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AIMS AND SCOPE

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

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

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

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

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

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All submissions are screened by a similarity detection software (iThenticate by CrossCheck).

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3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged in the title page of the manuscript.

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The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2016 - http://www.icmje.org/icmje-recommendations.pdf). Authors are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.istanbulmedicaljournal.org. Manuscripts submitted via any other medium will not be evaluated.

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Title page: A separate title page should be submitted with all submissions and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
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- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

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

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

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Methods, Results, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

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

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

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

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INSTRUCTIONS TO AUTHORS

Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

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

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

Table 1. Limitations for each manuscript type

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

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

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

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

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

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

References

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

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

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

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

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

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

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

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

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

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

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

REVISIONS

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

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal’s webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

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EDITORIAL

Dear My Collogues,

For the last seven years, I was honored to serve as publishing manager, associate editor and finally editor of the İstanbul Medical Journal, and I am completing my mission with this last issue of 2019. I am handing editorial duty to Dr. Feray AKBAŞ.

In these seven years, we have carried out several essential duties as the editorial board for the development of the necessary infrastructure for academic publishing. Some critical work was done, such as making a website, obtaining an electronic ISSN number, making electronic copies of all old printed archives, and making all past issues accessible on the website. In addition to these, long waiting times due to the printing of 8-10 articles in an issue was overcome by increasing the annually published issues from 4 to 6, and by increasing the number of articles per issue regularly over the years. Additionally, the number and type of reviewers in our reviewer pool was increased dramatically during this period, and the number of reviewers was increased by five times compared to 7 years ago. We managed to enter a large number of international indexes, and by making our journal fully published in English, we made essential progress in international recognition and accessibility. Also, it was possible to receive and publish some articles from vast geographic area such as far Asia or North America. I am grateful to “Aves” and “Galenos” for their contributions and efforts in composing and publishing at international standards while the attempt to enter the global indexes.

I had the opportunity to work together with Dr. Cüneyt MÜDERRİSOĞLU in the previous editorial board, and I would like to commemorate him respectfully once again. Also, I would like to express my gratitude to Dr. Hayri POLAT, Dr. Gürhan ÇELİK, Dr. Mehmet Salih GÜREL, Dr. Behiye Pınar GÖKSEDEF, Dr. Serkan SARI, Dr. Turgut KARABAĞ, Dr. Nevra DURSUN and new editor Dr. Feray AKBAŞ, for their efforts, understanding and support during this long period.

I would like to thank Özgür YİĞİT, the owner of the journal and the head of the Istanbul Training and Research Hospital, for the opportunity to take part in the editorial board of the Istanbul Medical Journal.

I wish happy New Year all of you.

My best regards,

MD, Tevfik Fikret ÇERMİK

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EDITORIAL

Son yedi yıldır, öncesinde yazı işleri müdürü, yardımcı editör ve sonrasında editör olarak hizmet vermekten onur duyduğum İstanbul Medical Journal dergisindeki görevlerimi bu sayıyla birlikte tamamlıyor ve editörlüğü sayın Dr. Feray Akbaş'a devrediyorum.

Yedi yıllık bu dönemde dergimizin akademik yayıncılık için gerekli olan alt yapısının geliştirilmesi için editöryel kurul olarak önemli çok sayıda çalışma gerçekleştirdik. Bir web sitesi kurulumu, elektronik ISSN numarasının alınması, tüm eski basılı arşivin elektronik kopyalarının çıkarılması ve web sitesinde tüm eski sayıların ulaşılır hale getirilmesi gibi bazı temel çalışmalar yapıldı. Bunun yanında bir sayıda 8-10 makale basılması nedeniyle uzun baskı bekleme süreleri, gerek baskı periyodunun yıllık 4 sayıdan 6 sayıya çıkarılması, gerekse sayı başına basılan makale sayılarının yıllar içinde düzenli bir şekilde arttırılması nedeniyle sorun olmaktan çıkarıldı. Yine hakem havuzumuzda yer alan hakem sayı ve çeşidinde bu dönemde önemli bir artış kaydedilerek 7 yıl öncesine göre hakem sayımız 5 kat arttırılarak makale değerlendirilme sürelerinde iyileştirmeler gerçekleştirildi. Bu periyotta çok sayıda uluslararası indekse girmeyi başardık ve dergimizi artık tamamen İngilizce makale basar hale getirerek uluslar arası tanınırlık ve ulaşılabilirlik konusunda önemli yol aldık. Dergimize yine bu dönemde Uzak Asya'dan, Kuzey Amerika'ya ulaşan geniş bir coğrafyadan makale gönderimi ve bunların bir kısmının basımı mümkün olabildi. Dergimizin temel hedefleri olan üst düzey uluslararası indekslere girme çabası devam ederken uluslararası standartlarda dizgi ve basımında "Aves" ve "Galenos" yayınevlerine göstermiş oldukları katkı ve emeklerinden dolayı teşekkürü bir borç biliyorum.

Bu uzun dönemde, editöryel kurulda öncelikle beraber çalışma fırsatı bulduğum merhum Dr. Cüneyt Müderrisoğlu saygıyla anıyorum. Ayrıca Dr. Hayri Polat, Dr. Gürhan Çelik, Dr. Mehmet Salih Gürel, Dr. Pınar Göksedef, Dr. Serkan Sarı, Dr. Turgut Karabağ, Dr. Nevra Dursun ve yeni editörümüz Dr. Feray Akbaş'a göstermiş oldukları emeklerinden ve şahsıma göstermiş oldukları anlayış ve destek dolayısıyla şükranlarımı sunuyorum.

Dergimizin bugüne gelmesinde hemen her konuda yoğun desteğini gördüğümüz İstanbul Eğitim ve Araştırma Hastanesi başhekimi ve hastanemiz adına dergimizin sahibi Dr. Özgür Yiğit'e dergimizde çalışma fırsatını bana vermesi nedeniyle teşekkür ediyor ve şahsında yeni editöryel kurulumuza önümüzdeki dönemde başarılar dilerim.

2020 eşiğinde olduğumuz bu sayı vesilesiyle tüm yazar ve okuyucuların yeni yıllarını kutlarım.

Saygılarımla,

Dr. Tevfik Fikret ÇERMİK

İstanbul Med J 2019; 20(6): 492–6
DOI: 10.4274/imj.galenos.2019.36034

A Magical Key to Female Sexual Dysfunction, Sexual Counseling

Kadın Cinsel Disfonksiyonunda Sihirli Bir Anahtar: Cinsel Danışmanlık

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ABSTRACT

This study aimed to express the steps, importance, and benefits of sexual counseling given to women with sexual problems. Sexuality is a complicated process that is shaped by the interaction of many emotional, mental, and behavioral elements. Having a sexual relationship and being able to do it without any problems is an important aspect that affects women's quality of life. Studies on sexuality have improved rapidly within the last 20 years. However, due to such factors as condemnation, shyness, unawareness, misbeliefs, or limited opportunities, women with sexual problems may still fail to find solutions to their problems. Sexual counseling is the assistance provided to clients and couples to eliminate a lack of knowledge, correct wrong information and beliefs, and informing them about sexual myths. Sexual counseling helps women to overcome the problems that they perceive unsolvable and to live sexuality freely.

Keywords: Sexual dysfunction, sexual function, sexuality, sexual counseling

ÖZ

Cinsellik, duygu, düşünce ve davranışsal pek çok unsurun karşılıklı etkileşimi ile şekillenen karmaşık bir süreçtir. Cinsel ilişki yaşayabilmek ve bunu herhangi bir sorun yaşamadan yapabilmek kadınların yaşam kalitesini etkileyen önemli bir boyuttur. Cinsellikle ilgili çalışmalar son 20 yılda hızlı bir gelişme kaydetmiştir. Fakat buna karşın kadınlarda ayıplanma, utanma, farkında olmamak, yanlış inançlar ya da imkanların sınırlı olması nedeniyle cinsel problem yaşayan kadınlar bu sorunlarına bir çözüm bulamayabilirler. Cinsel danışmanlık cinsellikle ilgili bilgi eksikliğinin giderilmesi, yanlış bilgilerin ve inançların düzeltilmesi, cinsel mitler hakkında bilgilendirme amacıyla danışanlara veya çiftlere yardımcı olmaktır. Cinsel danışmanlık, kadının çözümsüz gördüğü cinsel problemlerini aşmasına ve cinselliğini özgürce yaşamasına destek olur.

Anahtar Kelimeler: Cinsel disfonksiyon, cinsel fonksiyon, cinsellik, cinsel danışmanlık

Introduction

Sexuality is the social behavior of individuals or couples. Religious or social effects change an individual's response to sexuality. Masters and Johnson connect sexual response to two fundamental physiological changes: the increase in the blood flow of some parts of the body and the increase in muscle tension. Besides, an analysis of female orgasm indicates three key points called physiological, psychological, and sociological. In this regard, according to Masters and Johnson, fear of performance or social pressures reveal themselves as failure to reach orgasm for women and erection problems for men (1,2).

Sexuality is a multidimensional concept that requires physical and emotional participation. Sexuality and sexual intercourse should not be limited only with the genital system. The genital system forms the majority of sexuality, but as it does not approach the human body as a whole, it is limited only with reproduction. Focusing only on the genital area during sexual intercourse puts skin -the largest erogenous area in the human body- into second place. In this regard, clients and their partners should be encouraged to identify the erogenous areas in their body (3). On the other hand, factors that have effects on sexual health include physiological and emotional health, alcohol and substance use, familial relations, sexual abuse experienced in the past, and other traumatic events (4).

This study addresses the importance of sexual counseling for women and counseling for sexual dysfunctions.

Sexual Counselor

In order to give sexual counseling, one needs to receive comprehensive training, mainly on personal and couple therapies. Such a training process should also include a kind of internship (5).

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A sexual counselor should have a holistic view while evaluating the client, and s/he should not ignore some moral and legal issues. Boundaries of the therapy should also be identified well (6).

Issues such as honesty, privacy, and confidentiality should be prioritized. Information provided by the client should be welcomed attentively, and the sessions should be conducted in a professional framework. Couples may sometimes be given assignments (7).

Sexual Dysfunctions and Counseling

Sexual Desire Disorders

Diagnostic and Statistical Manual of Mental Disorders - fifth edition (DSM-V) defines sexual desire disorder as "persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity that causes marked distress or interpersonal difficulty". Diagnosis requires a "recurrent and persistent" complaint. The current prevalence of sexual dysfunction in women is reported to be between 30% and 60%. The most prevalent female sexual dysfunction in women is "sexual desire and arousal disorder" (8).

A decrease in sexual desire and sexual activity could cause problems between couples. Significant differences in sexual desire between couples might cause disappointment and tension between the couples (9). People who have sexual desire disorder are far from having sexual fantasies and satisfying themselves sexually (10).

Assessment of people who experience a decrease in sexual desire should include several factors such as the couples' age, hormone features, physical health, and frequency of sexual activity. The person's psychological strength, limitations, values, and attitudes should be identified. Besides these, one of the factors that affect sexual desire is anxiety. Anxiety could prevent pleasure. Another critical factor that affects sexuality is the interaction between couples, which is negatively affected by such factors as anger, lack of communication, and power conflicts. Each spouse's family features, religious beliefs, cultural differences, attitudes, and values contribute to the sexual life of couples. To solve these kinds of problems, the individual should be approached holistically, and trained about sexual intimacy. The counselor should consider various reasons and be flexible in the treatment of sexual desire disorder (11).

Clinical assessment: The evaluation of the person with a sexual desire disorder should include the formation of hypotheses about the reasons for the problem. First impressions, personal responses, relationships, and collective lives should be investigated. In the early period of the treatment, aims and couples' expectations should be identified. Besides, the client should be asked questions for the evaluation of her sexual relationship (3). Sessions at the clinical assessment phase involve the questioning of sexual fantasies and thoughts, sexual activity and its frequency, and the situations disturbing the client. These kinds of sessions also involve privacy issues and the client's viewpoint about her relationship. Starting from the beginning of the treatment, the client should be observed in terms of her negative thoughts about self, spouse, and family. This assessment helps to identify the direction of the therapy. Besides, the use of new psychometric tools for the clinical assessment of counselors has been approved. Female sexual dysfunction can be assessed using valid and reliable sexual function scales such as the Female Sexual Function Index (FSFI) (9,12).

Positive treatment results for people who have sexual desire problem could be maintained under some appropriate conditions, which include the followings:

- Couples' having common sexual desire,

- Couples' having no psychiatric problem,

- The client's willingness to sharing her negative past experiences,

- Identification of the factors that cause stress and anxiety,

- Elimination of the negative thoughts about sexual desire,

- Ability to discuss with the spouse about the treatable difficulties in their relationship,

- Sharing negative religious beliefs (11).

Reasons such as anxiety, depression, and bad body image prevent the treatment of sexual desire disorder. Lack of sexual desire is a complicated issue for the individual. Pessimism is a reaction in case of failure. The counselor should support his/her client in order to solve the problem. Besides, by asking more questions, the counselor should manage the process in terms of the way s/he contributes to the solution for lack of sexual desire. Throughout the treatment process, clients learn about sexual satisfaction slowly. These people should learn to have control over their feelings, behaviors, and sexual satisfaction (10).

Clinical approach: Treatment of sexual desire disorder should primarily include individual and relational issues. The treatment aims to bring sexual desire back. The success of the treatment in these kinds of patients is to maintain satisfaction in the relationship. In some cases, people create personal expectations for themselves. Disappointments might happen when these expectations are not met. The woman might think that she is not valued enough, which could cause a lack of sexual desire. The counselor should be able to reveal these expectations accurately (3).

An overall analysis of the clients who have sexual problems indicates that what couples wonder and worry about is whether their spouse desires them. Pleasure and desire decrease as anxiety increases. The main purpose of the treatment for lack of sexual desire is to eliminate this anxiety. The counselor should start the therapy by explaining the aim and the problems. Another therapy method could be objecting to the ideas that maintain anxiety. For this, the definition of sexuality and sex should be expanded, and focusing solely on sexual intercourse should be prevented (13).

Another case that should be focused on the therapy process is the emotional process that develops during the therapy. The counselor asks couples to explain their feelings to each other so that emotional barriers can be eliminated. The counselor should support the couples' erotic thoughts and fantasies, using which s/he should make perceptions positive (11).

Another side of the therapy is the discussion about the client's sexual desires, needs, and preferences. Some misbeliefs may not be eliminated

without talking with the counselors. Systemic assignments could be given regarding sexual intimacy and fantasies. Individual assignments could include physical exercises, fantasizing, guided masturbation, review of visual materials, or regular use of sex materials. Assignments for couples may include discussing sexual and emotional needs and exercises for the solution to the problems (10).

Sexual Arousal Disorders

DSM-V defines sexual arousal disorder as a lack or absence of desire for sexual activity or fantasies, or lack or absence of sexual excitement/pleasure during sexual intercourse (14). American Urological Association divides sexual arousal disorders as primary, secondary, and situation-specific. Through a detailed history taken from the client, the counselor should identify whether this problem is related to the sexual desire problem, or the decrease in sexual desire developed secondarily. Sexual arousal is a complicated issue to assess. There are limited findings of normal arousal, which is dependent on living conditions, age, and sexual experiences. The physiological response that an individual gives to sexual stimulation is not always at the same level (3).

Changes in the genital area happen with the increase in the bloodstream in the vaginal and clitoral area. A bloodstream increase in the middle wall of the vagina leads to lubrication. A bloodstream increase in the clitoral area leads to fullness and sensory changes (15).

Sexual arousal has both psychological and physical aspects. Some psychological aspects include sexual expectation, anticipatory sexual behaviors, psychic arousal, and sensory extension. Physical aspects of sexual arousal include swelling in vagina entrance, wetness, lubrication, and tingling sensation. The identification of each aspect separately is essential for the treatment of sexual arousal disorder (16).

Sexual problems such as sexual arousal disorder deteriorate women's quality of life and affect their relationships with their partners. While there are cardiovascular, neurologic, and psychological cases accompanied by this case, cancer, and its treatment could also cause sexual arousal disorder. Besides, surgical menopause, which causes a decrease in estrogen hormone, also affects sexual arousal. In addition to these medical cases, cognitive, emotional, and psychodynamic factors cause changes in sexual functions, too (3).

Clinical assessment: Assessment of the person with sexual arousal should be done thoroughly, and the counselor should keep in mind that the information provided by the client might be insufficient (16).

In the first assessment, with an interview session that takes about 45 to 60 minutes, a complete psychosocial, medical, and psychosexual history are taken. Finding out what causes stress in women with sexual arousal disorder has excellent contributions to the treatment. Besides, external genital organs should be examined. Some methods used for genital stimulations include photoplethysmography for the evaluation of the genital stimulus, measurement of labial temperature, Gold Sheffield electrode, and Doppler ultrasonography of clitoral blood flow (17).

Clinical approach: Approach to women's sexual arousal problem includes five rules:

1. The woman's and her partner's views on sexual intercourse are essential because each has a different point of view.

2. The woman's psychology and psychopathology, which includes her ideas, values, or general notions, should be evaluated.

3. The woman and her partner should be evaluated as a whole in terms of the relationship.

4. The couple's family and social life should be observed.

5. The effects of social, cultural, and historical factors should be identified in the evaluation phase (16).

Orgasmic Disorders

DSM-V defines orgasmic disorders as delays in almost every sexual activity, a significant delay in orgasm, lack of orgasm, or low-intensity orgasm. Orgasmic disorder in sexual life could be lifelong or acquired, general or psychological, and caused by situational or both psychological and medical reasons. This dysfunction causes deterioration in interpersonal relationships and stress. The orgasmic disorder might have been caused by misinformation about sex, a decrease in sexual desire, perception of sexual identification, or the effects of medical treatments. Stress, tiredness, general health state, and other personal features also affect sexual desire and response in a negative way (14).

Evaluation of orgasmic disorder in women should include a detailed psychological, social, relational, and medical anamnesis. Besides, the counselor needs to understand the source of the sexual dysfunction. The woman's orgasm problem should be investigated in terms of its frequency, whether it is primary or secondary, and how long it has been experienced. Besides, some other changes that she is going through should be taken into consideration, and the woman's or couple's expectations from the treatment should be investigated (18).

Clinical assessment: It is not known which approach is the most successful one in the treatment of the female orgasmic disorder. Another problem that affects the success of a sexual counselor is the duration of the dysfunction. If dysfunction has been experienced for a long time, and if the woman is applying it as a norm in her life, it could be hard to make her get used to a new change (19).

Clinical approach: Instruction of effective sexual arousal techniques could be helpful for the female orgasmic disorder. Guided masturbation is also an effective method. The counseling process includes instructions for women about how to reach orgasm, about ways of reaching orgasm, and about revealing her body. The woman is guided about understanding what stimulates her, which practices give pleasure to her, or which practice is hard or unpleasant during sexual intercourse. In the first phases of the exercises, the woman is suggested to use a mirror to know her genital organs. She is recommended to have sexual fantasies in order to increase her sexual response, feel her senses, and change her negative thoughts about masturbation. Some women ignore their sexuality and feel guilty during their sexual relationships. Therefore, fantasies should aim to improve the woman's perspective of self as a sexual individual. These fantasies should include both emotional and physical aspects of sex, and sexual function should involve the participation of both aspects. After these exercises are completed, the

next step is to guide the client to sexual intercourse. Supplementary stimulators might be needed at this stage. Coital intercourse during sexual intercourse is important as it increases orgasm frequency by enhancing clitoris contact (19,20).

Dyspareunia

DSM-V defines dyspareunia as permanent or recurrent pain during sexual intercourse, which is not related to vaginismus or a decrease in lubrication. Pain during sexual intercourse harms sexual life. Secondary sexual disorders could also accompany the pain. This case causes negative changes in female sexual behaviors, harmful behaviors, deterioration in partner relationships, a decrease in self-confidence, and mood disorders. Women with Dyspareunia state that they have severe pain during coitus. Besides, they also have pain in penetration cases such as during vaginal tampon or gynecologic examination. Although pain during sexual intercourse is thought to develop mostly during menopause due to a decrease in vaginal elasticity, it is reported to be prevalent mostly between the ages of 18 and 24 (21,22).

Clinic assessment: Several factors may cause physical pain during sexual intercourse. Pain may be caused by congenital anomalies of the genital system, urinary system infections, and acute or chronic diseases. A decrease in estrogen values following physical menopause or surgical menopause -due to its effects on the vagina- could cause pain during sexual intercourse. Episiotomy or other gynecological surgical procedures could cause painful sexual intercourse. Besides, woman's negative thoughts, sexual taboos, stress or anxiety, and lack of sexual education also, despite not causing pain alone, are among factors that increase pain (23,24). Assessment should be done in terms of the exact location of pain during sexual intercourse, severity and type of pain, whether the pain develops before or after penetration, how long the pain lasts, whether it is continuous or occasional, whether there is pain without sexual stimulus, and the time when the pain is felt during sexual intercourse. The effects of pain on the couple's sexual life should also be identified. With this purpose, patients could be administered scales such as FSFI that assesses sexual life (25,26).

Clinical approach: The most important phase of therapy in painful sexual intercourse is training. Patients generally think that the problem will be solved at the beginning of the counseling. However, the related literature indicates that it is quite hard to eliminate the pain. Instead, the client should be asked to tell about her expectations. The purpose of counseling is to help couples to maintain a satisfying sex life again. The counselor should know the source of the problem well. As facing the pain will scare the client, she might avoid mentioning her real problem. Besides, it is important to tell women who experience pain during sexual intercourse that their pain is real. The client should be asked to keep a diary that indicates under which conditions the pain is the lowest and under which ones it is the highest (26). The client could be taught relaxation techniques and exercises. Women who experience pain during sexual intercourse usually avoid observing their genital areas. It is important to help them accept their genital organs again. They could be taught Kegel exercises. The client should be told that the ultimate purpose is not to increase the frequency of sexual intercourse but to increase sexual desire, stimulus, and satisfaction. This situation decreases anxiety and helps to focus on the interviews to be conducted. Besides, in order to maintain recovery in sexual life, the woman should find herself attractive. The counselor should make the client have the self-belief that she is cognitively and behaviorally attractive. The client could be recommended to read an erotic book or watch a video before sexual intercourse or when she is alone at home. She should be told that as masturbation increases sexual desire and stimulation, she should masturbate. The client should be informed about the importance of sexual stimulation before penetration. Many couples focus on sexual intercourse. The client should be explained that sex involves many cases that involve satisfaction and orgasm. Pain during sexual intercourse may cause couples to be deprived of many experiences (23,27).

Conclusion

The purpose of sexual counseling is to help clients or couples to cover a lack of knowledge about sexuality, to correct wrong information and beliefs, and to learn about sexual myths. The aim in sexual counseling is to decrease the woman's sexual fears and worries, increase her emotional and sexual response, decrease her anger at her husband, help her experience new emotional and sexual techniques, increase communication between couples, eliminate thoughts that distract attention during sexual intercourse, and decrease her prejudices about having orgasm. Therefore, sexual counseling is a magical key that could be used in solving women's sexual problems, setting their sexual life free, and increasing their quality of life.

Ethics

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Nanomaterials and Their Effects on Health

Nanomalzemeler ve Sağlık Etkileri

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ABSTRACT

Nanotechnology, which includes many potential applications, is described as the technology of the future and the industrial revolution of the 21st century. The effect of nanotechnology is particularly evident in nanomaterials (NMs) used for chemicals, pharmaceuticals, and personal care products. Properties such as nanoscale size, large surface area, and surface activity make NMs attractive for many applications. It is estimated that more than 1600 nanoscale products are on the market today and that by 2020, more than six million employees will be exposed to engineered nanoparticles (NPs).

Due to the observed changes in the physical, chemical, and toxicological properties of the material in parallel with the decreasing particle size, it is predicted that NPs may cause adverse effects on biological systems. However, due to the relative novelty of nanotechnology, there is a lack of knowledge about the ways humans are exposed to NPs and the possible adverse health effects of NPs. Knowledge of the effects of long-term exposure to engineered NPs on human health is based on *in vitro* studies, *in vivo* animal studies, and a limited number of human exposure studies. In our country, there are no studies in this field. A better understanding of the health effects of NPs, which is expected to have increased production in our country soon, is a scientific necessity to be dealt with for the safe use of NMs. Therefore, it is aimed to evaluate the effects of NPs on human health in the light of current information and to draw attention to the dangers that may develop.

Keywords: Nanomaterials, nanotechnology, nanoparticle, health effects

ÖZ

Pek çok potansiyel uygulama içeren nanoteknoloji, geleceğin teknolojisi ve 21. yüzyılın endüstriyel devrimi olarak nitelenmektedir. Nanoteknolojinin etkisi özellikle kimyasallar, ilaç ve kişisel bakım ürünleri için kullanılan nanomalzemelerde görülmektedir. Nano-ölçekli boyutu, geniş yüzey alanı ve yüzey aktivitesi gibi özellikler nanomalzemeleri çok fazla uygulama için ilgi çekici kılar. Günümüzde 1600'den fazla nanoboyutlu ürünün piyasada bulunduğu ve 2020 yılına kadar altı milyondan fazla çalışanın mühendislik ürünü nanopartiküllere maruz kalacağı tahmin edilmektedir.

Küçülen parçacık boyutuyla paralel olarak malzemenin fiziksel, kimyasal ve toksikolojik özelliklerinde gözlenen değişiklikler nedeniyle nanopartiküllerin, biyolojik sistemler üzerine olumsuz etkilere neden olabileceği öngörülmektedir. Bununla birlikte, nanoteknolojinin göreli yeniliği nedeniyle, insanların nanopartiküllere maruziyet yolları ve nanopartiküllerin olası olumsuz sağlık etkileri hakkında bilgi eksikliği vardır. Mühendislik ürünü nanopartiküllere uzun süreli maruziyetin, insan sağlığı üzerine etkileri hakkındaki bilgi birikimi, *in vitro* çalışmalar, *in vivo* hayvan çalışmaları ve sınırlı sayıdaki insan maruziyet çalışmalarına dayanmaktadır. Ülkemizde ise bu alanda yapılmış çalışma bulunmamaktadır. Yakın zamanda ülkemizde de üretim artışı beklenen nanopartiküllerin sağlık etkilerinin daha iyi anlaşılması, nanomalzemelerin güvenli kullanımı için, ele alınması gereken bilimsel bir zorunluluktur. Bu nedenle makalede güncel bilgiler ışığında nanopartiküllerin insan sağlığı üzerine etkilerinin değerlendirilmesi ve böylece gelişebilecek tehlikelere dikkat çekmek amaçlanmıştır.

Anahtar Kelimeler: Nanomalzeme, nanoteknoloji, nanopartikül, sağlık etkileri

Introduction

Nanotechnology, a rapidly growing science that integrates engineering with biology, chemistry, and physics, is regarded by scientists as the industrial revolution of the 21st century (1). When the dimensions of solid material are reduced to nanometer (nm) dimensions, their physical and chemical properties change. In order to take advantage of these features, we still lack serious information about the health effects of nanomaterials (NMs), which have been increasing in production in recent years (2).

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NMs are potentially useful nanoscale materials with unique properties. The International Organization for Standardization defines the term "NM" as "material with any external dimension in the nanoscale or having internal structure or surface structure in the nanoscale". One nm is defined as the one billionth of a meter, and "nanoscale" is used to express length range approximately from 1 nm to 100 nm (3).

Properties such as nanoscale size, large surface area, and surface activity make NMs interesting for many applications (4). In a study conducted in 2011, the number of NMs produced as a consumer product by 24 countries worldwide was found to increase from 212 to 1317 (5). It is estimated that more than 1600 nanoscale products are on the market today, and more than 6 million employees will be exposed to engineered nanoparticles (NP) by 2020 (6).

NMs are used in many areas such as computer chip technology, automotive catalytic converters, air and space vehicles, food, cosmetics (lipstick, sunscreens, anti-aging creams), dental prostheses and orthopedic implants (7,8). There are more than 800 consumer products with different NM types. It is thought that a person consumes an average of 1012 NPs per day in a standard diet due to food additives (7).

In addition to consumer products, nanoscale molecules are also used in the drug transport system as nanotransporters. Nanotransporter systems have been developed to provide advantages such as reducing drug degradation and loss, preventing possible side effects, increasing drug biocompatibility, and being able to transport the drug in various regions in a controlled manner. These drug transport systems are divided into various classes, such as micelles, dendrimers, liposomes, NPs, and carbon nanotubes (CNT) (9,10). Each has advantages and disadvantages. In the future, it is thought that the release and effect of drugs will happen via nanotransporters with "compliance and time" adjustment through controlling toxicity and regional effects by clinicians and researchers (11). However, since most clinical research reports for nanomedicine products focus mainly on the therapeutic efficacy of drugs, human biosecurity information is limited. In order to evaluate the human biosafety of nanomedicine products in clinical studies, it has been reported that a standardized test battery should be developed, including all indices of blood chemistry, carcinogenic, teratogenic, mutagenic toxicities and immune, nervous and reproductive systems (12).

NMs are grouped according to their size, morphology, production methods, and compositions. Nanostructures are divided into three according to size: a) One-dimensional nanostructures, commonly referred to as thin films, are technologies used in computer chips, anti-reflective coatings and sunglasses, b) two-dimensional nanostructures are nanowires and CNT used in separation and filtration technologies, c) three-dimensional nanostructures include perforated structures, colloids and quantum structures in atomic structure (13). NMs can be a pipe, rod, wire, or sphere according to their morphological structures. Depending on their source, they can be categorized, as engineered NPs and incidental NPs. Engineered NPs are particles produced to use nanometer-specific size-dependent properties (e.g., conductivity, spectral properties, biological distribution). Incidental NPs are defined as NPs that are either formed from anthropogenic sources (e.g., cigarette smoke, diesel fuel exhausts, industrial by-products) or naturally (e.g., marine spray, volcanic ash). Engineered NMs, including NP and nanofibers, are divided into four classes according to compounds: a) carbon-based materials (CNT, graphene, fullerene), b) metal-based materials (quantum dots, nanosilver, nanogold, titanium dioxide), c) dendrimers (nanoscale polymers) and d) composites (7).

Clinical and Research Effects

Nanoparticle Exposure

In addition to occupational exposure to NPs, direct human exposure with medical applications, and air pollution in the environment is a significant concern (14). NPs are taken into the human body through various exposure routes such as respiration, skin, and gastrointestinal tract during the production and consumption processes (15). The size of the nanostructures is very small, and their mass is relatively light. Therefore, especially in the working environment, the main entry route for NP is the respiratory system (15,16). The size of the airborne particles reaching the airways affects the depth of the airways through which the particles can enter and their target organs (2). The primary deposition site of the NP, which is several tens of nanometers in size, is the alveolar area. From the NP reaching the alveoli, those within a range of several nm may reach the systemic circulation through the alveolar wall (17). Thus, they are translocated into secondary organs such as the liver, spleen, and kidney (18). It is estimated that the translocation of the inhaled NP into the circulation and secondary organs is less than 1% of the total mass-based amount. However, this rate is based on estimates from animal studies, and there is a lack of information on the biokinetics of inhaled NP and its long-term effects on humans (19).

Dermal exposure may occur during the application of topical creams and other drug treatments or accidental exposure (20). However, there are controversial data about the dermal absorption of NP. In contrast to studies reporting that NP cannot penetrate the dermis, Oberdörster et al. (21) demonstrated the penetration of various NPs in the dermis and translocation into the systemic circulation through the lymphatic system and regional lymph.

NPs may also enter the body indirectly after mucociliary clearance in the nasal region or directly through the gastrointestinal tract as a result of food, water, cosmetics, and drug consumption (20,21). Without dosimetry and particle kinetics data, it is currently difficult to accurately assess the potential toxicity of foodborne NMs. Besides the direct effects of foodborne NMs, chronic NP exposure is thought to play a role in the development of inflammatory diseases with the potential to disrupt the normal microbiota balance in the gastrointestinal tract (22).

Limited to engineered materials, injections, and implants are also possible routes of exposure. Intravenous and oral administration has a faster systemic effect compared to other routes (23). Since these particles can easily pass into the circulatory system, they can reach the lymph and nervous system and reach many organs, including the brain (24). Also, injected NPs are rapidly absorbed by the liver and kidneys from the circulatory system (18).

The Effects of Nanoparticles on Health

The health effects of NPs may vary depending on the number of physicochemical properties such as size, shape, surface properties, composition, solubility, aggregation/agglomeration, and the presence of mutagens and transition metals in the particles (25). Many engineered NPs have increased surface reactivity and, therefore, may cause local damage by inducing inflammation at the site of accumulation and the formation of reactive oxygen species (ROS) (26,27). NP-induced ROS plays a crucial role in cell and tissue toxicity (28). Overproduction of ROS can trigger oxidative stress, which causes the cells to fail normal physiological redox reactions; thus, it leads to DNA damage, deterioration in cell signaling, changes in cell motility, cytotoxicity, apoptosis and the onset of cancer (29).

ROS are associated with different stages of carcinogenesis, including epigenetic changes, DNA damage, and protein and lipid changes (29). Metal-based NPs, especially silver, gold, and titanium, are essential for ROS production and genetic damage (30). In a recent study, workers with occupational exposure to metal oxide NMs in 14 factories producing and using NMs in Taiwan were evaluated for the first time for epigenetic alteration (methylation) and oxidative DNA damage. In this study, oxidative stress biomarkers and DNA methylation of 87 employees with exposure to metal oxide NMs (titanium dioxide, silicon dioxide, and indium dioxide) and 43 employees with no exposure were compared, and exposure to metal oxide NMs has been shown to cause methylation, oxidative damage to DNA, and lipid peroxidation (31).

It is vital to assess genotoxicity to protect employees from the potentially harmful effects of engineered NPs. Since many commonly used genotoxicity tests are adapted for soluble chemicals rather than particulates, genotoxicity test results for NPs are skeptical (4). However, some *in vitro* and *in vivo* studies have provided useful information on the relationship between NP exposure and genotoxicity in the working environment (32). In the study of Lindberg et al. (33), it was shown that genotoxic changes occurred in pulmonary epithelial cell culture with low doses of carbon CNT and graphite nanofiber exposure. Subsequently, in Lindberg et al. (33) study, human lymphocyte cells were exposed to single-walled CNT (SWCNT), and multi-walled CNT (MWCNT) in low and moderate doses (6.25-300/g/mL) and this finding was confirmed by demonstrating chromosomal abnormalities (33). The point that should be considered in these studies is that genotoxic effects have been observed at the exposure levels expected in occupational environments (2).

From the experimental results, a study was conducted to evaluate potential genotoxic effects of NMs in humans and found significant changes in the messenger RNA and non-coding expression profiles in the sera of workers (eight workers) exposed to MWCNT for more than six months compared to those without exposure (seven workers). Also, described pathways and signaling networks have revealed the potential of MWCNT to produce carcinogenic results in humans as well as pulmonary and cardiovascular effects, similar to rodents previously exposed to MWCNT (34).

As the size of the particles reaching the airways becomes smaller, the depth of the airways through which the particles can enter increases, and thus their effects on the target organs change. In studies evaluating the relationship between particle size and lung inflammation and toxicity, engineered NPs and coarse particles were compared, and a higher rate of lung inflammation and toxicity response to NPs was observed (35,36).

NPs are thought to cause pathological changes in the lung regardless of dose. In two independent studies, mice exposed to SWCNT at doses of 3.3-16.6 mg/kg and 10-40 ug/mouse have developed a strong acute inflammatory response, with the development of pulmonary fibrosis leading to impaired pulmonary function (37,38).

Although we have limited data on engineered NPs, many epidemiological studies have shown a direct coherence between the increased amounts of incidental NP produced in indoor air and the increased adverse health effects associated with cardiovascular disease. There is a strong link that supports the relationship between inflammation and coronary heart disease because inflammation has been proven to be directly associated with atherosclerosis (39). Data from human studies support the link between PM air pollution and the development of cardiac responses leading to atherosclerosis (40). In the review of epidemiological studies, Delfino et al. (41) have clearly demonstrated pathophysiological changes that induce cardiovascular diseases by exposure to ultra-fine particles. In a recent animal study, titanium NPs have been shown to affect ventricular cardiomyocytes besides indirect inflammatory effects directly. In rodents exposed to intratracheal titanium dioxide NPs, shortened repolarization time, increased cardiac conduction and excitability rate, and ventricular arrhythmia were observed (42).

Although there are few epidemiological studies showing the direct effect of engineered NPs on human health in the literature, the known health effects of NMs in the guideline published by WHO in 2017 including all the studies conducted were divided into nine categories: Acute toxicity, skin corrosion/irritation, eye damage/irritation, respiratory and skin sensitization, genotoxicity, carcinogenicity, reproductive system toxicity, specific target organ toxicity following single exposure and specific target organ toxicity following repeated exposure. In the guideline (19), the effects of 11 NMs on human health were for summarized as follows:

Fullerene: There is evidence that it does not cause acute toxicity, skin, eye, respiratory damage, genotoxicity, and specific target organ toxicity after repeated exposure, but data are lacking for other hazard categories.

SWCNT: There is evidence of genotoxicity and specific target organ toxicity after repeated exposure (low level of evidence). There is evidence that it does not cause acute toxicity, eye and skin damage, and respiratory/skin sensitization. There is no data showing that it causes reproductive system toxicity and specific target organ toxicity after a single exposure. It has been classed as group 3 (those that cannot be classified as carcinogenic in humans) by the International Agency for Research on Cancer (IARC).

MWCNT: There is evidence of eye damage (strong grade of evidence), genotoxicity (strong grade of evidence), carcinogenicity (moderate grade of evidence), and specific target organ toxicity following repeated exposure (moderate grade of evidence). There is evidence that it does not cause acute toxicity, skin damage, respiratory/skin sensitization, and reproductive system toxicity. There is no evidence of specific target organ toxicity following a single exposure. MWCNT-7 has been classed as

group 2B (possibly carcinogenic in humans) by IARC and other MWCNTs as group 3 (those that cannot be classified as carcinogenic in humans).

Silver NPs: There is evidence of respiratory/skin sensitization (moderate grade of evidence), and specific target organ toxicity following repeated inhalation and oral exposure (strong grade of evidence). There is evidence that they do not cause acute toxicity, eye damage, and genotoxicity. There is no evidence of carcinogenicity and specific target organ toxicity following a single exposure.

Gold NPs: There is evidence of specific target organ toxicity following repeated inhalation exposure (strong grade of evidence). There is no data for other classes.

Silicon dioxide: There is evidence of specific target organ toxicity following repeated inhalation exposure (strong grade of evidence). There is evidence that it does not cause acute toxicity, eye and skin damage, respiratory and skin sensitization, genotoxicity, and reproductive system toxicity. There is no data for carcinogenicity and specific target organ toxicity following a single exposure.

Titanium dioxide: There is evidence of reproductive system toxicity (moderate grade of evidence) and specific target organ toxicity (strong grade of evidence) following repeated inhalation exposure. There is evidence that it does not cause acute toxicity, skin and eye damage, respiratory and skin sensitization, and genotoxicity. There is no data for specific target organ toxicity following a single exposure. It has been classed as group 2B (possibly carcinogenic in humans) by IARC.

Cerium dioxide: There is evidence of specific target organ toxicity following repeated inhalation exposure (moderate grade of evidence). There is evidence that it does not cause acute toxicity. There is no data available for other hazard classes.

Dendrimers and nanoclays: There is no data on hazard classes.

Zinc oxide: There is evidence of specific target organ toxicity following repeated inhalation exposure (moderate grade of evidence). There is evidence that they do not cause acute toxicity, skin and eye damage, genotoxicity, and reproductive system toxicity. There is no data on respiratory/skin sensitization, carcinogenicity, and specific target organ toxicity following a single exposure.

As a result, it is emphasized in the guideline that prudence should be taken against engineered NPs that we do not yet know the health risks and that the proactive approach should minimize the exposure of workers (19).

Conclusion

Features such as nanoscale size, large surface area, and surface activity make NMs appealing for many applications. Therefore, nanoscale materials are increasingly used in many areas of daily life, such as industry, science, pharmacy, medicine, electronics, communications, and consumer products. Although it is predicted that NPs may cause adverse effects on biological systems due to the observed changes in the physical, chemical and toxicological properties of the material in parallel with the decreasing particle size, unfortunately, there is still a lack of data about the ways people are exposed to NP and the possible negative health effects of NPs. Toxicological assessment of these new materials is a scientific necessity that needs to be addressed in order to recognize risks, avoid potential hazards, and safe use of NPs. Although humans have been exposed to unwanted NPs for the long-term due to combustion processes, the recent increase in engineered production of NMs requires further investigation into potential toxicity and adverse health effects after exposure. Since the potential health effects of newly engineered NMs have not been sufficiently tested, a prudent approach should be adopted until they reach reliable results.

Ethics

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - G.S., B.P.; Design - G.S., B.P.; Supervision - G.S., B.P.; Analysis and/or Interpretation - G.S., B.P.; Literature Search - G.S., B.P.; Writing Manuscript - G.S.; Critical Review - G.S., B.P.

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Perinatal and Medical Risk Factors in Children with Attention Deficit Hyperactivity Disorder, Autism Spectrum Disorder or Specific Learning Disorder: Comparison Between Diagnostic Groups

Dikkat Eksikliği Hiperaktivite Bozukluğu, Otizm Spektrum Bozukluğu veya Özgül Öğrenme Bozukluğu Olan Çocuklarda Perinatal ve Tıbbi Risk Faktörleri: Tanı Grupları Arası Karşılaştırma

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ABSTRACT

Introduction: Epigenetic changes in the pathogenesis of neurodevelopmental disorders, including prenatal and early life exposures, are becoming as appealing as hereditary genes. This study aimed to investigate possible pre-pubertal environmental and developmental risk factors for children with Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), and Specific Learning Disorder (SLD).

Methods: The study included 98 children (24 ADHD, 24 SLD, 26 ASD, 20 controls) aged 7-12 years. The diagnostic evaluation was based on the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders and Schedule for Affective Disorders and Schizophrenia for School-age Children-present version. Parents completed socio-demographic data form for clinical evaluation, and The Wechsler Children's Intelligence scale was used to assess cognitive skills.

Results: In our study, low parental education level, parental unemployment, low-income, and history of psychiatric disorders in first-degree relatives were associated with SLD risk, prematurity, and early self-regulation difficulties were associated with ASD risk, and history of allergy was associated with ADHD risk.

Conclusion: In this study, the presence of many different risk factors that play a possible role in neurodevelopmental disorders suggests that further epigenetic studies are needed.

Keywords: Specific Learning Disorder, autism spectrum disorder, attention deficit hyperactivity disorder, developmental characteristics, risk factors

ÖZ

Amaç: Nörogelişimsel bozuklukların patogenezinde doğum öncesi ve erken yaşam dönemi maruziyetlerini içeren epigenetik değişiklikler, kalıtsal genler kadar ilgi çekici olmaya başlamaktadır. Bu çalışmada puberte öncesi dönemde dikkat eksikliği hiperaktivite bozukluğu (DEHB), otizm spektrum bozukluğu (OSB) ve özgül öğrenme bozukluğu (ÖÖB) tanılı çocuklar için olası çevresel ve gelişimsel risk faktörlerinin araştırılması amaçlanmıştır.

Yöntemler: Çalışmaya 7-12 yaş aralığında 98 çocuk (24 DEHB, 24 ÖÖB, 26 OSB, 24 kontrol) alınmıştır. Tanısal değerlendirmede Amerikan Psikiyatri Birliği Ruhsal Bozuklukların Tanısal ve Sayımsal El Kitabına dayalı görüşme, Okul Çağı Çocukları için Duygulanım Bozuklukları ve Şizofreni Görüşme Çizelgesi-şimdi versiyonu kullanılmıştır. Klinik değerlendirmede ebeveynler tarafından sosyo-demografik veri formu doldurulmuştur ve bilişsel değerlendirmede Wechsler Çocuklar İçin Zeka ölçeği kullanılmıştır.

Bulgular: Çalışmamızda düşük ebeveyn eğitim düzeyi, ebeveyn işsizliği, düşük gelirli aile ve birinci derece akrabalarda psikiyatrik hastalık öyküsü ÖÖB riski ile, prematürite öyküsü ve erken dönem kendini düzenleme güçlükleri OSB riski ile, allerji öyküsü DEHB riski ile ilişkili bulunmuştur.

Sonuç: Bu çalışmada nörogelişimsel bozukluklarda olası rol oynayan pek çok farklı risk faktörü bulunması ileri epigenetik çalışmalara ihtiyaç olduğunu göstermektedir.

Anahtar Kelimeler: Öğrenme bozukluğu, otizm spektrum bozukluğu, dikkat eksikliği hiperaktivite bozukluğu, gelişimsel özellikler, risk faktörleri

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Introduction

Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), and Specific Learning Disorder (SLD) are the most common neuropsychiatric disorders in childhood. These disorders are classified under the heading of Neurodevelopmental Disorders in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Neurodevelopmental disorders occur early in development and are characterized by developmental disabilities that lead to disruptions in individual, social, educational, or occupational functionalities.

ADHD is a heterogeneous developmental disorder characterized by inattention, impulsivity, and hyperactivity. It is common among neurodevelopmental disorders, and the current diagnostic criteria are met in 5.3% of school-aged children worldwide and 8% throughout Turkey (1,2). DSM-5 defined ASD as a neurodevelopmental disorder that starts in early childhood with impairment in social interaction, repetitive behaviors, and circumscribed interests. In a study report published by "US Centers for Disease Control and Prevention" in 2014 among children aged eight years, the prevalence of ASD was reported as 1/68 (3). There are few studies regarding the prevalence of autism in children in Turkey, and school-age autism prevalence has been reported to be approximately 12/10000 (4). SLD is defined as a neurodevelopmental disorder that lasts for at least six months despite appropriate interventions, including difficulties in learning and using school skills. The difficulties these children experience are beyond the "expected situation" given their age and general cognitive skills, and it cannot be explained by delay in cognitive development in general. They may experience difficulties in academic, attention, organizing, ordering, and social-emotional fields (5). Its incidence has been reported to be 3-10% among school-age children (6).

Neurodevelopmental disorders show a high level of heredity and have shared genetic risks. Epigenetic changes, including prenatal and early life exposures in the pathogenesis of neurodevelopmental disorders, are becoming as appealing as hereditary features (7). Many risk factors such as prenatal maternal stress, poor intrauterine environment, postpartum maternal depressive mood, short duration of breastfeeding, low birth weight, prematurity, and education of the mother have been defined for ADHD, ASD, or SLD (8-12). In the literature, it was seen that the risk factors and developmental characteristics of children with SLD were not examined sufficiently in our country.

Determination of risk factors for ADHD, ASD, and SLD, which are the most common neurodevelopmental disorders of childhood, is an essential objective for child mental health research and developmental psychology. We aimed to contribute to the literature by comparing these three diagnoses with similar phenomenological and etiological features in terms of socio-demographic and developmental/clinical features in a cohort from Turkey. In light of this information, this study aimed to investigate possible pre-pubertal risk factors for children with ADHD, SLD, and ASD.

Methods

Participants

Our study has a single-center, cross-sectional, case-control study design. The study cohort included 24 children (7-12 years) diagnosed as ADHD, 24 children (7-12 years) diagnosed as SLD, 26 children (7-12 years) diagnosed as ASD and 24 healthy controls (7-12 years) who applied to Ondokuz Mayıs University Faculty of Medicine Health Application and Research Center Child and Adolescent Psychiatry Outpatient Clinic. The diagnoses of the patient groups were made by clinical interviews based on DSM-5, and participants with a Wechsler Children's Intelligence Scale-R (WISC-R) score of less than 70 were excluded from the study. The standard exclusion criteria in patient groups were as follows: comorbid psychotic disorder, bipolar disorder, eating disorder, substance use disorder, neurological disease, or loss of consciousness for more than one hour due to trauma, unstable or chronic medical disease, and known visual and hearing deficits. Also, the presence of SLD or ASD findings in the ADHD group, the presence of ASD comorbidity in the SLD group, and the presence of SLD comorbidity in the ASD group were identified as exclusion criteria. The healthy control group was selected from children who had more than 70 points in WISC-R and who had no history of psychiatric or medical illness.

The study was approved by Ondokuz Mayıs University Clinical Research Ethics Committee (B.30.ODM.0.20.08/632-745 dated: 15.02.2017). Informed consent was obtained from the parents of the children.

Application

After the diagnostic evaluation of the case groups identified for our study, patients, healthy controls, and their families were informed about our research. Socio-demographic data form, which was used to re-evaluate the inclusion and exclusion criteria of the study, was completed by researches following socio-demographic data, medical history, family history, prenatal, perinatal, and postnatal period information, developmental stages information obtained from the parents of the participants. The comorbidities were evaluated using Schedule for Affective Disorders and Schizophrenia for School-age Children-Present - Turkish Adaptation (SADS-P-T) (13,14).

Statistical Analysis

Data were analyzed with IBM SPSS v23.0 (Chicago, USA). The normality of the data was examined by the Shapiro-Wilk test. One-way ANOVA was used to compare quantitative data with a normal distribution. Kruskal-Wallis test was used to compare non-normally distributed data, and the source of the difference was examined by the Mann-Whitney U test with Bonferroni correction. The correlation between categorical data was examined by chi-square test. The significance level was accepted as $p<0.05$.

Results

A total of 98 participants, including 24 children with SLD, 24 children with ADHD and 26 children with ASD according to DSM-5, and 24 healthy controls without any psychiatric diagnosis, completed the study. It was seen that 78.6% (n=77) of the children included in the study

were male, and 21.4% (n=21) were female. The mean age and gender distributions were similar between the groups. There was a significant difference between the groups in terms of maternal (p<0.001) and paternal education level (p=0.001), maternal (p<0.001) and paternal employment status (p=0.006), monthly income (p<0.001) and history of mental disorders in first-degree relatives (p=0.007) (Table 1).

When the prenatal, perinatal and postnatal characteristics of the subjects included in the study were examined, the presence of a history of mental problems during pregnancy (p=0.009), premature birth (p=0.027) and allergy (p=0.021) showed a significant difference between the groups (Table 2).

Significant differences were found between the groups in terms of firstword acquisition (p=0.012), sentence generation (p<0.001), and self-regulation as expressed by the mother (p=0.013) (Table 3).

The children in the study group were evaluated with (SADS-P-T) during the study in terms of present mental disorders. There was no difference between the patient groups in terms of the presence of comorbid disorders (Table 4).

Discussion

Neurodevelopmental disorders are coexisting and persistent disorders in the development of cognitive or motor functions during childhood. In this study, the main clinical gain of focusing on neurodevelopmental disorders is to draw attention to early risk characteristics of mental disorders in childhood and early adolescence. The fact that neurodevelopmental disorders show similar male gender predominance and neurocognitive disorder suggests that there may be similar causal pathways leading to different disorders (15). Epigenetic

Table 1. Socio-demographic characteristics of cases

	SLD	ADHD	ASD	Control	Test statistics	p
Age	9 (7-12)	9 (7-12)	9.5 (7-12)	10 (7-12)	$\chi2$=5.753**	0.124
Gender						
Male	16 (66.7)	18 (75.0)	23 (88.5)	20 (83.3)	$\chi2$=4.036*	0.258
Female	8 (33.3)	6 (25.0)	3 (11.5)	4 (16.7)		
Maternal education (years)	5 (0-16)[a]	11 (0-16)[ab]	8 (5-15)[ab]	13 (5-20)[b]	$\chi2$=18.853**	<0.001
Paternal education (years)	5 (3-12)[a]	11 (1-16)[ab]	11 (5-15)[b]	13 (5-20)[b]	$\chi2$=16.572**	0.001
Maternal employment status, (working) n (%)	2 (8.3)[a]	9 (37.5)[b]	7 (26.9)[ab]	17 (70.8)[c]	$\chi2$=21.638**	<0.001
Paternal employment status, (working) n (%)	19 (79.2)[a]	23 (95.8)[ab]	26 (100.0)[b]	24 (100.0)[b]	$\chi2$=12.457*	0.006
F-M status (together), n (%)	22 (91.7)	23 (95.8)	25 (96.2)	23 (95.8)	$\chi2$=0.689*	0.876
Consanguinity between parents (yes) n (%)	2 (8.3)	2 (8.3)	7 (26.9)	2 (8.3)	$\chi2$=5.737*	0.125
Monthly income (TL)						
<1300	8 (33.3)	3 (12.5)	2 (7.7)	0 (0.0)	$\chi2$=25.374*	<0.001
1300-4500	15 (62.5)	19 (79.2)	21 (80.8)	14 (58.3)		
>4500	1 (4.2)	2 (8.3)	3 (11.5)	10 (41.7)		
Mental disorders in first degree relatives (yes) n (%)	13 (54.2)[a]	9 (37.5)[ab]	5 (19.2)[ab]	3 (12.5)[b]	$\chi2$=12.097*	0.007

SLD: Specific Learning Disorder, ADHD: attention deficit hyperactivity disorder, ASD: autism spectrum disorder, a-c: there is no difference between groups with the same letter, *: pearson chi-square test statistic, **: Kruskal-Wallis test statistic

Table 2. Evaluation of prenatal, perinatal and postnatal characteristics of cases

	SLD	ADHD	ASD	Control	Test statistics	p
Maternal age	29 (17-39)	27 (18-38)	24 (19-35)	32 (18-41)	$\chi2$=8.2	0.050
Smoking during pregnancy n (%)	4 (16.7)	4 (16.7)	2 (7.7)	1 (4.2)	$\chi2$=2.952	0.399
Mental problems in pregnancy n (%)	14 (58.3)[a]	14 (58.3)[a]	10 (38.5)[ab]	4 (16.7)[b]	$\chi2$=11.622	0.009
Delivery method						
NSVD	8 (33.3)	9 (37.5)	10 (38.5)	8 (33.3)	$\chi2$=3.428	0.753
C/S	16 (66.7)	14 (58.3)	16 (61.5)	16 (66.7)		
Forceps	0 (0)	1 (4.2)	0 (0)	0 (0)		
Prematurity	2 (8.3)[ab]	1 (4.2)[ab]	7 (26.9)[b]	0 (0)[a]	$\chi2$=14.255	0.027
Birth complication n (%)	2 (8.3)	3 (12.5)	3 (11.5)	2 (8.3)	$\chi2$=0.372	0.946
Asphyxia n (%)	3 (12.5)	2 (8.3)	1 (3.8)	2 (8.3)	$\chi2$=1.25	0.741
Incubator n (%)	2 (8.3)	5 (20.8)	4 (15.4)	0 (0)	$\chi2$=5.911	0.116
Seizure n (%)	1 (4.2)	4 (16.7)	1 (3.8)	1 (4.2)	$\chi2$=4.349	0.226
Allergy n (%)	2 (8.3)[a]	10 (41.7)[b]	5 (19.2)[a]	3 (12.5)[a]	$\chi2$=9.778	0.021

SLD: specific learning disorder, ADHD: attention deficit hyperactivity disorder, ASD: autism spectrum disorder, $\chi2$: pearson chi-square test statistic, a-b: there is no difference between groups with the same letter

mechanisms, as well as high inheritance, can help explain how the same risk factors lead to different clinical characteristics. In this study, environmental factors, developmental and clinical features of children with neurodevelopmental disorders were determined. In the literature, when the etiological factors causing intellectual disability are examined, it is reported that approximately 30% are genetically based (16). In our study, children with normal intelligence performance were included in the study, considering that it would contribute to the evaluation of environmental and developmental risk factors as independent risk factors.

When the education levels of the parents were examined, it was seen that the parents of children with SLD had a lower educational level than the other parents. The mothers of all three patient groups are significantly less unemployed than the control group. The fathers of children with SLD had a significant unemployment rate. When the monthly income reflecting the socio-economic level was examined, the groups with the lowest monthly income were children with SLD and ADHD, respectively. The results of both the family structure and the socio-demographic characteristics of the parents cannot exclude the effect of lack of interest and enviromental stimulus. However, the importance of socio-demographic factors in children with SLD is emphasized in the literature. Low levels of parental education and low socio-economic status were thought to be risk factors for academic difficulties. The low socio-economic status may indicate parental educational difficulties and possible learning disability in the parents as well as a risk factor involving specific environmental conditions (17). Meta-analysis studies show that the socio-economic structure of parents has a substantial impact on students' academic achievement. The support systems provided at home provide the basis for the academic success of the students. It has been found that schools with higher socio-economic status have many significant advantages, such as teaching arrangements, materials, teacher experience, and teacher-student ratio (18). The presence of many confounding factors makes it difficult to establish a causal relationship between socio-economic status and academic achievement. However, advanced parental education levels may indicate that children with SLD can receive effective education in

Table 3. Evaluation of developmental stages of cases

	SLD	ADHD	ASD	Control	Test Statistics	p
Word (months)	12 (9-36)[b]	12 (7-48)[b]	21 (7-48)[a]	12 (9-24)[b]	$\chi2$=10.9	0.012
Sentence (months)	24 (12-36)[b]	24 (12-60)[b]	36 (15-60)[a]	18 (11-48)[b]	$\chi2$=23.9	<0.001
Walking (months)	16 (9-36)	12 (8-30)	12 (10-24)	12 (9-18)	$\chi2$=7.9	0.050
Toilet (months)	36 (18-72)	36 (24-54)	36 (1-60)	27 (20-36)	$\chi2$=7.4	0.061
Breasting feeding (months)	10.5 (0-42)	21 (0-42)	10.5 (2-36)	18 (5-27)	$\chi2$=2.7	0.448
Self-regulation						
Difficult	9 (37.5)[a]	7 (29.2)[a]	14 (56)[b]	3 (12.5)[a]	$\chi2$=10.714	0.013
Easy	15 (62.5)	17 (70.8)	11 (44)	21 (87.5)		

SLD: specific learning disorder, ADHD: attention deficit hyperactivity disorder, ASD: autism spectrum disorder, a-b: there is no difference between groups with the same letter, $\chi2$: Kruskal-Wallis test statistic

Table 4. Distributions of cases according to current mental disorders determined by SADS-P-T

	SLD		ADHD		ASD	
	n	%	n	%	n	%
ADHD	15	62.5	0	0	21	80.8
GAD	7	29.2	4	16.7	1	3.8
SAD	5	20.8	2	8.3	2	7.7
OCD	2	8.3	0	0	4	15.4
Primary Enuresis	3	12.5	4	16.7	0	0
Primary Encopresis	2	8.3	1	4.2	0	0
ODD	14	58.3	17	70.8	2	7.7
Behavioral Disorder	5	20.8	2	8.3	1	3.8
Social Phobia	2	8.3	2	8.3	6	23.1
Tic disorder	1	4.2	1	4.2	0	0
Secondary Enuresis	0	0.0	0	0.0	1	3.8
Secondary Encopresis	0	0.0	0	0.0	1	3.8
Specific Phobia	11	45.8	7	29.2	9	34.6
Major depression	4	16.7	0	0.0	0	0
Comorbid disorder (yes)	22	91.7	19	79.2	24	92.3

$\chi2$=2.505, p=0.286. SLD: Specific Learning Disorder, ADHD: attention deficit hyperactivity disorder, ASD: autism spectrum disorder, GAD: generalized anxiety disorder; SAD: separation anxiety disorder, OCD: obsessive-compulsive disorder, ODD: oppositional defiant disorder, $\chi2$: pearson chi-square test statistic

intervention and management processes. As a result, low education status and unemployment of parents can be considered as an environmental and/or genetic risk factor for SLD in their children. There is a need for family-based studies in this area.

When the mental illnesses of the first-degree relatives of the cases were examined, it was seen that children with the neurodevelopmental disorder had higher rates than the control group. This rate, which reaches a significant level in children with SLD, is consistent with the relevant literature findings of neurodevelopmental disorders with a high level of heredity and shared genetic risk (19).

Prenatal, perinatal, and postnatal period data of the cases were examined. Psychological problems during pregnancy were significantly higher in the patient group. In the studies conducted, it is emphasized that exposure to perinatal stress may be one of the critical and practical epigenetic factors in neurodevelopmental diseases, particularly in the pathogenesis of ADHD and ASD (20,21). It has been reported that physical and mental stress experienced during pregnancy may play a role in the etiology by causing changes through hypothalamic-pituitary-adrenal axis feedback mechanisms in children (22). When the birth weeks were examined, a significant prematurity history was found in the ASD group. It has been reported that the prevalence of prematurity is increased, especially in ADHD and ASD diagnostic groups and that there may be an increased risk between prematurity and these diseases (23,24). Our study supports that prematurity is a risk factor for ASD diagnosis. Allergy history was significantly higher in the ADHD group compared to the other patient groups and control group. In the literature, allergy skin test positivity was found to be high in ADHD patients, and in community-based studies, it was shown that there was a significant relationship between ADHD and allergic/autoimmune diseases (25,26). It has been reported that genes related to the immune system may be associated with ADHD, and hypersensitivity to environmental factors such as foods may contribute to the development of ADHD (27). Our results indicate that allergy history may be a risk factor in the ADHD group of neurodevelopmental disorders.

There was no significant difference between the groups in terms of smoking during pregnancy, mode of delivery, intra-partum complications, asphyxia, incubation, and seizure history. The smallness of our sample group may not have made a significant difference between the groups. In the literature, conflicting results can be seen in studies examining risk factors and perinatal conditions exposed during pregnancy. These results may arise from the methodological differences of the studies (28).

When the developmental stages of the cases were examined, it was seen that ASD patients with normal intelligence levels reached the developmental stage of saying at least two meaningful words and generate a sentence with at least two words at a later age. Delay in language development was not a significant clinical feature for ADHD and SLD. One of the essential features of infancy and early childhood is self-regulation. This skill has biological basics and is influenced by maturation and experience. Self-regulation is regulating the motor activity, affect, and increased and decreased endocrine and autonomic responses. It includes attachment-detachment, attention, behavioral inhibition, and self-appeasement (29). When the infancy and early childhood periods of participants were examined, it was seen that children with ASD had significant difficulty in developing these skills, and they were defined as “difficult babies” by their mothers.

The diagnostic groups were evaluated for the present psychiatric disorders with SADS-P-T. The most common associations in the diagnosis groups were ADHD and oppositional defiant disorder (ODD) in the SLD group, ODD and Specific Phobia in the ADHD group, and ADHD and Specific Phobia in the ASD group. The incidence rates of comorbid disorders were consistent with the literature (30,31). It was found that 92% of the SLD group, 79% of the ADHD group, and 92% of the ASD group had at least one comorbid psychiatric diagnosis. It was found that the high incidence rate in the SLD and ASD groups was highly dependent on the comorbidity of ADHD.

Study Limitations

In our study, although there was no age and gender difference between the groups, equal gender recruitment within the groups could make the groups more homogeneous. The comorbid diagnosis of the patient groups may have impaired the homogeneity of the groups. Taking larger samples by checking all the comorbidities will strengthen the study data. Information from families may be considered as a limitation as it may show recall bias.

Conclusion

Regarding the independent risk factors investigated in this study, parental education level, parental employment status, monthly income of the family and psychiatric disease history in first degree relatives were related to SLD risk, history of prematurity and early self-regulation difficulties were related to ASD risk, and allergy history was related to ADHD risk. No significant single risk factor for all groups was identified. This suggests that further studies are needed to learn about the many different risk factors that contribute to neurodevelopmental disorders and to show how they can potentially interact.

Ethics Committee Approval: The study was approved by Ondokuz Mayıs University Clinical Research Ethics Committee (B.30.ODM.0.20.08/632-745 date: 15.02.2017).

Informed Consent: Informed consent was obtained from the parents of the children.

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Fluid Management in Cesarean Section with Spinal Anesthesia: A Retrospective Study

Spinal Anestezi Uygulanan Sezaryen Olgularında Sıvı Yönetimi: Retrospektif Çalışma

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ABSTRACT

Introduction: Spinal anesthesia is a widely used and preferred method for elective cesarean section operations. However, one of the critical side effects is hypotension. In this study, we aimed to compare the effects of fluid replacement preferences on hemodynamics in elective cesarean sections by retrospectively examining the patient files.

Methods: We retrospectively searched the anesthesia files dated between 01.11.2017 and 31.10.2018, and reviewed elective cesarean section data undergoing spinal anesthesia. Hemodynamic parameters, fluid replacement, ephedrine use, need for additional medication, nausea, and vomiting were recorded. Patients were divided into two groups as crystalloid group (group C) and crystalloid + colloid group (group CC).

Results: Compared to baseline, systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and mean arterial pressure (MAP) values were significantly lower in both groups after spinal anesthesia. SAP, DAP, and MAP values were significantly lower in group C at the 3rd and 6th minutes compared to group CC. Total ephedrine dose was significantly higher in group C, and the number of patients receiving ephedrine was significantly higher in group C.

Conclusion: We suggest that co-administration of crystalloid and colloid is more effective than colloid alone in preventing hypotension in patients undergoing spinal anesthesia in elective cesarean section and that it may prevent complications due to high dose fluid replacement.

Keywords: Spinal anesthesia, hypotension, fluid replacement

ÖZ

Amaç: Spinal anestezi elektif sezaryen ameliyatları için yaygın kullanılan ve tercih edilen bir yöntemdir. Bununla birlikte önemli yan etkilerinden birisi de hipotansiyondur. Çalışmamızda elektif sezaryenlerde sıvı replasman tercihlerinin hemodinami üzerine etkisini retrospektif olarak karşılaştırmayı amaçladık.

Yöntemler: Hastanemizde 01.11.2017-31.10.2018 arası aylara ait anestezi dosyaları geriye dönük taranarak spinal anestezi uygulanan elektif sezaryen verileri incelendi. Hastaların hemodinamik parametreleri, sıvı replasmanı, efedrin kullanımı, ek ilaç ihtiyacı, bulantı ve kusma olup olmadığı kaydedildi. Sadece kristalloid verilenler grup K, kristalloid ve kolloid birlikte verilenler grup KK olarak adlandırıldı.

Bulgular: Her iki grupta da spinal anestezi uygulaması sonrası sistolik arteriyal basınç (SAB), diastolik arteriyal basınç (DAB), ortalama arteriyal basınç (OAB) ölçümleri giriş değerlere göre anlamlı olarak düşük bulundu. grup K'de 3. ve 6. dakika SAB, DAB, OAB değerleri grup KK'ye göre anlamlı olarak düşük saptandı. Efedrin kullanılan hasta sayısı ve kullanılan toplam efedrin dozu grup K'de anlamlı olarak yüksek bulundu.

Sonuç: Elektif sezaryenlerde spinal anestezi uygulanacak hastalarda hipotansiyonun önlenmesinde kristalloid ve kolloidin birlikte uygulanmasının sadece kolloid uygulanmasına göre daha etkili olup yüksek doz sıvı replasmanına bağlı komplikasyonları da önleyebileceğini düşünmekteyiz.

Anahtar Kelimeler: Spinal anestezi, hipotansiyon, sıvı replasmanı

Introduction

Numerous maternal deaths have been reported due to complications of general anesthesia, including oxygenation insufficiency and aspiration-related complications caused by complicated and unsuccessful tracheal intubations, and regional anesthesia has been preferred for these reasons (1-3). Spinal anesthesia is widely used for emergency and elective cesarean section operations due to the rapid onset of action and adequate anesthesia. However, the most common side effect is hypotension, and the incidence can be reduced by up to 40% despite treatments and applications to prevent it. Pregnant women at term are more prone to spinal anesthesia-related hypotension, and this is due to aortocaval compression, uterine contractions, engagement of the fetal

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head, and rapid development of sympathetic blockade. Supine position, hypovolemia, spinal, and epidural block increase the incidence and severity of aortocaval compression (4,5).

Crystalloid infusion before spinal anesthesia is a common method to prevent hypotension; however, this does not always prevent hypotension. It is known that the clinical and intraoperative use of colloid solutions is highly effective on hypotension (6).

In this study, elective cesarean sections performed in our hospital in 2018 were retrospectively reviewed. We aimed to compare hypotension and other hemodynamic parameters of patients who received crystalloid infusion alone and who received crystalloid + colloid infusion.

Methods

Patient Selection

Following University of Health Sciences, İstanbul Training and Research Hospital Ethics Committee (decision no: 1505, date: 09.11.2018), the files of the patients who underwent elective cesarean section under spinal anesthesia between 01.11.2017 and 31.10.2018 were retrieved from Hospital Information Management Systems and examined retrospectively. The necessary consent for interventions, treatments, and using the data are included in the patient files. Since it was a retrospective study, consent was not obtained from the patients. The data of patients who were given preoperative 10 mL/kg crystalloid infusion (group C) and preoperative 5 mL/kg crystalloid + 5 mL/kg colloid infusion (group CC) were recorded. We examined the anesthesia files of the patients and compared the effect of preoperative fluid type between the two groups on hypotension and other hemodynamic parameters.

In our clinic, preoperative fluid replacement is performed by anesthesiologists to prevent maternal hypotension. One group of anesthetists routinely used 10 mL/kg crystalloid 15-20 minutes before spinal anesthesia for fluid replacement to prevent maternal hypotension, while the other group used 5 mL/kg crystalloid + 5 mL/kg colloid infusion.

Hypotension was considered as a 30% decrease from baseline mean arterial pressure (MAP), and bradycardia was accepted when the heart rate (HR) was below 50 beats/min. Intravenous bolus ephedrine was administered in hypotension, and atropine was administered in bradycardia. Spinal anesthesia was performed with a 26 gauge quincke-tipped spinal needle in the sitting position from the L3-4 or L4-5 interval, and the dose of heavy bupivacaine used was administered according to the patient's height. The amount of drug used in spinal anesthesia, the level of intervention, the diameter and type of the needle used were retrospectively analyzed and recorded from the anesthesia file.

The files were examined retrospectively for age, height, weight, American Society of Anesthesiologists (ASA) physical status classification system category, total ephedrine used, time of ephedrine use, further drug use, presence of nausea and vomiting, and bleeding. Systolic arterial pressure (SAP), diastolic arterial pressure (DAP), MAP, HR, and saturation values (SPO_2) were measured at baseline, after intrathecal drug administration and at 3rd, 6th, 9th, 12th, 15th minutes during surgery.

Statistical Analysis

SPSS 16.0 statistical package program was used for statistical analysis of the data. Descriptive statistics of numerical variables were expressed as mean ± standard deviation, while categorical variables were expressed as frequency (n) and percentage (%). Kolmogorov-Smirnov or Shapiro-Wilk tests were used to determine whether the data fit the normal distribution. Pearson chi-square test or Fisher's exact chi-square test was used for the analysis of categorical data. A paired t-test or Wilcoxon test was used for the analysis of continuous variables. The level of significance was set at $p<0.05$.

Results

In this study, 186 patient files were examined. Thirty-six patients were excluded due to lack of data, severe systemic disease, multiple pregnancies, morbid obesity, height below 150 cm, and being under 18 years of age. There were 65 patients in group C and 85 patients in group CC.

Age, weight, height, and ASA scores of the patients were similar in both groups, and there was no statistically significant difference. The mean age of the patients was 29.6±6 years in group C and 28.7±7 years in group CC. The mean height of the patients was 161±2 cm in group C and 162±4 cm in group CC. The mean weight of the patients was 63±8 kg in group C and 62±9 kg in group CC. In group C, there were 45 ASA 1 patients and 20 ASA 2 patients. In group CC, there were 51 ASA 1 patients and 34 ASA 2 patients.

In both groups, baseline SAP, DAP, and MAP values were significantly higher than those measured after spinal anesthesia (Table 1). SAP, DAP, and MAP values at 3rd and 6th minutes were significantly lower in group C than in group CC (Table 2).

The number of patients receiving ephedrine was 43 (66.2%) in group C, and this was significantly higher than 25 patients (29.4%) receiving ephedrine in group CC. Total ephedrine dose was significantly higher in group C than in group CC (7.0±6.6 mg vs 3.2±5.8 mg) (Table 3).

Table 1. Measured SAP, DAP and MAP values of the groups

	Group CC, (n=85)			Group C, (n=65)		
	Baseline	After spinal anesthesia	p*	Baseline	After spinal anesthesia	p*
Heart rate, beats/min	85.6±12.0	86.4±12.8	0.552	86.4±11.2	85.7±13.3	0.743
Systolic blood pressure, mmHg	122.7±16.4	115.6±12.9	<0.001	125.8±14.7	113.9±9.0	<0.001
Diastolic blood pressure, mmHg	74.2±14.0	66.6±10.8	<0.001	76.2±9.3	65.2±12.7	<0.001
Mean arterial pressure, mmHg	90.4±13.4	82.9±10.7	<0.001	92.8±10.0	81.4±10.7	<0.001

*: Paired t-test. SAP: systolic arterial pressure, DAP: diastolic arterial pressure, MAP: mean arterial pressure

Atropine requirement was not detected in both groups. In both groups, no additional medication was required. Nausea rates were similar in both groups. The mean bleeding was similar in both groups, and there were no additional complications.

Discussion

Patients undergoing cesarean section have potential risks related to anesthesia as well as complications of surgical operation. Regional anesthesia has been preferred in recent years because of its advantages such as the patient being conscious, lack of aspiration risk, and not causing respiratory depression in the newborn (3).

In addition to the advantages of spinal anesthesia in cesarean section, maternal hypotension due to sympathetic blockade is the most common and undesirable effect of spinal anesthesia, and severe hypotension may cause fetal acidosis and neonatal depression by decreasing uterine and intervillous blood flow. It may cause maternal nausea and vomiting (7).

Although the validity of pre-loading with crystalloid and colloid solutions before spinal anesthesia is discussed today, it is still the most commonly used method to prevent hypotension (8,9). It was emphasized that hypotension would be prevented by increasing the intravascular volume by giving 10-15 mL/kg crystalloid solution in a short time before spinal intervention (10). However, other studies have shown that intravascular crystalloid application does not have a sufficient effect on the incidence of hypotension due to spinal anesthesia (11). In recent years, Jackson et al. (12) have suggested that 1000 mL crystalloid infusion has no difference in preventing hypotension after cesarean section in comparison to 200 mL and that pre-hydration should be abandoned. Park et al. (13) reported that loading the patients with a volume higher than 10 mL/kg before cesarean delivery did not provide an advantage. In another study, it was emphasized that hydration with crystalloid given before spinal anesthesia caused more pronounced hypotension than hydration after spinal block (14). In a study performed with colloids to prevent hypotension due to spinal anesthesia in cesarean operations, it was emphasized that intravascular administration of 5% albumin was effective, but albumin solutions were expensive, and that gelatin and starch solutions were as effective as 5% albumin in expanding intravascular volume with less cost (12,15).

Studies have shown that colloids remain in the vascular area for a longer period by showing the superiority of colloids over crystalloid in preventing post-spinal hypotension in elective cesarean operations (6,11). Ueyama et al. (16) similarly showed that only 28% of the lactated ringer solution administered at 30th minutes remained in the intravascular area, while this rate was 100% with the HES solution. However, in recent years, some studies have shown that colloid pre-hydration, as well as crystalloid, is inadequate in reducing hypotension due to spinal anesthesia. Buggy et al. (17) concluded that although 500 mL colloid pre-hydration kept SAP levels higher, it did not reduce the incidence of hypotension and ephedrine use when compared to groups with or without crystalloid pre-hydration. In the study of Baraka et al. (11), 7 mL/kg intravascular administration of 3% gelatin in electrolyte solution led to a significant increase in central venous pressure and showed less hypotension after spinal anesthesia compared with intravascular administration of equal volume of isotonic sodium chloride. In their study, Idehen et al. (18) compared the incidence of hypotension in cases of cesarean section and found that hydration with crystalloid/colloid fluid combination for 15 minutes showed better efficacy in the prophylaxis of hypotension compared with colloid.

In a meta-analysis by Ripollés et al. (19) including 11 randomized clinical trials and 990 patients, they reported that the use of colloids provided a significant reduction in the incidence of spinal anesthesia-induced hypotension compared to crystalloid. Similar to other studies, BP levels were found to be significantly lower in patients treated with crystalloid infusion compared to the group treated with colloidal plus crystalloid hydration in our study.

Administration of high doses of crystalloid leads to peripheral and pulmonary edema (20). Crystalloids are thought not to have sufficient

Table 2. SAP, DAP and MAP values of the groups measured at 3 and 6 minutes after spinal anesthesia

	Group CC, (n=85)	Group C, (n=65)	p*
3. min. Heart rate, beats/min	80.2±10.2	82.2±13.6	0.324
3. min. Systolic blood pressure, mmHg	102.2±9.5	96.1±16.1	0.007
3. min. Diastolic blood pressure, mmHg	64.9±10.9	59.7±10.5	0.004
3. min. Mean arterial pressure, mmHg	77.3±9.2	71.8±10.5	0.001
6. min. Heart rate, beats/min	83.4±11.2	82.0±9.1	0.417
6. min. Systolic blood pressure, mmHg	99.4±10.3	96.1±13.2	0.094
6. min. Diastolic blood pressure, mmHg	66.9±12.1	61.6±12.3	0.009
6. min. Mean arterial pressure, mmHg	77.7±9.6	73.1±11.7	0.009

*: unpaired t-test. SAP: systolic arterial pressure, DAP: diastolic arterial pressure, MAP: mean arterial pressure, min: minute

Table 3. Number of patients receiving ephedrine and dose of ephedrine

	Group CC, (n=85)	Group C, (n=65)	p
Number of patients receiving ephedrine (%)	25 (29.4%)	43 (66.2%)	<0.001*
Total dose of ephedrine, mg	3.2±5.8	7.0±6.6	<0.001#

*: chi-square test, #: t-test

effect on its own due to the rapid redistribution to the intravascular compartment. A high amount of crystalloid infusion may cause pulmonary edema by disrupting oxygen transport in the blood. It is stated that excessive fluid replacement will increase extravasation by diluting plasma proteins (13). In our study, total crystalloid infusion dose was not over 10 mL/kg in both groups, and no additional complications were detected.

In addition to the advantages of colloids, there are disadvantages of pre-loading with colloids such as higher cost, hemodilution effect, fluid overload, and anaphylactoid reaction risk (21). Also, it is known that colloids administered at high doses have adverse effects on the coagulation profile (22). In our study, the amount of bleeding was similar to the crystalloid group in patients treated with colloid plus crystalloid, and we think that this result is due to low dose colloid administration. Also, anaphylaxis and similar reactions were not observed in both groups.

Conclusion

In this study, we think that the co-administration of crystalloid and colloid is more effective in preventing hypotension due to spinal anesthesia in cesarean operations than colloid alone. We also think that the use of crystalloid and colloids together is more effective in avoiding the side effects of high dosing of crystalloid or colloid infusions in preoperative fluid selection.

Ethics Committee Approval: Following University of Health Sciences, İstanbul Training and Research Hospital Ethics Committee (decision no: 1505, date: 09.11.2018), the files of the patients who underwent elective cesarean section under spinal anesthesia between 01.11.2017 and 31.10.2018 were retrieved from Hospital Information Management Systems and examined retrospectively.

Informed Consent: Since it was a retrospective study, consent was not obtained from the patients.

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Sedation for Colonoscopy: Comparison of Remifentanil and Alfentanil Combined with Propofol/Midazolam

Kolonoskopi için Sedasyon: Propofol/Midazolam ile Kombine Edilen Remifentanil ve Alfentanil'in Karşılaştırılması

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ABSTRACT

Introduction: Different drug combinations are used in patients who underwent colonoscopy for safe sedation and early discharge. Remifentanil and alfentanil are short-acting narcotic analgesic agents. A short-acting anxiolytic agent, midazolam has a potent sedative efficiency when combined with narcotic analgesics. In this study, we aimed to compare the effectiveness of the two opioids that have not been previously compared in the literature, combined with propofol/midazolam in patients who underwent colonoscopy.

Methods: One hundred eighty-nine patients aged over 18 years who underwent diagnostic and/or therapeutic colonoscopy were included in the study. 1 mg midazolam + 5µg kg-1 alfentanil + 1 mg kg-1 propofol were administered in the alfentanil group (group A), while 1 mg midazolam + 0.1 µg kg-1 min-1 remifentanil + 1 mg kg-1 propofol were administered in the remifentanil group (group R). Hemodynamic data, Modified Steward scale (MSS), Visual Analog scale (VAS), additional propofol doses, total procedure time, awake time, recovery time, and side effects were recorded during the procedure. After the procedure, all patients were transferred to the recovery room, and the Modified Aldrete scale (MAS) values were recorded.

Results: There was a statistically significant difference between the groups in terms of total propofol and additional propofol doses ($p<0.05$), with additional propofol dose being higher in group A compared to group R ($p<0.05$). Awake time was similar between the groups. Recovery time was longer in group A compared to group R ($p<0.05$). No significant difference was observed in the side effects between both groups.

Conclusion: Although the low dose of midazolam combined with propofol/remifentanil and propofol/alfentanil provided adequate sedation and analgesia, we believe that remifentanil is an ideal choice for daily procedures like colonoscopy because of its advantages resulting from its pharmacological properties.

Keywords: Alfentanil, colonoscopy, remifentanil, sedation

ÖZ

Amaç: Kolonoskopi işlemi uygulanan hastalara güvenli sedasyon ve erken taburculuk amacıyla farklı ilaç kombinasyonları kullanılmaktadır. Remifentanil ve alfentanil kısa etkili narkotik analjezik ajanlardır. Kısa etkili bir anksiyolitik ajan olan midazolam narkotik analjeziklerle kombine edildiğinde güçlü bir sedadif etkinliğe sahiptir. Kolonoskopi işlemi altındaki hasta da sedasyon amacıyla literatürde karşılaştırılmamış 2 opiodin propofol/midazolam ile kombinasyonunun etkinliğini karşılaştırmayı amaçladık.

Yöntemler: Çalışmaya tanı ve/veya tedavi amaçlı kolonoskopi uygulanan 18 yaş üzeri yüz seksen dokuz hasta alındı. Alfentanil grubunda (grup A) 1 mg midazolam + 5 µg kg-1 alfentanil + 1 mg kg-1 propofol ve remifentanil grubuna (grup R) 1 mg midazolam + 0.1 µg kg -1 dk-1 remifentanil + 1 mg kg-1 propofol uygulandı. Hemodinamik veriler, Modifiye Steward skalası (MSS), Görsel Analog skala (VAS), ek propofol dozları, toplam işlem süresi, uyanma süresi, iyileşme süresi ve yan etkiler işlem sırasında kaydedildi. İşlem sonrası tüm hastalar derlenme odasına transfer edildi ve Modifiye Aldrete skalası (MAS) değerleri kaydedildi.

Bulgular: Total propofol ve ek propofol dozlarında gruplar arasında istatistiksel olarak anlamlı farklılık saptanmıştır ($p<0.05$), ve grup A da grup R ye göre propofol ek dozunun daha yüksek olduğu gözlenmiştir ($p<0.05$). Uyanma süresi gruplar arasında benzerdi. Derlenme süresinin grup A'da grup R'ye göre daha uzun olduğu tespit edildi ($p<0.05$). Gruplar arasında yan etkilerde anlamlı farklılık saptanmamıştır.

Sonuç: Propofol/remifentanil ve propofol/alfentanil ile kombine edilen düşük doz midazolam etkili sedasyon ve analjezi sağlamasına rağmen, remifentanilin, farmakolojik özelliklerinden doğan avantajları nedeniyle kolonoskopi gibi günlük işlemler için ideal bir seçim olduğuna inanıyoruz.

Anahtar Kelimeler: Alfentanil, kolonoskopi, remifentanil, sedasyon

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Introduction

Currently, colonoscopy is a standard imaging procedure used for the diagnosis, treatment, and follow up of many colorectal diseases (1). Safe sedation and early discharge are the essential parameters in daily procedures requiring sedation such as colonoscopy (2). Considering the increase in colonoscopies, there is an increasing demand for intravenous (IV) analgesics and sedatives. Increased demand and recent developments in the pharmacological area lead to the use of drugs with a broad therapeutic index, and the drugs are rapidly metabolized to inactive metabolites (3). The agents used for sedation should not cause respiratory depression, hemodynamic instability, and severe side effects (2). Therefore, propofol is increasingly used in many countries due to its excellent effect in moderate sedation, very short terminal half-life, rapid discharge, and rapid recovery from sedation (3,4). Remifentanil is a short-acting narcotic analgesic with a short elimination time under 10 minutes. Biotransformation is rapid and complete; therefore, the infusion time has a minimal effect on the awake time of patients (5). Alfentanil is a narcotic analgesic that has a rapid effect onset very short action time, and potency approximately 1/3 of fentanyl. Midazolam is a short-acting anxiolytic agent with a strong sedative effect when combined with IV narcotic agents. The combination of propofol with a low dose of short-acting opioids and benzodiazepine is a good alternative for safe sedation and analgesia without increasing the rate of adverse effects. The total propofol dose is reduced due to the synergistic effect of the drugs in this combination (6-9).

Unlike the other studies in adult patients who underwent colonoscopy procedure, in the present study, we aimed to compare additional propofol dose, awake times, recovery times, and side effects of low dose midazolam combined with propofol/alfentanil and propofol/remifentanil, in adult patients who underwent colonoscopy procedure.

Methods

The study was performed with the approval of the Necmettin Erbakan University Meram Faculty of Medicine Ethical Committee (decision no: 2017/1109) in concordance with the Declaration of Helsinki. Written informed consent was received from all patients. In this study, a prospectively stored database and medical records of patients who underwent diagnostic and/or therapeutic colonoscopy in Necmettin Erbakan University Meram Faculty of Medicine between January 2017 and November 2017 were reviewed. We used G Power Software to determine the sample size. The sample size was calculated based on recovery time (10-12). We found that a total of 180 patients (90 patients for each group) would be needed to compare the two groups with 90% power, 5% type I error level, and 25% effect size for the F test. We enrolled 200 patients in accounting for the possibility of exclusion.

Patients who were aged over 18 years, had American Society of Anesthesiologists (ASA) physical status I-III and who underwent colonoscopic examination for diagnosis and treatment under sedation with a low dose of midazolam combined with propofol/remifentanil and propofol/alfentanil, were included in the study. Patients aged less than 18 years, having ASA IV-V and patients with opioid and/or sedative addictions, pregnancy, psychiatric/emotional disorder, patients undergoing an emergency or inpatient colonoscopy, and other endoscopic procedures in addition to colonoscopy were excluded from the study. Patients with an incomplete procedure for any reason and patients with inadequate bowel preparation were excluded from the final analysis.

Two hundred patients who underwent colonoscopy under sedation with the combination of remifentanil-propofol-midazolam or alfentanil-propofol-midazolam were included in the study. Eleven patients were excluded from the final analysis (Figure 1).

The age, gender, body mass index, and ASA of one hundred eighty-nine patients were recorded. All colonoscopy procedures were performed by the same experienced endoscopist using high-resolution video colonoscopies (EC-530WL3, Fujinon, Fujifilm Corporation, Japan). All patients were monitored according to the ASA standards in the colonoscopy room. Heart rate (HR), mean blood pressure (MBP), and peripheral oxygen saturation (SpO_2) were measured and recorded (Petaş KMA 800). Measurements were repeated every 5 minutes during the procedure. Intranasal oxygen (6 L min^{-1}) was administered to the patients. After peripheral IV cannulation, 6 mL kg^{-1} hr^{-1} standard saline infusion was initiated, and 1 mg midazolam (1 mg mL^{-1}, 5 mL; Deva Holding, İstanbul, Turkey) was administered to all patients. Sedation was induced with 5μg kg^{-1} alfentanil (Rapifen® Johnson & Johnson, İstanbul, Turkey) + 1 mg kg^{-1} propofol (Propofol, Fresenius, İstanbul, Turkey) in the alfentanil group (group A), and 0.1 μg kg^{-1} min^{-1} remifentanil (Ultiva, Glaxo Smith Kline, İstanbul, Turkey) + 1 mg kg^{-1} propofol in the remifentanil group (group R). Propofol (10-20 mg) was added according to the Modified Steward scale (MSS) in order to maintain at 2-4 (Appendix 1) (13).

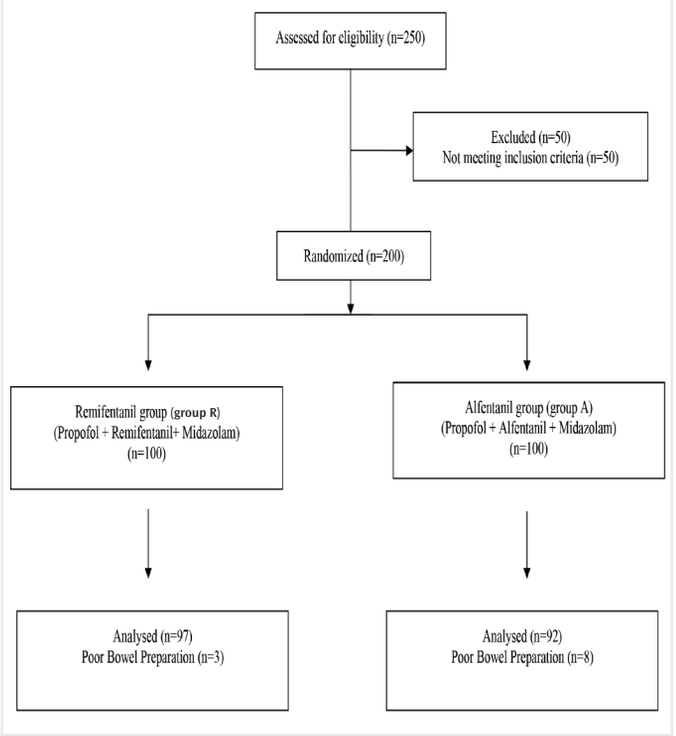

Figure 1. Flow diagram of the study

Additional propofol doses were recorded. The pain level of the patients was assessed by a Visual Analog scale (VAS) [no pain (0) - severe pain (10)] at every 5-minute interval during the colonoscopy procedure. Systolic blood pressure under 90 mmHg was accepted as hypotension, and HR under 50 beats min^{-1} was accepted as bradycardia. The fluid infusion rate of patients who developed hypotension was increased by three folds. An additional fluid infusion was continued for 10 minutes. Vasopressor (ephedrine) administration was planned in patients who had no response to liquid infusion. Atropine (0.01 mg kg^{-1}; IV) was given to patients in case of bradycardia. SpO_2 less than 90% was accepted as hypoxemia. When SpO_2 was determined less than 90% during the follow-up, a jaw thrust maneuver was performed. If SpO_2 persisted as less than 85% despite the jaw thrust maneuver, all of the infusions were stopped, and assisted ventilation was performed. It was planned that, if SpO_2 less than 85% took more than 30 seconds, then the procedure would be interrupted, and an antagonist agent (flumazenil, naloxone) would be administered. Cardiopulmonary side effects (hypotension, bradycardia, and hypoxemia), nausea, vomiting, and the treatment were recorded in all patients. The colonoscopic procedure was waited for 60 seconds after the administration of the drugs. Total procedure time was defined as the time between the initiation and completion of colonoscopy. Awake time was defined as the time from the end of colonoscopy until consciousness (0-4) score 4, according to the MSS, and the recovery time was defined as the time from the end of colonoscopy until Modified Aldrete scoring (MAS) 10 was achieved. After the procedure, all patients were transferred to the recovery room, and vital findings and MAS values were recorded. MAS, which is a 10-point scale, was used for assessing the recovery time (Appendix 2) (12). Patients were followed up until MAS 10 and then discharged.

Appendix 1

Patient Sedation Score

Consciousness 0 1 2 3 4

Airway 0 1 2 3

Activity 0 1 2

Modified Steward Score

Consciousness (0-4)

4- Fully awake, eyes open, conversive

3- Lightly asleep, eyes open intermittently

2- Eyes open on command

1- Response to ear pinching

0- No response

Airway (0-3)

3- Opens mouth, coughs on command

2- Opens mouth, clear airway, weak cough

1- Airway obstruction relieved by head extension

0- Airway obstruction needing jaw retraction/oropharyngeal airway

Activity (0-2)

2- Raising arm on command

1- No purposeful movement

0- No movement

Appendix 2

Modified Aldrete Scores

Activity (0-2)

2- Able to move four extremities voluntarily or on command

1- Able to move two extremities voluntarily or on command

0- Able to move 0 extremities voluntarily or on command

Respiration (0-2)

2- Able to deep breathe and cough freely

1- Dyspnea or limited breathing

0- Apnea

Circulation (0-2)

2- Blood Pressure ± 20% of Pre-anesthetic level

1- Blood Pressure ± 20-50% of Pre-anesthetic level

0- Blood Pressure ± 50% of Pre-anesthetic level

Consciousness (0-2)

2- Fully awake

1- Arousable on calling

0- Not responding

O_2 Saturation (0-2)

2- Maintains >92% on room air

1- Needs O_2 inhalation to maintain O_2 saturation >90%

0- Saturation <90% even with supplemental oxygen

Table 1. Basic characteristics of the study groups

Characteristics	Remifentanil group, (n=97)	Alfentanil group, (n=92)	p
Age (mean ± SD) (year)	53.97±14.23	51.92±15.11	0.344
Gender (male/female)	50/47	44/48	-
BMI (mean ± SD) (kg/m^2)	24.30±4.3	25.01±5.2	0.516
ASA classification n (%)			
I	37 (38.1%)	36 (39.1%)	-
II	42 (43.3%)	38 (41.3%)	-
III	18 (18.6%)	18 (19.6%)	-
Baseline MBP, (mean ± SD), mmHg	88.45±9.28	85.56±9.91	0.040
Baseline HR, (mean ± SD), beat/min	81.25±11.46	81.14±12.51	0.947
Baseline SpO_2, (mean ± SD), %	97.03±1.25	97.86±1.35	0.839

BMI: body mass index, ASA: American Society of Anesthesiology, MBP: mean blood pressure, HR: heart rate, SpO_2: peripheral oxygen saturation, n: number of patients, SD: standart deviation

Statistical Analysis

Data obtained were analyzed using SPSS 20.00 software (Statistical Package for Social Sciences Inc. Chicago, IL). The continuous variables are expressed as mean ± standard deviation (SD) or number (%); whereas categorical variables are expressed as number and percentages (%). The normality of the data was tested with Kolmogorov-Smirnov test. Since there was no normal distribution, continuous variables were analyzed with the Mann-Whitney U test. Comparison of two groups and analysis of categorical variables were made using the chi-square test. P values <0.05 were considered statistically significant.

Results

A total of 200 patients who underwent colonoscopy under sedation were included in the study. Eight patients from group A and three patients from group R were excluded from the study because of inadequate bowel preparation. Ninety-nine of the patients were male (52%), and the two groups were similar in terms of gender (p>0.05). The baseline characteristics of the patients were the same in the two groups (Table 1).

A statistically significant difference was determined between total propofol doses and additional propofol doses, with propofol doses being higher in group A than in group R (p<0.05). There was no statistically significant difference in awake time between the groups (p>0.05). Recovery time was longer in group A than in group R (p<0.05). The mean total dose of sedatives and analgesics administered during mean procedural times are presented in Table 2.

In both groups, MBP and HR values decreased compared to baseline values, but mean arterial pressure, HR, and SPO_2 values were not statistically significantly different between the groups.

No statistically significant difference was determined in the VAS and MSS scores between the groups. The VAS score range was 0-3 and 0-4 (mean ± SD: 0.16±0.45/0.21±0.41), while MSS score range was 1-3 and 1-4 (mean ± SD: 1.68±0.87/1.8±0.98) in the remifentanil and the alfentanil group, respectively.

There was no statistically significant difference between the groups in the MBP and SPO_2 and HR values in the recovery room. Though a statistically significant difference was determined between the groups in MAS recovery scale values recorded in the recovery room (RR) at RR3rd, RR5th, RR10th, and RR15th minutes (p<0.05), while no difference was observed at other time points (Figure 2).

There was no bradycardia in any patients in group A, but two patients experienced bradycardia in group R (p=0.166). Three patients (3.3%) in group A and five patients (5.2%) in group R developed hypotension (p=0.721), and none of the patients required a vasopressor agent. The numbers of patients who experienced hypoxemia and underwent interventions were similar between the two groups. Sedation related complications are given in Table 3.

Discussion

In this study, though a significant difference was determined in additional propofol dose and recovery times compared to the remifentanil group and alfentanil group in adult patients during the colonoscopic procedure, there was no difference in awake times and side effects.

The use of propofol as the single agent has recently occupied a significant place for sedation of the patients under colonoscopy because of rapid awake and recovery times it provides and also its safety (14). However, the analgesic effect of propofol is limited, and higher doses that increase the risk of deep sedation are required when it is used as a single agent.

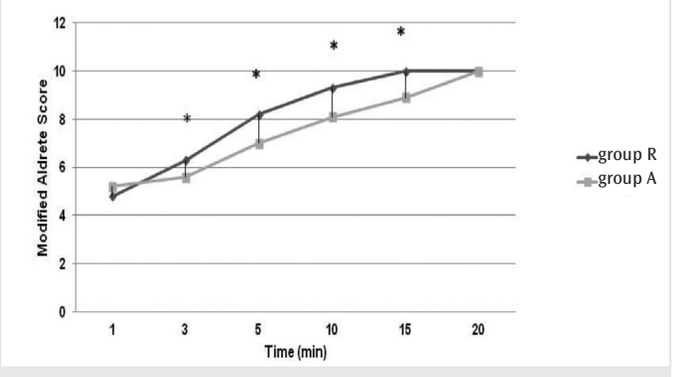

Figure 2. Comparison of MAS between groups

*: p<0.05, group R: remifentanil group, group A: alfentanil group, RR: recovery room, MAS: modified Aldrete scores

Table 2. Sedative/analgesic doses, procedure-related times

Total dose, mean ± SD	Remifentanil group, (n=97)	Alfentanil group, (n=92)	p
Midazolam, mg	1	1	-
Remifentanil, µcg	81.42±34.85	-	-
Alfentanil, µcg	-	371.08±73.37	-
Total propofol, mg	88.17±22.97	110.11±41.26	<0.001*
Additional propofol, mg	13.96±21.34	36.89±42.56	<0.001*
Procedure related times (mean ± SD) min			
Total procedure time	12.07±4.07	13.15±3.57	0.054
Awake time	5.9±0.89	6.1±1.10	0.158
Recovery time	12.36±1.42	14.68±1.41	<0.001*

n: number of patients, *p<0.05, SD: standart deviation, min: minimum

Table 3. Complications associated with the sedation during, n (%)

	Remifentanil group, (n=97)	Alfentanil group, (n=92)	p
Hypoxemia			
SpO_2<90	2 (2.1)	5 (5.4)	0.269
SpO_2<85	6 (6.2)	2 (2.2)	0.280
Chin lift	2 (2.1)	5 (5.4)	0.269
Mask ventilation	6 (6.2)	2 (2.2)	0.280
Systolic hypotension <90 mmHg	5 (5.2)	3 (3.3)	0.721
Use of vasopressors	0	0	0.501
Bradycardia <50 beats/min	2 (2.1)	0	0.166
Vomiting	0	0	0.501

n: number of patients, SpO_2: peripheral oxygen saturation, min: minimum

Bolus administration related to a short half-life of propofol facilitates the occurrence of "sedation waves" via which deep sedation peaks and respiratory depression may be replaced by the risk for superficialization and agitation during colonoscopy (15). The addition of opioids and benzodiazepine to propofol for pain control during colonoscopy procedure increases the sedative effects of propofol, and thus provides avoiding of propofol overdose (16).

Patients sedated only with propofol need higher dose additional propofol than the patients sedated with the combination of alfentanil/midazolam and with midazolam alone (9). In a study with incremental propofol administration in the midazolam/fentanyl and midazolam/fentanyl/ketamine groups, propofol dose was found to be significantly lower in the second group (11). In the pre-anesthetic administration of fentanyl and propofol with and without midazolam, propofol consumption is lower in the midazolam (0.05 mg kg^{-1}) group (17).

In our study, an additional dose of propofol was lower in the remifentanil group, compared to the alfentanil group.

In the case of midazolam alone for sedation, duration of hospitalization, and recovery time are prolonged (9). Whereas recovery times were similar in the combination of 1-2.5 mg midazolam with propofol and opioids (6,9,10), recovery time was prolonged when midazolam dose was used as 2.5 mg and higher (9).

The slow metabolization of benzodiazepines could prolong the recovery time, reducing the turnover rate and efficiency of the endoscopic unit (1). In the present study, midazolam was administered in all patients at 1 mg dose because of its effect on recovery time.

In a study comparing safety and effectiveness of small dose alfentanil and fentanyl at balanced propofol sedation for deep sedation, recovery time was around 15 minutes (10). Similarly, recovery time was found as around 15 minutes in balanced propofol sedation targeting moderate sedation for colonoscopy (1). It was underlined for the same result obtained in these two studies that only 1 mg administration of midazolam in the second study might provide an advantage on recovery time (10). In the present study, midazolam used at 1 mg revealed the difference between action times of opioids. Both short action time of remifentanil and a low additional dose of propofol have been effective in the short recovery time in group R.

In a study that combined midazolam and propofol with alfentanil, fentanyl, and remifentanil in order to maintain sedoanalgesia during cardioversion, it was shown that time of achieving MAS 8 was shortest in the remifentanil group and longest in the fentanyl group, and there was no statistical difference between alfentanil and remifentanil groups (8). In this study, no difference was found in the alfentanil and remifentanil since the additional dose of propofol was not administered, while in our study, this time was longer because of the high additional dose of propofol in the alfentanil group.

In our study, VAS and MSS values were observed as minimal in both groups, compatible with the literature (10).

The use of sedative agents improves endoscopic performance and increases compliance with the procedure. However, the probability of moderate complications related to sedation should be considered (18,19). Respiratory depression caused by sedation and hemodynamic instability can occur during colonoscopy, but the prevalence of adverse effects requiring antagonist agent is low (20). Drug-induced hypoventilation may cause hypoxemia and carbon dioxide retention. Pulse-oximetry is a useful indicator of oxygenation (21). When propofol is administered concomitantly with an opioid, it causes less respiratory depression (8). In our study, patients were monitored with pulse oximetry, and no significant difference was observed in terms of SpO_2 between the two groups. In our study, the blood pressure of patients was monitored non-invasively before, during, and after the procedure. Following drug administration, a reduction was observed in MBP and HR values compared to basal in both of the groups. There was no statistically significant difference in the MBP and HR values between the groups at other times. Generally, 90 mmHg systolic blood pressure is adequate to perfuse tissues in the lying position. Lower blood pressure values cause inadequate perfusion and require intervention. A decline in HR and/or cardiac output volume decreases the blood pressure at the same time. Therefore, blood pressure and HR should be recorded before, during, and after the endoscopy. Also, a more profound fall in blood pressure may occur in the hypovolemic patient. Volume support can be beneficial; therefore, it can be suggested in order to prevent hypotension due to propofol (21).

None of our patients required antagonist agents, and there was no difference related to cardiovascular complications between the two

groups. The complication rate was similar to other studies, complications were treated conservatively, and there was no need for endotracheal intubation (8,10).

There was no nausea and vomiting in our study groups. This might be due to the antiemetic effect of propofol. Studies have reported that propofol and the opioid combination provided not only analgesia and amnesia, but also decreased the frequency of nausea and vomiting (14,22). Nausea and vomiting are the common adverse effects of opioids. Excessive distension of the stomach and colon during the procedure can also cause nausea and vomiting (21).

The sedative patients were discharged from the RR when they met discharge criteria (23). The probability of early discharge from PACU is an essential feature in the care of outpatients and produces better service and lower costs (24). Time to discharge was determined as 15 minutes according to the Modified Post-anesthetic Discharge Criteria (11). In another study, time to discharge was determined as 20 minutes in patients administered deep sedation (25). In our study, time to discharge was determined as 15 minutes.

Study Limitation

There were limitations to our study. First, this study was performed in a center with only one gastroenterologist and anesthesiologist, and follow up was performed by an independent research nurse. Therefore, the results were difficult to generalize. A multiple-center clinical trial might solve this limitation.

Conclusion

In the present study, a low dose of midazolam combined with propofol/remifentanil and propofol/alfentanil provided effective sedation and analgesia. Less propofol consumption and shorter recovery times were observed in the remifentanil group. We believe that low dose midazolam combined with propofol/remifentanil is a vital anesthetic option in pain control during colonoscopy and can be safely and effectively used in daily practice because of its advantages related to the pharmacological characteristics of remifentanil.

Ethics Committee Approval: The study was performed with the approval of the Necmettin Erbakan University Meram Faculty of Medicine Ethical Committee (decision no: 2017/1109).

Informed Consent: Written informed consent was received from all patients.

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Author Contributions: Surgical and Medical Practices - R.D., M.K.; Concept - Ş.A., Ç.S.; Design - Ş.A., Ç.S.; Data Collection and/or Processing - F.Ç., G.H., R.D., M.K.; Analysis and/or Interpretation - G.H., R.D., M.K.; Literature Search - F.Ç., G.H., Ç.S.; Writing Manuscript - Ş.A., G.H., S.T.U.

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Clinical Uses of Lactate and Lactate Clearance in Carbon Monoxide Poisoning

Karbon Monoksit Zehirlenmesinde Laktat ve Laktat Klirensinin Klinik Kullanımı

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ABSTRACT

Introduction: This study aimed to investigate lactate and lactate clearance and to determine the feasibility of the use of lactate clearance for assessing treatment efficacy in carbon monoxide (CO) poisoning.

Methods: All patients aged 18 years and older with CO intoxication between 01.06.2016 and 28.02.2018 were included. COHb levels, initial (lactate-1), and post-treatment control lactate (lactate-2) levels, lactate clearance, type of treatment [normobaric, or hyperbaric oxygen therapy (HBOT)] were recorded. The receiver operating characteristic curve was configured to establish a cut-off point of initial lactate level with the calculated area under the curve (AUC) to predict the need for HBOT.

Results: A total of 103 patients were included. There was a moderate correlation between COHb and lactate-1 (r=0.49; p<0.001) and a weak correlation between COHb and lactate clearance (r=0.291; p=0.003). A significantly higher increase was observed in lactate clearance in the HBOT group (p=0.017). The AUC value of initial lactate in predicting the need for HBOT was 0.708.

Conclusion: The initial lactate level and lactate clearance are rapidly performed and effective markers that may be used in CO intoxication. Especially lactate clearance may provide valuable information in predicting the need for HBOT and assessing treatment efficacy as a monitorization marker.

Keywords: Lactate, lactate clearance, carbon monoxide poisoning, emergency department

ÖZ

Amaç: Çalışmamızda karbonmonoksit (CO) zehirlenmesinde laktat ve laktat klirensi düzeylerinin araştırılması ve laktat klirensinin tedavi etkinliğini değerlendirmede kullanılabilirliğinin belirlenmesi amaçlanmıştır.

Yöntemler: 01.06.2016-28.02.2018 tarihleri arasında acil serviste CO zehirlenmesi tanısı alan 18 yaş ve üzeri tüm hastalar çalışmaya dahil edildi. COHb düzeyi, başvuru (laktat-1) ve tedavi sonrası laktat (laktat-2) değerleri, laktat klirensi, uygulanan tedavi türü [gereksinime göre normobarik veya hiperbarik oksijen tedavisi (HBOT)] kaydedildi. Receiver Operating Characteristic (ROC) eğrisi çizilerek HBOT ihtiyacını öngörmek için başvuru laktatın eşik değeri ve eğri altında kalan alan (AUC) hesaplandı.

Bulgular: Toplam 103 hasta çalışmaya dahil edildi. COHb ve laktat-1 arasında orta düzeyde korelasyon (r=0,49; p<0,001) varken; COHb ve laktat klirensi arasında ise zayıf bir korelasyon (r=0,291; p=0,003) saptandı. HBOT alan grupta laktat klirensi istatistiksel olarak anlamlı düzeyde daha yüksekti (p=0,017). HBOT ihtiyacını öngörmede başvuru laktat düzeyinin AUC değeri 0,78 olarak saptandı.

Sonuç: Başvuru laktat düzeyi ve laktat klirensi CO zehirlenmesinde kullanılabilecek hızlı ve etkin belirteçlerdir. Özellikle laktat klirensinin, HBOT ihtiyacını öngörmede ve tedavi etkinliğinin değerlendirilmesinde bir izlem parametresi olarak klinisyene faydalı bilgiler sunabileceğini düşünmekteyiz.

Anahtar Kelimeler: Laktat, laktat klirensi, karbon monoksit zehirlenmesi, acil servis

Introduction

Carbon monoxide (CO) intoxication is one of the most common causes of intoxication-related deaths (1,2). The tissue hypoxia-ischemia combination that the formation of the carboxyhemoglobin (COHb) molecule with higher oxygen affinity creates, is the most important mechanism in the pathophysiology of CO intoxication (3). Although CO intoxication is diagnosed on the basis of a history of exposure and elevated serum COHb level, it has been reported that the measured COHb level is an inadequate predictor of disease severity and prognosis (4,5).

Lactate is a biomarker known to reflect tissue hypoxia, which has been related to prognosis in many disorders. Lactate clearance reflects the rate of lactate removal from the blood (6). The efficacy of lactate clearance

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for treatment guidance in sepsis has led to the performance of studies to evaluate the feasibility of its use in critically ill patients with systemic involvement due to other diseases (7,8). Although several studies reporting a correlation between initial lactate levels and disease severity in CO exposure have been recently published, there are a limited number of studies examining lactate clearance in CO intoxication (9-12).

In our study, it was aimed to investigate lactate and lactate clearance levels and to determine the feasibility of the use of lactate clearance for assessing treatment efficacy in CO poisoning.

Methods

Study Design and Setting

Our study was conducted in an emergency department where 250.000 patients are admitted annually. A local ethics committee approval (Ankara Keçiören Training and Research Hospital Ethics Committee, decision no: 2012-KAEK-15/1674, date: 23.05.2018) was obtained before the study onset. All patients aged 18 years and older who were diagnosed with CO intoxication in the emergency department between the dates of 01.06.2016 and 28.02.2018 were included. All patient data were obtained by retrospectively scanning hospital records and patients' files. The COHb level measured from peripheral venous blood gas sample was above 10% in smokers and above 5% in non-smokers among patients reporting CO exposure was accepted as CO intoxication. Patients with missing data, oncological or hematological disorders, chronic inflammatory disorders (rheumatoid arthritis, vasculitis), and pregnant subjects were excluded. Demographic data, Glasgow Coma scale (GCS) scores, initial COHb levels, initial (lactate-1) and post-treatment control lactate (lactate-2) levels, lactate clearance [lactate clearance = (lactate-2)-(lactate-1)], type of administered treatment [normobaric (NBOT) or hyperbaric oxygen therapy (HBOT), depending on the need] were recorded. The lactate-1 level was determined as the lactate level in the first blood gas following emergency department admission. In the patients administered only NBOT, the lactate-2 level was considered as the lactate level measured 4 hours after treatment initiation in the emergency department. When the patient was referred from the emergency department for HBOT, the lactate-2 level was recorded as the lactate level in the first-ever blood gas examination taken after the hyperbaric oxygen session. Venous blood samples obtained from patients with suspected CO intoxication were taken with heparin-containing injectors and studied with the Gestat 1825 (Japan) device. Patients with syncope, loss of consciousness, seizures, coma, focal neurological deficits, and signs of acute myocardial ischemia, or a blood COHb level >25% were referred to HBOT. Other patients were administered %100 NBOT with a reservoir mask.

Statistical Analysis

Study data were analyzed with IBM SPSS 20.0 (Chicago, IL, USA) statistical software package. The normality of distribution for discrete and continuous variables was tested using the Kolmogorov-Smirnov test. As the continuous variables did not have a normal distribution, they were expressed as median, minimum, and maximum, while the categorical ones were displayed as number and percentage (%). Categorical variables were compared using the chi-square test and continuous variables with the Mann-Whitney U test. Correlation analysis between continuous variables was done with Spearman's correlation test. Receiver operating characteristic (ROC) curves were configured to establish cut-off point of plasma lactate level with the calculated area under the curve (AUC) and 95% confidence interval. A p-value <0.05 was considered significant.

Results

A total of 131 patients were diagnosed with CO intoxication during the study period. Twenty-eight patients were excluded due to missing data, and so a total of 103 patients with CO intoxication were included in the study for statistical analyses. Sixty-eight percent of the study population was female. The most common presenting symptom was headache (78%). Demographic data and laboratory results were presented in Table 1.

An analysis of the correlation coefficients and their significance between COHb levels and initial lactate levels and lactate clearance revealed a significant, moderate correlation between COHb and lactate-1 (r=0.49; p<0.001). There was a statistically significant and weak correlation between COHb and lactate clearance (r=0.291; p=0.003) (Table 2).

Nineteen (17%) patients received HBOT. Those patients had a significantly higher median initial lactate level compared to the NBOT group (p=0.006). A significantly higher increase was observed in the lactate clearance in the HBOT group (p=0.017). An analysis of percentage changes of the lactate levels after the therapy revealed that the drop in

Table 1. The demographic characteristics of the patients (n=103)

Age median (min-max)	42 (18-87)
Gender n (%)	
Male	33 (32%)
Female	70 (68%)
COHb level (%) median (min-max)	21.4 (7.1-51.8)
Presentation symptoms [n (%)]	
Headache	80 (78%)
Nausea	61 (59%)
Dizziness	55 (53.6%)
Syncope	13 (12.3%)
GCS score median (min-max)	14.98 (14-15)
Hyperbaric oxygen therapy n (%)	19 (17.9%)
Lactate 1 median (min-max)	2.9 (0.3-9.3)
Lactate 2 median (min-max)	1.3 (0.1-7.20)
Lactate clearance median (min-max)	0.33 (-8.33-0.96)
Troponin median (min-max)	1.7 (0.0-184.3)

COHb: carboxyhemoglobin, GCS: Glasgow Coma score, min: minimum, max: maximum

Table 2. Correlation coefficients between COHb levels and lactate-1, lactate clearances

Variables	Correlation coefficient	p
Lactate-1	0.490	0.000
Lactate clearance	0.291	0.003

COHb: carboxyhemoglobin

lactate level was significantly higher in the HBOT group compared to the NBOT group (p=0.039) (Table 3).

A ROC analysis was performed, and the AUC was calculated to find out the cut-off level for the initial lactate level to predict the need for HBOT. The AUC value was found to be 0.708 (0.567-0.850) (p=0.006) (Figure 1). Accordingly, when the cut-off value was taken 1.75 mmol, the sensitivity and specificity values of initial lactate were 77% and 56%, respectively.

Discussion

In the present study, which we evaluated lactate and lactate clearance levels in CO intoxication, we found three important results. Firstly, we found a higher admission lactate level among patients with CO intoxication, which reflects tissue hypoxia occurring secondary to hypoperfusion in CO intoxication. Secondly, initial lactate levels were significantly higher in the HBOT group than the NBOT group. Clinicians need to subjectively evaluate injuries occurring secondarily to hypoxia for deciding to proceed with HBOT in CO intoxication. Our result suggests that lactate, a direct indicator of tissue hypoxia, maybe a suitable marker for use in decision making regarding the appropriate treatment modality before overt signs arise. Following this thought, we found that the AUC value of initial lactate in predicting the need for HBOT was 0.708. Lastly, we found a greater lactate clearance in patients administered HBOT than those who were not. Therefore, we believe that, by reflecting the improvement occurring in tissue hypoxia, lactate clearance may be used to evaluate treatment response.

Table 3. Comparison of lactate-1, lactate-2 and lactate clearance levels according to treatment groups

Variables	Received HBOT	Received NBOT	p
Lactate-1	3.6 (1-9.3)	1.8 (0.3-7.1)	0.006
Lactate-2	1.2 (0.6-3.4)	1.3 (0.1-5.2)	0.514
Lactate clearance	0.51 (-0.25-0.80)	0.27 (-2.3-0.96)	0.017
Lactate change	51% (-25-80)	33% (-66-95)	0.039

HBOT: hyperbaric oxygen therapy, NBOT: normobaric oxygen therapy

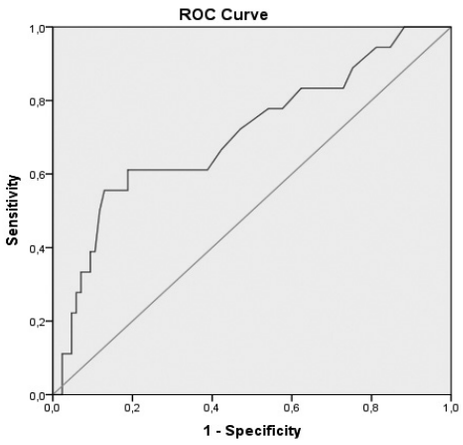

Figure 1. Receiver operating characteristic curve of the initial lactate to predict the need for hyperbaric oxygen therapy

ROC: receiver operating characteristic

The diagnosis of CO intoxication is classically made by an exposure history and COHb level (4). As COHb impairs oxygen-carrying capacity and tissue oxygen use independently of the oxygen amount, intoxicated patients may have normal oxygen saturation and partial oxygen pressure in arterial blood gas analysis. Furthermore, studies in the literature have underlined that the COHb level inadequately reflects intoxication-related acidosis and various complications, including delayed neurological sequelae (5,12). For this reason, a rapid, reproducible, and effective marker is needed to monitor tissue hypoxia. By reflecting tissue hypoxia, which is the last step in the pathophysiology of many disease states, lactate has recently proved its value in a variety of disorders (8,13). In CO intoxication, a significant correlation was reported between initial lactate and COHb levels by Moon et al. (12) (r=0.493, p<0.001), Doğan et al. (9) (r=0.738, p<0.001), Cervellin et al. (11) (r=0.54, p<0.001) and Emektar et al. (10) (r=0.588, p<0.001). We also found a moderately strong correlation between lactate and COHb (r=0.490; p<0.001). The differences of correlation strength between our study and the others in the literature may be due to the heterogeneity of disease severity among the study populations and differences between initial median COHb levels.

The most important decision made by the clinician regarding management is whether HBOT or only NBOT would be administered. Unfortunately, clear criteria regarding the use of HBOT in this indication have not yet to be defined. Subjective criteria widely used in clinical practice include end-organ injuries secondary to hypoxia (1). Thus, predicting hypoxia severity early in the course before ischemia occurs would bring the clinician one step forward in the disease management. As lactate starts to increase after the mitochondrial oxidative capacity is overwhelmed, it may warn the clinician about the severity of tissue hypoxia in advance of ischemic injury (14). Cervellin et al. (11) and Icme et al. (15) reported a more significant lactate increase among patients treated with HBOT. Doğan et al. (9) found higher lactate levels in patients with mental status changes and the need for HBOT compared to those without; they also reported an AUC level of 0.83 for plasma lactate levels in predicting HBOT need (9). In agreement with the literature, we found a higher admission plasma lactate level among patients that received HBOT and found an AUC value of 0.708 for predicting HBOT need. Based on this observation, we believe that higher lactate levels may warn clinicians about the severity of tissue hypoxia and the need for HBOT.

As it is a static parameter, it has been thought that a single lactate measurement is rather useful for risk prediction. As it indirectly reflects an improvement in tissue hypoxia, lactate clearance is thought to assume a more effective role in clinical monitorization (8). Many studies have reported the usefulness of lactate clearance for treatment monitoring and predicting prognosis in sepsis, severe sepsis, and septic shock (7,16,17). Nevertheless, several studies have reported that its use is not limited to sepsis. Wada et al. (18) reported that a higher lactate clearance might be useful for differentiating patients without active bleeding among those with upper gastrointestinal bleeding. Odom et al. (19), in a large trauma series, found that lactate clearance was an independent predictor of mortality. Zhang's meta-analysis reported that lactate clearance is a useful biomarker for predicting mortality among critically ill patients (8). Slottosch et al. (20) underlined that lactate

clearance measurement was more effective at rating treatment efficacy and determining prognosis than a single lactate measurement among patients undergoing extracorporeal membrane oxygenation. There is limited knowledge on the role of lactate clearance in intoxications. Liu et al. (21) reported that lactate clearance might be used for determining prognosis in acute paraquat intoxication. Emektar et al. (10), in the only study that, to our best knowledge, examined the relationship between treatment modalities and lactate clearance in CO intoxication, found a greater lactate clearance (64%) in patients receiving HBOT than those receiving no such therapy (52%), which they attributed to a more rapid lactate clearance depending on treatment type. We found a greater lactate clearance among patients receiving HBOT than those receiving NBOT. We think that this result is due to reduced lactate production secondary to a more effective reduction of tissue hypoxia by HBOT. Also, we think that, in this way, it is possible to evaluate the treatment efficiency by observing both inter-sessional lactate clearance among patients receiving HBOT and at certain time intervals among those receiving NBOT. Similarly, in cases that HBOT is not chosen as the therapy modality or NBOT is thought to be enough while making treatment decisions, inadequate lactate clearance may indicate an insufficient improvement in tissue hypoxia and guide clinicians toward HBOT. We, therefore, believe that lactate clearance may be used as a monitoring tool for treatment response in CO intoxication as in other critical diseases.

Study Limitations

Our study has some limitations. First of all, as this was a single-center study, our results are not generalizable to all centers. Secondly, erroneous data in the hospital records may have influenced the study results owing to its retrospective design. Additionally, neurological and cardiac involvement was not considered. As our hospital was not a hyperbaric center, cases admitted via ambulance were relatively milder CO intoxication cases than those who presented on an outpatient basis. Therefore, based on the assumption that our patient population may not have had adequate heterogeneity, we did not compare disease severity and lactate and lactate clearance. The above parameters were only compared with the need for HBOT. We think that this was one of the major limitations of our study.

Conclusion

In the present study, we determined that the initial lactate level and lactate clearance are rapidly performed and effective markers that may be used in the diagnostic and treatment processes of CO intoxication. We believe that particularly lactate clearance may provide valuable information in predicting the need for HBOT and assessing treatment efficacy as a monitorization marker.

Ethics Committee Approval: A local ethics committee approval (Ankara Keçiören Training and Research Hospital Ethics Committee, decision no: 2012-KAEK-15/1674, date: 23.05.2018).

Informed Consent: Retrospective study.

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The Effect of Erythropoiesis-Stimulating Agents on Platelet Aggregation in Peritoneal Dialysis Patients

Periton Diyaliz Hastalarında Eritropoietin Stimüle Eden Ajanlar Kullanımının Trombosit Agregasyonu Üzerindeki Etkisi

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ABSTRACT

Introduction: Erythropoietin (Epo) is a hormone that is synthesized in the kidneys and that stimulates the erythropoiesis in the bone marrow. Epo has effects apart from the erythropoiesis. In chronic renal failure (CRF) patients, hemorrhagic diathesis is observed, and Epo production is decreased. Erythropoiesis-stimulating agents (ESAs) are widely used in the treatment of renal anemia in these patients. Our study aimed to investigate the effect of ESAs use on platelet aggregation in peritoneal dialysis (PD) patients due to CRF.

Methods: Forty-three PD patients were included in the study. Seventeen patients had been using ESAs for anemia for at least three months (ESAs user group). Twenty-six patients were not using ESAs since they did not have indications (non-ESAs user group). Platelet aggregation measurement from the whole blood was carried out in each patient by a multiplate device. The calculated values [area under the curve (AUC), aggregation, and velocity] were recorded. The results were evaluated statistically, and $p<0.05$ was accepted as statistically significant.

Results: In the non-ESAs user group, the mean hemoglobin level was found higher when compared to the other group, and this difference was statistically significant ($p<0.001$). The percentage of transferrin saturation was found higher in the ESAs user group ($p=0.021$). It was observed that AUC, aggregation, and velocity values were lower in the ESAs user group, and the result was not statistically significant (p values were 0.202, 0.329, 0.290, respectively).

Conclusion: ESAs use in PD patients did not have any effect on platelet aggregation. Further prospective studies involving platelet aggregation tests before and after ESA treatment in dialysis patients are needed.

Keywords: Platelet aggregation, erythropoiesis-stimulating agents, peritoneal dialysis

ÖZ

Amaç: Eritropoietin (Epo), böbrekler tarafından sentez edilen ve kemik iliğinde eritropoezi uyaran bir hormondur. Epo hormonunun eritropoez dışında etkileri de mevcuttur. Kronik böbrek yetmezliği (KBY) hastalarında kanama diyatezi görülür ve Epo üretimi azalmıştır. Bu hastalarda renal aneminin tedavisinde eritropoietin stimüle eden ajanların (ESAs) kullanımı yaygındır. Çalışmamızın amacı; KBY nedeniyle periton diyalizi (PD) uygulayan hastalarda, ESAs kullanımının trombosit agregasyonu üzerindeki etkisini araştırmaktı.

Yöntemler: Çalışmaya 43 PD hastası dahil edildi. En az üç ay süreyle ve anemi nedeniyle ESAs kullanımı olan 17 hasta mevcuttu (ESAs kullanan grup). Endikasyonu olmadığından 26 hasta ESAs kullanmıyordu (ESAs kullanmayan grup). Multiplate cihazı ile her hastanın tam kandan trombosit agregasyon ölçümü yapıldı. Hesaplanan değerler [eğrinin altında kolon olan (AUC) agregasyon ve velozite] kaydedildi. Sonuçlar istatistiksel olarak değerlendirildi. $P<0.05$ istatistiksel anlamlı kabul edildi.

Bulgular: ESAs kullanmayan grupta, diğer gruba kıyasla ortalama hemoglobin seviyesi daha yüksek bulundu ve bu farklılık istatistiksel anlamlıydı ($p<0,001$). Ortalama transferrin satürasyonu, ESAs kullanan grupta, diğer gruba göre daha yüksek saptandı ($p=0,021$). ESAs kullanan grupta, diğer gruba kıyasla AUC, agregasyon ve velozite değerlerinin daha düşük olduğu görüldü; sonuç istatistiksel anlamlı değildi (p değerleri sırasıyla 0,202; 0,329; 0,290).

Sonuç: PD hastalarında ESAs kullanımının trombosit agregasyonu üzerine etkisi yoktu. Diyaliz hastalarında ESAs tedavisinden önce ve sonra trombosit agregasyon testlerinin yapıldığı ileriye dönük çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Trombosit agregasyonu, eritropoietin sitümüle eden ajanlar, periton diyalizi

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Introduction

Erythropoietin (Epo) is a hormone that is synthesized in the kidneys, which provides the continuity of erythropoiesis by protecting the erythrocytic precursors colony-forming unit-erythroid, and burst-forming unit-erythroid cells against the apoptosis (1). Epo hormone has some effects apart from the erythropoiesis. It can provide regeneration both on muscular tonus and on gonadal and cognitive functions with its anti-apoptotic feature, as well as its autocrine, paracrine, and endocrine effects (2).

Chronic renal failure (CRF) disrupts the adhesion and aggregation of platelets with the extended bleeding time (3). Vascular erythrocytes drag platelets towards the vessel wall and increase their contact with each other. Also, they both perform the secretion of adenosine diphosphate (ADP) and the inactivation of prostacyclin. Using the erythropoiesis-stimulating agents (ESAs) in patients with CRF may improve the functions of the platelet through increasing the hematocrit (4). Thrombotic complications in uremia are due to increased platelet aggregation and hypercoagulopathy (5). Long-term ESAs treatment increased the level of platelet cytosolic calcium that is stimulated by the thrombin from low to normal, independent from the hematocrit and blood pressure values in the rats of which CRF was created (3). It was determined that in experimental animals of which high doses of Epo were given in the short-term, platelet aggregation was increased, and the level of plasma soluble p-selectin was increased (6). Our study aimed to investigate the effect of ESAs use on platelet aggregation in peritoneal dialysis (PD) patients due to CRF.

Methods

Patients Selection Evaluation

Forty-three patients (22 females, 21 males) who are in the standard PD program (continuous ambulatory or automated peritoneal dialysis) were included in the study. The patients were randomly selected from the outpatient nephrology clinic of Kocaeli University Faculty of Medicine between the years 2011-2012.

The inclusion criteria of the study were volunteering, being 18 to 80 years old, and receiving PD at least for three months. The exclusion criteria were determined as; possessing diabetes mellitus, thrombocyte adhesion or aggregation defects, using aspirin or NSAI drugs in the last two weeks, or undergoing an infectious disease.

Committee approval was obtained for the study from Kocaeli University Ethics Committee (decision no: 2011/64, date: 27.06.2011). Informed consent was obtained.

A certain amount of blood was drawn from each patient who consulted to nephrology outpatient clinic for routine biochemical markers, following fasting of at least eight hours, and the results were assessed in the laboratory. The samples, which were drawn from each patient for exact blood count, were put into tubes that contain ethylenediaminetetraacetic acid, were analyzed in Cell-Dyn 3700 (Abbott Laboratories, Philippines), which operates with combined impedance and Multi-Angle Polarized Scatter Separation flow cytometry method. Percentage of transferrin saturation (100 x serum iron/TIBC) was studied with Abbott architect original kit. Seventeen PD patients with anemia (ESAs users) were using recombinant human erythropoietin (rHuEpo) by subcutaneous route for more than three months and with a dosage of 75-150 IU/kg/week and since there was not any indication, rHuEpo treatment was not performed on 26 PD patients (non-ESAs users).

Platelet Aggregation Study

The platelet aggregation values of each patient were recorded by measuring them in Multiplate (Dynabyte medical, Munich, Germany) device with multiple electrode aggregometry methods that can carry out measurements from whole blood. The increasing impedance due to platelets that adhere to the sensor of the device is transformed into aggregation unit (AU), and it is printed as a graph against time. Three values are calculated regarding platelet aggregation:

a) The area under the curve (AUC): Its unit is AU x minute,

b) Aggregation: Its unit is AU,

c) Velocity: Its unit is AU/minute.

Whole blood, which was drawn from each patient into a hirudin blood tube, was studied in the laboratory with a multiplate device between 30 and 120 minutes. Three hundred µl of blood was taken into a hirudin blood tube and inserted in the test cell, and after a three-minute incubation by adding 300 µl isotonic NaCl, platelet aggregation measurement was carried out by adding 31 µl (10 µmol/L) ADP.

Statistical Analysis

SPSS 15.0 version was used for the statistical analysis of the study. The significance measurement between the groups of PD patient (ESAs users and non-ESAs users) was conducted with independent samples t-test for markers which comply with a normal distribution. Mann-Whitney U test was used for the variables that do not comply with a normal distribution. In the subgroup of patients, the chi-square test was used to analyze the gender parameter. $P<0.05$ was accepted as statistically significant.

Results

According to the CRF etiology, 23 of the patients had hypertension, 11 of them had chronic glomerulonephritis, three of them had autosomal dominant polycystic kidney disease, one of them had amyloidosis, one of them had obstructive nephropathy, and four of them had idiopathic etiology. According to the outpatient clinic controls for the last three months, the patients were separated into two groups, ESAs users (n=17) and non-ESAs users (n=26). There was a statistically significant difference between the two groups in terms of age and gender parameters (p values were 0.001, 0.012, respectively). Biochemical data and demographic findings of PD patients were given in Table 1.

The mean hemoglobin level was found higher in the non-ESAs user group when compared to the other group, and this difference was statistically significant ($p<0.001$). The percentage of transferrin saturation was detected higher in the ESAs user group when compared to the other group ($p=0.021$). Platelet aggregation values of ESAs user and not-ESAs user PD patients were compared in terms of AUC, aggregation, and velocity. It was observed that AUC, aggregation, and velocity values were

lower in the ESAs user group. The results were not statistically significant (p values were 0.202, 0.329, 0.290, respectively). Platelet aggregation values of PD patients were presented in Table 2.

Discussion

In our study, we have investigated the effect of ESAs use on platelet aggregation in PD patients. However, aggregation values in the ESAs user group were not statistically significant, and they were lower than the other group. Also, hemoglobin level was lower in patients who were using ESAs. Furthermore, the percentage of transferrin saturation was higher in the ESAs user group. This is probably because of ESAs use in anemic patients despite normal transferrin saturation (>20%).

ESAs treatment in the experimental CRF model demonstrated the increase of platelet cytosolic calcium level (3). Although there are contradictory results in recent studies, ESAs treatment was also effective in platelet aggregation by increasing hemoglobin and hematocrit. Increased hematocrit may improve platelet function (4). Also, an inverse relationship was determined between platelet aggregation and the level of hemoglobin in hemodialysis (HD) patients. In the same study, an inverse relationship was found between platelet aggregation and the level of serum Epo in HD patients who were not given recombinant (rHuEpo) (7). An inverse relationship was reported between platelet aggregation and hematocrit in patients who are under the aspirin treatment and have coronary artery disease (8). There was not a relationship between platelet aggregation and hematocrit in healthy patients after the corrections were made regarding their age and gender (9).

In the study of Taylor et al. (10), ESAs user and non-ESAs user dialysis patients were compared to each other in terms of platelet aggregation. The study results pointed that platelet aggregation values changed and increased with ESAs treatment both in HD and PD patients, but in another study, ESAs treatment had not any effect on platelet aggregation and activation in continuous ambulatory PD patients (11).

In our study, the number of female patients was higher than male patients in ESAs user group, and the mean age of them was lower than the non-ESAs user group. Platelets of healthy women have both increased aggregation and activation potential (12). However, rHuEpo increased platelet aggregation induced by ADP in both male and female donors in a study of healthy and young individuals. Unlike women, a lower rHuEpo dose was used for effective platelet aggregation in men (13). Both thrombotic events and hospital mortality rates increased with age (14). In a study by Verdoia et al. (15), the mean values of the ADP test were higher in the elderly than patients under the age of seventy. However, no association was found between platelet aggregation and age in healthy individuals (9). In our study, subjects were randomly selected while forming the groups. Age and gender homogenization could not be achieved between the groups. Therefore, it may be challenging to interpret the available data.

There are some limitations in the study design. HD patients were not included in the study, and a control group of healthy volunteers could

Table 1. Biochemical data and demographic findings of PD patients

	ESAs user group (n=17) Mean ± standard deviation	Non-ESAs user group (n=26) Mean ± standard deviation	p
Age (year)	41±9.2	52.7±9.9	0.001
Gender (female)	13	9	0.012
Dialysis duration (month)	41.7±22.1	40±23.5	0.823
Total Kt/V (week)	2.2±0.9	2.4±0.9	0.35
Hemoglobin (g/dL)	9.3±1.3	11.3±1.8	<0.001
Leukocyte (mm^3)	6898±1949	7253±1683	0.529
Platelet (mm^3)	235430±72800	266690±71450	0.258
Serum CRP (mg/dL)	0.5±0.4	1±0.9	0.168
Serum albumin (g/dL)	3.4±0.4	3.5±0.3	0.359
Serum ferritin (ng/mL)	797±620	479±352	0.15
Transferrin saturation (%)	38.9±16.9	28.6±10.8	0.021
Systolic blood pressure (mmHg)	151±20	142±21	0.153
Diastolic blood pressure (mmHg)	89±13	86±13	0.342

PD: peritoneal dialysis, ESAs: erythropoiesis-stimulating agents, CRP: C-reactive protein

Table 2. Platelet aggregation values of PD patients

Platelet aggregation values	ESAs user group (n=17) Mean ± standard deviation	Non-ESAs user group (n=26) Mean ± standard deviation	p
AUC (AUxminute)	646.2±301.3	748.3±215.1	0.202
Aggregation (AU)	121.4±63.4	136.7±38.3	0.329
Velocity (AU/minute)	14.5±6.2	16.4±5.6	0.290

PD: peritoneal dialysis, AUC: area under the curve ESAs: erythropoiesis-stimulating agents AU: aggregation unit

not be formed. Our study is cross-sectional and observational, and platelet aggregation measurement was carried out by separating in PD patients into two groups as using ESAs for at least three weeks and the non-ESAs users. The basal platelet aggregation values of patients before ESAs treatment were not studied. Furthermore, serum Epo levels could not be determined additionally.

Conclusion

As a result, ESAs use in PD patients did not have any effect on platelet aggregation. Rather than ESAs use, serum hemoglobin levels may be more effective on platelet aggregation in patients. Further prospective studies involving platelet aggregation tests before and after ESAs treatment in PD patients are needed.

Ethics Committee Approval: Committee approval was obtained for the study from Kocaeli University Ethics Committee (decision no: 2011/64, date: 27.06.2011).

Informed Consent: Informed consent was obtained.

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Investigation of Subclinical Cardiotoxicity in Chronic Leukemia Patients with Non-invasive Tests

Kronik Lösemi Hastalarında Subklinik Kardiyotoksisitenin Non-invazif Testler ile Araştırılması

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ABSTRACT

Introduction: This study aimed to investigate the left ventricular function and electrocardiographic findings in patients with chronic leukemia receiving and not receiving chemotherapy during a one-year follow-up.

Methods: A total of 111 patients with chronic leukemia were included in the study. Electrocardiographic and mechanical findings of the heart were evaluated by surface 12-lead electrocardiogram and 2-dimensional transthoracic echocardiography, and cardiac troponin (cTn) was evaluated for myocyte damage and B-type natriuretic peptide marker for heart failure at baseline, 6th month and 12th month.

Results: During the study, a total of six patients reached the endpoint, including two patients to primary endpoint (atrial fibrillation) and four patients to secondary endpoint (non-cardiac death). However, asymptomatic hemodynamic and electrocardiographic changes were observed in all patients who did not reach the endpoint. There was a quantitative decrease in left ventricular ejection fraction and an increase in the rate of diastolic dysfunction. Increased incidence of fragmented QRS, and prolongation of QT interval and QT dispersion, which are important indicators of possible cardiac events, were detected. cTn levels were observed to be at the upper limit of the normal range. All these findings show that myocardial damage has begun in the study patients, even if it is asymptomatic.

Conclusion: In order to prevent future cardiac events in this patient group, these changes need to be taken into consideration and closely monitored.

Keywords: Chronic leukemia, heart failure, cardiotoxicity

ÖZ

Amaç: Kemoterapi alan ve almayan kronik lösemi tanılı hastalarda 1 yıllık izlemde sol ventrikül fonksiyonunun ve elektrokardiyografik bulgularının araştırılması amaçlanmıştır.

Yöntemler: Kronik lösemi tanılı 111 hasta çalışmaya alındı. Başlangıçta, 6. ve 12. aylarda kalbin elektrokardiyografik ve mekanik bulgularına yüzeyel 12-derivasyonlu elektrokardiyogram ve 2-boyutlu transtorasik ekokardiyografi ile, bunun yanında miyosit hasarının önemli belirteci olan kardiyak troponin (cTn) ve kalp yetersizliğinin belirteci B-tipi natriüretik peptid düzeyleri bakılıp karşlaştırıldı.

Bulgular: Çalışma süresince 2 hasta birinci (atriyal fibrilasyon), 4 hasta ikinci sonlanım noktası (kardiyak olmayan ölüm) olmak üzere toplam 6 hasta sonlanım noktasına ulaştı. Ancak asıl önemli olan sonlanım noktasına ulaşmayan hastaların tamamında, asemptomatik olmak ile beraber, takipte hemodinamik ve elektrokardiyografik değişiklikler gözlendi. Sol ventrikül ejeksiyon fraksiyonunda kantitatif olarak düşme görülürken diyastolik disfonksiyon görülme oranında da artış görüldü. Olası kardiyak olayların önemli göstergeleri olan fragmante QRS görülme oranında artış, QT intervali ve QT dispersiyonunda uzama olduğu tespit edildi. cTn düzeyinin normal aralığın üst sınırında seyrettiği görüldü. Bunların hepsi çalışma hastalarında, asemptomatik olsa bile, miyokard hasarının başladığını, ancak daha başlangıç aşamasında olduğunu göstermektedir.

Sonuç: Bu hasta grubunda gelecekteki olası kardiyak olayların önlenebilmesi için bahsi geçen değişikliklerin daha başta dikkate alınması ve yakın takip gerekmektedir.

Anahtar Kelimeler: Kronik lösemi, kalp yetersizliği, kardiyotoksisite

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Introduction

Despite all the advances in medicine, cardiovascular diseases (CVD) and malignancies are the leading causes of death in the world (1). Although there is enough information about diagnosis and treatment when CVD and malignancies are evaluated separately, there is not enough information about how a treatment strategy if both diseases occur in the same individual.

Although it has been shown in many studies that agents used in chemotherapy (CT) adversely affect left ventricular (LV) function, there are not many studies in the literature showing the effect of malignant blood diseases on LV function (2-4). For this purpose, in this study, the effects of the primary effects of the disease on the mechanical and electrocardiographic functions of the heart were investigated.

Lymphoproliferative diseases such as leukemia and lymphoma are diseases that have effects on many organs through inflammation and mediators such as cytokines, hormones, etc. (5). It is also possible to think that it may negatively affect heart function using various mediators released into the environment. Myocardial injury may result in cardiomyopathy (CMP) and heart failure (HF). HF can be in the form of a decrease in LV ejection fraction (LVEF), or EF can be preserved. In recent studies, HF with preserved EF accounts for 50% of HF (6-8).

Tests and markers used in the diagnosis and prognosis of myocardial injury or developing HF in cancer patients include a surface 12-lead electrocardiogram (ECG), 2-dimensional transthoracic echocardiography (TTE), cardiac troponin (cTn), B-type natriuretic peptide (BNP), and some other blood markers (9-11).

High sensitivity cTn has been suggested to be used in the diagnosis of diseases other than non-myocardial infarction. An increase in cTn levels in the early and late post-CT period is associated with an increased incidence of cardiac events (12). Abnormal ECG findings are observed in the majority of patients with HF that developed as a result of myocardial injury (13,14). Again, TTE is an excellent method for demonstrating cardiac function. While it is a good test to show the size of the cardiac cavities and LVEF, it also helps to show HF with preserved EF (15,16).

Fifty percent of the asymptomatic patients with normal LVEF after CT have diastolic dysfunction (16). Significant echocardiographic changes after CT can be observed in most cases, while no signs and clinical symptoms of cardiotoxicity are present (17). The abovementioned biomarkers may help detect structural damage due to cardiotoxicity at an early stage.

The specific treatment of HF caused by CT has not been widely studied. Angiotensin-converting enzyme (ACE) inhibitors (ACEi) increased LVEF in breast cancer patients treated with epirubicin; therefore, ACEi should be part of the treatment of LV dysfunction in cancer patients. It has been shown that the addition of β-blockers (Bb) to ACEi in LV dysfunction following doxorubicin and imatinib treatment improves LVEF more significantly than those receiving ACEi alone. LVEF was significantly improved with the combined treatment of ACEi and Bb in CT-induced CMP (18,19).

This study aimed to investigate the LV function and electrocardiographic findings in patients with chronic leukemia receiving and not receiving CT during a one-year follow-up.

Methods

Between March 2014 and April 2015, 111 chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL) patients who were followed in the hematology outpatient clinic of Cerrahpaşa Medical Faculty were included in the study.

Each patient was informed about the scope of the study, and written consent was obtained for participation in the study. The study was evaluated by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee, and ethical approval was obtained (decision no: 83045809/604.01/02-14160).

At the beginning of the study, the patient's history was taken, and the risk factors (RF) were questioned. Initial physical examinations were performed, blood samples were analyzed, resting ECG and TTEs were recorded, and the same procedures were repeated at 6 and 12 months. The analyzed data were compared in all of the patients, as well as between age (median age of 55) and gender subgroups.

Inclusion Criteria

Patients over 18 years of age (with or without CT) with a diagnosis of CML and CLL were included. Patients with a history of CVD, HF, and CMP, signs of LV hypertrophy on ECG, stroke, atrial fibrillation (AF), and malignant arrhythmia were not included in the study.

Endpoints

The primary endpoints were hemodynamic impairment, symptomatic or asymptomatic LV systolic dysfunction (5-10% decrease in LVEF in TTE) or diastolic dysfunction of stage 2 and above, malignant arrhythmia (ventricular tachycardia, AF with rapid ventricular response), atrioventricular and interventricular blocks, cardiovascular mortality, and increase in cTn level 20% above 99. percentil of standard value. The secondary endpoints were death due to non-cardiac causes.

Electrocardiographic Parameters and Their Definitions

The ECGs of the patients were recorded in the supine position (Schiller AT-2 Plus, 9.025000C, Baar, Switzerland).

P Wave Dispersion: The difference between the longest p wave and the shortest p wave duration in the ECG.

QT dispersion: The difference between the longest QT interval and the shortest QT interval in the ECG.

Fragmented QRS (fQRS): The presence of r'- R'- s' - S' wave in any lead in the ECG (Figure 1).

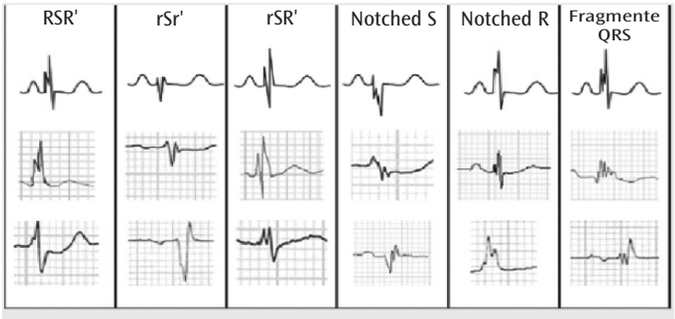

Figure 1. Fragmented QRS examples

Echocardiographic Evaluation

Two-dimensional images from apical 4th, 3rd and 2nd chambers, parasternal short and long axis in accordance with the recommendation of the AHA 2015 echocardiography guide using GE Vingmed System Five (GE Vingmed Ultrasound, Horten, Norway) and 2.5 MHz probe (70-80 frame) were obtained with standard methods in TTE, and cardiac cavities and wall thickness, systolic and diastolic ventricular functions of the patient were examined and calculated (20).

LVEF: After the mean systolic and end-diastolic volume measurements were obtained from three repeated measurements of apical four chambers and parasternal short-axis during consecutive heart cycles using the classical two-dimensional and modified Simpson rule method, the mean EF values obtained for each cycle were recorded.

Pulmonary Hypertension: Tricuspid regurgitation (TR) jet velocity was measured from apical four chambers, right ventricular entrance or parasternal short axis windows as much parallel as to continuous-wave Doppler insufficiency jet at the end of the diastole while the patient exhaled as much as possible and held the breath. The pulmonary artery systolic pressure (PASP) was calculated by excluding pulmonary stenosis, assuming right ventricular systolic pressure to be equal to PASP, using the Bernoulli equation from the TR rate and adding estimated right atrial pressure. PASP above 25mmHg was accepted as pulmonary hypertension (PH).

Diastolic Dysfunction: It was calculated by measuring e' by tissue Doppler, and E, A, E/A waves by checking transmitral jet velocities by PW Doppler.

Heart Failure: It was accepted as having an LVEF of 45% or less or diastolic dysfunction of stage 2 or more in TTE.

Statistical Analysis

In our study, we compared the findings of the patients in each of the three follow-up examinations, and gender subgroups and age subgroups (55 years of age was accepted as RF for CVD) were also compared among themselves. Statistical analysis was performed with SPSS v21.0. The statistical significance level was accepted as $p<0.05$. Normality assessments were made by Kolmogorov-Smirnov and Shapiro-Wilk tests. A chi-square test was used to compare categorical data, and the Mann-Whitney U test was used to compare continuous data. For repeated measures, ANOVA was used for continuous variables, and Cochran Q was used for categorical variables obtained during follow-up examinations. ANOVA test results were evaluated with Pillai's Trace. Post-hoc evaluations were performed with Bonferroni. When comparing the changes between groups, the model was evaluated by a single group. Significance in the Cochran Q test was assessed using the McNemar test as a post-hoc binary comparison test.

Results

Of the 111 patients in our study group, 67 were male, and 44 were female. The percentages of specific malignant diseases in our study group were similar: CML was 52.3%, and CLL was 47.7% (Table 1). In the age subgroup, CML and CLL rates were 72.2% and 27.8%, respectively, at <55 years of age, whereas it was 33.3% and 66.7% at >55 years of age. Accordingly, CML was significantly higher at <55 years, and CLL significantly higher at >55 years ($p<0.001$).

During the study, a total of six patients reached the endpoint, including two patients to primary endpoint (AF) and four patients to secondary endpoint (non-cardiac death). AF developed in two patients in the third and fifth months. Both were male, and one had CML, and the other had CLL. One of them had asymptomatic LV dysfunction (LVEF: 55% at baseline; 35% and 40% at follow-up). Four patients died in the second half of the study due to non-cardiac causes. Three of them were CLL, one was CML, and two were male, and two were female. All patients reaching the endpoint were above the median age of 55 years.

The Use of CT in Our Patients: As expected, it was significantly higher in CML patients than in patients with CLL (91.4% vs. 32.1%, $p=0.001$). Proportional to this, PR dispersion, f(QRS) and diastolic dysfunction were higher in the CML group ($p=0.01$; $p=0.05$; $p=0.03$, respectively, at baseline, first and second follow-up) (Table 2).

Table 1. Demographic features

Age (mean ± SD)	53.18±13.05	
Height (mean ± SD)	168.19±7.75	
Risk factors		
Smoking (n, %)	22	19.8
HT (n, %)	35	31.5
DM (n, %)	23	20.7
CRF (n, %)	0	0
Alcohol (n, %)	0	0
Hyperlipidemia (n, %)	18	16.2
Gender		
Male (n, %)	67	60.4
Female (n, %)	44	39.6
	111	100
Disease		
CML (n, %)	58	52.3
CLL (n, %)	53	47.7
Median age		
<55 (n, %)	54	48.6
≥55 (n, %)	57	51.4

SD: standard deviation, HT: hypertension, DM: diabetes mellitus, CRF: chronic renal failure, CML: chronic myeloid leukemia, CLL: chronic lymphocytic leukemia

Table 2. Comparison of electrocardiographic and dynamic changes in CML and CLL patients

	CML	CLL	p
Number (n)	58	53	-
CT rate (%)	91.4	32.1	0.001
PR dispersion (ms)	2.57±5.24	1.95±5.15	0.014
QT dispersion (ms)	27.45±13.71	24.83±15.72	0.036
fQRS (%)	63.7	47.1	0.05
Diastolic dysfunction (%)	65.5	47.1	0.039

CML: chronic myeloid leukemia, CLL: chronic lymphocytic leukemia, CT: chemotherapy, fQRS: fragmented QRS complex

When TTE findings were evaluated, EF was 62.0% at baseline, and 61.8% and 61.1% in the first and second follow-up, respectively. Even if there was only 0.2 and 0.9 decrease (<1.0) in the absolute value at follow-up compared to the baseline EF value (relative decrease of 1.45%), it was statistically significant (p=0.018). The mean PASP values were 22.48 mmHg at baseline and 22.94 mmHg and 24.06 mmHg, respectively, at follow-up. Although PASP did not meet the diagnostic criteria for PH, it was significantly increased in the second follow-up when compared to the baseline (p=0.001). The incidence of diastolic dysfunction was found in 35.2% of the patients at the beginning and in 36.2% and 47.6% of the patients, respectively. At the end of the follow-up, the diastolic dysfunction rate increased significantly in the second half of the follow-up period (p<0.001). The incidence of PH was 17.9% at baseline and 22.9% and 31.4%, respectively (p<0.001) (Table 3).

In our study, the mean value of PR dispersion calculated on ECG was 0 at baseline and then measured as 1.19±4.07 ms and 2.57±5.10 ms at the follow-up, respectively. It was found to increase significantly at the follow-up (p<0.001). The incidence of fQRS was 7.2% at baseline, and 20% and 46.7% at follow-up, respectively, and it increased significantly (p<0.001). The mean QT dispersion was 23.24±13.37 ms at baseline, while it was measured 25.14±15.48 ms and 26.48±14.44 ms during follow-up. It was increased significantly (p=0.004). Again, this increase was higher in men than in women (p=0.03) (Table 4).

The mean cTn value was measured as 0.0047±0.0028, 0.0053±0.0032 and 0.0067±0.0012, respectively, at baseline and at follow-up (p=0.012). cTN increase was continuous during follow-up (baseline vs. first follow-up: p<0.001; baseline vs. second follow-up: p=0.001; first follow-up vs. second follow-up: p=0.001) (Table 5).

Table 3. Transthoracic echocardiography findings

	Baseline	First follow-up	Second follow-up	p
EF (%)				
Total	62	61.8	61.1	0.018
Male	61.4	61.3	60.4	0.48
Female	63	62.7	62.3	0.48
<55 years	62.7	62.6	62.3	0.59
≥55 years	61.2	61.02	59.9	0.59
PASP (mmHg)				
Total	22.48	22.94	24.06	0.001
Male	22.34	22.67	24.27	0.001
Female	22.68	23.37	23.73	0.03
<55 years	22.58	23.4	23.8	0.045
≥55 years	22.38	22.49	24.3	0.001
DD (%)				
Total	35.2*	36.2	47.6*	<0.001*
Male	32.8	35.9	46.8	0.002
Female	34	36.5	73.1	0.03
<55 years	28.8	30.7	34.6	0.24
≥55 years	41.5	45.5	60.3	<0.001
PH (%)				
Total	17	22.9	31.9	<0.001
Male	14	20.3	34.3	<0.001
Female	21.9	26.8	26.8	0.44
<55 years	19.2	26.9	25	0.039
≥55 years	15	18.8	37.7	<0.001

*Difference between baseline and second follow-up, EF: ejection fraction, PASP: pulmonary artery systolic pressure, DD (%): diastolic dysfunction rate, PH (%): pulmonary hypertension rate

Discussion

The cytotoxic and cardiotoxic effects of CT agents used in the treatment of cancers are known to adversely affect the prognosis of the disease.

Table 4. Electrocardiographic parameter changes

	Baseline	First follow-up	Second follow-up	p
PR Dispersion (ms)				
Total	0	1.19±4.07	2.57±5.10	0.001
Male	0	1.95±5.08	3.52±5.95	<0.001
Female	0	0	1.10±2.85	<0.001
<55 years	0	0.48±2.47	2.60±5.85	0.11
≥55 years	0	1.89±5.11	2.55±4.23	0.11
f(QRS) (%)				
Total	7.2	20	46.7	<0.001
Male	10.9	26.5	48.4	<0.001
Female	2.4	9.7	43.9	<0.001
<55 years	7.6	11.5	34.6	<0.001
≥55 years	7.5	28.3	58.4	<0.001
QT Dispersion (ms)				
Total	23.24±13.37*	25.14±15.48	26.48±14.44*	0.004*
Male**	24.38±12.98	24.61±12.64	27.50±13.62	0.035**
Female**	21.46±13.93	25.98±19.24	24.88±15.67	
<55 years***	23.85±14.19	25.96±18.41	26.06±14.49	0.41***
≥55 years***	22.64±12.61	24.34±12.05	26.89±14.51	

*Difference between baseline and second follow-up, **Difference between genders ***Difference between age groups, f(QRS) (%) Fragmented QRS complex rate

Table 5. Changes in troponin level

Troponin (ng/dL)	Baseline	First follow-up	Second follow-up	p
Total	0.0047±0.0028	0.0053±0.0032	0.0067±0.012	0.012
Male*	0.0049±0.003	0.0058±0.0034	0.0076±0.014	0.22*
Female*	0.0043±0.0024	0.0044±0.0026	0.0054±0.009	
<55 years**	0.0040±0.0022	0.0040±0.0022	0.0041±0.0023	0.011**
≥55 years**	0.0054±0.0031	0.0066±0.0035	0.0093±0.017	

*Difference between genders, **Difference between age groups

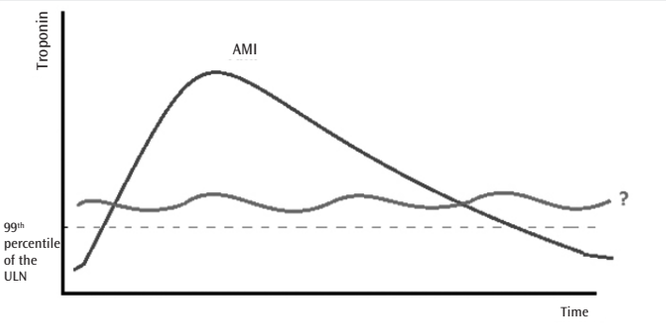

Figure 2. Troponin: course of troponin levels in AMI and non-ischemic conditions (a marker of cardiotoxicity during cancer treatment)

ULN: upper limit of normal, AMI: acute myocardial infarction, the course of troponin levels in non-ischemic conditions

However, the direct effect of the malignant disease itself in the chronic process on cardiac histopathology and functions is not known, and the number of studies to be attributed to the subject in the literature is limited (21,22). Therefore, in order to shed light on this issue, the effects of chronic leukemia disease (primary malignant disease of circulating blood) on the functions of the heart were investigated in patients without primary (documented) heart disease in this study. For this purpose, in our study, patients with a history of coronary atherosclerotic heart disease that is the major cause of the high prevalence of heart disease in adults were excluded. However, about half of the randomly selected cases had no major RFs. Also, the mean age of our patient group was lower than the level of atherosclerosis defined as a conventional RF (55 years for men, 65 years for women). Atherosclerosis, which occurs in younger than the expected age in the general population and is usually manifested by clinical manifestations, can be seen by the presence of several RFs (diabetes + 1 RF, 3 RFs without diabetes, and the presence of early cardio- and non-cardiovascular manifestations in hereditary first-degree relatives) and can be defined as "premature". In conclusion, the effect of atherosclerosis on the cardiovascular outcomes of the study in the medium and long-term follow-up was eliminated to some extent due to these demographic characteristics of the study group.

In our prospective study, we investigated cardiac involvement in chronic leukemia patients, and functional, electrocardiographic, and chemical concrete evidence of myocardial involvement was determined during the 1-year follow-up period in patients with or without CT treatment. According to this:

1. Echocardiographic findings showed that mechanical contractile functions (systolic and diastolic) of LV were impaired,

2. The increase in the frequency of f(QRS), reflecting changes in the depolarization and repolarization of the heart, and especially the calculated QT dispersion time in the ECG compared to baseline values were the electrocardiographic findings of myocardial damage and specifically developing LV remodeling,

3. cTn, which is the marker and/or product of the cytological physiopathological process underlying these findings, increased to the upper level of the standard (99th percentile of the reference level) and continued elevated cTn levels with fluctuations without showing the classic "delta pattern" for acute myocardial infarction (AMI) during follow-up was observed (Figure 2),

4. BNP, which is the sensitive and specific hemodynamic marker of elevated LV filling pressures proportional to the magnitude of myocardial damage, did not increase significantly in our asymptomatic patient group as expected.

In the literature, in studies in which the effects of CT are mostly examined and questioned in cancer patients, LV dysfunction in cancer patients was found to be non-homogeneous (asymptomatic, subclinical, manifested by signs and symptoms of prominent HF, and sudden cardiac death).

EF, which is the quantitative indicator of LV systolic function independent of CT in cancer patients, is a crucial marker even in asymptomatic patients with EF, and a decrease was found in our study compared to baseline values. However, since it cannot show microscopic myocyte damage, it may be insensitive to measure EF for early detection of global heart damage, and no correlation could be detected between clinical HF symptoms and signs and EF changes (9).

After CT, diastolic dysfunction was found in approximately 50% of asymptomatic patients with preserved LV systolic function in TTE, especially in early (<1 month) and mid-term (<3 months) (7). In the absence of clinical signs and symptoms of cardiotoxicity, structural pathologies in the myocardium (such as cardiomyocyte damage without cell death, hydropic degeneration, and interstitial edema) are the main pathological changes that impair myocardial compliance and relaxation function. In parallel to this, in our study, the incidence of diastolic dysfunction increased at the end of one year compared to baseline.

Systolic functional impairment occurs as a result of acute mass or persistent and minor loss of myocytes and LV remodeling. It may emerge with clinical, echocardiographic pump insufficiency, and severe clinical systolic dysfunction very early (with toxicity) or mostly late (with low flow syndrome). EF is an important prognostic marker in these patients (23).

Diastolic dysfunction may occur (be expected) before or at the beginning of a decrease in EF, as in acute myocardial ischemia or acute myocarditis, in light of the above physiopathological process. Therefore, early detection of cardiotoxicity (in the acute phase) is essential in terms of treatment and preventive measures in asymptomatic patients, as in our study (8).

Serial monitoring of cardiac bio- and/or electro-markers may be helpful in early detection of cardiotoxicity in the asymptomatic and subclinical stage during follow-up:

- The process leading to CMP caused by CT begins primarily with massive damage to cardiomyocytes (such as cTn elevation; 2X standard upper limit) and acute/subacute and chronic microscopic myocyte damage (≥standard upper limit) in the chronic period, and increasing mass loss of functional myocardium (elevation of BNP) leads to asymptomatic LV dysfunction.

- Diastolic dysfunction is often expected to occur earlier, probably due to edema formation as a result of inflammation reaction in myocardium due to CT and disruption of LV wall compliance (as in AMI and myocarditis) (24).

- In our study, the absolute but not significant decrease of EF in the follow-up and the significant increase in the frequency of diastolic dysfunction implied acute-subacute myocardial injury and involvement of the myocardium.

- Despite the myocardial functional and electrocardiographic changes observed in almost all of our patients (95%) after one year of clinical follow-up, almost all of them remained asymptomatic (clinically silent, subclinical). In these, the findings mentioned above pointing to acute and subacute myocardial damage were noted ("myocarditis-like" condition).

- In summary, LV dysfunction developed as a result of disruption of compliance due to initial acute-subacute interstitial edema causing in particular diastolic and relatively less systolic dysfunction.

The levels of cTn, which is the specific marker of myocardial damage and myocyte loss, were higher according to baseline and slightly above the upper limit of the standard reference value. Three findings reflecting myocardial physiopathology were: 1) myocardial damage is not massive as in AMI (transmural or subendocardial, myocardial infarction with or without ST-segment elevation), but microscopic, 2) the absence of a "delta pattern" during follow-up and continuous fluctuations above the upper limit of normal were a distinctive feature of chronic myocardial damage pathology rather than acute myocardial ischemia, 3) continuous fluctuating cTn levels could be the sign of smoldering fire. The clinical messages of this physiopathological process are a) "the best" is the ability to prevent or even regress the progression of LV remodeling with combined renin-angiotensin-aldosterone system (RAAS) inhibitor and Bb agents (19), b) "the worst" is that asymptomatic myocardial and electrocardiographic pathological changes, which can often be overlooked or ignored, may adversely affect prognosis by symptomatic HF (stage C HF), increased risk of sudden cardiac death in the long-term (>1 year, mean 19 months) and inhibiting and restricting the treatment of malignant disease.

In our study, because of the higher rate of CT in CML patients, PR dispersion, QT dispersion, f QRS, and diastolic dysfunction were higher in this group than in the CLL group. This may be due to the high rate of CT in patients with CML.

Conclusion

The subclinical diagnosis of cardiac dysfunction during CT is complicated, with the most important reason being that most of the patients are asymptomatic initially and during the short-to-medium period despite significant changes in noninvasive tests. Therefore, in order to prevent possible future cardiac events (with early RAAS inhibition and regulation of the CT program), these changes should be taken into consideration and monitored closely.

Ethics Committee Approval: The study was evaluated by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee, and ethical approval was obtained (decision no: 83045809/604.01/02-14160).

Informed Consent: Each patient was informed about the scope of the study, and written consent was obtained for participation in the study.

Peer-review: Internal peer-reviewed.

Authorship Contributions: Concept - T.O., R.E.; Design - R.E.; Supervision - R.E.; Resources - T.O.; Materials - T.O.; Data Collection and/or Processing - T.O.; Analysis and/or Interpretation - T.O., R.E.; Literature Search - R.E.; Writing Manuscript - T.O.; Critical Review - R.E., B.İ., B.K.A.

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Can VAP-1 Protein be used as a Biomarker in Thyroid Cancer?

VAP-1 Proteini Tiroid Kanserinde Biyobelirteç Olarak Kullanılabilir mi?

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ABSTRACT

Introduction: The aim of this study is to determine whether vascular adhesion protein-1 (VAP-1) glycoprotein can be used as a biomarker in thyroid cancer.

Methods: Retrospective analysis of the pathology results of patients who were operated for thyroid malignancy or multinodular goiter in our hospital was performed. A total of 46 patients, including 16 papillary carcinomas, ten follicular carcinomas, ten benign nodules, and ten healthy tissues, were included in the study. Patients with cancer other than thyroid cancer, who were pregnant, who had a chronic systemic disease, and impaired liver function tests were excluded from the study. The level of tissue VAP-1 was assayed by immunohistochemistry.

Results: In our study, 13 papillary carcinoma tissues, five follicular carcinoma tissues, six benign nodules, and one healthy tissue were stained positively. Although there was a statistically significant difference between papillary carcinoma and healthy tissue, no statistically significant difference was found between the other groups.

Conclusion: VAP-1 glycoprotein can be used as a biomarker in the diagnosis of papillary thyroid carcinoma.

Keywords: Thyroid cancer, VAP-1 protein, goiter

ÖZ

Amaç: Bu çalışmanın amacı, vasküler adhezyon proteini-1 (VAP-1) glikoproteinin tiroid kanserinde biyobelirteç olarak kullanılıp kullanılamayacağını belirlemektir.

Yöntemler: Hastanemizde tiroid malignitesi veya multinodüler guatr nedeniyle opere edilen hastaların patoloji sonuçlarının retrospektif analizi yapıldı. Çalışmaya 16 papiller karsinom, on foliküler karsinom, on iyi huylu nodül ve on sağlıklı doku olmak üzere toplam 46 hasta alındı. Tiroid kanseri dışında kanseri olan, gebe olan, kronik sistemik hastalığı olan ve karaciğer fonksiyon bozukluğu olan hastalar çalışma dışı bırakıldı. Doku VAP-1 seviyesi immünohistokimya ile test edildi.

Bulgular: Çalışmamızda 16 papiller karsinom olgusunun 13'ü, 10 foliküler karsinom olgusunun 5'i, 10 benign dokunun 6'sı ve 10 normal dokunun 1'i pozitif olarak boyanırken diğer olgular negatif olarak boyandı. Papiller karsinom ve normal doku arasında istatistiksel olarak anlamlı bir fark olmasına rağmen, diğer gruplar arasında istatistiksel olarak anlamlı bir fark bulunmadı.

Sonuç: VAP-1 glikoprotein papiller tiroid karsinomu tanısında biyobelirteç olarak kullanılabilir.

Anahtar Kelimeler: Tiroid kanseri, VAP-1 proteini, guatr

Introduction

Thyroid cancer is a common disease among head and neck cancers, and the incidence of it has been increasing all around the world (1). The five-year survival is only 59% in late-stage compared to nearly 100% for an earlier, localized stage (2).

Most of the patients present with a thyroid nodule, but only 5-15% of nodules are malignant (3). One of the most effective methods of decreasing mortality is the early diagnosis, and fine-needle aspiration cytology (FNAC) is most commonly used for this purpose (4). The use of FNAC can reduce unnecessary thyroid operations by 25% (5). Although malignant nodules can be detected by FNAC, 10% to 25% of thyroid nodules are diagnosed as indeterminate nodules (6). FNAC results may vary from non-specific cytology to malignancy, but as a result, the biomarker may be needed to support this outcome preoperatively. Given the limitations of diagnosis by FNAC, investigators have examined molecular markers as cytopathologic adjuncts to improve the accuracy of diagnostic testing of thyroid nodules. A major aim of the research is to

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improve upon the preoperative diagnosis of indeterminate nodules in order to avoid surgery for benign nodules. To reduce repetitive diagnostic tests and operations, there has been an extensive investigation into molecular markers that can be detected on FNAC specimens to stratify a patient's risk of malignancy more accurately.

Many biomarkers are used to differentiate between benign and malignant thyroid nodules, including cytokeratin-19, fibronectin-1, intracellular sodium/iodide, high molecular weight cytokeratin, cyclin D1, and galectin-3 (7,8). They can be used alone or in combination. A single biological marker is not yet able to distinguish between benign or malignant thyroid nodules. The ideal biomolecule that can make this distinction has long been the subject of research.

Vascular adhesion protein-1 (VAP-1), which is another promising glycoprotein marker, weighs 170 kDa. This protein is an endothelial adhesion molecule generally involved in the interaction between leukocytes and endothelial cells, including leukocyte rolling, adhesion, and transmigration into sites of inflammation (9). Recently, many studies have investigated the role of VAP-1 in cancers. In the head and neck, liver, and melanoma tumors, VAP-1 expression is found in intra-tumoral vessels (10-12). VAP-1 has been shown to enhance tumor growth in mice (13). In humans, serum VAP-1 is correlated with angiogenic factors in lung cancers and is more concentrated in metastatic prostatic cancers (14,15).

The primary aim of this study was to investigate tissue VAP-1 levels in benign and malignant thyroid lesions and to compare them with healthy tissue levels. We also aimed to determine whether VAP-1 could be used as a biomarker in thyroid cancer.

Methods

The pathology specimens of patients who underwent total thyroidectomy for thyroid malignancy or multinodular goiter were examined. The study was carried out in four groups, including papillary carcinoma, follicular carcinoma, benign tissue, and healthy tissue. The pathologic tissues of 53 patients were retrospectively reviewed. Patients with other cancers other than thyroid cancer, who were pregnant, who had a chronic systemic disease, and impaired liver function tests were excluded from the study. Of the 46 patients included in the study, 16 were papillary thyroid carcinoma (PTC), ten were follicular thyroid carcinoma (FTC), ten were benign nodules, and ten were healthy patients. Thyroid cancer patients underwent total thyroidectomy and neck dissection. The American Common Cancer Committee TNM classification system was used for staging. Our study was approved by the Ethics Committee of Ümraniye Training and Research Hospital (decision no: 165, date: 24.11.2017). For the study, approval was obtained from the patients.

Laboratory Study

VAP-1 (A-8: sc-166713; Santa Cruz Biotechnology) clone was used as the primary antibody. Paraffin blocks suitable for immunohistochemical analysis were selected, and 3-micron thick sections were taken on the poly-L-lysine coated slide. The immunohistochemical study was completed automatically on the VENTANA BENCHMARK XT device by the device instructions. The staining patterns in the tissue were evaluated as negative and positive.

Statistical Analysis

In this study, IBM SPSS Statistics Version 22 (IBM Turkish Limited Company, İstanbul, Turkey) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviations, and median value) were calculated. When the groups were evaluated together, nonparametric data were assessed by the chi-square test. We performed a receiver operating characteristic (ROC) curve analysis to evaluate the predictive value of VAP-1 for papillary thyroid cancer. Significance was assessed at $p<0.05$ levels.

Results

There were 46 patients in our study. Sixteen of the patients had PTC, ten of them had the FTC, ten with benign tissue, and ten with healthy tissue. The mean age of the patients included in the study was 43.6±5.2, 42.7±5.7, 43.7±4.7, and 43.4±5.2 years, respectively. Thyroglobulin (ng/mL) levels of the patients were higher in cancer patients than in benign and healthy tissues. In PTC and FTC patients, it was found to be 89.4±56.7 and 88.7±55.2, whereas it was 15.2±13.6 and 11.3±10.4 in benign tissue and healthy tissue, respectively. FT4 (pmol/L), thyroid-stimulating hormone (μIU/mL) values, and liver function tests were normal in all groups. Of the PTC patients, 14 were stage 1-2, two were stage 3-4, while eight of the FTC patients were stage 1-2, and two were stage 3-4 (Table 1).

In tissue staining, 13 of the PTC, five of the FTC, seven of the benign nodules, and one of the healthy tissues were stained positively while the others were negatively stained (Figure 1, 2) (Table 2).

Table 1. Demographic and laboratory values of patients

Characteristics	Papillary carcinoma	Follicular carcinoma	Benign tissue	Healthy tissue
Age	43.6±5.2 (n=16)	42.6±5.7 (n=10)	43.7±4.7 (n=10)	43.4±5.2 (n=10)
Tg (ng/mL)	89.4±56.7	88.7±55.2	15.2±13.6	11.3±10.4
FT4 (pmol/L)	12.5±4.7	13.4±3.8	14.1±2.6	11.50-23.12
TSH (μIU/mL)	3.5±3.1	3.6±3.4	3.2±2.3	3.1±1.6
Hepatic disease	-	-	-	-
Systemic disease	-	-	-	-
Thyroid cancer stage	-	-	-	-
I/II (n, %)	14 (87.5%)	8 (80%)	-	-
III/IV (n, %)	2 (12.5%)	2 (20%)	-	-

Tg:thyroglobulin, TSH: thyroid-stimulating hormone, FT4: Free T4, ng/mL: nanogram/milliliter, pmol/L: picomole/liter, μIU/mL: micro unit/milliliter, n: number of patients

When all groups were compared, a statistically no significant difference was found (p=0.48) (Table 3). Although there was a statistically significant difference in comparisons between PTC and healthy tissue groups (p<0.01), respectively, no significant difference was found between the other groups (p=1), (p=0,52), (p=1), (p=1), (p=0.52) (Table 4).

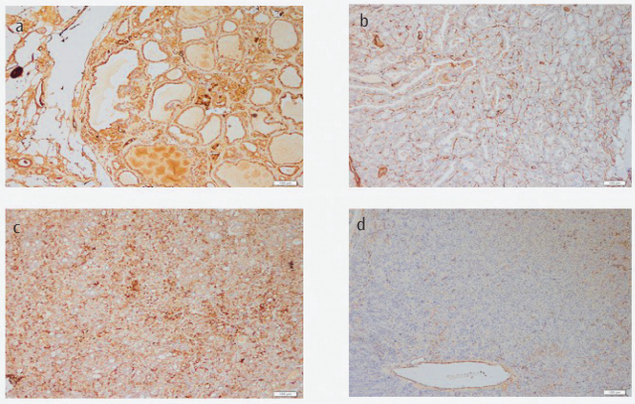

Figure 1. a) Papillary carcinoma positive staining. b) Papillary carcinoma negative staining. c) Follicular carcinoma positive staining. d) Follicular carcinoma negative staining

The area under the ROC curve was 0.83 (95% confidence interval, 0.65-1; p=0.007). The decision on optimal cut off value for tissue VAP-1 was based on maximizing the sum of sensitivity and specificity. The cut-off value of VAP-1 was 0.5 µg/mL, with a 78% specificity and 100% sensitivity (Figure 3).

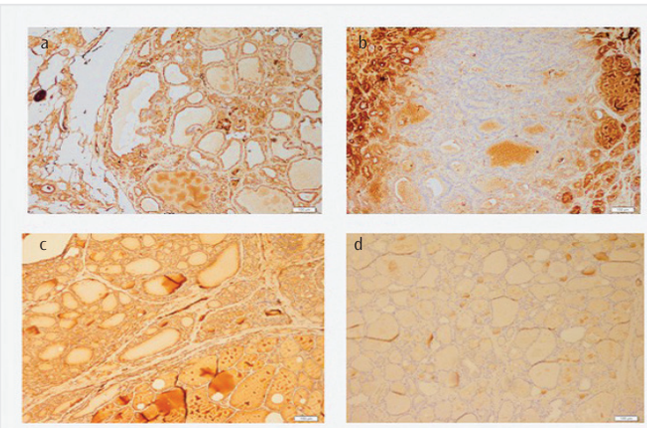

Figure 2. a) Benign tissue positive staining. b) Benign tissue negative staining. c) Healthy tissue positive staining. d) Healthy tissue negative staining

Table 2. Staining characteristics of the patients

	Positive stained	Negative stained
	n	n
Normal tissue	1	9
Benign nodule	7	3
Papillary cancer	13	3
Follicular cancer	5	5

n: number of patients

Table 3. Comparison of all groups together

	n	x^2	p
Papillary cancer	16	6.66	0.48
Follicular cancer	10		
Benign nodule	10		
Normal tissue	10		

Chi-square test, N: number of patients, p value ≤0.05

Table 4. Comparison of binary groups

Comparison of papillary cancer and normal tissue	**n**	**x^2**	**p**
Papillary cancer	16	6.25	0.01*
Normal tissue	10		
Comparison of papillary cancer and follicular cancer groups	**n**	**x^2**	**p**
Papillary cancer	16	6.25	1
Follicular cancer	10		
Comparison of papillary and benign nodules	**n**	**x^2**	**p**
Papillary cancer	16	6.25	0.52
Benign nodule	10		
Comparison of follicular cancer and benign nodules	**n**	**x^2**	**p**
Follicular cancer	10	0.00	1
Benign nodule	10		
Comparison of follicular cancer and normal tissue	**n**	**x^2**	**p**
Follicular cancer	10	0.00	1
Normal tissue	10		
Benign nodule and normal tissue comparison	**n**	**x^2**	**p**
Benign nodule	10	0.40	0.52
Normal tissue	10		
Chi-square test, N: number of patients, p value ≤0.05*			

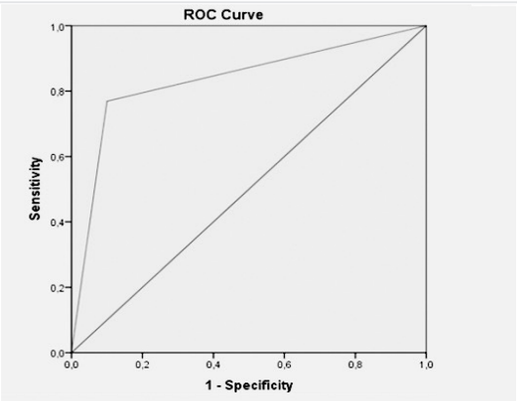

Figure 3. Receiver operating characteristic (ROC) curve. Tissue VAP-1 staining in papillary thyroid cancer and healthy tissue were used to draw the ROC curve, and the specificity, sensitivity, area under the ROC curve (AUC), and cut-off value were determined

VAP-1: vascular adhesion protein-1, AUC: area under the curve

Discussion

Biomarkers have been used for many years to detect thyroid cancer and to determine its prognosis (16). A marker that can identify benign and malignant thyroid nodules and predict their behavior is continuously sought. Difficulties in identifying thyroid nodules and determining their prognosis persist (17). For thyroid nodules, an accurate biomarker is necessary to measure the likelihood of preoperative malignancy.

The process of tumor growth and metastasis involves a variety of cell-cell and cell-extracellular matrix interactions mediated by cell adhesion molecules such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, platelet endothelial cell adhesion molecule-1, and selectins. During tumor growth and metastasis, each process requires cell adhesive interactions involving specific adhesion molecules and receptors (18,19). VAP-1 is one of the endothelial adhesion molecules, which is upregulated at sites of inflammation and mediates binding of lymphocytes to vessels of inflamed tissue (20). In many studies, serum VAP-1 levels are a significant predictor of the prognosis of cancer diseases.

The tissue and serum VAP-1 protein levels were significantly lower in colorectal cancer compared with healthy colon tissue (21). The low serum VAP-1 was associated with poor prognosis in patients with colorectal cancer (22). The low tissue VAP-1 may be part of a mechanism used by the tumor to prevent the recruitment of antitumor defense cells (21). The serum concentration of VAP-1 was significantly elevated in patients with gastric cancer, and clinicopathological analysis revealed that low serum VAP-1 levels in tumors were associated with tumor size increase, serosal invasion, lymph node metastasis, peritoneal dissemination and poor prognosis (23). Serum VAP-1 levels were also found higher in patients with hepatocellular cancer (24). In human breast cancer, tumor VAP-1 mRNA expression is associated with improved prognosis (25,26). In contrast, increased VAP-1 protein expression was found to be associated with poor prognosis in astrocytomas (27).

Hu et al. (28) find that serum VAP-1 levels are significantly lower in thyroid cancer group than in healthy control and benign thyroid nodule groups. Another important finding of their study is that serum VAP-1 has relatively high sensitivity and specificity in predicting thyroid cancer. In this study, we evaluated VAP-1 protein expression in different thyroid pathologies and healthy thyroid tissue at tissue level for the first time in the literature. In our study, 13 of 16 cases of PTC, five of ten cases of FTC, six of ten benign tissues, and one of ten healthy tissues were stained positively. Although there was a statistically significant difference between PTC and healthy tissue, no statistically significant difference was found between the other groups. The cut-off value of VAP-1 was 0.5 µg/mL, with a 78% specificity and 100% sensitivity for papillary carcinoma. Therefore, the combined application of ultrasonographic features and VAP-1 examination in FNA material could be a potential way to improve the accuracy of diagnosing PTC.

It was shown that the genes encoding chemokines CCL20, CXCL8, and the adhesion molecule L-selectin were overexpressed in PTC in comparison to healthy thyroid tissue, and these chemokines could be associated with tumor-related inflammation and lymphocyte infiltration (29). In human PTC, the density of lymphocytes is correlated with improved overall survival and lower recurrences (30,31). In our study, the rate of VAP-1 staining was higher in patients with PTC than in healthy tissues. This may be because the VAP-1 protein has a significant lymphocyte infiltration and migration effect, and the expression is increased to prevent the progression of the disease in cancer tissue.

FTC comprises between 10% and 15% of all differentiated thyroid cancers. This cancer usually presents later in life and is more aggressive than PTC (32,33). It is a malignant epithelial tumor showing follicular cell differentiation and lacking the nuclear diagnostic features of PTC (34). In this study, VAP-1 protein staining was found in half of the patients with FTC. However, statistical results could not be obtained to support the use of VAP-1 protein as a biomarker in this cancer type. Also, less VAP-1 staining in FTC than PTC may explain that the prognosis of FTC is worse than papillary cancer. Further studies are needed to investigate the effects of tissue VAP-1 protein expression on prognosis in FTC.

In this study, tissue VAP-1 protein staining was detected in six of ten patients with benign thyroid nodules. VAP-1 is upregulated at sites of inflammation, and it mediates lymphocyte binding to inflamed endothelium (35). Increased serum VAP-1 levels in chronic liver disease and multiple sclerosis compared to healthy individuals has been reported previously (36,37). Since VAP-1 levels can be detected in inflammatory tissues besides cancers, we thought that positivity detected in benign nodules might be related to inflammation at the tissue level. New data are needed to explain the pathophysiology of VAP-1 staining in benign thyroid nodules at the tissue level and the importance of this staining.

FNAC results may not yield accurate results in thyroid nodules, so positive or negative staining of FNAC material with VAP-1 protein may be helpful in the differential diagnosis. As a result, positive staining of VAP-1 protein in FNAC results may stimulate us for the diagnosis of papillary cancer. It can also help reduce the patient's follow-up or additional cost tests. To demonstrate that VAP-1 protein can be used as an important biomarker in thyroid cancer, studies may be needed in larger series. Further studies are needed to investigate the prognostic effects of VAP-1 on TPC.

Conclusions

Different amounts of VAP-1 staining were obtained in different thyroid pathologies. VAP-1 protein can be used as an important biomarker in TPC.

Ethics Committee Approval: Our study was approved by the Ethics Committee of Ümraniye Training and Research Hospital (decision no: 165, date: 24.11.2017).

Informed Consent: For the study, approval was obtained from the patients.

Peer-review: Externally peer-reviewed.

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

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

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A Retrospective Analysis of Patients Receiving Teleradiology Consultations for Computed Tomography in the Emergency Department

Serviste Bilgisayarlı Tomografi için Teleradyoloji Konsültasyonu Yapılan Hastaların Tanımlayıcı Bir Analizi

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ABSTRACT

Introduction: Teleradiology plays an essential role in the accurate and prompt diagnosis of patients in the emergency department (ED). This study aimed to analyze some factors affecting the use of teleradiology in EDs.

Methods: We retrospectively examined computerized tomography (CT) images taken in our ED over one month. We compared patients for whom emergency physicians (EP) requested an immediate report via teleradiology (group 1), and patients for whom they requested no report and assessed themselves (group 2), in terms of demographic characteristics, complaints, outcomes, and re-admission.

Results: The study population consisted of 1999 patients, 831 in group 1, and 1168 in group 2. The patients in group 2 were older (42.87±25.12 years) than those in group 1 (38.78±25.03 years) ($p<0.01$). The proportion of reports issued in forensic cases (85.8%) was significantly higher than that in non-forensic cases ($p<0.05$). EPs most commonly requested reports for patients presenting to the hospital due to abdominal pain ($p<0.05$). EP requested significantly more reports for patients admitted to the hospital and for subjects who died ($p<0.05$). The re-admission rate among patients who were discharged without teleradiology consultation was higher than the re-admission rate of those who were discharged after the teleradiology consultation ($p=0.01$).

Conclusion: Our findings show that teleradiology is most used in forensic cases, for patients with abdominal pain, who are admitted to clinics, and at after-hours.

Keywords: Emergency, teleradiology, computed tomography, abdominal pain

ÖZ

Amaç: Teleradyolojinin, acil servislerde hastalara zamanında ve doğru tanı konmasında önemli bir işlevi vardır. Bu çalışmamızda acil hekiminin teleradyolojiyi daha çok hangi durumlarda kullandığını inceleyerek, acil servislerde teleradyoloji kullanımını etkileyen faktörleri tespit etmek istedik.

Yöntemler: Bir ay boyunca acil servislerde çekilen bilgisayarlı tomografi (BT) görüntülerini retrospektif olarak inceledik. Acil hekiminin teleradyolojiden hemen raporlama istediği (grup 1) ve raporlama istemeyip kendisinin değerlendirdiği hastaları (grup 2); demografik özellikleri, şikayetleri, sonlanımları ve tekrar başvuru açısından karşılaştırdık.

Bulgular: Çalışmada toplam 1999 hasta olup, bunların 831'i grup 1 1168'i ise grup 2'ye aittir. Grup 2'deki (42,87±25,12 yıl) hastalar grup 1'dekilerden (38,78±25,03 yıl) daha yaşlıdır ($p<0,01$). Adli olgularda raporlanma oranı (%85,8) adli olmayanlara göre anlamlı düzeyde daha yüksektir ($p<0,05$). Acil hekimleri en fazla raporlamayı karın ağrısı şikayetiyle hastaneye başvurup abdomen BT çekilen hastalara istemiştir ($p<0,05$). Acil hekimi hastaneye yatırılan ve ölen olgulara taburcu olanlara göre daha fazla raporlama talep etmiştir ($p<0,05$). Teleradyoloji konsültasyonu yapılmadan taburcu edilen olguların acile tekrar başvuru oranı, teleradyolojiye konsülte edilip taburcu edilenlerinkinden anlamlı düzeyde daha yüksektir ($p=0,01$).

Sonuç: Bu araştırmada, adli olgularda, karın ağrılı hastalarda, hastaneye yatırılarak tedavi edilmesi gereken hastalarda ve mesai dışındaki saatlerde acile başvuran hastalarda teleradyolojinin daha fazla kullanıldığını tespit ettik.

Anahtar Kelimeler: Acil, teleradyoloji, bilgisayarlı tomografi, karın ağrısı

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Introduction

Emergency departments (ED) are units that serve a significant proportion of hospitals' patient populations and that have high mortality rates. In contrast to other fields, the nature of the case that will arrive next is unknown, and a multidisciplinary approach is generally required. It is, therefore, essential for arriving patients to be evaluated in detail and for the necessary tests and consultations to be performed promptly (1). The radiology unit plays a crucial role in early diagnosis and prompt treatment in the management of emergency patients (2). So, the emergency radiology has emerged as a subspecialty in parallel with the development of emergency medicine in recent years. The emergency radiology serves regardless of working hours, but staying in the hospital all the time is difficult for a radiologist. So the online radiology consultation service, known as teleradiology, helps us to solve this problem (3).

Teleradiology refers to the digital transfer of patients' radiological images [computed radiographs (CR), computed tomography (CT) and magnetic resonance imaging (MRI)] to a radiology specialist outside the center where the imaging was performed for consultation or evaluation. The use of teleradiology has spread in parallel to recent advances in picture archiving and communication systems (PACS) (4). The use of teleradiology in EDs is increasing rapidly, and this is making a significant contribution to reducing morbidity and mortality (5). The real increase in the use of teleradiology happened at the beginning of the 2000s. Between 2003 and 2007, teleradiology use increased from 15% to 50% (6). In the USA, teleradiology is used in the majority of imaging reports performed after-hours, and the level of use of teleradiology by radiologists is very high in private hospitals (7).

The teleradiology has been operating in our hospital since 2016. We examined the patients who underwent CT in our ED and searched for urgent teleradiology consultation demands of emergency physicians (EP). We aimed to determine the factors affecting the use of teleradiology in the ED by evaluating the differences between the patients who got teleradiology consultation urgently and who did not get.

Methods

Study Design and Population

This was a retrospective study conducted in the adult ED of a tertiary hospital. Before the study, the approval of the Clinical Research Ethics Committee of Adıyaman University was obtained (decision no: 2019/2-12). Since it was a retrospective study, no patient consent form was obtained. Our hospital is a tertiary health institution serving a city with a population of 600.000, and its ED operates by a 24-h shift system, involving four physicians (two emergency medicine specialists and two general practitioners). The hospital administration has contracted with a teleradiology company for evaluating the radiological images (CT and MRI), which were obtained in ED. So, all of the images in our ED have been evaluated by radiologists who were provided by the teleradiology company. Seven radiologists had a minimum of five years of radiology experience in the list of teleradiology company. These radiologists examined the images on a standard monitor in their home. There are radiologists in our hospital during working hours. However, they do not evaluate any radiological images (CR, CT, MRI), which were taken in our ED because of the lack of numbers of radiologists.

Patients presenting with any symptom and undergoing CT scan in the ED of our hospital in January 2019 were included in the study. The records of the patients included were examined retrospectively. We investigated the reason for CT scan, the time performed, whether the EP evaluated the results or requested an emergency report from teleradiology, the time it took to write the report, patients' demographic data, whether the case is forensic and patient outcomes. Legal cases mean events that require prosecution such as traffic accidents, firearm injuries, and stabbings. Then patients were divided into two groups, those for whom emergency teleradiology reports were requested immediately (group 1) and those for whom no teleradiology report was requested (group 2). Differences between the groups were investigated in order to elicit findings concerning teleradiology use in the ED. We also investigated the time taken to write reports and the factors affecting that time in group 1 patients. Additionally, the patients, who were discharged from ED after CT evaluation by EP (without any teleradiology report), were investigated for any re-admission in 24 hours. The cases that have missing data in their medical records were excluded from the study.

System Description and Design

The CT images in our ED were taken by a Multi-Detector- Row CT scanner (Mx 8000 IDT 16, Philips Medical Systems, Best, The Netherlands). Once radiological imaging has been performed, the images are sent by the technician performing the imaging to the EP and the teleradiology physician via the PACS system in DICOM format. The EP first evaluates them and tries to diagnose. The names of patients whom the physician is unable to diagnose are sent to the remote radiologist using the on-line messaging service (Skype®), together with any preliminary diagnosis. The available radiologist then performs an urgent assessment following receipt of the Skype® message from the EP, together with the images that appear on the teleradiology worklist. Once the images have been assessed, the teleradiology physician sends the report with an e-signature back to the emergency system. However, this report is preliminary, and the final report is created in 24 hours after a double-check by a second radiologist. Images for which the EP does not request a report are regarded as routine work, and reports for these are issued within three days at the latest under the contract with the company providing the hospital's teleradiology service. In urgent cases, reports must be issued within 40 min under the contract. The reporting duration in our study was calculated as the time elapsing between the EP sending a Skype® message to the radiologist, and the report appearing on the emergency system.

Statistical Analysis

Data analysis was performed on Statistical Package for the Social Sciences (SPSS, version 22.0, Chicago, IL, USA) software. $P<0.05$ was regarded as statistically significant. Data were expressed as mean±standard deviation and median values. Student's t-test was used in the analysis of quantitative data when data were normally distributed, and the non-parametric Mann-Whitney U test when data were not normally distributed. The chi-square test and Fisher's exact chi-square test were

used to compare qualitative data. Correlation between variables was investigated using Spearman's test for nonparametric data and Pearson's test for parametric data.

Results

During the study period, 2397 images from 1999 patients were evaluated. EPs requested a teleradiology report of 1152 images from 831 patients (group 1), while no emergency reports were sought for 1245 images from 1168 patients, with the EPs evaluating those images themselves (group 2). The mean age of the patients was 41.17±25.16 years (range, 0-104), with males comprising 1073 cases and females 926. The mean time to report being issued in group 1 was 35.76±33.63 min (range, 2-376), and the majority being issued in 20-39 min (43.6%) (Table 1).

Patients in group 1 were significantly younger than those in group 2 ($p<0.01$). Reports were issued for 40.6% of female patients, and 42.4% of males and gender did not affect report request rates ($p>0.05$). The urgent report rate of forensic cases was 85.8%, compared to 35.3% for non-forensic cases, and the difference was significant ($p<0.05$). In terms of outcomes, in group 1, urgent reports were requested for all the patients who died (100%), for 54.7% of hospitalized patients, and 39.2% of discharged patients. In group 2, 60.8% of cases (n=1038) discharged without teleradiology report, and 35 of these patients re-admitted to our ED within 24 hours, and 15 of them were hospitalized. Nine patients who were discharged after teleradiology reporting also re-admitted to ED, but none of them were hospitalized. The re-admission rate of discharged patients in group 2 (3.4%) was significantly higher than those in group 1 (1.3%) ($p=0.01$). A significantly higher proportion of urgent report requests were made for hospitalized patients, and patients who died, separately ($p<0.05$). The majority of imaging (67.3%) was performed at after-hours, and urgent report request rate was significantly lower at working hours ($p<0.05$). The complaint for which urgent reports were most commonly requested was abdominal pain, at 73.7%, while the lowest level of reports was requested for patients presenting due to headache (15.9%), and a significant relation was determined between complaints of patients and urgent report demand ($p<0.05$) (Table 2). Time to report delivery was not significantly affected by many variables such as the patient's age and gender, time of imaging, outcomes, and the patient's complaints ($p>0.05$).

Discussion

Our findings showed that we made greater teleradiology use in the ED in forensic cases, in patients with abdominal pain, in patients admitted to the clinics, and for images taken at after-hours. Deficiencies in diagnosis occur for such reasons as the large numbers of patients in EDs, the heavy workload, and physicians' lack of attention. As a natural result of this situation, malpractice litigations may be seen. The radiology department provides significant support to EPs in terms of accurate diagnosis, and fewer problems with the diagnosis are observed in EDs in which a radiology specialist is available on a 24-h basis (8). We, therefore, shared the responsibility in our ED by requesting radiologist

Table 1. Descriptive statistics

Variables	Urgently reported	Routinely reported	
	n (%)	n (%)	Total
Gender distribution			
Female	376 (40.6%)	550 (59.4%)	926
Male	455 (42.4%)	618 (57.6%)	1073
Total	831 (41.6%)	1168 (58.4%)	1999
Age distribution			
<18	172 (46.6%)	197 (53.4%)	369
18-44	336 (44.6%)	417 (55.4%)	753
45-65	168 (36.6%)	291 (63.4%)	459
>65	155 (37.1%)	263 (62.9%)	418
Region of body			
Head	419 (32.8%)	857 (67.2%)	1276
Cervical	102 (80.9%)	24 (19.1%)	126
Thorax	213 (56.6%)	163 (43.4%)	376
Abdomen	391 (74.5%)	134 (25.5%)	525
Pelvis	11 (50%)	11 (50%)	22
Extremity	16 (22.2%)	56 (77.8%)	72
Total number of films	1152 (48.1%)	1245 (51.9%)	2397
Turnaround time (minutes)			
<20	231	N/A	231
20-39	362	N/A	362
40-59	132	N/A	132
>60	106	1168	1274

Table 2. Comparison of factors that affect the reporting			
Variables	**Urgently reported**	**Routinely reported**	**p**
Age	38.78±25.03	42.87±25.12	<0.001
Gender			
Female	376 (40.6%)	550 (59.4%)	0.416
Male	455 (42.4%)	618 (57.6%)	-
Forensic case			
Yes	212 (85.8%)	35 (14.2%)	<0.001
No	619 (35.3%)	1133 (64.7%)	-
Outcome of patient			
Exitus	4 (100%)	N/A	<0.001
Hospitalized	157 (54.7%)	130 (45.3%)	-
Discharged	670 (39.2%)	1038 (60.8%)	-
Readmission of discharged patients			
Yes	9 (20.5%)	35 (79.5%)	0.01
No	661 (39.7%)	1003 (60.3%)	-
Period of filming			
08:01-16:00	222 (33.9%)	432 (67.1%)	<0.001
16:01-08:00	609 (45.3%)	736 (54.7%)	-
Complaints patient			
Trauma	330 (44%)	420 (56%)	<0.001
Headache	74 (15.9%)	391 (84.1%)	-
Chest pain	22 (38.6%)	35 (61.4%)	-
Abdominal pain	272 (73.7%)	97 (26.3%)	-
Dyspnea	59 (45.4%)	71 (54.6%)	-
Cognitive problems	74 (32.5%)	154 (67.5%)	-

reports to protect our own against malpractice litigations in cases the EP was unable to diagnose, and especially in forensic cases.

Studies have listed trauma, abdominal pain, and respiratory problems as the most common causes of presentations to the ED (9). Among these cases, patients with abdominal pain have a high possibility of misdiagnosis by EP. The cause of abdominal pain may sometimes not be identified, despite the use of assistant diagnostic tools such as CT (10). Nonetheless, the importance of CT in patients with abdominal pain should not be underestimated. Studies have reported that CT resulted in a modification of treatment in 42% of patients with abdominal pain, that it usually results in the administration of surgical treatment on time, and that it reduces repeated presentations to the ED (11,12). One study examining the increasing use of tomography revealed that the highest increase in requests in 1996-2007 was for abdominal CT, involving a 10-fold rise (13). However, another study also observed that EPs incorrectly evaluated radiological images and abdominal CT significantly more than radiologists (14,15). Moreover, the most significant discrepancy with images evaluated by radiologists was seen in tomographies of the neck and abdomen (16). So, the EP must receive support from a radiologist physician when evaluating abdominal CT (17). Another study showed that EPs evaluated cranial CTs to the same extent as radiologists (18). In our study, the patients with non-traumatic abdominal pain were the group for which CT reports were most frequently issued. Subjects with non-traumatic headache were the group with the lowest rate of CT reports. This shows that the condition in which EPs have the most significant difficulty evaluating and for which they most need to consult the teleradiology unit is abdominal pain, while they are better able to interpret cranial CT findings.

In recent years, an increasing number of advanced radiological tests have been used in the USA. However, this has not, in turn, increased emergency pathological diagnoses, and therefore hospitalization rates. Despite many endeavors to make less use of CT, EPs still insist on using the technique, either to avoid malpractice litigation or else because it is a readily available and rapid diagnostic guide (19,20). Also, the use of CT appears to significantly reduce waiting times in the ED among patients requiring to be admitted for treatment in clinics (21). In our study, 85.4% of patients undergoing radiological imaging were discharged. Moreover, non-report rates among discharged patients (60.8%) are also both high. The re-admission rate among these patients was 3.4%, and 42.9% of these re-admissions were hospitalized. So, EPs should avoid discharge of patients without teleradiology reports.

Presentations to the ED occurred after 17:00 h in 62.8% of adults and 72.5% of children in one study (22). Another study reporting that 59.5% of patients arrived at after-hours determined a rate of CT of 54.5% within that time frame (21). The primary aim behind the teleradiology use is

to support EPs in terms of diagnosis after-hours (7). The vast majority of our patients admitted to ED at after-hours, and the count of patients in which urgent report was requested after-hours was higher than those of at working hours. We have access to the teleradiology 24-h of day.

The principal contribution of the radiologist to the ED and patient care consists of imaging reports issued promptly and accurately. These reports prevent time loss of patients in the ED and unnecessary crowding (23). One study comparing teleradiology with radiological opinions by telephone showed that in the event of teleradiology being used, the time between imaging being performed and a report issued was less than 34 min (24). Agrawal et al. (25) reported a time of 34.03 min, and Shah et al. (16) of 28.46±9.20 min. In our study, we calculated a time of 35.76±33.63 min and the expected time (<40 min) was maintained in 71.4% of the cases.

CT use in ED increases with patient age. Patients aged over 65 constituted the group in which CT was most performed (26.7%), with the lowest rate of CT being observed in patients under nine (3%). This was attributed to chronic diseases increasing with age and to sensitivity over radiation exposure in children. In the same study, it was found that more CTs were scanned on female patients (20). In our study, CT was taken mostly in the 18-44 age group (37.7%), and for male patients. Trauma was the most common cause of presentation in our cases. We attributed this to traumas being particularly common in young men with active lifestyles.

Study Limitations

The main limitation in this study is that the patients whose radiological images were evaluated by EPs and discharged from the hospital were not analyzed for any discrepancy between the radiology interpretation performed by the EP and the radiologist. Because this paper is not a consistency study, and instead of that, we searched the records of these patients for any re-admission and hospitalization.

Conclusion

Our study findings identified forensic cases, patients presenting with non-traumatic abdominal pain, patients requiring admission to clinics, and presentations at after-hours as the factors affecting the teleradiology use in the ED. EPs should demand teleradiology reports for all images to avoid re-admissions. We think that teleradiology services are beneficial for EPs and should become more prevalent in competing with crowds in EDs worldwide.

Ethics Committee Approval: Before the study, the approval of the Clinical Research Ethics Committee of Adıyaman University was obtained (decision no: 2019/2-12).

Informed Consent: Since it was a retrospective study, no patient consent form was obtained.

Peer-review: Externally peer-reviewed.

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Contribution of the Diffusion Weighted Magnetic Resonance Imaging on Classification of Hepatic Hydatid Cyst Types

Karaciğer Kist Hidatiklerinin Tiplendirilmesinde Diffüzyon Manyetik Rezonans Görüntüleme Bulgularının Katkısı

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ABSTRACT

Introduction: The purpose of this study is to provide a classification of different types of hepatic hydatid cysts by measuring the mean apparent diffusion coefficient (ADC) and exponential apparent diffusion coefficient (EADC) using diffusion-weighted magnetic resonance imaging (MRI).

Methods: A total of 60 patients (42 female, 18 male) and 79 lesions were included in this retrospective study. The patients were diagnosed with hepatic cyst lesions for various reasons according to the hospital's abdominal MRI records, and therefore all patients had their diagnosis pathologically or serologically confirmed. ADC and EADC maps were obtained with values of b0, and b400 s/mm^2, and mean ADC and EADC values were calculated for each lesion. Then, the mean value calculated for each cyst type is compared.

Results: Regarding ADC values, we determined a statistically significant difference between types 1 and 4, types 2 and 4, and types 3 and 4 (p=0.001). When we compared EADC values, we found that EADC values of WHO type 4 lesions were higher than WHO type 1,2, and 5 lesions (p=0.001). Also, we divided our patients' lesions into two groups, namely active (types 1,2,3) and inactive (types 4,5) lesions. When we compared each group's mean ADC and EADC values, we determined a difference between active and inactive groups. When compared to inactive groups, ADC values of active lesions were higher, and EADC values were lower, as shown by statistics.

Conclusion: Our study shows that ADC and EADC values may be useful for the differentiation of type 4 lesions from other types, and distinguishing of active and inactive groups.

Keywords: Hydatid cyst, diffusion-weighted magnetic resonance imaging, apparent diffusion coefficient

ÖZ

Amaç: Bu çalışmada amacımız karaciğerde yerleşmiş olan farklı evrelerdeki kist hidatik lezyonlarının difüzyon ağırlıklı görüntüleme (DAG) ile ortalama ADC ve EADC değerlerini hesaplayarak, lezyonların evrelerine göre birbirinden ayrımında DAG'nin katkısı olup olmayacağını araştırmaktır.

Yöntemler: Çalışmamızda Ocak 2014-Mayıs 2015 tarihleri arasında hastanemizde kist hidatik tanısı almış, patolojik ya da serolojik olarak tanısı doğrulanmış ve herhangi bir sebeple üst batın MR tetkiki yapılmış 18-81 yaşları arasında, 60 hastaya (42 kadın, 18 erkek) ait 79 adet lezyon incelendi. b0 ve b400 değerinde elde edilen DAG'den her lezyonun ADC ve EADC haritası çıkarıldı. Daha sonra hidatik kist tiplerinin hesaplanan ortalama ADC ve EADC değerleri kantitatif olarak karşılaştırılmışır.

Bulgular: Çalışmamızda b400 değerinde, tip 1 ile 4 arasında, tip 2 ile tip 4 arasında, tip 3 ile tip 4 arasında ADC değerleri arasında istatistiksel yönden anlamlı fark olduğu tespit edildi (p=0,001). WHO kategorilerinin EADC değerleri karşılaştırıldığında kategorisi 4 olan hastaların EADC değerleri; WHO kategorisi 1,2,5 olan hastaların ADC değerlerinden anlamlı olarak yüksekti (p=0,001). Ayrıca lezyonları aktif (tip 1,2,3) ve inaktif (tip 4,5) olarak; iki gruba ayırdığımızda grup ortalamaları arasında istatistiksel açıdan anlamlı fark tespit edildi. Aktif lezyonların ADC ortalamaları, inaktif lezyonların ADC ortalamalarından yüksek, EADC ortalamaları, inaktif lezyonların EADC ortalamalarından düşüktü.

Sonuç: Bizim çalışmamız karaciğer hidatik kist hastalığında tip 4 lezyonların diğer sınıflardan ayırımında ve aktif ve inaktif grupların birbirinden ayırımında ADC ve EADC değerlerinin faydalı olabileceğini göstermektedir.

Anahtar Kelimeler: Hidatik kist, difüzyon ağırlıklı manyetik rezonans görüntüleme, görünür difüzyon katsayısı

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Introduction

Hydatid cyst disease is among the most important parasitic zoonosis threatening human and animal health around the world. They are lesions of benign nature and most frequently seen in the liver, although they can be located in almost any part of the body. Diagnostic methods for cystic echinococcosis are imaging, indirect immunological methods, and direct microscopic examination. While imaging methods are prioritized for clinical diagnosis, it is also essential to support it with parasitological and immunological diagnosis in order to make a differential diagnosis of the cyst from other cases such as a tumor, abscess, etc. (1).

Imaging findings of the hydatid cyst disease depend on the development stage of the cyst (2). As imaging findings change depending on the stage of the disease, there is an advantage of using different imaging methods at different stages. Depending on the stage when the disease is diagnosed, the treatment may require medical, surgical, and interventional radiological methods, or it may be enough to monitor the disease.

Ultrasonography (US) is a frequently preferred imaging method in the diagnosis of hydatid cyst disease thanks to its ease of use, non-invasiveness, and easy accessibility. Many classification schemes have been proposed based on the appearance of cysts on US. (2,3) The most frequently used are the classifications of Gharbi and WHO-IWGE (Table 1).

Computed tomography (CT) is highly diagnostic in the spread of the disease, preoperative evaluation of the disease, and detection of the complications if the patient is suspected of clinical, biochemical, and radiological hydatid cyst. Daughter cysts, degenerated membranes, and capsular and peripheral calcifications can be seen on CT. CT is sensitive enough to detect lesion localization and organ spread before the surgery. Additionally, it is superior to the US in visualizing complications (4,5). Unless there are suspected complications such as an opening in the biliary tract and infection, it is not necessary to use intravenous contrast agents (3).

Most of the magnetic resonance imaging (MRI) findings are similar to those identified on CT. This method allows for the precise visualization of the multiloculated or multicystic pattern with a "ring appearance", which can be seen in almost all cases. The ring appearance, considered belonging to the pericyst, causes hypointensity of this collagen-rich layer in T2-weighted sequences. This layer has a ring shape and is generally 2-5 mm in thickness. In some cases, signal loss further increases, and intensity is markedly reduced if there is calcification on the wall. In other epithelial cysts that can be seen in the liver, the wall is not that thick.

Table 1. World Health Organization-informal working group in echinococcosis and Gharbi classification of hydatid cysts

Gharbi	WHO	Us characteristics
Type1	CE1	Unilocular cyst + wall + internal echogenities
Type2	CE3	Detached membrane
Type3	CE2	Multivesicular, multiseptated cyst, daughter cysts
Type4	CE4	Heterogeneous cyst, no daughter vesicles
Type5	CE5	Cyst with a wall calcification

On the other hand, as the hydatid cyst varies according to stages, hepatoma, amoebic abscess, intraparenchymal hematoma, and hepatic adenoma are also considered in the differential diagnosis (6). Another finding that can be identified with MRI is peritumoral edema, which is seen in tumoral lesions but has never been seen in the hydatid cyst disease (7).

Diffusion-weighted imaging (DWI) is a method that can be obtained in a single breath-hold time. It does not require the use of a contrast agent and contributes to diagnosis in cases where benign-malignant differentiation of liver masses cannot be made with conventional sequences (8).

Apparent diffusion coefficient (ADC) maps are obtained in order to measure the diffusion size. Today, exponential ADC (EADC) measurements can also be made with the same systems as a new quantitative indicator. EADC maps allow clinicians to identify the lesion easily, and these maps can also provide quantitative data (9). The exponential map or image is calculated by dividing the diffusion-weighted image with maximum b-value by the b0 image. Mathematically, EADC shows the negative exponential value of ADC, and T2 is a diffusion-weighted artificial image with a similar contrast behavior to that of the high b-valued image not having an internal glare effect (10).

Methods

This study investigated 79 lesions of 60 patients (42 females, 18 males) between the ages of 18-81 who were diagnosed with hydatid cyst disease in our hospital, whose diagnosis was confirmed pathologically or serologically and who underwent upper abdomen MRI due to any reason, between January 2014-May 2015. Lesion classification was made retrospectively under the guidance of USI and T2-weighted images (WI). As they included atypical appearances and calcification, lesions with CT images for WHO type 4 and type 5 lesions were also included in the study. Ethics committee approval was received for this study from the Ethics Committee of İstanbul Training and Research Hospital (decision no: 2015/739).

The conventional MRI and DWI examinations of all cases were made using a 1.5-Tesla superconductive MRI device (Signa HDxt, GE Medical Systems, Milwaukee, Wisconsin, USA) and 8-channel body array coil. The maximum gradient strength of the MR device was 32 mTesla/m, and the gradient slew rate was 120 mT/m/s. DWI with b400 value was applied to patients in addition to their T1- and T2-weighted conventional MRI sequences. All of the T1- and T2-WI were applied in the axial and coronal plane.

DWI parameters were as follows; TR/TE: 4800/68 ms; turning angle: 90°; section thickness: 5.5 mm; FOV: 430 mm; NEX: 128x128/4.00. They were obtained by applying diffusion-sensitive gradients on each of the three directions (x, y, z) to the "Single-shot echo-planar" sequence on the 8 Coil body upper/flip axial plane. The first series in the image cluster of the sequence consisted of "Echo-planar-spin echo" T2-WI (b:0); the next three series consisted of images, which were the first series to which diffusion-sensitive gradients were applied separately on x, y, and z directions, and isotropic images obtained by calculating the projection of diffusion vectors on three directions. Isotropic images consisted

of images removing the signal changes depending on the direction, generated by the device by taking the cube root of the multiplication of signal intensities measured on x, y, z directions.

ADC and EADC maps were generated using a software (Functool) on a separate workstation (Advantage Workstation 4.4-GE Medical Systems).

ADC and EADC maps for each lesion were generated from DWI obtained using b0 and b400 values. For numerical evaluation, the measurements were made with a round "Region of Interest" at the largest size possible, away from the artifacts, calcific areas, vascular structures, and healthy tissues, under the guidance of T2-WI (Figure 1). By taking the average of ADC and EADC measurements of at least two consecutive sections for each lesion and three for large lesions, mean values were calculated for that lesion. Then, the mean ADC and EADC values of hydatid cyst types were quantitatively compared.

Statistical Analysis

When evaluating the results of the study, SPSS 21.0 statistical package was used for statistical analyses. When evaluating the study data, descriptive statistical methods (number, percentage, mean, standard deviation, median, minimum, maximum) were used. Pearson's chi-square test was used to compare qualitative data.

Regarding quantitative data, the Mann-Whitney U test was used to compare the parameters between two groups. Regarding multigroup comparison for quantitative data, the Kruskal-Wallis test was used to compare the parameters between the groups, and the Mann-Whitney U test was used to detect the group causing the difference. As there was a significant difference in the Mann-Whitney U test following the Kruskal-Wallis variance analysis, the significance threshold was determined as 0.005 after Bonferroni correction. Other results were evaluated in a 95% confidence interval with a significance level of $p<0.05$.

Results

A total of 60 patients (42 female, 18 male) and 79 lesions were included in the research. The subjects were diagnosed with hepatic cystic lesions for various reasons according to the hospitals archived records of abdominal MRI between January 2014 and May 2015, therefore they had their diagnosis pathologically or serologically confirmed. Lesions were classified according to WHO-IWGE using the US, CT, and MRI images in the system. Eight of the cases (10.1%) were 1.18 (22.8%) were 2.22 (27.8%) were 3.19 (24.1%) were 4.12 (15.2%) were 5.

Forty-three of the patients (72%) were female, and 17 (28%) were male. The mean age of the patients was 46.2±17.2 years (range: 18-81). The presence of a statistically significant age-related difference between the WHO categories was investigated using the Kruskal-Wallis variance analysis, and no difference was found (p=0.298). To evaluate the difference between the genders concerning WHO Categories, Pearson's chi-square analysis was used, and no significant difference was found (p=0.431).

The size variable consisted of the two longest different values. These two values were multiplied to calculate the mass volume. When the mass volumes of WHO categories were compared, there was no statistically significant difference (p=0.079). Using the maximum value measured for the size variable, the maximum mass measurement was calculated. When the maximum mass measurements of the WHO categories were compared, no statistically significant difference was found (p=0.103).

In our study, ADC values using the b400 value were calculated to be: 3.20 x 10^{-3} s/mm^2 for type 1 lesions, 3.06×10^{-3} s/mm^2 for type 2 lesions, 3.49×10^{-3} s/mm^2 for type 3 lesions, 2.33×10^{-3} s/mm^2 for type 4 lesions, and 2.58×10^{-3} s/mm^2 for type 5 lesions. We detected no statistically significant difference in terms of ADC values between type 1 and 4; type 2 and type 4; and type 3 and type 4 (p=0.001) (Figure 2).

EADC values using the b400 value were calculated to be: 1.91x10^{-2} s/mm^2 for type 1 lesions, 2.69×10^{-2} s/mm^2 for type 2 lesions, 2.74×10^{-2} s/mm^2 for type 3 lesions, 3.92×10^{-2} s/mm^2 for type 4 lesions, and 2.92×10^{-2} s/mm^2 for type 5 lesions. There was a statistically significant difference found when EADC values of WHO categories were compared (p=0.001). Therefore, the EADC values of patients with WHO category of 4 were higher than that of the patients with WHO categories of 1, 2, 5 (Figure 3).

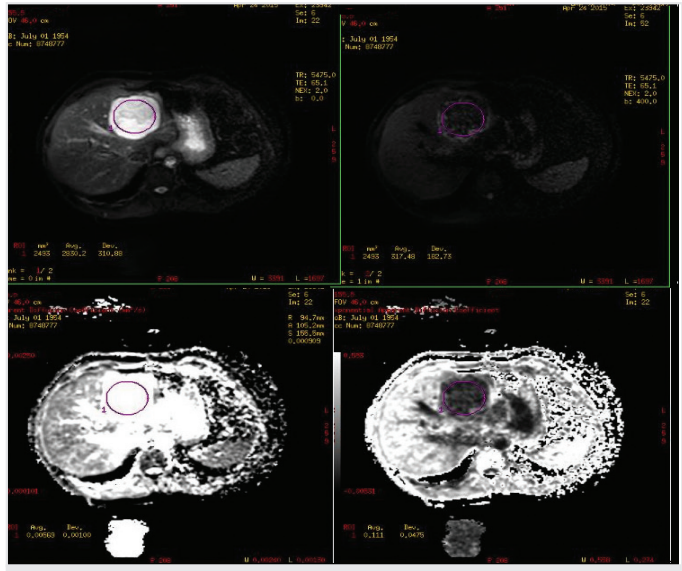

Figure 1. Image of the CE3 hydatid cyst lesion using b0 and b400 values measurements made from the ADC and EADC maps

ADC: apparent diffusion coefficient, EADC: exponential apparent diffusion coefficient

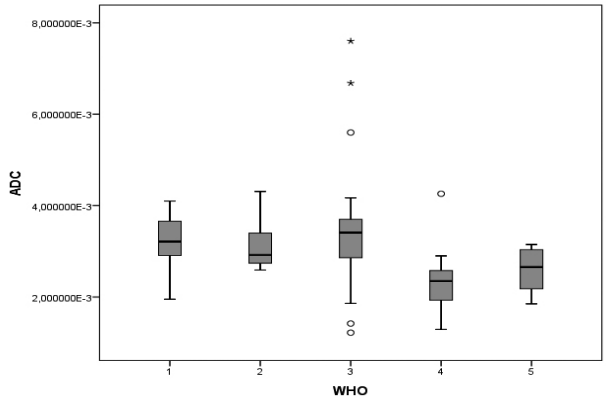

Figure 2. Apparent diffusion coefficient distribution by groups

ADC: apparent diffusion coefficient

In order to determine whether ADC means showed a statistically significant difference according to the lesion type, we divided the lesions into two groups as active (type 1,2,3) and inactive (type 4,5) lesions. There was a statistically significant difference between the group means (Mann-Whitney U=291.500; p=0.000, p<0.05). ADC means of the active lesions (0.003) were higher than that of the inactive lesions (0.002).

When the presence of a significant difference between the EADC means of the patients concerning the lesion type variable was investigated, the difference between the group means was found to be statistically significant (Mann Whitney U test: 407.000; p=0.001<0.05). EADC means of the active lesions (0.259) were lower than that of the inactive lesions (0.354) (Table 2).

Furthermore, during the evaluation regarding whether there was a significant difference between the mass volume mean values of the patients according to the lesion type variable, there was a statistically significant difference between the group means (Mann-Whitney U=543.500; p=0.044<0.05). The mass volume means of the active lesions (3834.080) were higher than that of the inactive lesions (2238.970).

When the presence of a significant difference between the maximum mass measurement means of the patients concerning the lesion type variable was investigated, the difference between the group means was found to be statistically significant (Mann-Whitney U=506.500; p=0.028 <0.05). The maximum mass volume means of the active lesions (63.188) were higher than that of the inactive lesions (46.800).

Discussion

MRI is one of the most important radiological diagnostic methods used in the detection and characterization of liver lesions (10). In recent years, the DWI examination, a technique not requiring the use of a contrast agent, has entered into use in the imaging of abdominal organs and has contributed considerably to lesion characterization (10-12).

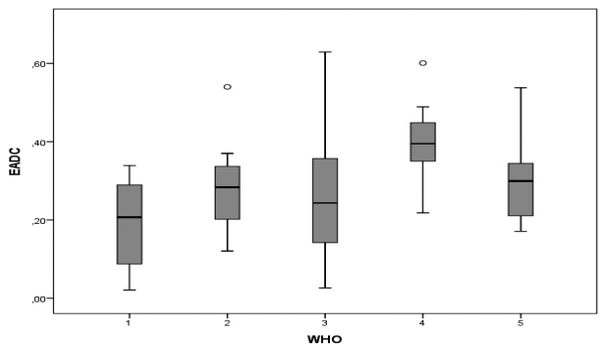

Figure 3. Exponential apparent diffusion coefficient distribution by groups

EADC: exponential apparent diffusion coefficient

DWI sequence is a method that can be obtained in a single breath-hold time, does not require the use of a contrast agent, and contributes to diagnosis in cases where benign-malignant differentiation of liver masses cannot be made in conventional sequences (8). Quantitative measurement of diffusion is possible today with ADC measurements.

High intensity of cell membranes in tissues with high cellularity like tumor tissues limits the diffusion of water protons. On the contrary, water molecules move more easily in cystic or necrotic tissues, and ADC of the water protons are identified as free. Therefore, diffusion MRI provides information about tissue cellularity and the integrity of cellular membranes. ADC value is the first one to be affected during the intracellular liquid increase resulting from the disruption in membrane permeability. The presence of the diffusion is observed as signal loss and in turn, a high value of ADC. On the other hand, limited diffusion in the tumor cell emerges in DWI with high signal intensity and in turn, low ADC values (8). Several studies in the literature demonstrate that ADC measurements are beneficial in the benign-malign differentiation of the lesions of the liver (8,10-12).

Today, EADC measurements can also be done by using ADC maps as a new quantitative indicator, which is the mathematically negative exponential value of ADC, with which the T2 glare effect is removed, and lesion visualization is increased (9,10). There are studies showing that EADC maps are beneficial in lesion identification similar to ADC and in some cases, even superior to ADC (13,14).

While hepatic hydatid cyst is a benign condition unless any complication develops, it is sometimes difficult to differentiate between stage 4 lesions and other liver masses because of them not having a pathognomonic radiologic appearance.

Although there is no study conducted using the b400 value, Oruç et al. (15) study measured ADC values using b0, b50 and b1000 values and investigated the role of DWI in the classification of hydatid cysts and differentiation between simple cysts and abscesses but found no significant difference related to b values. The study, which used the Gharbi classification, reported a statistically significant difference in ADC values of type 4 hydatid cysts compared to type 1 and type 3 hydatid cysts, similar to our study. This study did not include type 2 hydatid cysts due to the small number of lesions and type 5 lesions due to their calcifications, but they also concluded that DWI did not have a significant contribution to the differentiation of type 1 lesions from simple liver

Table 2. ADC and eADC values for determining active and inactive lesions

	Live lesion		Dead lesion		MW	p
	Mean	SD	Mean	SD		
ADC	0.003	0.001	0.002	0.001	291.500	0.000
EADC	0.259	0.144	0.354	0.108	407.000	0.001
Mass volume	3834.080	3604.286	2238.970	2168.429	543.500	0.044
Maximum mass measurement	63.188	33.761	46.800	21.188	506.500	0.028

ADC: apparent diffusion coefficient, EADC: exponential apparent diffusion coefficient

cysts. As MRI has some shortcomings in calcification imaging, the present study included type 5 lesions provided that there was a CT test conducted, and we found no statistically significant difference in the differentiation from other types except type 4 lesions.

Another study by Ceçe et al. (16) investigated the role of DWI in the classification of the hydatid cysts of the liver. The examination used the mean ADC maps generated from the measurements using b0, b500, and b1000 values in 44 lesions of 44 patients, which included 15 type 1, 11 type 2, 7 type 3, 5 type 4, and 6 type 5 according to the Gharbi classification. While this study did not evaluate the difference between b values, the mean ADC values were determined as follows: $2.48x10^{-3}$ mm^2 for type 1; $2.8010^{-3}\pm0.34$ s/mm^2 for type 2; $2.7010^{-3}\pm0.26$ s/mm^2 for type 3; $2.02\times10^{-3}\pm0.01$ s/mm^2 for type 4; and $2.18\times10^{-3}\pm0.1$ s/mm^2 for type 5. In the study, type 4 hydatid cysts could be differentiated from all other groups in the confidence interval of 95%, and the study claimed that they could be detected with 100% sensitivity and 100% specificity when the threshold value was taken as $\leq2.06\times10^{-3}$ for type 4 lesions. They also argued that type 1 lesions could be differentiated from type 2, type 4 and type 5; type 2 lesions from type 1, 4 and 5; type 3 lesions only from type 4; and type 4 lesions from 1, 2, 3, 5; and type 5 lesions from type 1, 2, and 4 (16).

Also, when two groupings were made as type 1, 2, 3 lesions and type 4, 5 lesions, diffusion MRI was found to be "excellent" in the differentiation of these two groups (16).

Koken et al. (17) study investigated 92 lesions of 54 patients by creating ADC maps using b50, b500, and b1000 values. When the ADC values were compared according to lesion groups, there was no significant difference between type 1 and 2, 3; type 2 and 3; type 3 and 4; or type 4 and 5.

Similar to our study, Koken et al. (17) suggested that a comparison of hydatid cyst types according to ADC values could be beneficial in the differentiation of type 1, 2, and 3 from type 4 and 5.

Another study by Sonmez et al. (18) retrospectively investigated 28 hydatid cysts and 22 simple cysts larger than at least 1 cm. Sixteen of lesions were type 1, and 12 were type 3., and there was no statistical difference between ADC values of lesions. Similar to Sonmez et al. (18), our study did not find any significant difference between type 1 and type 3 lesions classified according to Gharbi.

Hydatid cysts are lesions of benign nature, most frequently seen in the liver (1). Type 1, 2, and 3 cysts, according to both classifications, show a treatment indication. In recent years, percutaneous treatment of these lesions using the US (PAIR) has been preferred considering the surgery and the risks thereof. Also, some of the studies in the literature indicate that percutaneous treatment can be applied to type 4 lesions depending on the liquid component amount it contains (18-22).

The limitations of our study included having a retrospective design, less CE type 1 and CE type 5 lesions compared to other groups, and using only b0 and b400 values for ADC measurements. Although other studies in the literature detected no significant difference based on b values (15), we think that this may be open to further research and new developments as the number of related studies is limited. Furthermore, the susceptibility weighted sequence in MRI is also included in the evaluation of calcifications today, but the retrospective nature of our study did not allow us to include it in the present research.

Conclusion

Our study shows that ADC and EADC values can be beneficial in the differentiation of type 4 lesions from other classes, and active and inactive groups in hydatid cysts of the liver.

ADC and EADC values are also important in the differentiation of active and inactive lesions. ADC values of inactive lesions (CE type 4 and 5) were significantly lower than the CE type 1, 2, and 3 lesions, which are considered to be active.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of İstanbul Training and Research Hospital (decision no: 2015/739).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - Ö.A.; Concept - Ö.A., C.T.B., A.H.Y., Ö.K.; Design - Ö.A., C.T.B., A.H.Y., Ö.K.; Data Collection and/or Processing - Ö.A.; Analysis and/or Interpretation - Ö.A.; Literature Search - Ö.A.; Writing Manuscript - Ö.A.

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The Role of Advanced Technology Product Animations on Informing Patients with Gonarthrosis Preoperatively

Gonartrozlu Hastaların Preoperatif Bilgilendirilmesinde İleri Teknoloji Ürünü Animasyonların Rolü

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ABSTRACT

Introduction: This study aimed to investigate the effect of visual animations on the patient's knowledge and satisfaction level in the informing during informed consent of the patients scheduled for total knee replacement surgery.

Methods: A total of 139 patients who were diagnosed with gonarthrosis and scheduled for total knee replacement surgery in our clinic were included in the study. Verbal and written information about diagnoses, disease findings, scheduled surgery, operation stages, other treatment options other than the scheduled surgery, and specific complications of scheduled surgery were given to the patients. The information levels were measured with open-ended questions. After 35 days, on average, a visual animation that included the findings of their diseases and the stages of the surgery planned was shown. The impact of visual animations on the knowledge level and patient satisfaction were examined. The relation between this impact and the education level of the patient was also investigated.

Results: Visual animations statistically and significantly increased the knowledge level of patients and the level of their satisfaction in informed consent ($p=0.001$; $p<0.01$, respectively). It was determined that this increase was independent of the education level of the patients ($p>0.05$).

Conclusion: Visual animations are a simple, easy, and effective method for informing during informed consent.

Keywords: Informed consent, patient satisfaction, visual animations, gonarthrosis, total knee arthroplasty

ÖZ

Amaç: Bu çalışmanın amacı; total diz protezi ameliyatı planlanan hastalarda; aydınlatılmış onam esnasındaki bilgilendirmenin görsel animasyonlar ile desteklenmesinin hastadaki bilgi ve memnuniyet düzeyine etkisinin araştırılmasıdır.

Yöntemler: Kliniğimizde gonartroz tanısı alan ve total diz protezi ameliyatı planlanan 139 hasta çalışmaya dahil edildi. Hastalar; tanıları, hastalığın bulguları, planlanan ameliyat ve ameliyatın aşamaları, planlanan ameliyat dışındaki başka tedavi seçenekleri, planlanan ameliyata özgü komplikasyonlar hakkında sözlü ve yazılı olarak bilgilendirildi. Açık uçlu sorular ile bilgi düzeyleri ölçüldü. Ortalama 35 gün sonra hastalıklarının bulguları ve planlanan ameliyat aşamalarını içeren görsel animasyon uygulaması gösterildi. Görsel animasyonların bilgi düzeyine ve hasta memnuniyetine etkisi ile bu etkinin hastanın eğitim düzeyi ile ilişkisi araştırıldı.

Bulgular: Görsel animasyonlar; hastaların bilgi ve bilgilendirilmiş onam şeklinden duyulan memnuniyet düzeyini istatistiksel olarak anlamlı derecede artırmıştır ($p=0,001$; $p<0,01$). Bu artışın hastaların eğitim düzeyinden bağımsız olduğu belirlenmiştir ($p>0,05$).

Sonuç: Görsel animasyonlar aydınlatılmış onam esnasında yapılan bilgilendirmede basit, kolay, etkili bir yöntemdir.

Anahtar Kelimeler: Aydınlatılmış onam, hasta memnuniyeti, görsel animasyonlar, gonartroz, total diz artroplastisi

Introduction

Total knee arthroplasty is a surgical procedure that relieves pain in knee osteoarthritis, improves the functions of the knee joint, and increases the patient's quality of life (1). In the coming years, total knee replacement demand is expected to increase exponentially (1-3). It is a surgical procedure open to complications despite increasing demand, advances in implant design, excellent results, developments in the technique, and rehabilitation (1,3,4). Patients who undergo total knee replacement are usually elderly. This situation brings risks during and after surgery (5,6). Therefore, the patient should be sufficiently informed about the possible risks and complications of this operation. This informing is provided with the informed consent process. Informed consent is based on the decision-making principle of the person and forms the basis of the doctor-patient relationship (7). Every patient has the right

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to know and determine what shall be done to his/her body. The fact that legal regulations guarantee this right gives the health workers the responsibility of informed consent (8). Also, the lack of informed consent of the individuals before the medical procedure or the failure to obtain it appropriately causes essential ethical and legal problems in clinical practice (9). The conventional informed consent is generally in the form of insufficient written texts (10,11). Studies show that patients do not understand the main elements of the consent in their informed consent performed with written or verbal information (10,12-15). In particular, it is seen that elderly patients with gonarthrosis cannot read written informing texts, or they are too lazy to read them. In order for the information during the informing process to be permanent in the mind of the patient, the patient should be aware of stimuli and allow them to be stored in memory. The use of visual images and symbols during informing allows the individual to give more attention to the informing; also, images are more memorable than words (10,14,16). In the present study, it was aimed to evaluate the available knowledge levels of the patients who had gonarthrosis and were informed with standard verbal and written texts, and the changes in their levels of knowledge after visual animation.

Methods

Necessary permissions [İstanbul Training and Research Hospital, Clinical Research Ethics Committee; with (decision no: 757, date: 15.01.2016)] were obtained for the implementation of the research. A total of 139 patients, who were admitted in our clinic between January 2016 and September 2018 with gonarthrosis diagnosis, who were not relieved from their complaints despite conservative treatments, and who had undergone total knee arthroplasty, were included in the present study after their consents were received as volunteers in the study. Gender, age, educational status, diagnosis, and scheduled operation information of the patients were recorded. In the outpatient clinic conditions, the participating patients were informed verbally and in writing about diagnoses and the findings of their diseases, the planned surgery and the stages of it, other treatment options other than the planned surgery, and the complications of the planned surgery. Each informational stage was limited to six items in order to evaluate the results of the informing objectively (17-19). After verbal and written informing, available knowledge levels of the patients were determined by asking open-ended questions (20-23). The correct answers given to each open-ended question were scored with numbers 0-6 following the number of information given before. Zero point was given to the patient who did not know any of the items in the informational stage, and 6 points were given to the patient who knew all items (6 items) in the informational stage. After the surgery appointments were given to the patients, they were admitted to the orthopedics service to be operated after an average of 35 days (20-58). The animation showing the findings of their disease and the planned surgery stages (Knee Pro III version: 3.8.1, 3D4 Medical's NOVA3 technology application) was shown on the tablet computer (iPad Wi-Fi 128 GB Black; Apple, California) (Figure 1). Although there were no visual animations, explanations were made on other treatment options and complications specific to their surgery over the figures in the visual animations. The patients' knowledge levels after the animation representation were determined by asking the same open-ended questions again. The knowledge levels after the animation representation were also scored with numbers from 0 to 6 in the same way (the correct answers to each open-ended question are following the number of information given before). Zero point was given to a patient who did not know any of the items in the informational stage, and 6 points were given to a patient who knew all items (6 items) in the informational stage. Also, the satisfaction with the written-oral informed consent and the satisfaction with the visual animation and informed consent were scored with a number between 0-6. The data that were obtained in this way were compared statistically.

Statistical Analysis

Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) program was used for statistical analysis. In the assessment of the study data, the Mann-Whitney U test was used in the paired comparisons of the variables that did not show the normal distribution in the comparison of quantitative data in addition to the descriptive statistical methods. Kruskal-Wallis test was used in the comparison of three and more groups that did not show normal distribution. Wilcoxon signed ranks test was used for intra-group comparisons of the variables that did not show normal distribution. Statistical significance was evaluated at $p<0.01$ and $p<0.05$ levels.

Results

The distribution of the demographic characteristics of the patients participating in our study is shown in Table 1. When compared to the knowledge and satisfaction levels of the patients before the animation; after the animation, it was seen that there was a statistically significant increase in the levels of knowledge about the findings of disease, stages of surgery, alternative treatment options, information about surgery-specific complications, and the levels of satisfaction in the format of obtaining the consent (Table 2) ($p=0.001$; $p<0.01$, respectively). It was detected that there was no statistically significant difference in the relationship of the changes of the parameters according to before and after animation with the education status of the patients (Table 3) ($p>0.05$). Animations increase the knowledge and satisfaction levels of the patients independently from the level of education.

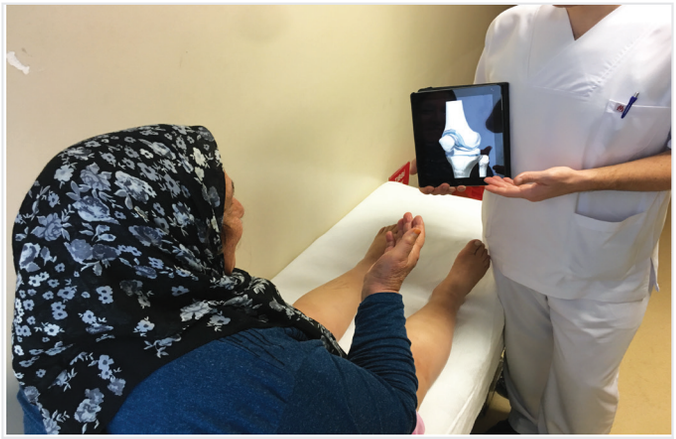

Figure 1. Image of patient watching visual animation

Discussion

Informed consent based on the principle of respect for autonomy before medical intervention is a legal obligation that should be implemented in many countries, including our country. A significant number of lawsuits against health professionals are caused by the lack of or insufficient informed consent (9,24,25). The patients' levels of understanding and remembering the information given in informed consent may be different. The informed consent procedure, which is very useful in the surgical decision making by patients together with the physician, cannot be sufficiently remembered by the patients after some time from surgery, and this may lead to some legal problems in the lawsuits of weak enforcement (9).

In a study examining the lawsuits related to knee arthroplasty, it was seen that the most common complications were the subject of the lawsuits. The authors have an opinion that most of the allegations that led to the lawsuits in question were not caused by frequent complications. It was seen that the patients sued the surgeons when the results of the surgery were different from their expectations. The authors presented an opinion that an unsatisfactory result according to patient expectations, is a frequent cause of the lawsuit (26). In a study examining the ethical aspects of informed consent in patients undergoing total knee arthroplasty, it was detected that all patients signed the informed consent. However, in this study, 20% of the patients stated that they could not get information about their diseases, 38% were not informed about the surgical procedure, 72% did not know about the possible complications, and 85% were not informed about the alternative

Table 1. Distribution of demographic characteristics

		Min-max	Mean ± SD
Age (year)		**54-78**	**66.63±4.36**
		n	**%**
Gender	Female	113	81.3
	Male	26	18.7
Education status	Literate	28	20.1
	Primary school	63	45.3
	Secondary school	20	14.4
	High school	23	16.5
	University	5	3.6

Min: minimum, Max: maximum, SD: standard deviation

Table 2. Changes in information and satisfaction levels before and after animation representation

		Verbal-written consent	Consent with animation	Change percentage	[a]p**
Knowledge about the findings of disease	Mean ± SD	2.72±0.66	5.02±0.65	92.93±41.73	0.001
	Min-max (median)	2-5 (3)	4-6 (5)		
Knowledge about the stages of scheduled surgery	Mean ± SD	2.46±0.62	5.21±0.73	123.47±59.77	0.001
	Min-max (median)	1-5 (2)	2-6 (5)		
Knowledge about other treatment options	Mean ± SD	2.68±0.51	3.53±0.66	36.09±37.04	0.001
	Min-max (median)	2-4 (3)	2-5 (3)		
Knowledge about complications	Mean ± SD	2.58±0.56	3.45±0.62	38.31±32.78	0.001
	Min-max (median)	2-4 (3)	2-5 (3)		
Satisfaction level	Mean ± SD	4.93±0.78	5.92±0.30	23.21±21.24	0.001
	Min-max (median)	3-6 (5)	4-6 (6)		

[a]Wilcoxon signed ranks test, **p<0.01, Min: minimum, Max: maximum, SD: standard deviation

Table 3. Change in the informing and satisfaction levels of patients according to education status

		Change percentages between before and after the animation				[c]p
		Literate (n=28)	Primary school (n=63)	Secondary school (n=20)	High school, university (n=28)	
Knowledge about the diagnosis of disease	Mean ± SD	100.3±40.73	90.87±41.66	92.5±37.65	90.48±46.74	**0.699**
	Min-max (median)	25-150 (100)	25-200 (100)	33-150(66.6)	0-150 (100)	
Knowledge about the scheduled surgery	Mean ± SD	125.6±75.56	126.98±53.25	105.42±41.73	126.31±67.3	**0.550**
	Min-max (median)	0-400 (100)	33.33-300 (150)	25-200 (100)	20-300 (100)	
Knowledge about other treatment options	Mean ± SD	30.36±33.96	32.8±35.41	41.25±40.24	45.54±40.86	**0.333**
	Min-max (median)	0-100 (33.33)	0-150 (33.33)	25-150(33.3)	0-150 (33.33)	
Knowledge about complications	Mean ± SD	36.9±28.09	35.71±31.37	41.67±38.04	43.15±37.06	**0.862**
	Min-max (median)	0-100 (50)	0-100 (33.33)	0-100 (41.67)	0-150 (33.33)	
Satisfaction level	Mean ± SD	24.64±16.44	19.13±19.75	23.75±17.54	30.6±28.73	**0.139**
	Min-max (median)	0-50 (20)	0-100 (20)	0-50 (20)	0-100 (20)	

[c]Kruskal Wallis test, Min: minimum, Max: maximum, SD: standard deviation

treatment methods. Also, about half of the patients signed the consent form without reading. It was stated that the readability and intelligibility of the consent form are low, and a short and understandable language should be used in consent form considering the educational status of the patients. It was also stated that multimedia resources should be used in the informed consent process (5).

In our study, the readability and intelligibility levels of the written consent forms were also found to be low in parallel with the study in question. When preparing the consent forms, the education level of the patients should be considered. However, since the educational level of the patients is different, it is not possible to prepare different consent forms for each education level. This non-practical situation will bring some ethical problems in addition to many difficulties. Visual materials, especially animations, can be easily understood by patients with every educational level, including even non-literate patients, and provides a possibility to watch many times. In another study that investigated the understanding of informed consent form in surgical interventions by patients, approximately one-third of patients stated that they did not know its importance despite having signed the informed consent form (20,27). In another similar study that investigated the comprehension of the informed consent process by the patients who were scheduled for surgery, most of the patients stated that they knew the informed consent process partially, and the majority of them did not know what the informed consent form they signed was. In this study, the author concluded that the patient's knowledge about the consent process was not sufficient (28). In our study, although we had a similar opinion before the visual material representation, it was found that the patients' satisfaction in the format of obtaining the consent was high after visual materials, and they had enough knowledge about the informed consent process with open-ended questions. Informing patients before the operation reduces the fear and anxiety of patients. In a randomized-controlled study that was conducted with informing (in video form) in addition to the written and oral form, it was demonstrated that the form of informing patients affected anxiety before surgery; and that informing that was carried out with visual materials decreased anxiety (29,30). In another similar study, before the surgery, the effect of informing as verbal or with pictures in CD-ROM on the anxiety of patients who will undergo the surgical procedure was investigated. The patients were divided into two groups. While verbal and written information was given to one group, the CD-ROM, which included pictures of surgery procedure, results, complications, and different periods of recovery, was shown to the other group. At the end of the study, it was determined that the anxiety levels increased significantly in both groups when the surgery day approached, but the anxiety of the group watching the CD-ROM was significantly lower than the other group. While there was no difference between the two groups in terms of understanding the complications of the surgical procedure, the score that showed the understanding of the subtleties and purpose of the surgical procedure was found to be higher in the group watching the CD-ROM (31). It was reported that the psychological preparation of the patient for the surgery decreased the duration of the hospital stay, the use of analgesics and the complications, and the training videos were effective in increasing the quality of life and the immune response. Also, in various studies, it was reported that preoperative video training would reduce medical costs and be effective in reducing the stress and anxiety associated with surgery (32,33). In our study, the surgical procedures shown in the animations were not performed on live tissue; they were performed on a limb in a virtual environment. Also, these animations did not contain disturbing images such as blood and purulent exudates. This implementation provides that the informed consent process is made more permanent and more satisfactory, by forming an environment in which patient-physician communication increases. Even though the patients were only informed with animations about the disease findings and the stages of the surgery; after the animation, it was seen that patients understood the other treatment options other than the scheduled surgery and the complications related to the operation better and there was a significant increase in their knowledge levels. We think that increasing the visual information about the disease and operation stages of the patients makes the previous information, which was given verbally and in written form, easier to understand and remember. There are some limitations to our study. As a result of our research, we could not find any visual animation applications explaining other treatment options of gonarthrosis and the complications that are specific to total knee arthroplasty. For this reason, we could not provide visual animation to our patients in this respect. We believe that this limitation of our study is also the limitation of visual animation designers. Another limitation of our study is that written/verbal and visual animation applications were carried out on the same patients. Although there was nearly one month's time interval, we still believe this might cause recall bias. The effect of age and gender could not be investigated in the study because the ages of our cases were close to each other, and most of them were female. Also, we did not consider providing information with visual animation proper in terms of the medicolegal approach, which is outside the standard application. For this reason, the control group could not be formed.

Conclusion

The thought of surgery creates anxiety in the person. This makes understanding of the written consent forms, which are already difficult to understand, more difficult. For this reason, the ways to obtain the informed consent form, which is clear, objective, engaging, and easier to understand for patients at all levels, are needed. The use of visual animations is a simple, easy, and effective method independent of the patient's level of education in informing patients. It also increases patient satisfaction and provides that the patient more easily understands postoperative care and complications.

Ethics Committee Approval: Necessary permissions [İstanbul Training and Research Hospital, Clinical Research Ethics Committee; with (decision no: 757, date: 15.01.2016)] were obtained for the implementation of the research.

Informed Consent: It was obtained.

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The Outcomes of Cataract Surgery in Small and Normal Pupillary Eyes with Pseudoexfoliation

Psödoeksfoliyasyonu Olan Küçük ve Normal Pupillalı Gözlerde Katarakt Cerrahisi Sonuçlarımız

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ABSTRACT

Introduction: To evaluate the outcomes of cataract surgery and anterior chamber parameters in pseudoexfoliation cases in our clinic.

Methods: The patients, who were admitted to our clinic between 01.03.2016 and 01.04.2019 and who were found to have cataract and pseudoexfoliation in the examination, were divided into two groups according to dilated pupillary diameter above and below 5 mm before cataract surgery. Preoperative and postoperative visual acuities, intraocular pressure levels, anterior chamber depths and perioperative posterior capsule opening, development of floppy iris syndrome and corneoscleral suture rates were evaluated.

Results: Sixty eyes of 60 patients, including 31 male (51.7%) and 29 female (48.3%) patients, with a mean age of 70.2±7.1 (range: 57-82) years, were included. Patients with pupillary diameter above 5 mm were included in group 1, and those below 5 mm were included in group 2. Preoperative and postoperative visual acuity according to Snellen chart, intraocular pressure and anterior chamber depths of patients in group 1 were 0.2±0.1 (range: 0.1-0.4) vs 0.6±0.2 (range: 0.2-1.0), 16.9±1.7 (range: 14-20) mmHg vs 15.2±1.2 (range: 12-17) mmHg, and 3.04±0.31 (range: 2.29-3.73) mm vs 3.81±0.38 (range: 2.48-4.36) mm, respectively. Preoperative and postoperative visual acuity according to Snellen chart, intraocular pressure and anterior chamber depths of patients in group 2 were 0.1±0.1 (range: 0.1-0.4) vs 0.7±0.2 (range: 0.3-1.0), 17.1±1.5 (range: 14-20) mmHg vs 16±1.5 (range: 12-19) mmHg, and 2.98±0.44 (range: 1.98-3.88) mm vs 3.99±0.54 (range: 3.29-5.46) mm, respectively. In group 1, three eyes (10%) had floppy iris syndrome, four eyes (13.3%) had posterior capsule rupture, and corneoscleral suture was performed in three eyes (10%). In group 2, one eye (3.3%) had floppy iris syndrome, one eye (3.3%) had posterior capsule rupture and corneoscleral suture was performed in one eye (3.3%). There was no statistically significant difference between two groups in terms of age, gender, development of floppy iris syndrome, posterior capsule rupture, corneoscleral suturing, preoperative

ÖZ

Amaç: Kliniğimizde psödoeksfoliyasyonlu olgulara uygulanan katarakt cerrahisi sonuçlarını ve ön kamara parametre değerlerini değerlendirmektir.

Yöntemler: 01.03.2016 ve 01.04.2019 tarihleri arasında kliniğimize başvuran, yapılan muayenede katarakt ve psödoeksfoliasyon saptanan olgular katarakt ameliyatı öncesi dilate pupilla çapına göre 5 mm'nin üzerinde ve altında olmak üzere iki gruba ayrıldı. Olguların ameliyat öncesi ve sonrası görme keskinlikleri, göz içi basıncı seviyeleri, ön kamara derinlikleri ile ameliyat esnasında arka kapsül açılması, gevşek iris sendromu gelişimi ve korneaskleral sütür atılması oranları değerlendirilmiştir.

Bulgular: Yaş ortalamaları 70,2±7,1 (57-82) olan, 31'i erkek (%51,7), 29'u kadın (%48,3) olmak üzere 60 hastanın 60 gözü dahil edildi. Pupilla çapı 5 mm'nin üzerinde olanlar grup 1'e, 5 mm'nin altında olanlar grup 2'ye dahil edildi. Grup 1'deki hastaların ameliyat öncesi ve sonrası Snellen eşeline göre görme keskinliği, göz içi basıncı ve ön kamara derinlikleri sırasıyla 0,2±0,1 (0,1-0,4), 0,6±0,2 (0,2-1,0); 16,9±1,7 (14-20) mmHg, 15,2±1,2 (12-17) mmHg; 3,04±0,31 (2,29-3,73) mm, 3,81±0,38 (2,48-4,36) mm olarak tespit edildi. Grup 2'deki hastaların ameliyat öncesi ve sonrası Snellen eşeline göre görme keskinliği, göz içi basıncı ve ön kamara derinlikleri sırasıyla 0,1±0,1 (0,1-0,4), 0,7±0,2 (0,3-1,0); 17,1±1,5 (14-20) mmHg, 16±1,5 (12-19) mmHg; 2,97±0,44 (1,98-3,88) mm, 3,99±0,54 (3,29-5,46) mm olarak tespit edildi. Grup 1'deki 3 (%10) gözde gevşek iris sendromu, 4 (%13,3) gözde arka kapsül yırtığı gelişmiş ve 3 (%10) göze korneaskleral sütür konmuştur. Grup 2'deki 1 (%3,3) gözde gevşek iris sendromu, 1 (%3,3) gözde arka kapsül yırtığı gelişmiş ve 1 (%3,3) göze korneaskleral sütür konmuştur. Her iki grup arasında yaş, cinsiyet, gevşek iris sendromu gelişimi, arka kapsül yırtılması, korneaskleral sütür konulması; ameliyat öncesi ve sonrası görme keskinliği, göz içi basıncı ve ön kamara derinlikleri arasında istatistiksel

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and postoperative visual acuity, intraocular pressure and anterior chamber depths (p=0.304, p=0.508 for male, p=0.509 for female, p=0.500, p=0.447, p=0.500, p=0.304, p=0.904, p=0.644, p=0.025, p=0.437, p=0.150, respectively).

Conclusion: Pseudoexfoliation is more likely to occur with small pupils. Both conditions involve an increased risk of complications during cataract surgery.

Keywords: Pseudoexfoliation, cataract, small pupil

seviyede anlamlı fark bulunmamıştır (sırasıyla; p=0,304, erkek için p=0,508, kadın için p=0,509, p=0,500, p=0,447, p=0,500, p=0,304, p=0,904, p=0,644, p=0,025, p=0,437, p=0,150).

Sonuç: Psödoeksfoliyasyonlu olgularda küçük pupilla ile karşılaşma ihtimali daha fazladır. Her iki durum katarakt ameliyat esnasında artmış komplikasyon riskini barındırır.

Anahtar Kelimeler: Psödoeksfoliyasyon, katarakt, küçük pupil

Introduction

Pseudoexfoliation is a gray-white, fibrogranular material that accumulates in the anterior lens surface, pupillary edge, iris and angle in the eye, and in the walls of vessels and tissues in the body (1-3).

An area where pseudoexfoliation accumulates in the eye is the corneal endothelial region. The pseudoexfoliation material deposited in this region causes alterations firstly in the functions of corneal endothelial cells, and changes the shape and number in later periods (4). In addition, pseudoexfoliation material deposited on the surface of the cornea may cause corneal curvature changes in cases with increased intraocular pressure (5). The other accumulation area of exfoliative material in the eye is the anterior chamber angle and lens zonules (4,6,7). The material deposited at the anterior chamber angle can cause resistance to the passage of the aqueous humor to the trabecular network, causing open-angle glaucoma (8). Exfoliative material accumulated in the zonules may damage the lens zonules and cause the development of zonular weakness (9). This situation may cause many complications such as loss of zonules, development of aphakia and loss of vitreous in cataract surgery (10,11). In the event that exfoliative material accumulates in the iris, pupillary dilatation occurs less during surgery and an increase in the complications of cataract surgery can be observed (12,13). Another site of pseudoexfoliation in the eye is the lens anterior capsule (14).

The primary accumulation of pseudoexfoliation material outside the eye is the arterial vessel walls. As a result of this accumulation, the probability of cardiovascular and cerebrovascular diseases increases (15,16).

Methods

Ethics committee approval was obtained from Pamukkale University Faculty of Medicine Medical Ethics Committee (decision no: 05, date: 05.03.2019). The study was conducted in accordance with the Declaration of Helsinki. Written and oral consent was obtained from the patients included in the study and their data were evaluated within the scope of the study.

Patients who presented to our ophthalmology outpatient clinic with low vision complaints between 01.03.2016 and 01.04.2019 and in whom the cause of vision loss was due to cataract were included in our study. Age, gender, preoperative maximum dilated pupillary diameters, preoperative and postoperative visual acuities, anterior chamber depths and intraocular pressures were recorded. Patients with eye disease other than pseudoexfoliation and cataract, patients with zonular dialysis, and patients with previous ocular trauma and surgery were not included in the study.

Anterior chamber depth measurements were performed before and one month after the surgery with the A-Scan ultrasonography under dim light when the pupil was in its natural state. Dilated pupillary measurements of all patients before and one month after the surgery with biomicroscope following 30 minutes after instillation with one drop of tropicamide (Tropamid 1%, Bilim), cyclopentalate hydrochloride (Cycloplegine 1%, Abdi İbrahim) and phenylephrine hydrochloride (Mydfrin 2.5%, Alcon) at intervals of 10 minutes. Visual acuity and intraocular pressure levels of all patients were measured before and one month after the surgery. Visual acuity level was recorded according to Snellen chart and intraocular pressure level was recorded according to applanation tonometer. All eyes were operated by the same surgeon with experience of over 1000 phacoemulsification surgeries with the same microscope, instruments and surgical instruments. As a surgical method, divide and eat method was used for the nucleus removal in all eyes. In the cases whose posterior capsule integrity was impaired during surgery, vitreous viscoelastic material was removed and the remaining nucleus and cortex were removed by aspiration. In these cases, a 3-part lens was implanted in the sulcus. At the end of the operation, corneoscleral sutures with 10/0 nylon sutures were placed in the patients with posterior capsule opening in the area near the main entrance. The side inlets were inflated with balanced salt solution and the operation was terminated.

Patients were divided into two groups as maximum pupillary dilatation diameter of above or below 5 mm. Preoperative and postoperative anterior chamber depths, visual acuity levels and intraocular pressures and intraoperative complications of the eyes in both groups were recorded.

Statistical Analysis

Statistical analysis was performed using SPSS 25.00 for Windows (SPSS Inc., Chicago, Illinois, USA) software using a paired t-test. Descriptive statistics were given as numbers and percentages for categorical variables. Pearson tests were performed for normally-distributed variables and Spearman tests were used for non-normally-distributed variables. $P<0.005$ was considered statistically significant.

Results

Sixty eyes of 60 patients, including 31 male (51.7%) and 29 female (48.3%) patients, with a mean age of 70.2±7.1 (range: 57-82) years, were

included. Nineteen (31.7%) patients had hypertension. There was no history of diabetes mellitus and alpha-blocker drug use in the patients included in the study. Patients with pupillary diameter above 5 mm were included in group 1, and those below 5 mm were included in group 2. The reference pupillary diameters for grouping were made according to the narrow and normal pupillary width specified in the referenced studies (17-19). Group 1 included 30 eyes of 30 patients, 15 men (50%) and 15 women (50%), with a mean age of 69.3±6.9 (range: 58-82) years and group 2 included 30 eyes of 30 patients, 16 men (53.3%) and 14 women (46.7%), with a mean age of 71.2±7.2 (range: 57-79) years. There was no statistically significant difference between two groups in terms of mean age, gender, hypertension, development of floppy iris syndrome, complications, corneoscleral suturing, preoperative and postoperative visual acuity, intraocular pressure and anterior chamber depths (p=0.304, p=0.508 for male, p=0.509 for female, p=0.478, p=0.500, p=0.447, p=0.500, p=0.304, p=0.904, p=0.644, p=0.025, p=0.437, p=0.150, respectively) (Table 1).

Visual acuity, intraocular pressure and anterior chamber depths were evaluated in both groups before and after surgery. Visual acuity and anterior chamber depth were significantly increased in both groups (p=0.000 and p=0.000 for group 1 and p=0.000 and p=0.000 for group 2, respectively), and intraocular pressure decreased significantly (p=0.000 for group 1 and p=0.013 for group 2) (Table 2).

Floppy iris syndrome developed in three eyes (10%) in group 1 and in one eye (3.3%) in group 2. Posterior capsule integrity was observed to be impaired in four eyes (13.3%) in group 1 and in one eye (3.3%) in group 2. In these five eyes, the nucleus material was not dislocated to the vitreous and the intraocular lens was implanted into the sulcus. Regarding eyes with impaired posterior capsule integrity, corneoscleral sutures were placed in three eyes in group 1 and in one eye in group 2. No statistically significant difference was found between two groups regarding the development of floppy iris syndrome and complications and corneoscleral suturing (p=0.500, p=0447, p=0.500, respectively).

Discussion

Cataract surgery is a necessary method to increase vision in patients with low vision due to cataract (20,21). In pseudoexfoliation cases, cataract causes a decrease in vision and surgical intervention is necessary to increase vision (22,23). Many studies have shown that pupillary dilatation in eyes with pseudoexfoliation is insufficient (24,25). In our study, 30 eyes with preoperative insufficient pupillary dilatation were evaluated. It has also been reported in many studies

Table 1. The mean values of group 1 and group 2 characteristics evaluated in the study and the statistical evaluation results of the differences between these two groups

	Group 1 (n=30)	Group 2 (n=30)	p
Age, years (range)	69.3±6.9 (58-82)	71.2±7.2 (57-79)	0.304
Gender (%)			
	15 Male (50%)	16 Male (53.3%)	Male=0.508
	15 Female (50%)	14 Female (46.7%)	Female=0.509
Hypertension (%)	6 (20%)	13 (43.3%)	0.478
Floppy iris syndrome (%)	3 (10%)	1 (3.3%)	0.500
Posterior capsule rupture (%)	4 (13.3%)	1 (3.3%)	0.447
Corneoscleral suturing (%)	3 (10%)	1 (3.3%)	0.500
Preoperative VA (range)	0.2±0.1 (0.1-0.4)	0.1±0.1 (0.1-0.4)	0.304
Postoperative VA (range)	0.6±0.2 (0.2-1.0)	0.7±0.2 (0.3-1.0)	0.904
Preoperative IOP, mmHg (range)	16.9±1.7 (14-20)	17.1±1.5 (14-20)	0.644
Postoperative IOP, mmHg (range)	15.2±1.2 (12-17)	16±1.5 (12-19)	0.025
Preoperative ACD, mm (range)	3.04±0.31 (2.29-3.73)	2.97±0.44 (1.98-3.88)	0.437
Postoperative ACD, mm (range)	3.81±0.38 (2.48-4.36)	3.99±0.54 (3.29-5.46)	0.150

*p<0.005. VA: visual acuity (Snellen chart), IOP: intraocular pressure, ACD: anterior chamber depth

Table 2. Preoperative and postoperative evaluation of eyes in group 1 and group 2 and the results of statistical evaluation of the difference between these values

		Preoperative	Postoperative	p
Group 1	VA (range)	0.2±0.1 (0.1-0.4)	0.6±0.2 (0.2-1.0)	0.000
	IOP, mmHg (range)	16.9±1.7 (14-20)	15.2±1.2 (12-17)	0.000
	ACD, mm (range)	3.04±0.31 (2.29-3.73)	3.81±0.38 (2.48-4.36)	0.000
Group 2	VA (range)	0.1±0.1 (0.1-0.4)	0.7±0.2 (0.3-1.0)	0.000
	IOP, mmHg (range)	17.1±1.5 (14-20)	16±1.5 (12-19)	0.013
	ACD, mm (range)	2.97±0.44 (1.98-3.88)	3.99±0.54 (3.29-5.46)	0.000

*p<0.005. VA: visual acuity (Snellen chart), IOP: intraocular pressure, ACD: anterior chamber depth

that the complications that can be observed in cataract surgery may increase in eyes with pseudoexfoliation. The reason for the increase in complications was reported to be insufficient pupillary dilatation and accompanying zonular damage to pseudoexfoliation (12,26). It has also been shown in some studies that the use of capsular tension ring and iris hook during cataract surgery is higher in these eyes than in normal eyes (27-29).

The rate of deterioration of posterior capsule integrity during cataract surgery in the general population was reported as 1.9% by Chakrabarti and Singh (30), as 0.68 by Chen et al. (31) and as 7.9% by Zare et al. (32). In our study, posterior capsule integrity was impaired during surgery in five eyes, including four eyes in group 1 and one eye in group 2. Thanigasalam et al. (33) reported that the incidence of posterior capsule rupture in eyes with pseudoexfoliation was 2.833 times higher than normal eyes. The incidence of posterior capsule rupture observed in our study was found to be 8.3%. This result seems to be compatible with the results of other studies. In studies evaluating populations that did not use any medication and had no additional disease, the rate of development of floppy iris syndrome was reported as 0.018% by Goyal et al. (34) and as 1.18% by Özer et al. (35). The rate of development of floppy iris syndrome in general populations was stated as 9.09% by Kaczmarek et al. (36) and as 4.1% by Neff et al. (37). Tzamalis et al. (38) reported the rate of development of floppy iris syndrome in the general population as 1.29% in women and 5.17% in men. In the literature, there is no study on the rate of development of floppy iris syndrome in patients with pseudoexfoliation. In our study, this rate was found to be 6.6%. This rate was found to be higher than that of Goyal et al. (34), Özer et al. (35), Neff et al. (37), and Tzamalis et al. (38)

Increased visual acuity after cataract surgery has been shown in many studies (39-41). In our study, the postoperative visual acuity level was found to be significantly increased compared to the preoperative visual acuity level. Various studies have shown that postoperative intraocular pressure is lower than preoperative values after cataract surgery (42-44). In our study, intraocular pressure values measured postoperatively were found to be statistically lower than preoperative intraocular pressure values. Several studies have shown that anterior chamber depth is increased after cataract surgery in eyes with and without pseudoexfoliation (45-48). In our study, anterior chamber depth was increased after cataract surgery similar to other studies.

Conclusion

There is an increased risk of complications in cataract surgeries in eyes with pseudoexfoliation. Increased surgical risk in cases where pupillary dilatation is insufficient has been shown to increase in many studies, but this risk increase can be reduced by increasing surgical experience.

Ethics Committee Approval: Ethics committee approval was obtained from Pamukkale University Faculty of Medicine Medical Ethics Committee (decision no: 05, date: 05.03.2019).

Informed Consent: Written and oral consent was obtained from the patients included in the study.

Peer-review: Externally peer-reviewed.

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Clopidogrel Resistance in Stroke Cases

İnme Olgularında Klopidogrel Rezistansı

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ABSTRACT

Introduction: Clopidogrel treatment is one of the standard treatments in terms of reducing mortality and morbidity in patients with cerebrovascular disease diagnosed with large artery atherosclerosis. However, resistance to clopidogrel treatment is a significant problem today. In this study, we aimed to retrospectively investigate clopidogrel resistance (CR) and related factors in patients with detected large artery atherosclerosis who were evaluated for cerebrovascular disease.

Methods: A total of 96 patients, including 31 females and 65 males, were evaluated in the neurology and neuroradiology clinics with the diagnosis of cerebrovascular disease. Age, gender, presence of CR, and complete blood count values [platelet count (PLT), platelecrit (PCT), mean platelet volume, white blood cells, platelet distribution width] were evaluated. Impedance Aggregometry was used to evaluate CR in the study. The results were given as the area under the curve. An adenosine diphosphate value higher than 46 U was taken as a resistance indicator. The relationship between blood tests and CR was investigated.

Results: CR was detected in 33.3% (n=32) of 96 patients. PLT (295.7±12.4) and PCT values (0.3±0.01) were significantly higher in patients with resistance than those without resistance ($p<0.005$).

Conclusion: This study shows that high PLT and PCT values can be used to predict CR.

Keywords: Cerebrovascular diseases, clopidogrel, resistance, platelet count, platelecrit

ÖZ

Amaç: Beyin damar hastalığı tanısı ile değerlendirilen ve büyük arter aterosklerozu saptanan hastalarda mortalite ve morbititenin azaltılması yönünden klopidogrel tedavisi standart tedaviler içinde yer almaktadır. Bununla beraber klopidogrel tedavisine karşı gelişen rezistans günümüzde önemli bir sorundur. Bu çalışmada, beyin damar hastalığı nedeni ile değerlendirilen ve büyük arter aterosklerozu saptanan hastalarda klopidogrel rezistansının (KR) incelenmesi ve ilişkili faktörlerin retrospektif olarak gözden geçirilmesi amaçlandı.

Yöntemler: Çalışmaya nöroloji ve nöroradyoloji kliniklerinde beyin damar hastalığı tanısı ile değerlendirilen KR'nin incelendiği, 31 kadın ve 65 erkek olmak üzere toplam 96 hasta dahil edildi. Tüm hastaların yaş, cinsiyet, KR varlığı, hemogram değerleri [platelet sayısı (PLT), platelekrit (PCT), ortalama trombosit hacmi, beyaz kan hücreleri, trombosit dağılım genişliği] retrospektif olarak değerlendirildi. Çalışmada KR'nin değerlendirilmesinde impedans agregometri kullanıldı. Sonuçlar eğri altında kalan alan cinsinden verildi. Adenozin difosfat değerinin 46 U değerinden yüksek olması rezistans göstergesi olarak alındı. KR varlığı ile incelenen tüm parametreler arasındaki ilişki değerlendirildi.

Bulgular: Toplamda 96 hastanın %33,3'ünde (n=32) KR saptandı. Rezistans gösteren hastaların PLT (295,7±12,4) ve PCT değerleri (0,3±0,01) rezistans göstermeyen hastalara göre anlamlı oranda daha yüksek bulundu ($p<0,005$).

Sonuç: Bu çalışma yüksek PLT ve PCT değerlerinin KR'yi öngörmede kullanılabilecek parametreler olduğunu göstermektedir.

Anahtar Kelimeler: Serebrovasküler hastalıklar, klopidogrel, rezistans, platelet sayısı, platelekrit

Introduction

Platelets (PLTs) play an essential role in the development of ischemic stroke in terms of pathophysiology of thrombosis formation (1). Clopidogrel, an antithrombotic agent that inhibits PLT activation via adenosine diphosphate (ADP), has proven efficacy and safety in preventing recurrent ischemic strokes (1). Clopidogrel is a second-generation thienopyridine derivative prodrug and is converted to its active metabolite by cytochrome P450 enzyme system (mainly CYP2C19)

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in the liver. It shows its antithrombotic effect by irreversibly inhibiting the ADP-P2Y12 receptor located in the PLT membrane (2-4). Clopidogrel given at the standard dose does not show a complete P2Y12 antagonism; in other words, it inhibits ADP-mediated PLT aggregation by 50% (5). Therefore, some patients receiving clopidogrel therapy do not have an adequate therapeutic response to the drug, and this phenomenon is also described as clopidogrel resistance (CR). This phenomenon, also known as the absence of ADP-mediated PLT inhibition with the use of therapeutic doses of clopidogrel, can be attributed to individual variability in PLT response to clopidogrel treatment and may be associated with recurrent thrombotic events or poor prognosis incidence due to treatment insufficiency (6).

The frequency of patients who do not respond to clopidogrel treatment varies between 4-30%, depending on the clinical use indications, the dose of the drug, the time of treatment initiation, and the test method to evaluate PLT functions (5,7). Currently, CR is characterized by PLT function (a measurement of the degree of PLT aggregation induced by *in vitro* ADP) and genetic polymorphism analysis (5,6). Evaluation of PLT function in cardiovascular and cerebrovascular diseases is important for predicting clinical outcomes and prognosis and determining the efficacy of antithrombotic therapy (2). In these studies, basal PLT parameters such as high PLT and plateletcrit (PCT), mean PLT volume (MPV), PLT distribution width (PDW), have been tried to correlate with CR (8,9), but the results are still controversial (10,11).

This study aimed to evaluate CR in patients diagnosed with large artery atherosclerosis during evaluation for stroke and to determine the routine biochemical parameters before clopidogrel treatment, thus evaluating whether biochemical markers could predict early PLT response and future clinical outcomes that might be associated with resistance.

Methods

Patients who were diagnosed clinically and radiologically with magnetic resonance imaging with cerebrovascular disease at İstanbul Training and Research Hospital, Clinic of Neurology and Neuroradiology between 29.09.2015 and 30.11.2017, and who were also diagnosed with large artery atherosclerosis or stenosis by brain computed tomography (CT) or MR angiography examinations during further evaluation were included in the study. A total of 96 patients (31 women and 65 men) with CR were evaluated retrospectively. The study was approved by the İstanbul Training and Research Hospital Ethics Committee of clinical trials (decision no: 1687). As the study included retrospective file scanning, informed consent was not obtained from the patients.

The patients were divided into two groups as patients with CR (CR+) and without CR (CR-). Age, gender, complete blood count parameters [PLT count, PCT, MPV, white blood cell count, PDW], and prothrombin time (PT-INR) were recorded retrospectively from patient files.

Patients with severe anemia, active hemorrhage, bone marrow disease, heparin-induced thrombocytopenia, blood transfusion, anticoagulant medication other than clopidogrel, or drug use that would affect PLT count were not included in the study.

Evaluation of Clopidogrel Resistance

Impedance aggregometry (Multiplate Analyzer, Dynabyte, Munich, Germany) was used to evaluate CR. For the test, blood was collected in 4 cc tubes containing hirudin and incubated for 30 minutes at room temperature. Blood was diluted 1:2 with 0.9% NaCl and stirred at 37 °C for 3 minutes. Then, 20 µl of ADP (6.4 Mmol) was added. Resistance changes caused by PLTs, which were aggregated and adhered to the electrodes in the test cell, were recorded with two pairs of electrodes. Increased resistance by PLTs adhering to the electrodes was converted to the aggregation unit (AU) by the device, and the time-aggregation graph was plotted. The area under the aggregation line Area Under the Curve, the parameter that best reflects platelet activity, was calculated. An ADP value of >46 U indicates no suppression, a value between 19-46 U indicates adequate suppression, and <19 indicates over suppression.

In our study, there was no control group to determine the reference range of the PLT function test. Test results may vary between races, with each center determining its own reference range will give more accurate results.

Statistical Analysis

The data of our study were expressed as mean ± standard error of the mean. The difference between CR+ and CR- patients was evaluated by the Mann-Whitney U test. A chi-square test was used to compare qualitative data. $P<0.05$ was considered statistically significant.

Results

Impedance Aggregometry Results: Clopidogrel Resistance

CR was detected in 32 (33.3%) of 96 patients (31 women and 65 men) diagnosed with large artery atherosclerosis according to the impedance aggregometry results. The mean age of CR+ patients was 70.4±1.5 years, and the mean age of CR- patients was 68.9±1.4 years. There was no difference between the two groups in terms of mean age ($p>0.05$). Fifty-nine percent of CR+ patients were male, and 41% were female, and 72% of CR- patients were male, and 28% were female. There was no significant relationship between CR and gender ($p=0.25$) (Table 1). When CR+ patients (n=32) were evaluated for possible co-morbidities, ten patients (31.25%) were found to have both hypertension and diabetes, eight patients (25%) had only hypertension, four patients (12.5%) had only diabetes, and ten patients had no chronic disease.

Biochemical Parameters

Routine complete blood count parameters and PT-INR values requested from the patients were compared between CR+ and CR- patients and the values of both groups are summarized in Table 1. The mean ADP value of CR+ patients was 67.5±4.4 U and thrombin receptor activating peptide (TRAP) value was 116.6±4, whereas the mean ADP value of CR- patients was 23.5±3.5 U and TRAP value was 88.7±3.5 (Table 1). As these two parameters are indicators supporting the accuracy of the Impedance Aggregometry test, a significant difference was found between the two groups as expected ($p<0.05$).

The mean PLT value of CR+ patients was 295.7±12.4, and the mean PLT value of CR- patients was 259.0±8.8 (Figure 1A). The mean PCT value

of CR+ patients was 0.3±0.01, and the mean PCT value of CR- patients was 0.27±0.01 (Figure 1B). Platelet and PCT values were higher in CR+ patients, and a statistically significant difference was found between the two groups (p=0.02 and p=0.0015) (Figure 1, Table 1).

Discussion

At present, antiplatelet drugs are proven treatment of atherothrombotic stroke in the prevention of secondary stroke. In the last 30 years, studies have shown that aspirin, ticlopidine, clopidogrel, and dipyridamole are effective in preventing recurrent stroke in patients with atherothrombotic stroke (12,13). Studies have shown that approximately 10-20% of patients undergoing antiplatelet therapy have a recurrent stroke (14). Repeated thrombotic event despite antiplatelet therapy raises antiplatelet drug resistance. Other commonly used definitions of this resistance are insufficiency of antiplatelet therapy, non-responsiveness, or inadequate efficacy.

In our study, 33.3% of 96 cases had CR. Studies on CR have reported different rates. In the study of Notarangelo et al. (15), this rate was stated as 30% and in the study by Wang et al. (7) as 11%. In general, CR varies between 4-30% depending on the clinical indications, starting dose, maintenance dose, time to start treatment, and PLT function test methods (16).

Studies have reported higher CR in women (17,18). However, although the rate of female patients in the CR+ group was higher than the rate of female patients in the CR- group, no significant relationship was found between CR and gender (Table 1). When the mean age was examined, no significant difference was found between the CR+ and CR- groups in support of previous studies (17,18).

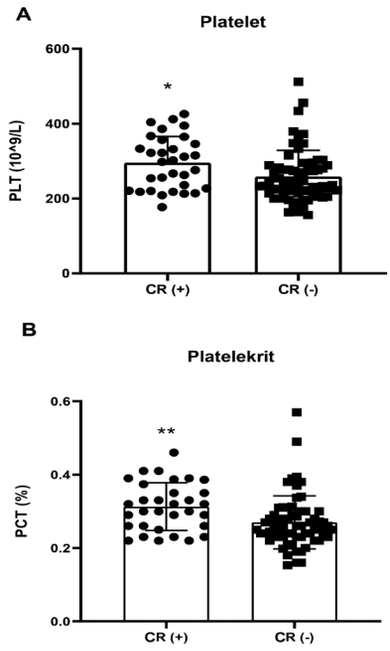

Figure 1. Platelet A) and plateletcrit B) values in patients with (CR+) and without (CR-) clopidogrel resistance. Data were expressed as mean ± standard error of the mean, and the comparison was made with the Mann-Whitney U test. *P<0.05. Individual data of CR+ and CR- patients were placed in round and square bar graphs, respectively

PLT: platelet, PCT: plateletcrit, CR: clopidogrel resistance

The main finding of our study was that the PLT and PCT values of the patients with CR were significantly higher than those without resistance. In studies conducted to date, baseline PLT values, which can easily be obtained from routine laboratory tests, are shown as simple and useful markers that can be used to predict CR (6). Our findings suggest that PLT count, and PCT, which is a measure of total platelet mass, can be used as parameters to predict CR.

Thrombus formation and PLT activation play an important role in the pathogenesis of ischemic cerebrovascular diseases (19,20). Estimates of PLT volume and count give information about PLT function and activation (20). PLT is a parameter reflecting PLT production, function, and aging (8), and high PLT values are noteworthy in patients showing CR in support of our study (6). Therefore, patients with elevated PLT levels before treatment may be prone to thrombosis.

It is assumed that PCT shows PLT count circulating in a unit of blood, similar to the hematocrit value for erythrocytes (21). In our study, PCT values were significantly higher in patients with CR. It has been proposed that high PCT values can be used as a useful parameter in predicting coronary slow-flow phenomenon associated with cardiovascular pathologies such as recurrent angina pectoris, acute myocardial infarction, and hypertension, and may be considered as a marker for more aggressive antiplatelet therapy (22). In support of this hypothesis, the findings of our study suggest that PCT value can be used as another parameter that can be evaluated together with the PLT count in predicting CR. However, larger scale and comprehensive studies are needed to establish the relationship between CR and high PCT values.

MPV is another commonly used parameter to evaluate PLT size and function (8). In the studies performed, MPV values were found to be

Table 1. Clinical and laboratory features of CR+ and CR- patients

Parametre	CR+ (n=32)	CR- (n=64)	p
Age	70.4±1.5	68.9±1.4	NS
Female, n (%)	12 (41)	18 (28)	NS
MPV (fL)	10.7±0.2	10.4±0.1	NS
PLT (10^9/L)	295.7±12.4*	259.0±8.8	0.01
PCT (%)	0.3±0.01**	0.27±0.01	0.0015
PDW (%)	13.2±0.5	14.4±1.8	NS
HB (g/dL)	12.9±0.3	13.4±0.2	NS
WBC (10^9/L)	8.8±0.4	8.2±0.3	NS
RBC (10^12/L)	4.5±0.1	4.7±0.07	NS
HCT (%)	39.4±0.8	40.7±0.6	NS
INR	0.95±0.02	1.02±0.04	NS
ADP (U)	67.5±4.4***	23.5±1.3	<0.001
TRAP (U)	116.6±4***	88.7±3.5	<0.001

Quantitative data were expressed as mean ± SEM, and the comparison was made with the Mann-Whitney U test. *p<0.05. Qualitative data (age) were given as n (%) and evaluated by the chi-square test

CR: clopidogrel resistance, MPV: mean platelet volume, PLT: platelet count, PCT: platelecrit, PDW: platelet distribution width, HB: hemoglobin, WBC: white blood cells, RBC: red blood cells, HCT: hematocrit, INR: international normalized ratio, ADP: adenosine diphosphate, TRAP: thrombin receptor activating peptide

significantly higher in patients with CR compared to patients responding to treatment (23,24). In a prospective study by Li et al. (25), PLT and MPV values were found to be significantly higher in the clopidogrel-resistant group in 152 coronary artery patients (CAD) treated with clopidogrel. It was observed that CR+ patients had more cardiovascular events in the 53-month follow-up period, and it was concluded that the increase in PLT and MPV was a risk factor for the development of CR in CAD (25). In our study, no statistically significant difference was found between CR+ and CR- patients in terms of MPV, whereas the PLT value was significantly higher in the CR+ group.

Study Limitations

The limitations of our study include the small number of patients and lack of evaluation of several related factors (especially CYP2C19 enzyme activity and genetic polymorphism, inflammation-related biochemical parameters such as C-reactive protein) due to the retrospective nature of our study.

Conclusion

We found a significant relationship between CR and PLT and PCT values in our study. This finding suggests that PLT and PCT values can be considered as parameters that can be used to predict CR. Considering that CR examination is costly and not performed in many centers, it may be appropriate to evaluate these findings with more large-scale prospective studies.

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Ethics Committee Approval: The study was approved by the İstanbul Training and Research Hospital Ethics Committee of clinical trials (decision no: 1687).

Informed Consent: As the study included retrospective file scanning, informed consent was not obtained from the patients.

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A Rare and Serious Complication of Percutaneous Renal Biopsy: Retroperitoneal Hemorrhage

Perkütan Böbrek Biyopsisinin Nadir ve Ciddi Bir Komplikasyonu: Retroperitoneal Hemoraji

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ABSTRACT

Renal biopsy is the gold standard diagnostic method in adults with the renal parenchymal disease. Retroperitoneal hemorrhage is one of the rare and most severe complications of percutaneous renal biopsy. The incidence of hemorrhagic complications due to interventional procedures in patients with enoxaparin use is 1.9-6.5%. Patients undergoing percutaneous renal biopsy under anti-coagulant therapy should be carefully monitored for this potentially fatal complication after a biopsy. In this case report, we presented a 45-year-old female patient who was admitted to our nephrology department for renal biopsy for unexplained proteinuria and hematuria. Because of mitral valve replacement history, a percutaneous renal biopsy was performed under low molecular weight heparin treatment. The follow-up and treatment process of retroperitoneal hemorrhage after the procedure were described.

Keywords: Hemorrhage, retroperitoneal area, renal biopsy

ÖZ

Böbrek biyopsisi renal parenkimal hastalığı olan erişkinlerde altın standart tanı yöntemidir. Retroperitoneal kanama perkütan renal biyopsinin nadir görülen ve en ciddi komplikasyonlarından biridir. Düşük molekül ağırlıklı heparin olan enoksaparin kullanılan hastalarda girişimsel işlemlere bağlı hemorajik komplikasyonların görülme insidansı %1,9-6,5 arasındadır. Anti-koagülan tedavi altında perkütan renal biyopsi yapılan hastalar biyopsi sonrası ölümcül olabilen bu komplikasyon nedeniyle dikkatli izlenmelidir. Bu yazımızda açıklanamayan proteinüri ve hematüri nedeniyle nefroloji servisimize renal biyopsi amacıyla yatırılan 45 yaşında kadın hasta sunulmuştur. Mitral kapak replasman öyküsü nedeniyle hastaya düşük molekül ağırlıklı heparin tedavisi verilerek perkütan renal biyopsi yapılmıştır. İşlem sonrası gelişen retroperitoneal hemorajinin takip ve tedavi süreci anlatılmıştır.

Anahtar Kelimeler: Hemoraji, retroperitoneal alan, renal biyopsi

Introduction

Renal biopsy is the most important diagnostic and prognostic approach in adults with a renal parenchymal disease (1-3). Indications for renal biopsy include proteinuria, acute renal injury, suspicion of systemic disease associated with renal dysfunction, unexplained renal dysfunction, chronic kidney disease, isolated microscopic hematuria, and graft dysfunction (4). The rare complications of percutaneous renal biopsy are pain, hemorrhage, arteriovenous fistula, Page kidney, perirenal soft tissue infection, and extra-renal organ puncture. In this article, we aimed to present a case with retroperitoneal hemorrhage, which is a rare but severe and fatal complication of renal biopsy.

Case Report

A 45-year-old female patient was admitted to our nephrology department for renal biopsy due to unexplained renal dysfunction, hematuria, and proteinuria. She had a history of essential hypertension for ten years, hyperlipidemia for five years, and mitral mechanical valve replacement (MVR) surgery. She was on warfarin sodium, atorvastatin, and ramipril. Laboratory results were as follows: hemoglobin (Hgb): 12.3 g/dL, platelet (Plt): 240x10^3/µL, international normalized ratio (INR): 3.4, urea: 54 mg/dL, creatinine (Cr): 1.5 mg/dL, +3 protein in complete urinalysis, 4 erythrocytes in urine microscopy, 2.6 g/day proteinuria on 24 hour urine analysis. Warfarin treatment was discontinued for MVR, and enoxaparin (low molecular weight heparin) was added to the treatment when the INR level was below 2 after close INR follow-up. The patient's enoxaparin treatment was stopped 24 hours before the biopsy. Pre-biopsy laboratory values were as follows: Hgb: 12 g/dL, Plt: 175x10^3/µL, prothrombin time (PT): 11.7 sec, INR: 1.01 and aPTT: 32.1 sec. Percutaneous left renal biopsy was performed by interventional radiology. After the biopsy, Hgb values were checked three times at 6-hour intervals, and no decrease

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was detected in Hgb values. The patient's physical examination was normal, and enoxaparin treatment was restarted at 20 hours after the procedure. During the follow-ups, she had a vague left side pain that did not cause rebound tenderness. The patient underwent a urinary system ultrasound examination followed by non-contrast abdominal tomography. There was a 94x98x200 mm hyperdensity, consistent with hematoma, in the para- and perirenal region causing anterolateral displacement of the left kidney and extending to the pelvic region, and that could not be clearly distinguished from the psoas muscle (Figure 1). During laboratory follow-up, the patient's Hgb value decreased to 7 g/dL. Inotropic treatment was started due to hemodynamic instability, and the patient was transferred to the intensive care unit. She had fever, and sepsis was considered according to qSOFA criteria, and meropenem and teicoplanin were started empirically with the suggestion of infectious diseases clinic. The patient underwent emergency hemodialysis because of uremic symptoms and detected values of urea: 130 mg/dL, Cr: 3.7 mg/dL, K: 5.56 mEq/L, pH: 7.0, bicarbonate: 11 mmol/L. A total of six units of erythrocyte suspensions were administered to the patient in the intensive care unit with the conservative follow-up recommendations of urology and interventional radiology clinics. The patient became hemodynamically stable, and she did not need hemodialysis. She had no active retroperitoneal hemorrhage, and Hgb value increased to 10 mg/dL, and Cr value decreased to 1.21 mg/dL in the service follow-up. The patient had regression in hematoma dimensions on control tomography, and she was discharged with warfarin treatment. Informed consent was obtained from the patient.

Discussion

Percutaneous renal biopsy is the gold standard method used in the diagnosis, treatment planning, and prognosis of renal diseases (5,6). As with any invasive procedure, this procedure has several complications. Retroperitoneal hemorrhage is one of these complications. Retroperitoneal hemorrhage can be seen as a result of trauma or as a complication of vascular lesions, tumors, surgical intervention, and anticoagulant therapy. Retroperitoneal hemorrhage due to enoxaparin is rare, and few cases have been reported so far (7-9). It is essential because of its high mortality.

Enoxaparin has a longer half-life than standard heparin, does not require anti-coagulation monitoring, the risk of heparin-induced thrombocytopenia is low, and the cost is less, thus making enoxaparin preferable. Also, hemorrhage complications are reported to be less than standard heparin (10).

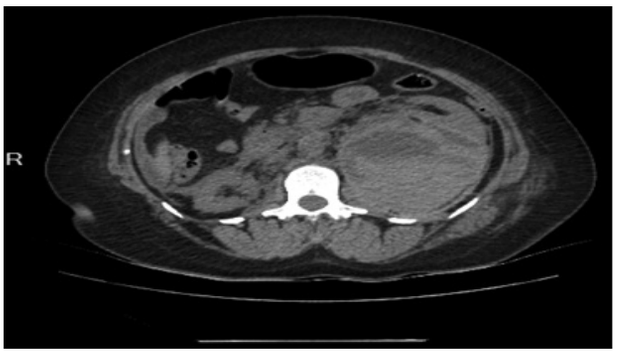

Figure 1. A 94x98x200 mm hematoma in the left retroperitoneal area, and anterolateral displacement of left kidney secondary to hematoma

In the presence of hypotension, tachycardia, and acute abdominal symptoms during treatment with enoxaparin, anticoagulant therapy should be discontinued immediately, and antidote protamine sulfate should be given. However, if more than 12 hours have elapsed since the hemorrhagic event, the use of protamine sulfate has no meaning (11-14). Hemodynamic monitoring should be performed, coagulation parameters should be monitored, and blood and blood product replacement should be performed. Invasive interventions should be avoided as much as possible. Evaluation should be performed by abdominal tomography, and other life-threatening conditions such as gastrointestinal bleeding and abdominal aortic aneurysm rupture should be ruled out in the differential diagnosis except for the detection of possible bleeding focus (11-15). Surgical intervention or embolization should be considered in patients with worsening of their general condition despite supportive treatment (14,15).

Conclusion

Hemorrhage risk after invasive intervention should be kept in mind in patients under enoxaparin treatment. In these cases, close hemodynamic follow-up, physical examination, and bleeding control should be kept in mind after the procedure, and anti-coagulant treatment could then be started.

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally and internally peer-reviewed.

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

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A Rare Complication of Ventriculoperitoneal Shunt: Asymptomatic Small Bowel Perforation

Ventrikülоperitoneal Şantın Nadir Bir Komplikasyonu: Asemptomatik İnce Barsak Perforasyonu

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ABSTRACT

A ventriculoperitoneal (VP) shunt is a standard treatment option for the treatment of hydrocephalus. Small bowel perforation is a rare complication of VP shunt placement. We describe a case and image findings of a 15-year-old male with VP shunt who had an asymptomatic small bowel perforation. He had a history of constipation and occasional abdominal pain. The imaging findings were confirmed surgically. The results of abdominal complications of VP shunts are excellent when diagnosed and treated early. Mortality and morbidity decrease significantly with early diagnosis and treatment, especially in asymptomatic bowel perforations. We also provide an overview of the current literature discussing previously reported cases, clinical features, and treatment.

Keywords: Small bowel perforation, VP shunt surgery, VP shunt complications

ÖZ

Ventrikülоperitoneal (VP) şant hidrosefalinin tedavisinde sık kullanılan bir tedavi seçeneğidir. İnce barsak perforasyonu VP şantın nadir bir komplikasyonudur. Çalışmamızda asemptomatik ince barsak perforasyonu olan 15 yaşındaki VP şantlı hastayı ve radyolojik bulgularını tanımladık. Olgunun kabızlık ve ara ara olan karın ağrısı öyküsü vardı. Görüntüleme bulguları cerrahi olarak doğrulandı. VP şantların abdominal komplikasyonlarının sonuçları erken teşhis ve tedavi edildiğinde mükemmeldir. Özellikle asemptomatik barsak perforasyonlarında erken tanı ve tedavi ile mortalite ve morbidite önemli ölçüde azalmaktadır.

Anahtar Kelimeler: İnce barsak perforasyonu, VP şant cerrahisi, VP şant komplikasyonları

Introduction

Ventriculoperitoneal (VP) shunt is a standard treatment option for the treatment of hydrocephalus. Early or late complications of VP shunt can be classified as mechanical, infectious, and functional. A rare mechanical complication of VP shunt is the migration of the catheter into the thoracic cavity, heart, bladder, hernia sacs, anus, and the distal portion of the scrotum causing infection and/or inadequate drainage of the cerebrospinal fluid (CSF). These complications may remain asymptomatic or sometimes cause mortality (1). In this report, we present a case with a VP shunt who had an asymptomatic small bowel perforation (terminal ileum) with an early and adequately description.

Case Report

Verbal and written informed consent were obtained from the patient who participated in this study. A 15-year-old male with a previous VP shunting due to meningomyelocele and hydrocephalus was evaluated because of abdominal pain and nausea. He had a history of constipation and occasional abdominal pain. Neurological and general physical examination was normal on physical examination. There was no fever, bowel sounds were normal, and there was no tenderness in the abdomen. Only white blood cell count (10:98 10e3/PL) and C-reactive protein (101 Mmg/L) were higher, and other parameters were normal in laboratory findings. There was no shunt dysfunction on the cranial computed tomography (CT) scan. An abdominal CT scan revealed a hyperdense catheter in the subcutaneous adipose tissue on the right abdominal

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lateral wall entering into the abdomen from the subcostal region. The catheter was lying within the right paracolic region, and the distal portion was seen inside the terminal ileum (Figure 1, 2). There was no free fluid or mesenteric fat tissue edema around the catheter. In operation, the shunt catheter tip perforating the terminal ileum was seen. There was a fibrotic tract around the catheter that did not allow fistula formation. The tract was opened, and the catheter was withdrawn. CSF flow within the catheter was seen. The peritoneal catheter was changed because of contamination. CSF microscopy and biochemistry were normal during surgery. Ventricular end and shunt valve protected because there was no central nervous system infection findings. The opening in the small intestine was closed by ligation from the tract around the entrance of the catheter. Two days after the operation, oral intake was started, and the patient was followed for eight months without any problem.

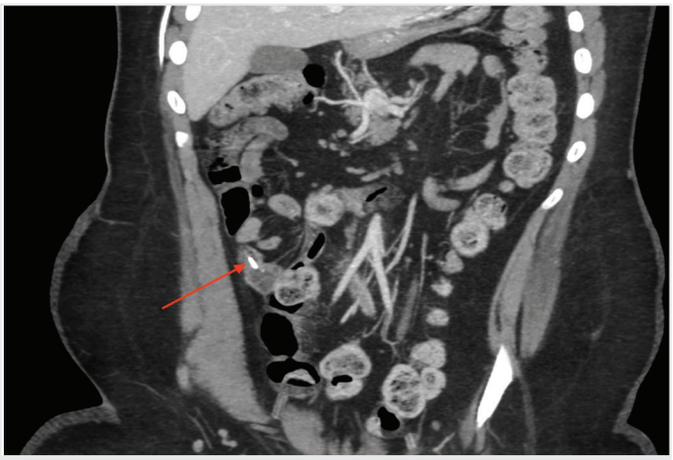

Figure 1. Ventriculoperitoneal shunt catheter appears to be in the terminal ileum in the coronal reformatted abdominal CT

CT: computed tomography

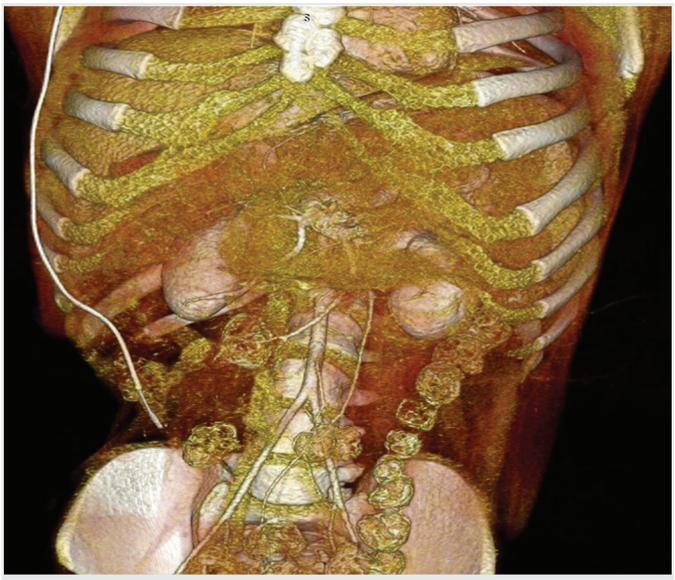

Figure 2. 3D VR image shows the catheter advancing in the right lateral wall of the chest and entering from the subcostal region into the abdomen

VR: virtual reality

Discussion

The incidence of VP shunt-related complications has been reported to be 24-47%, and the majority of these are late complications (2). Approximately one-fourth of these complications are intestinal volvulus, peritoneal pseudocyst, catheter penetration to the visceral organs, or protrusion through rectum, vagina, or urethra. Sometimes it can also penetrate the abdominal wall (3-5).

The incidence of perforation of the colon due to VP shunt in the gastrointestinal tract is reported to be between 0.1-0.7%. After the first case of Wilson and Bertran (6), more than 70 cases have been reported. Half of the cases were asymptomatic. It has been reported that VP shunt dysfunction or protrusion of the catheter tip from the natural orifices provides the diagnosis in symptomatic cases. Up to 70% of cases have been reported in children (1). The perforation mechanism is unclear. However, some possible mechanisms have been put forward. The main factor in perforation is repeated mechanical irritation by the relatively fixed catheter tip to the small bowel due to peristalsis. Among the mechanisms, it is the common main factor in the formation of perforation by the catheter, which is limited in the abdomen and which is repeated with intestinal peristalsis. It is also suggested that catheter may cause allergies and cause perforation with intestinal irritation and adhesion (7). It has also been reported that CSF with a high amount of protein will facilitate the formation of perforations by causing adhesions. It has been reported that the insufficiency of the bowel innervation, which causes weakness in the bowel motility, especially in children with spinal system anomalies, may increase the risk of perforation (8,9). Our case had a chronic constipation problem due to myelomeningocele. Although there is no information in the literature about how the length of the catheter in the abdomen affects the risk of perforation, the intra-abdominal peritoneal catheter was quite short in our case (about 10 cm). In our case, we think that the intraperitoneal portion of the catheter was too short, causing the catheter to remain in the same localization facilitated the formation of intestinal perforation with recurrent irritations. Shunt dysfunction and infection, which are the abdominal complication of the VP shunt, is defined as a result of examinations. CSF culture, cranial CT, abdominal X-ray, and abdominal CT help with identification. The most frequently isolated organism is *Escherichia Coli* (9).

Ultrasonography (US) usually provides sufficient information for the evaluation of intraabdominal complications of VP shunt. The most common intraabdominal complication is the pseudocysts, which are usually the liquid loculations formed at the distal end of the shunt catheter and which can be identified by the US. In the evaluation of complications such as catheter migration, the US may be inadequate. The most commonly described type of migration is the protrusion of the catheter tip through the anus. In patients with VP shunting, the location of the catheter tip, as well as whether there is folding in the catheter, should be considered during the radiological evaluation. In our case, no increase in the intraperitoneal fluid was observed, which is usually seen in shunt patients. In the axial CT sections, it was suspected that the catheter tip was in the lumen of the small bowel, and it was confirmed using 3D MPR CT images. In the presented case, the perforation diagnosis was made by abdominal CT. There was no evidence of meningitis. The

treatment of shunt-dependent gastro-intestinal tract perforation should be individual. Laparotomy should be performed to remove the shunt from the intestine and repair the fistula tract (1). There was no abscess or peritonitis in the abdomen. In cases where these complications are accompanied, laparotomy should be performed because the fistula tract will not close itself. The distal portion of the shunt should be revised with a new catheter. It should be kept in mind that there may be widespread adhesions, as in the case presented, and laparotomy incision should not be kept small.

Conclusion

The results of abdominal complications of VP shunts are excellent when diagnosed and treated early. Mortality and morbidity decrease significantly with early diagnosis and treatment, especially in asymptomatic bowel perforations. Because of adhesions, the surgical intervention must be performed with laparotomy.

Informed Consent: Verbal and written informed consent were obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

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

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

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Absence of the Left Circumflex Artery Detected by Coronary Computed Tomography Angiography

Sol Sirkümfleks Arter Yokluğunun Koroner Bilgisayarlı Tomografi ile Birlikte Saptanması

Aslı Tanrıvermiş Sayit, İlkay Çamlıdağ, Çetin Çelenk
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ABSTRACT

Congenital absence of the left circumflex artery (LCx) is a very rare congenital coronary anomaly. It is a benign incidental finding. Coronary computed tomography angiography (CTA) is the first choice imaging modality for non-invasive visualization of coronary artery anomalies. Also, it is fast and safe. Here, we present a case with an absent LCx detected by coronary CTA in a 20-year-old man with chest pain.

Keywords: Coronary computed tomography angiography, coronary arteries, anomalies, left circumflex artery

ÖZ

Sol sirkümfleks arterin konjenital yokluğu çok nadir görülen konjenital koroner bir anomalidir. İyi huylu tesadüfi bir bulgudur. Koroner bilgisayarlı tomografi anjiyografi, koroner arter anomalilerinin invazif olmayan görüntüleme yöntemleri arasında ilk tercih edilecek görüntüleme yöntemidir. Ayrıca, hızlı ve güvenilirdir. Biz burada, göğüs ağrısı olan 20 yaşında bir erkek hastada koroner bilgisayarlı tomografi anjiyografide saptanan sol sirkümfleks arter yokluğunu sunmayı amaçladık.

Anahtar Kelimeler: Koroner bilgisayarlı tomografi anjiyografi, koroner arterler, anomaliler, sol sirkümfleks arter

Introduction

Congenital anomalies of coronary arteries are uncommon, with an incidence between 0.64% and 1.3% (1). Although these anomalies are usually benign and patients are asymptomatic, it may sometimes cause life-threatening complications such as myocardial infarction, arrhythmia, or sudden death in 20% of patients (2). Coronary artery anomalies can be classified as anomalies and variations without a shunt, anomalies with a shunt, or congenital aneurysms. Anomalies and variations without a shunt include variations in coronary artery number, the origin of vessel ostium, myocardial bridging, segmental hypoplasia, stenosis, or atresia. Anomalies with a shunt include coronary artery fistulas and coronary arteries originating from the pulmonary artery (2). The congenital absence of the left circumflex artery (LCx) is very rare and results from the failure of LCx development in the left atrioventricular groove (3). Conventional coronary angiography (CCA) can be used for the diagnosis of coronary artery anomalies, but it is an invasive imaging method with a high radiation dose. Recently, coronary computed tomography angiography (CTA) has emerged as a non-invasive alternative for evaluation of coronary anatomy, particularly after the introduction of modern protocols allowing to perform coronary CTA with a low radiation dose (1). Moreover, it is a faster, safer, and non-invasive imaging modality with a higher accuracy rate. Here, we present a case with an absent LCx detected by coronary CTA in a 20-year-old man with chest pain.

Case Report

A 20-year-old male patient came to the emergency department with a complaint of chest pain. Physical examination and prior medical history were unremarkable. Cardiovascular examination was normal, with no additional sounds or murmur. Complete blood count, biochemistry, and cardiac enzymes [creatine kinase (CK), CK-MB, and troponin T] were within normal limits. Electrocardiogram revealed normal sinus rhythm, the normal axis with no ischemic changes. Also, echocardiography was normal, with no structural abnormalities, normal ejection fraction, and no regional dyskinesia. Upon continuation of the patient's angina, 64-section multislice coronary CTA was performed to exclude coronary artery disease or anomalies. Coronary CTA showed that the right coronary artery (RCA) originated from the right sinus of Valsalva, and the left main coronary artery (LMCA) originated from the left sinus Valsalva. Coronary CTA revealed a long LMCA (Figure 1), normal left anterior descending

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(LAD), and absence of LCx with superdominant RCA and no obstructive lesion of the coronary arteries (Figure 2). Lateral and posterior aspects of the left ventricle were supplied by a superdominant RCA and a large first diagonal artery (Figure 3). The patient was diagnosed with the absence of LCx. No treatment was planned because the patient had no arrhythmia. The patient was informed about his diagnosis, and he was discharged.

Informed consent was obtained from the patient.

Discussion

The congenital absence of LCx is very rare, and its incidence varies between 0.003-0.067% (3). Upon the absence of the LCx, the lateral wall of the left ventricle is supplied by a superdominant RCA or occasionally by multiple diagonal branches of LAD**.** Congenital absence of LCx is an incidental benign finding. However, it may cause significant symptoms in 20% of patients (4). Congenital coronary artery anomalies should be distinguished from pericarditis, myocarditis, myocardial infarction, and musculoskeletal tenderness, especially in patients with chest pain (5).

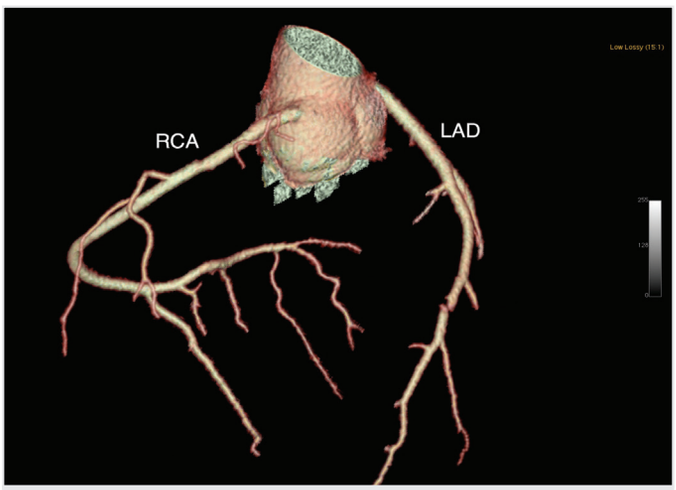

Figure 1. Three-dimensional volume-rendered (3D-VR) image shows the normal course of the right coronary artery and left anterior descending

RCA: right coronary artery, LAD: left anterior descending

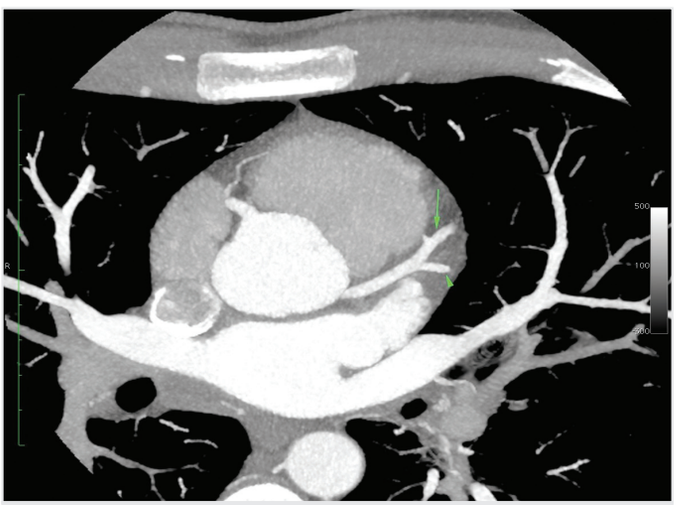

Figure 2. Coronary computed tomography angiography shows a long left main coronary artery, normal left anterior descending (arrow), first diagonal artery (arrowhead), and absence of left circumflex artery with superdominant right coronary artery

Transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), cardiac magnetic resonance imaging, coronary CTA and CCA can be used to diagnose coronary artery anomalies and to rule out other cardiac pathologies (4). TTE and TEE have limitations in diagnosing the coronary artery anomalies, including an inability to visualize the coronary arteries. CCA and coronary CTA are the preferred methods for the evaluation of coronary arteries (4). Asymptomatic patients with coronary artery disease who are low to an intermediate-risk group for the coronary artery disease, coronary BTA is the first choice imaging modality in order to exclude coronary artery anomalies due to being non-invasive, rapid, reliable and having a low radiation dose. Ghadri et al. (6) reported that the prevalence of coronary artery anomalies detected by coronary CTA was significantly higher than that of CCA (7.85% versus 2.02%; $p<0.01$). Also, coronary artery origin, course, termination of the coronary arteries, and their relationship to cardiac and non-cardiac structures can be better evaluated with coronary CTA than the CCA (4). Therefore, coronary CTA should be the first-line imaging method for the assessment of known or suspected coronary anomalies in patients with low risk for coronary artery disease**.** However, CCA should be performed in patients who are suspected of having coronary artery disease and will be undergoing interventional procedures during imaging (4). There is no specific treatment for the absence of LCx, but it should be differentiated from the total occlusion of Lcx because their treatment approach differs (4). If RCA is totally occluded in a patient with absent LCx, myocardial infarction may develop in the inferior, posterior, and lateral walls (5). Therefore, early diagnosis and treatment may be lifesaver in these patients.

In our case, the absence of LCx presented with superdominant RCA, and no stenosis or occlusion was detected in the coronary arteries. No specific treatment was given to the patient. The patient was discharged with information about his condition.

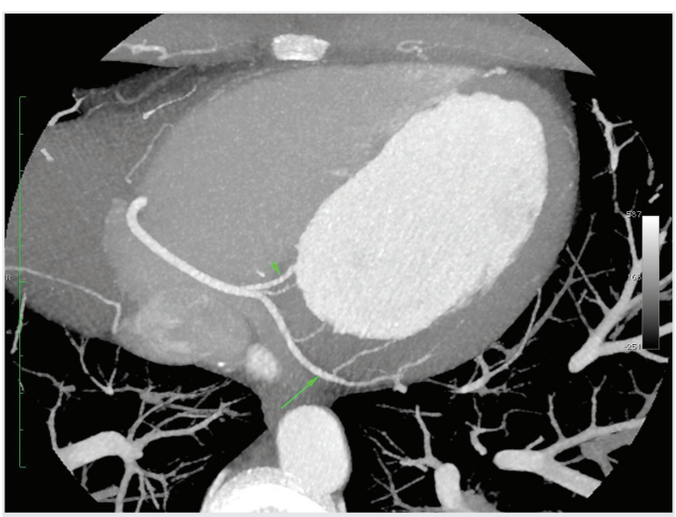

Figure 3. Coronary computed tomography angiography shows well-developed posterolateral branches (arrow) and posterior descending artery (arrowhead) of the right coronary artery

Conclusion

Congenital absence of LCx is an extremely rare anomaly of coronary arteries resulting from the failure of LCx development in the left atrioventricular groove. Coronary CTA should be the first-line imaging method for the assessment of known or suspected coronary anomalies in patients with a low risk for coronary artery disease**.** There is no specific treatment for the absence of LCx, but it should be differentiated from the total occlusion of LCx.

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

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

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Lumbar Ligamentum Flavum Cyst: Case Report

Lomber Düzeyde Ligamentum Flavum Kisti: Olgu Sunumu

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ABSTRACT

Ligamentum flavum cyst, a cystic lesion adjacent to the lumbar spine, is a rare cause of neurological symptoms and signs. It is usually seen in older ages. It is more common in the lower lumbar region than in the cervical region. Here, we aimed to discuss ligamentum flavum cysts in two cases.

In a 54-year-old male, a lumbar magnetic resonance imaging showed a ligamentum flavum cyst located at the right posterolateral of the spinal canal at the L3-L4 level, and spinal canal stenosis at this level. After the surgical removal of the cyst, the patient's symptoms entirely resolved. A 43-year-old female patient had a ligamentum flavum cyst on the left posterolateral of the spinal at L4-L5 level with thecal sac compression. Conservative treatment was planned, and the symptoms regressed during follow-up.

Keywords: Ligamentum flavum cyst, radiculopathy, lumbar vertebra, magnetic resonance imaging

ÖZ

Lomber vertebra komşuluğunda kistik bir lezyon olan ligamentum flavum kistleri nörolojik semptom ve bulguların nadir bir nedenidir. Genellikle ileri yaşlarda görülür. Alt lomber bölgede, servikal bölgeye göre daha sıktır. Burada iki olgu dahilinde ligamentum flavum kistlerini tartışmak amaçlanmıştır.

Elli dört yaşında erkek olguda, lomber magnetik rezonans görüntülemede, L3-L4 seviyesinde spinal kanal sağ posterolateralinde yerleşen bir ligamentum flavum kisti ve buna bağlı bu seviyede spinal kanalda daralma görüntülendi. Kist cerrahi yöntemle çıkartıldıktan sonra olgunun yakınmaları tamamen düzeldi. Kırk üç yaşında kadın olguda, L4-L5 düzeyinde sol posterolateralde tekal saka indentasyon gösteren, ligamentum flavum kisti saptandı. Hastaya konservatif tedavi planlandı ve takipte semptomların gerilediği görüldü.

Anahtar Kelimeler: Ligamentum flavum kisti, radikülopati, lomber vertebra, manyetik rezonans görüntüleme

Introduction

The term ligamentum flavum cyst is defined as a cystic formation arising from ligamentum flavum that is not lined with synovial epithelium (1). Ligamentum flavum cyst is a rare cause of spinal cord and nerve compression (2). It was first defined by Moiel et al. (3) in 1967. It occurs most frequently in the lower lumbar region (4). It may cause neurological complaints due to spinal canal stenosis or lumbar root compression (5). These cysts accompany degenerative changes in the spine. It can be distinguished from synovial and other degenerative spinal cysts based on localization and histopathological features (6). We aimed to present two cases of ligamentum flavum cysts that we diagnosed based on original magnetic resonance imaging (MRI) findings and confirmed one histopathologically.

Case Reports

Case 1

A lumbar MRI was requested for a 54-year-old male patient with low back pain, slow-developing gait disturbance, hip, and right leg pain. Neurological examination revealed normal motor functions, but sensory impairment in the right L4 dermatome. The patient's medical history included hypertension and diabetes. No pathology was observed in laboratory tests. Degenerative changes were observed on the direct X-ray of the lumbosacral vertebra. Multilevel facet arthropathy, more prominent in L3-L4, was observed in lumbar MRI. A 17x5.5 mm ligamentum flavum cyst, which was hypointense on T1-weighted images (T1WI) and hyperintense on T2-WI, was found at L3-L4 level. The cyst caused right lateral recess stenosis by compressing thecal sac and spinal

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cord from the right lateral side, and it was not related to the facet joint (Figure 1 a,b). At this level, significant stenosis was observed in the spinal canal due to cyst and ligamentum flavum hypertrophy. Since the patient refused, electromyography (EMG) was not performed. The cyst was surgically resected with hypertrophic ligamentum flavum, and partial L3-L4 hemilaminectomy was performed. Histopathological examination revealed myxoid and pseudocystic degeneration of the ligamentum flavum without synovial epithelium. In the postoperative period, the patient's symptoms improved, and he recovered without any problem. Informed consent was obtained.

Case 2

A 43-year-old female patient presented with chronic low back pain and progressive neurogenic claudication symptoms over a 6-month period. There were no features in her medical and family history. There was no motor or sensory disorder in her neurological examination. Deep tendon reflexes were normal. Laboratory tests were normal. MRI revealed a 11x8.5 mm ligamentum flavum cyst, which was hypointense on T1WI and hyperintense on T2WI, at L4-L5 level on the left with thecal sac indentation (Figure 2 a,b). Diffuse bulging of the disc and facet joint degeneration were detected at this level. EMG was not performed. Conservative treatment was planned because the patient did not accept the surgery, and the symptoms regressed during the follow-up. Informed consent was obtained.

Discussion

The term ligamentum flavum cyst is defined as a cystic formation originating from ligamentum flavum that is not lined with synovial epithelium (1). Ligamentum flavum cyst is a juxtafacet cyst, and it is thought that continuous stress caused by small recurrent trauma may cause cyst development (7).

While these cysts are frequently seen in lumbar vertebrae, they are also rarely found in cervical vertebrae (8). The most commonly reported level is L4-L5, the most mobile part of the vertebra, followed by L5-S1 and L3-L4 levels (4). Osteoarthritis, spondylosis, spondylolisthesis, and degenerative disc disease are common with vertebra cysts (9). Most ligamentum flavum cysts develop posterolaterally near the facet joint in the spinal canal (10). Most symptomatic cysts usually present with radiculopathy. The history and physical examination findings of these patients may resemble symptoms related to sciatica and disc herniation (11). Typically, cysts can cause radicular pain (97%), sensory (55%) or motor (39%) deficit, Lasèque sign (33%), abnormal reflexes (18%), and rarely present as cauda equina syndrome (1).

Ligamentum flavum cysts can be easily identified by MRI. The cysts are characteristically hypointense on T1WI and hyperintense on T2WI. The presence of blood, gas, air, or proteinaceous content may change the signal intensity (4). Conservative treatment has proved to be

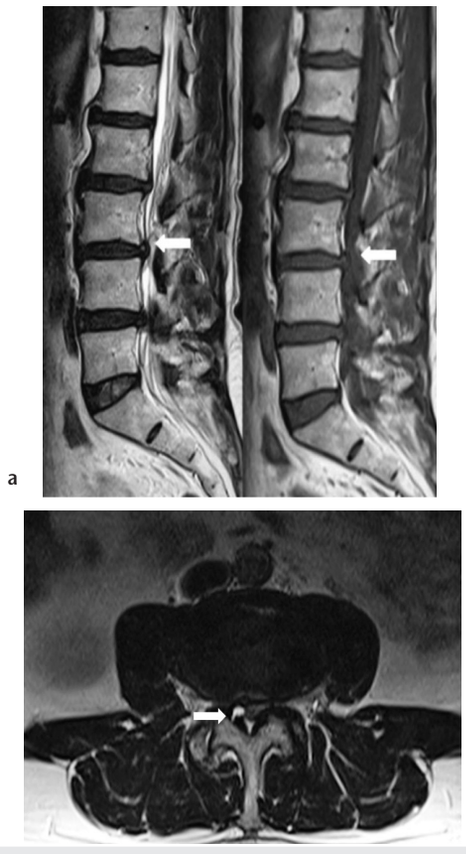

Figure 1. a) Sagittal T1-weighted imaging (T1WI) and T2-WI); b) axial magnetic resonance imaging showing cystic lesion (arrows) in the thickened ligamentum flavum at the L3-L4 intervertebral level, which is hypointense on T1WI and hyperintense on T2W images

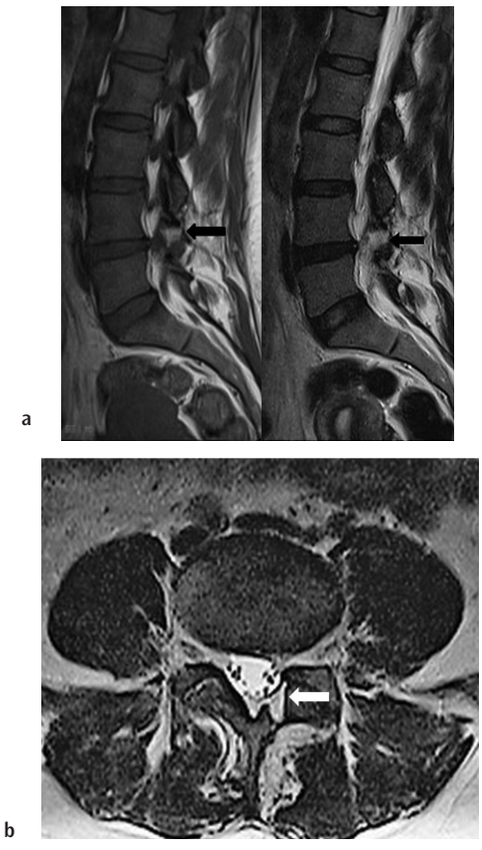

Figure 2. a) Sagittal T1-weighted imaging (T1WI) and T2-WI); b) Axial T2WI showing hyperintense cystic lesion (arrows) in the ligamentum flavum on the left at the L4-L5 intervertebral level

unsuccessful and has transient and unreliable short-term outcomes. Surgical treatment is the gold standard in patients with severe pain and neurological deficit (12). Surgical decompression with complete excision of the ligamentum flavum cyst is the most successful treatment strategy and has excellent results (12). Instrumentation is performed only if facetectomy is performed or other pathologies are present (8).

Although the ligamentum flavum cyst is a rare cause of spinal compression and radiculopathy, it should be considered in the differential diagnosis of cystic lesions of the lumbar spinal canal. Preoperative diagnosis is not easy due to its rare and nonspecific clinical and radiological findings. MRI is the best imaging method to help us with this.

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Isolated Esophageal İnvolvement in Pemphigus Vulgaris Confused with Esophageal Cancer

Pemfigus Vulgariste Özofagus Kanseri ile Karışan İzole Özofagus Tutulumu

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ABSTRACT

Pemphigus is a disease characterized by the formation of intraepithelial blisters due to acantholysis caused by immunoglobulin G antibodies against the keratinocyte cell surface holding the mucous membranes and skin. While the oral mucosa is the most affected region, all body cells with multilayered horizontal epithelia such as the conjunctiva, pharynx, larynx, esophagus, vagina, penis, and anus might be affected. Although few pemphigus cases with esophageal involvement have been reported, the incidence of actual involvement is thought to be higher. Our case was guided by an external endoscopy center because of the appearance of esophagus cancer. This pre-diagnosis was excluded in the endoscopic biopsy, and lesions regressed entirely with the treatment given for pemphigus. The co-existence of pemphigus vulgaris and esophagus squamous cell carcinoma has been reported. However, it has not been previously reported that the esophageal involvement of pemphigus, as in our case, has been confused with esophageal cancer. In this case report, we present a pemphigus case with isolated esophageal involvement in a pemphigus patient in clinical remission. We found it worthy of presentation because of the confusion with esophageal cancer due to an endoscopy result from an external center.

Keywords: Pemphigus, dysphagia, esophageal involvement, endoscopy

ÖZ

Pemfigus, mukozaları ve deriyi tutan keratinosit hücre yüzeyine karşı immünoglobulin G antikorların neden olduğu akantoliz nedeniyle intraepitelyal büllerin oluşması ile karakterize bir hastalıktır. Oral mukoza en çok etkilenen bölge iken, konjonktiva, yutak, larinks, özofagus, vajinal, penil ve anal mukoza gibi çok katmanlı epitelyumu olan tüm vücut alanları etkilenebilir. Pemfigus özofagus tutulumu olan az sayıda olgu bildirilmiş olmasına rağmen, gerçek tutulum insidansının daha yüksek olduğu düşünülmektedir. Olgumuz özofagus kanseri endoskopik görünümü nedeniyle dış merkezden hastanemize yönlendirilmişti. Bu ön tanı endoskopik biyopside dışlandı ve pemfigus için verilen tedavi ile lezyonlar tamamen geriledi. Literatürde, pemfigus vulgaris ve özofagus skuamöz hücreli karsinomun birlikte görüldüğü olgular bildirilmiştir. Ancak, bizim olgumuzda olduğu gibi pemfigusun özofagus tutulumunun özofagus kanseri ile endoskopik olarak karıştırıldığı bir olgu daha önce bildirilmemiştir. Bu olgu sunumunda, pemfigus vulgaris takibi sırasında izole özofagus tutulumu olan bir olgu sunuldu. Olgumuzu, dış merkez endoskopisinde özofagus kanseri ile tanıda karışıklık olması ve oral mukozal tutulum olmaksızın izole özofagus tutulumu göstermesi nedeniyle sunum yapmaya değer bulduk.

Anahtar Kelimeler: Pemfigus, disfaji, özofagus tutulumu, endoskopi

Introduction

Pemphigus is a disease characterized by the formation of intraepithelial blisters due to acantholysis caused by immunoglobulin G (IgG) antibodies against the keratinocyte cell surface holding the mucous membranes and skin (1). Pemphigus vulgaris (PV) is the most common and life-threatening subtype of pemphigus (1). While the oral mucosa is the most affected region, all body cells with multilayered horizontal epithelia such as the conjunctiva, pharynx, larynx, esophagus, vagina, penis and anus might be affected (2).

In this case report, we present a pemphigus case with isolated esophageal involvement in a pemphigus patient in clinical remission. We found it worthy of presentation because of the confusion with esophageal cancer (CA) due to an endoscopy result from an external center.

Case Report

A 55-year-old female patient complained of odynophagia and pain in her chest for about two months. The case was started proton pump inhibitor

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therapy and alginic acid at an external center with the diagnosis of esophagitis. Her symptoms did not improve. The case was diagnosed with a vegetative mass by esophagogastroduodenoscopy (EGD) and referred to gastroenterology unit of our hospital with the suspicion of esophageal CA. There was no biopsy at the external center, and the only suspicion of malignancy was noted due to endoscopic appearance and vegetative mass.

The patient was referred to our outpatient dermatology clinic from the gastroenterology department. She had been followed-up for pemphigus in our department since June 2008. No oral mucosal and skin lesions were observed on current physical examination (Figure 1). The patient's last pemphigus attack was two years ago in the form of eroded lesions in the oral mucosa. She had been in remission for one year and received prednisolone 4 mg once daily for three months. During endoscopy, a mucosal biopsy was recommended for the differential diagnosis of esophagus CA and esophageal involvement of pemphigus.

In the EGD, multiple erosions in the form of white plaques were observed on the esophageal surface (the lesion was seen to extend from the mucosa to the lumen in a single site), which continued 7-8 cm from 25 cm (Figure 2). It was observed that the esophageal mucosa was dissected when the endoscopic biopsy was performed. The endoscopic interpretation of the gastroenterologist was in the form of esophagitis dissecans superficialis (EDS) in favor of esophageal involvement by pemphigus.

The biopsy material was interpreted as insufficient, so the level of dissociation in the histopathology could not be seen clearly. However, there were no signs of malignancy in the biopsy, and the malignancy was excluded histopathologically. The case was diagnosed with PV with isolated esophageal involvement, both clinically and endoscopically. Thirty-two mg/day prednisolone and mycophenolate mofetil 360 mg twice a day were started. A control endoscopy was planned for the patient whose complaints regressed one month later. In the endoscopy, esophageal lesions regressed entirely (Figure 3). A gradual decrement was planned in the treatment of the patient whose lesions had regressed. Informed consent was obtained from the patient for the publication of this case report and images.

Discussion

PV is an uncommon autoimmune bullous disease in which bullae form as a result of acantholysis by IgG autoantibodies against intercellular antigens of stratified epithelia (1). PV can affect other mucosal surfaces such as those of the anus, genital mucosa, nasopharynx, conjunctivae, cervix, and esophagus (1,2). Although few cases with esophageal involvement of pemphigus have been reported, the incidence of actual involvement is thought to be higher (3)

Odynophagia and dysphagia are the most common symptoms of esophageal involvement. However, patients may be asymptomatic (3). In asymptomatic patients, most esophageal involvement is thought to be overlooked because endoscopy is not usually performed. Recent immunohistopathological studies have shown that esophageal involvement is higher than in previous reports (2). There are approximately 60 articles on PV involving the esophagus in the literature. The actual frequency is probably much higher. Blisters, erosions, and an easily separated esophageal mucosa (Nikolsky sign) are the most common findings on EGD. Calka et al. (2) found esophageal involvement in up to 46.15% PV patients by endoscopy. Mignogna et al. (4) found esophageal

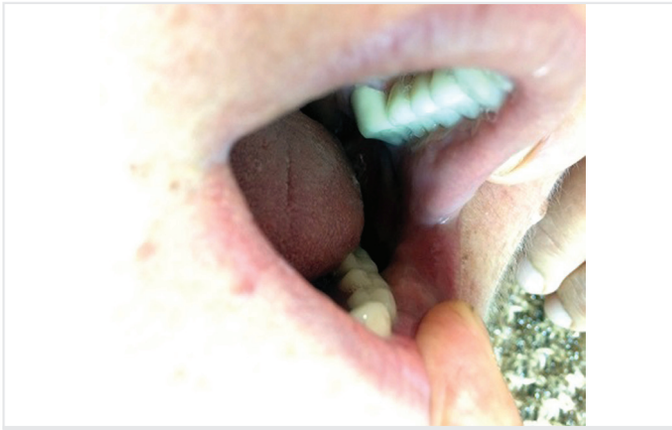

Figure 1. No oral mucosal lesions were observed in the present examination

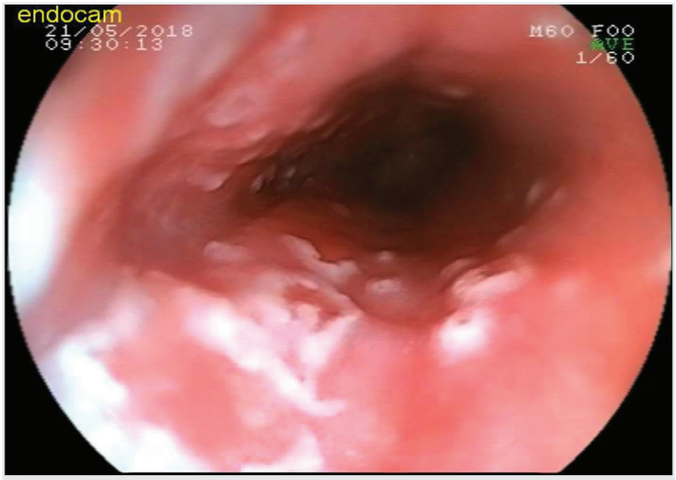

Figure 2. In the EGD, multiple erosions in the form of white plaque were observed on the esophageal surface (the lesion was seen to extend from the mucosa to the lumen in a single site), which continued 7-8 cm from 25 cm

EGD: esophagogastroduodenoscopy

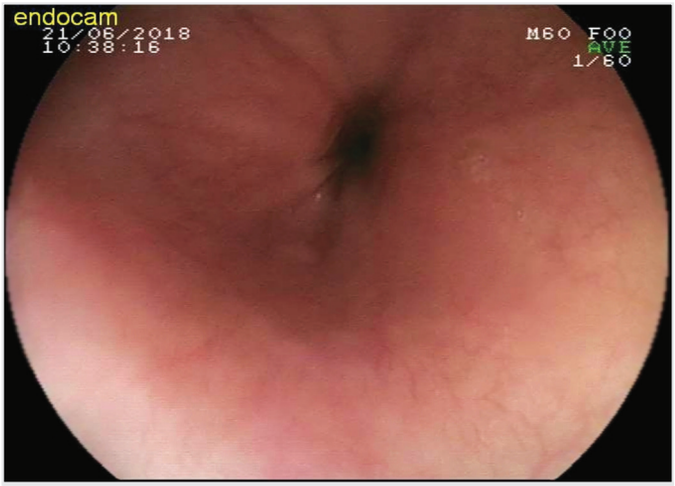

Figure 3. In the control endoscopy, esophageal lesions were completely regressed

involvement in five out of eight patients examined. Our case was referred by an external endoscopy center due to suspicion of esophageal CA. This pre-diagnosis was excluded in the endoscopic biopsy, and lesions regressed entirely with the treatment given for pemphigus.

The co-existence of PV and esophagus squamous cell carcinoma has been reported (5). However, it has not been previously reported that the esophageal involvement of pemphigus, as in our case, has been confused with esophageal CA. We excluded the suspicion of malignancy by esophageal biopsy.

Bullous diseases may influence the esophagus in such a way that there is sloughing of the entire mucous membrane (1). The composition of such an esophageal cast has been termed EDS (2). EDS is also incorporated with trauma, immunosuppression, smoking, and medication (5). This type of involvement may not always be seen in endoscopy, which may lead to confusion with other differential diagnoses such as candidal/infective esophagitis and steroid-induced esophagitis (6). In our case, we excluded malignancy and other preliminary diagnoses by biopsy, but because of the absence of full-thickness biopsy, we could not make a judgment about the place of decomposition and exact histopathological PV. At this stage, we endoscopically diagnosed PV in the patient, relying on the experience of the endoscopist. We also achieved a successful outcome with treatment for PV. In an endoscopy study, it was found that in skilled hands, the endoscopy was sufficient to determine the esophageal involvement of pemphigus (7). As in our case, endoscopic diagnosis can be made in those cases where there is inadequate material for a biopsy. However, the experience of the endoscopist and the suspicion of the diagnosis of pemphigus are important in these cases.

Esophageal involvement should be considered when there are symptoms such as dysphagia and odynophagia with a previous history of PV (8). The majority of patients with lesions in the esophagus are middle-aged women, as in our case. Most case reports in the literature define patients with PV as having either oral or cutaneous lesions at the time of diagnosis of esophageal involvement (9,10). At the same, in a study of esophageal involvement of pemphigus, oral mucosal involvement was reported in 87% of the patients (11). As in our case, isolated esophageal relapse is an unexpected condition without oral lesions.

We have described a case of PV in which the esophagus, which was previously misdiagnosed as esophagus CA, was seriously involved without skin or oropharynx involvement. Our case is valuable because it showed only isolated esophageal in a pemphigus patient in clinical remission without other skin and oral mucosa involvement. At the same time, no case has been reported in the literature in which esophageal involvement of pemphigus and esophagus CA were confused. For these reasons, we found it appropriate to publish.

Conclusion

Identification of the esophageal involvement of pemphigus may change the management requiring teamwork between dermatologists and the gastroenterologist. Endoscopic assessment is, therefore, necessary to discriminate between esophageal involvement of PV and other pathologies, which warrant significant differences in management. The endoscopic inspection should be applied carefully in talented hands for esophageal symptoms to decide the correct diagnosis and allow quick treatment.

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

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Development of Hodgkin Lymphoma in a Patient with Common Variable Immunodeficiency

Yaygın Değişken İmmün Yetmezlikli Hastada Hodgkin Lenfoma Gelişimi

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Anahtar Kelimeler: Yaygın değişken immün yetmezlik, Hodgkin hastalığı, lenfoma

Common variable immunodeficiency (CVID) is a primary immunodeficiency, which is characterized by insufficiency in the synthesis of immunoglobulins due to the disruption of B cell differentiation. The term "variable" in its name describes the heterogeneous clinical picture (infections, chronic lung disease, autoimmune diseases, gastrointestinal disorders, and malignancy) in this disease. Although the risk of developing malignancy in children with primary immunodeficiency is reported to be 4%, this rate is 10.000 times higher than healthy subjects of similar age. Non-Hodgkin lymphoma (NHL) accounts for 60% of malignancy in primary immunodeficiency patients (1). In the cohorts, the incidence of cancer in CVID patients was 15-21%. The most common malignancy was reported to be NHL, followed by gastric, breast, bladder, and cervix tumors (2-4). Our case shows that Hodgkin lymphoma may rarely develop in CVID and is presented to raise awareness.

Our 9-year-old patient had severe mental retardation and optic atrophy complications due to convulsion lasting 20 minutes on postnatal 35th day. He had used antiepileptic (carbamazepine) treatment that was started at the age of 5 months with the diagnosis of epilepsy for three years. Laboratory tests requested for frequent bronchitis (five per year), otitis (thirteen per year) and antibiotic use (each month) revealed hypogammaglobulinemia with immunoglobulin G (IgG): 365 mg/dL, IgA: <26 mg/dL, and IgM: <18 mg/dL. Lymphocyte subsets were normal. Anti-Rubella IgG was 19 U/mL, and anti-HBs was 148 mIU/mL in response to previous vaccines. Isohemagglutinin antibody was negative, and anti-HAV IgG (11.3 U/mL) and anti-CMV IgG (1 U/mL) titers against previous infections were weak positive. Fine needle aspiration biopsy of 3x4 cm lymphadenopathy (LAP) in the left cervical region, which was detected during intravenous immunoglobulin administration for the third time with the diagnosis of CVID, revealed abundant lymphoid cells, immunoblasts and Reed-Stenberg cells with distinct nuclei, some with single, some with more than one nucleus. Abdominal ultrasonography was normal. Neck ultrasonography showed a large number of pathological LAPs in the left jugular chain and supraclavicular region, with the largest being 32 mm in diameter in the left jugulodigastric region. Positron emission tomography/computed tomography revealed hypermetabolic LAPs in the left upper lower jugular and supraclavicular space in the left side of the neck (Figure 1 a,b), slightly increased uptake in the spleen parenchyma, and diffuse hypermetabolic appearance at the bone marrow, suggesting lymphoproliferative malignancy. Excisional biopsy specimens were positive for CD30/CD15, and Fascin staining (compatible with nodular sclerosis type), and the patient was diagnosed as Hodgkin lymphoma. EBV test by polymerase chain reaction was negative. (The patient's consent was obtained for presentation).

Despite the risk of toxicity, routine chemotherapy provided survival in 80% of patients with NHL. It has been proposed to reduce the dose of treatment, but survival in standard chemotherapy patients is reported to be better than in those receiving low-dose chemotherapy (1,5). In our case, Hodgkin lymphoma (stage 3A) was diagnosed five months after the diagnosis of CVID, and a reduced dose of ABVD (Adriamycin, Bleomycin, Vinblastin, Dacarbazine) was decided.

It should be known that the risk of malignancy is increased in CVID, and the physical examination should be performed in routine hospitalizations, and especially LAP should be considered. This will provide the patient with early diagnosis and treatment.

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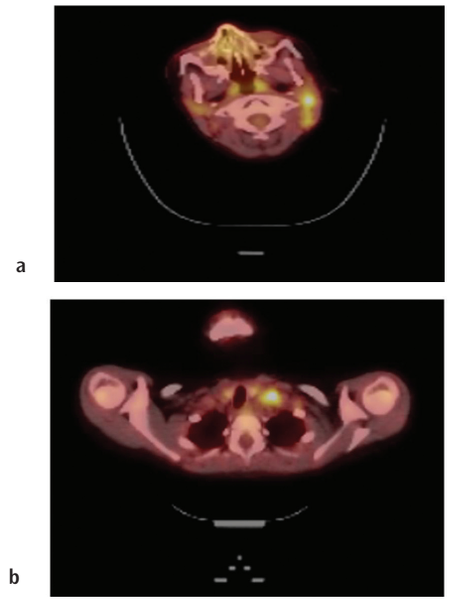

Figure 1. a,b) In the positron emission tomography/computed tomography report of our patient, mild hypermetabolic lymphadenopathy with conglomerate is observed on the left side of the neck (jugulo-digastric and supraclavicular lymph nodes)

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