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Bu dergi daha önceden *İnönü Üniversitesi Tıp Fakültesi Dergisi* ismiyle yayınlanan derginin devamıdır.
This journal was formerly published as *Journal of Inonu University Medical Faculty* and is the continuation of it.

AMAÇ ve KAPSAM

Turgut Özal Tıp Merkezi Dergisi (ISSN: 1300-1744) İnönü Üniversitesi Tıp Fakültesi'nin bilimsel içerikli resmi yayın organıdır. Mart, Haziran, Eylül ve Aralık aylarında olmak üzere dört sayı yayınlanmaktadır. Turgut Özal Tıp Merkezi Dergisi'nin hedefi tıp alanında yapılan, bilimsel açıdan nitelikli ve literatüre yeni bir katkı sunacak olan klinik ve deneysel araştırma yazılarını yayınlamaktır. Bölgesel sıklık ve özellik gösteren hastalıklarla ilgili yapılan çalışmalara değerlendirme ve basım aşamasında öncelik verilir. Bunun yayında, derginin hedef kitlesinde yer alan hekimler ve sağlık profesyonellerin eğitimine ve pratiğine katkı yapacak ve yazarlarla okuyucular arasındaki bilimsel iletişimi ve bilgi birikimini artıracak olan derleme yazıları, olgu sunumları, editöryal yorumlar, editöre mektuplar derginin kapsamına girmektedir.

Derginin yayın dili Türkçe ve İngilizce'dir. **Dergimize gönderilen makaleler değerlendirilip kabul edildikten sonra ingilizceye çevrilerek yayınlanmaktadır.** Dergiye gönderilen makaleler bağımsız hakemler tarafından çift kör hakemlik değerlendirme sistemine göre değerlendirilmektedir. Dergiye makale yazımı ile ilgili kurallar dergimizin web sitesinde (www.totmdergisi.org) ve yayınlanmış sayılarında mevcuttur.

Çevreyi ve doğayı koruma sorumluluğu çerçevesinde, derginin basılı nüshası sınırlı sayıda üretilmekte ve baskı asitsiz kâğıda yapılmaktadır. Ancak dergide yayınlanan tüm yazıların özet, tam metin ve diğer tüm dergi içeriklerine www.totmdergisi.org adresinden ücretsiz olarak ulaşılabilmektedir ve yazılar indirilebilmektedir.

Derginin mali giderleri İnönü Üniversitesi Tıp Fakültesi tarafından karşılanmaktadır. Dergiye gelir sağlamak amacıyla, bilimsel çerçevenin ve etik kuralların dışına çıkmayan ticari duyuru ve ilanlar dergide basılabilir. Dergiye ilan vermek için Editör ofisine başvurulmalıdır.

Baskı İzinleri: Baskı izinleri için başvurular dergi editör ofisine başvurulmalıdır.

İndekslenme: Türk Tıp Veri Tabanı, Türkiye Atıf Dizini, Index Copernicus, Directory of Open Access Journals, Türk Medline, EBSCO, CrossRef, Google Scholar, Akademik Dizi,

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Bu dergi daha önce ***İnönü Üniversitesi Tıp Fakültesi Dergisi*** ismiyle yayınlanan derginin devamıdır.

AIMS and SCOPE

Journal of Turgut Ozal Medical Center (ISSN: 1300-1744) is the scientific official journal of the Inonu University School of Medicine. It is published quarterly March, June, September and December. The essential aim of the Journal of Turgut Ozal Medical Center is to publish scientifically high quality clinical and experimental research articles on fields of medicine which can contribute to the literature data. Manuscripts on regionally frequent and specific diseases will be prioritized during evaluation and publication stages. In addition, review articles, case reports, editorials, letters to the editors and manuscripts on publication ethics and medical history, which can contribute to the education and practices of physicians and health sector professionals within the scope of the journal's target audience and which can increase the level of scientific communication between the authors and readers, are included in the scope of the journal.

The journal publishes articles in both Turkish and English languages. **Following the initial evaluation and reviewing, accepted articles are translated into English by professional translators; after a final reviewing process, all studies are published in English.** All articles are evaluated through a double-blind review process by independent and unbiased reviewers. Information on preparing and submitting manuscripts for publication and information on article evaluation process are available in Instructions for Authors page both online at www.jtomc.org and in printed issues of the journal.

In order to protect the environment, the journal is printed in limited numbers on acid-free paper. Full content of all manuscripts published by the Journal of Turgut Ozal Medical Center is available and can be downloaded at www.jtomc.org free of charge.

Financial expenses of the journal are covered by the Inonu University School of Medicine. In addition, in order to generate revenue for the journal, commercial announcements and advertisements which are within the scientific scope and ethic guidelines may be published in the journal. For advertisement arrangements the editorial office of the journal should be contacted.

Publishing Permissions: Applications for publishing permissions should be sent to the Editorial Office.

Indexing and Abstracting: Türk Tıp Veri Tabanı, Türkiye Citation Index, Index Copernicus, Directory of Open Access Journals, Türk Medline, EBSCO, CrossRef, Google Scholar, Akademik Dizin.

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This journal was formerly published as ***Journal of Inonu University Medical Faculty***.

YAZARLARA BİLGİ

GENEL BİLGİLER

Turgut Özal Tıp Merkezi Dergisi, tıp bilimlerinde yapılan orijinal araştırmaları, olgu sunumlarını, editöryal yorumları, editöre mektup ve derlemeleri yayınlar. Derginin resmi dili Türkçe ve İngilizcedir. **Dergimize gönderilen makaleler değerlendirilip kabul edildikten sonra ingilizceye çevrilerek yayınlanmaktadır.** Dergide yayınlanmak üzere gönderilen yazılar, araştırma ve yayın etiğine uygun olmalıdır.
Dergiye gönderilen yazıların daha önce yayınlanmamış veya bir başka dergiye yayın için teslim edilmemiş olması gerekir. Eğer makalede daha önce yayınlanmış alıntı yazı, tablo, resim vs. varsa makale yazarı yayın hakkı sahibi ve yazarlarından yazılı izin almak ve bunu makalede belirtmek zorundadır. Dergiye gönderilen makale biçimsel esaslara uygun ise, editör ve en az iki danışmanın incelemesinden geçip, gerek görüldüğü takdirde istenen değişiklikler yazarlarca yapıldıktan sonra yayınlanır. Tüm yazarların gönderilen makalede akademik-bilimsel olarak doğrudan katkısı olmalıdır. Kongre veya sempozyumlarda sunulan bildirilerin, bu etkinliklere ait kitapta tümüyle yayınlanmamış olması ve bu durumun bir dipnot ile belirtilmesi gerekir.
Makale Başvuruları: Dergiye gönderilecek yazılar dergimizin www.totmdergisi.org veya www.jtomc.org adresinde bulunan online makale gönderme sisteminden yapılır. Online başvuru dışında gönderilecek yazılar değerlendirmeye alınamayacaktır.
Yayın Hakkı: Yayınlanmak üzere kabul edilen yazıların her türlü yayın hakkı dergiyi yayınlayan kuruma aittir. Yazılardaki düşünce ve öneriler ve maddi hatalar tümüyle yazarların sorumluluğundadır. Makale yazarlarına yazıları karşılığında ücret ödenmez. Yazıları yayına kabul edilen yazarlar www.totmdergisi.org adresindeki "Yayın Hakkı Devir Formunu" makaleleri basılmadan önce dergi ofisine göndermek zorundadır.

YAZI ÇEŞİTLERİ

Dergiye yayınlanmak üzere gönderilecek yazılar şu şekildedir.
1. Orijinal Makale: Prospektif ve retrospektif her türlü klinik ve deneysel araştırmalar yayınlanabilmektedir. Yazarlar makalenin gereç ve yöntemler bölümünde kurumlarının etik kurullarından onay ve çalışmaya katılmış insanlardan "bilgilendirilmiş olur" aldıklarını belirtmek zorundadır. Çalışmada deney hayvanı kullanılmış ise yazarlar, makalenin gereç ve yöntemler bölümünde "Guide for the Care and Use of Laboratory Animals" prensiplerine uyduklarını ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadır.
Orijinal Makale Özeti: Türkçe ve İngilizce, 200-250 kelime arasında, amaç, gereç ve yöntemler, bulgular ve sonuç bölümlerinden oluşan yapılandırılmış özet gereklidir.
Orijinal Makalenin Yapısı: Giriş, Gereç ve Yöntemler, Bulgular, Tartışma, Sonuç, Teşekkür ve Kaynaklar bölümünden oluşur.
2. Derlemeler: Yalnızca yazılan derleme konusunun uzmanı ve konuyla ilgili çalışmaları olan yazarların derlemeleri ve davetli derlemeler kabul edilmektedir.
Derlemelerin Özeti: 200-250 kelime arasında, yapılandırılmamış, Türkçe ve İngilizce özet
Derlemelerin Yapısı: Konu ile ilgili başlıklar ve kaynaklar.
3. Olgu Sunumu: Nadir görülen ve tanı ve tedavide farklılık gösteren makalelerdir. Yeterli miktarda görsellerle desteklenmelidir. Olgu sunumlarında hastanın kimliğinin ortaya çıkmasına bakılmaksızın hastalardan "bilgilendirilmiş olur" alınmalıdır. "Bilgilendirilmiş Olur Formu" na www.totmdergisi.org adresinden ulaşılabilir.
Olgu Sunumu Özeti: 100-150 kelime arasında, yapılandırılmamış, Türkçe ve İngilizce
Olgu Sunumunun Yapısı: Giriş, Olgu Sunumu, Tartışma ve Kaynaklar bölümlerinden oluşmalıdır.
4. Editöryal: Dergi editörü ve editöryal kurul üyelerinin değerlendirme yazılarıdır. Özet ve anahtar kelimeler gerekmez.
5. Editöre Mektup: Son bir yıl içinde dergimizde yayınlanan makaleler ile ilgili veya bağımsız konularla ilgili okuyucuların değişik görüş, tecrübe ve sorularını içeren en fazla 1000 kelimelik yazılardır. Mektuba cevap editör veya makalenin yazarları tarafından yine dergide yayınlanarak verilir
Editöre Mektubun Yapısı: Başlık ve özet bölümleri yoktur. Kaynak sayısı en fazla 10 tanedir. Hangi makaleye ithaf olunduğu belirtilmelidir.

YAZIM KURALLARI

Dergimize gönderilecek yazılar Microsoft Word programında iki satır aralıklı yazılmalı, kenarlarda en az 3 cm boşluk bırakılmalıdır. Gönderilen yazılarda bölümler şu şekilde sıralanmalıdır: Türkçe ve İngilizce özet, anahtar kelimeler, ana metin, teşekkür, kaynaklar, tabloların her biri ve şekil alt yazıları. ilk sayfadan itibaren alt veya üst köşede sayfa numarası olmalıdır. Türkçe makalelerde Türk Dil Kurumunun Türkçe sözlüğü veya www.tdk.org.tr adresi esas alınmalıdır
Kısaltmalar: Kelimenin ilk geçtiği yerde parantez içinde verilir ve tüm metin boyunca o kısaltma kullanılır. Özet bölümünde kısaltma ve kaynak numarası kullanılmaz.
Anahtar Kelimeler: En az 3 adet, Türkçe ve İngilizce yazılmalıdır. Kelimeler birbirinden noktalı virgül (;) ile ayrılmalıdır. Türkçe anahtar kelimelerde Türkiye Bilim Terimleri'ndeki (bkz: http://www.bilimterimleri.com) terimler, İngilizce anahtar kelimelerinde MESH (Medical Subject Headings, www.nlm.nih.gov/mesh) terimleri esas alınmalıdır.
Teşekkür: Eğer çıkar çatışması, finansal destek, bağış ve diğer bütün editöryal (istatistik, dil) ve/veya teknik yardım varsa metnin sonunda sunulmalıdır.
Kaynaklar: Kaynaklar makalede geliş sırasına göre yazılmalı ve cümle sonunda bir boşluk bırakılıp noktadan önce parantez içinde yazılmalıdır. Kaynaklar listesi makalenin bitimi sonrası iki satır aralığı boşluk bırakarak makalede geçiş sırasına göre numaralandırılmak suretiyle yazılmalıdır. Kaynak yazımında, yazar sayısı 6 ve üzerinde ise ilk 6 yazar yazılıp sonrası için İngilizce kaynaklar için "et al." Türkçe kaynaklar için "ve ark."ifadesi kullanılmalıdır. Metinde geçtikleri sıraya göre kaynak sayısının editöre mektuplar için 10, olgu sunumları 15, araştırma makaleleri ve derlemeler için 50 ile sınırlı kalmasına özen gösterilmelidir. Kaynaklarda dergi adlarının kısaltılmış yazımları için "List of Journals Indexed in IndexMedicus" esas alınmalıdır (bkz: http://www.icmje.org). Kongre bildirileri, kişisel deneyimler, basılmamış yayınlar, tezler ve internet adresleri kaynak olarak gösterilemez. Online yayınlar için DOI numarası tek kabul edilebilir referanstır.
Kaynakların yazımı için örnekler:
Makale: Yazarlarının soyadları, isimlerinin baş harfleri, makale ismi, dergi ismi, yıl, cilt ve sayfa numarası belirtilmelidir. Örn: Short FL, Blower TR, Salmond GPC. A promiscuous antitoxin of bacteriophage T4 ensures successful viral replication. Mol Microbiol 2012;83:665-8.
Kitap: Kitap için yazarların soyadları ve isimlerinin baş harfleri, bölüm başlığı, editörlerin isimleri, kitap ismi, kaçıncı baskı olduğu, şehir, yayınevi, yıl ve sayfalar belirtilmelidir. İngilizce kitap: Underwood LE, Van Wyk JJ. Normal and aberrant growth. In: Wilson JD, Foster DW, eds. Williams' Textbook of Endocrinology. 1st editon. Philadelphia: WB Saunders; 1992. p. 1079-138. Türkçe kitap: Tür A. Acil Hava Yolu Kontrolü ve Endotrakeal Entübasyon. Şahinoğlu AH, editör. Yoğun Bakım Sorunları ve Tedavileri. 2. Baskı. Ankara: Türkiye Klinikleri; 2003. p.145-210.
Şekil, Resim, Tablo ve Grafikler: Şekil, resim tablo ve grafiklerin metin içinde geçtiği yerler ilgili cümlenin sonunda belirtilmelidir. Şekil, resim, tablo ve grafiklerin açıklamaları makale sonuna eklenmelidir. Şekil, resim ve fotoğraflar ayrı birer .jpg veya .gif dosyası olarak (pixel boyutu yaklaşık 500×400, 8 cm eninde ve 300 çözünürlükte taranarak) sisteme yüklenmelidir. Kullanılan kısaltmalar şekil, resim, tablo ve grafiklerin altındaki açıklamada belirtilmelidir. Daha önce basılmış şekil, resim, tablo ve grafik kullanılmış ise yazılı izin alınmalıdır ve bu izin açıklama olarak resim, tablo ve grafik açıklamasında belirtilmelidir. Resimler ve fotoğraflar renkli, ayrıntıları görülecek kadar kontrast ve net olmalıdır.

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INFORMATION FOR AUTHORS

GENERAL INFORMATION

Journal of Turgut Ozal Medical Center welcomes original articles, case reports, editorials, and letters to the editor and review articles on basic and clinical medical sciences. The official languages of the journal are Turkish and English. **Following the initial evaluation and reviewing, accepted articles are translated into English by professional translators; after a final reviewing process, all studies are published in English.** All manuscripts which will be published in the journal must be in accordance with research and publication ethics.

Manuscripts are received with the explicit understanding that they have not been published in whole or in part elsewhere, that they are not under simultaneous consideration by any other publication. Direct quotations, tables, or illustrations that have appeared in copyrighted material must be accompanied by written permission for their use from the copyright owner and authors. All articles are subject to review by the editors and referees. Acceptance is based on significance, and originality of the material submitted. If the article is accepted for publication, it may be subject to editorial revisions to aid clarity and understanding without changing the data presented. All authors should have contributed to the article directly either academically or scientifically. Presentations at congresses or in symposia are accepted only if they were not published in whole in congress or symposium booklets and should be mentioned as a footnote.

Manuscript submission: All manuscripts should be submitted by online system of journal at www.totmdergisi.org or www.jtomc.org. For consideration, all articles must be submitted online. Articles submitted in other forms will not be considered.

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CATEGORIES OF MANUSCRIPTS

Journal of Turgut Ozal Medical Center publishes the following types of articles:

1. Original Articles: Original prospective or retrospective studies of basic or clinical researches in areas relevant to medicine.

Abstract of Original Article: Turkish and English, 200-250 words, the structured abstract contain the following sections: objective, material and methods, results, conclusion. Editorial office will write Turkish abstract for non-native Turkish speakers.

Structure of Original Article: Introduction, Material and Methods, Results, Discussion, Acknowledgements, References sections must be included.

2. Review Articles: The authors may be invited to write or should be expert in that subject of review article.

Abstract of Review Article: Turkish and English, 200-250 words, without structural divisions. Editorial office will write Turkish abstract for non-native Turkish speakers.

Structure of Review Article: Titles or related topics and references.

3. Case Reports: Brief descriptions of a previously undocumented disease process, a unique unreported manifestation or treatment of a known disease process, or unique unreported complications of treatment regimens. They should include an adequate number of images and figures. Case reports should be accompanied by "Informed Consent" whether the identity of the patients is disclosed or not. The "Informed Consent Form" is available at www.inonutipdergisi.com

Abstract of Case Reports: Turkish and English, 100-150 words, without structural divisions. Editorial office will write Turkish abstract for non-native Turkish speakers.

Structure of Case Reports: Introduction, Case Report, Discussion, References.

4. Editorial: Special articles are written by editor or editorial board members. Abstract is not required for editorials.

5 Letter to the Editor: These are letters which include different views, experiments and questions of the readers about the manuscript that were published in this journal in the recent year and should not be more than 1000 words. The answer to the letter is given by the editor or the corresponding author of the manuscript and is published in the journal.

Structure of Letter to the Editor: There is no title and abstract. The number of references should not exceed 10. Submitted letters should include a note indicating the attribution to an article published in journal.

MANUSCRIPT PREPARATION

Manuscripts should be typed double-spaced with margins of 3 cm. Articles should be set out as follows: cover letter, title page, abstract and key words, main text, acknowledgment, references, tables and illustrations. Table and illustration pages should also include the heading or legend, and be numbered below or above the page.

Abbreviations: Abbreviations that are used should be defined in parenthesis where the full word is mentioned. For commonly accepted abbreviations and usage please use "Scientific Style and Format" (The CBE for Manual for Authors Editors and Publishers, 6th ed. New York: Cambridge University Press, 1994). Abbreviations should not be used in Abstract section.

Key Words: They should be written at least three and also should written Turkish and English. The words should be separated by semicolon (;), from each other. Key words should be appropriate to "Medical Subject Headings" (MESH) (please see www.nlm.nih.gov/mesh).

Acknowledgement: Conflict of interest, financial support, grants and all other editorial and/or technical assistance if present, must be presented at the end of the text.

References: References in the text should be numbered in parenthesis and listed serially according to the order of mentioning on a separate page, double spaced, at the end of the paper in numerical order. All authors should be listed if six or fewer, otherwise list the first six and add the et al. References should be limited 10 for letter to the editor, 15 for case reports, 50 for case reports and review articles. Journal abbreviations should conform to the style used in the Cumulated Index Medicus (please see www.icmje.org). Declarations, personal experiments, unpublished papers, thesis cannot be given as reference. DOI is only acceptable for online reference.

Reference Format for Journal Articles: Initials of authors' names and surnames, titles of article, journal name, date, volume, and inclusive pages must be indicated. Example:

Short FL, Blower TR, Salmond GPC. A promiscuous antitoxin of bacteriophage T4 ensures successful viral replication. Mol Microbiol 2012;83:665-8.

Reference Format for Books: Initial's of author's names and surnames, chapter title, editor's name, book title, city, publisher, date and pages must be indicated. Example:

Underwood LE, Van Wyk JJ. Normal and aberrant growth. In: Wilson JD, Foster DW, eds. Williams' Textbook of Endocrinology. 1st edition. Philadelphia: WB Saunders; 1992. p. 1079-138.

Figures, Pictures, Tables and Graphics: All figures, pictures, tables and graphics should be cited at the end of the relevant sentence. Explanations about figures, pictures, tables and graphics must be placed at the end of the article. Figures, pictures/photographs must be added to the system as separate .jpg or .gif files (approximately 500×400 pixels, 8 cm in width and scanned 300 resolutions. All abbreviations used, must be listed in explanation which will be placed at the bottom of each figure, picture, table and graphic. For figures, pictures, tables and graphics to be reproduced relevant permissions need to be provided. This permission must be mentioned in the explanation. Pictures and photographs must be in color, clear and with appropriate contrast to separate details.

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EDİTÖRYAL/EDITORIAL
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Change and Development

Şükrü Kartalcı

İnönü Üniversitesi Tıp Fakültesi, Psikiyatri Anabilim Dalı, Malatya

Established within the Faculty of Medicine, Inonu University, *Journal of Turgut Ozal Medical Centre* is a noteworthy medical journal that has been publishing original articles and case reports for almost 20 years. As a quarterly journal published on a regular basis, our journal has come along way since it was first launched thanks to the intensive efforts of many people behind the scenes.

As is the case in all institutions, our journal has experienced a recent administrative change. About four months ago, I was appointed as the chief editor of the *Journal of Turgut Ozal Medical Centre*. As the new editor-in-chief, it is my privilege to inform our readers about what we have done so far since my appointment to the post and our plans for the near future.

I'd like to start my address by thanking Dr. Ahmet Karadağ, who has provided invaluable contributions to our journal as the Editor-in-chief for two years, as well as Dr. Derya Doğan and Dr. Ergül Alçin, two conscientious editors of our journal, who also decided to vacate their posts as editors after the publication of our previous issue. It is due to their efforts that our journal has reached this point. Thanks to their contributions, our journal now uses an exclusive online article submission and reviewing system; this has, indeed, speeded up the submission process while also reducing the workload significantly. In addition to our new international Advisory Board, our journal is now printed in full colour printing with a new design. The previous efforts put into the journal increases our responsibilities while they also motivate us. In this regard, we believe that we should continue following the established goals.

Another significant change our journal has brought in is publishing the studies in English. Starting from late 2013, every single article or case report accepted for publication has been translated into English by a professional translator, as it was the case in last four issues. We are willing to continue publishing a fully English journal by getting these studies translated until the number of submissions written in English increases and as long as this is practicable.

Along with the administrative changes, we have also strengthened our editorial staff with editors from different areas. In this way, we hope to further shorten the evaluation period. Again, in line with our journal's objectives and previous agreements with various institutions, we have renewed journal's memberships to relevant organisations and were still able to publish this issue in time.

Our next most important objective is to improve the quality and diversity of articles our journal publishes. To become a truly international journal, there is need to have quality submissions from outside Turkey. This can be achieved by improving the accessibility of the journal while also securing a place for it among recognised publications of our field. To this end, we have applied to and received acceptance from ULAKBİM DergiPark online system, which is established within TUBITAK, and we were able to publish our previous issue on this database. Meanwhile, we have also applied to ScopeMed, an international online journal management system. I am happy to announce that our submission to ScopeMed has also been accepted and we will hopefully be able to use this online system starting from our next issue.

In order to improve the quality of our publications, we are planning to take the necessary steps to place our journal in PubMed and other internationally recognised indexes. To achieve this, our journal needs to be cited more. This is where we need the valued support of our readers. It is of great importance for us if you could kindly refer to the articles in our journal in your submissions to especially international publications.

We are aware of the fact that the main purpose of publishing a journal is to contribute to scientific knowledge and, for this purpose; we are trying to do our part by publishing *Journal of Turgut Ozal Medical Centre*. In order to add to the quality of our journal and continue publishing noteworthy studies with scientific value, I would like to mention that we are always open to your worthy criticism. I sincerely believe that you will provide us with invaluable contribution to achieve our goals.

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Levels of Neuron-Specific Enolase and S-100B in the Serum of Neonates in Early Diagnosis of Possible Neurotoxic Effects of Hyperbilirubinemia

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Abstract

Aim: The laboratory and imaging methods are not sufficiently sensitive to determine precisely the neurotoxic effects of bilirubin in neonates. The neuron-specific enolase and calcium binding protein B, which are sensitive biomarkers of cellular damage in the central nerve system, were used in the present study to demonstrate possible neurotoxic effects of bilirubin below 20 mg/dL. We hypothesized that neuron-specific enolase and calcium binding protein B might be helpful for our purposes.

Material and Methods: The present study included 33 full-term infants hospitalized for phototherapy treatment (patient group) along with 29 healthy full-term infants (control group). The serum bilirubin levels of the patient group were all below 20 mg/dl. Two serum samples were obtained from all 62 infants at an interval of at least 48hrs which were used for the measurement of bilirubin, calcium binding protein B, and neuron-specific enolase levels.

Results: There was no significant difference in terms of the serum levels of calcium binding protein B between the patient and control groups but there was a significant difference of the serum levels of neuron-specific enolase between the groups. In addition, there were no significant changes in the levels of calcium binding protein B and neuron-specific enolase among the patient group before and after the phototherapy.

Conclusion: We conclude that, considering the serum levels of calcium binding protein B and neuron-specific enolase, a serum bilirubin level of <20mg/dL had no neurotoxic effect on the central nerve system. The results of the present study are consistent with the accepted safe level of bilirubin, <20mg/dL, in a full-term newborn.

Key Words: Bilirubin Encephalopathy; Neonatal Hyperbilirubinemia; Neuron-Specific Enolase; Calcium Binding Protein B.

Hiperbilirubineminin Olası Erken Nörotoksik Etkilerini Belirlemede, Yenidoğanların Serumunda Neuron-Spesifik Enolaz ve S-100B Düzeyler

Özet

Amaç: Yenidoğanlarda bilirubinin nörotoksik etkisini tam olarak göstermede, kullanılan laboratuvar ve görüntüleme metodları yeterince hassas değildir. Çalışmamızda 20mg/dl'in altındaki bilirubinin muhtemel nörotoksik etkisini gösterebilmek için, santral sinir sistemindeki hücresel hasarı gösteren hassas belirteçler olan nöron-spesifik enolaz ve kalsiyum bağlayıcı protein B kullanıldı. Çalışmamız nöron-spesifik enolaz ve kalsiyum bağlayıcı protein B düzeylerini ölçmenin, bu amaç için uygun olabileceği hipotezi üzerine kurgulandı.

Gereç ve Yöntemler: Çalışmada fototerapi tedavisi için hastaneye yatışı yapılan 33 term bebek (hasta gurubu) ve 29 sağlıklı term bebek (kontrol grubu) yer aldı. Fototerapi alması gereken bebeklerin serum bilirubin düzeyleri 20mg/dl'nin altında idi. Bütün bebeklerden, bilirubin, nöron-spesifik enolaz ve kalsiyum bağlayıcı protein B seviyelerini ölçmek için, en az 48 saat arayla iki serum örneği alındı.

Bulgular: Hasta ve kontrol gruplarının kalsiyum bağlayıcı protein B seviyeleri arasında anlamlı bir fark bulunmadı fakat nöron-spesifik enolaz değerleri arasında anlamlı bir fark bulundu. Hasta grubunda fototerapi öncesi ve sonrası nöron-spesifik enolaz ve kalsiyum bağlayıcı protein B değerleri arasında anlamlı bir değişim gözlenmedi.

Sonuç: Kalsiyum bağlayıcı protein B ve nöron-spesifik enolaz serum düzeyleri referans alındığında, 20mg/dl'in altındaki serum bilirubin değerlerinin nörotoksik etkisi olmadığı sonucuna vardık. Bu çalışmanın sonuçları, term bebeklerde kabul edilen güvenli bilirubin seviyesi olan 20mg/dl ile uyumludur.

Anahtar Kelimeler: Bilirubin Ensefalopati; Neonatal Hiperbilirubinemi; Nöron-Spesifik Enolaz; Kalsiyum Bağlayıcı Protein B.

INTRODUCTION

Bilirubin encephalopathy can develop in newborn infants as a result of acute neurotoxic effects of bilirubin. Kernicterus, the most significant chronic complication of neonatal hyperbilirubinemia, is defined as a pathologic change as a result of the accumulation of bilirubin in basal ganglia and brain stem nuclei that can lead to persistent neurological sequelae and even death (1). Bilirubin at concentrations above the exchange transfusion levels has neurotoxic effects. However, neurotoxic effects and long-term minor sequelae related to unconjugated bilirubin below the exchange transfusion levels have not been identified in clinical or laboratory ways (2). The techniques that have been used to demonstrate bilirubin-induced encephalopathy include magnetic resonance imaging (MRI), brainstem auditory evoked potentials (BAEP), oto-acoustic emissions (OAEs), cochlear microphonic (CM) responses,

electroencephalography (EEG), and some biochemical laboratory tests (3,4). All these methods are not able to determine the level of bilirubin that will not cause encephalopathy in infants precisely or the level that will lead to kernicterus in newborns. Biomarkers such as neuron-specific enolase (NSE), Tau protein, calcium-binding protein B (S100B), neurofilament triplet protein, glial fibrillary acidic protein and, brain-specific creatine kinase (CK-BB) can be used to detect the degree of neuronal damage and central nervous system (CNS) pathology. S100B, a member of the S100 family, is produced primarily by astrocytes and is found in other tissues, especially in fat tissues (5,6). Increased levels of S100B after brain injury and ischemia owing to astrocyte damage have been reported and it is suggested that S100B can be used as a biomarker to determine the severity of cellular damage and prognosis (7-9).

Similar to S100B, increased levels of NSE have also been determined following brain trauma and brain pathology. Elevated cerebrospinal fluid (CSF), plasma, and serum levels of both NSE and S100B were reported following several acute neurological diseases (8-11). We hypothesize that NSE and S100B, which have been proven to be sensitive biomarkers for cellular damage of the CNS, might be helpful in determining cellular damages. Thus, the present study has been designed to show bilirubin neurotoxicity, if any, by measuring serum levels of NSE and S100B in newborns requiring phototherapy. We have investigated the effect of phototherapy on the levels of these two neuron-specific proteins.

MATERIAL AND METHODS

The present study included 62 full-term newborn infants with postnatal ages in the range of 2–20 days. The patient group consisted of 33 jaundiced newborns hospitalized for phototherapy and the control group consisted of 29 healthy full-term newborns from the post-delivery clinic or outpatient healthy infant clinic. All infants were born at a gestational age of at least 37 completed weeks and within appropriate for gestational ages. The inclusion criteria for the patient group contained the presence of hyperbilirubinemia with a total level of serum bilirubin (TSB) <20mg/dL. Infants with any other health problems were excluded. We have obtained the consent from the parents of all infants that were included in the study. The study was approved by the ethical committee of our hospital. The mean birthweight of the newborns was 2998 (±373) g in the patient group, and 3014 (±382) g in the control group. There were 18 males and 15 females in the patient group and 21 males and 8 females in the control group. In the patient group, 12 infants were born via caesarean section and 21 infants were born by spontaneous vaginal delivery. In the control group, 13 infants were born via caesarean section and 16 patients were born by spontaneous vaginal delivery. The Apgar score of all infants was ≥8 at 5 mins after birth.

We have used the phototherapy schedule recommended by the American Academy of Pediatrics to identify the infants requiring phototherapy (2). Serum samples of the patient group were obtained before phototherapy for the measurement of TSB, S100B and NSE. The serum levels S-100B and NSE were measured by an electrochemiluminescence device (Modüler E-170 Roche-Hitachi®, Tokyo, Japan). During the phototherapy sessions, the eyes of the infants were shielded and the genital areas were covered. A fluorescent lamp emitting blue light at wavelength 420–470nm was used as the light source and the distance between the phototherapy lamps and the infant was 30–40 cm. A second serum sample was collected from each infant in the patient group after the phototherapy, which at least lasted for 48 hrs. Baseline serum samples were collected from the control group of infants at the beginning of the study and again after ≥48hrs for the measurement of bilirubin, S100B, and NSE.

Statistical analysis were carried out with the Statistical Package for Social Sciences version 15.0 (SPSS Inc., Chicago, IL, USA). The results were expressed in percentages for categorical variables. Continuous variables were presented as mean± standard deviation or median [min – max] as appropriates. The χ^2 test was used to determine the relationship between categorical variables. Independent samples *t*-test was used for comparing the two groups if parametric test assumptions were satisfactory. If these assumptions were not satisfactory, Mann Whitney U test was preferred. Within the groups, differences were given by paired samples t test. Factors affecting the delta-S100 B and delta-NSE were analyzed by multiple linear regression analysis. The level of statistically significant difference was set at $p \leq 0.05$.

RESULTS

There was no significant difference between the groups with respecs to gender and mode of birth; but there was significant differences between birth weights (Table 1).

Table 1. The general characteristics of the infants

	Patient Group (n=33)	Control Group(n=29)	p
Gender, n (%)			
Male	18 (54.5)	21 (72.4)	0.234
Female	15 (45.5)	8 (27.6)	
Mode of birth, n (%)			
Vaginal	21 (63.6)	16 (55.2)	0.676
C/S	12 (36.4)	13 (44.8)	
Birth weight (g), mean±SD	2998±373	3456±456	<0.001

C/S: Cesarean section, SD: Standard deviation

The mean level of TSB in the patient group was 19.5 (±2.80) mg/dL before phototherapy and each infant in this group received phototherapy according to the recommended schedule. At baseline, the mean level of TSB in the control group was 2.5 (±2.00) mg/dL and no infant in this group required phototherapy according to the recommended phototherapy regulations.

At baseline, the mean level of S100B was 1.5 (±0.55) µg/L in the patient group and 1.6 (±0.51) µg/L in the control group. The mean level of NSE was 43.5 (±16.20) ng/mL in the patient group and 63.1(±31.20) ng/mL in the control group; but there was a significant difference between the two groups in terms of NSE levels at baseline and after 48 hours (Table 2).

Table 2. The comparison of patient and control groups in terms of TSB, S100B and NSE levels at baseline and after 48 hours

	Patient Group (n=33)	Control Group (n=29)	p
TSB levels (mg/dL), mean±SD			
At baseline	19.50±2.80	2.50±2.00	<0.001
After 48 hours	11.40±2.70	8.40±1.90	<0.001
S100B levels (µg/L), mean±SD			
At baseline	1.56±0.55	1.62±0.51	0.654
After 48 hours	1.70±0.62	1.43±0.43	0.055
NSE levels (ng/ml), mean±SD			
At baseline	43.5±16.2	63.1± 31	0.003
After 48 hours	41.4±11.0	59.7± 23	<0.001

TSB: Total serum bilirubin, NSE: Neuron specific enolase, SD: Standard deviation

Phototherapy was continued in the patient group for at least 48 h. The levels of TSB, S100B and NSE were measured after phototherapy. In the patient group, the mean levels of bilirubin, S100B and NSE were 11.4 (±2.70) mg/dL, 1.7 (±0.62) µg/L and 41.3 (±10.99) ng/mL, respectively, after 48 hrs of phototherapy. No significant difference was found in the levels of S100B and NSE before or after phototherapy in the patient group (Table 3). So, there was no correlation between the level of TSB and that of S100B or NSE (Table 4).

Table 3. The comparison of mean S100B and NSE levels of patient group before and after phototherapy

	Before Phototherapy	After Phototherapy	p
S100B (µg/L), mean±SD	1.56±0.55	1.70±0.62	0.362
NSE (ng/ml), mean±SD	43.53±16.20	41.37±10.99	0.423

NSE: Neuron specific enolase, SD: Standard deviation

Table 4. Multiple Linear Regression Analyses Results

		Beta* (95 % CI)	p-value
Delta S100 B	Constant	0,027 (-0,490 – 0,543)	0,918
	Patient Group	0,470 (-0,610 – 1,550)	0,387
	Delta TSB	0,013 (-0,058 – 0,085)	0,711
Delta NSE	Constant	4,377 (3,885 – 4,868)	<0,001
	Patient Group	0,380 (-0,649 – 1,408)	0,463
	Delta TSB	0,008 (-0,060 – 0,076)	0,805

* Coefficient of Regression, CI: Confidence Interval. p<0.05

In the control group, the mean level of bilirubin, S100B, and NSE after 48 hrs was 8.4 (±1.90) mg/dL, 1.4 (±0.43) µg/L, and 59.7 (±23.62) ng/mL, respectively, and there was no significant difference between the level of S100B and NSE before and after 48 hrs (Table 5).

Table 5. Comparison of the S100B and NSE levels of the control group

	At baseline	After 48 hours	p
S100B (µg/L), mean±SD	1.62±0.51	1.43±0.43	0.091
NSE (ng/ml), mean±SD	63.14±31.20	59.75±23.62	0.671

NSE: Neuron specific enolase, SD: Standard deviation

DISCUSSION

It is a common problem in newborns that hyperbilirubinemia can lead to serious neurological dysfunctions if treatment is inadequate or belated. Current clinical, laboratory, and imaging methods are not able to determine the precise level of bilirubin that will not cause encephalopathy in infants or the level that will lead to kernicterus in newborns (2). The use of neuron-specific biomarkers, such as NSE, Tau protein, S100B, neurofilament triplet protein, glial fibrillary acidic

protein, and CK-BB might be helpful for developing APT methods to demonstrate the neurotoxic effects of hyperbilirubinemia.

The calcium-binding protein S100B is a member of the S100 family that can be isolated from the brain tissue, where it functions as a neurotrophic factor and a neuronal developmental protein. Levels of S100B increase in patients with head injury and CNS pathology due to astrocyte damage (12-14). The serum level of S100B is higher in newborns with hypoxic ischemic encephalopathy (HIE) and it is reported that newborns with serum levels of S100B >12 µg/L frequently have fatal outcomes or develop cerebral palsy (15). S100B can be measured in CSF, urine, and serum (16). The serum levels of S100B can be high in preterm infants with intracranial hemorrhage or in newborns with HIE even in the absence of any other clinical, laboratory or ultrasonography findings (17,18).

NSE is a glycolytic dimeric enzyme found in neuronal and neuroendocrine cells of the central and peripheral nervous systems and constitutes 0.4–4% of the soluble proteins of the brain. Brain-specific NSE is an isoenzyme of the enolase that catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate in the glycolytic pathway. Increased levels of NSE have been determined in the CSF and serum of full-term infants with asphyxia and cerebral infarcts (19,20).

Infants with moderate hyperbilirubinemia can display neurological problems and developmental retardation. Transient changes in behavior and crying patterns have been demonstrated by brainstem auditory evoked response recordings in infants with bilirubin levels of 15–25 mg/dL (1). There are many reports that relate neurotoxic effects in full-term infants with TSB levels >20 mg/dL (21-23).

In the present study, we used S100B and NSE, which are sensitive biomarkers of neuronal damage, to demonstrate whether serum levels of TSB <20 mg/dL are safe for infants. There are few reports that associate S100B and NSE levels with hyperbilirubinemia. In their study investigating the serum level of NSE in a rat model of kernicterus, Semba and Kato have reported a three-fold higher plasma level of NSE and a >30-fold higher level of NSE in the CSF in the rat model controls (24). Akman *et al.* reported that the serum level of NSE has increased significantly in infants with auditory neuropathy due to hyperbilirubinemia, despite the lack of a significant association between bilirubin and the serum level of NSE (25). Okumus *et al.* have reported a significant increase in the serum levels of Tau and S100B in correlation with serum levels of TSB >19.1 mg/Dl (26).

We found no significant difference in terms of serum levels of S100B between the patients in the study and control groups. We found, however, a significant difference in the serum levels of NSE between the two groups. Meanwhile there was also significant difference between the groups with respect to birth weights. NSE is found in mature neurons and cells of neuronal origin. We did not study the gestational ages of the infants but the statistical difference of the serum leves of NSE can be attributed to immaturity of the infant brains in the patient group.

There was no significant change in the serum levels of S100B and NSE in the patient group before and after phototherapy. Thus, total bilirubin levels <20 mg/dL can be considered to be non-neurotoxic. There was no significant decrease in the serum levels of S-100B and NSE in the patient group after phototherapy; therefore, we concluded that there was no positive effect of phototherapy on the level of these neuron-specific proteins. In the present study, the mean serum level of TSB in infants receiving phototherapy was <20 mg/dL 19.5(±2.80) mg/dL, which might explain why we did not observe increased levels of NSE or S100B proteins.

CONCLUSIONS

Although the NSE and S100B proteins are sensitive to neuronal damage, assessment solely based on these proteins cannot eliminate the presence of bilirubin neurotoxicity. Thus, other imaging and laboratory methods are needed to demonstrate bilirubin-induced encephalopathy while studies with larger numbers of infants should be undertaken to resolve this issue.

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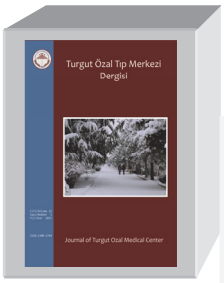

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An Investigation of Potential Risk Factors for Postoperative Urinary Retention Following Cesarean Section

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Abstract

Objectives: To investigate the risk factors for postoperative urinary retention following cesarean section.

Materials and Method: 135 female patients in Ankara Zekai Tahir Burak Woman's Health, Training and Research Hospital who underwent cesarean section were included in the study. Women who had postvoidal residual bladder with a volume of ≥150 ml measured by ultrasonography were the main group of patients. Women with postvoidal residual bladder with a volume of <150 ml were the control group patients. Demographic data such as age, parity, body mass index weight gain during pregnancy as well as obstetrical characteristics including gestational age and indications of cesarean section, number of cesarean section, anesthesia type, estimated blood loss during cesarean section, birth weight of newborn, presence of labor induction with intravenous oxytocin infusion before cesarean section were all among the data we collected throughout our research. At the end, a logistic regression model was performed to analyze the possible risk factors for postoperative urinary retention following cesarean section.

Results: We detected postoperative urenary retention in 21 (%15.6) patients. There were statistically significant relationships between the potential risks of postoperative urinary retention and the gain weight in the logistic regression model (Odds Ratio=20.8; 95; Confidence Interval=1.8-245.9; p=0.016), birth weight (>4000 gr) (Odds Ratio=0.1, 95%; Confidence Interval=0.0-0.5; p=0.002), birth induction before the cesarean section (Odds Ratio=0.2, 95%; Confidence Interval =0.0-0.8; p=0.027), and the presence of pain in the first urination after removing the urinary catheter (Odds Ratio=92.9, 95%; Confidence Interval =6.6-1299.0; p=0.001).

Conclusion: Postcesarean urinary retention risk increases if there is increased weight gain during pregnancy, macrosomic newborn delivery, cesarean section subsequent to labor induction, and high pain perception during the first urination after cesarean section.

Key Words: Urinary Retention; Cesarean Section; Risk Factors.

Sezaryeni Takiben Gelişen Postoperatif İdrar Retansiyonu İçin Potansiyel Risk Faktörlerinin Araştırılması

Özet

Amaç: Sezaryeni takiben gelişen postoperatif idrar retansiyonunun potansiyel risk faktörlerini araştırmak bu çalışmanın amacıdır.

Gereç ve Yöntem: Ankara Dr Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesinde Ocak 2014 ve Mayıs 2014 tarihleri arasında sezaryene alınan 135 hasta çalışmaya dahil edildi. Ultrasonografi ile işeme sonrası mesane hacmi ≥150 ml olan kadınlar çalışma grubu olarak olarak tanımlandı. İşeme sonrası mesane hacmi < 150 ml olan kadınlar ise kontrol grubunu oluşturdu. Bütün kadınlar yaş,parite,vücut kütle indeksi gibi demografik bilgileri ile gebelikte kilo alımı,gestasyonel yaş,sezaryen endikasyonu,sezaryen sayısı,anestezi tipi,sezaryen sırasında tahmini kan kaybı,yenidoğanın kilosu,sezaryen öncesi doğum indüksiyonunun varlığı açısından değerlendirildi. Lojistik regresyon modeli sezaryeni takiben gelişen postoperatif idrar retansiyonunun potansiyel risk faktörlerini analiz için yapıldı.

Bulgular: 21 (%15.6) kadında postoperatif idrar retansiyonu tespit edildi. Lojistik regresyon modelinde gebelikte kilo alımı (Odds Ratio =20.8; 95 Confidence Interval=1.8-245.9; p=0.016), doğum ağırlığı >4000 gram olan bebek doğurmak (Odds Ratio =0.1, 95% Confidence Interval=0.0-0.5; p=0.002) sezaryen öncesi doğum indüksiyonu (Odds Ratio =0.2, 95% Confidence Interval =0.0-0.8; p=0.027), idrar kateterinin çekilmesinden sonraki ilk işemede ağrı olması (Odds Ratio =92.9, 95% Confidence Interval =6.6-1299.0; p=0.001) sezaryeni takiben gelişen postoperatif idrar retansiyonunun potansiyel risk arasında istatiksel olarak anlamlı bulundu.

Sonuç: Sezaryeni takiben gelişen postoperatif idrar retansiyonu riski gebelikte fazla kilo alımı, makrozomik bebek doğurma hikayesi, sezaryenden önce doğum indüksiyonu alınması ve idrar kateterinin çekilmesinden sonraki ilk işemede ağrı olması gibi durumlarda artar.

Anahtar Kelimeler: İdrar Retansiyonu; Sezaryen; Risk Faktörleri.

INTRODUCTION

Cesarean section (CS) is one of the most common surgical procedures in obstetrics and its incidence increases globally day by day (1). With the technological and medical improvements, related complication rates have decreased seriously. However, CS may still cause some preventable morbidities that affect patient's quality of life negatively (2). Among these complications, postoperative urinary retention (POUR) is one that occurs rarely but can result in irreversible damage of bladder unless it is managed properly (3).

Although there is no consensus on the definition of POUR following CS today, most clinicians define this condition as the inability to void spontaneously within 6 hours after the removal of an indwelling bladder

catheter that requires catheterization or the postvoid residual bladder with a volume (PVRBV) of >150ml after spontaneous micturition which is identified by ultrasound or catheterization (4, 5).

Baldini et al. investigated the overall incidence and underlying mechanism of POUR associated with surgical procedure, anesthesia and analgesia type, and reported that urinary retantion is common after anesthesia and surgery (6). In the literature, most data about postpartum urinary retention focus on vaginal delivery while the exact role of the CS in this complication is still unknown (7). But the clinical risk factors related to POUR must be identified in order to take necessary cautions against poor outcomes of this condition. So we have designed this study to identify the potential risk factors that can help practitioners to predict the development of POUR following CS.

MATERIAL AND METHODS

One hundred and thirty-five term pregnant women, who underwent CS in the Department of Obstetrics, at Dr Zekai Tahir Burak Woman's Health Education and Research Hospital between January 2014 and May 2014, were included in this prospective observational case-control study. We obtained the approval from the Institutional Review Board and all the participants gave their written consents for the study.

The sample size was determined according to the results of the central limit theorem (8). We collected demographic data such as age, parity, body mass index (BMI), weight gain during pregnancy as well as as obstetrical characteristics including gestational age and indications of current CS, number of CSs, anesthesia type, estimated blood loss during CS, birth weight of newborn, presence of labor induction with intravenous oxytocin infusion before CS for all our patients.

We inserted a size of 16 Fr/Ch indwelling Foley catheter prior to cesarean delivery and removed it 24 hours in accordance with the CS hospital protocol. Patients were encouraged to void 6 hours after the removal of the Foley catheters. Immediately after the first void, the estimated PVRBV was measured by transabdominal ultrasonography. The longitudinal and transverse scan of the bladder that gave the greatest diameter were obtained with the transducer located in the midline above the symphysis pubis. The width (D1) and the anteroposterior diameter (D2) in the transverse plane along with the cephalocaudal diameter (D3) in the sagittal plane were all recorded.

Estimated PVRBV was calculated using the formula D1xD2xD3x0.7 (9). Women who had an estimated PVRBV ≥150ml or were inable to void within 6 hours after the removal of catheter were defined as the cases to be studied. The patients with an estimated PVRBV <150ml were the categorised as the control group. Postoperatively, all women were asked to score the worst pain experienced after CS and during the first void by using a 10 cm-line visual analogue scale (VAS: 0 cm- no pain, 10 cm- excruciating pain). Meanwhile it is important to mention that all women received the same mild postoperative analgesia protocol (tenoxicam 40 mg (IM) twice in 24hours). The postoperative ambulation time of all women were also recorded.

Statistical Program for Social Sciences (SPSS, Version 15.0; Chicago, IL, USA) was used to perform stastistical analysis of the study. The normal distribution of the variables was analyzed by the Kolmogorov–Smirnov test. The continuous variables with normal distribution are presented with mean ± standard deviation. Median (minimum-maximum) value is used where normal distribution is absent. Quantitative variables are given as numbers (percentages). The statistical comparison of the continuous variables with normal distribution was carried out by Independent-Samples t test while Chi-square ($\chi 2$) test was used for the quantitative variables. On the other hand, the statistical differences between the continuous variables with no normal distribution were analyzed by Mann–Whitney U test. Besides a logistic regression model was also performed to analyze the risk factors for POUR following CS. $P<0.05$ was considered statistically significant.

RESULTS

135 women who underwent CS volunteered to take part in this study. Of the 135 patients, 21 (15.6%) women were defined as the study group patients while the others (N=114, 84.4%) were the control group patients. In the study group, all women were able to void within 6 hours after the CS. Demographic and related obstetrical data of the groups are shown in Table 1. Mean weight gain during pregnancy was significantly greater in the case group (12.7±1.7 kg) than in control group (9.5±1.2 kg) p(<0.001) as well as the rate of newborn with a birth weight of >4000 g (p<0.01). In case group, labor induction with oxytocin and CS for cephalopelvic disproportion (CPD) is more common compared to the control group (p<0.01 and p=0.04, respectively). The women in the case group had higher postoperative median VAS scores than the control group (p=0.04). In addition, the first void after removal of the urinary catheter in the case group [VAS=9 (9-10)] was significantly more painful compared with the control group [VAS=8 (7-10)] (p<0.001). The other data listed in Table 1 shows no significant differences between the groups.

Analysis by logistic regression model has shown that weight gain during pregnancy (Wald (W)=5.8; Odds Ratio (OR)=20.8; 95% Confidence Interval (CI)=1.8-245.9; p=0.02), newborn birth weight >4000g (W=9.3; OR=0.1, 95% CI=0.0-0.5; p<0.01), labor induction before CS (W=4.9; OR=0.2, 95% CI=0.0-0.8; p=0.03), and the pain experienced during the first void after removal of the urinary catheter (W=11.3; OR=92.9, 95% CI=6.6-1299.0; p<0.01) were all statistically significant factors which effected the presence of POUR following CS.

Table 1. Demographic and obstetrical data of the study and control groups

	Cases (n=21)	Controls (n=114)	p
Age (years)	28.6±3.9	27.0±3.7	0.07*
Parity	2 (1-3)	2 (1-4)	0.54‡
BMI (kg/m²)	31.2±1.3	31.0±1.6	0.56*
Weight gain (kg)	12.7±1.7	9.5±1.2	<0.001*
Gestational age (days)	277.7±6.7	274.9±6.4	0.07*
Birth weight of the newborn (g)	3781.4±372.2	3623.5±347.8	0.06*
No. of those with >4000g (birth weight)	9 (42.9)	17 (14.9)	<0.01#
Anasthesia type			0.78#
General	6 (28.6)	36 (31.6)	
Spinal	15 (71.4)	78 (68.4)	
EBLV (mL)	692.9±92.6	736.5±144.7	0.18*
Duration of CS (minutes)	54.3±17.5	55.5±9.4	0.64*
Labor induction before CS	15 (71.4)	36 (31.6)	<0.01#
CS for previous uterine scar	6 (28.6)	48 (42.1)	0.25#
CS for CPD	6 (28.6)	13 (11.4)	0.04#
CS for arrest of dilation or descent	3 (14.3)	17 (14.9)	0.94#
CS for abnormal fetal heart pattern	3 (14.3)	24 (21.1)	0.48#
Time to first mobilization (hours)	9.6±1.8	9.3±1.7	0.91*
Postoperative VAS score	9 (8-10)	8 (8-10)	0.04‡
Voiding VAS score	9 (9-10)	8 (7-10)	<0.001‡

Values indicate mean ± standard deviation or median (minimum-maximum) values or numbers (percentages)
BMI: Body Mass Index, EBLV: Estimated Blood Loss Volume, CS: Cesarean Section, CPD: Cephalopelvic disproportion, VAS:Visual Analogue Scale
*Independent-Samples t test
‡ Mann-Whitney U test
# Chi Square test
p<0.05 is considered statistically significant

Table 2. Logistic regression model to compare Odds ratio of possible effective factors for postoperative urinary retention development following cesarean section

	Wald	p	OR	95% CI for OR	
				Lower	Upper
Weight gain	5.8	0.02	20.8	1.8	245.9
>4000g birth weight	9.3	<0.01	0.1	0.0	0.5
Anesthesia type	0.5	0.49	0.5	0.1	4.1
Labor induction with oxytocin	4.9	0.03	0.2	0.0	0.8
Presence of CPD	0.7	0.40	0.6	0.1	2.2
Postoperative VAS score	0.4	0.52	0.6	0.2	2.5
Voiding VAS score	11.3	<0.01	92.9	6.6	1299.0

OR: Odss Ratio, CI: Confidence Interval, CPD: Cephalopelvic disproportion, VAS:Visual Analogue Scale
p<0.05 is considered statistically significant.

DISCUSSION

This study has demonstrated that POUR following CS is a relatively common condition with an overall incidence of 15.6%. In the literature, the reported incidence rate for postcesarean urinary retention varies widely, between 5% and 33.3%, which, in fact, reflects its multifactorial etiology (including comorbidities, type of surgery, and type of anesthesia etc.) and that it lacks a uniform definition (7, 10).

The exact role of CS in developing POUR is still unknown. Chai et al, in a prospective study of 207 patients delivered by CS (both scheduled and unscheduled), reports that problems in progress of labor, resulting in an unscheduled CS, can be considered as the single most important risk factor of POUR (7). It is possible that during unsuccesful labor process, pelvic nerve plexuses in the pelvic soft tissue are affected by prolonged pressure of the fetus on the pelvic floor leading to tissue edema or impairment of the detrusor muscle from neuropraxia and, eventually, to urinary retention (11). In our study, labor arrest was not a risk factor for the development of POUR following CS. But we found that the pregnant women who gained much weight during pregnancy, had a cesarean delivery with a birth weight of >4000g, and those for whom labor was

induced by oxytocin infusion are by far more prone to have POUR following CS. Besides, although this is not statistically significant, the data evinced a trend towards POUR development when CS is performed due to CPD and the pain experienced is higher postoperatively. These findings suggest that the increasing abdominal pressure during pregnancy or labor may contribute to damages on pelvic connective tissues and nerves resulting in neurologic impairment of voiding function and, thus, urinary retention.

By using VAS score system, we were able to assess pain perception after CS and during first void after the removal of the urinary catheter interaction with POUR. We found that the women with POUR had statistically greater postoperative VAS scores than the women without POUR, but postoperative VAS score was not an independent risk factor for the development of POUR following CS in our regression model. On the other hand, the higher pain perception during first void after the removal of urinary catheter was presumably related to POUR. Traditionally, urinary catheterization is commonly used during CS to improve exposure of the lower uterine segment at the time of surgery as well as to prevent urinary bladder injury and avoid postoperative urinary retention (12, 13). However, catheterization has been shown as a main cause of urinary tract infections, greater postoperative discomfort, and pain (14, 15). It is possible to assume that the pain perception due to urinary catheterization may result in urinary retention by developing reflex urethral spasms.

It has been previously postulated that epidural anesthesia/analgesia with morphin was significantly associated with postcesarean urinary retention (16, 17) but the mechanism underlying the high incidence of urinary disturbances occurring after postoperative epidural morphine is unknown (10). In a review of postcesarean analgesia, it was stated that a single dose of spinal morphine at the time of CS can provide excellent analgesia of prolonged duration (18). Dahl et al., in a meta analysis on postcesarean analgesia, describe adverse effects of prolonged spinal morphine as pruritus, nausea, vomiting, early or delayed respiratory depression, and urinary retention (19). In our study, no epidural anasthesia was applied while the anesthesia type (spinal or general) was not found to be important in the development of POUR as we used the same type postoperative analgesia protocol in all patients.

Although POUR is not a well-understood clinical condition despite the fact that it results in bladder distention, it may lead to serious short and long term problems such as acute and chronic urinary tract infection, chronic voiding difficulties, and renal failure (20, 21). Thus, it is very important to diagnose POUR in its early stages and manage it properly.

In conclusion, POUR following CS seems as a relatively common complication in obstetric practices, but, since it is rarely reported in the published literature, the underlying mechanism is still not very commonly known. In this study, we suggest that all obstetricians should be aware of the development of POUR when the weight gain during pregnancy is more than normal, the birth weight of newborn is >4000g, the labor induction with oxytocin infusion is present, and the pain perception after removal of urinary catheter is high. The routine use of ultrasound to diagnose this condition during postoperative period may be beneficial whereas further studies with more participants are needed to clarify this topic.

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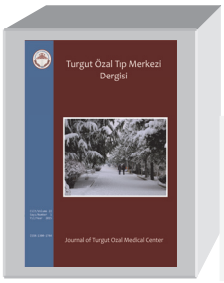

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Orthopedic Surgical Wound Infection: Microorganisms and Resistance Figures

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Abstract
Purpose: One of the most important and feared complications of modern orthopaedic surgery is postperative surgical wound infections. In this study, we aimed to investigate antimicrobial resistance rates of isolated microorganisms in wound infections after orthopaedic surgery.
Methods: Isolated bacteria were identified with conventional methods and automated system (Becton Dickinson Phoenix ID). Antimicrobial susceptibility of the strains were investigated according to Clinical Laboratory Standards Institute (CLSI) recommendations.
Results: Ninety six (37%) microorganisms were isolated from 257 wound specimens. These were: *Acinetobacter spp.* 24 (25%), *P. aeruginosa* 19 (20%), *S. aureus* 15 (16%), *E. coli* 10 (10%), *K. pneumoniae* 10 (10%), CNS 8 (8%), *P. mirabilis* 5 (5%), *Enterobacter spp.* 4 (4%), and Enterococcus spp. 1(1%), respectively. *Acinetobacter spp.* strains were resistant to imipenem by 92%, to amikacin by 83%, to ciprofloxacin by 89%, and to sulbactam-ampicillin (SAM) by 62%. 10% of *E. coli* and 40% of *K. pneumoniae* strains were extended to spektrulu beta-lactamase positive. 7% of *S. aureus*, 50% of CNS strains were methicillin resistant.
Conclusions: Considering local epidemiological data in the treatment of surgical wound infection is going to help increasing the chance of treatment success and reducing resistance rates by providing rational use of antibiotics.
Key Words: Antimicrobial Resistance; Microorganism; Orthopedic Surgical Wound İnfections.

Ortopedik Cerrahi Yara Enfeksiyonları: Mikroorganizmaların Direncine İlişkin Veriler

Özet
Amaç: Postoperatif dönemde modern ortopedik cerrahinin en önemli ve korkulan komplikasyonlarından biri cerrahi yara enfeksiyonlarıdır. Çalışmamızda ortopedik cerrahi sonrası bir yıllık sürede yara enfeksiyonlarından izole edilen mikroorganizmaların ve antimikrobiyallere direnç oranları araştırılmıştır.
Yöntem: İzole edilen mikroorganizmaların konvansiyonel yöntemler ve otomatize sistemle (Phoenix Becton Dickinson ID) tür tayini yapılmıştır. Elde edilen türlerin antimikrobiyal duyarlılık testleri Clinical Laboratory Standards Institute önerileri doğrultusunda çalışıldı.
Sonuçlar: İki yüz elli yedi yara örneğinden 96 (%37)'sında mikroorganizma izole edilmiştir. İzole edilen bakteriler sırasıyla *Acinetobacter spp.* 24 (%25), *P. aeruginosa* 19 (%20), *S. aureus* 15 (%16), *E. coli* 10 (%10), *K. pneumonia* 10 (%10), *Koagulaz negatif stafilokok (KNS)* 8 (%8), *P. mirabilis* 5 (%5), *Enterobacter spp.* 4 (%4) ve *Enterococcus spp.* 1 (%1) olarak belirlenmiştir. *Acinetobacter spp.* suşlarında imipeneme %92, amikasine %83, siprofloksasin %89 ve sulbaktam-ampisiline (SAM) %62 oranında direnç gözlenmiştir. *E.coli* suşlarında %10, *K.pneumonia* suşlarında ise %40 oranında GSBL (genişlemiş spektrumlu beta laktamaz) pozitifliği saptanmıştır. *S.aureus* suşlarının %7'si, KNS'lerin %50'si metisiline dirençli bulunmuştur.
Sonuç: Sonuç olarak; gelişen cerrahi yara enfeksiyonu tedavisinde lokal epidemiyolojik verilerin dikkate alınmasının tedavideki başarı şansını arttıracağını, akılcı ve rasyonel antibiyotik kullanımını sağlayarak direnç oranlarını azaltacağı kanısındayız.
Anahtar Kelimeler: Antibiyotik Direnci; Mikroorganizma; Ortopedik Yara Enfeksiyonu.

INTRODUCTION

The primary task of the skin is to prevent the invasion of pathogenic microorganisms into subcutaneous tissues and to avert the settling of pathogenic microorganisms by creating skin flora. Wounds are created by traumas. Post-traumatic disruption of skin integrity leads to colonisation and invasion of microorganisms in the subcutaneous tissues. This is followed by the damage in the immune system caused by the microorganisms in the wound area and, then, infection of the wound (1). Infection in the postoperative or wound healing periods may arise from patient's own flora, hospital environment, or operation equipment. Hospital-acquired (nosocomial) infection is usually caused by antimicrobial resistant bacteria. Therefore, this type of infection is difficult to treat, not to mention that it is also costly and has high complication rates (2). There is a significant increase in the number of surgical interventions with the developments in orthopaedic surgery in recent years. Despite the advancements and improvements in asepsis and antisepsis applications, method of sterilisation, operating room and intensive care facility conditions and surgical techniques, and several prophylactic antibiotic applications, one of the most important and feared

postoperative complications of modern orthopedic surgery is still infection of the surgical wound. Surgical wound infections developing in the postoperative period result in significant morbidity, mortality, loss of labor, extended hospital stay, and high costs (3). In spite of advances in diagnosis and treatment methods, irrational use of antibiotics and inadequate infection control policies give rise to microorganisms that develop rapid resistance even to the most effective antibiotics (4). Most of the orthopedic surgical wound infections are nosocomial (5). Therefore, systematic and realistic applications should be developed to reduce the risk of surgical wound infection caused by hospitals environment and staff.

This study aims at investigating the resistance rates of microorganisms and antimicrobial agents that have been isolated from wound infections in patients in inpatient and outpatient orthopaedics clinics in the postoperative period.

MATERIAL AND METHODS

Patients:

We have retrospectively studied the microorganisms isolated from wound samples of the postoperative patients from the inpatient and outpatient orthopaedics clinics of our hospital between June 2012 and June 2013. We have included the patients who developed infection in the early postoperative period (the first 4 weeks) in our hospital but did not receive any antibiotic treatment for the infection. Patients who had undergone operations in other centres and those who had previously received infection-related antibiotic treatment were excluded from the study.

Laboratory Tests:

The species identification of the isolated microorganisms was carried out by using conventional methods and an automatic system (Phoenix Becton Dickinson III). The in-vitro antimicrobial susceptibility of the isolated strains were determined according to the Clinical Laboratory Standards Institute criteria by using Kirby-Bauer disc diffusion method (Becton-Dickinson, Sparki Md, USA) on the automated system (6).

RESULTS

Within a period of 12 months, we isolated microorganism samples from 96 (37%) of the 257 postoperative patients from the inpatient and outpatient orthopaedics clinics. Of the 96 factors of the isolated wound samples, 72 (75%) were gram negative bacteria and 24 (25%) were gram positive bacteria. The most frequently isolated bacteria were acinetobacter spp. 24 (25%), Pseudomonas aeruginosa 19 (20%), Staphylococcus aureus 15 (16%), Escherichia coli 10 (10%), Klepsiell pneumonia 10 (10%), coagulase-negative staphylococci (CNS) 8 (8%), Proteus mirabilis 5 (5%), Enterobacter spp. 4 (4%), and Enterococcus spp. 1 (1%), respectively. We observed resistance in the Acinetobacter spp. strains to imipenem (92%), amikacin (83%), ciprofloxacin (89%), and SAM (62%). We detected beta-lactamase-positivity at an extended spectrum in E.coli (10%) and K. pneumoniae (40%) strains. There was no resistance to imipenem and amikacin in P. aeruginosa strains though these were resistant to ceftazidime, cefepime, piperacillin tazobactam with a resistance rate of 5%. 7% of the isolated S. aureus strains and 50% of the isolated KNS strains were methicillin-resistant while all strains were found to be resistant to vancomycin. The resistance rates of gram-positive strains showing their resistance to some antibiotics are given in Table 1; the resistance rates of gram-negative bacteria with respect to their resistance to various antibiotics are shown in Table 2.

Table 1. The resistance rates of gram positive strains.

Antimicrobial	*S.aureus* (n=15) Resistant (%)	KNS (n=8) Resistant (%)
Ciprofloxacin	1(%7)	3(%37)
Erythromycin	3(%20)	4(%50)
Gentamicin	1(%7)	1(%12)
Cefoxitin	1(%7)	4(%50)
Penicillin	11(%73)	7(%87)
Rifampin	1(%7)	4(%50)
Vancomycin	%0	%0
Tetracycline	3(%20)	3(%37)
Trimetoprim-Sulfametoxazol	2(%13)	2(%25)
Clindamycin	2(%13)	4(%50)
Ampicillin	4(%27)	-
Gentamicin 120	-	-
Streptomicin 300	-	-
Cloranfenicol	-	-

Table 2. The resistance rates of gram negative strains.

	E.coli (n=10) Resistant (%)	*K. pneumonia (n=10)* Resistant (%)	*Acinetobacter spp (n=24)* Resistant (%)	*P.aeruginosa (n=19)* Resistant (%)	Other Enterobactericeae (n=9) Resistant (%)
Ampicillin	8(%80)	-	-	-	4(%44)
Amoxicillin clavulanic acid	4(%40)	4(%40)	-	-	3(%33)
Cefoxitin	1(%10)	%0	-	-	-
Cefuroxime axetil	6(%60)	7(%70)	-	-	3(%33)
Cephalothin	7(%70)	8(%80)	-	-	4(%44)
Ceftazidime	1(%20)	4(%40)	18(%75)	1(%5)	1(%11)
Cefepime	1(%20)	4(%40)	22(%92)	1(%5)	1(%11)
Cefoperazone-sulbactam	%0	1(%10)	10(%42)	%0	%0
Piperacillin tazobactam	1(%10)	2(%20)	22(%92)	1(%5)	%0
Imipenem	%0	%0	22(%92)	%0	%0
Gentamicin	2(%20)	3(%30)	22(%92)	1(%5)	%0
Amikacin	%0	%0	20(%83)	%0	%0
Ciprofloxacin	1(%10)	1(%10)	19(%89)	1(%5)	%0
Netilmicin	-	-	17(%71)	%0	-
SAM	-	-	15(%62)	-	-
SXT	5(%50)	7(%70)	7(%39)	-	4(%44)
Tetracycline	4(%40)	7(%70)	8(%33)	-	5(%56)
ATM	1(%20)	4(%40)	-	1(%5)	1(%11)
CTX	2(%20)	4(%40)	19(%79)	14(%26)	1(%11)

DISCUSSION

Surgical wound infections is one of the major causes of mortality and morbidity in patients after surgery. Such infections delay the recovery of the clinical status of patients and lead to prolongation of hospital stay and increased costs (7). Since Joseph Lister's discovery of antiseptic applications in the 1860s, there has been an decrease in the high wound infection related postoperative morbidity rates. Currently, surgical wound infections constitute 14-16% of nosocomial infections which makes them the second most common type of infection among hospital-acquired infections (8). According to the Centre for Diseases Control and Prevention data, surgical wound infection is seen in 2-5% of all patients undergoing surgery (9). Depending on the surgeon, hospital, and surgical procedures, the incidence of surgical wound infections ranges from 1% to 40%. With an incidence rate of 22%, extending hospital stay with an average of 7.3 days, and increasing the hospital costs with an average of 3,152$, surgical wound infections is the second most common postoperative complication in Turkey (8).

Postoperative wound infection is the most important problem of modern orthopaedic surgery. It is very significant to conduct prophylaxis of infection consciously and effectively. Incomplete and incorrect treatment will develop resistance of bacteria and lead to increased morbidity and mortality rates (10). The post-surgical wound infection rates in Turkey have been reported by various researchers: Erbay et al. (11) 28%; Willke et al. (12) 20%; Geyik et al. (13) 36%; Yıldız et al. (14) 13%; and Demirtürk et al. (15) 16%. In our study, we isolated microorganisms in 96 (37%) of 257 wound samples of after orthopedic surgery and found out that 72 of these 96 (75%) were gram-negative bacteria while 24 (25%) were Gram positive bacteria.

In treating postoperative wound infections, regulating the treatment in the light of culture and antibiogram results will improve the success of treatment, shorten the length of hospital stay, and reduce costs. This will also increase the success rate of the practitioner and, with effective antibiotic use, block the dissemination of antibiotic-resistant strains (2). The reproduction of bacteria causing postoperative wound infection varies depending on the body area where the surgery is performed. Apart from patient's own bacterial flora, factors such as the already colonised bacterial species in hospital environments, particularly indoors in clinics, cause such infections (5). S. aureus, KNS, E. coli, and P. aeruginosa are among the most frequently isolated microorganisms in wound infections. Some of the isolation rates of these bacteria in Turkey have been listed below: Yurtsever et al. (2009) (16) E. coli 27%, P. aeruginosa 18%, S. aureus 18%, Acinetobacter baumannii 12%; Dogan et al. (2010) (2) E. coli 28%, P. aeruginosa 14%, S. aureus 15%; Demirturk et al. (2011) (15) E. coli 25%, P. aeruginosa 14%, S. aureus 28%; Bayram et al. (2013) (17); Acinetobacter baumannii 24%; P. aeruginosa 12%, S. aureus 11%, E. coli 10%. Some of the studies from abroad have provided the following rates: Guggenheim et al. (4) E. coli 14%, P. aeruginosa 12%, S. aureus 21% and Mulu et al. (18) E. coli 21%, KNS 21%, S. aureus 26%. In our study, the most common bacteria were Acinetobacter spp. (in 24 samples; 25%) and P. aeruginosa (in 19 samples; 20%). These are followed by S. aureus (in 15 samples; 16%), E. coli (in 10 samples; 10%), K. pneumoniae (in 10 samples; 10%), KNS (in 8 samples; 8%), P. mirabilis (in 5 samples; 5%),

Enterobacter spp. (in 4 samples; 4%), and Enterococcus spp.(in 1 sample; 1%), respectively. High rates of Acinetobacter spp. and P. aeruginosa are revealing in showing the differences between the studies in Turkey and abroad but our findings match with the findings of Bayram et al.'s 2013 study (17). Chim et al.'s (19) study conducted in Singapore also reports high rates of Acinetobacter spp. but they explain this by the high proportion of potential Acinetobacter spp. already endemic on the skin flora of the people of the region. In our study, the high isolation rates of Acinetobacter spp. and P. aeruginosa can be interpreted as a sign that shows that these bacteria is well-colonised in our hospital.

Because of their ability to maintain long-term viability in the external environment and be transmitted easily through contamination, acinetobacter species have increasingly become important nosocomial pathogens (20). With regards to epidemiological and clinical aspects of the bacteria, bacterial resistance profile is very crucial. The Acinetobacter spp. strains we isolated had multiple resistance to antimicrobials. The Acinetobacter spp. that have been isolated in a similar manner in other studies were also found to be highly imipenem-resistant with a rate of 92% (16-20). The emergence of strains with multiple resistance to antimicrobials causes treatment to fail and increases morbidity and mortality. In line with previous studies on wound infections, we isolated P. aeruginosa with a rate of 20% even though our strains were not resistant to multiple antibiotics (4,15 to 20). Carbapenems, however, were found to be highly sensitive to aminoglycosides and fluoroquinolones.

Unlike earlier studies, S. aureus was the third most common form in our study by 16%. MRSA rate was very low (7%) as well. In former studies conducted in our hospital, this rate was 31% in 2011 (21) and 43% in 2013 (22). CNSs were methicillin-resistant up to 50%. The highest resistance rate in S. aureus isolates was to penicillin with a rate of 73%. We did not detect any glycopeptide resistance. The resistance rates to other antibiotics were also notably low: 7% to ciprofloxacin, 20% to tetracycline, 20% to erythromycin, and 7% to gentamicin, respectively.

Within the family Enterobacteriaceae (E. coli, K. pneumoniae, Enterobacter spp., and P. mirabilis), the rapid spread of ESBL strains raises concern all over the world (23). In our study carried out in our hospital in 2010, we identified an ESBL rate of 28% (24). In Turkey, in general, the HITTITE-2 study that was conducted between 2005 and 2007 determined this ratio as 42% (25). In our study, the ESBL positivity rates were 10% and 40% for E. coli and K.pneumoniae strains, respectively. In accordance with our 2010 study, Guggenheim et al.'s retrospective study (4) evaluating the data of 20 years has found the most effective antimicrobials to be imipenem and amikacin for ESBL positive strains. E. coli strains were most resistant to ampicillin by 80% while they were also highly resistant to cephalothin (by 70%) and cefuroxime axetil (by 60%). K. pneumoniae strains were found to be unsusceptible to trimethoprim-sulfamethoxazole, tetracycline, and cefuroxime axetil by 70% and to cephalothin by 80%.

In short, it is very essential to have the knowledge of the type and in vitro sensitivity of microorganisms to achieve appropriate medical treatment for postoperative infections. We believe that considering local epidemiological data in the treatment of postoperative surgical wound infections will increase the chances of success of treatment, reduce the rate of resistance by providing rational use of antibiotics, and contribute to the quality of health services by reducing costs.

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Comparing Conventional and Digital Mammography in Patients With Microcalcifications

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Abstract

Objective: Microcalcifications are the primary mammographic abnormalities in 40% of nonpalpable breast cancers. The aim of this retrospective study is to compare the diagnostic value of conventional and digital mammography (CMG and DMG) by reviewing the histopathological results of microcalcifications evaluated with stereotactic biopsy together with these two methods.

Material and method: The mammography and stereotactic biopsy images and medical records of 464 females who had undergone wire localization for microcalcifications with CMG and DMG between May 2003 and May 2011 were retrospectively evaluated. The histopathology results were compared according to the positive and negative predictive values (PPV and NPV) and the BI-RADS classification.

Results: The histopathology was malignant in 57% (120/207) of the microcalcifications detected with CMG and 22.5% (58/257) of those detected with DMG. The malignant pathologies detected on CMG were infiltrative in 55% and in situ in 45%. The malignant pathologies detected on DMG were infiltrative in 43% and in situ in 56.9%. The microcalcifications detected on CMG were distributed as 30 BI-RADS 3 (PPV: 93.3%); 135 BI-RADS 4 (PPV:39%), and 42 BI-RADS 5 (PPV:100%) lesions and the total PPV was 66%. The microcalcifications detected on DMG were distributed as 1 BI-RADS 3 (PPD: 100%), 249 BI-RADS 4 (PPD: 20%), and 7 BI-RADS 5 (PPD:100%) cases and the total PPV was 22%.

Conclusion: Detecting microcalcifications, which are not visible on CMG, increases the 'false positivity' rate but the increase in the detection rate of in situ cancers with DMG can be accepted as an advantage of this method.

Key Words: Mammography; Digital, Conventional; Microcalcification.

Mikrokalsifikasyonlu Hastalarda Konvansiyonel ve Digital Mammografilerin Karşılaştırılması

Özet:

Amaç: Nonpalpabl meme kanserlerinin yaklaşık %40'ında mikrokalsifikasyonlar primer mammografik anormalliklerdir. Bu geriye dönük çalışmada, konvansiyonel ve digital mamografi (KMG ve DMG) eşliğinde stereotaktik biyopsi yapılan mikrokalsifikasyonların histopatolojik sonuçlarıyla beraber değerlendirilerek her iki yöntemin tanısal değerinin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Mayıs 2003-Mayıs 2011 yılları arasındaki DMG ve konvansiyonel KMG eşliğinde mikrokalsifikasyonlara yönelik tel lokalizasyonu yapılan 464 kadın olgunun mamografi ve sterotaktik biyopsi görüntüleri, radyoloji raporları, hastane iletişim sistemindeki patoloji raporları ve epikrizleri geriye dönük olarak incelenmiştir. Histopatoloji sonuçları, pozitif prediktif değer (PPD) ve negatif prediktif değerleri (NPD), BI-RADS klasifikasyonuna göre karşılaştırılmıştır.

Bulgular: KMG'de saptanan mikrokalsifikasyonların %57'si (120/207), DMG'de saptanan mikrokalsifikasyonların %22.5'i (58/257) malign histopatolojiye sahipti. KMG'de saptanan malign patolojilerin %55'ini infiltratif, %45'ini insitu kanserler oluşturmaktaydı. DMG'de saptanan malign patolojilerin %43'ünü infiltratif, %56.9'unu insitu kanserler oluşturmaktaydı. KMG'de saptanan mikrokalsifikasyonların 30'u BI-RADS 3 (PPD: %93.3); 135'i BI-RADS 4 (PPD: %39), 42'si BI-RADS 5 (PPD: %100) olarak bulundu. Total PPD %66'idi. DMG' de saptanan mikrokalsifikasyonların 1'i BI-RADS 3 (PPD:%100), 249'u BI-RADS 4 (PPD: %20), 7'si BI-RADS 5 (PPD: %100) idi. Total PPD %22 olarak bulundu.

Sonuç: KMG'de göremediğimiz mikrokalsifikasyonların DMG ile saptanabilir olmaları, 'yalancı pozitif' olgu sayısını arttırmaktadır ancak DMG 'nin insitu kanserleri daha fazla sayıda saptayabilmesi yöntemin avantajlarından biri olarak kabul edilebilir.

Anahtar Kelimeler: Mamografi; Dijital, Konvansiyonel; Mikrokalsifikasyon.

INTRODUCTION

Breast cancer is the most common malignant tumour in women. It constitutes 30% of all cancers in female patients while it is also responsible from 18% of cancer deaths in women (1). The life-long risk of breast cancer development in women is 7-10%. The importance of effective use of periodical physical examination and basic diagnostic methods for early diagnosis is unquestionable (1-3).

Mammography (MG) is the most effective imaging method known to detect breast cancer in its early stages. Studies suggest that early diagnosis of breast cancer reduces mortality in patients aged between 40 and 69 by 15-35% (4, 5). Microcalcifications constitute approximately 55% of breast lesions. Microcalcifications may be the first and/or only signs of premalignant conditions like atypical hyperplasia or early-stage malignant lesions like carcinoma in situ. Given that approximately 40% of non-palpable breast cancers are primary mammography abnormalities of microcalcifications, early detection of distribution and

nature of microcalcifications plays a key role in the diagnosis of breast cancer (6).

Until recently, due to its high spatial resolution, conventional mammography (CMG) was the primary imaging modality in breast screening programmes. Allowing practitioners to benefit from the convenience of computer environment with the development of digital systems and creating the basis for advanced technologies, the newly developed digital mammography (DMG) has replaced conventional methods. Studies conducted in the recent years have indicated that there are no major diagnostic differences between CMG and DMG. In this retrospective study, we aim to compare the diagnostic values of CMG and DMG by applying stereotactic biopsy to microcalcifications while also alternately evaluating the histopathologic results of both methods.

MATERIAL AND METHODS

In this study, we have performed a retrospective analysis of the stereotactic wire markings of 1988 patients who have undergone both imaging techniques for 8 years between May 2003 and May 2011 at Ankara Oncology Training and Research Hospital, Department of Radiology. We have excluded cases with missing data records, mammography and stereotactic biopsy images, radiology reports, pathology reports in hospital digital archives along with those who had undergone stereotactic biopsy with ultrasonography (US). At the end of the preliminary research, we have narrowed down the scope of our study to 464 female patients with complete data with regards to their MG guided wire localisation for microcalcifications.

Our department performed wire localisation to 207 patients with microcalcifications between May 2003 and December 2008 with CMG while 257 patients underwent wire localisation with DMG between January 2009 and May 2011. All assessments were simultaneously performed by two radiologists with experience in the field of breast imaging.

Mammographic examinations and stereotactic markings were all performed on a Lorad Selenia digital mammography unit (Hologic) and Flat SE (Metaltronica).

Characteristics of microcalcifications: We have studied all the MG images and reports registered in the hospital data management system. The distribution and morphological characteristics of microcalcifications have been assessed in accordance with the "American College of Radiology" (ACR) criteria and classified based on the "Breast Imaging Reporting and Data System" (BI-RADS).

Wire localisation: Wire localisation in our department is routinely applied as follows. We first inform the patient about the procedures and get their written consent. All patients are questioned about a possible existing anticoagulant therapy; those who are on anticoagulants are referred to related clinics. We start the MG-guided localisation by detecting the point of the lesion that is closest to the skin with the help of craniocaudal and full lateral radiographs. We perform the marking by using a single or multiple-hole compression plate with the mammography equipment. After calculating the lesion coordinates on the plate, we apply the needle parallel to the chest wall and perpendicularly to the skin. Reaching to the previously measured depth of the lesion, we completely, but slowly, reduce the compression on the breast. When the needle is in the desired location, we gently push the hook-tipped wire in and fix its location. At the end, we take a control mammogram that shows the latest breast-needle-lesion relationship.

All the cases that were marked with the needle-wire system at the radiology clinic were sent to surgical clinics on the same day and taken to the operating room at most within1 hour. The field marked with wiring, along with at least 1cm of the surrounding intact tissue, was removed under general anesthesia. Before sending them for pathological examination, the removed sections were first checked by specimen radiography. After confirming with specimen radiography that the desired section has been removed, we notify the surgical team.

The cases with benign histopathology have been invited for routine MG check-up in the 12th month of the treatment. Those with malign results have been referred to surgery.

Statistical Analysis: Categorical variables have been indicated in percentages (%). Positive predictive value (PPV) and negative predictive value (NPV) have been calculated according to the formula presented below:

$$\text{Positive Predictive Value} = \frac{\text{True positives (TP)}}{\text{Total positives (TP+FP)}} \times 100$$

$$\text{Negative Predictive Value} = \frac{\text{True Negatives (TN)}}{\text{Total Negatives (TN+FN)}} \times 100$$

TP value was used for the patients who, after the MG evaluation, were classified as BI-RADS 4 or BI-RADS 5 (very likely to be malignant) with histopathological malignancy while the TN value was used for patients who were classified as BI-RADS 3 (very likely to be benign) after the MG and diagnosed as histopathologically benign. Similarly, FP value was based on the patients who were classified as BI-RADS 4 or BI-RADS 5 following the MG evaluation results (very likely to be malignant) though with histopathologically benign diagnosis while FN value was used for patients who were classified as BI-RADS 3 (very likely to be benign) after the MG evaluation results but with histopathologically malignant diagnosis.

RESULTS

The US and MG-guided wire localisation applications for microcalcifications in our department between May 2003 and December 2008 constitute 20.1% (1032/207) (CMG)

of our patients while 26.8% of (257/956) (DMG) the patients underwent wire localisation between January 2009 and May 2011. 57% (120/207) of the detected microcalcifications (with CMG) and 22.5% (58/257) of the DMG-detected microcalcifications had malignant histopathology. 55% of the malignant pathologies diagnosed with CMG (63 IDC, 3 metaplastic) were infiltrating cancer cases while 45% were in situ cancers. 43% of the malignant pathologies diagnosed with DMG were infiltrating cancers while 56.9% were in situ cancer cases (Figure 1a, 1b).

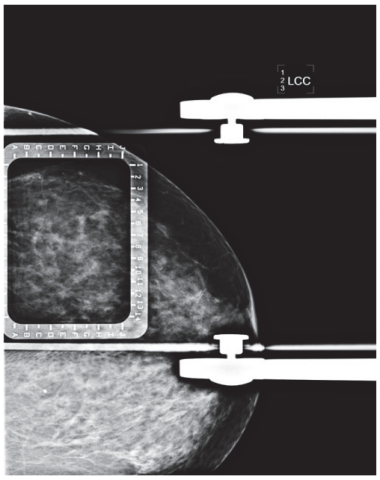

Figure 1a. Pulverulent microcalcifications on the CC graph on the outer frame of the window of the left.

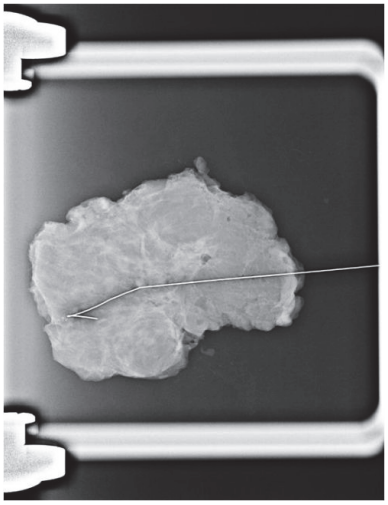

Figure 1b. The excised microcalcifications visible on the specimen MG following the wire localisation of the same patient in Figure 1a; the diagnosis is infiltrating ductal CA Grade 2.

41.3% of the benign pathologies detected with CMG and 45% of the benign pathologies detected with DMG were premalignant (moderate and severe epithelial hyperplasia, atypia) lesions. There were 30 BI-RADS 3 (NPV: 93.3%), 135 BI-RADS 4 (PPV: 39%), and 42 BI-RADS 5 (PPV: 100%) patients with microcalcifications diagnosed with CMG. The total PPV was 66%. There were 1 BI-RADS 3 (PPV: 100%), 249 BI-RADS 4 (PPV: 20%), and 7 BI-RADS 5 (PPV: 100%) patients with microcalcifications diagnosed with DMG. The total PPV was 22% (Table 1).

Table1. The correlation between the BI-RADS–histopathology results of microcalcifications diagnosed with DMG.

MAMOGRAPHY	MALIGNENT	BENIGN	TOTAL
BI-RADS 3	0(FN)	1(TN)	1
BI-RADS 4-5	58(TP)	198(FP)	256
TOTAL	58	199	257

DISCUSSION

Breast cancer is the most common malignant tumour in women and it constitutes about 30% of all cancers in women (1). Breast cancer occurs in one in every 10 women and it is responsible for one in every five of cancer-related deaths. Therefore, early diagnosis of breast cancer is of utmost importance to reduce mortality and morbidity (7). The number of detected non-palpable breast lesions has considerably increased due to the wide use of mammography screening in recent years (8).

Enabling storing, re-creating, and transferring data, DMG has become a valuable alternative to CMG. It is, thus, agreed that, due to its technical advantages, DMG may increase the rate of cancer detection. However, studies indicate that there are not many major diagnostic differences between CMG and DMG (9-11). Lewin et al. have examined 4,489 patients with both CMG and DMG only to find out that there was no significant difference in the rate of cancer detection between the two methods (9). Two large scale studies conducted by Skaane et al. have similarly shown that there was no significant differences in cancer detection between CMG and DMG (10,11). Pisano et al. have also failed to find significant differences between the two methods in terms of overall diagnostic accuracy though they have found some differences in the subgroups of their study. According to their study, women under the age of 50 in premenopausal or perimenopausal periods with dense and heterogeneous breast structures have proved to receive diagnosis significantly more accurately with DMG (12).

In the literature, the most frequent radio-morphologic criteria that can be regarded as an indication for biopsy are reported to be microcalcifications (13, 14). In our study, we have evaluated the microcalcifications that approximately formed 55% of the breast lesions during the screenings. The number of the wire localisation performed to cure microcalcifications and their application rate among other wire localisation applications were similar in CMG, which was used for 5,5 years, and DMG, which was used for 2.5 years. This is due to the rapid screening technology of DMG. We have detected more malignancies with CMG; and CMG was

more successful than DMG in diagnosing in situ cancers. However, considering the fact that microcalcifications are the only mammographic findings that can be detected in the early stages, DMG can be considered superior to CMG.

There were no significant differences between the two methods in terms of identifying premalignant lesions among benign pathologies. This finding is consistent with another study that compares CMG and DMG in terms of cellular atypia (15). The PPV for BI-RADS 4 (with CMG) was 39%; this was an overall of 66% for all categories. Our findings are also in line with other PPVs for microcalcifications (11%, 30%, 43%) (16-18). The PPV for BI-RADS 4 (with DMG) was 20%; this value was 22% for all categories.

In a similar study, in accordance with our reserach, PPVs for DMG were lower compared to CMG values (CMG: 20%; DMG: 12%) (19). This can be explained by the visibility of microcalcifications and higher number of biopsies resulting in high false positivity values. That the patients were not categorised according to breast density can be considered as a limitation of the study since DMG works with higher accuracy on dense breasts.

CONCLUSION

The fact that microcalcifications that are not visible with CMG can be detected with DMG raises the number of "false positive" cases though DMG's ability to identify in situ cancer types more accurately is one of its advantages.

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A Comparative Study of Radiation Doses and Treatment Area Dependence in Thermoluminescence Dosimetry Systems and Metal Oxide Semiconductor Field Effect Transistors

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Abstract

Aim: This study aims at examining the differences between thermoluminescense dosimeters and metal oxide semiconductor field effect transistors in terms of radiation doses at different photon energies treatment area dependence in patients who recieved radiotherapy at the Department of Radiation Oncology, İnönü University.

Material and Methods: Thermoluminescense dosimeter systems and metal oxide semiconductor fıeld effect transistors were used at 6MV and 25MV in the range of 25-1000 cGy radiation doses to examine radiation dose dependence. Results were evaluated by taking measurements of treatment areas 5x5, 10x10, 15x15, 20x20, 25x25, 30x30, and 40x40 cm², respectively, to specify treatment area dependence of these systems.

Results: In both thermoluminescense dosimeters (TLD) and metal oxide semiconductor field effect transistors (MOSFET), reading values at 6 MV and 25 MV photon energies remained up to 800 cGy. We observed that both systems deviate from linearity at doses above 800 cGy. In TLDs, we recorded a %±1 (6 MV photon energy) and %+4 (25 MV photon energy) change in reading values. This change was %±1 (6 MV photon energy) and %+4 (25 MV photon energy) in MOSFETs.

Conclusion: Both dosimeter systems have advantages and disadvantages in terms of accuracy and applicability. Being familiar with dosimeter systems is very important in identifying the accuracy of dose to be admisnistered.

Key Words: Radiotherapy; Invivo dosimeter; Thermoluminescense Dosimeter; Metal oxide semiconductor fıeld effect transistor; Linear accelerator.

Radyasyon Dozu ve Tedavi Alanı Bağımlılıklarının Termolüminesans Dozimetre Sistemleri ve Metal Oksit Yarıiletken Alan Etkili Transistörlerine Etkisi Üzerine Karşılaştırmalı Bir Çalışma

Özet

Amaç: Bu çalışmada, radyoterapi alan hastaların giriş dozunun belirlenmesi için İnönü Üniversitesi Tıp Fakültesi Radyasyon Onkolojisi Anabilim Dalı'nda kullanılan in vivo dozimetre sistemlerinin farklı foton enerjilerinde radyasyon dozu ve tedavi alanına bağımlılıklarının incelenmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmada termolüminesans dozimetre ve metal oksit yarıiletken alan etkili transistör invivo dozimetre sistemleri ile lineer hızlandırıcı cihazının 6 MV ve 25 MV foton enerjileri kullanılmıştır. Dozimetre sistemlerinin radyasyon dozu bağımlılığının incelenmesi için 25-1000 cGy radyasyon dozu aralığında ışınlamalar yapılmıştır. Sistemlerin tedavi alanına bağımlılığının belirlenmesi için ise sırasıyla 5x5, 10x10, 15x15, 20x20, 25x25, 30x30, 40x40 cm²'lik tedavi alanlarında ölçümler alınarak sonuçlar değerlendirilmiştir.

Bulgular: 6 MV ve 25 MV foton enerjilerinde artan radyasyon doz değerlerine bağlı okuma değerleri değişimi metal oksit yarıiletken alan etkili transistör dozimetre sisteminde lineer iken, temolüminesans dozimetrede 800 cGy'e kadar lineer, 800 cGy'den sonra ise lineerlikten saptığı gözlenmiştir. Artan tedavi alanı boyutuna bağlı okuma değerleri değişimi ise temolüminesans dozimetrelerde 6 MV foton enerjisi için %±1, 25 MV foton enerjisi için %+4 değerindedir. Metal oksit yarıiletken alan etkili transistör dozimetre sisteminde 6 MV foton enerjisinde değişim %± 1 iken 25 MV foton enerjisinde % ± 4 değerinde olduğu görülmüştür.

Sonuç: İnvivo dozimetrelerin birbirlerine göre bazı üstünlükleri vardır. Günlük kullanımda kullanıcıların dozimetre sistemlerini tanımaları ve ölçüm sonuçlarını etkileyecek özelliklerini bilmeleri, radyoterapi uygulanan hastaya verilen dozların doğruluğunun tespit edilmesi açısından oldukça önemlidir.

Anahtar Kelimeler: Radyoterapi; İn vivo Dozimetre; Termolüminesans Dozimetre; Metal Oksit Yarıiletken Alan Etkili Transistör; Lineer Hızlandırıcı.

INTRODUCTION

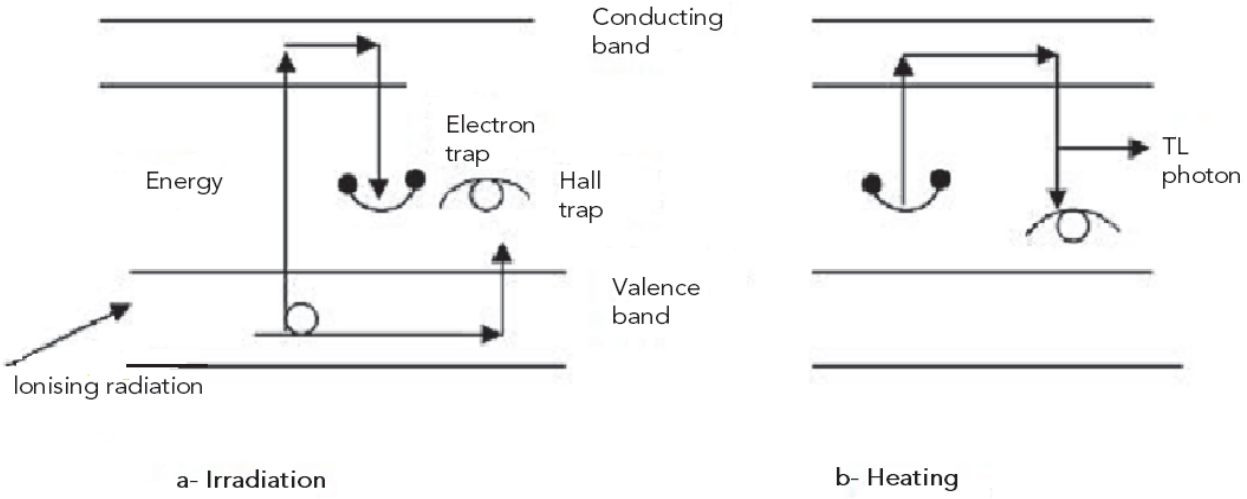
To control the dose to be administered in radiotherapy, it is very important to know that the target volume receives the defined dose accurately (1-3). To ensure that patients undergo targeted doses accurately and reliably, practitioners make use of in vivo dosimetry systems. By providing accurate data about the volume of the radiation patients should receive during the

treatment, and detecting possible dosimetric errors prior to the session, in vivo dosimeters prevent patients from taking less or more radiation than the planned doses (4).

For in vivo dosimetry measurements, practitioners use diodes and thermoluminescence dosimeters (TLD) (5). Metal oxide semiconductor field-effect transistors (MOSFET), radiochromic film dosimetry, conventional portal films, plastic scintillator dosimeters, electronic portal imaging, and gel dosimeters are among other dosimeters used in electronic radiation dosimetry measurements (6, 7).

Thermoluminescent dosimeters are based on the principle that a crystal with thermoluminescence properties becomes radiated through ionising and absorbs energy, which, in turn, is released in the form of thermoluminescence radiation as the crystal is exposed to temperature. Due to the defects in the structure of matter between conduction and valence bands or the presence of foreign atoms in itself, thermoluminescence crystal has quasi-steady energy levels. These energy levels create trap centres for the electrons and halls. When the matter is exposed to ionising radiation, some of the electrons in the valence band gain energy and move towards the conduction band or get caught in the electron traps in the forbidden energy gap (Figure 1a).

As a result of collisions, a portion of the electrons in the conduction band move to the valence band or get caught by the electron trap zone in the forbidden gap. When the crystal is heated, the electrons trying to avoid the traps and halls employ lower energy levels; whilst in lower energy levels, these electrons reflect their energy load in the form of thermoluminescent radiation (Figure 1b). The thermoluminescent radiation emitted from this phenomenon is proportional to the amount of radiation dose reflected on the crystal (8).



Figures 1a and 1b. Energy diagram of thermoluminescent crystal; **a)** irradiation **b)** heating.

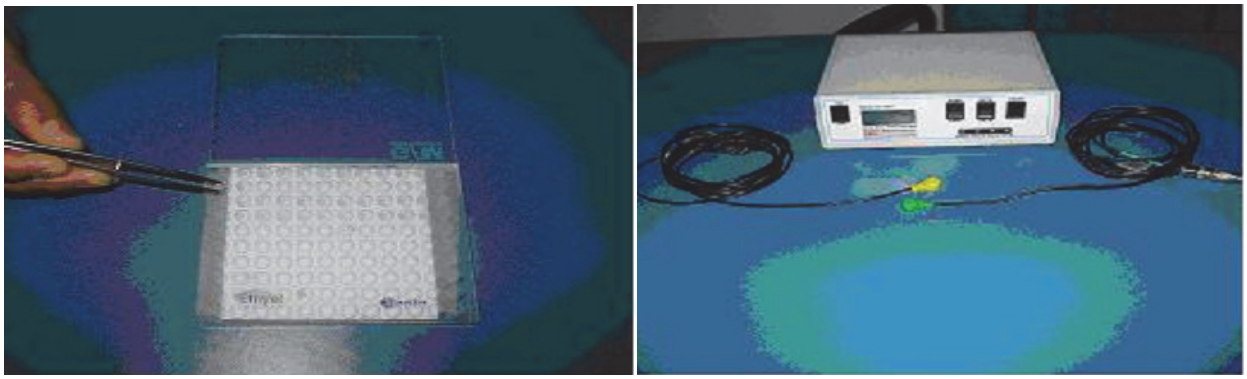
MOSFETs are either n-type or p-type semiconductors. N-type semiconductor is formed by the contribution of five-valence elements called donors. Each donor contributes to the free electrons of the semiconductor. In N-type semiconductors, majority carriers are the electrons while minority carriers are the holes. P-type semiconductor is formed by the contribution of the three-valence elements called the acceptors. Each acceptor is treated as an electron. In P-type semiconductors, the equivalent of the positive charge carriers are holes that move. Again, in P-type semiconductors, majority carriers are the holes while minority carriers are the electrons. As semiconductors are exposed to radiation, holes and electrons are formed; so the amount of the collected charge is proportional to the amount of radiation (9).

Although the physics underlying TLD and MOSFET detectors are different, both dosimeters are placed on the skin of patients during the irradiation. MOSFETs display the dose after irradiation directly, which allows a quick and easy way to identify the doses. While MOSFETs are dependent on energy and heat as they are also effected by radiation, they still have advantages like their high precision, repeatability, and stability (8, 10, 12-13). In TLDs, dose measurements are made after irradiation. So, there is need for a second reading system to obtain the post-dose irradiation. Although delays in reading is a disadvantage for TLDs as they cause low dose measurements, it is a low-cost system (8-11,14-16).

To determine the accuracy of the delivered dose and improve the quality of treatment, practitioners should be familiar with the dosimetry systems they are using and their features that may influence measurement results. This study aims to determine dose and treatment dependence of the patients. In this way, our study also aims at reducing errors in TLD and MOSFET applications, which are used to determine initial doses for radiation therapies.

MATERIAL AND METHODS

In this study, we have made use of TLD-100 chips, which are made up of LiF (lithium fluoride) crystals, and MOSFET dosimetry systems (Figure 2). Irradiation was carried out in a Linear Accelerator device (LINAC) (Electa-Precise) by using solid water phantom. First, we performed calibration on the dosimetry systems. In the second stage of our research, we examined the energy dependence of the systems, and in the third step, we performed measurements to investigate dependence on the therapy area.

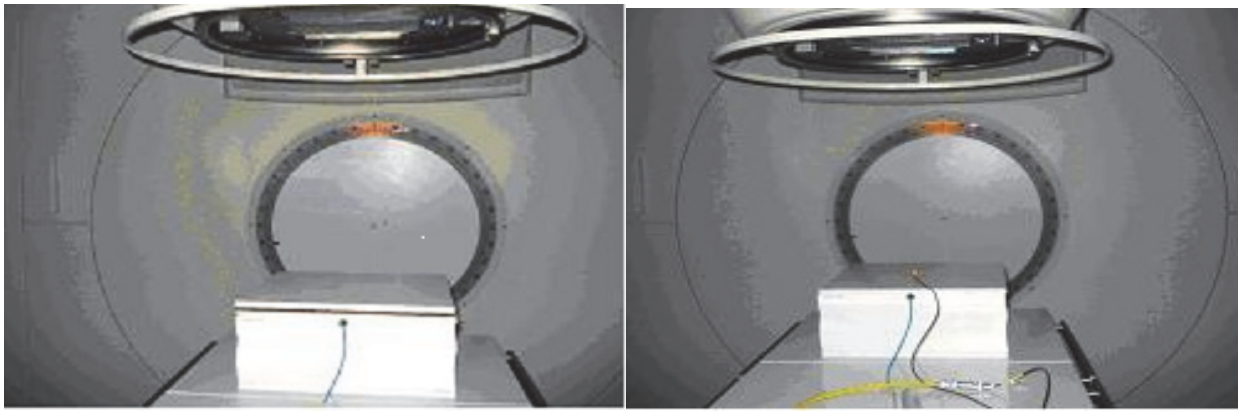


Figures 2a and 2b. **a)** TLDs **b)** MOSFETs

1) Calibration

Prior to the radiation measurement with TLD, we started the calibration and categorisation. We performed the following to stabilise 70 TLD crystals: to empty the traps in TLDs, we applied a annealing process by placing the crystals on metal trays. The annealing was performed in two stages: the long annealing process at 400 degrees C for 5 hours and the short annealing at 100 degree C for an hour. The annealed TLDs were then placed in a plexiglas tray in LINAC. The tray was 6 mm in diameter and 1mm in depth. Next, the crystals were irradiated at a radiation dose of 100cGy on a 5mm deep, 10x10cm2 treatment area, at a 100cm source skin distance (SSD). After the irradiation application and reading TLDs in the TLD reading system with the Winrems software, they were let loose in the traps. All these processes were repeated 10 times to increase the sensitivity of the dosimeters, to stabilize the dosimetry measurements, and to determine reproducibility. By using the Winrems software, we selected the best 15 TLD-100 chips (with a sensitivity rate of ±1%) from among seventy 1x3x3mm3 TLD-100 chips.

To let MOSFETs adapt to external factors such as temperature, pressure, and humidity, they were brought to the environment in which they would be used. In order to have a homogeneous dose, detectors were positioned to the isocenter as closely as possible. Since 100-200 cGy at a dose rate of 100 to 300 cGy/min is enough for calibration, we administered 100-200 cGy of radiation and recorded the values. After the calibration, we administered additional irradiation in the normal measurement mode of the dose monitor to confirm the calibration. The measurement sets used for irradiation in TLD and MOSFET are displayed in Figures 3a and 3b.



Figures 3a and 3b. **a)** Measurement set (TLD) **b)** Measurement set (MOSFET)

2) Determining Radiation Dose Dependence of the Dosimeters

We determined the irradiation dose dependence of the TLDs and MOSFETs, both of which are used in 6 MV and 25 MV photon energies in radiation therapy. The gantry (treatment head) and collimator on the LINAC were set to 0°. We placed ten PTW brand RW3 solid water phantoms (bulk density: 1,045g/cm^3; electron density: 3.43x1023e/cm^3; dimensions: of 40x40cm^2) on top of one another. The treatment area size was 10x10cm^2 and and the dosimeters were set in the centre 100 cm SSD from the treatment area; then, we performed radiation at 25, 50, 100, 200, 300, 400, 500, 600, 700, 800, 900, and 1000 cGy, respectively. Each irradiation session for each value was repeated 3 times and we took the average result of the three readings as the mean dependence rate.

3) Determining Treatment Area Size Dependence of the Dosimeters

Since photon input dose is dependent on collimator scatter factor (Sc) and phantom scatter factor (Sp), dosimeter readings may depend on the treatment area size (4, 9). Therefore, it is necessary to determine the treatment area dependence of the dosimetres.

In order to see the changes in the size of the treatment area and TLD readings, we placed the TLD 1cm below the center area of the solid water phantom and a cylindrical ion chamber 1,5 cm beneath the maximum dose depth. The SSD was 100cm and the treatment area size was adjusted to 5x5, 10x10, 15x15, 20x20, 25x25, 30x30, 35x35, and 40x40 cm^2, respectively. To minimise the effects of parameters on irradiation time, we performed irradiation at a constant irradiation volume of 100 MU. To increase the stability of the application, we repeated each process three times and averaged the results. All measurements were repeated for 6 MV and 25 MV.

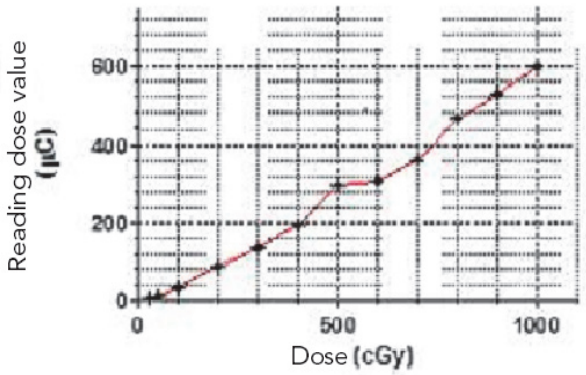
In order to see the changes in the size of the treatment area and diode readings, we repeated the measurements by placing a diode on the surface and in the centre of the solid water phantom and a cylindrical ion chamber 1,5 cm beneath the maximum dose depth. The readings for different therapeutic areas were normalised to the reading values of the treatment area of 10x10cm^2.

RESULTS

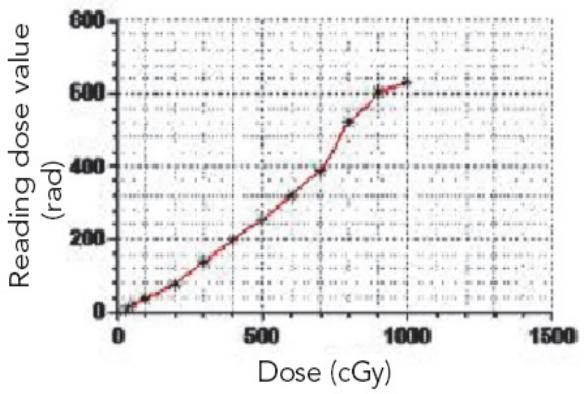
1) Radiation Dose Dependence:

TLD

Graphs 1 and 2, respectively, shows the radiation dose related changes of the readings at 6 MV and 25 MV photon energies in the range of 25-1000cGy.



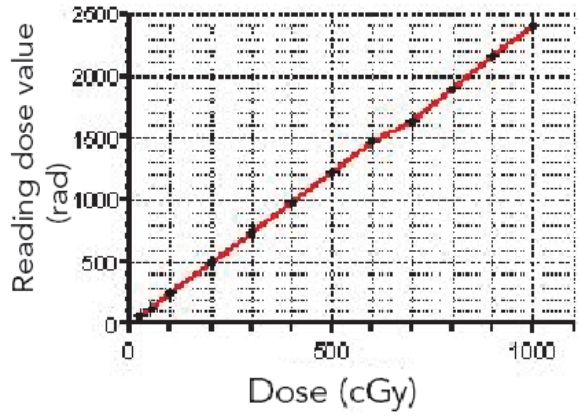
Graph 1. Radiation Dose Dependence of TLDs at 6 MV photon energy



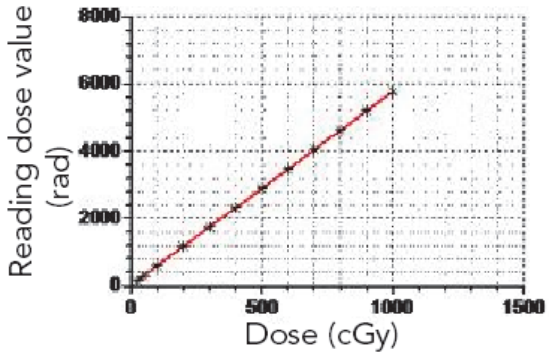
Graph 2. Radiation Dose Dependence of TLDs at 25MV photon energy

MOSFET

Graph 3 shows the radiation dose related changes of the MOSFETs at 6 MV photon energy in the range of 25-1000cGy while Graph 4 shows the radiation dose related changes at 25 MV photon energy.



Graph 3. Radiation Dose Dependence of MOSFETs at 6 MV photon energy



Graph 4. Radiation Dose Dependence of MOSFETs at 25 MV photon energy

In TLDs, radiation dose related changes at 6 MV and 25 MV were linear up to 800 cGy; these changes showed deviation after 800 cGy. In MOSFETs, radiation dose dependent changes were linear throughout both 6 MV and 25 MV measurements. Both dosimetry systems had a rising tendency in the readings as the photon energy increased; this rising inclination, eventually, is reflected in the graphs

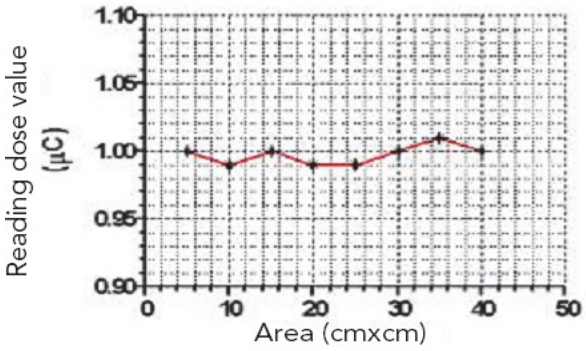
2) Treatment Area Size Dependence:

TLD

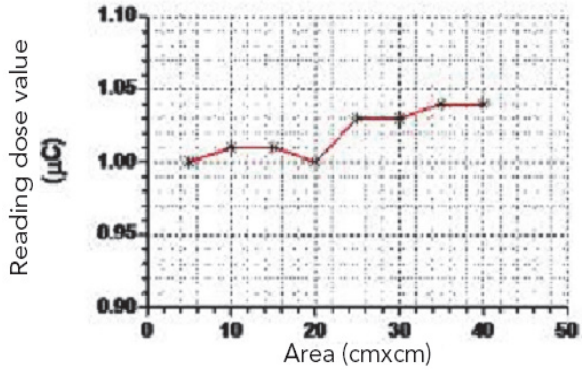
Graph 5 provides the changes observed in the area dependence of TLDs while SSD was 100 cm at 6 MV in 5x5, 10x10, 15x15, 20x20, 25x25, 30x30, and 40x40 cm^2 by using Elekta Precise LINAC device.Graph 6 presents the increase in the area dependence as the photon energy goes up to 25 MV; here, the maximum value for these changes was observed to be +4%.

MOSFET

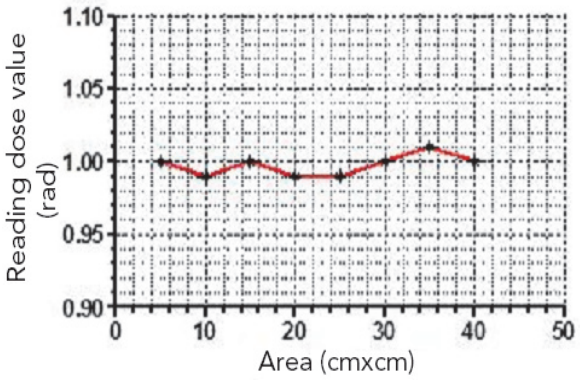
Graph 7 shows the changes observed in the area dependence of MOSFETs while SSD was 100cm at 6 MV in 5x5, 10x10, 15x15, 20x20, 25x25, 30x30, and 40x40 cm^2. At 6 MV and depending on the increase in the treatment area, the change in the reading value was +1%. Graph 8 presents the increase in the area dependence at 25 MV; here, the maximum value for these changes was observed to be +4%.



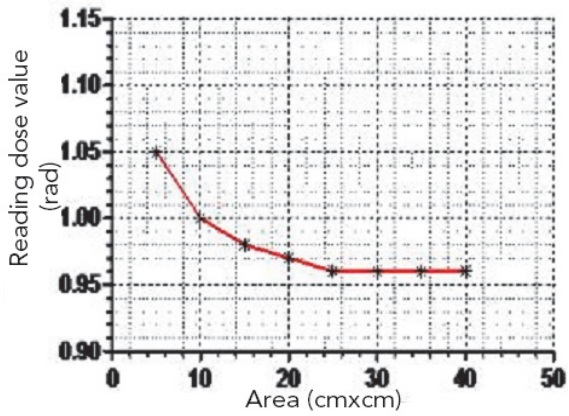
Graph 5. Treatment Area Dependence of TLDs at 6 MV photon energy



Graph 6. Treatment Area Dependence of TLDs at 25 MV photon energy



Graph 7. Treatment Area Dependence of MOSFETs at 6 MV photon energy



Graph 8. Treatment Area Dependence of MOSFETs at 25 MV photon energy

DISCUSSION

In radiation oncology, the accuracy of the radiation dose delivered to the patient is the most important part of the quality assurance programmes. In this study, we have compared the linearity of the dose-dependent change and dependence on the treatment area in TLD and MOSFETs, two devices used in radiotherapy, to find

whether these dosimetry systems are at ideal levels in terms of dose and area dependence.

Ideally, a dosimeter must show a linear change as radiation dose increases (8). In our study, TLDs maintained a linear change at 6 MV and 25 MV up to 800 cGy. However, above 800cGy, there were deviations in its linearity. A.J. Troncall et al. has perviously shown that the standard deviation was around 3% range in all doses in TLDs up to 1000 cGy (17). As far as our study is concerned, we believe that this deviation in linearity in terms of dose response above 800 cGy can be explained by the incapability of TLDs to respond to this increase in dose due to overloaded traps.

In MOSFETs, we observed an increase in reading values resulting from the increase in radiation dose. This change remained linear in both photon power levels up to 1000 cGy radiation dose. However, as it has been pointed out in other studies (11), when the amount of irradiation increases, there may be decreases in the response sensitivity of the diodes. We have observed that the change at 6 MV was smaller than it was at 25 MV in both photon energy levels. As a result of this, a further observation was the increase in the dependence on radiation dose due to the increase in energy levels (9).

Dependence on treatment area arises from scattered electrons and photons. The collimator scatter is added to the primary beam as the area enlarges, and accordingly, scattered radiation increases the amount of the absorbed dose (6).

For larger areas (40x40 cm^2), dosimetry system's dependence on the treatment area size may increase up to 5% in ion chamber measurement. This is due to the effect of the Sc, Sp, and collimator phantom scatter (Scp) on the dose distribution (8). At 6MV, the dependence to treatment area size was +1% for MOSFETs while the same value was ±1% for TLDs. At 25 MV, as the treatment area enlarged, the treatment area size dependence reached up to %± 4 in MOSFETs. This was up to +4% in TLDs.

CONCLUSION

Comparing TLDs and MOSFETs, it can be concluded that MOSFETs are more linear in terms of dependence on radiation dose. Apart from the daily fractionated doses, practitioners should prefer MOSFET to TLD by taking this deviation from linearity into consideration in TLDs especially in special applications like total body irradiation (TBI) and total skin electron irradiation (TSEI) that require fractional treatment doses above 800cGy. However, it should also be kept in mind that even MOSFETs share deformation at high doses of radiation. In dosimetry systems used at 6 MV, the increase in the treatment area size does not have an effect on reading though dosimetry systems should be calibrated by using appropriate calibration factors in line with the treatment area size at 25 MV photon energy.

MOSFET system is advantageous because it provides dose display, does not require secondary reading, and allows immediate detection and correction of potential errors. TLDs, on the other hand, are easier to use. TLDs can be easily placed on the skin and body cavities while they can also be used with random phantoms. TLDs do not require any additional components such as cables and electrometers during irradiation. MOSFETs get easily affected by changes in temperature and humidity. TLDs, compared to the diodes, are less affected by these changes.

To sum up, users should be familiar with the features of the dosimetry systems they are using to determine the accuracy of the administered dose. Therefore, by controlling the accuracy therapeutic doses, treatment quality increases while possible errors are minimised.

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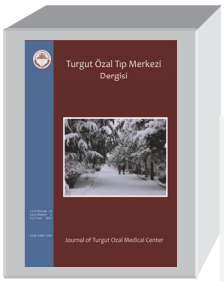

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An Evaluation of Catheter-Related Bloodstream Infections in Intensive Care Units

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Abstract

Aim: This study aims to study the risk factors that are related with the development of bloodstream infections in the patients hospitalized in intensive care units (ICUs).

Materials and Methods: We have prospectively examined the risk factors and microbiologic analyses of 18 patients with catheter-related blood stream infections (CR-BSI) who were selected from among 300 patients at ICU with central venous catheters (CVC) for 12 months (between August 2011 and August 2012).

Results: The mean duration of the catheterization was 15,19±5,977 days. The sensitivity and specificity of the time factor for receiving positive signal from cultures of CVC and blood samples were 88.8% and 93%, respectively. The CR-BSI attack rate was 20.9%. Metabolic disorders, duration of hospitalization in ICU, urinary catheterization, longer length of CVC duration, and whether CVC was used for other tests were found to be significant risk factors for the development of CR-BSI ($p<0,001$). Methicilin-resistant coagulase-negative staphylococcus (MRCNS) was detected in 6 (33.3%) cases while *Acinetobacter baumanii* was detected in 2 (11.1%) cases and polymicrobial agents were detected in 5 cases (27.7%). We also detected the following bacteria in 1 (5,6%) patient (for each) *Pseudomonas aeruginosa*, diphteroid bacilli, *Aeromonas veronii,* methicillin-susceptible *Staphylococcus aureus,* and *Klebsiella pneumoniae*.

Conclusion: In this study, metabolic disorders and CVC related factors were determined as risk factors for CR-BSI development. Taking these preventable factors into consideration and proper use of infection control measurements will provide significant decrease in CR-BSI rates. However, there is need for new scientific approaches on the diagnosis, treatment, and prevention for CR-BSI.

Anahtar Kelimeler: Central Venous Catheter; Catheter-Related Bloodstream İnfection; Intensive Care Unit, Bacteremia.

Yoğun Bakım Ünitelerinde Gelişen Kateter İlişkili Kan Dolaşım Enfeksiyonlarının İrdelenmesi

Özet

Amaç: Bu çalışmada, yoğun bakım ünitelerinde (YBÜ) yatan hastalarda gelişen kateter ilişkili kan dolaşımı infeksiyonları ile ilişkili risk faktörlerinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Bir yıllık sürede (Ağustos 2011-Ağustos 2012) yoğun bakım ünitelerinde takip edilen ve santral venöz kateter (SVK) takılan 300 hastada gelişen 18 kateter ilişkili kan dolaşımı infeksiyonu (KİKDİ) olgusundaki risk faktörleri ve mikrobiyolojik analizleri prospektif olarak araştırılmıştır.

Bulgular: Santral venöz kateterlerin takılı kalma süreleri ortalama 15,19±5,977 gündü. KİKDİ gelişen hastalarda SVK ve kan kültürlerinin sinyal pozitifleşmesinde zaman faktörünün duyarlılığı (sensitivity) %88,8, özgüllüğü (specifity) %93,0 olarak bulundu. KİKDİ atak oranı %20,9 olarak belirlendi. Metabolik bozukluklar, YBÜ yatış süresi, üriner kateterizasyon, SVK takılı kalma süresi ve çok amaçlı kullanılması KİKDİ gelişimi için anlamlı risk faktörleri ($p<0,001$) olarak belirlendi. Altı (%33,3) olguda metisilin-dirençli koagülaz-negatif stafilokok (MRKNS), 2 (%11,1) olguda *Acinetobacter baumanii*, birer (%5,6) olguda *Pseudomonas aeruginosa*, difteroid basil, *Aeromonas veronii*, metisilin-duyarlı *Staphylococcus aureus* (MSSA) ve *Klebsiella pneumoniae* ve 5 (%27,7) olguda polimikrobiyal etkenler saptandı.

Sonuç: Çalışmamızda, metabolik bozukluklar ve SVK kullanımına bağlı nedenlerin KİKDİ gelişiminde önemli faktörler olduğu saptanmıştır. Bu faktörlerin çoğunlukla önlenebilir olması, infeksiyon kontrol önlemlerinin doğru kullanılması ile KİKDİ oranlarında önemli düşüş sağlayacaktır. Ancak yine de KİKDİ tanımlanması, tedavisi ve korunma ile ilgili olarak yeni bilimsel yaklaşımlara ihtiyaç vardır.

Anahtar Kelimeler: Santral Venöz Kateter; Kateter-İlişkili Kan Dolaşımı İnfeskiyonu; Yoğun Bakım Ünitesi; Bakteriyemi.

INTRODUCTION

Because of the dense patient population, intensive care units apply more intravenous catheters than any other units (1). An important complication of intravenous catheter applications in critically ill patients is the development of a potential infection (2). Local cellulitis, septic thrombophlebitis, abscess formation, catheter-related bloodstream infection (CR-BSI), metastatic infections (osteomyelitis, endophthalmitis, arthritis, lung abscess, brain abscess), and endocarditis are among the major infectious complications of intravascular catheters (3).

The average incidence of CR-BSI in intensive care units ranges from 1,8 to 5,2 in 1000 catheter days (4). Therefore, CR-BSI is regarded as an important cause of nosocomial bacteria and for this reason it is often associated with longer duration of hospital stay, increased costs of treatment, and high morbidity and mortality (5). Determination of central venous catheter

infection rates and their risk factors are very significant in prevention and reducing the frequency of bloodstream infections (1).

This study aims at determining the relationship between the ICU patients to whom we administered CVC and CR-BSI attacks they developed as well as the risk factors associated with ICU stays and CVC.

MATERIALS and METHODS

Patients:

In this study, we have prospectively examined 300 patients who were admitted to the intensive care unit of Akdeniz University Hospital between August 2010 and August 2011 and to whom we placed CVC. We have only included those patients at 18 years of age and above whose CVC remained implemented during their hospital stay. Patients younger than 18, those who were monitored at ICU in other centres or were implemented CVC in other units, or those patients who had previously been to centres where CVC is commonly used such as dialysis and chemotherapy units or to other intensive care units (neonatal, pediatrics, coronary ICU) were excluded from the study. All 300 patients were grouped according to 'Health Care Associated Infections Identification Guide' published in 2008 by the Centres for Diseases Control and Prevention (CDC) (6). Accordingly, the control group was made of patients who did not have reproductive factors in the semiquantitative culture of their catheter tips, whose blood cultures were negative in terms of reproduction, and those who did not receive clinical CR-BSI diagnosis and adopted the thought of colonization (n=195).

Determining the Risk Factors:

The patient-associated factors (age, comorbid diseases, use of TPN, neutropenia, malignancies, organ failures, rheumatic diseases, transplantations, traumas) and ICU/CVC-associated factors (length of hospital stay, catheter type) were identified as possible risk factors. Our patients were followed with active surveillance methods based on clinical observation and laboratory data.

Microbiological Diagnosis:

We monitored the catheter insertion site and its surroundings in terms of signs of local infection during the time the catheter remained implemented. The semiquantitative culture was applied with roll on plate method. In addition, we simultaneously took quantitative blood culture samples from one end of the catheter and a peripheral vein. We determined the duration of time in which we detected positivity in the qualitative blood samples that we simultaneously obtained from the catheter lumen and peripheral vein. To assess the bacteria in the catheter lumen, we applied culture sampling following catheter sonication; these samples were incubated at 35°C for 48-72 hours and then their microorganism reproduction was recorded as "colony-forming unit" (cfu). Samples with 10^3 cfu bacteria per millilitre are labelled as infected catheter; in these samples, bacteremia was considered to be catheter induced. Blood cultures were studied on a BACTEC 9240 (Becton Dickinson, USA) fully automated blood culture system. The active antibiotic resistance was performed by disk diffusion method (Oxoid/UK).

Statistical Analysis:

The obtained data were statistically analysed by using SPSS (Ver-16.0, SPSS Inc., USA) software. Parametric test assumptions were studied by "Student's t-test" while the difference between the two matching samples were analysed by using "variance analysis." In cases when the parametric test assumptions failed, we applied "Mann-Whitney U," "Wilcoxon signed rank "and" Kruskall Wallis" tests. In order to determine the differences in the analyses, we employed a significance level of 95% (or α=0,05 as the margin of error).

RESULTS

During the course of our study, 105 patients in the study group developed 121 BCI attacks. 68 of these episodes were defined as "primary bacteremia." In addition to the clinical findings, 18 patients with active breeding of >15cfu/ml in their semiquantitative culture of the catheter tips and with microorganisms having the identical antibiotic resistance patterns in their central venous catheters, blood cultures, and catheter tips were identified as CR-BSI cases.

The mean duration in which the patients remained implemented with central venous catheters was 15,19 ± 5,977 days. In the 18 CR-BSI patients, according to the positivity of the blood samples simultaneously taken from CVC and a peripheral vein, the sensitivity of time factor was 88,8%, while the specificity of time factor was 93,0%. The episode rate in 18 patients who developed CR-BSI was 20,9%.

The parameters which were found with statistically significant in the development of CR-BSI episodes are presented in Table 1.

The following parameters were not found to be statistically significant (p>0.05) in the development of CR-BSI episodes: TPN use, advanced age, gender, CVE history, presence of a neurological disease or sequels, presence of COPD, neutropenia, hypertension, the presence of CVC-related complications, previous CVC insertion story, differences in anatomical regions where CVC was inserted, medical units that fitted CVC and whether these units implemented CVC under elective or emergency conditions, ICU admission history, diabetes (monitored), chronic liver disease, coronary artery disease or other heart diseases, and steroid use.

We detected gram-negative bacteria reproduction in 5 patients and gram-positive bacteria reproduction in 8 patients in the culture samples. The remaining five patients had reproductions of mixed pathogens, including gram positive and negative factors. The factors in reproduction and their sensitivities are shown in Table 2 in relation to the patients.

Table 1. The risk fcators that were found to be statistically significant for CR-BSI development in the 18 patients.

Risk Factor	Variable	P (<0.005)
Hyperglisemia (present)	12 (%66.6)	0.002
Hypoalbuminemia (present)	12 (%66.6)	0.026
Urinary Catheherisation Duration(days)	23.56±12.645	0.001
CVC imsertion time (hospitalization day)	4,06 ± 9,459	0.0011
The amount of time CVC remained inserted (days)	13,11 ± 4,391	0.0001
Multi-purpose CVC usage	13 (%72.2)	0.002
ICU stay (days)	27,17 ± 17,896	0.001

Table 2. Antibiotic susceptivity of the factors that simultaneously developed in the catheters and bloood samples of CR-BSI patients.

Patient No	Unit	Factor	Antibiogram Susceptivity Result
1	CVS ICU	*1. E. faecalis* *2. CNS* *3.C. albicans*	1. Genta **R**, Ampicillin, Streptomycin **S** 2. Methicillin **R** 3. Fluconazole **S**
2	CS ICU	*1. A. baumannii* *2. E. Cloacae*	1. **S:** Colistin, TMP, Tigecycline 2. **S:** Amikacin, Cipro, Cephotaxime, Cefepime, Genta, Imipenem, Levofloxacin, Sef/sub, TMP, Pip/tazo
3	R 1	*Difteroid basilli*	Susceptibility not examined.
4	R 2	*1. A. baumannii* *2. Acinetobacter spp.*	1. **S:** Colistin 2. **S:** Colistin, TMP, Tigecycline
5	R 2	*P. aeruginosae*	**S:** Amikacin, AZT, Ceftazidime, Cipro, Genta, Imipenem, Levo, Meropenem, Sef/sub, TMP, Pip/tazo
6	R 1	*CNS*	Methicillin **R**
7	R 2	*A. baumannii*	**S:** Amikacin, Colistin, Sef/sub
8	R 1	*CNS*	Metisillin **R**
9	R 2	*1. P.aeruginosae* *2. E.cloacae*	1. **S:** Amikacin, AZT, Ceftazidime, Cipro, Genta, Imipenem, Levofloxacin, Meropenem, Sef/sub, TMP, Pip/tazo 2. **S:** Amikacin, Cipro, Cefepime, Genta, Imipenem, Levo, TMP
10	R 2	*K. pneumoniae*	**S:** Amikacin, Cephotaxime, Cefepime, Cefoxitin, Cipro, Genta, Imipenem, SAM, Sef/sub, TMP, Pip/tazo
11	CVS ICU	*S. aureus*	Methicillin **S**
12	R 1	*CNS*	Methicillin **R**
13	R 1	*CNS*	Methicillin **R**
14	R 2	*A. baumannii*	**S:** Ceftazidime, Cipro, Colistin, Genta, Imipenem, Meropenem
15	DICU	*CNS*	Methicillin **R**
16	R 2	*1. S. epidermidis* *2. A. baumannii*	1.Methicillin **R** 2. Colistin **S:**
17	R 2	*Aeromonas veronii*	**S:** Ceftazidime, Cipro, Cefepime, Genta, Levo, TMP, Pip/tazo
18	CVS ICU	*S. warnerii*	Methicillin **R**

Abbreviations: S: susceptible; R: resistant; Genta: gentamicin; TMP: trimetoprim-sulfametoxazol, Cypro: ciprofloxacin, AZT: aztreonam, sef/sub: cefoperazone-sulbactam, pip/tazo: piperacillin-tazobactam, SAM: ampicillin-sulbactam.

DISCUSSION

CVCs are the most common cause of nosocomial infections; as of today, they are the third most common nosocomial infection types with an incidence rate of 14% (7, 8). CVCs are reported to constitute 40% of all bacteraemia, and 50% of nosocomial bacteremia (5). When diagnosed and treated in early stages with protective measures taken, these infections are clinical situations that can reduce morbidity and mortality rates (9, 10).

The culture positivity rate in CVCs ranges from 6 to 24%. In a multicenter study conducted in France, the positivity rate of blood cultures taken from the catheter was found to be 24%; according to this study, this rate varies between 5% and 47% among other centres included in the research (11). In this study, we have examined the episodes of 18 CR-BSI patients in the intensive care unit of an eminent research and training university hospital for a one-year period. Throughout the study period, the frequency of CR-BSI episodes among 86 primary bacteraemia cases was 20.9%. Studies show that incidence rate of CR-BSI attacks varies from 2% to 10% among other primary bacteraemia cases. However, reports also indicate that this rate increases up to even %40 in high-risk patient groups such as patients with advanced ages, burns, and organ transplantation and trauma histories (12).

Today, hospitals recommend that inserted catheters should be used up to 15-20 days unless patients develop complications. In this study, the patients in the study group remained with inserted catheters for 15.19 ± 5.977 days. Our statistical analysis has shown that there is a risk factor for CR-BSI when patients remain with inserted catheters for a long time (Table 1). Other risk factors for the development of CR-BSI in our study were found to be long ICU stay, long durations of time urinary catheters remain implemented, late CVC insertion, and long periods of time CVCs remain inserted. The statistically significant relationship between the total length of time catheter remains inserted and CR-BSI suggests that the proposed rules for asepsis may not have been followed during the time catheter remains inserted though the implementation of the catheter may have complied with the procedures for asepsis and that there might have been deficiencies in terms of the catheter insertion conditions. We believe that late insertion of the catheter as a risk factor indicates that this has caused an increase in the length of intensive care unit stay; this may have been caused by contamination during catheter insertion resulting in an increase in skin contamination rates of pathogens.

Öncü et al.'s 12-monthprospective study (13) has reported the CR-BSI rate to be 16,7% in a university hospital. They have also suggested that duration of catheterisation and catheter insertion area are among significant risk factors for the development of CR-BSI. The same study also argues that there are significant differences between catheters inserted into the jugular vein and catheters inserted in the subclavian region in terms of their effect on CR-BSI development (22,7% and 11,9%, respectively).

In our study, we detected metabolic disorders in 121 (40.3%) of our patients. Hyperglycaemia was the most common metabolic disorder in the ICU patients included in our study. The fact that hyperglycaemia has a negative effect on neutrophil functions, phagocytosis, and cytokine activity while it also provokes the growth of microorganisms may be regarded as the reason behind this result. Recent studies have shown that aggressive treatments to keep blood glucose levels at 80-110 mg/dl do not actually have any positive effects on long-term mortality though such approaches are reported to have reduced the risk of bacteremia development (14).

In our study, we have determined that presence of hypoalbuminemia is effective on the formation of CR-BSI attacks; in this respect, our study affirms the results of Kritchevsky et al.'s extensive research (15). A 2006 study conducted in Zonguldak Karaelmas University Training, Research, and Practice Hospital to examine bacteremia/BSI risk factors has found TPN use as an important risk factor (16). In this study, microorganisms that were found to be active are as follows (in order of their frequency): CNS, S. aureus, Enterococcus spp., Candida spp., Klebsiella spp., and P. aeruginosa, respectively. CNS was the responsible factor behind CR-BSI in 60% of TPN patients who remained with inserted CVCs for a long time (17).

Studying our 18 CR-BSI patients in terms of the distribution of active factors, we found out that CNS bacteria were the most common pathogens (27.8%). We believe that this high frequency rate is a result of patients' skin flora. Considering the sensitivity of these factors, we discovered that they were all methicillin-resistant, which is an important evidence that makes us think that these bacteria are nosocomial. While one of the two A. baumannii isolates was susceptible to all antibiotics, the other was resistant to amikacin, colistin and cefoperazone/sulbactam, ceftazidime, cefepime, quinolines, and carbapenems.Each one of the P. aeruginosa and K. pneumoniae strains were found to be sensitive to all antibiotics. Moreover, one of the isolated E. cloacae was found to be able to produce inducible beta-lactamase (Table 2).

The surveillance studies show that the most commonly produced factors in CR-BSI are CNS, S. aureus, aerobic gram-negative bacilli, and C. albicans. Although the distribution of the active factors is well known, determining antibiotic resistance patterns, especially in empirical treatment, is also important. In the treatment of CR-BSI, which can cause serious morbidity and mortality, every hospital should assess their own factor distribution and resistance rates, and, as it was the case in our study, plan the empirical therapy according to the resistance profile if the centre has high rates of resistance (13).

In conclusion, our study has put forward that some of the mistakes we have observed in CVC applications as well as uncontrolled metabolic problems constitute significant risk factors for the development of CR-BSI. We believe that bringing new regulations and corrective attempts will lead to a decline in the development of CR-BSI. Apart from reducing the incidence of CR-BSI, such studies will significantly contribute to the reduction of economic loss and infection related deaths.

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Antagonism of the Effect of Rocuronium with Sugammadex in a Patient with Myasthenia Gravis

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Abstract
Myasthenia Gravis (MG) is an autoimmune disorder which is characterized by the decrease of number, function, and capacity of ach receptors in muscle-nerve junctions. Anaesthesia is important patients with MG especially when they need muscle relaxants, which is a risky condition due to the possibility of postoperative residual neuromuscular blockage. Before the discovery of Sugammadex, colinesterase inhibitors were used to reverse the effects of non-depolarising muscle relaxants to treat MG patients. In these cases, practitioners had to deal with several side effects in MG patients. Sugammadex encapsules the steroid structured muscle relaxants and immediately reverses their effects. Therefore, anaesthesiologists started to use Sugammadex to decrease the need of postoperative residual blockage and mechanical ventilation. In this case report, we aim to share our experiences of Sugammadex use and relate readers how it eliminated the effect of rocuronium in an MG patient who underwent VATS.
Key Words: Myasthenia Gravis; Rocuronium; Sugammadex.

Myastenia Gravisli Hastada Rokuronyum Etkisinin Sugammadeks ile Antagonize Edilmesi

Özet
Myastenia Gravis (MG), kas sinir kavşağında asetilkolin reseptörlerin sayı ve fonksiyon kapasitesinin azalması ile karakterize otoimmun bir hastalıktır. Myastenia gravisli hastaların kas gevşetici kullanılması gereken durumlarda artmış postoperatif residüel nöromusküler blokaj riski nedeniyle anestezisi önem arz etmektedir. Sugammadeksin keşfinden önce non depolarizan kas gevşeticilerin etkisini geri döndürmede kullanılan kolinesteraz inhibitörleri spesifik bir antagonist olmadığı gibi aynı zamanda MG hastaların tedavisinde de kullanılmaktadır. Bu durum MG'li hastalarda istenmeyen etkilere yol açabilmektedir. Sugammadeks steroid yapılı kas gevşeticileri enkapsule ederek etkilerini hızlı bir şekilde ortadan kaldırır. Bu özelliğinden dolayı MG'li hastalarda postoperatif rezidüel blok ve mekanik ventilasyon gereksinimini azaltmak amacıyla anestezistler tarafından kullanılmaya başlanmıştır. Bu olgu sunumunda, VATS yapılan bir hastada rokuronyumun etkisinin sugammadeksle antagonize edilmesi ile ilgili deneyimimizi paylaşmayı amaçladık.
Anahtar Kelimeler: Myastenia Gravis; Rokuronyum; Sugammadeks.

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease affecting neuromuscular transmission. Ophthalmoplegia, ptosis, and muscle weakness resulting from repetitive movements characterise the disease (1). The fact that autoantibodies that develop against the acetylcholine receptors reduce the number of acetylcholine receptors brings about sensitisation against non-depolarizing muscle relaxants (NDMBAs) in varying degrees while the effect of depolarising muscle relaxation is prolonged (1). In such cases, local and regional anaesthesia is usually the first option while neuromuscular blockade is also necessary for many surgical procedures (2). If the use of neuromuscular agents is required, practitioners should apply a short or medium term non-depolarising agent titrated with neuromuscular monitoring (1). These agents should be administered by taking their risks and benefits into consideration due to the fact that cholinesterase inhibitors may cause residual blocking and cholinergic crisis (2).

A newly developed drug with its cyclodextrin structure, Sugammadex is capable of undoing neuromuscular blockade performed by steroid muscle relaxants at all levels. Sugammadex selectively encapsulates steroid muscle relaxant molecules and quickly eliminates their effect (3).

In this study, we aim to share our experiences of an MG patient who underwent video-assisted thoracoscopic surgery (VATS) during which we antagonised the effects of rocuronium by using Sugammadex.

CASE REPORT

A 48-year-old male patient (86kg) was diagnosed with myasthenia gravis following a series of tests performed 2 months ago when he presented with repetitive muscle weakness and ptosis complaints. The results of these tests also showed thymus hyperplasia. When the 2x60 mg/day pyridostigmine treatment did not help in declining the complaints, the patient was scheduled for a thymectomy surgery with VATS. The patient did not undergo any premedication before the operation. The

noninvasive arterial blood pressure, electrocardiography, and pulse oximetry was monitored. The neuromuscular block was placed in the left ulnar nerve with train-of-four (TOF) method for monitoring.

After a 2-to-3-minute preoxygenation with 100% O2, the induction of anaesthesia was achieved with 100 mcg of fentanyl and 180 mg of propofol. After the loss of eyelash reflex, the patient was ventilated with a mask. Then we performed TOF calibration, we administered 40 mg of rocuronium as the induction dose. As the TOF value dropped down to 0% 95 seconds after the rocuronium injection, the patient was intubated with a 37 F left double-lumen tube. The anaesthesia was maintained at 50% O2 - 50% air and we administered 6% desflurane controlled air ventilation and 0.5 mcg/h remifentanil infusion. After checking the location of the tube with fiberoptic bronchoscope in the left lateral position, we started one lung ventilation. During the intraoperative process, the hemodynamic data of the patient were stable and the patient did not need additional muscle relaxants. Following a 170-minute operation, we stopped the remifentanil and desflurane and put the patient in supine position. The TOF value was 60% and we started 200 mg iv sugammadex. In 60 seconds, the TOF value rose up to 93% and, after 2 minutes, the patient had spontaneous 450-500 ml breathing creating 20-25 cmH2O negative pressure along with spontaneous opening of the eyes upon which we extubated the patient. In the postoperative period, the patient spent 4 hours in the intensive care unit with stable hemodynamic data. We did not observe any residual neuromuscular blockade either. So we transferred the patient to the service floor.

DISCUSSION

Myasthenia gravis is an autoimmune disease of the neuromuscular junction characterized by development of autoantibodies (IgG) against postsynaptic acetylcholine receptors. Patients suffer from skeletal muscle weakness and fatigability as well as exacerbations and remissions. It often accompanies thymus gland abnormalities. Hyperplasia of the thymus gland is seen in more than 70% of the patients while 10%-15% of the patients have thymoma. In addition to pharmacological treatment, thymectomy is a widely applied surgical treatment option for MG patients (1).

VATS is considered to be an alternative method to minimal invasive surgery due to decreased postoperative pain, early mobilisation, and shorter hospital stay it offers. However, unlike open surgery, VATS requires one lung ventilation (OLV). Because OLV requires a double lumen endobronchial tube (DLT), a deeper muscle relaxation is needed compared to single-lumen tube application (2). However, anaesthesiologists do not prefer to use muscle relaxants in patients with MG. If using muscle relaxant is really ineluctable, practitioners should use low doses of agents with short and medium-term effects and monitor the neuromuscular cycle (1).

A great number of studies report that short-term mivacurium was safely used in MG patients after reducing the dose which ensured suitable intubation conditions as well as seamless extubation in the postoperative period in the majority of patients (4, 5). Because of plasmapheresis or pyridostigmine administration, butyrylcholinesterase activity may be decreased in myasthenic patients, which may eventually result in prolonged mivacurium connected blockade in the preoperative period.

Long-acting neuromuscular blocking drugs should be avoided in MG patients. By reducing the effect of NDMBAs like rocuronium, vecuronium, and cisatracurium by 50%, adequate muscle relaxation can be achieved in MG patients (2). Before the development of Suggamadex, cholinesterase inhibitors were the only option to fix the non-depolarizing muscle relaxant related neuromuscular block. Because these agents may be ineffective when used chronically and since they are able to induce cholinergic crisis, which is almost impossible to clinically distinguish from myasthenia crisis, they should be used with caution in myasthenic patients (1).

Several anaesthetic techniques have been used in myasthenic patients. Central nerve blocks can be preferred to peripheral nerve blocks in extremity surgery methods. For patients under general anaesthesia, this can be achieved either by total intravenous anaesthesia or inhalation anaesthetics (4-7). In such cases, practitioners usually prefer anaesthesia based on volatile agents. Since inhalation anaesthetics can provide muscle relaxation, myasthenic patients's need for additional muscle relaxants during the operation is minimised. Due to MG patients' low blood solubility, practitioners favour desflurane and sevoflurane (7). In our case, we preferred desflurane as the inhalation anesthetics and finalised the operation without the need of additional muscle relaxants. Kiran et al. (8) have shown that sevoflurane has provided adequate muscle relaxation in MG patients undergoing sternal thymectomy.

Sugammadex is able to swiftly eliminate the effect of even a steroid-based NDMBA in the first 3 minutes of application. According to the density of the block, 2 to 16 mg/kg of Sugammadex may be administered (3). The studies and case reports on the use of the drug on patients with MG have shown that 2-4 mg/kg Sugammadex helps practitioners extubate patients smoothly without the need for mechanical ventilation (2, 9, 10).

In their case report of an MG patient, Karaman et al. (11) have shown that using Sugammadex, the specific antidote of rocuronium, not only helps good intubation and surgical conditions but also eliminates the need for postoperative mechanical ventilation.

In their study on 10 patients who underwent VATS due to MG, Sungur et al. (2) have similarly reported that they have successfully antagonised the effects of rocuronium by using Sugammex. They further state that all of their

patients were extubated in the operation room without any residual neuromuscular signs in the postoperative period.

RESULTS

In MG patients, there is always the risk of an increased susceptibility to non-depolarizing muscle relaxants along with a likewise increased risk of residual blocks in postopertatif period. However, studies and case reports on patients with MG, parallel to our case, have shown that Sugammadex is successful in quickly antagonising the effects of steroid muscle relaxants while it also eliminates mechanical respiratory support requirements in the postoperative period.

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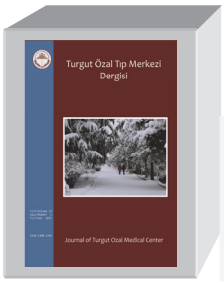

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Laparoscopic Transanal Endoscopic Microsurgery via Single-Port: A Case Report

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Abstract
Transanal endoscopic microsurgery is a minimally invasive procedure for the pathologies in the rectum. Transanal endoscopic microsurgery can be performed using a laparoscopic single port. In this study, we intended to represent our first case in which we used the singleport laparoscopic transanal endoscopic microsurgery for the excision of a rectal polyp. The single port was incorporated into the anal canal and then this port was fixed by sutures to the perianal area. The polyp was entirely resected with the help of standard and two angled laparoscopic surgical instruments. There were no postoperative complications and the patient was discharged on the first postoperative day. The histopathological examination revealed that focal high-grade dysplasia detected in the resection material surgical margins were negative. As a result, resection of rectal polyp in the anal canal by applying single-port laparoscopic surgery with the help of hand tools was found to be safe and feasible.
Key Words: Rectal Polyp; Single Port; Transanal Endoskopik Microsurgery.

Tek Port ile Laparoskopik Transanal Endoskopik Mikrocerrahi: Bir Vaka Takdimi

Özet
Transanal endoskopik mikrocerrahi, rektumda bulunan patolojiler için minimal invaziv bir girişim olup, tek portun transanal endoskopik mikrocerrahide kullanımı mümkündür. Bu çalışmada, merkezimizde ilk kez tek port transanal laparoskopik cerrahi yöntemi ile yaptığımız rektal polip eksizyonu olgusunun sunumunu amaçlandık. Tek port, anal kanala yerleştirildikten sonra perianal bölgeye sütürlerle tespit edildi. Standart ve açılı laparoskopik cerrahi aletler yardımı ile rektumdaki polip rezeksiyonu tam kat gerçekleştirildi. Operasyon sonrası komplikasyon gelişmeyen hasta postoperatif birinci günde taburcu edildi. Histopatolojik incelemede, fokal yüksek dereceli displazi tespit edilen rezeksiyon materyalinin cerrahi sınırları negatif idi. Sonuç olarak, rektal polip rezeksiyonunun, anal kanala tek port uygulanarak laparoskopik cerrahi el aletleri yardımıyla rezeksiyonunun mümkün ve güvenli olduğu görüldü.
Anahtar Kelimeler: Rektal Polip; Tek Port; Transanal Endoskopik Mikrocerrahi.

INTRODUCTION

The development of carcinoma, one of the rectal polypoid adenomas, is widely accepted to be the cause of rectal cancer (1). Transanal endoscopic microsurgery (TEM) is one of the surgical methods developed for the incision of polyps localised in the rectum (2). It was first applied by Gerhard Buess about 20 years ago; then, in a more improved form, it was first implemented by Marco Lirici in 2003 (3).

Next, with the introduction of single-port laparoscopy, transanal single-port polypectomy (TASPP) became an alternative method for the resection of rectal polyps. Single-port transanal polypectomy requires costly laparoscopic instruments and experienced operators in addition to the fact that it also takes a long period of time to learn the surgical procedures (4). The aim of this case report is to present the transanal single-portpolypectomy excision of a high-grade dysplastic polyp that developed in the rectum.

CASE REPORT

A 66-year old female patient presented in our General Surgery Outpatient Clinic with rectal bleeding and abdominal pain. We biopsied from the 1x1,5 cm polypoid lesion that the colonoscopy located on the rectum posterior wall, 10cm through the anal canal. We decided to apply surgery as the biopsy result reported the sample to be a high-grade dysplastic adenomatous polyp. The patient was positioned in the lithotomy position under general anesthesia. Three-input single port was placed in the anal canal with sutures on the perianal skin (Figure 1).

We inflated the rectum with suitable air pressure. Located 10cm from the anal canal, the polyp, about 1x1,5cm in diameter and located on the rectum posterior wall, was entirely excised with the help of a vessel sealing device and single port tools (Figure 2).

The bleeding control was achieved. The resection area was not sutured. The whole operation took about 80 minutes. We did not have any complications throughout

the operation. The patient was discharged on the first postoperative day. The patient's pathology reported the case to be one of high-grade dysplasia with clean surgical margins. The check-up in the 3rd postoperative month showed the colonoscopy to be normal and the patient did not have any fecal incontinence. After the rectal port usage, we did not observe any complications in this case despite the risk of anal sphincter dysfunction.

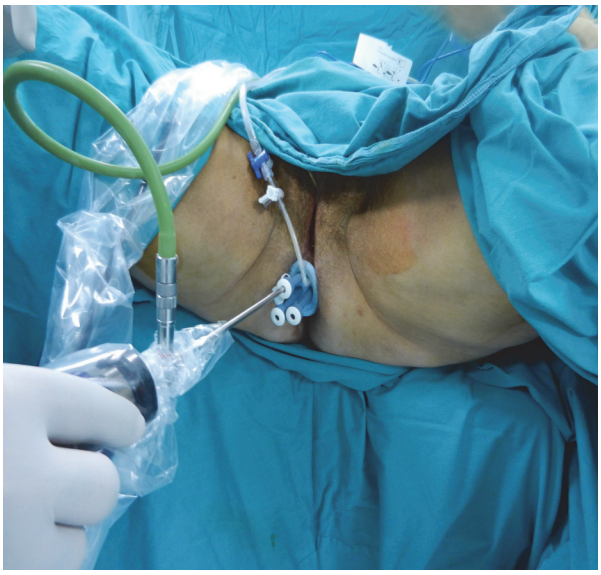

Figure 1. The application of the three-input single-port into the perianal area with sutures.

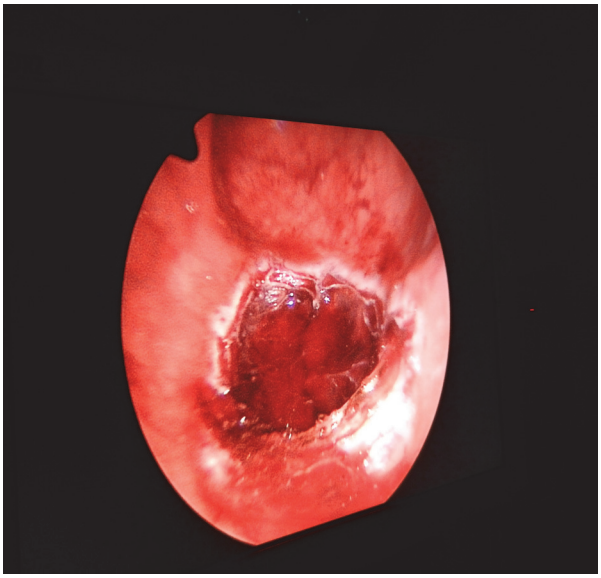

Figure 2. The view of the 1x1,5cm polyp located on the rectum posterior wall after the excision.

DISCUSSION

Transanal single-port polypectomy has proved to be a popular and effective procedure since it was developed 20 years ago. With its minimal invasive nature, easy implementation, and applicability, the method may be considered as an effective method. Low complication rates (9%) compared with local excision, safer procedures, and low recurrence rates (4-13%) are among the advantages of this application (5, 6, 7, 8). In some series, though they are few in number, it has been reported that the recurrence rates in the TEM procedures were higher than the ones in the radical surgery (2, 9, 10).

The number of post-TEM procedure complications such as rectal bleeding, suture opening, and perforation was reported to be 3-10% (11). Another complication that negatively affects the quality of life of patients is incontinence. In a series of operations conducted by Endreseth et al., incontinence rate was about 6% (10). However, we did not come across any of the reported complications like bleeding, perforation or incontinence. Except for the length of the operation, we did not observe any negative influence of the TEM procedure on the anal sphincter. In single-port transanal surgeries, the single-port may cause less damage since it is flexible.

We used standard single incision laparoscopic surgery tools (SILS) throughout our surgery. Although they are difficult to use in narrow areas of the rectum, they may still be considered advantageous since they allow the use of the vessel sealing devices while they also facilitate polyp resection. Assuming that applying sutures on the surgical resection area may cause submucosal abscess, we preferred to leave the resection area open.

Finally, it can be stated that transanal endoscopic microsurgery, which can be applied at one time, is an effective method in low-risk rectal cancer patients and resectable rectal polyp cases.

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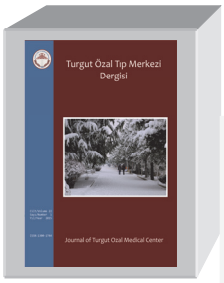

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HELLP Syndrome with Long-Lasting Severe Sepsis: A Case Report

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Abstract
Preeclampsia is a disease manifesting itself in the second half of pregnancy, and characterised by hypertension and proteinuria. It affects 5% to 7% of pregnant women all over the world making it the most common cause of maternal and fetal morbidity and mortality. HELLP syndrome (Hemolysis-Elevated Liver enzymes-Low Platelets) occurs in about 4%-20% of the preeclamptic pregnant women and it is often associated with high maternal and perinatal morbidity and mortality rates. HELLP syndrome may require monitoring in the intensive care unit because of the increased morbidity and mortality rates it brings about as a result of potential complications such as acute respiratory distress syndrome (ARDS), intracerebral hemorrhage, acute renal failure, hepatic rupture, disseminated intravascular coagulation, and septic shock. We aim to present the case story of a long-lasting but successful postoperative treatment for severe sepsis of a patient with HELLP syndrome who was monitored in our intensive care unit after a caesarean section.
Key Words: Pre-eclampsia; HELLP Syndrome; Maternal Morbidity And Mortality; Sepsis; Thrombocytopenia.

HELLP Sendromu Olan Hastada Uzun Süren Ciddi Sepsis: Bir Olgu Sunumu

Özet
Preeklampsi; hipertansiyon ve proteinuri ile karakterize, gebeliğin ikinci yarısından sonra görülen bir hastalıktır. Tüm dünyada gebelerin %5 ile %7'sini etkileyen, maternal ile fetal mortalite ve morbiditenin birinci nedenidir. HELLP sendromu (Hemolysis-Elevated Liver enzymes-Low Platelets) ise preeklamtik gebelerin yaklaşık %4-20'sinde görülen, yüksek maternal ve perinatal morbidite ve mortalite ile ilişkili bir tablodur. HELLP sendromlu hastalarda akut sıkıntılı solunum sendromu (ARDS), intraserebral kanama, akut böbrek yetersizliği (ABY), hepatik rüptür, yaygın damar içi pıhtılaşma bozukluğu (YDİPB) ve septik şok gibi komplikasyonlar maternal morbidite ve mortalite artması nedeniyle yoğun bakım ihtiyacı ortaya çıkabilmektedir. Sezeryan sonrası postoperatif dönemde yoğun bakım ünitesinde takip ettiğimiz ve uzun süren ciddi sepsis nedeniyle tedavi ettiğimiz HELLP sendromlu bir hastanın sunulması amaçlanmıştır.
Anahtar Kelimeler: Preeklampsi; HELLP Sendromu; Maternal Morbidite ve Mortalite; Sepsis; Trombositopeni.

INTRODUCTION

Characterised by hypertension, proteinuria, and manifesting itself in the second half of pregnancy, preeclampsia is the initial cause of fetal and maternal morbidity and mortality affecting 7%-5% of pregnant women in the world (1). Its pathophysiology still unknown, preeclampsia is thought to result from reduced organ perfusion and endothelial damage (2). As a serious complication of pregnancy, preeclampsia is also associated with maternal inflammatory response and increase in endothelial cell activation (3).

HELLP syndrome occurs in about 4-20% of preeclamptic pregnant women and it is associated with high maternal and perinatal morbidity and mortality. Due to complications such as ARDS, intracerebral haemorrhage, acute renal failure, hepatic rupture, and septic shock, patients with HELLP syndrome may suffer from increased maternal morbidity and mortality and, thus, may require intensive care (4).

In this paper, we aim to present the case of a patient with postoperative HELLP syndrome who was monitored in the intensive care unit due to prolonged severe sepsis.

CASE REPORT

The 33-year-old patient who was being followed due to preeclampsia had seizures in the 33rd week of her pregnancy and was brought to the emergency department. The emergency laboratory test values were as follows: Hg: 12.9g/dL; Htc: 36.3%; and leukocyte value: 16,650 uk/L. The other results, including the bilirubin values, were normal. The pregnancy was terminated with emergency caesarean section under general anesthesia. Developing postoperative metabolic acidosis, the patient was intubated and taken to the intensive care where we started mechanical ventilation. The vital signs on her admission to the postoperative intensive care unit were as follows: arterial blood pressure: 160/105mm Hg; heart rate: 125 beats/mins; oxygen saturation: 99%; and body temperature: 36 degrees C.Her APACHE score was 29 while the SOFA

score was 10. The laboratory figures on her admission to the intensive care unit admission were listed as: Hg: 8.8 g/dL; Htc: 26.4%; number of leukocytes: 22.07 UK/L; platelets: 28000mm3; PT: 14 secs; PTT: 30,2 secs; INR: 1,2; BUN: 15mg/dL; creatinine: 0.39mg/dL; AST: 2319 u/L; ALT: 1035 U/L; LDH (lactate dehydrogenase): 1153 U/L; total bilirubin: 3.57mg/dL (N=0.3 to 1.2); direct bilirubin: 0.02mg/dL (N=0.01 to 0.02); indirect bilirubin: 3.55mg/dL (N=0 to 1.1), respectively. Because the patient had anaemia, we administered 3 units of red blood cells and 2 units of thrombocyte apheresis suspension. To control hypertension, we started 5 microg/kg/min of nitroglycerin infusion. Because of the high levels of arterial blood pressure on the second day, we started esmolol infusion. Considering that the patient had anaemia, leukocytosis, thrombocytopenia, and critically high LFT (liver function tests) results, we began to consider the possibility of HELLP syndrome and re-planned the treatment (Table 1).

Because the patient had leukocytosis, her PaCO2 was 29.7 mm/Hg, and heart rate was 105-120 beats/min, we decided that the patient had "Systemic inflammatory response syndrome" (SIRS) and started the support treatment without delay. We started fluid resuscitation, oxygen support, nutritional support, and empiric antibiotics (ceftriaxone 2x1g/day). In order to find the underlying causes, we collected culture for infection but did not observe any multiplication in the samples. The LFTs began to decline on the second day of hospitalisation as platelets increased to normal values. The LFT enzymes eventually reached the normal values on the fourth day. On the second day of her admission, the patient's BUN figure was 37mg/dL, creatinine was 2.41mg/dl, WBC values were 30.89 UK/L, and lactate value was 3.4 mM/L. Considering a potential ARF, we started to provide fluid therapy and to follow urine output. As BUN/creatinine reached 143/7.3 IU/L on the sixth day, we applied renal replacement therapy (hemofiltration). All biochemical values of the patient during her hospitalisation are shown in Table 1. On the 8th day the patient's hospitalisation, leukocytosis and procalcitonine were 4.1 ng/ml upon which we decided to take cultures to investigate the focus of infection. During her hospital stay, the patient developed three serious gram (-) sepsis and septic shocks. In the first episode of sepsis (on the 8th day), we detected Klebsiella pneumonia reproduction in her blood and urine cultures. The sensitivity profile was identified to have imipenem, meropenem, amikacin, colistin, and trimethoprim-sulfometoksozol so we started to give meropenem 3x500 mg. In the second episode of sepsis (on the 13th day), we detected Pseudomonas Aeruginosa reproduction. In accordance the patient's antibiotic susceptibility profile (sensitive to colistin only), we applied colistin. Despite adequate antibiotic treatment, we identified Acinetobacter Baumannii reproduction in her urine culture samples on the 18th day of her hospitalisation. This was probably due to hypotension (MAP <65 mmHg), tachycardia (132 beats/min), and leukocytosis (21,000 uk/L) the patient developed throughout. Parallel to the sensitivity profile of the patient, we added 2x50 mg of tigecycline to the already continuing colistin treatment. Due to the ongoing hypotension regardless of the appropriate fluid replacement, and keeping the possibility of a septic shock in mind, we applied vasopressor therapy that would keep MAP at around 65-90 mmHg (dopamine 5-20 ug/kg/min; norepinephrine 1-30 g/min), CVP 8-14 cmH2O, and 250 to 1000 ml of crystalloid solution in every 15-30 minutes to keep urinary output at >0.5 ml/kg/min. We also started oxygenation maintaining SaO2>92% value and blood transfusion keeping hematocrit >30% figure. Nutrition is very essential in patients with sepsis since they are in a catabolic process; to this end, we administered a daily amount of 25-30 kcal/kg (ideal body weight) of calorie support. On the 30th day of hospitalisation, the patient was discharged having entirely declined parameters infection and hemodynamic stability.

At the end, we explained the patient that the details of her case would be published in a scientific article and obtained her consent.

Table1. The biochemical parametres of the patient during hospital stay.

	Hg ($gr\ dL^{-1}$)	Leucocyte ($uK\ L^{-1}$)	Thrombocyte (mm^3)	AST ($IU.\ L^{-1}$)	ALT ($IU.\ L^{-1}$)	LDH ($IU.\ L^{-1}$)	CRP ($mg\ ml^{-1}$)	Procalcitonin ($ng\ ml^{-1}$)
Day 1	8,8	22,07	28000	2319	1035	1153	140	25
Day 2	13,1	19,53	118000	1189	446	850	155	18
Day 5	9,8	21,00	76000	63	85	550	168	15
Day 8	9,2	20,46	172000	65	54	250	167	4,61
Day 13	8,8	17,20	585000	49	28		85	4,83
Day 18	10,7	21,00	212000	59	47		194	4,86
Day 30	9,2	14,68	172000	56	40		45	0,74

AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; CRP: C-reactive proteins

Endothelial cell injury and inflammation are responsible for the pathophysiology of preeclampsia. HELLP syndrome, which is characterised by microangiopathic hemolytic anemia, hepatic dysfunction, and thrombocytopenia, is a serious complication of pregnancy that can lead to maternal and fetal mortality by affecting many systems.

Microangiopathic hemolysis, one of the major features of the HELLP syndrome, is related to hemolytic anemia (5). Hemolysis is followed by the destruction of red blood cells, which, in turn, leads to an increase of serum LDH levels and a decrease in the hemoglobin concentration. Therefore, hemolysis can be diagnosed by considering high LDH and indirect bilirubin values (6). In our case,hemolysis was present since the patient's

admission to the intensive care unit; the presence of anaemia, and high LDH and indirect bilirubin values support our argument.

DISCUSSION

Early diagnosis and effective treatment are required to achieve the best outcome for both mother and baby. In HELLP syndrome, the termination of birth should be the first step of definitive treatment (6). Some authors state that some time should be spared for supportive treatment but it is very risky to choose this option and requires the consent of both the practitioner and the family (7). As in the case presented here, the preferred method to terminate pregnancy should be cesarean section. After the removal of the placenta, symptoms tend to regress slowly. Generally, even after 48 hours after the birth, laboratory values may still show deterioration though results are expected to improve in the next 48 hours. In our case, the clinical picture did not improve within the first 96 hours. During this period, the patient had severe fever, leukocytosis, and high procalcitonin values though we did not observe reproduction in her culture results. However, after the eight day, having determined the foci of infection, we were able to concentrate on the long-lasting severe sepsis and sepsis-related organ failures.

There is controversy regarding the treatment of HELLP syndrome. Practitioners have tried several different approaches most of which were therapeutic solutions such as dexamethasone, several blood products, and magnesium sulfate (8).

Endothelial damage, vasospasm, platelet activation, and reduction of EDRF emissions (endothelium-derived relaxing factor) are among the pathogenesis of HELLP syndrome and acute renal failure. ARF is a serious clinical condition characterized by sudden decrease in renal function and azotemia. It rarely accompanies preeclampsia and eclampsia pathologies with an incidence and mortality rate of 7,3% and 13%, respectively (9). Our patient had ARF and we had to perform continuous renal replacement therapy (hemofiltration) in order to secure the kidneys and to eliminate the complications connected to renal failure.

While procalcitonin is a specific and sensitive marker of systemic bacterial infections in our today, it also shows the severity and presence of preeclampsia in patients without infections (10). In our case, the high levels of procalcitonin since her hospitalisation explain the long period of time our patient had to spend in the intensive care unit and, thus, the severity of the case. Despite the fact that the relationship mechanisms between preeclampsia and some types of infections, especially urinary tract infections, are not clearly defined, such relationships are now known to exist for sure. Infection is not usually regarded as the direct cause of preeclampsia but the presence of a strong relationship between preeclampsia in sepsis and inflammatory processes are distinctly defined (11). As the focus of infection, we have similarly detected repeated Klebsiella pneumonia and Acinetobacter baumannii reproduction in the urine and blood cultures and Pseudomonas aeruginosa reproduction in sputum culture. Many studies show that E.coli and Klebsiella pneumonia are the most frequent factors for urinary tract infections in pregnant women (12).

Chronic hypertension and pre-eclampsia are high risk assets in maternal sepsis. Chronic hypertension has already been determined as risk factor for severe sepsis progression independent of preeclampsia. This is because, compared to normotensive pregnant women, patients with chronic hypertension are more likely to develop critical hypo-perfusion at high blood pressures, which can ultimately trigger severe sepsis (11).

CONCLUSION

The most common obstetric problems in intensive care units are eclampsia and HELLP syndrome and both has high maternal and fetal morbidity and mortality rates. Especially patients with HELLP syndrome with a history of convulsion should be closely monitored in intensive care units after cesarean section since clinical conditions may worsen in such patients; in this way, reducing rate of complications will also reduce morbidity and mortality in due course. To improve survival in sepsis during pregnancy and the postpartum period, early diagnosis, keeping the infection source under control, and targeted therapy are all very essential. To achieve this, practitioners should apply adequate fluid therapy, appropriate antibiotics, and central hemodynamic monitoring.

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Fatal Herpes Simplex Virus Infection in Darier's Disease

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Abstract
Darier disease is an autosomal dominant disorder characterized by small, hyperkeratotic papules localised on the trunk especially in the seborrheic regions. Vegetation and infections in the intertriginous areas are common in this disease while treatment is not usually satisfying. While the urea or lactic acid containing moisturizers, topical steroids, and topical retinoids are used in mild cases, systemic retinoids are preferred in severe cases. Kaposi varicelliform eruption caused by herpes simplex virus is rare but a well-defined complication. Clinical findings of this viral infection, which are usually uncommon, may delay diagnosis and treatment. Here, we report the case of a patient with Darier's disease treated with corticosteroids who later developed fatal herpes simplex virus infection despite the aciclovir therapy.
Key Words: Darier's Disease; Herpes Simplex Infection; Fatal Herpes Simplex Infection.

Darier Hastalığında Fatal Herpes Simpleks Virüs Enfeksiyonu

Özet
Darier Hastalığı, otozomal dominant kalıtımla geçen, klinik olarak gövdede ve özellikle seboreik alanlarda lokalize, küçük, hiperkeratotik papüllerle karakterize bir hastalıktır. Hastalıkta intertriginöz alanlarda vejetasyon ve infeksiyonlar sıktır. Tedavisi genellikle tatmin edici değildir. Hafif olgularda üre veya laktik asit içeren nemlendiriciler, topikal steroidler, topikal retinoidler kullanılırken, şiddetli olgularda sistemik retinoidler tercih edilir. Herpes simpleks virüsünün neden olduğu Kaposinin variselliform erüpsiyonu hastalığın nadir görülen fakat iyi tanımlanmış bir komplikasyonudur. Bu viral enfeksiyonun alışılmışın dışındaki klinik bulguları, sıklıkla tanıda ve tedavinin verilmesinde gecikmelere neden olabilir. Burada kortikosteroid tedavisi alan bir Darier hastasında takipleri esnasında gelişen ve asiklovir tedavisine rağmen fatal seyreden, herpes simpleks virüs enfeksiyonu sunulmaktadır.
Anahtar Kelimeler: Darier Hastalığı; Herpes Simpleks Enfeksiyonu; Fatal Herpes Simpleks Enfeksiyonu.

INTRODUCTION

Also known as keratosis follicularis or Darier-White disease, Darier's disease is an inherited disease characterised by keratinisation disorders with skin, nails, and mucous membrane involvement (1). Clinically, it manifests itself especially on the seborrheic areas of the skin like the forehead, scalp, nasolabial and retroauricular folds, chest, and back in skin colour or as yellow-brown, oily, wart-like papules. Changes in the nails provide important clues in the diagnosis. Longitudinal white and red lines, longitudinal ridges and grooves on the nails along with subungual hyperkeratosis are common signs practitioners often come across. The most pathognomonic indication is V-shaped grooves on the free edge of the nails. In addition to that, kaposi varicelliform eruption (KVE) caused by herpes simplex virus is a rare but well-recognized complication (2-4).

The unusual clinical manifestations of this viral infection cause delays in the diagnosis and treatment processes (2). This study presents a fatal case of herpes simplex virus infection in a Darier's disease patient taking corticosteroid therapy.

CASE REPORT

A 55-year-old female patient, who was also a Darier's disease patient for 30 years with a history of routine follow-ups, was admitted to our clinic with extensive lesions all over the body. The dermatological examination showed expansive erythematous, hyperkeratotic, and some of them verrucous, papules on the face, trunk, and extremities as well as eroded and extensively macerated plaques under the abdomen and around the groin. There were brown longitudinal ridges on the fingernails (Figures 1, 2, and 3).

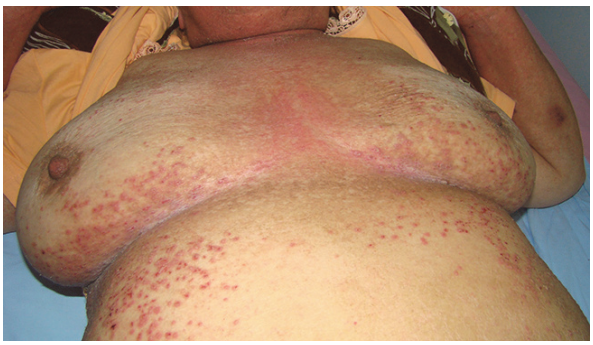

Figure 1. Lesions on the trunk

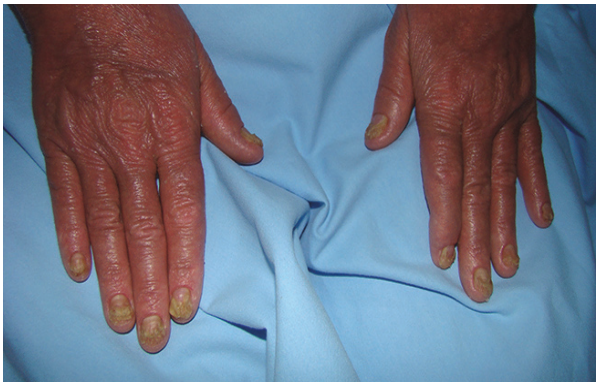

Figure 2. Lesions on the nails

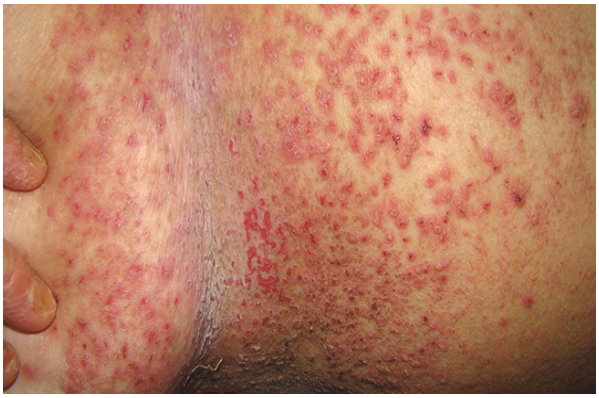

Figure 3. Lesions beneath the breasts.

The patient had been using 25 mg acitretin for the last 6 months. We learnt that she had not been on any other drugs. The patient reported that she had been given triamcinolone acetonide bulbs twice in the last two months due to the increase in her complaints although she added that the treatment did not work. The biopsy obtained from the pustular area on the back of the hand showed hyperkeratosis in the epidermis and dyskeratotic cells undergoing suprabasal decomposition. The results were consistent with Darier's disease. The routine laboratory tests did not show any further issues.

Upon observing widespread eczematous skin lesions, we started a systemic methylprednisolone 60 mg/day treatment. The samples obtained from the sharp-edged plaques with activation on the edges and the native preparation obtained from the tongue were considered positive, which urged us to start systemic and topical antifungal medication. In the follow-up sessions, we observed that the patient developed umbilicated vesicular lesions that could only be measured in millimetres. Apart from this, the Tzanck test was also positive. Therefore, we urgently applied 3x250 systemic acyclovir parenterally.The PCR results of the samples from the vesicular lesions on the trunk showed that HSV-1 was positive. The patient developed respiratory distress thus we started antibiotic treatment (imipenem + cilastatin 4x500mg, teicoplanin 1x400mg). Despite all the treatments we applied, the patient developed systemic dissemination and we lost the patient due to acute respiratory distress syndrome.

DISCUSSION

Darier-White disease is an autosomal dominant inherited disease that is characterised by keratinisation changes in the skin and mucous membranes only. Especially hairline, temples, ears, and hairy scalp on the face and seborrheic areas like the chest, back, and flexures disclose skin coloured follicular or parafollicular, dirty yellow, reddish, brown hard papules which eventually turn to yellowish-brown extensive squams. Vegetation and infections are common around the intertriginous areas (5). In our case, too, the patient had superficial fungal infection on the intertriginous areas. Herpes simplex skin infections tend to be more common in Darier's disease (3, 4). Herpes simplex infections are generally self-limiting infections. However it may lead to severe muco-cutaneous tables, systemic involvement, and fatal results in immunocompromised patients (4, 7, 8). In our case, we observed lesions while applying the systemic steroid therapy.

Disseminated zoster HIV infection gives way to cellular immune system damages like hematopoietic stem cell and solid organ transplantation (3, 9).

Herpes simplex infections in Darier's diseases is very rare. Nikkels A.F. et al.'s Darier's patient on corticosteroids who developed fatal herpes simplex infection is one of the few reports in the literature (4).

We think that our case, in which the patient developed fatal herpes simplex infection while receiving steroid therapy, is worth sharing due to its rarity.

This case report has been presented as a poster study at 23rd National Dermatalogy Congress.

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A Case of a Difficult Airway Control during Glottic Tumor Biopsy

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Abstract
Glottic tumors might cause severe airway problems due to their location. Manipulations with endotracheal intubation may increase the severity of airway problems. This case reports presents our experience with a patient who was admitted with acute disphonia and respiratory stress, diagnosed with laryngeal tumor following CT, and underwent biopsy under general anesthesia. In the light of similar cases in the literature, our report aims to present airway management of this patient who had to go through difficult ventilation and intubation during the anesthesia induction due to a glottic mass.
Key Words: Glottic Mass; Difficult Ventilation; Tracheostomy.

Glottik Kitle Direk Biyopsisi Sırasında Gelişen Zor Hava Yolu Olgusu

Özet
Glottik yerleşimli tümörler, yerleşim yerine bağlı olarak ciddi hava yolu sorunlarına yol açabilmektedir. Endotrakeal entübasyon sırasındaki manipülasyonlar, hava yolu sorunlarını daha da arttırabilir. Larenkste kitle nedeniyle ses kısıklığı ve solunum sıkıntısı hastanemize başvuran hastaya glottik kitle biyopsisi nedeniyle genel anestezi uygulandı. Bu olgu sunumunda glottik yerleşimli kitlesi olan hastanın anestezi indüksiyonunda karşılaştığımız zor ventilasyon ve zor entübasyon sonrası başarı ile sonlandırılan hava yolu kontrolünü literatür eşliğinde sunmayı amaçladık.
Anahtar Kelimeler: Glottik Kitle; Zor Ventilasyon; Trakeostomi.

INTRODUCTION

Depending on size and location, masses in the hypopharynx can cause severe airway problems (1, 2). Patients who are not yet diagnosed with mass in the hypopharynx may present at the ER with progressive respiratory distress and cyanosis complaints. Without quick and effective intervention, such patients can develop airway related cardiovascular dysfunction, hypoxia, brain damage and even lose their lives (3). Anaesthesia may be required for those patients who present with upper airway obstruction symptoms throughout the diagnosis of the case and possible surgical intervention. Practitioners are advised to commence anaesthesia by taking the necessary precautions against a possible airway challenge in such applications (4). In our report, we aim to present our experience of a successfully applied anaesthesia for airway control in a diagnosis and treatment targeted direct biopsy case for a glottic located mass despite the difficult ventilation and intubation that preceded the process.

CASE REPORT

A 44-year-old male patient, who had a 30 years/30-a-day smoking history no known systemic diseases, was admitted to our hospital with hoarseness. The indirect laryngoscopy showed that the right vocal cord had motion with adequate rima glottis opening and that the left vocal cord had paralysis. A biopsy under anaesthesia with direct laryngoscopy was planned for the patient. The preoperative assessment for the anaesthesia showed normal physical examination results and laboratory values. The patient was taken to the operating room where we performed ECG, measured the heart rate (HR), applied arterial oxygen saturation (SpO2), and checked non-invasive arterial blood pressure (ABP). HR was 90 beats/min, ABP was 130/80 mmHg, and SpO2 was measured 97%, respectively. The patient's Mallampati score was Class I. The head and neck examination was normal. However, assuming that the ventilation and intubation after the anaesthesia induction might prove to be difficult due to the mass located on the left cord vocal, we made the necessary preparations. We kept a fiberoptic bronchoscopy set, a stylet, a laryngeal mask, flat blade, a jet ventilation system, and an emergency tracheostomy kit ready to use in the operation room. We got the written consent from the patient and his relatives for the anaesthesia and surgical procedures after informing them about the anaesthesia method and the planned surgical procedures. We intravenously applied propofol (2 mg/kg) and fentanyl (1 mcg/kg) for the induction of anaesthesia. After an unproblematic ventilation, we applied rocuronium bromide (0.5 mg/kg) as muscle relaxant. After the patient developed resistance in the first minute of the ventilation, we decided to perform emergency intubation. The results of the laryngoscopy

we performed was assessed as Grade I according to Cormack and Lahen classification. It was observed that the solid mass completely obstructed the subglottic stenosis. We tried the endotracheal tubes (ETT) numbers 6, 5.5, and 5, respectively, for the intubation. But the ETT failed to reach the subglottic narrowing. Once the ventilation failed, the patient developed rapid desaturation and we decided to open an emergency tracheostomy without delay. With stable hemodynamic findings after the tracheostomy, we continued the surgery. As observed in the direct laryngoscopy, we found a mass, possibly emerging from the left band and anterior commissure, impacting the glottic narrowing. We applied a total excision to the mass that almost totally obstructed the opening (Figures 1-2). The patient was transferred to the intensive care unit after the operation.

Figure 1. The mass that almost totally obstructs the glottic narrowing as observed in laryngoscopy.

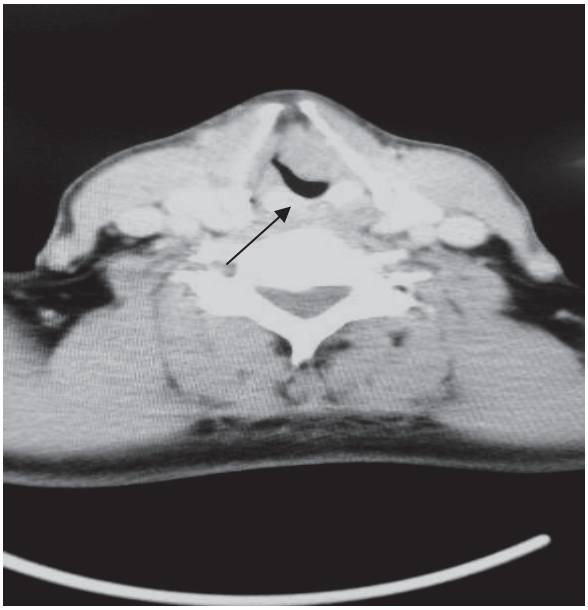

Figure 2. The CT image of the mass that blocks the larynx passage.

DISCUSSION

The application of anaesthesia is especially important in all surgical procedures related to airway. The administration of anaesthesia in surgery of glottic tumours may accompany serious issues such as strenuous intubation and ventilation due to narrowed airway, difficulties in managing airway control during direct laryngoscopy and rigid bronchoscopy, and problems in maintaining airway control during surgery. In such cases, preparations for alternative methods of airway control should be planned prior to surgery and necessary probes should be made ready in the operation room. As it was the case in our patient, the airway control after the induction of anaesthesia may fail with smaller intubation tubes in glottic tumours while it is also possible for intubation and ventilation to fall short as ETTs do not reach out because of the mass that almost entirely blocks the glottic opening. In our case, we tried the endotracheal intubation three times. Failing that, we decided to apply emergency tracheostomy believing that further applications might cause trauma in the tumour tissue, bleeding, rupture of the tumoral mass, and eventually obstruction of small airways as the severed parts may move to the lower segments of trachea. It should be noted that mask ventilation and endotracheal intubation can be difficult in these patients after the implementation of the muscle relaxant agents. In case of a possible obstructed airway, a fiberoptic bronchoscopy set, a stylet, a flat blade, a laryngeal mask, a jet ventilation system, and an emergency tracheostomy kit should be available in the operation room (5). In our case, because the patient rapidly developed desaturation, we decided to apply tracheostomy without trying other methods to save time. In such cases, practitioners should make a preliminary assessment by maintaining spontaneous breathing with supplemental oxygen before the application of muscle relaxant (5).

The fundamental task of an anaesthesiologist is to ensure airway safety and to make necessary preoperative preparations by planning alternative airway control methods in surgeries for diagnosis and treatment. As it was the case in our patient, practitioners should consider the possibility that masses may totally block the airway after the application of muscle relaxants in cases where masses largely obstruct the tracheal lumen. It should also be kept in mind that practitioners may choose to administer intubation with fiberoptic bronchoscope or perform tracheostomy to ensure airway control maintaining spontaneous breathing under sedation when laryngoscopy intubation is not be feasible.

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Spontaneous Chylothorax (A Case Report)

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Abstract

Chylothorax is caused by the distruption or obstruction of the thoracic duct or its tributaries that result in leakage of chyle into the pleural space. A 3.5-year-old male patient without significant past medical history was admitted to the outpatient clinic of our hospital with persistent coughing. The initial chest radiograph demonstrated consolidation and effusion in the left lung upon which we performed thoracentesis. The pleural fluid had milk-white color. The biochemical analysis showed that its density was 1015 with pH: 7, glucose: 168 mg/dl, triglyceride: 2101 mg/dl, and WBC: 590/mm^3. We started the treatment by offering a low-fat diet and somatostatin 3 µgr/kg/h. The chest tube was removed on the 25th day after the cessation of chylous pleural fluid from the tube in addition to the improvement that was visible on the chest radiograph; the patient was discharged. We would like to emphasize that chylothorax may occur very rarely but spontaneously and the use of somatostatin therapy may reduce the need for surgical intervention.

Key Words: Spontaneous Chylothorax; Somatostatin; Chest Tube.

Spontan Şilotoraks (Bir Olgu Sunumu)

Özet

Şilotoraks, duktus torasikus ya da dallarının bozulması ya da tıkanıklığına bağlı olarak plevral aralığa şilöz sıvının sızmasıdır. Öncesinde herhangi bir yakınması bulunmayan 3,5 yaşında erkek hasta, öksürük ve hırıltılı solunum şikayetleriyle başvurdu. Akciğer grafisinde sol akciğerde konsolidasyon ile birlikte plevral efüzyon saptandı. Kapalı sualtı drenaja alınan hastanın efüzyon sıvısının görünümü süt beyaz renkte, pH 7, dansite 1015, trigliserit 2101 mg/dl, glikoz 168 mg/dl, lökosit 590 mm^3 bulundu. Plevral efüzyon sıvısı kültüründe üreme olmadı. Bu bulgularla hastaya şilotoraks tanısı konuldu. Yağdan fakir diyetle birlikte somatostatin 3 µgr/kg/saat başlandı. Somatostatin tedavisine 2 hafta devam edilen hasta 25. günde toraks tüpü çıkarılarak taburcu edildi. Şilotoraksın çok nadiren de olsa spontan gerçekleşebileceği, tedavide somatostatin kullanımının cerrahi müdahale ihtiyacını azaltabileceği vurgulandı.

Anahtar Kelimeler: Spontan Şilotoraks; Somatostatin; Göğüs Tüpü.

INTRODUCTION

Chylothorax is defined as the accumulation of lymphatic fluid in the pleural cavity due to damaged ductus thoracicus. It is one of the rare causes of pleural effusion in childhood. It is also often seen as a complication in children who undergo cardio-thoracic surgery though it may also rarely follow blunt chest trauma or sudden hyperextension of the spine (1, 2).

This study presents the case of a 3,5-year-old boy who developed spontaneous chylothorax despite its unknown etiology while putting emphasis on the effectiveness of somatostatin in the patient's treatment.

CASE REPORT

A 3,5-year-old male patient presented with coughing and wheezing that had been going on for the last few days before which he did not have any other symptoms except for constipation. The physical examination revealed the following: body temperature: 37.1°C; pulse: 110 beats per minute; respiratory rate: 32 per minute; O_2 saturation: 92%; and blood pressure: 100/70 mmHg. The patient did not have any dysmorphic features and he had a medium general condition. While listening to the lungs for dyspnea and tachypnea, the respiratory sounds in the left lung decreased. As the examination of the left lung showed consolidation, the ultrasound examination of the thorax revealed an 8 cm-thick pleural effusion on the left (Figure 1).

The laboratory test results were as follows: hemoglobin: 12.3 mg/dL; hematocrit 34%; WBC 6580 mm3 (78% PNL); urea 11 mg/dL; total protein 5.9 g/dL; albumin 3.2 g/dL; triglycerides 50 mg/dL; LDL 10 mg/dL; CRP (-), respectively. After inserting the chest tube, we applied underwater seal and found out that the patient's effusion liquid had a milky white look with pH 7, density 1015, triglycerides 2101 mg/dL, glucose 168 mg/dl, and WBC 590 mm3 (82% lymphocytes) (Figure 2).

The pleural effusion liquid was unremarkable and PPD was negative. These findings confirmed the diagnosis of chylothorax. The thorax CT applied showed no etiologies. The patient started a fat-poor diet along with octreotide, a somatostatin analogue (3 mg/kg/hrs iv), and dobutamine (5 mg/kg/mins iv) treatment. We maintained the somatostatin treatment for 2 weeks. Observing decline in the signs of a potential heart failure during the follow-up, we cut the dobutamine treatment. We terminated the chest tube application on the 25th day of the treatment as the signs of chyle came to an end. The patient was discharged and advised to attend the follow-up examinations. The findings of the physical and radiographic examinations were normal at the first follow-up after a week (Figure 3).

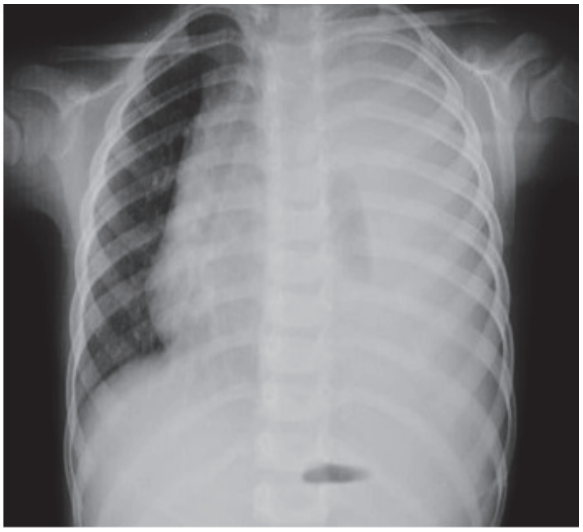

Figure 1. The dense view of consolidation in the lung in the first examination.

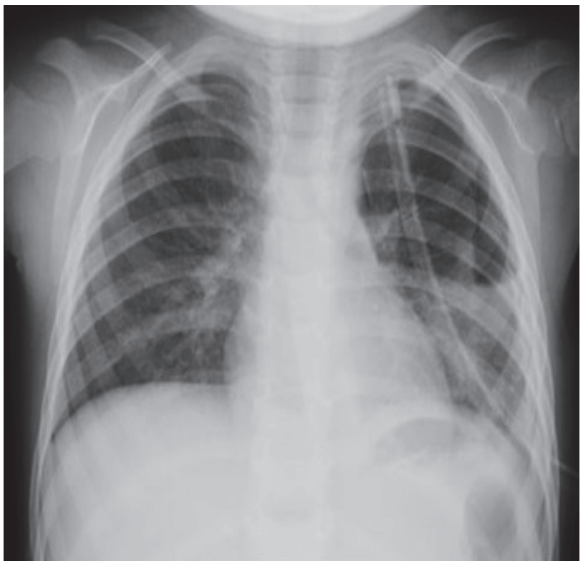

Figure 2. The view of the effusion liquid after the application of underwater seal.

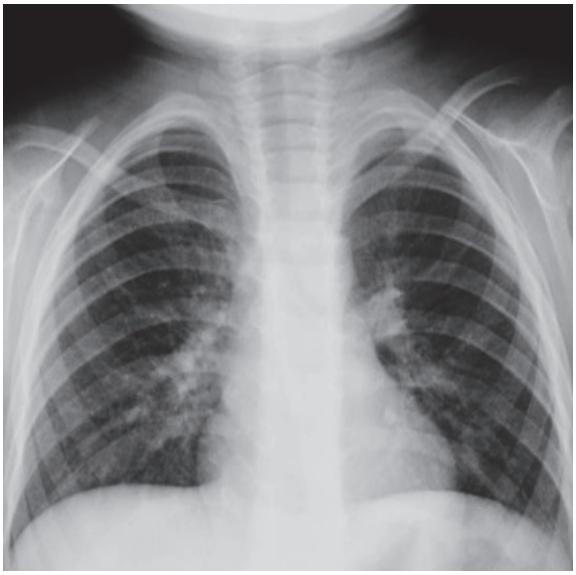

Figure 3. The follow-up radiograph view after the treatment (week 4)

DISCUSSION

Chylothorax, which is characterised by the accumulation of lymphatic fluid in the pleural space following damage in the ductus thoracicus, is one of the rare causes of pleural effusion. The incidence rate of chylothorax is unknown. The etiology of chylothorax is often seen as the post-cardio-thoracic surgery complications in children while left subclavian catheter applications, blunt chest trauma, stab wounds, gunshot wounds, and sudden hyperextension of the vertebrae may also lead to chylothorax (1-3). In addition, the disease may accompany Down syndrome, genetic disorders such as Turner's syndrome, malignancies such as lymphoma and neuroblastoma, and chronic infectious diseases like tuberculosis and histoplasmosis (4). In our case, we failed to determine the cause of chylothorax either in the patient's history, laboratory findings, or after the physical and radiological examinations. However, we think that the reason for the chylothorax development can be secondary to the continuous constipation-related contraction during discharge. The treatment method of chylothorax is poorly defined. Therefore, applied treatments are usually conservative. Reduced high-protein low-fat diet, total parenteral nutrition (TPN), somatostatin analogues (octreotide), and pleural drainage are among the existing major treatment options (5).

Octreotide is a long-acting somatostatin analogue. By influencing the central nervous system, gastrointestinal tract, and the organs of the endocrine system, it reduces the production of many hormones such as insulin, glucagon, growth hormone, thyroid stimulating hormone (TSH), gastrin, secretin, vasoactive intestinal peptide (VIP), motilin, and biliary and pancreatic polypeptide. Although the action mechanism is not known exactly, it may also reduce the production of chylous effusion by

decreasing venous blood flow in the liver and spleen, and by reducing fat absorption in the intestine (6, 7).

Octreotide may be applied in intravenous (iv) infusion doses from 0,3 to 10 mg/kg/hour while it may also be administered subcutaneously in 3 doses of 20 to 70 mg/kg/day. However, the most common method is to use the intravenous infusion (4, 8). While it is debatable how much the treatment will be continued, it is often advised to go on the treatment 3-5 days after the withdrawal of chylous fluid drainage (9).

On the first day of pleural drainage, we extracted 550ml of liquid (about 2 mL/kg/hr). Despite the decreasing amount of leakage after the dietary regulation at the follow-up, the chylous liquid continued to come out (1mL/kg/hr) upon which we started the somatostatin treatment on day 5 of the treatment and continued the somatostatin application for two weeks. With the somatostatin treatment, the chylous fluid extraction decreased, and eventually stopped.

In the treatment of resistant chylothorax cases, the risk of infection increases as the length of hospital stay becomes longer. Also the loss of oil-rich lymphatic fluid leads to fluid and electrolyte imbalance, malnutrition, and immunodeficiency. Buttiker et al. have detected 1000 cells/ml in the chylous effusion of the 92% of their 39 chylothorax cases and that 90% of these cells were lymphocytes (10). In chylothorax, prognosis may vary depending on the underlying etiologies. Chylothorax is reported to have subsided in more than 80% of cases within 4 weeks without requiring any surgical intervention (11). For those patients with active chylous after 4 weeks, following lymphangioscintigraphy, practitioners consider surgical treatment in accordance with the damage done (12). Our patient improved in the 4th week of the medical treatment without the need for surgical intervention.

Chylothorax may spontaneously develop in childhood. The use of somatostatin analogs with a chest tube in medical treatment will reduce the need for surgical intervention.

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The Role of Radiotherapy in Gliomatosis Cerebri: Two Case Reports

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Abstract
Gliomatosis cerebri is a rare diffuse involvement of the central nervous system by a malignant glioma that permeates the brain extensively without destroying the neural architecture. It involves more than two of the lobes. Oligodedroglial component can be predictive for a better prognosis. This is a report of two patients: a 33-year-old female patient and a 58-year-old male patient. A stereotactic biopsy was performed for our first patient. She was diagnosed with grade 2 astrocytoma. The second case was a grade 3 patient who was diagnosed with tumour infiltration in line with gliomatosis cerebri. Both cases underwent external beam radiotherapy at 44 Gy and 50 Gy, respectively, with a helical tomotherapy device. The patients tolerated the cure quite well and no acute complications (except for grade 1 skin reactions) were observed during the therapy. Radiotherapy volume and treatment dose are still controversial in the treatment of gliomatosis cerebri. Partial or whole brain radiotherapy can be applied.
Key Words: Gliomatosis Cerebri; Radiotherapy; Tomotherapy.

Gliomatozis Serebride Radyoterapinin Yeri: İki Olgu Deneyimi

Özet
Gliomatozis serebri, oldukça nadir görülen, beyinde en az iki lobu tutan, nöral yapıların korunduğu, diffüz neoplastik glial hücre proliferasyonudur. Oligodedroglial komponent varlığı prognoz açısından daha iyidir. Olgularımız 33 yaşında bayan ve 58 yaşında erkek hastadır. Birinci olgumuzda stereotaktik biyopsi yapılmış. Grade 2, astrositom olarak değerlendirilmiş. İkinci olgumuz ise biyopsi sonucu Grade 3, Gliomatozis serebri ile uyumlu tümör infiltrasyonu olarak değerlendirilmiş. Hastalarımıza Helikal Tomoterapi cihazında sırasıyla 44 Gy ve 50 Gy eksternal radyoterapi uygulandı. Hastalar tedaviyi iyi tolere etti ve tedavi süresince grade 1 cilt reaksiyonu dışında akut komplikasyon gözlenmedi. Gliomatozis serebride radyoterapi volümü, tedavi dozu tartışmalıdır. Tüm beyin veya parsiyel radyoterapi uygulanabilmektedir.
Anahtar Kelimeler: Gliomatozis Serebri; Radyoterapi; Tomoterapi.

INTRODUCTION

Gliomatosis Cerebri (GC) is a rare diffuse neoplastic glial cell proliferation that involves at least two lobes of the brain while keeping neural structures undamaged. It was first described by Nevin in 1938. It is categorised as a neuroepithelial tumour by the World Health Organization (WHO) (1, 2).

The optimal treatment for GC is not yet clear. Due to diffuse involvement, surgical intervention is limited to biopsy in GC. Radiotherapy and chemotherapy are among the preferred treatment modalities. Many studies have shown that radiotherapy can at least stop GC's progress and sometimes cure the disease. However the effect of radiotherapy on the survival rate is unknown. Here, we would like to share the cases of two patients with GC, a disease with a very low incidence rate.

CASE REPORT

Case 1: A thirty-three-year-old female patient consulted to a doctor with headache and weakness about 7 months ago. The cranial magnetic resonance (MR) imaging showed diffuse infiltrative involvement in the right frontal, temporal, parietal regions as well as in the left frontal region (Figure 1). The patient underwent stereotactic biopsy. The histopathological result was evaluated as Grade 2 astrocytoma. The patient was given six cycles of temozolomide chemotherapy. Due to the progress in the lesions, the patient was referred to the department of radiotherapy.

Case 2: A fifty-eight-year-old male patient was admitted to the hospital with weakness in his legs 3-4 months ago. The MRI revealed diffuse involvement in the left frontal and right insular regions along with the right frontal cortex. After the stereotactic biopsy, the histopathological findings showed that the patient had Grade 3 GC-related tumor infiltration.

We performed computed tomography in the supine position. After achieving proper immobilization (flat headboard and head thermoplastic mask) and contrast enhanced planning, CT scans were taken with 3 mm slice thickness target volumes and contours for organs at risk were created within the Velocity treatment planning system fused with MRI scans. We delineated the clinical target volume (CTV) by using the tomography and MRI findings. The hyperintense involvement on the T2 sequence on MR was evaluated as CTV while PTV (planning target volume) was delineated by adding 5mm to CTV (Figure 2).

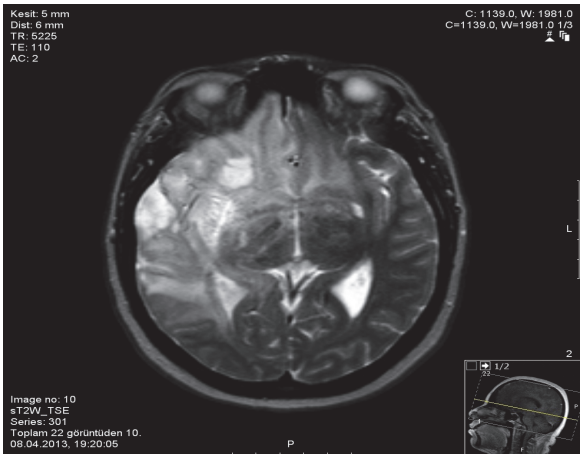

Figure 1. The MRI view of Case 1.

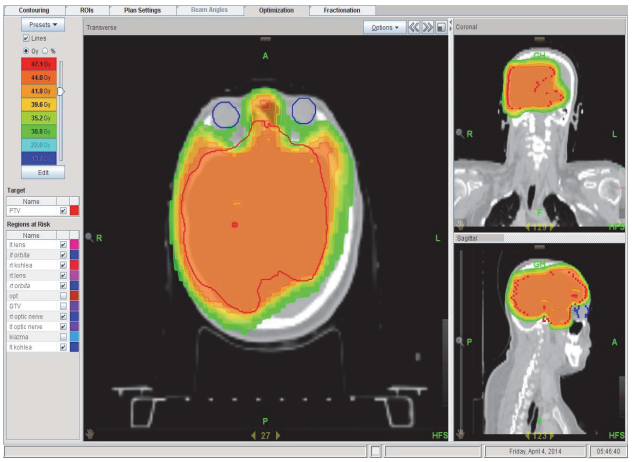

Figure 2. The planning image of Case 1.

We administered 44Gy with 2Gy fraction dose for the first patient and 50Gy with a fraction dose of 2Gy for the second patient. We planned to have a target dose of 95% of PTV, for which the planning treatment objectives were to cover at least 95% of the PTV with the 95% isodose. Prior to each treatment session, we performed MV-CT imaging and, after setting the PTV localisation, we initiated the treatment with a Helical Tomotherapy device. Throughout the radiotherapy, we did not observe acute complications other than grade 1 skin reactions; the patients tolerated the treatment well.

Both of our patients were still alive six months after the radiotherapy. The current cranial MRI shows that the disease is stable without any progress as in the case they were in when they first presented at our clinic.

DISCUSSION

GC is a very rare brain malignancy. The WHO diagnostic criteria for GC are involvement of at least the two of the lobes of the brain despite well-protected brain architecture, the presence of a necrotic area in the middle and cellular structure. It can be differentiated from other diffuse infiltrating gliomas by the lack of a mass in the middle and that it does not bring about tissue destruction (2, 3).

Because of its variable clinical features, it is difficult to diagnose GC. It can be seen in every age group. Its clinical symptoms are quite variable though headache, fatigue, and muscle weakness are among the most common symptoms.

The gold standard in the diagnosis of GC is the T2-weighted MR imaging. The common MRI finding is the diffuse infiltration from the cortex towards the sulcus and the loss of the boundary between the gray matter and white matter. FLAIR sequence is also good at revealing the extent of the lesion, callosum infiltration, and cortical involvement (4, 5). Though it is less revealing compared to MRI, brain positron emission tomography (PET / CT) imaging can also help in showing the extension of the tumour. It has been found out that the grey matter looks less hypometabolic than it is normally viewed in PET/CT. Therefore, radiological and histopathological correlation is important in the diagnosis of GC (6).

Many series have shown that radiotherapy contributes to survival. Survival rate varies from 1.5 to 55 months in several studies (7, 8). However, it should be kept in mind that some studies relate longer survival periods because they consider the start of complaints as the beginning of the survival time while other studies take the biopsy date as the start of the survival period (9). Survival in patients who do not undergo radiotherapy is highly variable (between 1 week and 15 years), the average being 3-6 months (8, 10).

Tallibert et al.'s survey of the ANOCEF database and the literature analyses 296 GC patients in terms of age, sex, histology, survival, and treatment. Their study relates that the median age of incidence is 42 (1 month-85 years) with a median survival rate of 14.5 months. This was 36 months in oligodendroglial GC, 14 months in mixed GC, and 11 months in astrocytic GC, respectively ($p<0.001$). Oligodendroglial component was found to be a good prognostic factor. Because oligodendrogial components are more common in male patients and because male patients are usually younger, the survival rate for these patients was higher (17 months to 11.5 months). The survival rate of the 105 patients who did not receive radiotherapy was 11 months (ranging between 1 month and 16 years). Radiotherapy has been found to have a positive effect in clinical and radiological improvement, but the full impact on survival could be detected (11).

Radiotherapy has proven to be an effective method in a 30-patient MD Anderson series. 87% of these patients have shown radiological improvement while 70% have come up with clinical improvement at the end of the treatment. The median survival rate was 18 months. Younger patients and patients with non-glioblastoma histology had higher survival rates (12).

Another modality in GC's treatment is temozolomide chemotherapy. Temozolomide is an agent used in malignant gliomas and Gliomatosis Cerebri (13, 14). It is hoped that temozolomide therapy, accompanied by radiotherapy, may lead to better results, but there is a need for further studies on this issue.

Both of the patients presented in this report are stable after the radiotherapy. The location, dose, or volume of radiotherapy in GC patients is still not clear. There is need for further studies on this subject.

Due to the new display methods and developments in molecular techniques, we learn more about GC each day. As we keep learning more about GC, we will be able to shape our treatment strategies for this disease in the coming years. In the light of the available information on GC, we can conclude that cranial radiotherapy may be a successful method in treating GC.

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Current Approaches to Esophageal Variceal Bleeding

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Abstract
Esophageal varices are collateral veins at the distal esophagus between gastric and azygos veins arising following increased portal pressure. Vein pressure above 10 mmHg is regarded as portal hypertension, in which portal vein-hepatic vein pressure gradient is increased. This status is seen as "clinically important portal hypertension" and it is most common in liver cirrhosis. Acid and esophageal variceal bleeding is the result of portal hypertension, which are the signs of advanced disease with poorer survival rates. Esophageal varices develop in 30% of the patients with compensated cirrhosis and 60-70% of the patients with decompensated cirrhosis. Varice development incidence is around 4-12% in cirrhotic patients without varices. Esophageal variceal hemorrhage has high recurrence, mortality, and morbidity rates requiring immediate medical treatment and these constitute approximately 10% of upper gastrointestinal bleeding, which is one of the major causes of mortality in patients with cirrhosis. Bleeding develops in 30% of the cirrhotic patients with esophageal varices diagnosed during endoscopy. The mortality of the first bleeding episode ranges from 25 to 70% and after the first bleeding episode re-bleeding occurs at a rate of 75-80% in six to twelve months. Variceal diameter, grade, degree of red dots, and cirrhosis are among the factors that increase the risk of variceal bleeding. The risk of bleeding in Grade 1 varices is 8% and a higher grade increases the risk of bleeding four to five folds. Pharmacological endoscopic and antibiotic treatment constitutes the basis for esophageal variceal bleeding treatment. In this study, we aimed to evaluate the current approaches to esophageal variceal bleeding.
Key Words: Esophageal Variceal Bleeding; Portal Hypertension; Cirrhosis.

Özofagus Varis Kanamalarına Güncel Yaklaşımlar

Özet
Özofagus varisleri portal kan basıncının artmasına bağlı, özofagusun distalinde gastrik venler ile azigos ven arasında geşilen kolaterallerdir. Portal ven basıncının 10 mm Hg'nin üzerinde olmasına portal hipertansiyon denilir. Portal hipertansiyonda portal ven – hepatik ven basınç gradiyenti artmıştır. Bu durum "klinik olarak önem arz eden portal hipertansiyon" olarak adlandırılmaktadır ve en sık karaciğer sirozunda karşılaşılır. Karaciğer sirozu olan hastalarda asit oluşumu ve özofagus varis kanamalarının olması ilerlemiş hastalık belirtileridir ve bu hastaların beklenen yaşama süresi oldukça kısalmıştır. Kompanze sirozlu hastaların %30'unda dekompanze sirozlu hastaların %60-70'inde özofagus varisi gelişmektedir. Varisi olmayan sirotik hastalarda yıllık varis oluşum hızı %4-12 dolayındadır. Özofagus varis kanaması yüksek rekürrens, mortalite ve morbidite oranına sahip acil medikal tedavi gerektiren hastalıklardan biridir. Özofagus varis kanamaları üst gastrointestinal sistem kanamalarının yaklaşık %10'unu oluştururlar ve sirozlu hastalarda başlıca mortalite nedenlerindendir. Özofagus varis kanaması, endoskopik olarak özofagus varisi saptanan sirotik hastaların %30'unda gelişmektedir. İlk kanama epizodunun mortalitesi % 25-70 arasında değişmektedir ve ilk kanama sonrası varislerin % 75-80'inde altı ay ya da bir yıl içinde yeniden kanama meydana gelir. Varis çapı, grade, kırmızı noktalanmalar ve siroz derecesi varis kanaması riskini arttıran faktörlerdir. Grade 1 varislerde kanama riski %8 iken grade arttıkça kanama riski 4-5 kat artmaktadır. Özofagus varis kanamalarında tedavinin temelini farmakolojik, endoskopik ve antibiyotik tedavisi oluşturur. Bu çalışmada özofagus varis kanamalarına güncel yaklaşımlar ele alınmıştır.
Anahtar Kelimeler: Özofagus Varis Kanaması; Portal Hipertansiyon; Siroz.

Esophageal variceal bleeding occurs in enlarged submucosal veins due to esophageal shunts as a result of portal hypertension (PHT).

Pathophysiology

PHT is defined as the increase in blood pressure in the portal venous system. Portal pressure can be indirectly estimated by hepatic venous gradient. Normal hepatic venous pressure gradient is less than 5 mmHg. In cirrhosis, in the context of Ohm's law (Pressure= vascular resistance X blood stream), patients may develop increased intrahepatic vascular resistance and PHT due to the blood stream flowing towards portal venous system (Figure 1).

Intrahepatic resistance is increased in two ways: mechanical and dynamic. The mechanic component is connected to development of intrahepatic fibrosis. Whereas, the dynamic component occurs due to the induced vasoconstriction in the portal veins. Intrehepatic vascular tonus is regulated by endogenous vasoconstrictors such as norepinephrine, endothelin-1, angiotensin-2, thromboxane, leukotrienes as well as vasodilators such as nitric oxide. PHT, which leads to acid and variceal bleeding in cirrhosis, is caused by the deterioration of the balance between these vasoconstrictors and vasodilators (1-3).

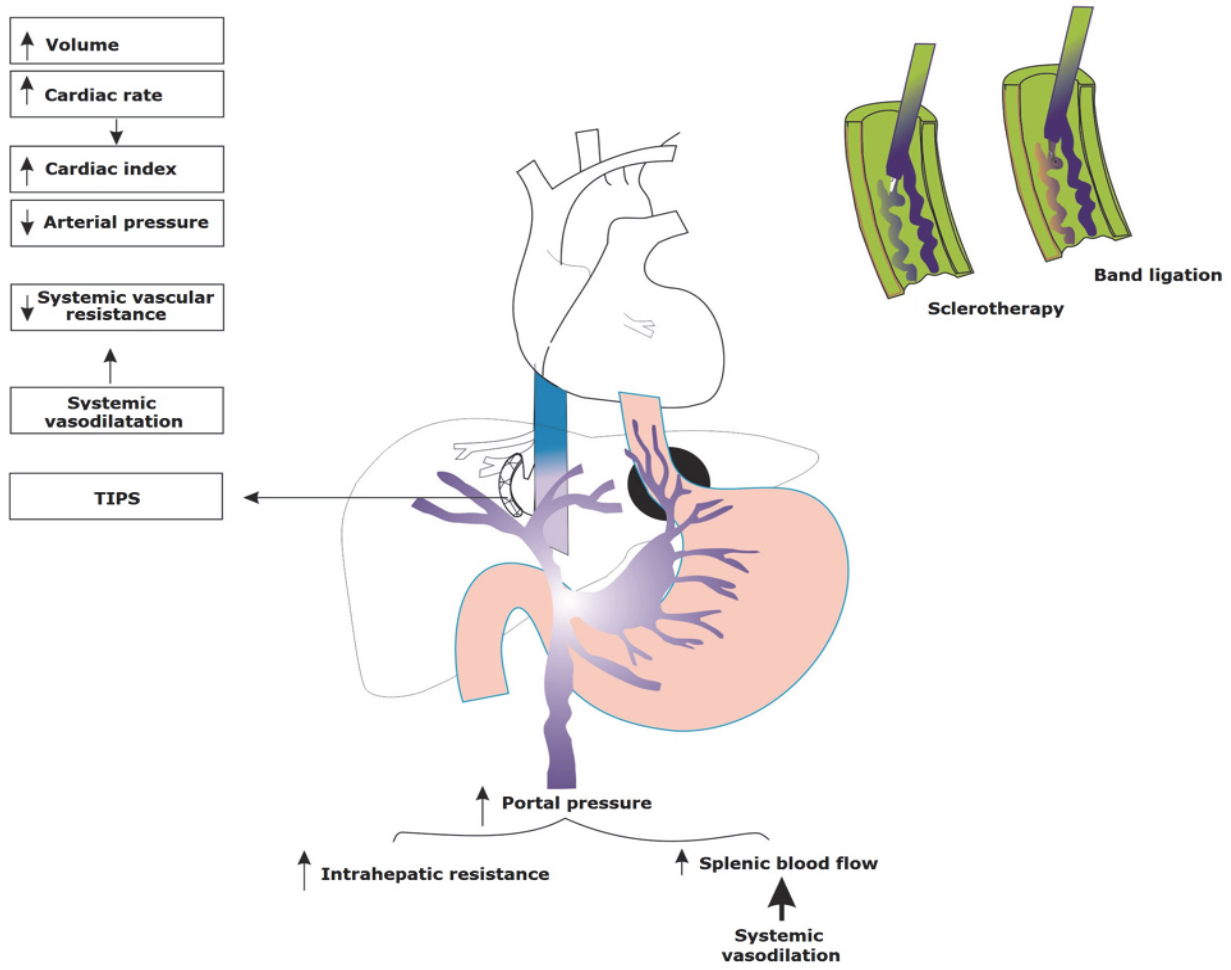

Figure 1. The pathophysiology of portal hypertension; based on Nina D. et al.'s diagram (1).

PHT is characterized by hyperdynamic circulation resulting from splanchnic and systemic arterial vasodilation, and, in turn, increased cardiac outflow and decreased systemic vascular resistance. Splanchnic arterial dilatation develops due to endogenous vasodilators such as glucagon and vasoactive intestinal peptides and it leads to increased portal blood flow. The emerging PHT creates portacaval pressure difference. Hence, portosystemic venous collaterals develop in order to try to reduce this pressure difference. Esophageal varices generally drain down to azygos veins and they are considered to be one of the most important collaterals due to their tendency to bleed. Esophageal varices develop when the hepatic venous pressure difference exceeds 10mmHg (4). All the factors such as deterioration in liver disease, patient's diet, ethanol intake, physical execise, and increased intra-abdominal pressure that contribute to high PHT values increase variceal bleeding and acid formation (5, 6). Aspirin and non-steroidal anti-inflammatory drugs may increase the tendency for bleeding by changing the variceal wall structure. In addition, bacterial infections may also be effective on the formation of varices and the risk of bleeding.

Esophageal Variceal Bleeding

Variceal bleeding has been one of the diseases with high risk of recurrence, mortality, and morbidity rates and it requires urgent medical treatment. The prevalence of varicose veinin cirrhotic patients is about 50%. In the presence of PHT, annual growth rate of varicose vein is between 4 and 12 %. Pharmacological, endoscopic, and antibiotic treatment form the basis of varicose vein treatment. Endoscopy is the most valuable diagnostic method. Varicose vein observed in endoscopy are generally classified in three grades.

- Grade 1: Observed in a single column; disappearing air application; depressed by endoscopy.
- Grade 2: Observed in more than one columns; cannot be depressed by fluid resuscitation or endoscopy.

- Grade 3: Multiple intercorrelated varicosis; occupying more than 2/3 of the lumen space; cannot be depressed by giving air or endoscopy

Varicose diameter, grade, red dots, and degree of cirrhosis are factors that increase the risk of variceal bleeding. In grade 1 varices, the risk of bleeding is 8 %, but as the grade increases, the risk of bleeding also increases up to 4-5 times. 30-35% of chronic liver of patients with varicose veins bleed within 2 years and they share a mortality rate of about 30-50 %.

Gastroesophageal Varicose Veins

Endoscopic screening is the best technique; today there is no other technique indicating the presence of esophagogastric varices than endoscopic screening. In patients with esophageal varices, prevalence of gastric varices is also high. Gastroesophageal varices are divided into 2 groups:

Type 1: This is the most common type of esophageal varices. They can be 2-5 cm below the cardio-esophageal junction. The risk of bleeding is about 12%, which is less than the bleeding percentage in other types.

Type 2: They are the varices that spread towards the fundus. They have two subgroups. The first subgroup only occupies the fundus (with a bleeding risk of 80%, the highest bleeding risk among varicose veins) while the other group spreads over the antrum and corpus.

Pharmacological Treatment

Vasopressin/Terlipressin: Vasopressin is a potent splanchnic vasoconstrictor agent. In many countries, it has been discontinued due to its severe vascular side effects. Terlipressin, however, is the equivalent of vasopressin and it reduces hepatic venous pressure gradient, variceal pressure, and azygos blood flow by showing similar effects as vasopressin. Terlipressin has been proven to reduce variceal bleeding compared to placebo. In addition, it protects the renal function of patients with hepatorenal syndrome by reducing the activation of renal vasoconstrictor system. However, terlipressin may increase ischemic complications in patients who are in shock. Therefore, the use of this drug in patients with cardiovascular diseases such as heart failure, arrhythmia and hypertension is contraindicated (7, 8).

Somatostatin, Octerotid, Vapreotide: Somatostatin reduces the hepatic venous pressure gradient, variceal intraocular pressure, and azygos blood flow. However, its hemodynamic effects are temporary and require continuous infusion. Also, information on the idea that it reduces the need for blood transfusion and balloon tamponade is controversial. Terlipressin is as as effective as somatostatin in bleeding control. Octreotide and vapreotide have longer half-life than somatostatin and they are more useful in the treatment of PHT. Octreotide reduces the hepatic venous pressure gradient and azygos blood flow but does not affect the varices pressure. Moreover, the effect of octreotide is temporary and even this effect is controversial. It prevents the postprandial increase in hepatic blood flow while it also seems to reduce variceal bleeding and increase the success of endoscopic treatment (1, 7, 9, 10). Published randomized controlled studies show that Octreotide is not more effective than placebo in the prevention and control of variceal bleeding (11). Some studies also show that vapreotide, which is a long-acting counterpart of somatostatin, reduces the need for blood transfusion when it is given before endoscopic treatment; besides, it is only found to be more effective than the group treated by endoscopy (12). With regard to the use of somatostatin and its counterpart drugs, there is almost no major complications and toxic effects.

Endoscopic Treatment:

In variceal bleeding, endoscopy is a commonly used technique in both the diagnosis and treatment of the bleeding. Three types of endoscopic techniques are commonly used: Endoscopic band ligation, sclerotherapy, and endoscopic variceal occlusion by using adhesives.

Endoscopic band ligation: Today, it is the first choice for esophageal variceal hemorrhage. Only up to 5-8 tapes should be used in every session. Sessions should be implemented with intervals of 2-3 weeks until varices are entirely obliterated or shrunk. Endoscopic band ligation is a relatively less complicated operation compared to sclerotherapy. After ligation, occasional moderate bleeding can be observed due to ulcer developing in the area.

Endoscopic Sclerotherapy: There are several sclerosing agents such as polydocanol, ethanolamine, ethanol, tetradecyl sulfate, and sodium morruat. The effects of these agents are similar. In each session, an injection of sclerosing with total volume of 10-30 ml can be administered inside or around the varices. Sessions continue with intervals of 1-3 weeks until varices are obliterated. Thereafter, since the probability of re-occurrence of the varices is up to 70 %, endoscopic follow-ups are required with intervals of 3-6 months. Retrosternal pain, dysphagia, and sclerotherapy related ulcer bleeding can be observed due to sclerotherapy. Esophageal perforation and stricture due to sclerotherapy may also develop though this is quite rare.

Variceal Obliteration by using Adhesives: This treatment is more suitable for patients who have suffered from gastric or gastroesophageal variceal bleeding in the past. Generally, practitioners use N-butyl-2-cyanoacrylate in this method. 1 ml adhesive is injected at one time and only up to 3 injections are implemented in each session. The most serious complication of this treatment is the possibility of embolization in the pulmonary system, spleen, and the brain.

Transjugular Intrahepatic Portosystemic Shunt (TIPS):

TIPS refers to providing a new path between the hepatic and portal vein via jugular vein in the liver (Figure 1). Here, the purpose is to prevent variceal bleeding by reducing portal pressure. TIPS reduces portal pressure,

but there is a risk of encephalopathy. In most cases, encephalopathy responds to standard treatments but in some cases, it may be neccessary to reduce the diameter of the shunt. 5% of encephalopathy patients do not respond to treatment; in this case, practitioners need to stop the flow in the shunt. In addition, from time to time, stenosis or thrombosis may develop in the shunt. In recent years, there are studies that report that stents wrapped with polyether urethanes tend to get clogges less than conventional stents.

Other Treatment Options:

Balloon tamponade: Balloon tamponade is a bridging therapy for TIPS and portosystemic shunts in cases with massive and uncontrolled bleeding. The most frequently used tube is the modified 4-lumen Sengstaken-Blakemore tube. In gastric varices, practitioners prefer Linton-Nachlas tube which has a wider lumen.

Porto-Systemic Shunt: After the introduction of TIPS, the use of surgical shunts has dramatically decreased. The implementation of surgical shunts are complicated operations that require experience. This method can be useful in patients for whom TIPS is technically impossible and when the liver functions of the patient are not severely decreased.

If the bleeding is still unstoppable despite all attempts, procedures such as percutaneous transhepatic embolisation, devascularization-transection, or transplantation can be considered as last resources.

Practical Treatments:

Variceal bleeding should be treated in intensive care units. The treatment can include nonspecific treatment options like fluid replacement or antibiotic treatment therapies as well as patient-specific methods like pharmacological and endoscopic treatments (Figures 2, 3).

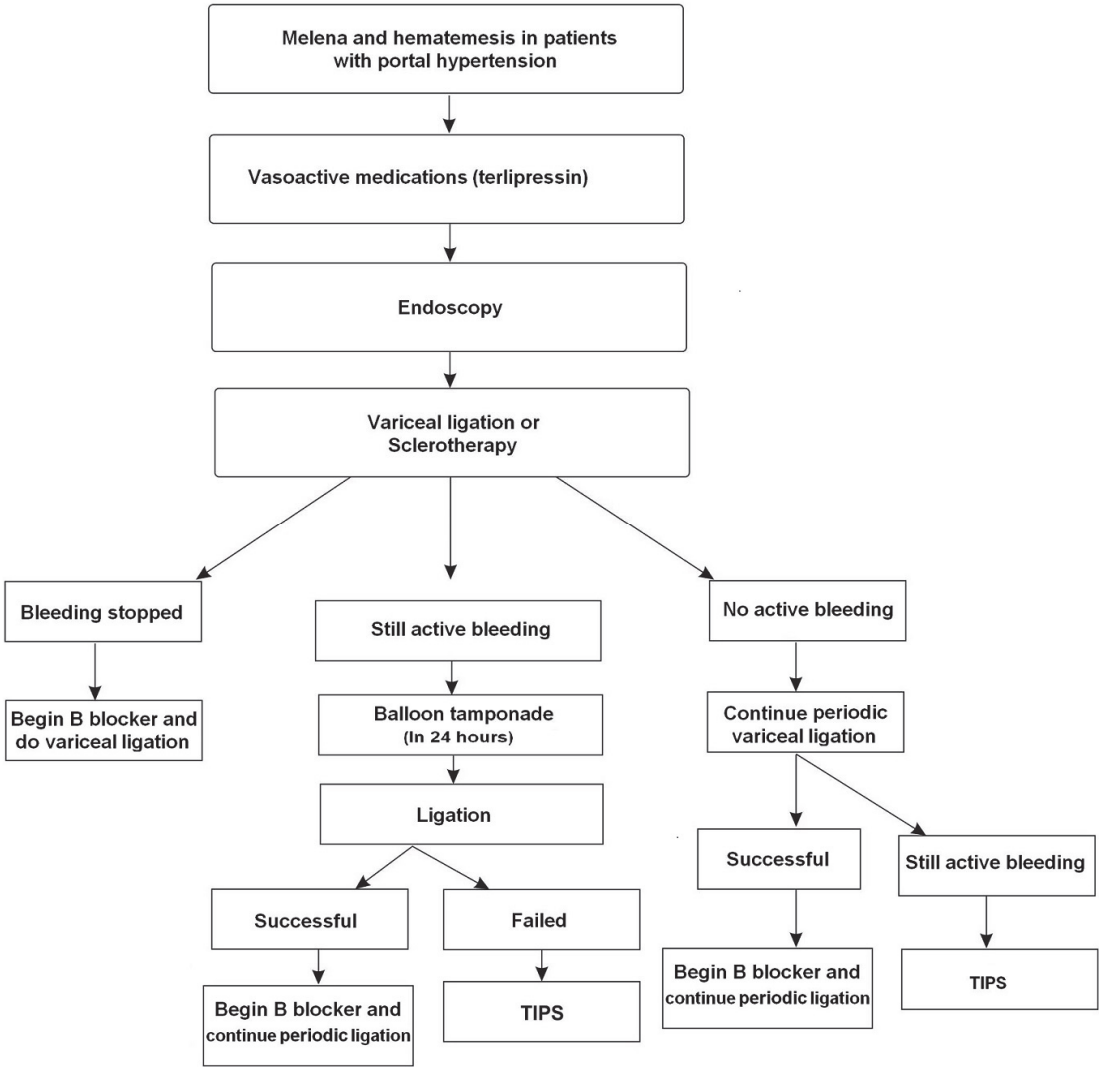

Figure 2. Approach algorithm for patients with active esophageal variceal bleeding.

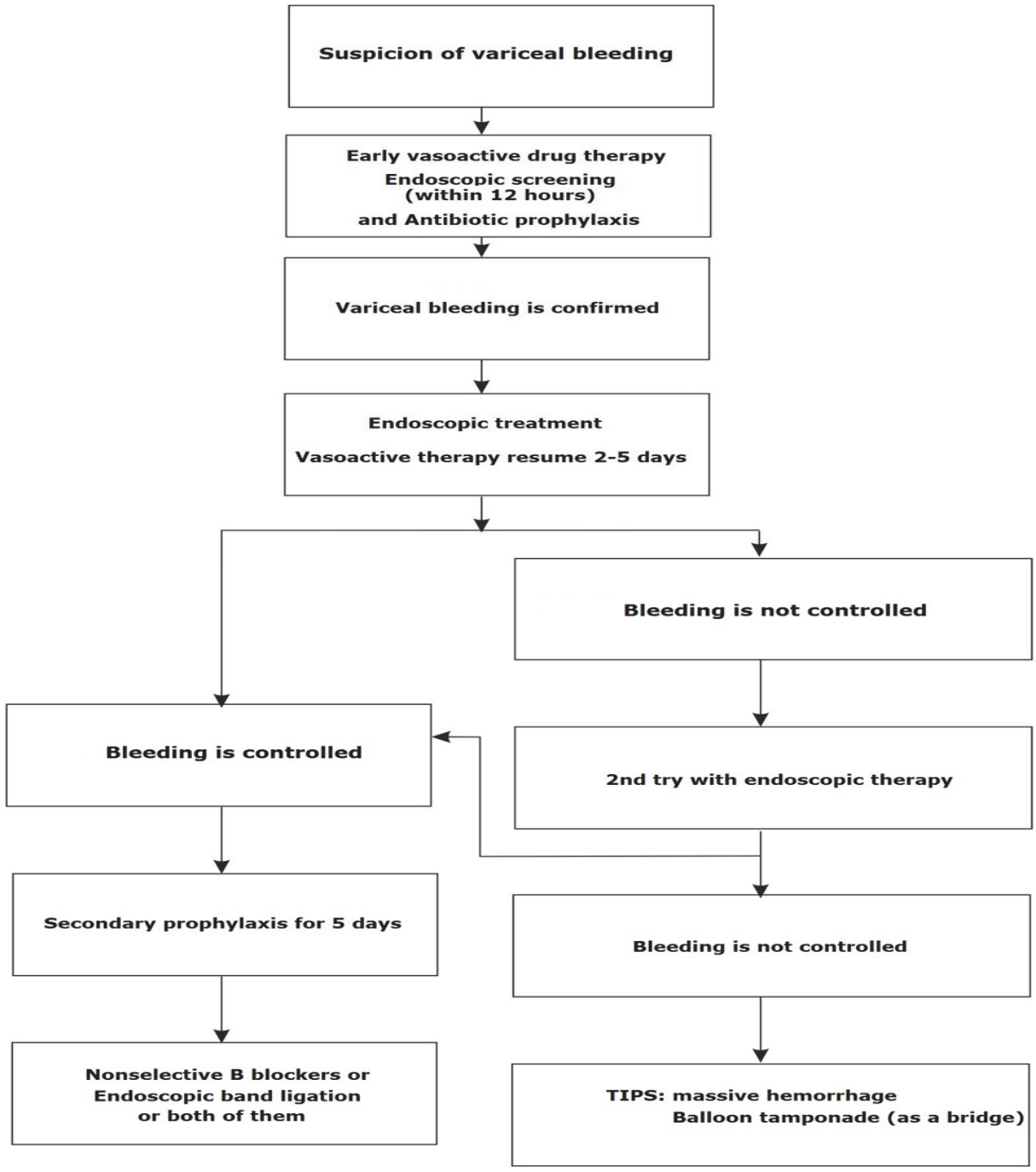

Figure 3. Approach algorithm for patients with variceal bleeding.

Practical Recommendations for the treatment of acute variceal bleeding (1):

-Variceal bleeding is medically an emergency case and must be treated in intensive care units.
-Blood replacement should be carried out carefully.
-Red blood cells should be maintained at a hemoglobin level of 70 to 80 g/L.
-Plasma expanders should be used for hemodynamic stability and renal perfusion.
-Antibiotic prophylaxis
-Endoscopic treatment should be given as quickly as possible (within the first 12 hours of admission to hospital).

-Treatment should include vasoactive drugs along with endoscopic therapy and a specific treatment.
1) One of the following drugs should be started as soon as possible immediately after admission to the hospital prior to endoscopic treatment (to be administered for the first 2-5 days):
-Terlipressin: 1-2 mg every 4 hours
-Somatostatin: 250µg bolus; then 250µg infusion therapy every hour
-Octreotide: 25-50µg/h infusion and 50-100µg bolus if required
-Vapreotide: 50 mg bolus and 50 mg/h infusion.
2) If possible, practitioners should first consider endoscopic band ligation or endoscopic sclerotherapy. Tissue adhesives can be applied in acute gastric variceal bleeding (such as N-butyl-2-cyanoacrylate)
-Should vasoactive drugs and endoscopic treatment fall short, endoscopic treatments or TIPS can be reapplied.

Nonspecific treatment:

The purpose of the non-specific treatment is to correct hypovolemia and prevent complications. Blood replacement should be applied with erythrocyte suspension by keeping the hemoglobin level at 70-80 g/L. Practitioners should avoid over transfusion which brings about recurrent bleeding and increases the risk of continuous bleeding (14). Plasma expanders are used to maintain hemodynamic stability and renal perfusion pressure. To this end, either crystalloids or colloids can be preferred but it should also be kept in mind that crystalloids are known to be less harmful.

25-50% of the patients may develop infections in cirrhosis related esophageal variceal bleeding. Controlling bleeding is difficult in infected patients; death rate is higher in such cases. Early antibiotic prophylaxis is beneficial both for survival and bleeding control. The preferred protocol is generally the application of 400mg of norfloxacin twice a day for two weeks (15).

The routine nasogastric tube application is not recommended at this stage. Although we do not know for sure if lactulose prevents encephalopathy, practitioners are recommended to apply lactulose in encephalopathic patients (16).

Specific Treatment

Intravenous vasoactive medications should be started right after admission to the hospital and maintained for 2-5 days. Due to its possible side effects, vasopressin is not recommended for routine applications. Endoscopy should be scheduled within 12 hours of admission. For this, stomach should be emptied - if needed, with a nasogastric tube. It is useful to apply 250mg of intravenous erythromycin 30-60 minutes before the procedure (1).

Endoscopy is highly beneficial in locating and treating the source of bleeding. The first step could be to achieve homeostasis with the help of band ligation or sclerotherapy. In patients with gastric or gastroesophageal variceal bleeding, N-butyl-2-cyanoacrylate and endoscopic obliteration should be preferred. Band ligation can also be administered in patients with gastroesophageal reflux. Should vasoactive and endoscopic treatments prove to be insufficient for the treatment, practitioners may try a second endoscopic intervention. It should be remembered that TIPS is a method that should be considered in the second step of the procedure.Balloon tamponade can also be applied as a bridging treatment against massive bleeding. TIPS and surgical shunt operations can be applied as life-saving treatments if bleeding does not stop or gets complicated despite all these preventive approaches (1, 16).

The effects of various methods for variceal bleeding on portal flow, resistance, and pressure are given in Table 1.

Table1. The effects of various methods for variceal bleeding on portal flow, resistance, and pressure.

Treatment	Portal Flow	Portal Resistance	Portal Pressure
Vasoconstrictors	↓↓	↑	↓
Vasodilators	↓	↓	↓
Endoscopic Treatments	--	--	--
TIPS/Surgical shunt	↑	↓↓↓	↓↓↓

Prophylactic Approaches (Figure 4):

There are three main to prevent variceal bleeding:

- By obstructing variceal development (pre-primary prophylaxis),
- By preventing bleeding when the varice develops (primary prophylaxis),
- By preventing recurrent bleeding (secondary prophylaxis).

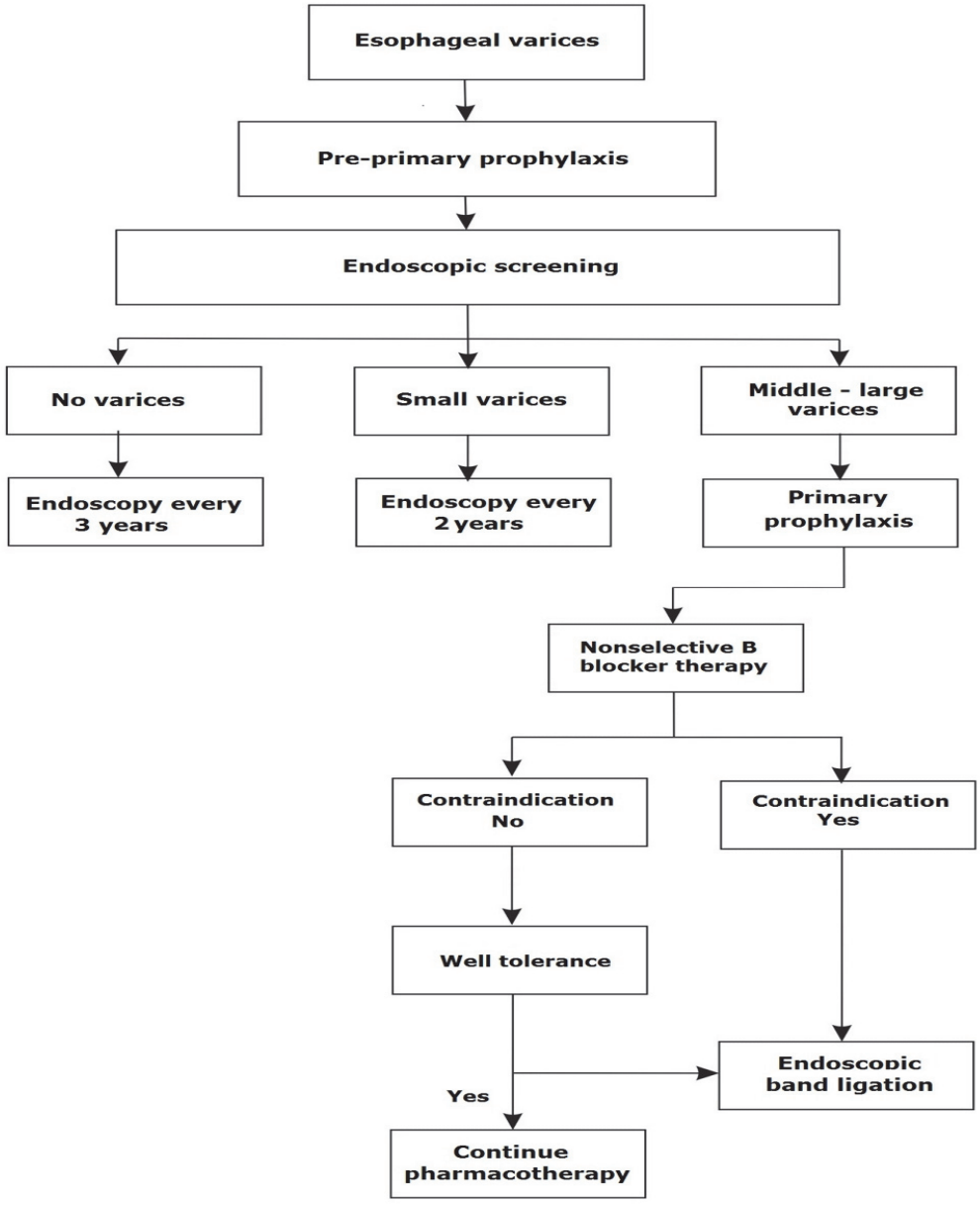

Figure 4. Prophylactic approach algorithm.

Pharmacological Treatment:

Pharmacological agents can be used both for treatment and prophylaxis.

β-blockers: They reduce portal pressure by reducing portal blood flow. Decrease in portal blood flow is caused by the decrease in the cardiac output due to β1 blockage and to the arteriolar splanchnic vasoconstriction that results from the reaction of the alpha receptors against β2 receptor blockage. Nonselective beta-blockers like propranolol, nadolol, and timolol are better than selective beta1 blockers in reducing hepatic venous pressure gradient. Up to a 15% drop can be achieved with nonselective beta-blockers in hepatic venous pressure gradient (17). Nonselective beta blockers may help reduce the volume of bleeding if not provide a significant reduction in hepatic venous gradient by reducing intra-varice pressure and azygos blood flow. It has been reported that using propranolol in cirrhotic patients prevents increase in physical activity related portal pressure while also mitigating bacterial translocation. Although it is still arguable, propranolol is also thought to be effective in reducing postprandial portal pressure peaks. The effect of treatment with beta-blockers can be measured by measuring hepatic venous pressure gradient. Many studies have shown that gradient below 12mmHg or 20% of the base value is considered to be a sign of the absence of variceal hemorrhage (18). However, the impact of hepatic

venous pressure gradient on the survival is controversial. Moreover, some researchers also think that gradient measurement is not cost-effective because it is an invasive method that can be applied only in some centers as a clinical practice (19, 20).

Nitrates: The vasodilator influence of nitrates (reduction in vascular tonus and intra-hepatic resistance) is not fully understood yet. It is probable that it may be effective through nitric oxide release. Isosorbide monohydrate is the only nitrate that is reported to be effective in randomized trials (21). It reduces the hepatic venous pressure gradient while also increasing the impact of propranolol. However, it should be known that isosorbide monohydrate has systemic effects such as hypotension. Nitrates may be used along with vasopressin and its analogous drug, terlipressin.

Pre-Primary Prophylaxis

The results of the studies on this issue are not compatible with one another. The International Baveno consensus recommends that beta-blockers should not be used in primary prophylaxis (22).

Primary Prophylaxis

After the diagnosis of cirrhosis, endoscopic variceal screening should be applied within 3 years in patients without varicose veins and within 2 years in patients with minor varicose veins. The following check-ups should be planned according to the initial size of varicose veins. Endoscopic follow-up is not necessary in patients with large varicose veins; practitioners should start primary prophylaxis with propranolol or nadolol for these patients. Endoscopic variceal band ligation may be considered in medium to large size varicose veins in primary prophylaxis though there is still no clear information regarding the long-term benefits of this application. Therefore, for now, band ligation is only recommended in primary prophylaxis if there are potential issues concerning the use of nonselective beta-blockers. In patients with medium and large size varicose veins, treatment involving nonselective beta-blockers reduces the frequency of the first bleeding episodes. Nonselective beta-blockers are traditionally administered twice a day whereas doses may be modified according to patient's tolerance. Recent pharmacodynamic studies imply that applying 80-160mg of propranolol has a long-acting effect and, thus, this can be sufficient in daily single doses. In all cases, the aim should be to achieve 20-25% reduction in heart rate with a heart rate of 55 beats/min. The use of isosorbide monohydrate alone is not effective in the prophylaxis of variceal occlusion and is not recommended (23).

Recommendations for the primary prophylaxis of variceal bleeding (1, 16):

1. Endoscopic variceal screening should follow the diagnosis of cirrhosis in all patients. Proceeding follow-ups should be scheduled by the degree of liver dysfunction and the size of varices.
2. Nonselective beta-blockers may be initially used in medium or large varicose veins. Treatment should be adjusted according to patient's needs and tolerance. In this group of patients, if the use of beta-blockers brings about contraindication and patient finds it hard to tolerate the therapy, endoscopic band ligation can be initiated.
3. Nonselective beta-blockers can be useful in patients with red, small size varicose veins or Child-Pugh C.
4. General dosage for beta blockers is as follows: propranolol 80-160mg/dl, nadolol 80 mg/dl.
5. Beta-blocker dose should be set to cause a 20-25% decrease in the heart rate to maintain it at 55 beats/min.

Secondary prophylaxis (Figure 5):

All patients who survived the first episode of bleeding should receive treatment for possible secondary bleeding. Risk factors for recurrent bleeding are summarised in Table 2. For the first step of treatment in the prophylaxis for recurrent bleeding, practitioners often employ both pharmacological and endoscopic therapies. Pharmacological treatment consists of nonselective beta-blockers; at this point, practitioners are advised to initiate an isosorbide monohydrate-proparanolol combination but this is not usually regarded as a favourable option. Endoscopic therapy for the treatment of varicose veins is one of the effective ways of treatment to cure recurrent bleeding. Compared with placebo, endoscopic sclerotherapy alone provides significant improvement in mortality rates and recurrent bleeding (22). Today, since it can reduce the risk of recurrent bleeding and due to its advantage to decrease varicose vein structure formation, band ligation is preferred to sclerotherapy. Administrating band ligation and sclerotherapy at the same time has not proved to be more effective than band ligation alone (24). However sclerotherapy may be preferred to band ligation if the patient's case is unsuitable for the latter. Endoscopic band ligation has been reported to be more effective in the prophylaxis of recurrent haemorrhage after a nadolol and sucralfate combination administration (25). As of now, we do not have sufficient data about the effect of the administration of this combination alongside with sclerotherapy. If nonselective beta-blocker and/or band ligation treatments fail in the secondary prophylaxis, salvage therapy options should be considered. Both TIPS and surgical shunts are efficacious in the prevention of recurrent bleeding. While TIPS is more effective than endoscopic treatments, surgical shunts are also more effectual than endoscopic sclerotherapy. Unfortunately, the impact of neither TIPS nor surgical shunts on survival is clear and both pose a risk to encephalopathy (26, 27).

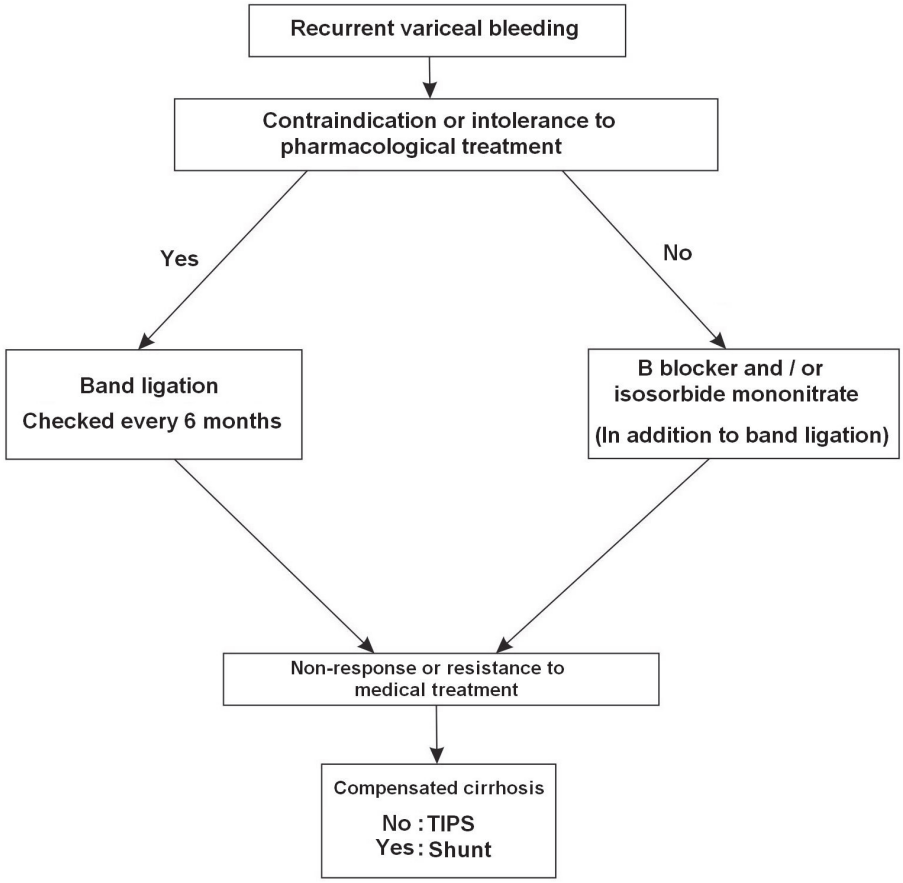

Figure 5. Approach algorithm for recurrent variceal bleeding.

Table 2. Risk factors for recurrent variceal bleeding.

Early recurrence of bleeding (within 6 weeks)	Late recurrence of bleeding (after 6 weeks)
Age (>60)	Cirrhosis Grade
Severe initial bleeding	Red-spotted varicose veins
Acid	Acid
Renal failure	Hepatoma
Identifying active bleeding in endoscopy	Alcoholism
Red-spotted varicose veins and clogs	

Recommendations for secondary prophylaxis (1, 16, 22):
-For patients who do not receive primary prophylaxis, practitioners should opt for nonselective beta-blockers and/or endoscopic band ligation.
-For patients who receive beta-blockers in the primary prophylaxis, practitioners should check whether patients have been administered appropriate doses.
-If the doses are sufficient, practitioners should add band ligation to beta-blocker therapy.
-If the doses are not at intended levels, practitioners should adjust the dose though they may still need to apply band ligation.
-If there are contraindications to beta-blockers or patients cannot tolerate the doses, practitioners should then apply band ligation.
-If band ligation falls short in primary prophylaxis, practitioners should perform TIPS. For all patients with Child-Pugh B-C in particular, liver transplantation should be considered.

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Effects of Environmental Chemicals and Drugs on Reproductive Endocrine System

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Abstract
Commonly found in ecosystems, endocrine disruptors are a large group of natural or synthetic compounds and xenobiotics that are toxic to the endocrine system of a living organism. The pesticides, herbicides, and hormonally active substances that are widely used in agriculture and industrial compounds are among the endocrine disruptors. Endocrine disrupters interfere with the immune system, thyroid functions, reproductive systems, and intrauterine life of a living organism. Endocrine disruptors show their oestrogenic, anti-oestrogenic, antiandrogenic, and androgenic effects by activating hormone biosynthesis, secretion, transport, degradation, receptors, or postreceptors. Effects of endocrine disruptors on male genital tract can be observed in estrogenic effects that cause delayed puberty, and, more importantly, reduction in androgen production of Leydig cells. Promycine, linuron, vinclozin, p,p'DDT, dioxin, phthalates, genistein, resveratrol, and bisphenol A are among the natural or synthetic chemicals that alter Leydig cell function. On the other hand, endocrine disruptors such as diethylstilbesterol, dichlorodiphenyltrichloroethane/dichlorodiphenyl-dichloro ethylene , methoxychlor, bisphenol A, polychlorinated biphenyls A, polychlorinatedbiphenyl, dioxins, and phthalates cause premature thelarche and precocious puberty with their estrogenic effects in girls. Atrazine, trenbolan acetate, lead, and vinclozis are among the other endocrine disruptors that may cause late puberty in girls. This article is a review of the recent publications that study the influences of endocrine disruptors on endocrine systems during puberty and adolescence, the growth and development periods of children.
Key Words: Endocrine Disruptors; Reproductive System; Children.

Cinsel Gelişimi Etkileyen Çevresel Faktörler ve İlaçlar

Özet
Ekosistem üzerinde çok yaygın olarak bulunan ve sayıları giderek artan doğal veya sentetik, hormonal olarak aktif, endokrin sisteme toksik olan maddelere ve ksenohormonlara endokrin bozucular denmektedir. Çevrede bulunan veya tarımda kullanılan haşere ilaçları, bitki koruyucular, bitkilerin hızlı büyümesini artıran hormonal ilaçlar ve endüstriyel maddeler endokrin bozucuların listesini oluşturmaktadır. Endokrin bozucular intrauterine döneme etki ederek konjenital malformasyonlara yolaçabildiği gibi; postnatal dönemde üreme, immun sistem ve tiroid fonksiyonlar üzerine de olumsuz etki gösterirler. Endokrin bozucular hormonların biyosentezini, salınımını, transportunu veya yıkımını reseptör veya postreseptör aktivasyon yoluyla etkileyerek; östrojenik, antiöstrojenik, antiandrojenik veya androjenik etkiler ile gösterirler. Endokrin bozucuların erkek genital sistem üzerine etkileri, östrojenik etkilerinden dolayı daha çok gecikmiş puberte olarak gözükmektedir ve en önemli etkisini Leydig hücrelerinin androjen üretimini azaltarak göstermektedir. Özellikle promycine, linuron, vinclozin, p,p'DDT, dioxin, fitalatlar, genistein, resveratrol ve bisphenol A Leydig hücre fonksiyonunu etkileyen doğal veya sentetik kimyasallar arasında yer almaktadır. Kızlarda ise diethylstilbesterol, dichlorodiphenyltrichloroethane /dichlorodiphenyl-dichloro ethiylene, methoxyklor, bisphenol A, polychlorinatedbiphenyl, dioxinler ve fitalatlar gibi endokrin bozucular, östrojenik etkileri ile erken telarş ve puberte prekoksa neden olmaktadır. Kızlarda geç puberteye neden olan endokrin bozucular ise atrazin, trenbolan asetat, kurşun ve vinclozindir. Bu yazı endokrin bozucuların, hızlı büyüme dönemindeki çocukluk çağı ve adölesanların sürekli gelişim ve değişim halinde olan endokrin sistemleri üzerine etkilerini son yayınlar ışığında gözden geçirmektedir.
Anahtar Kelimeler: Endokrin Bozucular; Cinsel Gelişim; Çocuklar.

Sexual development gains momentum in the embryonic period and adolescence. Environmental factors that affect human ecosystems have potential influence on especially these two processes in life in terms of endocrine function and, particularly, of sexual development (1). Increasing in number with a widespread effect on humans, these natural or synthetic, and hormonally active substances and xenohormones are called endocrine disruptors (ED). EDs are toxic substances to the endocrine system (2). The list of EDs includes environmental and crop protection substances like insecticides and pesticides as well as hormonal drugs and industrial substances which allow rapid growth of plants (3, 4). Because they experience constant physiological change and are in a process of growing up all the time, children are more prone to get affected by such a toxically charged environment (5). In addition, because genes in children that enable cellular development, DNA replication, and DNA repair along with genes that control the metabolism of endogenous and exogenous agents are more easily influenced by EDs, children have more susceptibility to these agents (6, 7).

In the last 10 years, especially, there have been extensive studies on EDs. Under several subtitles and

with clinical findings like infertility, obesity and so on, these studies have focused on investigating the effect of EDs and determining the effect mechanisms and environmental contamination of some synthetic and steroidal substances that act like endocrine disruptors on the molecular level (8).

While EDs may cause congenital malformations by affecting the fetus in the intrauterine phase, they may also have toxic effects on reproductive and immune systems as well as thyroid functions in the postnatal period that can even lead to an increase in obesity in childhood (6). By influencing endocrine and reproductive systems, EDs affects the human body through enzymatic means such as nuclear receptors, steroid hormone receptors (estrogen receptors), neurotransmitter receptors (serotonin, dopamine, norepinephrine receptors), orphan receptors (aryl hydrocarbon receptor), and steroid biosynthesis and/or metabolism (9). Through receptor or post-receptor activation, EDs affect the biosynthesis, release, transport, or destruction of hormones; in this way, they create oestrogenic, anti-oestrogenic, androgenic, or antiandrogenic effects (10-12). Mimicking numerous hormonal effects in a very good way, therefore, EDs show different clinical signs in boys and girls (13) (Table 1).

Table 1. The potential effects of endocrine disruptors on genital system.

	Fetal/Neonatal	Prepubertal	Pubertal
Male	Intrauterine growth restriction Undescendent testes Hypospadias	Premature pubarch	Small testes and high FSH Early puberty Delayed puberty
Female	Intrauterine growth restriction	Premature thelarche Peripheral precocious puberty Premature pubarch	Secondary central precocious puberty Polycystic ovary syndrome Delays in ovulatory cycles

FSH: Follicle stimulating hormone

The effects of endocrine disruptors on male sexual development:

The occurrence of secondary sexual characteristics in males before the age of 9 is defined as early sexual maturation (14). Most endocrine disruptors have oestrogenic effects; they employ androgenic effects less. Therefore, ED-related early puberty is less common in males; delayed puberty, however, is a more common condition in boys (13) (Table 2).

Table 2. The effects of some specific EDs on male genital system.

	Effects on animal models	Potential effects on humans	Potential effect mechanism
Vinclozolin	Hypospadias, undescendent testes		Delay in DNA metilation of germ cells (Epigenetics)
DES	Hypospadias, undescendent testes, micropenis	Hypospadias, undescendent testes, micropenis, epididymal cyst	Increase in oestrogen receptor expression in the epididyme, increase in IGFB3 levels
DDT	Decrease in fertility	Undescendent testes	
DDE		Undescendent testes	
Phthalates	Dcerease in anogenital distance, undescendent testes, oligospermia	Dcerease in anogenital distance and leydig cell functions, hypospadias	Decrease in testosterone synthesis
PCB	Decrease in spermatogenesis, delayed puberty	Decrease in penis size, delayed sexual maturation, decrease in fertility, cancer in fetal testes	
BPA	Abnormal growth in prostate and urethra		Increase in oestrogen in the hypothalamus, increase in androgen receptor expression in the prostate

DES: diethylstilbestrol, DDT: dichlorodiphenyltrichloroethane, DDE: dichlorodiphenyldichloroethylene, PCB: polychlorinated biphenyls, BPA: bisphenol A, IGFB3: insulin-like growth-binding protein 3

Endocrine disruptors have various effects on male reproductive system and the most important of these is reducing the androgen production in Leydig cells (10). Experiments on humans and animals have both shown that males may suffer from inadequate masculinization and malformation of the genitalia due to ED-affected fetal Leydig cell dysfunction. Inadequate development of Leydig cells in the adolescence may also manifest itself as decreased libido and spermatogenesis (10). EDs affecting Leydig cell function are shown in Table 3 (13):

By inhibiting the binding of androgen to androgen receptors and inhibiting steroidogenesis in Leydig cells, EDs specified in the table bring about incomplete masculinization. EDs are one of the reasons of the diseases defined under the title "testicular dysgenesis syndrome." This syndrome may surface in the form of cryptorchidism, hypospadias, testicular cancer, and decrease in semen quality (10).

Since obesity is now a common phenomenon all over the world with an increasing rate of frequency and prevalence, it does not only effect humans but also animal species by increasing the average weight. This has caused an increase in the number of studies concentrating on the relationship between ED and obesity. Some of these publications have attempted to explain this relationship by EDs influence in reducing Leydig cell function and increased oestrogenic effects (15).

Table 3. Natural and synthetic chemicals that effet Leydig cell formation.

Chemicals	Effect mechanism	Area of use and sources
Procymidone	Androgen receptor antagonist	Fungicide
Linuron	Androgen receptor antagonist	Herbicide
Vinclozolin	Androgen receptor antagonist	Fungicide
p,p'DDT	Androgen receptor antagonist	Pesticide
Dioxin	Aryl hydrocarbon receptor antagonist	Carbon hydrocarbons
Phthalates	Peroksizom proliferator activated receptors (PRARs)	Plastic materials
Genistein	Oestrogen receptor stimulator	Soy-based food
Resveratrol	Oestrogen receptor stimulator	Red wine, red grapes
Bisphenol A	Oestrogen receptor stimulator	Polycarbonate plastic materials

McGray et al. have demonstrated the androgen receptor antagonist effects of pesticides like procymidone, linuron, vinclozolin, and p,p'-DDT on quails (16,17). Phthalates, which is especially commonly used in plastic toys, create adverse effects on male reproductive system during certain stages of development by inhibiting steroidogenesis of the Leydig cells (10).

A member of the polychlorinated dibenzop-dioxin groups, 2, 3, 7, 8 tetra chlodibenzo-p-dioxin (TCDD) is an industrial product that affects Leydig cells by disrupting steroidogenesis and decreasing sex steroids and LH receptor expression. It also causes inactivation in steroid hormones through cytochrome P450 induction (10, 18).

Cheng CY et al.'s 2011study has shown that environmental toxic substances like Bisphenol A and cadmium distort the occludin/20-1/focal adhesion kinase (FAK) complex in the blood-testis barrier while also affecting the Sertoli cells (19). Again, Haeba et al. have conducted a study to examine the effect of vinclozolin on vertebrates by applying the substance on Dapnia Manga, a plankton. This study has demonstrated that vinclozolin has antiandrogenic effects on male Dapnia Manga as it reduced the rate of reproduction (20).

Methoxychlor (MXC) leads to damage in the sexual behaviours of adult male quails. After a study conducted on Japanese quails for two generations, Ottinger et al. have pointed out that MXC-exposed male quails have shown abnormalities in sexual behaviour while also these males have had less hypothalamic, catecholamine, and plasma steroid hormones (21). Having replaced DDT, methoxychlor is an insecticide that has been in use in fruit and vegetable production for years. By injecting MXC to quail eggs, Ottinger et al. have also shown that this substance causes impaired sexual behaviour in male offsprings in the long term (21). The reason for selecting quails in this type of studies is the well-defined reproductive endocrinology and reproductive behaviours of the quail.
Ottinger et al. have investigated the effects of estradiol, ethinyl estradiol, atrazine, methoxychloro DES, genistein, vinclozolin, p.p'DDE, and trenbolone acetate on male reproductive function and reproductive behaviours and concluded that these substances limit reproductive behaviours. However, they have also pointed out that the effect may change according to EDs and dose, even creating inverse effects at times (10).

It is known that catecholamines have stimulant effects on reproductive function and behaviours. As much as it affects water balance, vasopressin, for instance, is known to have a modulatory effect on sexual behaviour (10). Because as studies on invertebrates have proved, vasopressin and vasotocin found in the stria terminalis and amygdala of the male brain contain more neuronal cells with a higher intensity. For example, vasotocin has a direct effect on the sexual behaviours of male quails (22).

To investigate the effect of alcohol as an ED, Anderson et al. have conducted a research on adolescent males during puberty (23). As a result of this research, they have concluded that alcohol decreases testis weight, sperm count and motility, and the effect of sperms on fertilisation while it also causes an abnormal increase sperm incidence.

Biologically natural phytoestrogens, isoflavone found in soybean and genistein found in other plants are 1000-fold less active than normal oestrogen (E2). However, when injected into male quail egg embryos, these substances impair sexual development; these embryo subjects have also shown a decrease in immunostaining due to arginine vasotocin (AVT) in the hypothalamus (24). Similarly, after being injected into embryos, DDE and 2,2-bis (4-chlorophenyl)-acetic acid (DDA), two

active metabolites of DDT, have reduced mating ability (24, 25).

The effects of endocrine disrupters on female sexual development:

The development of secondary sexual characteristics in females before the age of 8 is defined as early sexual maturation (14). Many EDs have oestrogenic effects and they may result in early thelarche and precocious puberty in girls (13) (Table 4).

Table 4. The effects of some specific EDs on female genital system.

	Effects on animal models	Potential effects on humans	Potential effect mechanism
Vinclozolin	Multisystemic malfunction, tumours		Affected DNA metilation of germ cells (Epigenetics)
DES	Susceptibility to malignincies	Vaginal adenocarcinoma in babies whose mothers use DES during pregnancy	Increase in oestrogen receptor expression in the epididyme, decrease in IGFB3 levels
DDT/DDE	Precocious sexual maturation	Precocious puberty, increase in breast cancer risk	Neuroendocrine effects through aryl hydrocarbon receptors and oestrogen receptors
BPA	Breast ductus anomalies, precocious puberty	Abortions	Apoptotic activity inhibition in breast tissues
PCB	Neuroendocrine effects, behavioural shifts		Effects on oestrogen and neurotrasmitter receptors
Dioxins	Breast ductus development anomalies		Aryl hydrocarbon receptor inhibition through cytokinesis 2
Phthalates		Premature thelarche	

DES: diethylstilbestrol, DDT: dichlorodiphenyltrichloroethane, DDE: dichlorodiphenyldichloroethylene, PCB: polychlorinated biphenyls, BPA: bisphenol A, IGFB3: insulin-like growth-binding protein 3

EDs with estrogenic effects in females have been identified by many researchers. These are estradiol (an endogenous oestrogen receptor (ER) agonist), diethylstilbestrol (a medicament), genistein (a soy phytoestrogen), methoxychlor (a pesticide), and PCB-126 (an industrial substance) (8).

It has been reported that oestrogen given to rodents before the onset of sexual maturation causes early opening of the vagina, which corresponds to breast development in humans (11, 26). It has also been pointed out that some phytoestrogens that contain isoflavones such as genistein (found in soybeans and soy-based products) and daidzein give rise to early vaginal opening and increase in the uterus width (25, 26). For example, the daidzein, genistein, and total isoflavone were significantly high in the serum of Korean girls with central pubertas praecox (27). However, some studies suggest that isoflavones do not distinctly lead to early puberty in girls (28). Still, it is accepted that the oestrogen-dependent tissues of children who feed on a isoflavone-rich diet are affected by isoflavones. However, once affected, these tissues do not always result in early puberty (as in the case of increase in uterine elevation in mice), proliferation of the vaginal epithelium, or increase bone density. In light of all these studies on various effects of EDs such as phytoestrogens, which have estrogenic effects, have led researchers to study the effect mechanisms of phytoestrogens. Bateman et al. have detected decrease in GnRH secretion in mice that were exposed to phytoestrogens. They have explain this with the decrease in the fibre density in anteroventral periventricular and arcuate nucleus stimulated by kisspeptin, a peptide that is normally located in the hypothalamus and stimulates GnRH (29). Methoxychlor (MXC) is a pesticide that has been used as an alternative to DDT for a long time. Experiments in rats have shown that subjects exposed to MXC in the fetal period have early vaginal opening in future sexual development (30).

Bisphenol A (BPA), which can be found in plastic toys and plastic bottles, causes early vaginal opening and early puberty in female rats despite the fact that it has weak oestrogenic effects (31). In addition to these effects, BPA is also known as a teratogen and carcinogen substance. It is known that mice are under higher risk of breast cancer in adulthood when they are exposed to oestrogen for long periods of time in fetal period. As a carcinogen substance, BPA, when applied to fetuses in long terms, gives rise to maturity in the mammary glands in mice. Early prepubertal BPA exposure accelerates the onset of puberty in female mice. The effects of Bisphenol A, all of which are carried out through its impact on the hypothalamus, influence oestrogen receptors and accelerate the onset of puberty in female rats (32). As Bisphenol A brings about an increase in the density of the fibres of paraventricular, ventromedial, and arcuate nuclei in the hypothalamus, it results in changes in the reproductive functions of mice. As a result, the effect of BPA is focused on these certain nuclei in the hypothalamus, which in turn, gives rise to increase in weight gain in female rats and, thus, impairs the reproductive function. The morphogenesis of the mammary glands of fetuses exposed to perinatal BPA

also changes (33). Of course, this effect is also created by influencing oestrogen receptors.

Phthalates are a type of EDs usually found in soaps, shampoos, plastic items, cosmetic ingredients, and intravenous and PVC medical tubes (11, 34). Phthalates have systemic impact. The effects of phthalates have been a subject of research in recent years and through these studies it has been proved that they have adverse effects on the course of pregnancy, semen quality, thyroid functions, respiratory system, and neuromotor development of children while they also cause precocious puberty especially in girls (35). It has also been reported that they even increase the risk of allergies and asthma prevalence, reduce muscle mass in boys, and cause hypersensitivity. But its effects on reproductive functions are of greater importance. Studies have pointed out that phthalates reduce LH, free testosterone, and sex hormone binding protein levels (35). Indeed, there were high levels of phthalate in the urine samples of girls with precocious puberty and early thelarche (34-36). Another study has shown that phthalates give way to early vaginal development and an increase in the size of the uterus in girls (37).

Kakeyema et al. have shown that giving dioxin and polychlorinated dibenzodioxins in small doses to female mice has resulted in precocious puberty. Their study has proven that dioxin type EDs cause early maturation of hypothalamo-pituitary axis and early development of genitalia (38). A study conducted on immigrants living in Belgium reports that they have found high levels of p,p'-DDE, a DDT metabolite, in the urine samples of 84% of the girls with precocious puberty. This ED effect has been explained by the stimulation of the hypothalamo-pituitary axis due to weak oestrogenic effect. To analyse the effect mechanism of p,p'-DDE, some researchers have studied the impact of this metabolite on the Mullerian duct in girls during the gonadal development (39).

The toxic effects causing the increase in delayed puberty in girls in the last decades have been explained by EDs such as lead, vinclozolin (a fungicide with an androgenic effect), DDT and its metabolite DDE, trenbolone acetate (a anabolic androgen receptor agonist), and atrazine (a herbicide).

Some researchers have reported that, once applied to embryos trenbol acetate influences female reproductive functions and causes delayed puberty (40). Toxic effects of lead, which is another ED causing late onset of puberty in girls, have been the subject of several studies. For example, lead, even at very low doses, delays puberty in female mice (41). In another outstanding research, Mendola et al.'s survey of PubMed data base articles published between 1997 and 2007 has reported lead to be the most influential toxic substance that effects reproductive system of girls (42). Another study analysing the relationship between blood lead levels and puberty prolongation has pointed out that the onset of puberty varies depending on blood lead levels (43). There is an inverse relationship between high blood lead levels in girls during puberty and inhibin B hormone, a sign of follicular development (44). Although these studies indicate that high lead levels delay follicular growth and puberty, low inhibin B levels in girls with delayed puberty should be regarded as a warning sign to check lead levels. However, in contrast to these findings, another study on 192 healthy girls has demonstrated that lead does not have any effects in breast development (45).

Another ED that is toxic for female reproductive system is atrazine. Particularly those with agricultural jobs are exposed to atrazine. The amount of atrazine in the drinking water also poses a problem for public health. To investigate the toxic effects of atrazine in patients, it is adequate enough to study the urinary atrazine mercapturate levels (46). The toxic effect of atrazine manifests itself by disrupting the oestrogen-based hormonal balance of the female reproductive system in favour of androgens. Some researchers assert that this effect may also manifest itself by increasing the rate of preterm births (47). A study conducted in Illinois, the United States, has demonstrated that females between the ages of 18 and 40 who were exposed to atrazine had irregularities in menstrual cycles, elongation in the follicular phase, and increase in infantile ovulatory cycles (48).

Other EDs that may cause late onset of puberty in girls are vinclozolin and Bisphenol A (BPA). It has been found out that while vinclozolin reduces the gestation period and number of pregnancy as well as increases the percentage of abortions, and BPA also has an increasing effect on the number of abortions (49).
Parallel to the time spent in urban life, the amount of toxic substances that threaten public health also increases. Toxic substances effect all systems of human health in varying degrees. Such toxic substances are especially effective during the fetal period, period of rapid growth in childhood, and adolescence along with the ever changing endocrine system during these periods. Endocrine disruptors (EDs) have oestrogenic, anti-oestrogenic, androgenic, and antiandrogenic effects. EDs usually manifest themselves by disrupting the hypothalamo-pituitary axis and changing the hormone balance. Clinically, these effects may point to early puberty or late puberty. Although there are many drugs and toxins that have been identified as EDs, it is for sure that we still live in a world of many unidentified substances that we are exposed to in our everyday lives. To see the effect of these substances on future generations, there is need for extensive research and experiments on humans and animals.

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Spontaneous Cecum Perforation Associated with Entero-Behçet

Enterobehçete Bağlı Spontan Çekum Perforasyonu

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Dear Editor,

First identified by Hulusi Behçet in 1937 and its etiology still unknown, Behçet's disease is a chronic multi-systemic vasculitis that can affect almost every organ and system. Entero-behçet disease refers to the gastrointestinal system involvement. In a study conducted in Turkey, the gastrointestinal involvement rate of Behçet's disease in Turkey was found to be 1,4% (1). In this letter, we aim to provide a case of isolated cecal perforation connected to entero-behçet. A thirty-six-year-old female who had a known story of Behçet's disease was admitted to our emergency department with abdominal pain. The physical examination showed common defence and rebound tenderness in the abdomen. The patient's WBC values were high (15000). We have observed free fluid in the right lower quadrant abdominal and the pelvis in the pelvic ultrasound. The patient did not have a story of steroid use. We did not observe any pathologies in the gynecological examination either. We decided to apply emergency exploration. The exploration showed perforation foci in two different areas in the cecum the largest of which was 1 cm. Thus we agreed to apply ileocecal resection was performed double barrelled ileo-colostomy. The patient was discharged in good health on postoperative day 5. The postoperative pathology report was consistent with vasculitis and entero-behçet.

We closed the double barrel and colostomy by administering end to end anastomosis after 6 months. Behçet's disease may manifest itself with vasculitis related chronic abdominal pain as well as vasculitis, secondary ischemia, necrosis, and perforation that cause acute abdomen issues (2). Having considered the appendicitis induced pathologies and gynaecological pathologies on the foreground, we decided to apply an exploration by using a standard MC-Burney incision. We found two perforated areas on the back wall of the cecum prior to the operation. Then we expanded the incision towards the right and upwards. Because the inside of the abdomen was contaminated and the patient had a history of Behçet's disease, we considered the application of anastomosis unsafe. Instead we performed double barrelled ileo-colostomy followed by ileo-cecal resection. We were able to establish full exploration by extending standard MC-Burney incision laterally and upwards during the surgery. We discharged the patient without any issues on postoperative 5th day.

We closed the double barrel and colostomy by applying end to end anastomosis after 6 months. There are studies reporting intestinal involvement and perforation due to intestinal involvement in Behçet's disease. Practitioners should keep in mind the possibility of entero-behçet related intestinal ischemia and perforation in Behçet's disease patients with acute abdominal symptoms. In these patients, applying midline incision as the surgical incision method will facilitate the exploration. In such cases, surgical exploration should be made carefully.

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The Case of a Diplopia and Visual Impairment Developing Patient after Spinal Anaesthesia

Spinal Anestezi Sonrası Diplopi ve Görme Bozukluğu Gelişen Bir Hasta Olgusu

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Dear Editor,

Blocking subarachnoid nerve roots with local anaesthetics brings about intense sensory and motor block. Although spinal anaesthesia is an very reliable method when it is applied with suitable approaches, it can still lead to back pain, severe neurological damages, and even to death. Complications like diplopia, headache, hearing loss, tinnitus, nausea, vomiting, and loss of consciousness may follow spinal anaesthesia (1). Among these complications, diplopia is very rare. In some cases, intracranial hypotension due to cerebrospinal fluid (CSF) leakage is known to give way to damages in the sixth cranial nerve which in turn leads to diplopia (2).

In this letter, we aim to present the anaesthetic management of a patient who developed diplopia and visual impairment after spinal anaesthesia.

A 27-year old male patient with no additional pathology in his medical history was taken to the operation room for a planned inguinal hernia repair. Before the operation, the non-invasive blood pressure was 135/77 mmHg while the heart rate was 75 beats/mins and SpO2 was 98%. After achieving pre-hydration with 500 mL 0.9% NaCl, we applied the spinal anaesthesia in sterile conditions in sitting position with a 22-gauge spinal needle through the L3-4 range by administering 12.5 mg 0.5% bupivacaine. Following the anaesthesia application, in the 10th minute, the sensory block level was T8-10 but in the 30th minute of the operation, the patient developed blurred vision and diplopia. At the end of the operation, now hemodynamically stable, the patient was taken to the recovery room. We administered 500 mL of colloid in the recovery room and monitored the patient for neurological symptoms, hemodynamics, and block level. The visual impairment problem recovered within an hour while the patient was neurologically and hemodynamically stable with declined sensory block. After the puncture application, due to a possible CSF leak, we sent the patient back to the service floor with suggestions of bed rest, hydration through fluid intake, and analgesia. With no pathologies following the postoperative neurologic and ophthalmologic examinations and imaging, the patient was discharged on the second day of his hospitalisation.

The incidence of diplopia after spinal anaesthesia ranges between 1/300 and 1/8000. The incidence rate has actually fallen down as the less traumatic needles replaced formerly used spinal needles that were more likely to bring about complications. In more than 80% of patients, diplopia is reported to improve spontaneously within 2 weeks to 8 months. Although emerging intracranial hypotension is generally thought to effect all cranial nerves except for I-IX and X, cranial nerve VI is reported to be the most affected nerve due to its length in the intracranial area. The formation mechanism is described as the development of local ischemia and function failure due to stretching of nerve caused by intracranial hypotension (3).

Our patient underwent spinal anaesthesia in one sitting without any difficulty. The spinal anaesthesia related CSF loss after puncture varies depending on the thickness and type of the needle as well as the patient group. Using thinner and pencil-point spinal needles helps reduce the frequency of CSF loss after puncture. To secure the volume of CSF, patients are recommended to have bed rest and fluids to maintain hydration.

Serious complications may occur during and after spinal anaesthesia. Practitioners need to be careful when applying the required techniques. Underlining the importance of informing patients about possible risks and of monitoring patients closely in order to recognise probable temporary or permanent complications, we wanted to share our experienced with the readers.

This study was presented at the 47th Turkish Anaesthesiology and Reanimation Congress (20-24 November 2013, Antalya).

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Life-Threatening Poisoning Associated with Henbane Plant

Hayatı Tehdit Eden Ban Otu Zehirlenmesi

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Dear Editor,

Hyoscyamus Niger (HN) is a very common and highly hallucinogenic plant which contains anticholinergic agents. The HN is found in every region in Turkey. It is 25-80 cm tall with yellowish, purple flowers. As an annual herbaceous plant, it opens up with a lid-like cover when it is ripe and contains many seeds in its fruits. HN is commonly known as "stinking nightshade" or "black henbane;" in Turkey, HN is defined as "Ban Plant" (Ban Otu) or "Crazy Bat" (Deli Bat). There are 6 different types of henbane in Turkey. Black henbane and maize henbane are the kinds used in medicine. Maize henbane grows in and around Malatya in Turkey. Its leaves contain hyoscyamine, scopolamine (hyoscine), and several tropane alkaloids. Glycosides is found in the entire body of the plant, though it is dense in the seeds (1). The oral intake can cause central and peripheral anticholinergic effects. It is known that HN poisoning leads to anticholinergic syndromes. In this case report, we are presenting the life-threatening poisoning of a family of four after the accidental oral intake of HN.

10 minutes after cooking and consuming a plant in their garden, which was reported to be HN, all members of the family developed nausea, vomiting, visual and speech disorders, dry mouth, altered consciousness, and palpitations. The investigation about the plant has identified it to be HN. The initial evaluation at the ER revealed that the 77-year-old father of the family had clinical signs like meaningless speech, agitation, visual hallucinations, dilatation in both pupils, difficulty in movement, facial flushing, and respiratory distress. The results of this patient's ER examination was as follows: arterial blood pressure (BP): 90/60mm Hg; heart rate (K): 60/mins; filiform pulse; oxygen saturation (SpO2): 94%. The 67-year-old mother similarly had nausea, vomiting, palpitations, dry mouth, and agitation. This patient had 95/60mm Hg arterial blood pressure, 80/mins heart rate, and SpO2 was 98%. There were two other patients; a male and a female, both aged 37. These patients also had nausea, vomiting, and palpitations.The routine laboratory findings of the patients were normal. Considering this revealing clinical picture, we diagnosed the patients with poisoning related central anticholinergic syndrome (CAS). To monitor the patients closely, we transferred the patients to the intensive care unit. We performed ECG, BP, and SpO2 monitoring for each patient.We provided supportive breathing with oxygen masks (5L/min). We applied gastric lavage with nasogastric tube and gave each patient 1mg/kg of activated charcoal. Because the patients did not show any signs of physostigmine, we started a symptomatic treatment. Developing superficial breathing, we administered 3mg of intravenous (iv) midazolam which was followed by an endotracheal intubation. Next we started intermittent positive pressure ventilation (IPPV) with mechanical ventilator support. The arterial blood gas values of the patient was then hemodynamically stable. Achieving strong spontaneous respiration 24 hours after the intubation, the patient was extubated. Other patients received symptomatic treatment. With no further complaints and stable hemodynamics, the patients were discharged after 48 hours.

HN poisoning is a rare kind of poisoning in the literature. HN is reported to have caused central anticholinergic syndrome (SAS) due to the alkaloids it contains. Because of its anticholinergic properties, the intake of HN brings about central and peripheral symptoms (2). Central effects may, in turn, result in confusion, anxiety, delirium, hallucination, myoclonus, dysarthria, choreoathetosis, hyperactive deep tendon reflexes, convulsions, and coma. The peripheral anticholinergic effects that may surface are mydriasis, peripheral vasodilation, hyperpyrexia, tachycardia, urinary retention, decreased gastrointestinal motility, decreased secretions, and respiratory depression. In the treatment of patients with suspicion of intoxication, practitioners should ensure respiratory and circulatory continuity and start antidote treatment in case of gastrointestinal decontamination and other similar conditions that require such treatment (1).

Our patients had both central and peripheral anticholinergic symptoms. Because the signs and symptoms were typical, we were able to initiate the treatment without delay. We needed to provide mechanical ventilation support for the patient who developed respiratory failure and loss of consciousness. In such cases, patients should be monitored closely in terms of tachyarrhythmias and cardiac state, which may develop depending on the degree of vagal impact on the sinoatrial node. Physostigmine, an

acetylcholinesterase inhibitor, may be required in patients with dysrhythmia, significant hypertension, uncontrolled hyperpyrexia, convulsions, and coma (3). If physostigmine could not be found, practitioners should consider symptomatic treatment.

The oral intake of henbane may cause anticholinergic side effects. We believe that close follow-up, respiratory support, and symptomatic treatment may prevent mortality and morbidity resulting from the potentially life-threatening intoxication due to henbane intake.

Kind Regards

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