow health-related aspects of the issue (2). It is really difficult for women to decide to have induced abortion and their decisions are influenced by their religious beliefs, personal values and attitudes of the society towards abortion. Induced abortion is an issue still debatable and upon which there is not an agreement in Turkey, where 99% of the population is Muslim. Although there have been numerous studies about attitudes towards induced abortion in the world (8-17), there is not a comprehensive study on the issue in Turkey.

The aim of this study was to reveal attitudes of the married women towards induced abortion and the variables likely to affect their attitudes.

Methods

Sample

This study had a descriptive design and the study population included 64.382 married women aged 15-49 years in the city of Manisa, Turkey. Based on a prevalence of 50% in the smallest sample, the size of which is unknown (5% of standard deviation and 95% of confidence interval), the study sample was calculated as 383. When the sample group was determined, the stratification of the family health care center (FHCC) regions as high, medium, and low socio-economic level was taken as the basis (based on the Manisa Provincial Health Directorate data). The numbers of the FHCCs were written on papers and 11 FHCCs were selected from each stratum via draw. Proportional stratified sampling was used and 383 women were contacted. Data were collected face-to-face from women who gave informed consent. Approval was obtained from Ethical Committee of Celal Bayar University Faculty of Medicine and the Health Directorate of Manisa (decision no: 5.1, date: 04.01.2012).

Three data collection tools were developed by the researchers in the light of the relevant literature: "Socio-demographic Information Form" composed of 15 questions, "Attitude Inventory of Induced Abortion" including 14 items and "Knowledge of Induced Abortion Form" including 12 questions. They were piloted on 10 women to test their understandability and practicality. Data collected during piloting the tools were excluded from the analysis. It took 10-15 minutes for the participants to complete all the tools.

Socio-demographic Information Form

It includes questions regarding age, education, income and perceived income, family type, place where participants lived the longest, perceived piety, number of pregnancies, number of living children, previous induced abortion, use of family planning methods, receiving information about induced abortion, education and employment status of spouses and induced abortion status of relatives.

Attitude Inventory of Induced Abortion

It was developed by researchers to determine attitudes towards induced abortion. First, the researchers prepared a list of 30 items in the light of the literature. The list was sent to five experts specialized in the issue and they were requested to evaluate the items in terms of understandability, appropriateness and discriminativeness. In accordance with suggestions and recommendations of the experts, the items were revised and the number of the items was decreased to 14. Thus, the content validity of the inventory was achieved. Of the 14 items, six (1-6 items) were positive and eight (7-14 items) were negative statements. It is a Likert scale and the items were evaluated on a five-point scale: five points for "strongly agree", four points for "agree", three points for "neither agree nor disagree", two points for "disagree" and one point for "strongly disagree". Negative statements were scored in reverse order. The Cronbach alpha value of the inventory was 0.78. The questions of the inventory were prepared by the researchers based on the literature. Only reliability analysis (Cronbach alpha value and expert opinions) was performed in the study. Since the inventory was not designed as a scale, the validity analyzes were not performed.

The highest and the lowest scores to be obtained from the inventory were 70 and 14 points, respectively. High scores indicate a positive attitude towards induced abortion and low scores indicate a negative attitude.

Knowledge of Induced Abortion Form

It was developed by the researchers to evaluate the knowledge of the paritcipants on induced abortion. The questions are about the definition of induced abortion, legal aspects, problems likely to arise after the procedure and consent of the spouse for the procedure. It includes 12 items and the scores are based on the number of correct answers. Each correct answer is scored as 1, and the lowest and the highest scores to be obtained are 0 and 12, respectively.

To evaluate perceived piety, a question that was taken from the study "religion, secularism and the veil in daily life survey" by KONDA was used (18).

Statistical Analysis

Obtained data were analyzed by SPSS 16.0. Data were expressed as mean, standart deviation, numbers and percentages. Chi-square test, independent Samples t-test, Mann-Whitney U test, variance analysis, correlation and multiple linear regression analysis were used where appropriate.

Results

The mean age of the participants was 31.28±7.91 years. Of all participants, 53.3% were primary school graduates and dropouts of primary school and illiterate; 80.4% were unemployed; 40.9% were married to graduates, primary school graduates and dropouts of primary school and illiterate; 76.0% had a nuclear family; 76.2% had a perceived income equal to their expenses and 57.1% lived the longest

in Manisa. Seventy percent of women defined themselves as religious persons. Fifty point two percent of women were informed about induced abortion and the mean score for their knowledge of induced abortion was 6.97±2.01 (minimum: 0, maximum: 11.00, median: 7.00). Eighty-two point two percent of the women were using a modern family planning method. Evaluation of reproductive status of women showed that the mean number of pregnancies was 2.13, the mean number of living children was 1.59 and 16.5% of women had at least one induced abortion (Table 1).

There was a higher degree of agreement with the idea that "induced abortion is a sin" and that "induced abortion is a murder". The degree of agreement with the ideas that "women can have induced abortion if pregnancy is life-threatening for the mother", "if a pregnant woman is mentally ill" and "if a baby with a disability is likely to be born" was also high. Women had a higher rate of agreement with the item "induced abortion is interference with a woman's body". In addition, the rate of agreement with the idea that "if a woman has induced abortion, it should be kept secret" was high. The rate of agreement with the items "induced abortion is shameful" and "induced abortion should be banned" was low (Table 2).

Older women, women with higher education, employed women, women with a nuclear family, women with a perceived income higher than their expenses, women who lived in a city the longest, women defining themselves as nullifidians or who did not fulfil religious rituals, women

Table 1. Descriptive characteristics of participants

Characteristics		n	%
Age 31.28±7.91 minimum: 16, maximum: 49, median: 30	16-25 years	106	27.7
	26-35 years	165	43.1
	36-45 years	88	23.0
	46 years or older	24	6.3
Education	Graduates and dropouts of primary school, illiterate	204	53.3
	Secondary school graduates	77	20.1
	High school graduates	67	17.5
	University graduates	35	9.1
Employment status	Employed	75	19.6
	Unemployed	308	80.4
Spouses' education*	Graduates and dropouts of primary school and illiterate	150	40.9
	Secondary school graduates	70	19.8
	High school graduates	103	29.1
	University graduates	36	10.2
Family	Nuclear	291	76.0
	Extended	80	20.9
	Broken	12	4.2
Perceived income	Lower than expenses	66	17.2
	Equal to expenses	292	76.2
	Higher than expenses	25	6.5
Insurance*	Yes	369	96.9
	No	13	3.1
Place where participants lived longest*	Village	71	18.7
	Town	87	22.9
	City	217	57.1
Self-definitions of religiosity*	Someone with no religious conviction	2	0.5
	Someone who does not believe in religious obligations	1	0.3
	Believer who does not fulfil religious obligations	87	22.7
	Religious person who strives to fulfil religious obligations	269	70.2
	Fully devout person fulfilling all religious obligations	23	6.0
Number of pregnancies	2.13±1.60 minimum: 0, maximum: 12, median: 2		
Number of living children	1.59±1.24 minimum: 0, maximum: 6, median: 2		
Number of induced abortions	0	320	83.5
	1	53	13.9
	2	9	2.3
	3	1	0.3

Table 1 contiuned

Using family planning methods*	Modern	282	81.9
	Conventional	61	17.7
	None	1	0.4
Induced abortion status of relatives*	Yes	200	53.1
	No	177	46.9
Receiving information about induced abortion*	Yes	188	49.8
	No	191	50.2
Scores for knowledge of induced abortion	6.97±2.01 minimum: 0, maximum: 11, median: 7		
Total		**383**	**100**

*Twenty-four women whose spouse died or who got divorced did not answer the question about the education level of the spouse, eight women did not answer the question about the place where they lived the longest, one woman did not answer the question about health insurance, one woman did not answer the question about religiosity, 39 women did not answer the question about using family planning methods, six women did not answer the question about induced abortion status of their relatives and four women did not answer the question about receiving information about induced abortion

Table 2. Mean scores for items in attitude inventory of induced abortion

Items	Mean ± SD
1. If pregnancy poses a threat to a mother's life, induced abortion can be carried out	3.81±1.05
2. Induced abortion can be performed if a mother is mentally ill	3.50±1.13
3. Induced abortion is an interference with a woman's body	3.36±1.18
4. Induced abortion should be performed if a baby with a disability is likely to be born	3.18±1.24
5. Induced abortion can be performed to terminate unwanted pregnancies	2.73±1.22
6. Induced abortion can be performed if the baby cannot not be cared for	2.66±1.22
7. Induced abortion should be banned	3.40±1.23
8. Whatever the circumstances are, induced abortion should never be performed	3.32±1.23
9. Induced abortion is shameful	3.27±1.21
10. If a woman has induced abortion, it should be kept secret.	3.07±1.21
11. Induced abortion can only be performed in cases of rapes	2.96±1.24
12. Induced abortion is unnecessary; God takes care of everybody	2.84±1.26
13. Induced abortion is a murder	2.37±1.24
14. Induced abortion is a sin	2.25±1.18

SD: standard deviation

with a previous induced abortion, women with a relative having a history of induced abortion, women using a modern family planning method, women with a higher number of children and women having higher scores for knowledge of induced abortion received significantly higher scores on Attitude Inventory of Induced Abortion (p=0.001) (Table 3).

Multivariate analyses showed that women at an older age, women with higher education, women with a nuclear family, women with fewer living children, women with a previous induced abortion, women using a modern family planning method, women defining themselves as nullifidians or who did not fulfil religious rituals, and women having high scores for knowledge of induced abortion had a more positive attitude towards induced abortion. Thirty-four percent of the variance in the scores for attitudes towards induced abortion could be explained by the number of living children, family types, age, previous induced abortion, using family planning methods, education, scores for knowledge of induced abortion and self-definitions of religiosity. Other variables should be considered to explain the rest of the variance (R^2=0.34, p<0.05) (Table 4).

Discussion

This study conducted to reveal women's attitudes towards induced abortion showed that the attitudes of women were contradictory, i.e. a negative attitude caused by religious beliefs and a positive attitude caused by their needs. The religious elements in the items caused women to exhibit a negative attitude towards induced abortion; on the other hand, medical and social needs enabled a positive attitude towards induced abortion. Although three-fourths of the women considered themselves as religious, their religious beliefs did not turn out to have a negative impact on their attitudes towards induced abortion as expected.

The item which reflects a positive attitude towards induced abortion and with which the women had a higher degree of agreement was "if the pregnancy poses a threat to the mother's life, induced abortion can be carried out", and this higher agreement is consistent with the literature (8-11,13,19-21).

Table 3. Distribution of scores on attitude inventory of induced abortion according to descriptive characteristics

Descriptive characteristics (n)	Total X ± SD	t/f/X²	p
Age groups*			
30 yrs and young (203)	41.25±8.78	t=-3.21	p=0.001
Older than 30 yrs (180)	44.13±8.76		
Education levels**			
Illiterate+literate (55) a	38.32±7.35	f=19.99	p=0.000, a<b<c
Primary school graduates (224) b	41.80±8.49		
High school graduates and those having higher education levels (104) c	46.71±8.97		
Employment status			
Unemployed (308)	41.57±8.58	t=-4.74	p=0.000
Employed (75)	46.85±8.86		
Family			
Nuclear (288)	43.90±8.70	t=5.15	p=0.000
Extended+broken (95)	38.66±8.23		
Perceived income			
Lower than expenses (66) a	40.68±8.66	X2=3.88	p=0.143
Equal to expenses (292) b	42.94±8.89		
Higher than expenses (25) c	43.76±8.88		
Place where one lived the longest**			
Village/small town (71) a	41.46±9.24	f=5.10	p=0.002, a=b<c
Town (87) b	40.48±9.03		
City (217) c	43.86±8.41		
Self-definitions of religiosity***			
Not believing any religions + not fulfilling religious duties (91) a	48.20±8.49	X^2=51.24	p=0.000, a>b=c
Attempting to fulfil religious duties (269) b	41.09±8.28		
Having religious beliefs and fulfilling religious duties (23) c	38.13±7.61		
Having had induced abortion			
Yes (63)	47.36±8.52	t=4.78	p=0.000
No (320)	41.66±8.65		
Having relatives with a history of induced abortion			
Yes (200)	43.71±8.37	t=2.36	p=0.018
No (177)	41.57±9.17		
Using family planning methods**			
Using modern family planning methods (282)	43.32±8.58	t=4.61	p=0.000
Using conventional methods or not using any methods (62)	37.66±9.40		
Number of living children	1.70±1.20 minimum: 0, maximum: 6, median: 2	r=-0.200	p=0.000
Scores for knowledge of induced abortion	6.97±2.01minimum: 0 maximum: 11 median: 7	r=0.331	p=0.000

*Pearson correlation coefficient for age and total scores for the inventory r=0.124 p=0.015; **Posthoc test Tukeys b test; ***Posthoc test Mann-Whitney U test; ****Pearson correlation value: r

Evidence from both this study and other studies emphasizes maternal health. In addition, the mothers were found to have a more positive attitude towards induced abortion in cases of unwanted pregnancy, babies with disabilities and maternal mental illnesses, which is consistent with results of the studies by Dimoula et al. (8), Betts (9), Hill (10), Becker et al. (11), Esmer (19), Balakrishnan et al. (20), Palermo (21) and Geary et al. (22).

The most unfavourable attitude towards induced abortion was reflected in the women's responses to the items "induced abortion is a sin" and "induced abortion is a murder, which is comparable with the results of the studies by Baykan et al. (5), Dimoula et al. (8), Norris et al. (12), Vieira (13), Saka et al. (23), Serap (24) and Erol et al. (25). However, it was striking that although the women considered induced abortion as a sin or a murder, they tended to have a positive attitude to the issue when it was necessary.

Table 4. Stepwise multiple regression analysis for explanation of scores on attitude inventory of induced abortion

Scores for attitudes towards induced abortion* (n=383), R^2=0.34	ß	p
Constant	-	0.000
Age (number)	0.170	0.003
Family type (nuclear family: 0 / extended family: 1)	-0.156	0.002
Number of children alive (number)	-0.246	0.000
Having had induced abortion (yes: 0 / no: 1)	-0.229	0.000
Using family planning methods** (modern family planning methods: 0 / conventional family planning methods: 1)	-0.135	0.006
Self-definitions of religiosity (being religious: 0 / not being religious or not fulfilling religious duties: 1)	0.111	0.021
Scores for knowledge of induced abortion (number)	0.193	0.000
Education (high school or higher education: 0 / primary school: 1)	-0.121	0.028

*The final single factor model was based on the significant variables age, number of children alive, education, employment, family type, place where one lived the longest, perceived religiosity, having induced abortion before, having a relative with a history of induced abortion, using family planning methods and scores for knowledge of induced abortion

A higher rate of agreement with the items "induced abortion is shameful" and "induced abortion should be kept secret" underlines the stigmatization of induced abortion. Norris et al. (12) and Moore et al. (26) also mentioned a stigma over induced abortion.

Although half of the women reported that they had been offered information about induced abortion, the results obtained from the responses to Knowledge of Induced Abortion Form showed that they did not have sufficient knowledge and needed training for it. Dimoula et al. (8) also revealed that women had insufficient knowledge of induced abortion.

Women over the age of 30 had a more favourable attitude towards induced abortion than those aged 30 and younger. Although there has been change in marriage age, Turkey is still a country where people get married at young ages. These couples have enough children at young ages as they planned (3). Therefore, it can be considered that older women do not want to have unwanted pregnancies and have a positive attitude towards induced abortion, which is congruent with the results of the studies by Balakrishnan et al. (20), Hollá (27) and Norup (28), Stricker and Danigelis (29), Esposito and Basow (30).

Women living in a nuclear family had a more positive attitude towards induced abortion than those living in an extended family. It may be that the women with an extended family were more dependent on traditions and customs and more conservative, but that those with a nuclear family could make their own decisions freely and had more opportunities to express their opinions (31).

The scores for attitudes towards induced abortion had an inverse linear relationship with the number of living children. Women with fewer living children were most likely to use modern family planning methods and want to have a small family. Balakrishnan et al. (20) and Remennick et al. (32) also showed that women with fewer children had a more favourable attitude towards induced abortion.

Women who had a previous induced abortion had a more positive attitude towards induced abortion than those who did not have induced abortion. This might have been due to the latter group of women's lack of experience in induced abortion. Erol et al. (25), Esposito and Basow (30) and Hollis and Morris (33) also revealed that women who had experienced induced abortion more frequently attempted to undergo this procedure than those who did not have such experience. However, it should be kept in mind that women who had induced abortion before might be using this procedure as a method of preventing pregnancy. In fact, the rate of induced abortion was 16.5% in this study, which is higher than the rate in Turkey (10%) (3). Therefore, women presenting for induced abortion should be informed about contraceptives and the contraceptives should be easily available to them.

Women using modern family planning methods had a more positive attitude towards induced abortion than those not using any family planning methods and those using conventional methods. In the literature, it has been noted that there is a direct relation between social status and access to and use of family planning methods (3,34,35). The two most important variables determining the social status of women are education and employment (36). In this study, we also found that women with higher education displayed a more positive attitude towards induced abortion. As a result, social status and determination to have children of women using a modern family planning method might affect women's attitudes towards the issue (37).

Considering the processes of accepting and rejecting abortion since ancient times, all religious systems had different approaches and practices, and each system of beliefs has harboured different interpretations of abortion (38). Studies conducted on this issue so far have shown the effects of religious beliefs on induced abortion (9,14-17,19-21,28,32). In this study, which was conducted in Turkey where 99% of the population is Muslim, the women defining themselves as religious had a more negative attitude towards induced abortion, but their negative attitude disappeared in conditions such as possibility of negative effects on mothers' and babies' psychological and social health, and rapes.

As the scores for knowledge of induced abortion increased, the scores for attitudes towards the issue also increased, and there was a positive linear relationship between them. Knowledge on its own is not enough to change individuals' attitudes; however, it can be one of the leading effects on changes. Rich background information allows individuals to evaluate issues from a wider perspective, which helps them to have more tolerant and favourable attitudes and behaviour (39). In this study,

women with higher scores for knowledge of induced abortion also had a more favourable attitude towards the issue, which is consistent with the results of the studies by Esposito and Basow (30) and Banerjee et al. (40).

Women with high school and higher education had a more favourable attitude towards induced abortion, which is congruent with evidence reported by Betts (9), Olaitan (14), Fawcett et al. (15), Bahr and Marcos (16), Roman and Lester (17), Esmer (19), Balakrishnan et al. (20), Palermo (21), Norup (28) and Remennick et al. (32). As the education level of women increases, they receive scientific, updated information from health institutions instead of family members and other people around them (3,37). In addition, as education levels increase, women become more autonomous and make decisions about their bodies. This may have a positive effect on women's attitudes towards induced abortion. However, women with lower education levels may have to give birth in cases of unwanted pregnancies due to various social, cultural and religious factors.

Study Limitations

Our study has some limitations. Data were collected from a sample of married women living in the city of Manisa, Turkey. Therefore, the findings represent only this population and cannot not be generalized to the general population. Failure to perform all methodological analyses of the inventory is another limitation of the study. Future qualitatively designed studies with larger samples are needed to confirm these findings.

Conclusion

The results of the study revealed that attitudes of the women towards induced abortion were affected by their religious beliefs, but that women were flexible enough to have a positive attitude towards the procedure in medical and social conditions. Although about half of the women noted that they received information about induced abortion, they had low scores for their knowledge, which suggests that the quality of education given should be questioned. The rate of women presenting for induced abortion indicates unfulfilled needs for family planning methods. For these reasons, couples should be informed about family planning methods and induced abortion by health institutions, and these services should be available to them. The results of the study revealed some variables affecting induced abortion; however, both qualitative studies and quantitative studies with larger sample sizes are needed to elucidate other factors likely to affect the issue.

Ethics Committee Approval: Approval was obtained from Ethical Committee of Celal Bayar University Faculty of Medicine and the Health Directorate of Manisa (decision no: 5.1, date: 04.01.2012).

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Comparison of Cutting Diathermy and Scalpel in Terms of Delay in Wound Healing and Scar Appearance in Skin Incision: A Prospective Observational Study

Deri İnsizyonunda Yara İyileşmesinde Gecikme ve Skar Görünümü Açısından Bistüri ile Koterin Karşılaştırılması: Prospektif Gözlemsel Çalışma

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ABSTRACT

Introduction: Traditionally, a scalpel is used for surgical incisions. The aim of this study was to compare cutting diathermy and scalpel in terms of wound healing or cosmetic appearance in skin incision.

Methods: The study was performed in patients with Pfannenstiel incision in a gynecology and obstetrics clinic. Half of the skin incision of the same patient was made with cautery and the other half was made with scalpel. The part of the incision made with cautery was compared with the incision made with scalpel in terms of wound healing and cosmetic appearance. The assessments were based on the observer scale of the "The Patient and Observer Scar Assessment scale" (POSAS). Evaluations were performed as single blind (observer-blinded, but not surgeon) in the short term (postoperative 15th day) and long term (45th day).

Results: A total of 73 women with Pfannenstiel incision were evaluated. The median age of the patients was 33 (21-52) years. The total POSAS scores of the parts opened with scalpel were not statistically different from those opened with cautery both at the 15th and 45th days (27.3±5.2 vs 27.0±5.1, p=0.88 for 15th day; 11.8±3.2 vs 11.0±4.1, p=0.56 for 45th day).

Conclusion: The study showed that using cautery in cutting mode had no effect on poor wound healing and cosmetic appearance in Pfannenstiel incisions compared to the use of scalpel. This result encourages surgeons to make a skin incision with cautery.

Keywords: Incision, scalpel, cautery, scar

ÖZ

Amaç: Geleneksel olarak, cerrahi insizyonlar için bir bistüri kullanılır. Bu çalışmanın amacı, yara iyileşmesi ve deri insizyonunun kozmetik görünümü açısından koter ile bistüriyi karşılaştırmaktır.

Yöntemler: Çalışma kadın hastalıkları ve doğum kliniğinde Phannenstiel insizyonu olan hastalarda yapıldı. Aynı hastanın deri insizyonunun yarısı koterin kesme modu ile, diğer yarısı neşter ile açıldı. Koter ile açılan insizyon kısmı, yara iyileşmesi ve kozmetik görünüm açısından neşter ile açılan kısım ile karşılaştırıldı. Değerlendirmeler POSAS (Hasta ve Gözlemci Skar Değerlendirme ölçeği) puanlama ölçeğinin gözlemci kısmına dayandırılmıştır. Değerlendirmeler kısa vadede (postoperatif 15. gün) ve uzun vadede (45. gün) tek kör (gözlemci kör fakat cerrah değil) olarak yapıldı.

Bulgular: Pfannenstiel insizyonu olan toplam 73 hasta değerlendirildi. Hastaların ortanca yaşı 33 (21-52) idi. Bistüri ile açılan bölümlerin toplam POSAS skorları, 15. ve 45. günlerde koter ile açılanlara göre istatistiksel olarak farklı değildi (15. gün için 27,3±5,2 ve 27,0±5,1 p=0,88; 45. gün için 11,8±3,2, p=0,56).

Sonuç: Çalışma, bistüri kullanımı ile karşılaştırıldığında, kesme modu koter kullanımının, Pfannenstiel insizyonlarında kötü yara iyileşmesi ve kozmetik görünüm olarak bir etkisi olmadığını göstermiştir. Bu sonuç, cerrahları koter ile deri insizyonu açmaya teşvik eder.

Anahtar Kelimeler: Insizyon, bisturi, koter, skar

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Introduction

Today, electrosurgical instruments are widely used in surgical procedures. Many publications have reported that the use of electrocautery is acceptable instead of traditional scalpel, even for skin incision (1-7). On the other hand, there are concerns about the use of diathermy in the skin incision due to fear of causing large scars and improper tissue healing (8-10).

In this study, scalpel and electrocautery were compared in terms of wound healing and cosmetic appearance. The difference of this study from previous studies is that these two techniques are compared in the same patient, thus eliminating the patient-related parameters.

Methods

This study was carried out between June 2018 and November 2018 in Gynecology and Obstetrics Clinic of Istanbul Training and Research Hospital. Local Clinical Research Ethics Committee approval was obtained for the study (decision no: 2011-KAEK-50). Patients scheduled for operation with a Pfannenstiel incision were selected as the study cohort. Exclusion criteria were a previous Pfannenstiel incision, morbid obesity, diabetes, patients aged 65 years and older, patients under 15 years of age, presence of any skin disease at the incision site. Informed consent was obtained from the patients for the study.

Half of the skin incision of the same patient was made with electrocautery in cutting mode (40-50 watt) and the other half was made with scalpel in order to obtain two identical observation sites. The part of the incision made with cautery (right side) was compared with the part made with scalpel (left side). Comparisons were made as single blind (observer-blinded, but not surgeon) when the patient came for control on the 15th and 45th days. Evaluated parameters were delayed wound healing and scar appearance. Patient and Observer Scar Assessment scale (POSAS) v2.0 observer scale was used for these evaluations. The observer scale of the POSAS consists of six items (vascularity, pigmentation, thickness, relief, pliability and surface area). All items are scored on a scale ranging from 1 ("like normal skin") to 10 ("worst scar imaginable"). The sum of the six items results in a total score of the POSAS observer scale. All parameters should preferably be compared to normal skin on a comparable anatomic location. The total minimum score of the POSAS scale is 6 and the maximum score is 60. Observations were made by the same team throughout the study.

Statistical Analysis

Mean and standard deviation for POSAS score, and median and minimum-maximum values for age of the patients were used for descriptive statistics. Shapiro-Wilk test was used for normality distribution of groups. Chi-square test was used for the analysis of qualitative independent data. SPSS 22.0 program was used in the analysis. A p value <0.05 was considered to indicate statistical significance.

Results

A total of 73 patients with Pfannenstiel incision were evaluated. The median age of the patients was 33 (21-52) years. The total POSAS scores of the incision parts made with scalpel were not statistically different from those made with cautery both at the 15th and 45th days (27.3±5.2 vs 27.0±5.1 p=0.88 for 15th day; 11.8±3.2 vs 11.0±4.1 p=0.56 for 45th day) (Tables 1 and 2) (Figures 1-4).

Table 1. Comparison of short term (15th day) the patient and observer scar assessment scale scores (mean ± standart deviation) of cautery and scalpel

	Cautery	Scalpel	p*
Vascularity	6.4±2.0	5.3±1.6	0.08
Pigmentation	2.3±0.4	2.3±0.9	0.98
Thickness	4.6±1.8	4.8±1.0	0.90
Relief	4.5±0.2	4.6±0.9	0.56
Pliability	4.0±0.7	4.4±0.1	0.27
Surface area	5.5±1.0	5.6±0.7	0.91
Total score of the POSAS	27.3±5.2	27.0±5.1	0.88

All items are scored on a scale ranging from 1 ("like normal skin") to 10 ("worst scar imaginable"), *Chi-square test
POSAS: patient and observer wound scale rating scale

Table 2. Comparison of long term (45th day) the patient and observer scar assessment scale scores (mean ± standart deviation) of cautery and scalpel

	Cautery	Scalpel	p*
Vascularity	1.4±0.3	1.3±1.1	0.85
Pigmentation	2.4±0.4	2.0±0.9	0.08
Thickness	1.6±1.7	1.1±1.0	0.78
Relief	3.1±0.4	2.7±0.9	0.76
Pliability	1.0±0.8	1.4±0.1	0.27
Surface area	2.3±1.0	2.5±0.7	0.51
Total score of the POSAS	11.8±3.2	11.0±4.1	0.56

All items are scored on a scale ranging from 1 ("like normal skin") to 10 ("worst scar imaginable"), *Chi-square test
POSAS: patient and observer wound scale rating scale

Figure 1. Appearance of skin incision at the 15th day

Figure 2. Appearance of skin incision at the 45th day

Figure 3. Long-term (45th day) appearance

Figure 4. Appearance of skin at the 15th day

Discussion

In this study, half of the Pfannenstiel skin incision in the same patient was made with an electrocautery and the other half with a scalpel. These two halves were compared at the 15th and 45th days. According to the results of the study, the effects of cautery and scalpel on wound healing and cosmetic were not different.

In the literature, many studies have compared the scalpel with cautery in skin incision. These studies have shown that these two techniques have similar cosmetic and wound healing results (1-7). The difference of this study is that these two techniques are compared in the same patient. With this comparison method, the parameters affected by the differences between the patients were eliminated. This study, unlike the previous studies, is a self-controlled study. Each case is its own control, thus the conditions that could affect wound healing are equalized.

The stages of wound healing proceed in an organized way and follow four processes: hemostasis, inflammation, proliferation and maturation., Angiogenesis, fibroplasia and re-epithelialization occur in the proliferation phase (11,12). The proliferation phase in a wound healing process is completed in the first two weeks (13). The maturation phase, also referred as the remodeling phase of wound healing, is when the collagen is remodeled from type 3 to type 1 and the wound is completely closed. Generally, remodeling begins approximately 21 days after an injury and can last for months (11-13). In the present study, the surgical incision was evaluated at two separate times. The initial evaluation was performed at the 15th day when the proliferative phase was completed. In addition, patients were evaluated at the sixth week (45th day) when they were called for a follow-up examination.

Conclusion

POSAS patient scale was not used. The patients had difficulty in evaluating both halves of the Pfannenstiel incision separately and did not provide any objective results. Therefore, POSAS observer scale was used for evaluations.

In this study, it was observed that the use of cautery in cutting mode in Pfannenstiel incisions had no effect on poor wound healing and poor cosmetic. In fact, surgeons have experienced that the use of cautery for incision is more advantageous for bleeding control. This result of the study encourages surgeons to make a skin incision with a cautery.

Ethics Committee Approval: İstanbul Training and Research Hospital, Clinical Research Ethics Committee (decision no: 2011-KAEK-50).

Informed Consent: Informed consent was obtained from the patients for the study.

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Is Component Separation a Safe Method in Incisional Hernias?

İnsizyonel Hernilerde Komponent Seperasyon Tekniği Güvenli Bir Yöntem midir?

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ABSTRACT

Introduction: Incisional hernias after abdominal surgical procedures cause morbidity, significant loss of labor and affect quality of life. In this study, we investigated whether component separation (CS) technique is a safe method in patients with incisional hernia. We evaluated the results of this technique in terms of wound infection and recurrence.

Methods: Thirty incisional hernia cases operated with CS technique between February 2012 and February 2014 were included in the study. Demographic data, body mass index (BMI), American Society of Anesthesiologists (ASA) score, defect size, wound complications and recurrences after one-year follow-up were evaluated.

Results: Seventeen patients were female and 13 were male. The mean age of the patients was 54.8 years (range: 29-76). The mean BMI of the patients was 26.8 kg/m^2 (range: 20.5-32.9). The mean hernia transverse diameter was 9.6 cm (range: 6.5-23). Mortality was not observed in any of the patients. Wound problems were observed in six of 30 patients in CS repair, and recurrence was observed in three of these patients. Recurrence was observed in only one of the remaining 24 patients without a wound problem. Recurrence was found to be statistically related to wound problem. There was also a significant relationship between BMI, hernia transverse diameter, ASA score and recurrence.

Conclusion: In selected cases, CS technique is a safe technique for incisional hernia repair. It can be performed by paying attention to wound problems.

Keywords: Component separation, wound infection, recurrence

ÖZ

Amaç: Abdominal cerrahi girişimler sonrasında ortaya çıkan insizyonel herniler önemli oranda işgücü kaybına, morbiditeye neden olur, yaşam kalitesini etkiler. Bu çalışmada insizyonel hernili hastalarda Komponent Seperasyon (KS) tekniğinin güvenli bir yöntem olup olmadığını araştırdık. Bu tekniğin; yara yeri enfeksiyonu ve nüks açısından sonuçlarını değerlendirdik.

Yöntemler: Şubat 2012- Şubat 2014 tarihleri arasında hastanemizde KS tekniği ile ameliyat edilen 30 insizyonel herni olgusu çalışmaya dahil edildi. Hastaların demografik bilgileri, vücut kitle indeksi (VKİ), Amerikan Anesteziyoloji Derneği (ASA) skoru, defektin boyu, yara komplikasyonları ve bir yıllık takip sonrası nüksler değerlendirildi.

Bulgular: Hastaların 17'si kadın, 13'ü erkekti. Hastaların yaş ortalaması 54,8 (29-76) idi. Hastaların VKİ ortalaması 26,8 kg/m^2 (20,5-32,9) idi. Bu hastaların ortalama fıtık transvers çapı 9,6 cm (6,5-23) idi. Hastaların hiçbirinde mortalite izlenmedi.

KS onarımında 30 hastanın altısında yara yeri problemleri gözlenirken bu hastaların üçünde nüks gözlendi. Yara yeri problemi olmayan 24 olgunun ise sadece birinde nüks gözlendi. Yara yeri problemi olan hastalarda nüks istatistiksel olarak ilişkili bulundu. VKİ, fıtık transvers çapı yüksekliği ve ASA skoru ile de nüks arasında anlamlı ilişki saptandı.

Sonuç: İnsizyonel herni onarımında uygun olgularda komponent separasyon tekniği güvenli bir tekniktir. Yara problemlerine dikkat edilerek uygulanabilir.

Anahtar Kelimeler: Komponent seperasyon, yara yeri enfeksiyonu, rekürrens

Introduction

The incidence of incisional hernias (IHs) after median incisions is between 2-11%, with a recurrence rate of 30-50% after primary repair of IH (1). The incidence of hernia is smaller in small incisions. IHs cause significant labor loss, morbidity and even mortality (2,3). They continue to constitute one of the major problems of surgery due to their frequent incidence and high morbidity. The only treatment option for IHs is surgery. Treatment of IHs includes primary repair and repair with prosthetic materials. Prosthetic material application is the primary option when there is not enough intact tissue (4). Component separation (CS) is based on a functional abdominal wall-shaping concept using autologous tissue (5). The use of patient's own tissues is an advantageous method as it

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reduces the cost compared to meshed repair. The likelihood of a foreign body reaction is thus reduced.

Etiologic factors in IH formation can be classified as modifiable and non-modifiable. Modifiable etiologic factors include obesity, incision pattern, suture material used and wound infection. Non-modifiable etiologic factors include age of the patient, general body weakness and other chronic diseases [chronic obstructive pulmonary disease (COPD), malignancy, prostatism, etc.] of the patient (6-8). CS technique was first described by Ramirez et al. (9) in 1990.

The aim of this retrospective study was to investigate the recurrence, wound complications and general complications of patients who were diagnosed with IH and operated by CS technique, and to compare these rates with the literature.

Methods

This study was started after the approval of the İstanbul Okmeydanı Training and Research Hospital Ethics Committee (decision no: 48670771-514.10). This was a clinical retrospective study. Informed consent was obtained from all patients.

Thirty cases of IH operated by CS technique in our hospital between February 2012 and February 2014 were included in the study. The criteria for inclusion in the study were patients older than 18 years, patients with an abdominal midline IH and patients with transverse diameter of the fascia defect greater than 5 cm. Age, gender, body mass index (BMI), transverse diameter of hernia, and American Society of Anesthesiologists (ASA) score were recorded. Wound infections and recurrences after 1-year follow-up were noted. Table 1 shows the demographic characteristics and recorded physical examination findings of the operated patients.

All patients received 1 g of first generation cephalosporin (İbrahim Etem-menarini, İstanbul, Turkey) one hour prior to surgery. The operations were performed under general anesthesia in supine position. Second generation cephalosporin (Nobel, İstanbul, Turkey) was given orally for 5 days after surgery. A urinary catheter was inserted during the surgery. Two subcutaneous aspirating drains were routinely inserted in each patient. 10% povidone iodine was used as skin antiseptic. Each patient was dressed with antiembolic socks and embolism prophylaxis was performed with low molecular weight heparin (Sanofi-aventis, İstanbul, Turkey) in patients with a BMI over 30.

Following the preparations described above, the skin is opened with a midline incision to include the previous incision scar. The intestines and other organs are dissected from the ventral abdominal wall (Figure 1). In this way, the lateral border of the rectus abdominis muscle can be accurately recognized through the abdomen. The skin and subcutaneous tissue are dissected from anterior rectus sheath and external oblique aponeurosis 5 cm lateral to the rectus sheath. As the perforating branches of the epigastric artery are cut, blood supply to the skin is at risk. Because the blood supply is then only dependent

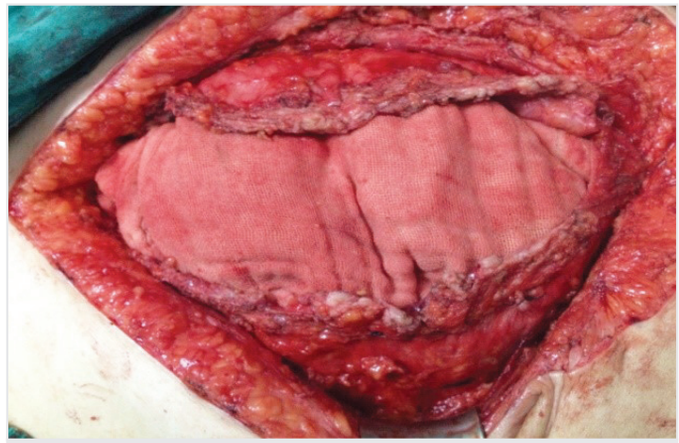

Figure 1. Dissected view of hernia sac, intestines and other organs from ventral abdominal Wall

Table 1. Demographic characteristics and physical examination findings of operated patients

Features	Patient group (n=30)	n	%	Mean ± SD
Gender	Female	17	56.7	1.433±0.504
	Male	13	43.3	
Age (WHO)	Young (18-65 years)	24	80.0	3.10±0.844
	Middle-aged (66-79 years)	6	20.0	
	Elderly (80-99 years)	0	0	
BMI	Underweight (<18.5 kg/m^2)	0	0	1.70±0.876
	Normal (18.5-24.9kg/m^2)	7	23.3	
	Overweight (25-29.9kg/m^2)	20	66.7	
	Obese (30 -34.9 kg/m^2)	3	10.0	
ASA score	ASA 1	15	50.0	1.30±0.651
	ASA 2	11	36.7	
	ASA 3	2	6.7	
	ASA 4	2	6.7	1.30±0.65
HTD	Small (6-10 cm)	24	80.0	
	Medium (11-14 cm)	3	10.0	
	Large (>15 cm)	3	10.0	

WHO: World Health Organization, BMI: body mass index, ASA: American Society of Anesthesiologists, HTD: hernia transverse diameter

on the intercostal arteries and the branches of the pudendal artery. In this case, the epigastric perforating vessels should be preserved. The aponeurosis of the external oblique muscle is incised 1-2 cm lateral to the rectus abdominis muscle. If the incision in the aponeurosis is made correctly, fatty cell tissue is exposed. If the muscle is seen, the incision is not in the right place. The myoaponeurosis of the external oblique muscle is transected longitudinally along its length. Seven to ten cm muscular part of the external oblique muscle in the thorax wall extending cranially is added to the transection. With this extension, the rectus abdominis muscle can be maximally medially rotated in the upper abdomen. Connections to the ribs should be dissected to fully mobilize the rectus abdominis muscle. The external oblique muscle is separated from the internal oblique muscle up to the midaxillary line using the avascular plane between the two muscles. This mobilization is very important, since fibrous connections between the muscles will prevent optimal medial displacement of the rectus abdominis muscle. It is very important to determine the plane between the internal and external oblique muscles correctly. Transection of the internal oblique muscle may lead to abdominal wall rupture, because the transverse abdominal muscle is too weak to withstand intraabdominal pressure. In addition, neurovascular structures can be easily damaged as they lie between the internal oblique and transverse abdominal muscles. As a result, the abdominal wall muscles are denervated. With this technique, rectus muscle can be advanced unilaterally 3-5 cm on the upper edge, 7-10 cm in the waistline, and 1-3 cm in the lower abdomen (Figure 2). An additional 2-4 cm advance can be achieved by separating the posterior sheath of the rectus abdominis muscle. The posterior sheath is incised along its entire length close to the midline. The rectus abdominis muscle is easily separated from the posterior rectus sheath. The abdominal wall is sutured continuously in the midline with non-absorbable or slow-absorbing sutures through the fascia. The suture length should be at least 4 times the wound in the fascia. Drains are placed under the skin. Defects up to 28 cm at waist level can be closed in this way (Figure 3).

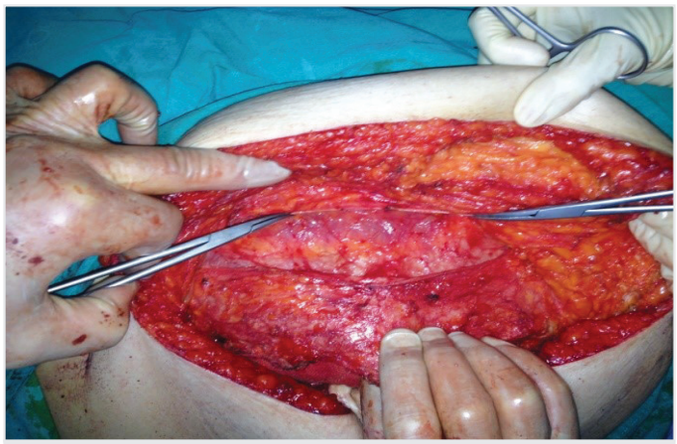

Figure 2. Longitudinal excision of external oblique aponeurosis

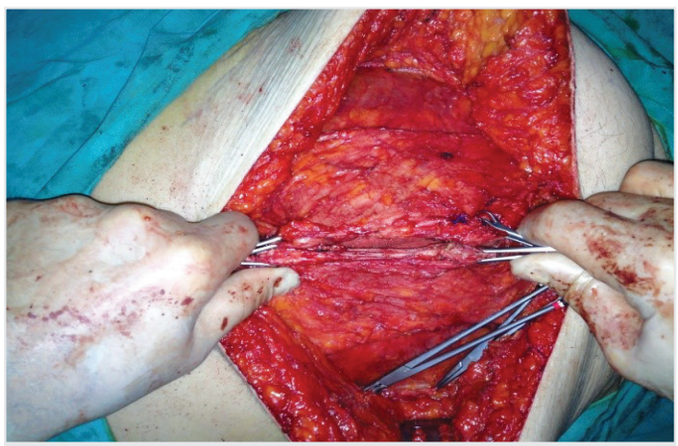

Figure 3. Completed version of bilateral separation

Statistical Analysis

The findings of the study were analyzed with SPSS 13.0. Descriptive statistics (mean, standard deviation) were used in the evaluation of qualitative data. X^2 test was used for comparison of qualitative data. Student's t-test was used to analyze the quantitative data. The results were evaluated with 95% confidence interval and level of significance was $p<0.05$.

Results

Thirty patients were operated with this technique. The mean transverse diameter of hernia was 9.6 cm (range: 6.5-23). Seventeen patients were

Table 2. The relationship between demographic characteristics and physical examination findings and recurrence in patients who underwent component separation

Patients		n	Mean ± SD	p
Gender	Recurrence	4	1.250±0.50	0.44
	No recurrence	26	1.461±0.50	
Age	Recurrence	4	3.250±0.50	0.59
	No recurrence	26	3.076±0.89	
BMI	Recurrence	4	3.750±0.50	0.02
	No recurrence	26	2.730±0.45	
ASA score	Recurrence	4	3.500±0.57	0.03
	No recurrence	26	1.423±0.50	
HTD	Recurrence	4	2.750±0.50	0.00
	No recurrence	26	1.076±0.27	

BMI: body mass index, ASA: American Society of Anesthesiologists, HTD: hernia transverse diameter

Table 3. Relation between wound problem and recurrence in patients who underwent component separation

Patients		n	p
Patients with wound infection	Recurrence	3	0.02
	No recurrence	3	
Patients without wound infection	Recurrence	1	0.121
	No recurrence	23	

*chi-square tests (p<0.05 is significant)

female and 13 were male. The mean age of the patients was 54.8 years (range: 29-76). The mean BMI of the patients was 26.8 (range: 20.5-32.9). Mortality was not observed in any of the patients.

Gender, age, BMI, ASA scores, and hernia transverse diameter were separately grouped. No statistically significant relationship was found between age and gender and recurrence. There was a significant relationship between hernia transverse diameter, BMI level and ASA score and recurrence (p=0.02, p=0.03, p=0.00, respectively) (Table 2).

Wound problems were observed in six of the 30 patients who underwent surgery with this technique, and recurrence was observed in three of these patients. Recurrence was observed in only one of the 24 patients who did not have any wound problems. The statistical evaluation revealed a p value of 0.02 and recurrence was found to be statistically related with wound problems (Table 3).

Discussion

IH is the post-operative disruption of the integrity of the fascia that is closed and herniation of peritoneum from this defect (10). It develops in 2-23% of abdominal operations (11-13). IH repair is a serious operation with mortality and morbidity, and a good pre-operative evaluation of the patient may reduce post-operative problems (13). In the repair of IH, many methods are used, ranging from primary closure, mesh placement and closure with laparoscopic method. There are many studies in the literature related to these and primary closure can be performed in small defects, whereas mesh or CS is better in larger defects. CS was found to be superior to prosthetic material, but similar recurrence rates were determined after 24 months of follow-up (14). In the literature, recurrence rates have been reported between 0-28% in patients undergoing tension-free CS technique (15-16). In our study, this rate was found to be 13.3%.

Wound complications are relatively common due to the formation of large wound surfaces. Hematoma and seroma formation are the most common complications. Infection rates are between 0-40% (17). In most cases, these complications can be treated conservatively. Similar complications were observed in our patients and one patient had severe wound problems. Although there was no statistically significant difference in the single randomized controlled study, more hematoma and seroma developed in the mesh group, and re-operation rates due to wound complications were significantly higher in the prosthetic mesh group. In the same study, no difference was found between using and not using mesh during CS in terms of hernia recurrence during 3 year follow-up (18). Attention should be paid to perforating vessels to reduce wound complications and to preserve vascularization of the skin (17). Laparoscopic approach is preferred by most surgeons because it allows for less general and wound complications, lower recurrence rates, shorter hospital stay and faster recovery (19).

The most important indicator of reliability in incisional hernia repair is recurrence. Most recurrences occur in the first 2 years, with recurrence risk for 10 years. The most common cause of recurrence is wound infection and other causes are obesity, COPD and surgical error (20). Recurrence occurred in four of 30 patients who underwent CS technique. There was a statistically significant correlation between recurrence and postoperative wound infection, obesity, hernia transverse diameter, and higher ASA scores. Attention can be paid to the use of drains to reduce the incidence of wound problems, thus recurrence rates (21). Obese patients need to be supported to lose weight and the skin vascularization should be protected as much as possible (22). There are publications reporting that wound infection is more common in obese patients (23). In our series, recurrence rate was found to be significantly higher in patients with high BMI.

Conclusion

We think that the CS technique can be safely applied in the repair of large incisional hernias by paying attention to wound infection.

Ethics Committee Approval: This study was started after the approval of the İstanbul Okmeydanı Training and Research Hospital Ethics Committee (decision no: 48670771-514.10).

Informed Consent: Informed consent was obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Author Contributions: Concept - U.A.; Design - U.A; Data Collection and/or Processing - U.A., T.B.; Analysis and/or Interpretation - U.A., T.B.; Literature Search - U.A., T.B.; Writing Manuscript - U.A., T.B.

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

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Investigation of Laboratory Parameters That Differentiate Complicated Appendicitis from Simple Appendicitis in Adults

Yetişkinlerde Komplike Apandisiti Basit Apandisitten Ayıran Laboratuvar Özelliklerinin Araştırılması

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ABSTRACT

Introduction: Acute appendicitis is one of the most common abdominal emergencies. In this study, we aimed to investigate preoperative laboratory parameters in patients with simple and complicated appendicitis.

Methods: The medical records of patients over 40 years of age with histopathologically diagnosed acute appendicitis between January and December 2015 were retrospectively reviewed. The patients were divided into two groups as simple and complicated. The relationship between appendicitis subgroups and laboratory parameters including white blood cell count, neutrophil count and percentage, lymphocyte count and percentage, basophil count and percentage, platelet count, mean platelet volume, plateletcrit, platelet distribution width was investigated. Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) were also analyzed in these groups.

Results: A total of 156 patients were included in the study. Twenty-three patients (14.7%) had simple appendicitis and the mean age of all patients was 50.5±8.5 years. Male and elderly patients had more complicated appendicitis. In univariate analysis, percentage of neutrophils, lymphocyte count and percentage, lymphocyte count and percentage, basophil percentage, plateletcrit, NLR and PLR values were significantly different between the groups. However, in the multivariate logistic regression analysis comparing simple and complicated appendicitis data, only NLR value was found to be significant.

Conclusion: Neutrophil percentage, lymphocyte count and percentage, basophil percentage, plateletcrit and NLR were associated with complicated appendicitis in patients over 40 years of age, but only NLR was significant in multivariate analysis. However, these parameters can be used to distinguish complicated appendicitis at presentation.

Keywords: Acute appendicitis, adult, complicated appendicitis, laboratory

ÖZ

Amaç: Akut apandisit en sık görülen abdominal acillerden birisidir. Bu çalışmada basit ve komplike apandisit hastalarında preoperatif laboratuvar değerlerini incelenmeyi amaçladık.

Yöntemler: Ocak-Aralık 2015 tarihleri arasında histopatolojik olarak akut apandisit tanısı konulmuş 40 yaş ve üzeri hastaların tıbbi kayıtları retrospektif olarak incelendi. Hastalar basit ve komplike olarak iki gruba ayrıldı. Beyaz kan hücresi sayımı, nötrofil sayısı ve yüzdesi, lenfosit sayısı ve yüzdesi, bazofil sayısı ve yüzdesi, trombosit sayısı, ortalama trombosit hacmi, plateletkrit, trombosit dağılım genişliği ve apandisit alt grupları arasındaki ilişki araştırıldı. Aynı zamanda nötrofil/lenfosit oranı (NLR) ve trombosit/lenfosit oranı (PLR) da bu gruplarda analiz edildi.

Bulgular: Kırk yaş üzeri 156 hasta çalışmaya dahil edildi. Hastaların 23'ü (%14,7) basit apandisitti ve tüm hastaların yaş ortalaması 50,5±8,5 yıl olarak saptandı. Erkek ve yaşlı hastalarda daha fazla komplike apandisit saptandı. Tek değişkenli analizde nötrofil yüzdesi, lenfosit sayı ve yüzdesi, lenfosit sayısı ve yüzdesi, bazofil yüzdesi, plateletkrit, NLR ve PLR değerleri gruplar arasında anlamlı farklı bulundu. Basit ve komplike apandisit verilerinin karşılaştırıldığı çok değişkenli lojistik regresyon analizinde sadece NLR değeri anlamlı bulundu.

Sonuç: Kırk yaş üstü hastalarda nötrofil yüzdesi, lenfosit sayısı ve yüzdesi, bazofil yüzdesi, plateletkrit ve NLR'nin komplike apandisit ile ilişkili olduğu ancak sadece NLR'nin çok değişkenli analizde anlamlı olduğu saptandı. Buna rağmen bu parametreler başvuruda komplike apandisitin ayırt edilmesinde kullanılabilir.

Anahtar Kelimeler: Akut apandisit, yetişkin, komplike apandisit, laboratuvar

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Introduction

The lifetime risk of acute appendicitis is approximately 8%, and although it is one of the most common abdominal emergencies, its pathogenesis is still poorly understood. It is thought to be a multifactorial clinical picture caused by mechanical, infectious and genetic processes leading to appendix inflammation (1). Appendicitis can be seen as simple or uncomplicated (inflammation of the appendix with or without phlegmonous changes in surrounding tissues) or complicated appendicitis (inflammation of the appendix causing gangrene or perforation with or without abscess formation). Perforation may occur in 13-20% of patients presenting with acute appendicitis (2). Although it has long been assumed that simple appendicitis will eventually lead to a complicated form, recent data raise doubts that different forms of biological appendicitis may exist. Although general appendicitis rates decrease, the rate of patients presenting with perforated appendicitis or after the onset of symptoms does not decrease (3). Acute complicated appendicitis causes serious problems such as wound infection, intraabdominal abscess formation, postoperative intestinal obstruction, prolongation of recovery and hospital stay and increased cost. In addition, whether appendicitis is complicated or not has an important role in determining the treatment method to be selected. Therefore, early recognition of complicated appendicitis cases is critical by making a distinction between complicated and simple appendicitis. Although many studies have been published regarding the prediction of complicated appendicitis, there is no definite method to differentiate preoperative complicated appendicitis from simple appendicitis (4-6).

In this study, we aimed to investigate the preoperative laboratory characteristics of simple and complicated appendicitis in patients over 40 years of age diagnosed with acute appendicitis histopathologically.

Methods

This study was performed retrospectively on the medical records of the patients who were diagnosed as acute abdomen and underwent appendectomy (open and laparoscopic) between 01.01.2015-31.12.2015 in the Emergency Medicine Clinic of İstanbul Training and Research Hospital, University of Health Sciences. The study was started after the approval of the hospital İstanbul Training and Research Hospital Ethics Committee (decision no: 759).

All patients who underwent appendectomy for acute appendicitis were included in the study. Of these patients, patients with no histopathological appendicitis, patients under 41 years of age, patients with missing data, and patients who underwent incidental appendectomy during surgery for any other reason were excluded from the study.

Demographic characteristics of all patients, initial vital signs recorded on admission, laboratory values including leucocyte, neutrophil count, neutrophil percentage, lymphocyte count, platelet count, mean platelet volume (MPV), plateletcrit and platelet distribution width (PDW) values were recorded. Neutrophil/lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by lymphocyte count, and platelet/lymphocyte ratio (PLR) was calculated by dividing the platelet count by lymphocyte count.

The operation records and histopathology reports were examined, and the widest and longest dimensions of the excised appendix material were noted. Infiltration of muscularis propria with polymorphonuclear cells was accepted as histological acute appendicitis.

All patients included in the study were divided into two groups as simple and complicated appendicitis. Patients with perforated or gangrenous appendix or patients with periappendiceal abscess were included in the complicated appendicitis group. Patients with histopathological findings consistent with perforation or gangrene from patients who were included in the simple appendicitis group by intraoperative evaluation were also included in the complicated appendicitis group. Patients without intraoperative and histopathological perforation or gangrenous features, and patients without periappendiceal abscess formed simple appendicitis group.

Statistical Analysis

Statistical analysis was performed using SPSS 15.0 (SPSS Inc. Chicago, IL, USA). The normality of continuous variables was evaluated by Kolmogorov Smirnov test. Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as number and percentage. Chi-square test was used for comparisons between categorical variables. Student's t-test was used for comparison of the normally distributed parameters and Mann-Whitney U test was used for the comparison of non-normally distributed parameters. The effect level was investigated by univariate and multivariate logistic regression. Sensitivity, specificity and odds ratios were calculated for the factors that differentiated between simple and complicated appendicitis groups. All analyzes were performed at 95% confidence interval. Statistical significance was accepted as $p<0.05$.

Results

The records of 550 patients who underwent appendectomy during the one-year period were reached. Three hundred and eighty-two patients (69.5%) were excluded because they were 40 years or younger. Histopathology reports of the remaining 168 patients revealed normal appendicitis in 12 (7.1%) patients. In conclusion, this study was carried out with 156 patients who underwent appendectomy for acute appendicitis. In the operation notes and histopathological examination of 133 patients (85.3%), no pathology could be detected for inclusion to the complicated group. The remaining 23 patients (14.7%) had pathological findings of complicated appendicitis in at least one of the operation notes or histopathological examinations.

The mean age of the patients was 50.5±8.5 years (range: 41-79 years). The mean age of the patients in the complicated appendicitis group (56.3±10.9 years) was higher than the mean age of the patients in the simple appendicitis group (49.5±7.7 years) ($p=0.004$). Seventy-nine patients (50.6%) included in the study were male. The incidence of complicated appendicitis was higher in male patients than in female patients (21.5% vs 7.8%, respectively, $p=0.016$). All laboratory values of simple and complicated appendicitis cases are shown in Table 1. The relationship between increased NLR and increased risk of complicated appendicitis is shown in Figure 1.

When univariate logistic regression analysis was performed, age, gender, lymphocyte count, percentage of neutrophils, percentage of

Table 1. Comparison of simple and complicated groups according to the characteristics of the patients included in the study

Variable	All patients		Simple appendicitis	Complicated appendicitis	p
	Mean ± SD	Min-Max	Mean ± SD	Mean ± SD	
Length of appendix (cm)	6.5±1.6	3.0-13.0	6.5±1.7	6.7±1.5	0.538
Width of appendix (cm)	1.0±0.7	0.3-8.0	1.0±0.7	1.2±0.5	0.002
Leukocyte count (109/L)	13.1±4.5	1.0-30.1	12.9±4.3	14.2±5.4	0.245
Platelet count (109/L)	249.8±62.8	82.0-538.0	252.7±61.4	233.0±69.3	0.165
Neutrophil count (109/L)	10.3±4.3	0.2-28.7	10.1±4.2	12.0±5.0	0.092
Lymphocyte count (109/L)	1.9±0.9	0.2-4.7	2.0±0.8	1.4±1.0	0.003
Neutrophil percentage (%)	76.9±11.7	20.0-96.4	75.6±11.8	84.2±7.7	<0.001
Lymphocyte percentage (%)	16.8±10.0	2.0-65.2	17.9±10.2	10.2±6.1	<0.001
MPV (fL)	9.9±1.0	7.0-12.5	10.0±1.0	9.6±0.9	0.100
Plateletcrit (%)	0.2±0.1	0.1-0.6	0.3±0.1	0.2±0.1	0.025
PDW (%)	16.2±0.9	14.9-26.5	16.2±1.0	16.1±0.4	0.498
Urea (mg/dL)	29.6±11.1	14.9-85.2	28.5±9.6	36.2±16.3	0.035
Creatinine (mg/dL)	0.8±0.2	0.3-1.9	0.8±0.2	1.0±0.4	0.001
Glucose (mg/dL)	118.8±34.4	78.0-330.0	118.6±36.4	119.8±21.7	0.232
NLR	7.3±6.9	0.3-46.9	6.4±5.9	12.5±9.7	<0.001
PLR	166.8±126.4	48.3-936.4	151.3±89.7	256.0±233.4	0.005

MPV: mean platelet volume, SD: standard deviation, Min: minimum, Max: maximum, fL: femtoliter, PDW: platelet distribution width, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio

Table 2. Logistic regression analysis

Variable	Univariate model					Multivariate model				
	OR	95% CI			p	OR	95% CI			p
Age	1.09	1.03	-	1.14	0.001	1.09	1.03	-	1.15	0.002
Gender	3.24	1.20	-	8.74	0.020	3.54	1.18	-	10.60	0.024
Lymphocyte count	0.41	0.23	-	0.75	0.003					
Neutrophil percentage	1.11	1.04	-	1.18	0.001					
Lymphocyte percentage	0.87	0.80	-	0.94	0.001					
PCT	0.00	0.00	-	0.35	0.028					
Urea	1.05	1.02	-	1.09	0.005					
Creatinine	14.39	2.66	-	77.76	0.002					
NLR	1.10	1.04	-	1.17	0.002	1.09	1.03	-	1.15	0.005
PLR	1.00	1.00	-	1.01	0.004					

PCT: plateletcrit, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, OR: odds ratio, CI: confidence interval

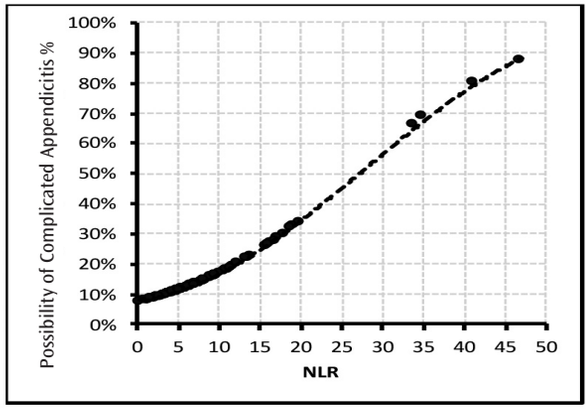

Figure 1. Risk graph of NLR increase and possibility of complicated appendicitis

NLR: neutrophil/lymphocyte ratio

lymphocytes, percentage of basophils, plateletcrit (PCT), urea, creatinine, NLR, PLR values were observed to differentiate complicated and simple appendicitis. In the multivariate logistic regression, significant and independent efficacy of age, gender, and NLR was found to differentiate simple and complicated appendicitis (Table 2).

Discussion

Acute appendicitis is the most common surgical cause of acute abdomen affecting all age groups. Complicated acute appendicitis is a serious problem with prolonged recovery and length of hospital stay and increased cost, which adversely affect clinical outcome and treatment outcomes. Being simple or complicated is important in determining the treatment method to be selected in appendicitis. In this study, preoperative laboratory values of adult acute appendicitis patients were investigated and the role of these values in differentiating complicated and simple appendicitis was demonstrated. Age, gender, lymphocyte

count and percentage, percentage of neutrophils, percentage of basophils, PCT, urea, creatinine, NLR, PLR and appendix diameter were found to be associated with complicated appendicitis.

In this study, we found significant differences between the groups in terms of demographic characteristics such as age and gender. The mean age of the patients in the complicated appendicitis group was higher than the patients in the simple appendicitis group. There are similar reports in the literature (7). This can be explained by the fact that acute appendicitis occurs more frequently with atypical symptoms in elderly patients and the diagnosis is more difficult than in younger patients. Similarly, in accordance with the literature, we found that complicated appendicitis was more common in male patients.

There are many reports in the literature regarding the association of complete blood count parameters with underlying inflammatory or infectious pathologies. Leukocyte elevation is quite common in the diagnosis of acute appendicitis, but it is a non-diagnostic condition. Yang et al. (8) reported that the increase in the percentage of leukocytes and neutrophils correlated with the degree of appendiceal inflammation. Paragiotopoulou et al. (9) reported that leukocyte count might be used in the diagnosis of appendicitis but that it was not suitable for differential diagnosis of perforated acute appendicitis. In our study, leukocyte and neutrophil counts were not significantly different but the percentage of neutrophils was significantly higher in complicated acute appendicitis cases. The physiological leukocyte response due to triggering factors causes an increase in neutrophil count and a decrease in lymphocyte count. NLR, which is calculated by the ratio of these two parameters to each other, is used as an inflammatory parameter reflecting this physiological response (10,11). Kahramanca et al. (12) reported that NLR is a parameter that can be used both in the diagnosis of appendicitis and in the differential diagnosis of complicated and non-complicated appendicitis. Similarly, in our study, NLR was significantly higher in patients with complicated acute appendicitis.

There are reports in the literature that express the relationship between platelet activation and pathophysiological process in inflammatory diseases. Assuming that platelet size is associated with activity and functionality, the assumption is that larger platelets are younger and more reactive. It is reported that PLR, calculated by the ratio of platelet count to lymphocyte count, can help predict complicated appendicitis (13). Similarly, in our study, PLR value was found to be significantly higher in patients with complicated appendicitis. MPV is the MPV in the blood and is calculated by dividing the PCT value by the platelet count. There are conflicting publications on the change of MPV in acute appendicitis. While some publications report a decrease in acute appendicitis (14), some reports report an increase (15). There are also reports in the literature stating that there is no relationship between MPV and acute appendicitis (16). In our study, we did not find any significant difference between MPV values in simple and complicated acute appendicitis groups. We thought that this might be due effects of other inflammatory causes on MPV that we could not detect. Aydogan et al. (17) reported that PDW values were significantly higher in perforated acute appendicitis cases. In another study, Fan et al. (16) reported an increase in PDW in patients with acute gangrenous appendicitis when compared with healthy control group. However, there are also studies reporting no significant difference in PDW values in complicated acute appendicitis (14). Similarly, in our study, we did not find any significant difference in PDW value between simple and complicated acute appendicitis groups.

Tanrikulu et al. (18) reported that appendiceal wall thickness, diameter and length were risk factors for perforation in their measurements of excised surgical material in patients with acute appendicitis. In our study, we did not find any relationship between length and complicated appendicitis. However, there was a positive correlation between appendix diameter and complicated appendicitis.

There were some limitations in our study. First of all, our study is a single-center study, so it is not sufficient to apply the results to the general population. Evaluations were made according to the results of a single laboratory. Therefore, no comment can be made about changes after follow-up or treatment. In addition, no additional research has been conducted on the presence of hematological malignancy.

Conclusion

In this study, age, gender, lymphocyte count and percentage, neutrophil percentage, basophil percentage, PCT, urea, creatinine, NLR and PLR values were significantly different between simple and complicated appendicitis patients, but multivariate analysis showed that only age, gender and NLR were significant and independent factors in differentiating complicated appendicitis.

Ethics Committee Approval: The study was started after the approval of the hospital İstanbul Training and Research Hospital Ethics Committee (decision no: 759).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Özlem D., Ö.D.; Design - Özlem D., Ö.D.; Data Collection and/or Processing - Özlem D., Ö.D.; Analysis and/or Interpretation - Özlem D., Ö.D.; Literature Search - Özlem D., Ö.D.; Writing Manuscript - Özlem D., Ö.D.

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Necrotizing Pneumonia in a Diabetic Child Successfully Treated with Pneumonectomy

Pnömonektomi ile Başarılı Bir Şekilde Tedavi Edilen Nekrotizan Pnömonili Diyabetik Çocuk

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ABSTRACT

Diabetic patients may experience more severe *Staphylococcus aureus*-related respiratory tract infections such as necrotizing pneumonia (NP). A 13-year-old girl with uncontrolled diabetes mellitus was admitted to pediatric intensive care unit (PICU) with diabetic ketoacidosis and respiratory distress. Her initial evaluation revealed diffuse pneumonic infiltration that progressed to NP within days. She was intubated and placed on mechanical ventilator (MV) support. Positive inotropes and broad-spectrum antibiotics were initiated. Methicillin-resistant *S. aureus* was isolated from blood and pleural specimen cultures. In spite of aggressive medical treatment, infection could not be controlled and lobectomy was performed. However, the patient was fistulized and right total pneumonectomy was performed on the 16th and 29th days of PICU admission. She gradually got better and was weaned from MV. On the 59th day, she was discharged oxygen-free from the hospital. Early surgical intervention should be considered for the treatment of NP resistant to medical therapy.

Keywords: Diabetes, child, necrotizing pneumonia, pneumonectomy

ÖZ

Diyabetik hastalar, nekrotizan pnömoni (NP) gibi daha ağır seyirli *Staphylococcus aureus* ile ilgili solunum yolu enfeksiyonları yaşayabilirler. Düzensiz takipli diabetes mellitus tanılı 13 yaşındaki kız hasta, diyabetik ketoasidoz ve solunum sıkıntısı tanılarıyla çocuk yoğun bakım ünitesine (ÇYBÜ) yatırıldı. İlk değerlendirmesinde pnömonik infiltrasyon tespit edilen hasta NP tanısıyla entübe edildi ve mekanik ventilatör (MV) desteğine bağlandı. Pozitif inotrop ve geniş spektrumlu antibiyotikler başlanıldı. Kan ve plevral örnek kültüründe metisiline dirençli *S. aureus* üremesi görüldü. Agresif medikal tedaviye rağmen enfeksiyonu kontrol altına alınamayan hastaya lobektomi yapıldı. Fistülize olan ve hayatı tehlikesi devam eden hastaya ÇYBÜ'ye yatışının 16 ve 29. günlerinde sağ total pnömonektomi ameliyatları yapıldı. Kliniğinde iyileşme görülen ve MV'den ayrılan hasta 59. günde hastaneden oksijensiz taburcu edildi. Medikal tedaviye dirençli NP tedavisinde erken cerrahi girişim hayat kurtarıcı olabilir.

Anahtar Kelimeler: Diyabet, çocuk, nekrotizan pnömoni, pnömonektomi

Introduction

Diabetes mellitus (DM) is a metabolic disorder that has been reported with increasing incidence in children. It is estimated that approximately 65.000 new cases under the age of 15 are diagnosed each year in the world (1). Diabetic children, particularly those with uncontrolled diabetes, are more prone to infectious diseases including skin and soft tissue structures, urinary tract and respiratory system when compared to healthy subjects (2).

Staphylococcus aureus is an important cause of respiratory tract infections. Especially, methicillin-resistant strains can lead to progressive necrotizing pneumonia (NP) with a high mortality rate (3). Although medical and supportive therapy remains the first-line treatment options, early surgical interventions should be performed in resistant cases (4).

Herein, we report a child with uncontrolled type 1 DM who was hospitalized in pediatric intensive care unit (PICU) for NP that was successfully treated with right total pneumonectomy.

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Case Report

A 13-year-old female was admitted to PICU with the preliminary diagnoses of respiratory distress and diabetic ketoacidosis. Her medical history revealed that she was diagnosed as type 1 DM at the age of 8 years and was on subcutaneous insulin treatment. However, she was irregularly followed-up because of non-compliance.

On presentation, she was confused and agitated. Her Glasgow Coma scale score was 10 and her vitals were as follows: heart rate: 139/min, blood pressure: 107/57 mmHg and respiratory rate: 45/min. She was dyspneic and severely dehydrated. Her respiratory sounds were diminished at the right middle zone and percussion revealed dullness. Other system examinations were unremarkable.

In the laboratory evaluation, white blood cell count was 13.000/mm^3 (neutrophil 87%). Acute phase reactants were significantly increased [C-reactive protein: 545 mg/L (normally <5) and procalcitonin: 43.56 mcg/L (normally <0.02)]. Metabolic acidosis was detected in venous blood gas analyses (pH=7.07, CO_2=19.8 mmHg, HCO_3=5.7 mmol/L BE=-23.7 mmol/L). Plasma blood glucose was 628 mg/dL. She was intubated and placed on pressure support-synchronized intermittent mandatory ventilation (PS-SIMV) with the following settings: positive inspiratory pressure: 20 cmH_2O, frequency: 22/min, I/E ratio:1:2.4 and positive end-expiratory pressure: 7 cmH_2O.

In addition to pleural effusion, chest radiography showed diffuse pulmonary opacity with air bronchogram in the right lung, dominantly in the lower zone (Figure 1A). Intravenous hydration, bicarbonate and insulin therapies were started. After blood cultures were taken, empirical teicoplanin (10 mg/kg/dose loading, with 12-hour intervals for 3 times, then 10 mg/kg/day) and meropenem (100 mg/kg/day) were initiated. Tube thoracotomy drainage was performed and exudative pleural specimen was sent for culture. She was started dobutamine (10 mcg/kg/min) and noradrenaline (0.1 mcg/kg/min) perfusion due to refractory hypotension. Echocardiographic examination was normal. Amikacin (15 mg/kg/day) and fluconazole (10 mg/kg/day) were added due to worsening medical condition. Abdominal ultrasonography was normal except for grade 1 renal parenchymal damage. Hemoglobin A1 level was 9.2%.

On follow-up, blood and pleural specimen cultures yielded methicillin-resistant *S. aureus* (MRSA) growth. Teicoplanin was tapered to linezolid (10 mg/kg/dose, three times a day) therapy. However, fever and increased acute phase response persisted. Chest computerized tomography (CT) performed on the 7th day revealed consolidation in the right middle and lower lobe, which evolved into necrosis and pneumatocele with accompanying pleural fluid (Figure 1B). She was tapered to subcutaneous insulin treatment after blood glucose control was achieved.

On the 10th day of PICU admission, the thorax tube was extracted. However, she was still febrile and dependent on intensive support MV. On the 12th day, the radiologic features were complicated by large cavitation in the right lower lobe and a newly developed bronchopneumonic infiltrative lesion in the left lower lobe (Figure 1C). Linezolid was stopped after 10 days and vancomycin was started (60 mg/kg/day). Despite aggressive medical treatment, infection could not be localized and right lower lobectomy was performed on the 16th day of admission.

On follow-up, tracheal aspirate specimen culture yielded *Stenotrophomonas maltophilia* and *Candida albicans* growth. Meropenem was stopped. Fluconazole was tapered to caspofungin therapy (50 mg/m^2/day after a loading dose of 70 mg/m^2), and ciprofloxacin (20 mg/kg/day) and trimethoprim (TMP)-sulfamethoxazole (12 mg TMP/kg/day) were added.

On the 24th day, she experienced a sudden decrease in hematocrit levels. Control chest CT was performed on suspicion of pulmonary hemorrhage. In addition to newly developed bronchiolar infiltration in ground glass opacities in the right lower lobe, hemorrhagic fluid collection was observed in the right hemithorax (Figure 1D). She was given erythrocyte and plasma transfusion, and pentaglobulin treatment (5 mL/kg/day for five days). Meanwhile, tigecycline (1.2 mg/kg/dose every 12 hours) was added.

A multidisciplinary council of pediatric and chest surgeons agreed on the necessity of right pneumonectomy because of progressive course. On the 29th day, right pneumonectomy and tracheostomy operations were performed. During follow-up, bronchoscopy was performed because of insufficient ventilation and suspected air leak on chest X-ray, and parenchymal fistula was detected in the right residual segment. On the 41th day, fistula closure was performed.

Postoperative control chest X-ray and CT revealed that right lung was totally removed. Also, there was no evidence of infiltration in the upper and lower lobes of the left lung, which was consistent with improvement (Figure 2A, B). Her general condition and ventilation improved over time. She was tapered to home ventilation on PS-SIMV mode, and then to continuous positive airway pressure support and

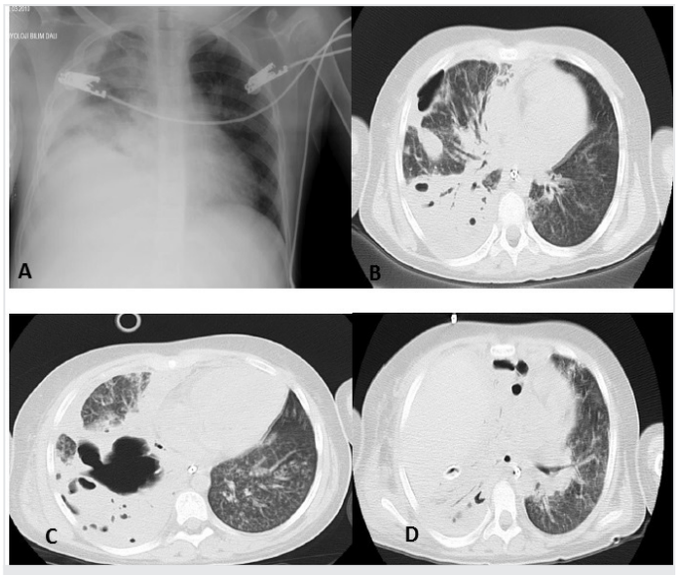

Figure 1A. Postero-anterior chest X-ray. Day 1, diffuse pulmonary opacity with air bronchogram and pleural effusion in the right lung. **1B.** Computerized chest tomography (CT). Day 7, Consolidation in the right middle and lower lobe, which evolved into necrosis and pneumatocele with accompanying pleural fluid. **1C.** CT. Day 12, large cavitation in the right lower lobe, newly developed bronchopneumonic infiltrative lesion in the left lower lobe. **1D.** CT. Day 24, hemorrhagic fluid collection in the right hemithorax and newly developed bronchiolar infiltration in ground glass opacities in the right lower lobe

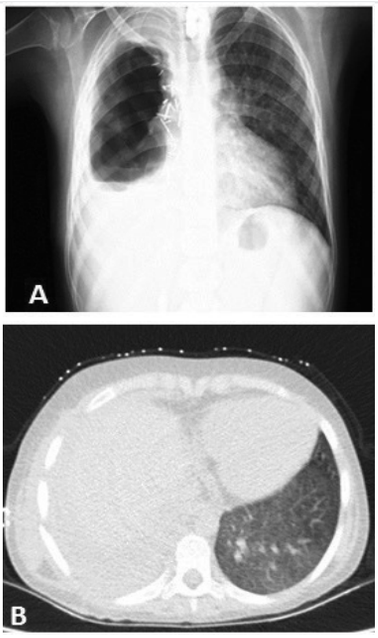

Figure 2A. Postero-anterior chest X-ray, **2B.** Computerized chest tomography on day 42, right pneumonectomy and prominent improvement in left lung

easy-breathe on the following days. On the 52nd day of admission, she was transferred to inpatient clinic and discharged oxygen-free from the hospital one week later. Informed consent was obtained from the parents of the patient for publication.

Discussion

The incidence of community-acquired MRSA infections has been increasing in recent years (5). In addition, type 1 DM is declared as a risk factor for *S. aureus*-related infections (5). Literature data agree that nasal colonization of *S. aureus* is a predisposing factor for infection and that there is an increased incidence of nasal *S. aureus* colonization in diabetic patients (6). Ahluwalia et al. (7) reported a positive correlation between hemoglobin A1 levels and incidence of nasal *S. aureus* colonization in diabetic patients. Similarly, our patient was diagnosed as type 1 DM five years ago and she was non-compliant with the proper follow-up, thus having a high hemoglobin A1 values.

MRSA-associated NP may have a potentially progressive and fatal course (3). Linezolid or glycopeptide antibiotics (vancomycin/teicoplanin) should be included as part of the initial regimen to treat MRSA-related pneumonia (8). Tigecycline should be reserved for complicated cases and should be selected as the final option since it is not Food and Drug Administration (FDA) approved before 18 years of age (9). Our patient presented with respiratory distress secondary to community-acquired pneumonia. Since she was septic and distressed at presentation, empirical broad-spectrum antibiotherapy including teicoplanin was started initially. On her follow-up, empyematous material and blood culture revealed MRSA growth. As her pulmonary findings progressed under teicoplanin treatment, we preferred to taper linezolid because of its high penetration into lung tissue.

Despite effective medical treatment, persistent fever and respiratory distress should raise the suspicion of pulmonary necrosis (10). Similarly, chest CT confirmed NP in our patient. During follow-up, alternating vancomycin and finally tigecycline therapy was tried due to accompanying MRSA bacteremia. However, the progression of infection could not be inhibited.

Although medical and supportive treatment is preferred initially for the treatment of NP, surgery should not be delayed in resistant cases (4). The main indications for surgery include persistent fever, persistent respiratory distress, and sepsis despite aggressive medical treatment (11). The type of surgical resection is based on the extent of pulmonary necrosis and should be as conservative as possible. Thoracoscopic decortication without lung resection, wedge resection and lobectomy are the preferred surgical options (11). Pneumonectomy may be required if the necrotizing process involves multiple lobes (12). Because of the fulminant course of the infection, surgery was inevitable for our patient. Although lobectomy was tried initially, it was unable to control the infection. Therefore, pneumonectomy was performed. With the success of metabolic control, pneumonectomy was well-tolerated in our patient.

Conclusion

This case was reported to emphasize the importance of appropriate control of DM, in addition to awareness of early surgical consultation for patients with NP resistant to effective medical therapy.

Informed Consent: Informed consent was obtained from the parents of the patient for publication.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - G.A., M.K.; Design - G.A., E.Ç.; Supervision - F.G.S., S.H.T.; Data Collection and/or Processing - G.A., M.K., A.Ç.; Analysis and/ or Interpretation - A.S., K.N., A.Ç.; Literature Search - G.A., M.K. K.N.; Writing Manuscript - G.A., M.K.; Critical Review - A.S., S.H.T., A.Ç., K.N.

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

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A Case of Sarcoidosis with Diffuse Cavitary Lesion in the Lung

Akciğerde Yaygın Kaviter Lezyon İzlenen Sarkoidoz Olgusu

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ABSTRACT

Sarcoidosis is a granulomatous disease of unknown origin, which affects many organs and systems, and is often seen in young adults. The most common organ involved in sarcoidosis is the lung and various radiological features are observed. Bilateral hilar lymph node enlargement is the most common finding, followed by interstitial lung disease. Primer cavitary sarcoidosis is very rare. In this article, we present a case of sarcoidosis diagnosed by mediastinoscopy who had a history of contact with tuberculosis and diffuse cavitary lung lesions and hilar lymphadenopathies on thoracic computed tomography. Sarcoidosis should be kept in mind in the differential diagnosis of cavitary lesions of lung.

Keywords: Cavitary, sarcoidosis, hilar

ÖZ

Sarkoidoz, nedeni bilinmeyen, sıklıkla genç erişkenlerde görülen birçok organ ve sistemi etkileyen granülomatöz bir hastalıktır. Sarkoidozda en sık tutulan organ akciğer olup, çeşitli radyolojik görünümler izlenir. Bilateral hiler lenf nodu genişlemesi en sık bulgudur ikinci olarak interstisyel akciğer hastalığı izlenir. Primer kaviter sarkoidoz oldukça nadir izlenmektedir. Bu yazıda, tüberküloz temas öyküsü olan, akciğer bilgisayarlı tomografisinde hiler lenfadenopatileri ve yaygın kaviter lezyonları izlenen mediastinoskopi ile sarkoidoz tanısı konan olgu sunulmuştur. Kaviter lezyonların ayırıcı tanısında sarkoidozu vurgulamak için sunduk.

Anahtar Kelimeler: Kaviter, sarkoidoz, hiler

Introduction

Sarcoidosis is defined as a granulomatous disease of unknown origin that occurs in young adults, usually affecting many organs and systems such as hilar lymphadenopathy, lung infiltration, eye and skin findings, heart, liver, nervous system, musculoskeletal system, and peripheral lymph nodes. The most commonly involved organ is the lung and is responsible for the morbidity and mortality of the disease. Diagnosis is usually based on clinical, laboratory and radiological findings, including histopathologic findings (epitholoid cell granuloma without caseification) that can be demonstrated in more than one system and exclusion of other causes of granulomatous inflammation (1). Pulmonary tomography may show various radiological involvements (2). Bilateral hilar lymph node enlargement is the most common radiological finding and the second most common pattern is interstitial lung disease. Typical findings in high-resolution computed tomography are perilymphatic micronodules, fibrotic changes and bilateral perihilar opacities. Atypical appearances, mass-like or alveolar opacities, honeycomb cysts, miliary opacities, mosaic attenuation, tracheobronchial involvement, pleural disease, and cavitary involvement are rare (3). Acinar or nodular disease in the lung parenchyma is common in young individuals (4). Primary cavitary sarcoidosis is very rare and observed at a rate of <0.8% (5). The cavitation of parenchymal lesions was observed as 10% in end-stage disease (6). In this article, a case of primary cavitary sarcoidosis is presented with the literature.

Case Report

A 22-year-old female patient presented to outpatient clinic with complaints of cough and sputum production. She did not have a known history of systemic disease. She had a recent history of oral cefuroxime axetil (2x500 mg) and clarithromycin (2x500 mg) use for 7 days. The patient was a housewife and had no occupational exposure. The patient had a history of tuberculosis contact. On physical examination, respiratory sounds were evaluated as slightly rough. Posteroanterior chest X-ray showed a cavitary appearance in the right lung at the level of fourth rib.

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Complete blood count and biochemistry parameters were evaluated as normal. Purified protein derivative (PPD) test, sputum ARB and routine blood tests were requested. PPD was negative and sputum ARB samples were evaluated as negative five times. Cytoplasmic-anti neutrophil cytoplasmic antibodies, Perinuclear anti-neutrophil cytoplasmic antibodies and antinuclear antibody values were negative. Thoracic computed tomography showed diffuse mediastinal lymphadenopathies, ground glass areas and cavitary lesion in the right apex. Endobronchial Ultrasound (EBUS) was performed and no endobronchial lesion was observed. The sample taken from subcarinal lymphadenopathy was evaluated as fibrotic tissue fragments suspected for granulomatous inflammation. For definitive diagnosis, the patient was evaluated by mediastinoscopy. The results of upper and lower paratracheal lymph nodes were presented as non-necrotizing granulomatous inflammation. Serum ACE level was 72 U/L and urine calcium level was normal. During the follow-up period, lesions compatible with erythema nodosum developed in the lower extremity of the patient. The patient was evaluated as sarcoidosis and 20 mg oral prednisone was started. Clinical and radiological response was observed. A regression of the cavitary lesion was observed on the posteroanterior radiograph of the patient, complaints reduced and the patient was followed-up. Informed consent was obtained from the patient.

Discussion

Sarcoidosis is characterized by granulomatous inflammation with lymphadenopathy, pulmonary infiltration and eye and skin lesions. It is more common in young adults and women, and 70% of patients are young adults between the ages of 20-40 (7,8). The incidence of sarcoidosis in our country has been reported as 4/100.000 (9). Our case was a 22-year-old woman and was included in the population in which the disease is common.

The most common organ involved in sarcoidosis is the lung. Pulmonary involvement occurs in 95% of all cases (10). Symptoms such as dry cough (30%), dyspnea (28%), chest pain (25%), wheezing and rarely hemoptysis may occur in patients with pulmonary involvement (11). Our case was admitted to the outpatient clinic with complaints of dry cough and sputum production. Due to sputum production, sputum culture and acid-resistant bacteria examination in sputum were requested. ARB was negative for five times and there was no growth in non-specific and tuberculosis cultures.

It should be kept in mind that extra-pulmonary organs and tissues may be affected while taking anamnesis in a patient with sarcoidosis and extra-pulmonary symptoms should be questioned. Extra-pulmonary involvement is usually associated with pulmonary involvement in sarcoidosis (12). Extra-pulmonary involvement is most commonly seen in the liver, spleen, eye, peripheral lymph nodes and skin. Neurological involvement, cardiac involvement, chronic hypercalcemia, chronic uveitis, cystic bone lesions, lupus pernio, nasal mucosa involvement and nephrocalcinosis are extra-pulmonary involvements with poor prognosis. Therefore, diagnosis and treatment of extra-pulmonary involvement is important to reduce morbidity and mortality in sarcoidosis (13). Although there are no symptoms, basal tests (complete blood count, biochemical tests, urinalysis, 24-hour urine calcium, electrocardiography, PPD and eye examination) should be performed to evaluate extra-pulmonary sarcoidosis (12). In our case, complete blood count and biochemistry tests were unremarkable. PPD was evaluated as anergic. Eye examination was normal.

The presence of hypercalcemia is an important finding in supporting the diagnosis of sarcoidosis. It is caused by increased production of 1,25-dihydroxyvitamin D3 from alveolar macrophages due to increased 1-alpha hydroxylase activity. Hypercalciuria is frequently seen due to hypercalcemia (1,11). Serum and urine calcium levels were within normal limits in our patient.

Because sarcoidosis is a systemic, autoimmune, inflammatory disease, laboratory tests demonstrating systemic inflammation are often positive. Elevated sedimentation and CRP levels are common. Chronic disease anemia, lymphopenia, eosinophilia and thrombocytopenia may be seen. Elevated ACE serum level is an important feature in sarcoidosis and has been reported with a frequency of 40-90% (1,11). The hemoglobin value, lymphocyte count and eosinophil count were within normal limits in our patient. Serum ACE level was 72 U/L and it was high. In addition to sarcoidosis, elevation of serum ACE may occur in diseases such as silicosis, human immmunodeficiency virus (HIV) infection, liver cirrhosis, diabetes mellitus, Gaucher's disease, histoplasmosis and aspergillosis. There was no history of occupational or environmental exposure for silicosis. In our case, HIV RNA and anti-HIV were negative, blood glucose levels were within normal limits, liver functions were normal, serum galactomannan was negative and histoplasma antibody was negative.

The diagnosis of sarcoidosis is made by combining clinical, radiological and laboratory findings; however, the gold standard is histopathological diagnosis. The suspicion of sarcoidosis is frequently raised by chest X-ray findings, because 90-95% of the patients have pathological changes in chest radiographs. The radiological findings of sarcoidosis are quite broad spectrum and bilateral hilar lymph node enlargement is the most common finding, followed by interstitial lung disease. Scadding divided sarcoidosis into four stages according to changes in chest X-ray (12) (Table 1). The posteroanterior chest X-ray of our case showed a cavitary appearance of approximately 2 cm in diameter in the right lung at the level of fourth rib, and the hili were bilaterally wide. Radiologically, it was evaluated as stage 2.

Typical signs of sarcoidosis in HRCT are perilymphatic micronodules, fibrotic changes, and bilateral perihilar opacities. Atypical appearances, mass-like or alveolar opacities, honeycomb cysts, miliary opacities, mosaic attenuation, tracheobronchial involvement, pleural disease and cavitary involvement are rare (3). Computed tomography of our case revealed diffuse mediastinal lymphadenopathies, ground glass areas

Table 1. Scadding staging in sarcoidosis according to chest X-ray findings

Stage 0	**Normal**
Stage 1	Bilateral hilar adenopathy, normal lung parenchyma
Stage 2	Hilar adenopathy with pulmonary infiltration
Stage 3	Pulmonary infiltration without hilar adenopathy
Stage 4	Pulmonary fibrosis

and a 2x2.30 cm diameter cavitary lesion in the right apex. It has been suggested that cavitary lesions may be associated only with sarcoidosis as well as associated diseases, especially aspergilloma (14-16). In the study of Rockhoff and Rohadgi (6), cavitation of parenchymal lesions was observed as 10% in end-stage disease. In a study by Freundlich et al. (5), it was reported that cavitary lesions were present in 0.6% of patients with pulmonary sarcoidosis based on chest X-ray, and Mayock et al. (17) reported that cavitary lesions were present in 8.3% of sarcoidosis patients. The natural course of these lesions is highly variable; they can spontaneously resolve, stabilize or worsen, and their course may result in various complications such as hemoptysis, pneumothorax and aspergilloma (18-20). No pneumothorax, hemoptysis and aspergilloma were observed during the follow-up of our case, and the cavitary lesion regressed under steroid therapy.

Biopsy is required for definitive diagnosis in patients with suspected sarcoidosis by radiological and other laboratory methods. Transbronchial biopsies play an important role in the histological diagnosis of lung lesions. As another diagnostic method, EBUS has gained importance in recent years. In sarcoidosis, lymph nodes in areas adjacent to the bronchi often enlarge, and they can be reached with EBUS and needle biopsy can be done. However, mediastinoscopy can be performed with general anesthesia and biopsy can be performed from mediastinal lymph nodes in patients who cannot be diagnosed by EBUS. The well-circumscribed epithelioid non-necrotizing granulomas are typical histopathologic findings of sarcoidosis (11). Transbronchial biopsy was evaluated as non-diagnostic and CD4/CD8 ratio was 4 in bronchoalveolar lavage fluid. Because of mediastinal diffuse lymphadenopathies, EBUS was performed and no endobronchial lesion was observed, and the sample taken from subcarinal lymphadenopathy was evaluated as fibrotic tissue fragments suspected for granulomatous inflammation. *Mycobacteria Tuberculosis* polymerase chain reaction was evaluated as negative in tissue samples. For definitive diagnosis, the patient was evaluated by mediastinoscopy. The results of upper and lower paratracheal lymph nodes were presented as non-necrotizing granulomatous inflammation, and our case was evaluated as sarcoidosis.

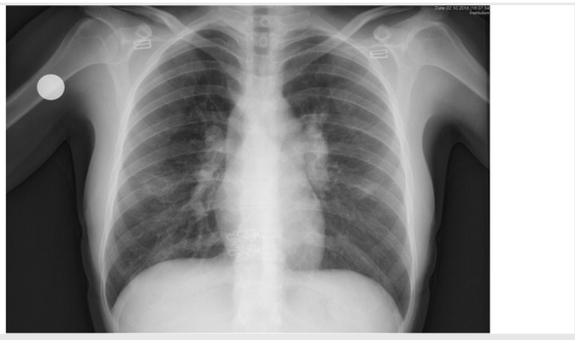

Figure 1. Posteroanterior chest X-ray of the patient

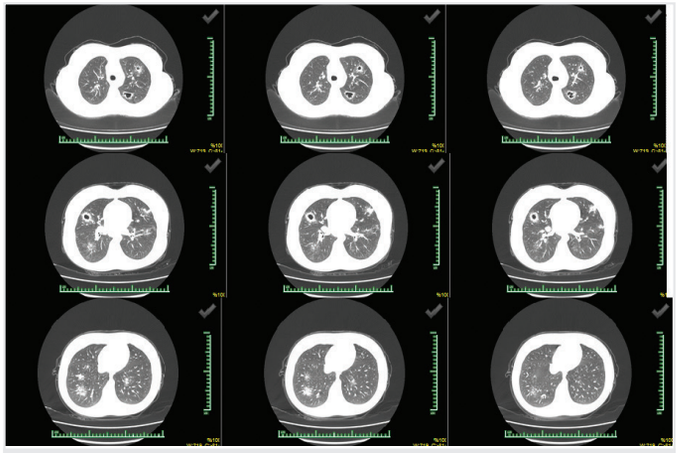

Figure 2. Thorax computed tomography images of the patient

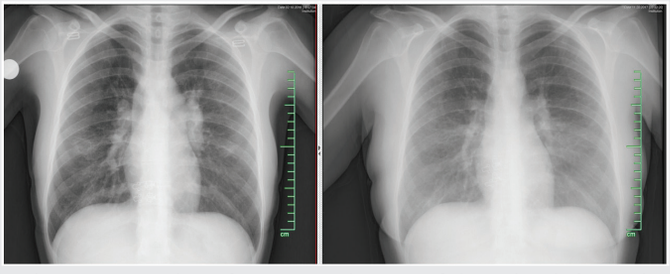

Figure 3. Comparison of posteroanterior X-ray of the patient before and after treatment

There is no consensus on treatment algorithm and the appropriate dose and duration of use of the drugs used in the treatment of sarcoidosis. Corticosteroids are the first-line and most commonly used treatment agents. In pulmonary involvement, more than 70% of patients respond with clinical and radiological response to corticosteroid therapy. However, it has been reported that 25-50% recurrence may occur in corticosteroid dose reduction or discontinuation (11). Treatment can be started with prednisolone 20-40 mg daily (12). Although doses above 20 mg per day are generally not required in patients with pulmonary involvement, the daily requirement for prednisolone dose may exceed 20 mg in cardiac and neurological involvement. In the follow-up, it should be aimed to reduce to the lowest dose of corticosteroid to control symptoms. The recommended corticosteroid treatment duration and dose reduction schemes are different. While Huninghake et al. (21) recommend that the corticosteroid dose be reduced and discontinued within 6 months after the start of treatment, Winterbauer et al. (22) recommend that the treatment be continued for at least 1 year against the risk of relapse. Second-line drugs may be used in patients with uncontrolled disease activity and symptoms despite corticosteroid treatment, with exacerbation following reduction of corticosteroid dose and with prominent side effects due to corticosteroid treatment. These drugs include chloroquine, hydroxychloroquine, methotrexate, azathioprine, leflunomide, mycophenolate mofetil, cyclosporine, pentoxifylline and minocycline. Cyclophosphamide, anti-Tumor necrosis factor agents, rituximab and thalidomide have also been reported in treatment-resistant and severe cases (23). The treatment of our case was 20 mg oral prednisone. At the end of the second month, her cavitary lesion and complaints regressed.

Conclusion

Sarcoidosis was diagnosed in a young female patient who had a history of tuberculosis contact and cavitary lesion in our country where tuberculosis was endemic, and clinical and radiological response to steroid treatment was observed in a short time. We presented our case

of cavitary sarcoidosis because it is rare and there is no case report and/ or series of cavitary sarcoidosis cases in our literature. We believe that we need larger case series on sarcoidosis.

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.E.G., D.T.; Design - M.A.Ö.; Supervision - F.E.G.; Resources - B.Z.Y.; Materials - D.T.; Data Collection and/or Processing - F.E.G., D.T.; Analysis and/ or Interpretation - D.T., M.A.Ö.; Literature Search - F.E.G.; Writing Manuscript - F.E.G.,; Critical Review - L.C., M.A.Ö.

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A Rare Case in Rheumatology Clinical Practice: Pachydermodactyly

Romatoloji Pratiğinde Nadir Bir Olgu: Pakidermodaktili

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ABSTRACT

Pachydermodactyly (PDD) is a benign, acquired digital fibromatosis characterized by asymptomatic and progressive swelling of periarticular soft tissue, and is usually seen in young men. The etiology of PDD is not fully understood, but is thought to be due to the result of recurrent mechanical stimulation. PDD is usually diagnosed by clinical evaluation. There are thick collagen bundles and collection of dermal mucin in the histopathology. Treatment is not indicated due to benign prognosis. Rheumatologic diseases, particularly rheumatoid arthritis, affecting the joints of the hands should be considered in the differential diagnosis due to the similarity of the joint involvement.

Keywords: Pachydermodactyly, proximal interphalangeal joint, painless swelling

ÖZ

Pakidermodaktili (PDD), genellikle genç erkeklerde görülen, periartiküler yumuşak dokunun asemptomatik, ilerleyici şişliği ile karakterize benign edinsel dijital fibromatozdur. PDD'nin etiyolojisi tam olarak bilinmemekle beraber muhtemelen tekrarlayan mekanik stimülasyonun bir sonucudur. Tanı genellikle klinik olarak konur. Histopatolojide kalın kollajen demetleri ve dermal musin birikimi vardır. Benign seyir gösterdiğinden tedavi genellikle endike değildir. Başta romatoid artrit olmak üzere el eklemlerini etkileyen romatizmal hastalıklar, eklem tutulumunun benzerliğinden dolayı, ayırıcı tanıda düşünülmelidir.

Anahtar Kelimeler: Pakidermodaktili, proksimal interfalangial eklem, ağrısız şişlik

Introduction

Pachydermodactyly (PDD) is a benign, skin fibromatosis characterized by asymptomatic painless periarticular swelling in the proximal interphalangeal (PIP) and sometimes metacarpophalangeal (MCP) joints, often affecting young adult males. The etiology is not fully understood, but mechanical trauma is thought to be responsible. Histopathologically, there is an accumulation of dermal collagen histopathologically (1). Rheumatological diseases, particularly rheumatoid arthritis (RA), affecting the joints of the hands should be considered in the differential diagnosis due to the similarity of the joint involvement (2).

We would like to draw attention to this rare situation, which should be considered in rheumatology clinical practice as it causes painless joint swelling.

Case Report

A 22-year old male patient was referred to our outpatient clinic with the complaint of swelling of the 3rd PIP joint of the right hand for the last 2.5 years. Symmetrical swelling was observed around the PIP joints of digits 3-4 bilaterally (Figure 1).

The patient had previously undergone methotrexate treatment in another medical center with the diagnosis of RA, but the patient discontinued the treatment on his own request as no benefit was obtained. There was no pain in the joints of the hands, no morning stiffness and no night pain. The results of the systemic examinations were unremarkable. There was no family history of psoriasis or rheumatologic disease. On the physical examination, there were joint swellings in the 4th and more evidently in the 3rd PIP joints of the right hand and the 3rd and 4th PIP joints of the left hand. There was no tenderness with palpation and range of motion was complete. In the laboratory tests, the results of the complete blood count, liver function tests, kidney function tests, erythrocyte sedimentation rate, C-reactive protein, thyroid stimulating hormone test and urinalysis were normal. Hepatitis markers, antinuclear antibody, rheumatoid factor, anti-cyclic and citrullinated peptide antibody were negative. Periarticular soft tissue swelling was observed on the direct

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Figure 1. Photographic image of bilateral hands. Symmetrical swelling around proximal interphalangeal joints of digits 3-4 bilaterally

Figure 2. Hand radiograph showings soft tissue swelling around the proximal interphalangeal joints without joint narrowing or bony erosions

Figure 3. Magnetic resonance imaging reveals soft tissue swelling of the third to fourth proximal interphalangeal joints of the hand without articular or bony abnormality

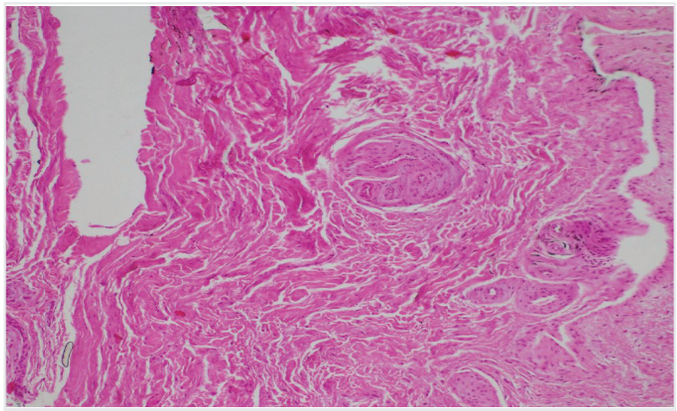

Figure 4. Skin biopsy specimen exhibits marked hyperkeratosis and thickened dermis with collagen deposition (hematoxylin and eosin, x100)

radiograph, but there was no sclerosis, joint space narrowing, erosion or periosteal reaction (Figure 2).

There was no evidence of inflammation in the PIP joint on ultrasonographic evaluation. Thickening of the subcutaneous tissue was detected on magnetic resonance imaging (MRI) of the hand, but no evidence could be associated with synovitis (Figure 3).

A biopsy was performed from the lateral of the 3rd PIP joint of the right hand with a preliminary diagnosis of PDD, and hyperkeratosis and thickened dermis with collagen deposition were detected (Figure 4).

The patient was diagnosed with PDD after evaluation of the clinical, laboratory, radiology and biopsy findings. The patient was given information that PDD is a non-inflammatory disease with a benign course.

Written informed consent was obtained from the patient for details to be published in this study.

Discussion

PDD is a rare digital fibromatosis, which was first reported by Basex et al. (3) in 1973 and was then named PDD by Verbov (4) in 1975. To date, approximately 150 cases of PDD have been reported in literature (5). It is characterized by soft tissue swelling especially in the lateral part of the PIP joints of the 2nd-4th fingers of adolescent males. It is approximately 4 times more commonly in men (2). There are also familial cases as case reports in the literature (6). Although the etiology is not fully understood, mechanical trauma is a precipitating factor in 44% of patients (2). Continuous pulling and docking of the fingers can be seen in some occupations (athletes, musicians, computer users, farm workers) and also in subjects with Asperger syndrome and obsessive compulsive disorder. Therefore, a psychiatric consultation is essential (1,7). Bardazzi et al. (8) defined PDD in 5 subtypes: a) classical (which affects multiple joints and is due to repeated microtrauma, b) localized (which affects only one joint), c) transgradient (which affects the dorsum of the hand and MCP areas), d) familial and e) the form associated with tuberous sclerosis.

There is no specific laboratory finding for the diagnosis. The acute phase proteins are normal and there are no specific autoantibodies for the disease. No periarticular osteoporosis, periosteal reaction, erosion, osteophyte or cysts are observed on radiographs, only soft tissue swelling. No pathological findings such as synovitis, capsulitis, tendinitis or hypervascularization apart from soft tissue swelling are found on MRI screening (9). In histopathological examination, PDD is characterized by hyperkeratosis and achantosis of the epidermis, and

thick collagen bundles and increased fibroblasts in the dermis. The cytological appearance of the fibroblasts is benign. There may also be mucin accumulation in the interstitium in varying degrees and the number of elastic fibers may be decreased (10). When collagen analysis is performed, the amount of collagen type 3 and 5 is higher. Collagen fibers are less uniform and of smaller diameter in electronmicroscopy (1,2).

Chen et al. (1) proposed the diagnostic criteria of no symptom of the patient, no morning stiffness, no pain with movement and tenderness with palpation, finger swelling especially on the ulnar or radial side, but not peripheral, normal laboratory test results, and only soft tissue swelling on X-ray.

In the differential diagnosis, there should be consideration of rheumatologic diseases such as juvenile idiopathic arthritis and RA, bone diseases such as spina ventosa, and pachydermatoperiostosis (11), skin diseases such as knuckle pads (12) and foreign body granuloma, and genetic causes such as Thiemann's disease (2).

There is no universally accepted treatment option. It may be useful to avoid mechanical stimulation. Some cases improved with oral tranilast, intralesional triamcinolone injection and surgical excision of fibrotic tissues. Tranilast is an anti-allergic drug, which inhibits collagen synthesis (13,14). No treatment was applied to the current patient, but as he had a habit of pulling his fingers, he was advised to discontinue this habit. The patient was referred to the psychiatry clinic for consultation.

PDD is a rare benign disease. As it causes swelling in the PIP joints, differential diagnoses must consider rheumatologic diseases, primarily RA. Loss of function, restricted range of motion, no morning stiffness and no pathology determined with laboratory and imaging methods, are significant characteristics. Correct recognition of PDD prevents unnecessary referrals and tests and, most importantly, inappropriate treatment.

Informed Consent: Written informed consent was obtained from the patient for details to be published in this study.

Peer-review: Externally and internally peer-reviewed.

Author Contributions: Concept - A.Ü.E., A.N.D., İ.S., C.Ç.; Design - A.Ü.E., A.N.D., İ.S., C.Ç.; Supervision - A.Ü.E., A.N.D., İ.S., C.Ç.; Data Collection and/or Processing - A.Ü.E., İ.S.; Analysis and/ or Interpretation - A.Ü.E., A.N.D., İ.S., C.Ç.; Literature Search - A.Ü.E., İ.S., C.Ç.; Writing Manuscript - A.Ü.E., İ.S.; Critical Review - İ.S., C.Ç.

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Laparoscopic Resection of the Schwannoma of the Colon: Case Report and Review of the Literature

Laparoskopik Kolon Schwannom Rezeksiyonu: Olgu Sunumu ve Literatür İncelenmesi

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ABSTRACT

Schwannomas are slowly growing nerve sheath tumors originating from Schwann cells (neural crest) of neural tissue and are usually known to have benign behavior. Although they are usually observed in the head, neck and extremities, they can rarely be encountered in gastrointestinal system without Von Recklinghausen's disease. They constitute 2-6% of all gastrointestinal tract submucosal tumors. The preoperative diagnosis of schwannoma is difficult and treatment is radical excision. Herein, we describe a case of schwannoma of the ascending colon that was resected with laparoscopic right hemicolectomy in the light of the literature.

Keywords: Schwannoma, Von Recklinghausen's, right hemicolectomy

ÖZ

Schwannomlar nöral kılıfta Schwann hücrelerde köken alan; sıklıkla kafa, boyun ve ekstremitelerde gözlenen yavaş büyüyen tümörlerdir. Kolon ve rektumda Von Recklinghausen ile ilişkisiz primer schwannom görülmesi oldukça nadirdir. Tüm gastrointestinal kanal submukozal tümörlerin %2-6'sını oluştururlar. Preoperatif tanı alması zor olup, tedavisi radikal cerrahi eksizyondur. Biz bu yazıda çıkan kolonda schwannomu olan ve laparoskopik sağ hemikolektomi uyguladığımız olguyu literatür eşliğinde anlatmayı amaçladık.

Anahtar Kelimeler: Schwannom, Von Recklinghausen, sağ hemikolektomi

Introduction

Schwannomas constitute 1% of gastrointestinal benign tumors (1). Regarding gastrointestinal tract, its rate is 83% for the stomach and 12% for the small intestine (2). Colorectal localization is very rare. They are slow-growing, usually benign, encapsulated tumors and constitute 2-6% of all gastrointestinal tract submucosal tumors (3,4). Local and distant metastasis rates are 30% and 2%, respectively (1). The incidence is equal in women and men, and the age of onset is 60-70 years (2). In this article, we describe a 67-year-old schwannoma case diagnosed postoperatively.

Case Report

A 67-year-old male patient was admitted to our clinic with fatigue. The patient's medical history was unremarkable. The laboratory tests were within normal limits except for hemoglobin value of 5.8 g/dL and hematocrit value of 28.8%. A colonoscopy was performed following detection of a 3.5x4 cm polypoid mass at the cecum and ascending colon in abdominal computed tomography (Figure 1). The lesion was approximately 3 cm and located at the ascending colon, and was reported to be an ulcerated, polypoid gastrointestinal stromal tumor (GIST). A biopsy was obtained and was reported to be lymphoma or leiomyoma. Laparoscopic right hemicolectomy was performed. There

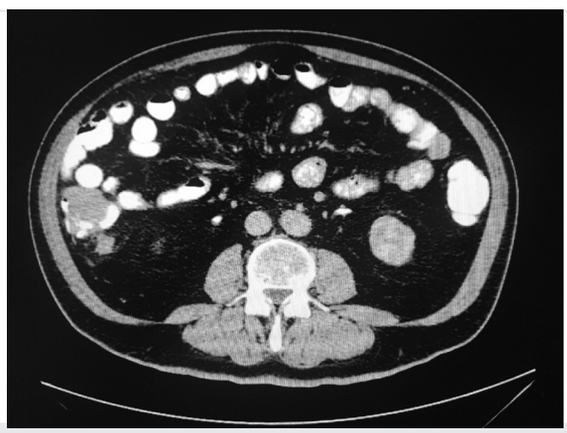

Figure 1. Computed tomography image

This was presented as a poster in 21st National Congress of Surgery in 2018.

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was no complication in the patient after a hospitalization period of 5 days. Pathology report was "4x3.8x3 cm non-invasive tumor with Ki-67 4%, mitotic index <1, CD117, CD34, desmin negativity and S100 positivity, compatible with schwannoma. Thirty-three lymph nodes were sampled and no metastasis was detected. The patient, who is in the 5th month of the follow-up, is uneventful. Written informed consent was obtained from the patient.

Discussion

Schwannoma was first reported by Verocay (4) in 1910. It mostly originates from Aurbach's plexus in the gastrointestinal tract and it has a sessile polyp structure growing towards the lumen. It has pedicled polyp appearance when originates from Meisiner's plexus (2). Diagnosis by biopsy is difficult due to submucosal growth pattern (1). Diagnosis is usually made by postoperative immunohistochemistry. Although schwannoma is a benign tumor with slow growth, it may show malignant transformation if left untreated. It causes symptoms such as abdominal pain, obstruction and rectal bleeding caused by other polypoid lesions (5). In our case, it was detected in a patient who was examined due to anemia and no similar case has been reported in the literature.

Schwannomas regarded as one of the subtypes of GISTs are diagnosed by immunohistochemical examination. They are CD117 (KIT), CD34, CK5, spinal muscular atrophy and desmin negative. They generally show positive staining for S100 protein and vimentin (5). Having a Ki-67 proliferative index of ≥5% and tumor diameter greater than 5 cm increases the probability of malignancy. In addition, mitotic activity rate of >5 mitosis is also a parameter that increases the risk of metastasis and recurrence (6). In our case, Ki-67 was 4%, the tumor was 4 cm in the widest part and the mitotic index was <1.

The general opinion in the treatment is complete local excision. Radical resection and lymphadenectomy are acceptable if there is no definitive pre-operative diagnosis. Nowadays, laparoscopic colectomies are widely used compared to conventional methods with less hospital stay, less postoperative pain and cosmetic superiority without increasing the risk of complications. We also performed a laparoscopic right hemicolectomy in this case. Since there was no pre-operative diagnosis, we added lymphadenectomy. There was no complication or recurrence during follow-up.

Conclusion

Schwannomas are tumors diagnosed postoperatively and their treatment is en bloc resection. Laparoscopic approach can be performed safely as in other gastrointestinal tumors.

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally and internally peer-reviewed.

Author Contributions: Concept - B.B.; Design - R.G.I.; Supervision - Ö.A.; Resources - B.B.; Materials - Ö.A.; Data Collection and/or Processing - B.B.; Analysis and/ or Interpretation - R.G.I.; Literature Search - B.B.; Writing Manuscript - Ö.A.; Critical Review - R.G.I.

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Aggressive Fibromatosis of the Chest Wall: A Case Report with Magnetic Resonance Imaging and Histopathological Findings

Göğüs Duvarı Agresif Fibromatozisi: Manyetik Rezonans Görüntüleme ve Histopatolojik Bulguları ile Birlikte Olgu Sunumu

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ABSTRACT

Fibromatosis represents a group of fibroblastic proliferations that vary from benign to intermediate in biological behavior. It can be classified as superficial or deep. Aggressive fibromatosis (AF) does not cause distant metastasis, the potential for local invasion and recurrence is very high. AF can be seen in various sites, including extra-abdominal, abdominal wall and intra-abdominal locations. It is rare in the extra-abdominal area and may involve the muscles of the shoulder, pelvis and thigh. AF of the chest wall is rare, representing only 8-10% of all deep fibromatoses. Cross-sectional imaging modalities, especially magnetic resonance imaging (MRI), can be used to detect, characterize and show the extension of these tumors into adjacent tissues. MRI is superior to CT in the radiological evaluation of soft tissues. The signal intensity of AF varies depending on the collagen and water content of the cell. A radical surgical resection strategy with a safe margin (2-3 cm) remains the standard therapeutic approach for AF. However, radiotherapy is a significant treatment challenge, especially for young women. Herein, we present a 25-year-old female patient with recurrent chest wall AF extending to the breast, along with clinical findings, MR images, and histopathological findings.

Keywords: Aggressive fibromatosis, chest wall, ultrasonography, magnetic resonance imaging

ÖZ

Fibromatozis biyolojik davranışı benign ve intermediate arasında değişen bir grup fibroblastik proliferasyonu temsil eder. Yüzeyel ve derin olarak sınıflandırılabilir. Agresif fibromatozis (AF) uzak metastaz yapmaz ancak lokal invazyon ve rekürrens potansiyeli çok yüksektir. AF, ekstraabdominal, intrabdominal ve karın duvarında olmak üzere çeşitli yerlerde görülebilir. Ekstraabdominal alanda nadir olup omuz, pelvis ve uyluk kaslarında görülebilir. Göğüs duvarının AF'si nadir olup tüm derin fibromatozların yalnızca %8-10'unu temsil eder. Kesitsel görüntüleme yöntemleri, özellikle manyetik rezonans görüntüleme (MRG), bu tümörleri saptamak, karakterize etmek ve komşu yumuşak dokulara yayılımını göstermek amacıyla kullanılabilir. MRG, yumuşak dokuların radyolojik değerlendirmesinde bilgisayarlı tomografiye (BT) oldukça üstündür. AF'nin sinyal intensitesi hücrenin kollajen ve su içeriğine bağlı olarak değişkenlik göstermektedir. AF'nin standart tedavisi güvenli marjlı (2-3 cm) radikal cerrahi rezeksiyondur. Bununla birlikte, radyoterapi, özellikle genç kadınlar için önemli tedavi yöntemlerindendir. Biz burada meme dokusuna uzanımlı rekürren göğüs duvarı AF'si olan 25 yaşında bayan hastayı klinik bulguları, MRG görüntüleri ve histopatalojik bulguları ile birlikte sunmayı amaçladık.

Anahtar Kelimeler: Agresif fibromatozis, göğüs duvarı, ultrasonografi, manyetik rezonans görüntüleme

Introduction

Fibromatosis is a benign, slow-growing tumor without any metastatic potential (1). These tumors are classified as superficial or deep (2). Deep fibromatosis, also known as desmoid tumors or aggressive fibromatosis (AF), can be intra-abdominal, within the abdominal wall, or extra-abdominal. In several studies, 28-69% of AF tumors were intra-abdominal (mesenteric or pelvic) or in the abdominal wall, and the remainder were extra-abdominal (3), 8-10% of which were located in the chest wall (4). There is a slight preponderance in females and the peak incidence occurs in the third and fourth decades of life. AF is more aggressive in younger patients with recurrence rates of up to 87%. Although AFs occur sporadically, they can also be seen as a part of familial adenomatous polyposis (FAP) and Gardner's syndrome (5). The estimated prevalence of sporadic AF in the general population is 2-4 per million per year, but the incidence of FAP-related AF is 3.5-32% (6).

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Herein, we present a 25-year-old female patient with recurrent chest wall AF extending to the breast with clinical, magnetic resonance imaging (MRI) and histopathological findings discussed.

Case Report

A 25-year-old female patient was admitted to the hospital with complaint of right breast swelling. Physical examination revealed a hard palpable mass in the right breast that was affixed to the chest wall. The patient had undergone right mastectomy for a 2x3.5 cm mass with a histopathological diagnosis of AF approximately 3 years ago. Contrast-enhanced and non-contrast-enhanced MRI of the breast and thorax were performed for the new palpable breast mass and they revealed a 6x9 cm irregular-shaped mass with irregular margins extending into the right breast. The mass was isointense on T1-weighted images (T1-WI) (Figure 1) and hyperintense on fat-suppressed T2-WI. After intravenous contrast administration, the mass showed heterogeneous enhancement (Figure 2). MRI demonstrated invasion of the pectoral and intercostal muscles and the ribs. Fine needle aspiration biopsy was performed. Microscopically, the tumor was composed of fibroblastic spindle-shaped cells embedded in abundant collagenous tissue without epithelial components. Mitosis and atypia were not observed (Figure 3). The tumor cells were immunoreactive for smooth muscle actin and negative for desmin, CD34, and S100. The proliferation rate assessed by the Ki-67 labeling index was <1%. This phenotype was consistent with the diagnosis of fibromatosis. Based on these findings, radiotherapy was recommended first and then a wide surgical excision was decided.

The patient gave informed consent for publication of the case.

Discussion

AF tumors are fibrous and fibrohistiocytic, and account for only 0.03% of all neoplasms (7,8). Their etiology is not exactly known, but genetic, endocrine, and traumatic factors may play a role (6).

AF may arise in virtually any part of the body, but extra-abdominal AFs are rare. They have a predilection for the upper torso, including the upper arm (28%), chest wall/paraspinal region (17%) and head/neck (10-23%) (3). Chest wall AF tumors that extend through the breast have rarely been reported in the literature (9).

In ultrasonography, AF appears as an irregular hypoechoic mass with posterior acoustic shadowing, simulating a malignancy (3). In computed tomography (CT), AF appears as a non-specific soft tissue mass that may have ill-defined margins with contrast enhancement. Attenuation of these tumors is variable, described as lower than, similar to, and higher than that of skeletal muscle. MRI is considered superior to CT for detecting, characterizing, and showing the extension of the AF tumor to adjacent tissues. The signal intensity of these tumors is variable and depends on cellular variability, collagen content, and water content. T1-WI most often demonstrates lesions with hypointense or intermediate signal intensity (isointense to muscle). On T2-WI, signal intensity is usually intermediate (isointense to muscle), occasionally with the presence of hypointense bands corresponding to collagen bundles. Lesions may also feature low or high signal intensity on T2-WI according to their contents (3,7). Band-like regions of low signal intensity on T1-WI and T2-WI are more diagnostically important. These low signal intensity bands are common (62-91%) in AF compared to other neoplastic lesions and are related to the collagenized, hypocellular bands seen on gross pathologic examination. These collagenized bands do not show contrast enhancement following gadolinium administration. This characteristic enhancement pattern has a sensitivity of 91%. These low signal intensity bands are very useful for diagnosing AF (10). However, areas of low

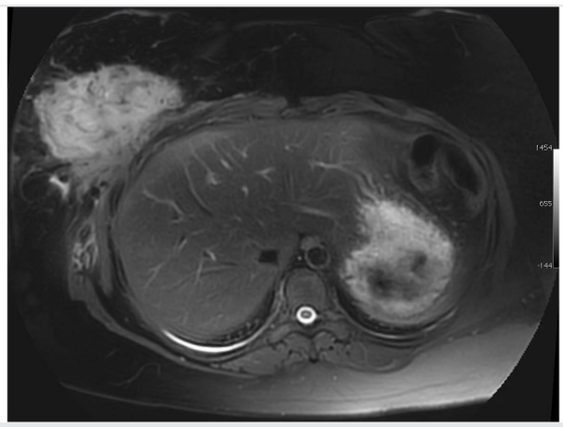

Figure 1. Axial T2-weighted fat-suppressed magnetic resonance image showing a large ill-defined heterogeneous mass in the right anterolateral chest wall extending to the breast that was hyperintense to skeletal muscle

Figure 2. Axial T1-weighted fat-suppressed gadolinium-enhanced magnetic resonance image showing a heterogeneously enhancing mass. Lesion margins could not be distinguished from the adjacent ribs and intercostal muscles

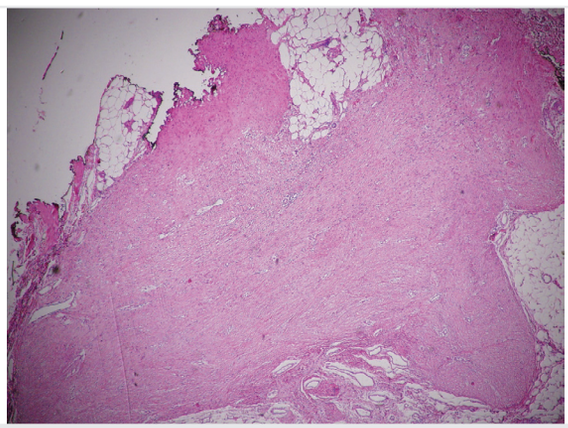

Figure 3. Histological features. Section stained with hematoxylin and eosin reveals uniform spindle cells (x100 magnification)

T2-W signal are not specific to AF and may be seen in other lesions. Consequently, densely calcified mass, elastofibroma, granular cell tumor, desmoplastic fibroblastoma and malignant fibrous histiocytoma/ fibrosarcoma should be kept in mind in the differential diagnosis of soft-tissue lesions with prominent areas of low signal intensity on T1-WI and T2-WI (3). In our case, the lesion was hypointense on T1-WI and hyperintense on T2-WI, without low signal intensity bands.

Surgical therapy, radiotherapy, systemic medical therapy, hormone therapy, anti-inflammatory drugs and tyrosine kinase inhibitors can be used to treat AF (10). However, the most effective and important treatment is aggressive surgical resection with negative margins (2-3 cm), as these tumors are locally aggressive with a high rate of recurrence. Incompletely excised lesions with positive surgical margins have a particularly high rate of local recurrence (1). Adjuvant radiotherapy is also recommended to reduce the risk of local recurrence despite negative margins (6,10). However, radiotherapy is generally recommended only for unresectable tumors, gross or microscopic residual disease and recurrent disease (10). Our patient presented with a recurrent lesion within 3 years and was not given radiotherapy after surgery. Therefore, the treatment approaches were discussed and aggressive surgical resection was recommended after radiotherapy.

Although radiotherapy is useful to effect tumor death, early and late complications should always be kept in mind. In addition, monitoring should be done for radiation-induced breast carcinomas after radiotherapy for anterior chest wall tumors in young women (2). Postoperative radiotherapy was not applied to our patient due to her age. However, she presented with a newly developed recurrent chest wall tumor within 3 years. Therefore, a multidisciplinary approach should be followed for the treatment of these lesions.

Informed Consent: The patient gave informed consent for publication of the case.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - A.T.S., M.E., F.K., İ.K.B.; Concept - A.T.S., M.E.; Design - A.T.S., M.E.; Data Collection and/ or Processing - A.T.S., F.K., İ.K.B.; Analysis and/ or Interpretation - A.T.S., M.E.; Literature Search - A.T.S.; Writing Manuscript - A.T.S.

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Penetrating Lung Injury Caused by a Close-range Blank Cartridge: Case Report

Yakın Mesafeden Kurusıkı Merminin Neden Olduğu Penetran Akciğer Yaralanması: Olgu Sunumu

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ABSTRACT

A 17-year-old male was brought to the emergency department with chest injury by a gunshot from a blank cartridge (BC). No bullet or fragment was seen in the radiological examination. The patient underwent left thoracotomy for hemopneumothorax. Chest injuries due to BCs have rarely been reported in the literature. The word "blank" gives people a false sense of safety. Although BC ammunition does not contain any bullets or parts coming out of the barrel, it can lead to serious injury or even death, especially at contact or close-range.

Keywords: Blank cartridge, barrel, gas pressure, gas jet

ÖZ

On yedi yaşındaki erkek hasta sol göğsünden Kurusıkı (KS) silah yaralanması nedeniyle acil servise getirildi. Radyolojik incelemede mermi veya parçası görülmedi. Hastaya hemopnömotoraks nedeniyle sol torakotomi yapıldı. KS silahlara bağlı göğüs yaralanmaları nadiren literatürde bildirilmiştir. "kurusıkı" veya "boş" kelimesi, insanlara yanlış bir güvenlik duygusu verir. KS mühimmat herhangi bir mermi çekirdeği veya namludan çıkan bir parça içermemesine rağmen özellikle temas veya yakın atış mesafesinde ciddi yaralanmalara hatta ölümlere bile yol açabilir.

Anahtar Kelimeler: Kurusıkı mermi, namlu, gaz basıncı, gaz jeti

Introduction

Blank cartridges (BCs) were originally designed and manufactured for the training purposes of the Prussian army. Today, these weapons or ammunition are used in military training maneuvers or funerals, pointing the start of races in starting pistols and in entertainment industries such as in historical re-enactments, theatre, and movie special effects. BC defines a particular type of ammunition that discharges sound and gas flares, but no bullet or shot (1). Contrary to their production purpose, BCs have become very popular in society and amongst criminals due to their low prices, being easily available, being easily transformed into firearms and their uncertain legal status. Therefore, morbidity and mortality due to BCs are increasing (2). Several cases have been presented in the literature since its was first described by Hamilton in 1865 (3). Herein, we present a rare case of penetrating lung injury due to a gunshot by a BC pistol.

Case Report

A 17-year-old male patient was brought to the emergency department with chest pain and shortness of breath due to the penetrating chest trauma from a gunshot injury. His physical examination on admission was as follows: conscious, cooperative oriented, BP: 97/66 mmHg, heart rate: 122/min, body temperature: 37.4 °C and saturation: 91% with oxygen. Vital signs were consistent with hypovolemic shock. He was pale and somnolence. At first glance, there was a single circle entrance wound at the left 4th intercostal space in the midclavicular line which was 32x39 mm in size and had clot and bleeding around without an exit wound. The wound was partially covered with soot. There was limited emphysema in the subcutaneous soft tissues extending from the left lateral chest wall to the right hemithorax (Figure 1A). The left lung was less involved in breathing and breathing sounds were less heard in the lower region of the left hemithorax. The chest X-ray and contrast-enhanced chest tomography (CT) demonstrated entrance wound over the 4th intercostal space, irregularly shaped subcutaneous emphysema extending from the left lateral chest wall to the right hemithorax and left hemopneumothorax with a possible bullet trajectory from the upper lobe of the left lung to the lower superior lobe segment with hyperdense consolidation (Figure 1B, 1C and 1D). No bullet or fragment was seen in radiological

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examination. A left tube thoracostomy was performed at emergency room settings because of the hemopneumothorax. First, a huge air leak and approximately 650 mL of blood were drained after chest tube insertion. Therefore, he underwent left thoracotomy. During operation, no injury was observed in the ribs. It was seen that the gas jet passed through the thorax by lacerating the pectoral and intercostal muscles, and left lung was collapsed, and that the pleural cavity was filled with approximately 250 mL of blood (Figure 2). There were tissue losses in the lingular segment of the upper lobe (Figure 3) and the superior segment of the lower lobe in the form of a puncture mark of approximately 15 mm. Anterior pericardium showed moderate hemorrhages, but there were no ruptures and bleeding. Wedge resection of the lingular segment of the upper lobe and the superior segment of the lower lobe was performed.

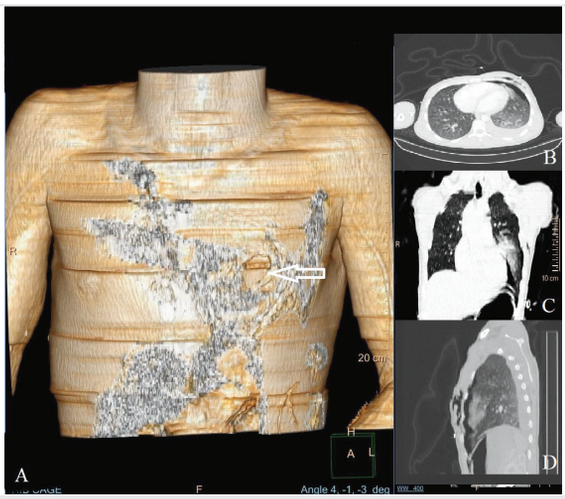

Figure 1 (A). The three-dimensional reconstruction image showed single entry wound in the left 4th intercostal space without an exit wound (white arrow) and subcutaneous emphysema extending from the left lateral chest wall to the right hemithorax (irregularly shaped black and white area); **(B)** Axial **(C)** Coronal and **(D)** Sagittal views of contrast-enhanced chest tomography demonstrated bullet entrance over the left 4th intercostal space, subcutaneous emphysema with a possible bullet trajectory from the left lung upper lobe to the lower lobe superior segment with hyperdense consolidation

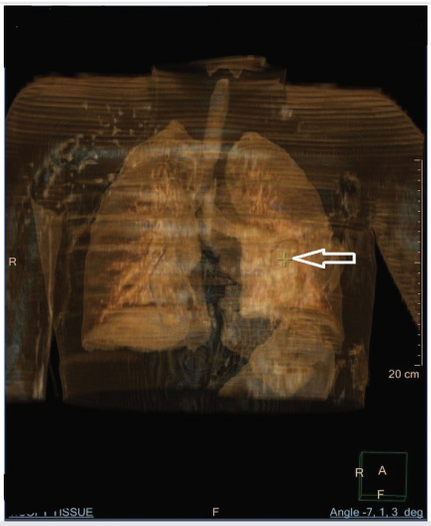

Figure 2. 3D reconstruction image of entry wound (white arrow) and hyperdense consolidation of the left lung

No additional organ injury was detected in the chest. He was followed up in the intensive care unit postoperatively and recovery was uneventful. He was discharged on the postoperative 9th day without any complaints. Written informed consent was obtained from the patient for publishing the individual medical records.

Discussion

Ballistic is the branch of science that examines the movement of the bullet. The possession and use of conventional firearms throughout the world is determined by strict rules and monitored at the same rate. It is sad that this does not apply to BCs (4). For this reason, in most of the countries as well as in Turkey, BCs are often used for celebrations such as national days, weddings and military farewell parties and sports activities especially football and basketball games. BCs are generally not considered firearms and regarded as harmless or as toys. According to the law issued in 2008, anyone over the age of 18 can easily buy BC pistols if they are not punished for more than a year from opposition to Law No. 6136 on firearms and knives. The laws on weapons and knives also do not need administrative control and supervision by law enforcement officers (1,4). Therefore, they are sold unlicensed or with few restrictions, and their use is poorly supervised. BC pistols, as required by law, cannot fire any bullet or fragments, and cannot include metal parts that can be removed by daily tools. However, with the replacement of barrel by criminals, they become capable of firing metal or plastic parts placed in the front part of the conventional bullet or cartridge. Under certain circumstances, even without making any changes, they can cause severe injuries and even deaths in their legal status (4). In the last 30 years, an increase in suicide, murder and accident rates has been reported. Deaths are mostly caused by head, neck, chest and substantial vessel injuries. Thoracic injuries are rare (5).

Bullets with a velocity more than 609.6 m/s are called high-energy bullets, whereas those with a velocity less than 457.2 m/s are called low-energy bullets (6). From a ballistic aspect, BCs act as low-energy weapons, mostly in civilian use. The differential diagnosis between conventional ammunition and BC injury is very complex and almost impossible (2,4,5). This was the case in our report. Initially, we thought it was a

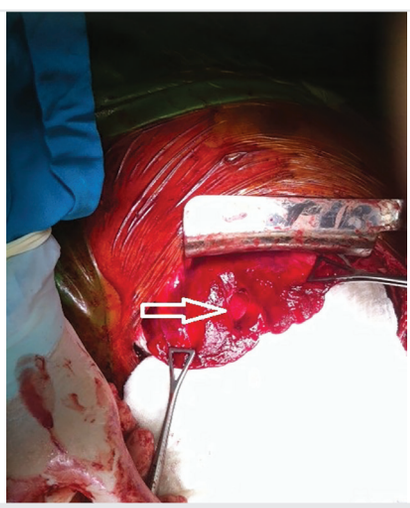

Figure 3. Tissue loss in the lingular segment of the upper lobe (white arrow)

conventional gunshot wound. It was evaluated as BC injury regarding the absence of an exit wound and a bullet and the anamnesis. The types of damages are laceration, penetration, crushing/contusion and a temporary cavity for a shorter term. In BCs, tissue damage is caused by two primary mechanisms, consisting of gas jet-borne barotrauma that are induced by the striking wave of gunpowder explosion and thermal damage (6). A hyperdense contusion demonstrating bullet trajectory through the thorax to the in front of the pericardium was found in our case (Figure 2). Nevertheless, BCs are generally loaded with black powder or nitrocellulose that detonates rather than burns. Nitrocellulose combustion creates 2000-3000 °C heat in the barrel and 1500 °C at the tip, and thermal injury is caused by flame burn. As with other firearms, BC is available in several loads and caliber sizes. Its shot distance is reported to be 20 cm in the user manual. This depends on the type of BC, such as revolver or pistol and the length of the barrel and the caliber of the bullet. A 9 mm cartridge fired from a revolver handgun with a barrel length of 105 mm with a pressure wave at 1200 to 1500 m/s will create 950 mL/g gas pressure with nitrocellulose and 280 mL/g with black powder. The pressure in the barrel drops to 200 bar and drops to 5, 3, and 1 bar at distances 3, 5 and 10 cm from the tip, respectively. The energy intensity represents the energy that 1 cm^2 is exposed to, and can be equivalent to 0.75, 0.27 and 0.1 J/mm^2 at 0, 5 and at 10 cm, respectively. It reaches 0.1 J/mm^2, which is the required energy to penetrate the human skin, even at 10 cm away from the barrel. In a recent study performed using revolver and pistol with pigskin and ballistic gel, 9 mm bullets were fired, and the mechanical destruction was found to be between 22 mm to 61 mm with a mean of 40 mm. When a BC is fired, the gas jet that emerges in an explosion in the barrel acts as a bullet at close or contact range. This pressure or invisible bullet can be powerful enough to penetrate the soft tissue and even bones (2,5). Considering the skin defect and the entrance wound in our case, we think that a 9 mm cartridge was used, although we did not have any ballistic information because the criminal and gun could not be seized. We suppose that subcutaneous emphysema in the patient is due to close range or contact shot. BC should be considered as a common gunshot injury and surgical treatment should be offered if necessary. In spite of the injury leading to hemopneumothorax and lung injury, we believe that the reason why mortality was not observed was the fact that major vascular structures of the left lung were not affected.

Conclusion

Chest injuries due to BCs have rarely been reported in the literature. The word “blank” gives people a false sense of safety. It is evident that BCs are used for purposes other than production purpose. The prevention of criminal use of these weapons is in the hands of the lawmakers and manufacturers. Lawmakers should strictly supervise their registration, sales and use as equivalent to firearms. Manufacturers should use new substances that produce lower pressure instead of black powder or nitrocellulose flour in the cartridge. Although there are no bullets in the BCs, precautions should be taken as deaths and serious injuries can occur if BCs are fired at very close distances.

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Intraspinal Bullet Migration: A Rare Case Report

İntraspinal Mermi Migrasyonu: Nadir Bir Olgu Sunumu

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ABSTRACT

Bullet migration is rarely reported in the literature. Herein we represent a case of penetrating gunshot injury with bullet migration from thoracic T7 spine to T10. A 34-year-old man was admitted to the emergency department with a gunshot wound on his left shoulder without an exit wound. He was paraplegic. Left hemopneumothorax and humeral fractures were detected on radiological examination. So far, the number of cases with migration is 30, including ours. Treatment is complex and still controversial. All spinal gunshot injuries should be treated as elective cases unless there are life-threatening or other major organ injuries requiring immediate surgery.

Keywords: Intraspinal, bullet, migration

ÖZ

Literatürde mermi migrasyonu nadiren bildirilmiştir. Burada torakal T7 omurgadan T10'a mermi migrasyonu olan penetran ateşli silah yaralanması olgusunu sunuyoruz. Otuz dört yaşındaki erkek hasta çıkış deliği olmadan sol omzunda vurularak acil servise başvurdu. Paraplejikti. Sol hemopnömotoraks ve humerus kırığı radyolojik incelemede görüldü. Şimdiye kadar, olgu sayısı bizimki de dahil olmak üzere otuzdur. Tedavisi karmaşıktır ve hala tartışmalıdır. Yaşamı tehdit eden veya acil ameliyat gerektiren diğer önemli organ yaralanmaları olmadığı sürece tüm spinal ateşli silah elektif olgu olarak tedavi edilmelidir.

Anahtar Kelimeler: İntraspinal, mermi, migrasyonu

Introduction

Spinal gunshot injury (GSI) is a devastating event with severe morbidity and mortality. The expected lifelong healthcare cost for a 25-year-old patient with tetraplegia is more than $4.5 million per patient in 2011, even if labor loss is not involved. Although initially it was regarded as only a type of military injury, its frequency has increased with the increased use of civilian firearms, especially in urban areas. It is the third most common cause of spinal trauma after traffic accidents and falls from height. However, when only the downtown area is taken into consideration, it ranks the second following falls from the height. In the last decade, an increase in spinal cord trauma has been observed in injuries caused by explosions especially in the military zones. This situation seems to be increasing. Of all the victims, one fourth are men and the incidence is highest in the third decade (1). Thoracic injuries range from simple superficial injuries to life-threatening injuries. A penetrating bullet generally follows a straight trajectory in the body. It may either exit the body or trap inside a tissue. The incidence of gunshot injuries that perforate and trap within the spinal canal is quite low, and migration of a bullet through the spinal canal is rarely reported in the literature (2,3). Herein we present a case of a penetrating GSI of the thoracic spine at T7 with the migration of the bullet within the spinal canal to T10.

Case Report

A 34-year-old man was admitted to our emergency department with chest pain and shortness of breath due to the penetrating GSI. During his first consultation, his general condition was as follows: unconscious, uncooperative, oriented, BP: 77/48 mmHg, heart rate: 166/min, body temperature: 37.4 ºC and saturation: 88% without oxygen. Vital signs were consistent with hypovolemic shock. He was pale and sleepy. On his first physical examination, there was a round entrance wound, 9x6 mm in size with clot which was over the left shoulder without an exit wound (Figure 1 Red arrow). There was limited emphysema in the subcutaneous soft tissues of the left lateral chest wall, the left lung was less involved in respiration, and decreased breathing sound was heard in the upper

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zone of the left hemithorax. The patient was paraplegic with complete loss of sensation below the T4 segment. His poor general status and unstable vital signs allowed limited radiological screening. Chest X-ray was unremarkable. However, contrast-enhanced chest computed tomography (CT) scan demonstrated a subcutaneous emphysema in the lateral wall of the left hemithorax, left hemopneumothorax with a maximum thickness of 30 mm in the left hemithorax, a fractured left humerus, a possible bullet trajectory from the left lung upper lobe posterior, hyperdense consolidation in lower lobe superior and basal segments (Figure 1 White arrows) and bullet entrance at the left inferolateral border of T7 vertebral body into the spinal canal (Figure 2 White Arrow). Bone fragments were also observed in the spinal canal. The bullet migrated inferiorly to the T10 vertebral level (Figure 3). A left tube thoracostomy was performed for hemopneumothorax at emergency room settings. At first, air and more than 1500 cc blood were drained after chest tube insertion. Therefore, the patient underwent an immediate left thoracotomy due to hemothorax and a posterior thoracic laminectomy following a trauma study. The bullet was not removed, the wound tract was irrigated and the dura was tightly closed (Figure 4 White arrow). He was kept intubated in the intensive care unit under sedation for two days postoperatively. No postoperative complication was observed. The patient was discharged on the 9th day of hospitalization and transferred to a rehabilitation unit. The patient's recovery was uneventful except for paraplegia. Two years after the surgery, the patient had no neurological impairment. Written informed consent was obtained from the patient for publishing the individual medical records.

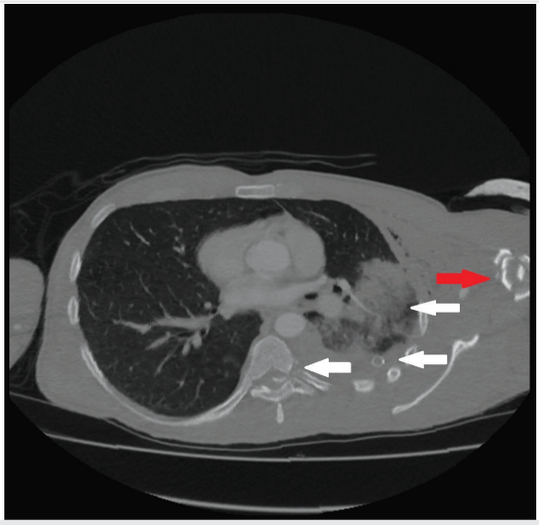

Figure 1. Axial computed tomography scan demonstrates fracture of the left humerus (red arrow), left hemopneumothorax, chest tube and possible trajectory of bullet in the upper lobe (white arrows)

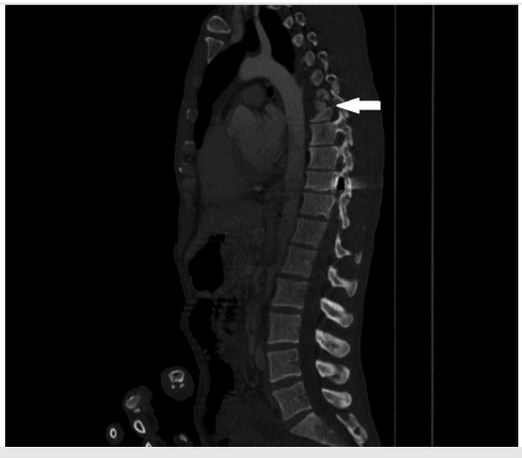

Figure 2. Sagittal computed tomography scan demonstrates the entrance of the bullet from the left inferolateral border of T7 vertebral body (white arrow) and intracanalicular bone fragments

Discussion

GSI of the spine are mainly caused by suicides, accidents, and assaults. They account for 13-17% of all spinal cord injuries each year (2). The

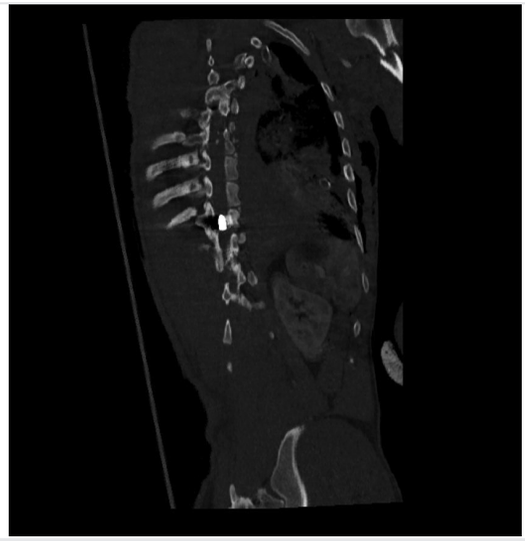

Figure 3. Sagittal computed tomography scan shows the bullet lodged within the spinal canal at T10 level

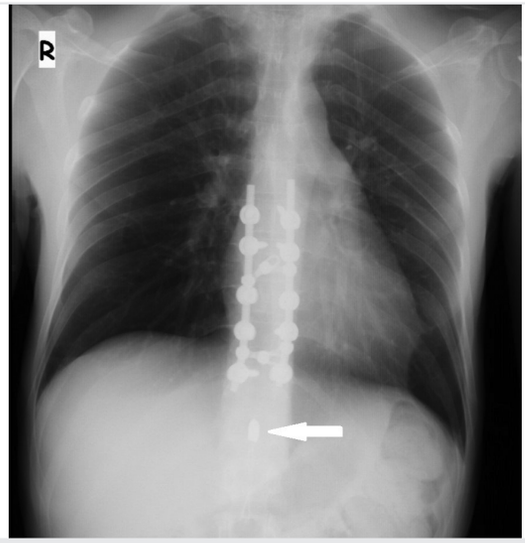

Figure 4. Patient's postoperative X-ray showing the bullet located at T10 level (white arrow)

most common site is thoracic spine (66%), followed by lumbar spine (17%) and cervical spine (6%). Approximately 40% of the patients are shot from the back and 19% are shot in the chest. In thoracic vertebrae, the canal/cord ratio is less than that of the lumbar spine and cervical spine, so the bullet is more destructive in the thoracic region than in other spine levels. In most reported cases, the migration is directed caudally. It has been observed that migration typically occurs between T10 and first sacral vertebra, as the relative narrowing of the spinal canal above the level of T10 is considered a primary factor in limiting the migratory distance and direction. It can result in varying degrees of severe and structural neurological deficit including infections, radiculopathy, paralysis, hydrocephalus, and Lhermitte's sign depending on the site of bullet impact (2). Bullets cause significant damage to the surrounding tissue along the trajectory due to the dispersion of both thermal and kinetic injury. The weapons with a velocity higher than 609.6 m/s are called high-energy bullets, whereas those with a velocity lower than 457.2 m/s are called low-energy bullets. Our case includes an injury due to a low-energy bullet. As in our case, low-energy bullets have different types of wounds. The types of damage include laceration, penetration, crushing/contusion and a temporary cavity for a shorter term. As described in the literature, our patient had a bullet trajectory showing linear extension from the left upper to the lower lobe in the anterior-posterior plane (Figure 1). The bullet passed through the thorax and stopped at the T10 vertebral level (4). As in our case, weapons with low energy in civilian use are much more different than those used in military. Low-energy or civilian GSI almost always causes direct contact or injury due to vertebral fractures that further increase existing damage, while high-energy or military weapons can cause cord injury leading to paralysis with the spread of high energy through the soft tissue and massive necrosis of the cord. In the literature, 49-83% of patients had a complete injury, 12-43% had an incomplete injury and 17-20% had cauda equina injury (5-7).

Intraspinal gunshot wounds and consequential damage are difficult to assess only with symptoms. Further radiological techniques should be employed to better identify the damage. The radiological examination, usually with conventional direct X-ray and non-contrast-enhanced CTs, is often used to locate the bullet and to detect bone fractures or fragments. Although magnetic resonance imaging (MRI) has advantages and is preferred in all spinal examinations, its use is controversial due to the possibility of bullet migration with a strong magnetic attraction, which may cause more soft tissue or neurological damage in GSIs. Todnem et al. (6) used MRI for an intraspinal bullet and showed that the MRI could be safely used in GSIs with bullet from low-speed civil injuries where the bullet was coated with non-ferromagnetic metals such as copper. However, this does not apply to high-speed steel military GSIs. As in our case, ballistic data are often absent in medical settings and, like most; they need to be treated urgently. Therefore, the use of MRI is rare. We used contrast-enhanced thorax CT.

Although the migration of a bullet in the skull to the central nervous system is known since 1916, reports of bullet migration in the spinal canal are rare in the following several decades. In 1982, Tanguy and his colleagues published the first intraspinal bullet migration. There are a limited number of reports from the last 36 years describing intraspinal migration specifically. Since then, the number of cases increased from 14 in 2000 to 30 in 2018, including our case (Table 1) (3,6). Most reported cases were caudal and cephalad migration has been reported only in 4 cases (7).

Treatment is complex and still controversial. Some authorities advocate conservative treatment and others advocate surgery. While civil literature recommends conservative non-surgical treatment, surgery for for exploration and debridement of the wound and removal of the bullet is recommended in times of war. Differences in the pathophysiology of both injuries may cause this. Bumpass et al. and Yashon et al. recommend conservative therapy for low-speed injuries unless there is infection or persistent cerebrospinal fluid (CSF) leaks. Heiden et al. and Stauffer et al. have shown that surgical intervention, regardless of the type of injury, provides no additional benefit. Methylprednisolone has no further advantages.

Interestingly, despite the absence of clear guidelines for surgery, there is consensus on surgery in the presence of persistent CSF fistula and infection, neurological deterioration, severe pain, bullet migration, vertebral instability, and finally cauda equine syndrome. In the literature, the first one is the most crucial evidence for surgery. Even GSI is asymptomatic initially; it causes a robust fibrotic reaction and becomes symptomatic within a few years. The bullet and metals in the full metal jacket destroy the axons and myelin, and cause a significant amount of gliosis in the spinal cord tissue. This effect is higher in copper but less in lead. There is limited number of cases in the literature (1,3,6,7).

Surgical removal of an intraspinal bullet may be further complicated by positional migration during operation. The position of the patients may change the final location of the bullet at any time due to the gravitational forces, breathing movements or the physiological movements of the cerebrospinal fluid. In the literature, the period has been reported to continue up to 27 years after the injury (6). This difficult situation was solved by ultrasonography (US) in a recent article. The authors used an electric motor drill for L5 laminectomy to avoid the bracing effect of bone rongeur. If rongeur has a repulsive effect, it is more doubtful for an electric motor drill not to have a vibration to create a propelling effect (1). This situation needs discussion and verification.

Although injury gives rise to hemopneumothorax and spinal cord injury, we believe that the reason why death did not occur in our case was the fact that major vascular structures of the left lung were not affected. In our case, the bullet could not be removed. The bone fragments in the spinal cord were removed and dural tear was tightly closed to prevent leakage and infection. However, none of the complications mentioned above have been encountered so far. These should be checked at every possible stage during surgery. We believe that the use of US is beneficial in cases where conventional intraoperative radiology fails. However, we believe that this should be confirmed by case series.

Table 1. Summary of all cases of migrating spinal bullets reported in the literature, including the treatment modality used and outcome measures

Authors	Year	Age/gender	Primary entrance	The entry point in the spine	The initial location of the bullet in the spine	Intraoperative location of the bullet	Pre-treatment neurological status	Treatment	Surgical findings	Post-treatment neurological status
Arasil	1982	22/F	Cranium	-	C4	C4	Lhermitte's sign	C3-C4 laminectomy	-	Complete recovery
Tanguy	1982	10/M	Cervical spine	C6	C6	S2	No neurological deficit initially Meningitis 3 months later	Conservative initially, S1-S2 laminectomy Three months later	-	Complete recovery
Kerin	1983	17/M	Cranium	-	L4	L4	(R) hemiparesis, hemianesthesia, perianal pain, urinary hesitancy	L4 laminectomy	-	Recovery of perianal pain, urinary hesitancy
Karim	1986	18/M	Abdomen	T11-T12	L4-L5	L4-L5	(L) leg pain, (L) drop foot, low back pain	Hemilaminectomy	Dura intact	Complete recovery
Soges	1988	27/M	Abdomen	T11-12	S1-S2	Migrated upwards	Loss of sensation (L) in legs, urinary urgency, perianal anesthesia	Sacral laminectomy	-	Complete recovery
Yip	1990	17/M	Thoracic Spine	T7	S1	S1	Paresthesias in both feet diminished ,perianal sensation	S1 laminectomy	-	Partial recovery
Young	1993	19/F	Cranium	-	C5	-	Asymptomatic	C5-C6	-	No change laminectomy
Conway	1993	35/M	Abdomen	-	L4-L5	L4-L5	Cauda equina after nine years	L4-L5 laminectomy	Dura intact, reactive fibrosis	Near complete recovery
Avci	1995	30/F	Abdomen	-	S1	L4	S1 hypoesthesia, loss of Achilles reflex, plantar flexion weak	L4-S1 laminectomy	Dura intact at L4 and S1 level. No CSF fistula at both sites	Complete recovery
Oktem	1995	20/M	Chest	T6	S2	-	Paraplegia	Conservative	Dural tear at T6 level with no spinal cord injury on postmortem examination	No change
Tekavcic	1996	21/M	Cervical Spine	C6	T10	T10	Paraplegia, wrist flexion weak	C6-T4 and T9-T10 laminectomy	Dural tear at both sites. The dural tear was replaced by lyophilized dura.	No change
Rajan	1997	24/M	Right mastoid	C1	T6 to S2 over Three years	-	Mild weakness of (L) upper limb, right foot hypoesthesia	Conservative	-	Complete recovery
Gupta	1999	25/M	Chest	-	S1	L3. Head elevation lead bullet migration to L5	Radicular symptoms, bilateral foot drop, urinary retention, S1-S4 hypoesthesia	L5-S2 laminectomy	-	Complete recovery
Kafadar	2006	44/M	Abdomen	L1	S2	S2	Paraplegia	S1-S2 laminectomy	Dura was greyish black at S2	Partial recovery
Singh	2007	20/M	Lumbar spine	L5	L4-L5	L2. Head end elevation lead to bullet migration at L3-L4	A backache, left foot numbness	L3-L4 laminectomy	-	Complete recovery

Cagavi	2007	28/M	Abdomen	L3	S2	S2	Paraparesis, anesthesia below L3, loss of anal tone	L3 and S2 laminectomy	Dural tear at L3. Dura closed using fascial graft	Partial recovery of paraparesis, improvement of anal tone
Rawlinson	2007	16/M	Cervical Spine	C3	T1-T2	-	Quadriplegia	Conservative	-	Partial recovery
Moon	2008	50/M	Lumbar spine	L3	L2	L2	A backache, bilateral leg pain, right gastrocnemius, right extensor hallucis weakness, bladder, bowel incontinence	Initially conservative, later L2-L3 laminotomy	-	Partial recovery
Ben	2008	14/F	Lumbar spine	L3	L3 to S1, S1 to L3 and finally T12	Head elevation lead to bullet migration to L5-S1	Radiculopathy	L5-S1 laminotomy	-	Complete recovery
Castillo Rangel	2010	36/F	Cranium	-	T4 over	T4	Quadriplegia, T4 sensory loss	T4 laminectomy,	-	Partial recovery
Jun	2010	42/M	Abdomen	L1	S2	S2	Cauda equina syndrome	L1, S2 laminectomy	Bone fragments in the canal at L1	Near complete recovery
Farrugia	2010	22/M	Chest	T12-L1	L5-S1	S1	Right ankle dorsiflexion weak, right foot numbness	-	Autopsy-Dural tear at T12 and epidural hematoma and lacerate cauda equina	Died during thoracotomy and laparotomy
Hunt	2012	24/M	Thoracic Spine	T8-T9	T9-T10	-	Paraplegia, the sensory level at D8	Conservative	-	Partial recovery
Ghori	2014	35/M	Thoracolumbar spine	T12-L1	L5-S1	L5-S1	No deficit initially, cauda equina 15 months later	L5 laminectomy	-	Complete recovery
Bordon	2014	27/M	Lumbar spine	L2-L3	S1-S2	L5	Hypoesthesia in perianal area and inside of both thighs, no muscle weakness, normal sphincters	L5-S1 laminotomy	-	Complete recovery
Ruy	2015	30/M	Abdomen	Probably T12-L1	L2-L3	L2-L3	Neurogenic claudication after one year	L3 laminectomy	-	Complete recovery
Chan	2015	27/M	Lumbar spine	L2	S1	L4-L5	Bilateral drop foot and bilateral reduced sensation in S2 to S4 dermatomes 48 h later	L5 laminectomyspine	-	Complete recovery
Koban	2016	29/M	Abdomen	L2	L3	L3	No deficit	L3/partial L2 laminectomy	No CSF fistula	-
Baldawa	2016	32/M	Abdomen	L2-L3	S1	L4-L5	Paresthesias in both feet, radiculopathy, loss of sensation in bilateral L5, S1 dermatome, perianal sensory loss, lax anal tone	L4-S1 laminectomy	No dural tear or CSF fistula	Complete recovery
Present case	2018	34/M	Chest	T4	T7	T10	Paraplegic with complete sensory loss below T4 segment	Thoracotomy and thoracic vertebra laminectomy	Bone fragments in the canal at T7	No change

Conclusion

The pathophysiology of GSI is complex. The critical factor that determines the amount of tissue damage depends on the amount of energy delivered to the affected tissues. Ballistics, whether the bullet is low-energy or high-energy, should be considered in treatment. Surgical indications should be clear. All GSI patients should be treated as elective cases unless there are other major organ injuries requiring immediate surgery. Surgery should be performed by a specialist team with the support of radiological imaging. Concomitant injuries further increase the complexity of the pathology. Treatment, especially surgical procedure, needs a multidisciplinary approach and should be individualized, thus considering hemodynamic factors, associated injuries, the extent of the neurological damage and the location of the bullet.

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