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INSTRUCTIONS FOR AUTHORS

AIM AND SCOPE

The Journal will not consider manuscripts any that have been published elsewhere, or manuscripts that are being considered for another publication, or are in press. Studies previously announced in the congresses are accepted if this condition is stated. If any part of a manuscript by the same author(s) contains any information that was previously published, a reprint or a copy of the previous article should be submitted to the Editorial Office with an explanation by the authors

A technical review is performed to confirm that all of the required documentation has been submitted and to conduct a preliminary evaluation of the manuscript and supplementary files to assess suitability for the Journal. The manuscript will be returned to the Author in the event of any deficiency.

Pediatric Practice and Research Journal operates a blind review process. Contributions deemed suitable are then typically sent to a minimum of two independent expert reviewers in the field of study to assess the scientific quality of the paper.

The Editor/Editors are responsible for the final decision regarding acceptance or rejection of articles. The Editor's decision is final. If necessary, author(s) may be invited to submit a revised version of the manuscript. This invitation does not imply that the manuscript will be accepted for publication. Revised manuscripts must be sent to the Editorial Office within 4 (four) weeks, otherwise they will be considered as a new application. The corresponding author will be notified of the decision to accept or reject the manuscript for publication.

Statements and suggestions published in manuscripts are the authors' responsibility and do not reflect the opinions of the Editor, Associate Editors and the Editorial Board members.

The manuscript will not be returned to the authors whether the article is accepted or not. Copyright fee is not paid for the articles published in the journal. A copy of the journal will be sent to the corresponding author.

Language of the Journal

The official languages of the Journal are Turkish and English. The manuscripts that are written in Turkish have abstracts in English, which makes the abstracts available to a broader audience.

Authorship Criteria

After accepted for publication, all the authors will be asked to sign "Coyright Transfer Form" which states the following: " This work is not under active consideration for publication, has not been accepted for publication, nor has it been published, in full or in part (except in abstract form). I confirm that the study has been approved by the ethics committee. " All authors should agree to the conditions outlined in the form.

Pediatric Practice and Research Journal has agreed to use the standards of the International Committee of Medical Journal Editors. The author(s) should meet the criteria for authorship according to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. It is available at www.icmje.org.

Ethical Responsibility

The protocol of clinical research articles must be approved by the Ethics Committee.

In all studies conducted on humans, the "Material and Method" section was approved by the relevant committee or the Helsinki Declaration of Principles (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/).

It should be stated in the text that all persons included in the study signed the am Informed Consent Form ".

The articles submitted to the Pediatric Practice and Research Journal will be deemed to have been conducted in accordance with the Helsinki Declaration of Principles, and have received ethical and legal permissions and will not be held responsible.

If the "Animal" item was used in the study, the authors stated that in the Material and Method section of the article, they protect the animal rights in their studies in accordance with the principles of Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) and that they have received approval from the ethics committees of their institutions. must specify.

In case reports, Informed Consent a should be obtained from patients regardless of the identity of the patient.

If the article includes the institution (directly or indirectly) providing financial support for the commercial connection or work, the authors; the commercial product used, the drug, the company has no commercial relationship with, or if there is any relationship (consultant, other agreements, etc.), the editor must inform the presentation page.

If Ethics Committee Approval is required in the article; the received document should be sent with the article.

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The manuscript should be submitted to the Academic Plagiarism Prevention Program by the authors.

It is the authors' responsibility to ensure that the article complies with the ethical rules.

Policy of Screening for Plagiarism

The manuscripts are scanned by the Journal using the iThenticate program for determination of plagiarism and non-ethical situations. Pediatric Practice and Research Journal will immediately reject manuscripts leading to plagiarism.

TYPES OF MANUSCRIPT

Manuscripts should be submitted online via www.pprjournal.com

Original Articles should not exceed 3000 words and should be arranged under the headings of Abstract (not more than 300 words), Introduction, Materials and Methods, Results, Discussion, Conclusion and References.

Case Reports should not exceed 1000 words and 10 references, and should be arranged as follows: Abstract, Introduction, Case Report, Discussion and References. It may be accompanied by only one figure or table.

Letter to the Editor should not exceed 500 words. Short relevant comments on medical and scientific issues, particularly controversies, having no more than five references and one table or figure are encouraged. Where letters refer to an earlier published paper, authors will be offered right of reply.

Reviews are not accepted unless written on the invitation of the Editorial Board.

PREPARATION OF MANUSCRIPTS

All articles submitted to the Journal must comply with the following instructions:

a) Submissions should be doubled-spaced and typed in Arial 10 points.

b) All pages should be numbered consecutively in the top right-hand corner, beginning with the title page.

c) The title page should not include the names and institutions of the authors.

d) The manuscript should be presented in the following order: Title page, Abstract (English, Turkish), Keywords (English, Turkish), Introduction, Materials and Methods, Results, Discussion, Conclusion, Acknowledgements (if present), References, Figure Legends, Tables (each table, complete with title and foot-notes, on a separate page) and Appendices (if present) presented each on a separate page.

Title

The title should be short, easy to understand and must define the contents of the article.

Abstract

Abstract should be in both English and Turkish and should consist "Aim, Materials and Methods, Results and Conclusion". The purpose of the study, the setting for the study, the subjects, the treatment or intervention, principal outcomes measured, the type of statistical analysis and the outcome of the study should be stated in this section (up to 300 words). Abstract should not include reference. No abstract is required for the letters to the Editor.

Keywords

Not more than five keywords in order of importance for indexing purposes should be supplied below the abstract and should be selected from Index Medicus Medical Subject Headings (MeSH), available at www.nlm.nih.gov/meshhome.html.

Text

Authors should use subheadings to divide sections regarding the type of the manuscript as described above. Statistical methods used should be specified in the Materials and Methods section.

References

In the text, references should be cited using Arabic numerals in parenthesis in the order in which they appear. If cited only in tables or figure legends, they should be numbered according to the first identification of the table or figure in the text. Names of the journals should be abbreviated in the style used in Index Medicus. The names of all authors should be cited when there are six or fewer; when seven or more, the first three should be followed by et al. The issue and volume numbers of the referenced journal should be added.

References should be listed in the following form:

Journal article

Teke Z, Kabay B, Aytekin FO et al. Pyrrolidine dithiocarbamate prevents 60 minutes of warm mesenteric ischemia/reperfusion injury in rats. Am J Surg 2007;194(6):255-62.

Supplement

Solca M. Acute pain management: Unmet needs and new advances in pain management. Eur J Anaesthesiol 2002; 19(Suppl 25): 3-10.

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Online article not yet published in an issue

Butterly SJ, Pillans P, Horn B, Miles R, Sturtevant J. Off-label use of rituximab in a tertiary Queensland hospital. Intern Med J doi: 10.1111/j.1445-5994.2009.01988.x

Book

Sample1: Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

Sample 2: Sümbüloğlu K, Akdağ B. Regresyon Yöntemleri ve Korelasyon Analizi. Hatiboğlu Yayınevi: Ankara; 2007.

Chapter in a book

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. I n: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93113.

Journal article on the Internet

Abood S. Quality improvement initiative in nursing homes: The ANA acts in an advisory role. Am J Nurs [serial on the Internet] 2002 [cited 12 Aug 2002]; 102. Available from: www.nursingworld.org/AJN/2002/june/wawatch.htm

Website

Cancer-pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources [updated 16 May 2002; cited 9 Jul 2002]. Available from: www.cancer-pain.org

An organization as an author

The Intensive Care Society of Australia and New Zealand. Mechanical ventilation strategy in ARDS: Guidelines. Int Care J Aust 1996;164:282-4.

Acknowledgements

The source of financial grants and the contribution of colleagues or institutions should be acknowledged.

Tables

Tables should be complementary, but not duplicate information contained in the text. Tables should be numbered consecutively in Arabic numbers, with a descriptive, self-explanatory title above the table. All abbreviations should be explained in a footnote. Footnotes should be designated by symbols in the following order: *,†, ‡, §, ¶.

Figures

All illustrations (including line drawings and photographs) are classified as figures. Figures must be added to the system as separate .jpg or .gif files (approximately 500x400 pixels, 8 cm in width and at least 300 dpi resolution). Figures should be numbered consecutively in Arabic numbers and should be cited in parenthesis in consecutive order in the text.

Figure Legends

Legends should be self-explanatory and positioned on a separate page. The legend should incorporate definitions of any symbols used and all abbreviations and units of measurements should be explained. A letter should be provided stating copyright authorization if figures have been reproduced from another source.

Measurements and Abbreviations

All measurements must be given in metric system (Système International d'Unités, SI). Example: mg/kg, µg/kg, mL, mL/kg, mL/kg/h, mL/kg/min, L/min, mmHg, etc. Statistics and measurements should always be given in numerals, except where the number begins a sentence. When a number does not refer to a unit of measurement, it is spelt out, except where the number is greater than nine.

Abbreviations that are used should be defined in parenthesis where the full word is first mentioned. Some common abbreviations can be used, such as iv, im, po, and sc.

Drugs should be referred to by their generic names, rather than brand names.

Editorial Correspondence

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YAZARLARA BİLGİ

AMAÇ ve KAPSAM

Pediatric Practice and Research Dergisi, dört ayda bir yayımlanır ve üç sayı ile bir cilt tamamlanır. Dergi; pediatri ile ilgili tüm nitelikli klinik ve deneysel araştırmaları, olgu sunumlarını ve editöre mektupları yayımlar.

Pediatric Practice and Research Dergisi, bilimsel yayınlara açık erişim sağlar. Dergi basımından hemen sonra, makalelerin tam metinlerine ücretsiz ulaşılabilir.

Dergide yayımlanmak üzere gönderilen yazıların daha önce başka bir yerde yayımlanmamış veya yayımlanmak üzere gönderilmemiş olması gerekir. Daha önce kongrelerde sunulmuş çalışmalar, bu durum belirtilmek koşuluyla kabul edilir. Makale, yazar(lar) ın daha önce yayımlanmış bir yazısındaki konuların bir kısmını içeriyorsa bu durum belirtilmeli ve yeni yazı ile birlikte önceki makalenin bir kopyası da Yayın Bürosu'na gönderilmelidir.

Gerekli tüm belgelerin sunulduğunu teyit etmek ve dergiye uygunluğunu değerlendirmek için makale ve ek dosyaların ön değerlendirmesini yapmak üzere teknik bir inceleme yapılır. Herhangi bir eksiklik olması halinde makale yazara iade edilecektir. Pediatric Practice and Research Dergisi kör bir inceleme süreci yürütmektedir. Uygun görülen yazılar daha sonra makalenin bilimsel kalitesini değerlendirmek için çalışma alanında en az iki bağımsız uzmana gönderilir. Editör / Editörler makalelerin kabulü veya reddi ile ilgili nihai karardan sorumludur.

Editörün kararı kesindir. Gerekli olduğu durumlarda, yazar(lar) dan düzeltme istenebilir. Yazardan düzeltme istenmesi, yazının yayımlanacağı anlamına gelmez. Bu düzeltmelerin en geç 21 gün içinde tamamlanıp dergiye gönderilmesi gereklidir. Aksi halde yeni başvuru olarak değerlendirilir. Sorumlu yazara yazının kabul veya reddedildiğine dair bilgi verilir.

Dergide yayımlanan yazıların etik, bilimsel ve hukuki sorumluluğu yazar(lar)a ait olup Editör, Editör Yardımcısı ve Yayın Kurulu'nun görüşlerini yansıtmaz.

Dergide yayımlanması kabul edilse de edilmese de, yazı materyali yazarlara geri verilmez. Dergide yayımlanan yazılar için telif hakkı ödenmez. Bir adet dergi, sorumlu yazara gönderilir.

Derginin Yazı Dili

Derginin yazı dili Türkçe ve İngilizcedir. Dili Türkçe olan yazılar, İngilizce özetleri ile yer alır. Yazının hazırlanması sırasında, Türkçe kelimeler için Türk Dil Kurumundan (www.tdk.gov.tr), teknik terimler için Türk Tıp Terminolojisinden (www.tipterimleri.com) yararlanılabilir.

Yazarlık Kriterleri

Dergide yayınlanması uygun bulunan tüm yazıların araştırma ve yayın etiğine uygun hazırlandığı, varsa sağlanan fonun kaynağının tanımlandığı, başka yerde yayımlanmadığı veya yayımlanmak üzere gönderilmediği, çalışmaya katılan tüm yazarlar tarafından yazının son halinin onaylandığı, yayımlanacak yazı ile ilgili telif haklarının dergiye devredildiği, tüm yazarların imzaları ile "Yayın Hakkı Devir Formu"nda belirtilmesi gerekir.

Pediatric Practice and Research Dergisi, Uluslararası Tıp Dergileri Editörleri Kurulu'nun (International Committee of Medical Journal Editors) "Biyomedikal Dergilere Gönderilen Makalelerin Uyması Gereken Standartlar: Biyomedikal Yayınların Yazımı ve Baskıya Hazırlanması (Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication)" standartlarını kullanmayı kabul etmektedir. Bu konudaki bilgiye www.icmje.org adresinden ulaşılabilir.

Etik Sorumluluk

Etik Sorumluluk / Kurallar: Klinik araştırma makalelerinin protokolü Etik Komitesi tarafından onaylanmış olmalıdır.

İnsanlar üzerinde yapılan tüm çalışmalarda "Gereç ve Yöntem" bölümünde çalışmanın ilgili komite tarafından onaylandığı veya çalışmanın Helsinki İlkeler Deklarasyonu'na (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/) uyularak gerçekleştirildiğine dair bir cümle yer almalıdır.

Çalışmaya dahil edilen tüm kişilerin Bilgilendirilmiş Onam Formu'nu imzaladığı metin içinde belirtilmelidir.

Pediatric Practice and Research Dergisi'ne gönderilen makalelerdeki çalışmaların Helsinki İlkeler Deklarasyonu'na uygun olarak yapıldığı, kurumsal etik ve yasal izinlerin alındığı varsayılacak ve bu konuda sorumluluk kabul edilmeyecektir.

Çalışmada "Hayvan" öğesi kullanılmış ise yazarlar, makalenin Gereç ve Yöntem bölümünde hayvan haklarını Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) prensipleri doğrultusunda koruduklarını, çalışmalarında ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadır.

Olgu sunumlarında hastanın kimliğinin ortaya çıkmasına bakılmaksızın hastalardan "Bilgilendirilmiş rıza" alınmalıdır.

Makalede ticari bağlantı veya çalışma için maddi destek veren kurum (doğrudan veya dolaylı) mevcut ise yazarlar; kullanılan ticari ürün, ilaç, firma ile ticari hiçbir ilişkisinin olmadığını veya varsa nasıl bir ilişkisinin olduğunu (konsültan, diğer anlaşmalar vs.), editöre sunum sayfasında bildirmek zorundadır.

Makalede Etik Kurul Onayı alınması gerekli ise; alınan belge makale ile birlikte gönderilmelidir.

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Makale yazarlar tarafından akademik intihal önleme programından geçirilmelidir.

Makalenin etik kurallara uygunluğu yazarların sorumluluğundadır.

İntihal Taraması Politikası

Makaleler, intihal ve etik olmayan durumların belirlenmesi için iThenticate programı kullanılarak Journal tarafından taranır. Pediatric Practice and Research Dergisi intihallere yol açan makaleleri derhal reddedecektir.

YAZI TÜRLERİ

Yazılar, elektronik ortamda www.pprjournal.com adresine gönderilir.

Orijinal makaleler, 3000 sözcük sayısını aşmamalı, "Öz (en fazla 300 kelime), Giriş, Gereç ve Yöntem, Bulgular, Tartışma, Sonuç, Kaynaklar" bölümlerinden oluşmalıdır.

Olgu Sunumu, "Öz, Giriş, Olgu Sunumu, Tartışma, Kaynaklar" şeklinde düzenlenmelidir. En fazla 1000 sözcük ile sınırlıdır. Sadece bir tablo veya şekil ile desteklenebilir.

Editöre Mektup, yayımlanan metinlerle veya mesleki konularla ilgili olarak 500 sözcüğü aşmayan ve beş kaynak ile bir tablo veya şekil içerecek şekilde yazılabilir. Ayrıca daha önce dergide yayınlanmış metinlerle ilişkili mektuplara cevap hakkı verilir.

Yayın Kurulu'nun daveti üzerine yazılanlar dışında derleme kabul edilmez.

MAKALENİN HAZIRLANMASI

Dergide yayınlanması istenilen yazı için aşağıdaki kurallara uyulmalıdır.

a) Yazı; iki satır aralıklı olarak, Arial 10 punto ile yazılmalıdır.
b) Sayfalar başlık sayfasından başlamak üzere, sağ üst köşesinde numaralandırılmalıdır.
c) Online makale sistemine yüklenen word dosyasının başlık sayfasında (makalenin adını içeren başlık sayfası), yazarlara ait isim ve kurum bilgileri yer almamalıdır.
d) Makale, şu bölümleri içermelidir: Her biri ayrı sayfada yazılmak üzere; Türkçe ve İngilizce Başlık Sayfası, Öz, Abstract, Anahtar Sözcükler, Keywords, Giriş, Gereç ve Yöntem, Bulgular, Tartışma, Sonuç, Açıklamalar (varsa), Kaynaklar, Şekil Alt Yazıları, Tablolar (başlıkları ve açıklamalarıyla beraber), Ekler (varsa).

Yazının Başlığı

Kısa, kolay anlaşılır ve yazının içeriğini tanımlar özellikte olmalıdır.

Özetler

Türkçe (Öz) ve İngilizce (Abstract) olarak yazılmalı, Amaç, Gereç ve Yöntem, Bulgular ve Sonuç (Aim, Materials and Methods, Results, Conclusion) olmak üzere dört bölümden oluşmalı, en fazla 300 sözcük içermelidir. Araştırmanın amacı, yapılan işlemler, gözlemsel ve analitik yöntemler, temel bulgular ve ana sonuçlar belirtilmelidir. Özette kaynak kullanılmamalıdır. Editöre mektup için özet gerekmemektedir.

Anahtar Sözcükler

Türkçe Öz ve İngilizce Abstract bölümünün sonunda, Anahtar Sözcükler ve Keywords başlığı altında, bilimsel yazının ana başlıklarını yakalayan, Index Medicus Medical Subject Headings (MeSH)'e uygun olarak yazılmış en fazla beş anahtar sözcük olmalıdır. Anahtar sözcüklerin, Türkiye Bilim Terimleri'nden (www.bilimterimleri.com) seçilmesine özen gösterilmelidir.

Metin

Yazı metni, yazının türüne göre yukarıda tanımlanan bölümlerden oluşmalıdır. Uygulanan istatistiksel yöntem, Gereç ve Yöntem bölümünde belirtilmelidir.

Kaynaklar

Pediatric Practice and Research Dergisi, Türkçe kaynaklardan yararlanmaya özel önem verdiğini belirtir ve yazarların bu konuda duyarlı olmasını bekler.

Kaynaklar metinde yer aldıkları sırayla, cümle içinde atıfta bulunulan ad veya özelliği belirten kelimenin hemen bittiği yerde ya da cümle bitiminde noktadan önce parantez içinde Arabik rakamlarla numaralandırılmalıdır. Metinde, tablolarda ve şekil alt yazılarında kaynaklar, parantez içinde Arabik numaralarla nitelendirilir. Sadece tablo veya şekil alt yazılarında kullanılan kaynaklar, tablo ya da şeklin metindeki ilk yer aldığı sıraya uygun olarak numaralandırılmalıdır. Dergi başlıkları, Index Medicus'ta kullanılan tarza uygun olarak kısaltılmalıdır. Kısaltılmış yazar ve dergi adlarından sonra nokta olmamalıdır. Yazar sayısı altı veya daha az olan kaynaklarda tüm yazarların adı yazılmalı, yedi veya daha fazla olan kaynaklarda ise üç yazar adından sonra et al. veya ve ark. yazılmalıdır. Kaynak gösterilen derginin sayı ve cilt numarası mutlaka yazılmalıdır.

Kaynaklar, yazının alındığı dilde ve aşağıdaki örneklerde görüldüğü şekilde düzenlenmelidir.

Dergilerdeki yazılar

Teke Z, Kabay B, Aytekin FO et al. Pyrrolidine dithiocarbamate prevents 60 minutes of warm mesenteric ischemia/reperfusion injury in rats. Am J Surg 2007;194(6):255-62.

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Ek sayı (Supplement)
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Henüz yayınlanmamış online makale
Butterly SJ, Pillans P, Horn B, Miles R, Sturtevant J. Off-label use of rituximab in a tertiary Queensland hospital. Intern Med J doi: 10.1111/j.1445-5994.2009.01988.x

Kitap
Örnek 1: Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.
Örnek 2: Sümbüloğlu K, Akdağ B. Regresyon Yöntemleri ve Korelasyon Analizi. Hatiboğlu Yayınevi: Ankara; 2007.

Kitap bölümü
Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. I n: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93113.

İnternet makalesi
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Yazar olarak bir kuruluş
The Intensive Care Society of Australia and New Zealand. Mechanical ventilation strategy in ARDS: Guidelines. Int Care J Aust 1996;164:282-4.

Açıklamalar
Varsa finansal kaynaklar, katkı sağlayan kurum, kuruluş ve kişiler bu bölümde belirtilmelidir.

Tablolar
Tablolar metni tamamlayıcı olmalı, metin içerisinde tekrarlanan bilgiler içermemelidir. Metinde yer alma sıralarına göre Arabik sayılarla numaralandırılıp tablonun üstüne kısa ve açıklayıcı bir başlık yazılmalıdır. Tabloda yer alan kısaltmalar, tablonun hemen altında açıklanmalıdır. Dipnotlarda sırasıyla şu semboller kullanılabilir: *, †, ‡, §, ¶.

Şekiller
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Metin içindeki kısaltmalar, ilk kullanıldıkları yerde parantez içinde açıklanmalıdır. Bazı sık kullanılan kısaltmalar; iv, im, po ve sc şeklinde yazılabilir.

İlaçların yazımında jenerik isimleri kullanılmalıdır.

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Assessment of Cardiac Electrophysiological Alterations in Physically Active Children Using Ventricular Repolarization Parameters and Index of Cardiac Electrophysiological Balance

Kardiyak Elektrofizyolojik Değişikliklerin Fiziksel Olarak Aktif Çocuklarda Ventriküler Repolarizasyon Parametreleri ve Kardiyak Elektrofizyolojik Denge İndeksi (iCEB) Kullanılarak Değerlendirilmesi

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Abstract

Aim: Regular physical activity induces cardiovascular adaptations in children, which may affect ventricular repolarization which leads to arrhythmogenic risk. This study evaluates cardiac electrophysiological changes in children engaged in regular sports activity, using electrocardiographic ventricular repolarization parameters and the index of cardiac electrophysiological balance (iCEB), comparing them with non-athletic peers.

Material and Method: A total of 160 healthy children aged 5–18 years were enrolled, including 79 athletes and 81 non-athletes. Athletes had engaged in organized sports for at least 1 year, with a minimum frequency of three 60-minute sessions per week. Baseline demographics, blood pressure, and electrocardiographic variables (QT, QTc, Tp-e, iCEB, and iCEBc) were recorded and analyzed.

Results: Sinus bradycardia was observed in 26.4% of athletes. Heart rate was significantly lower in athletes compared to controls ($p<0.001$). Prolonged PR, QRS, QT, and Tp-e intervals were noted in the athletic group ($p<0.05$). iCEBc values were significantly lower in the athlete group, suggesting altered electrophysiological balance. No pathological ECG findings requiring sports disqualification were identified.

Conclusion: Physiological adaptations in athletic children can lead to measurable alterations in cardiac electrophysiology. Evaluation of repolarization parameters and iCEB may aid in early identification of children at risk of arrhythmia, thereby enhancing preparticipation cardiovascular screening protocols.

Keywords: Pediatric sports cardiology, electrocardiography, ventricular repolarization, iCEB, arrhythmia risk

Öz

Amaç: Düzenli fiziksel aktivite, çocuklarda kardiyovasküler adaptasyonlara yol açar ve bu durum ventriküler repolarizasyonu etkileyerek aritmojenik risk oluşturabilir. Bu çalışma, düzenli spor aktivitesi yapan çocuklarda elektrokardiyografik ventriküler repolarizasyon parametreleri ve kardiyak elektrofizyolojik denge indeksi (iCEB) kullanılarak kardiyak elektrofizyolojik değişiklikleri değerlendirmeyi ve bunları atletik olmayan akranları ile karşılaştırmayı amaçlamaktadır.

Gereç ve Yöntem: 5–18 yaş arasında toplam 160 sağlıklı çocuk çalışmaya dahil edilmiştir; bunların 79'u sporcu, 81'i ise spor yapmayanlardan oluşmaktadır. Sporcular en az 1 yıldır düzenli olarak haftada üç kez 60 dakikalık organize spor aktivitelerine katılmaktadır. Temel demografik veriler, kan basıncı ve elektrokardiyografik değişkenler (QT, QTc, Tp-e, iCEB ve iCEBc) kaydedilip analiz edilmiştir.

Bulgular: Sporcuların %26,4'ünde sinüs bradikardisi gözlenmiştir. Sporcuların kalp hızı, kontrol grubuna göre anlamlı derecede düşük bulunmuştur ($p<0,001$). Atlet grubunda PR, QRS, QT ve Tp-e interval sürelerinde uzama saptanmıştır ($p<0,05$). iCEBc değerleri atlet grubunda anlamlı derecede daha düşük olup, elektrofizyolojik dengenin değiştiğini düşündürmektedir. Spor yapmayı engelleyecek patolojik EKG bulgusu tespit edilmemiştir.

Sonuç: Atletik çocuklarda fizyolojik adaptasyonlar kardiyak elektrofizyolojide ölçülebilir değişikliklere yol açabilir. Repolarizasyon parametreleri ve iCEB'nin değerlendirilmesi, aritmi riski taşıyan çocukların erken tespitinde yardımcı olabilir ve böylece spor öncesi kardiyovasküler tarama protokollerinin etkinliğini artırabilir.

Anahtar Kelimeler: Pediatrik spor kardiyolojisi, elektrokardiyografi, ventriküler repolarizasyon, iCEB, aritmi riski

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1. INTRODUCTION

The increasing emphasis on physical fitness and its widely acknowledged benefits has resulted in a surge in organized sports participation among children and adolescents worldwide. Physical activity is not only instrumental in enhancing musculoskeletal strength and metabolic efficiency but also plays a vital role in promoting cardiovascular health from an early age. However, as the pediatric population increasingly engages in competitive sports, concerns about exercise-induced cardiac alterations and their potential to unmask latent arrhythmogenic conditions have gained prominence (1,2).

Regular endurance training elicits several physiological changes in the cardiovascular system, collectively known as the "athlete's heart." These adaptations include sinus bradycardia, increased stroke volume, and ventricular hypertrophy (3,4)—phenomena largely attributed to enhanced parasympathetic tone and myocardial efficiency. While typically benign, these changes can sometimes overlap with pathological features seen in cardiomyopathies and conduction disorders, thereby complicating clinical assessments.

Parameters of ventricular repolarization, which is the interval from the beginning of the QRS complex to the end of the T wave on the electrocardiogram, derived from surface electrocardiography (ECG)—such as QT interval, corrected QT (QTc), and the T-peak to T-end interval (Tp-e)—serve as useful non-invasive markers in evaluating electrical heterogeneity and arrhythmogenic potential (5,6). In recent years, the index of cardiac electrophysiological balance (iCEB), calculated as the QT interval divided by the QRS duration (QT/QRS), has been introduced as a novel marker to assess the balance between cardiac depolarization and repolarization. It provides an electrocardiographic surrogate for the cardiac wavelength (λ), which is pivotal in understanding arrhythmogenesis (7-9).

Despite the growing body of literature on iCEB in adult populations, particularly in the context of drug-induced torsadogenic risk, its application in pediatric sports cardiology remains sparse . Our study is one of the first to explore iCEB and its heart rate–corrected version (iCEBc) in healthy children participating in organized sports. By comparing these indices and classical repolarization parameters between athletic and non-athletic children, we aim to contribute valuable insights into their utility in preparticipation cardiovascular risk assessment.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara Atatürk Sanatorium Training and Research Hospital Scientific Studies Ethics Committee (Date: 17.07.2024, Decision No: 120). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants and their legal guardians.

Study Design and Population

This prospective observational study was conducted at the Pediatric Cardiology outpatient clinic of the University of Health Sciences, Ankara Atatürk Sanatoryum Training and Research Hospital, between July 2024 and February 2025. A total of 160 healthy children and adolescents aged 5–18 years were enrolled. The study population was divided into two groups:

- **Athlete group (n=79):** Participants who had been regularly engaging in organized sports activities for at least one year, with a minimum of three training sessions per week, each lasting no less than 60 minutes.
- **Control group (n=81):** Age- and sex-matched children with no history of regular sports participation.

Exclusion criteria included the presence of congenital heart disease, chronic illness, any form of arrhythmia, or use of medications known to affect cardiac conduction or repolarization.

Clinical and Anthropometric Evaluation

All participants underwent a detailed medical history assessment and physical examination. Data collected included age, sex, body weight, height, body mass index (BMI), and brachial blood pressure. BMI was calculated using the standard formula: weight (kg) / height^2 (m^2).

Blood pressure measurements were taken in a seated position after 5 minutes of rest using an automated upper-arm blood pressure monitor (NIHON KOHDEN BSM-2301K). Participants were instructed to avoid talking or moving during the measurement.

Electrocardiographic Assessment

A standard 12-lead resting electrocardiogram (ECG) was recorded using a Nihon Kohden ECG-2350 device at a paper speed of 25 mm/s and a voltage calibration of 10 mm/mV. The following parameters of all ECGs were reviewed independently by one experienced blinded pediatric cardiologist (**Figure 1**):

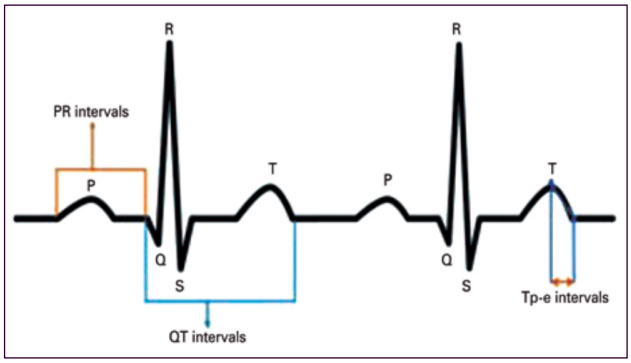

Figure 1. Demonstration of PR, QT and Tp-e intervals in electrocardiogram

- Heart rate (beats per minute)
- PR interval (ms) was measured from the first visible upward of the P wave to the QRS complex starting point
- QRS duration (ms) was calculated as the time from the beginning of the Q wave to the end of the S wave.
- QT interval (ms) was defined as from the beginning of the QRS complex to the end of the T wave
- Corrected QT (QTc) using Bazett's formula (10) (QT/√RR)
- Tp-e interval (ms), defined as the interval between the peak and end of the T wave
- Tp-e/QT and Tp-e/QTc ratios

In addition, the index of cardiac electrophysiological balance (iCEB) was calculated as QT/QRS, and the corrected index (iCEBc) was calculated as QTc/QRS.

Classification of Sports Activity

Athletic participants were further categorized according to the cardiovascular demands of their sports based on the Bethesda classification (11):

- Low demand (e.g., golf, cricket)
- Low- moderate demand (e.g., table tennis, volleyball)
- Moderate demand (e.g., football, swimming)
- High moderate demand (e.g., basketball, wrestling)
- High demand (e.g., rowing, boxing)

Training frequency (days/week), duration (minutes/session), and total training experience (months/years) were recorded.

Statistical Analysis

Statistical analysis was conducted using SPSS version 25.0 (IBM Corp., Armonk, NY). Data distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean±standard deviation or median (interquartile range) as appropriate. Categorical variables were expressed as frequencies and percentages.

Group comparisons were made using the independent samples t-test or Mann-Whitney U test for continuous variables and chi-square test for categorical variables. Correlation coefficients and statistical significances for relationships between variables, at least one of which was not normally distributed or ordinal, were calculated using the Spearman Test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

The study included 160 participants, consisting of 93 males (58.1%) and 67 females (41.9%), with a mean age of 11.9±2.9 years. The athlete group (n=79) and the control group (n=81) were similar in terms of age, sex distribution, height, weight, and body mass index (BMI) (p>0.05 for all). Mean systolic and diastolic blood pressures were also comparable between the two groups (**Table 1**).

Table 1. Demographic and Clinical Characteristics of Study Groups

	Athlete (n=79)	Control (n=81)	P
Gender(female/male)	29/50	38/43	0.19
Age (years)	12.05±2.91*	12.71±3.33*	0.18
Height (cm)	152.17±19*	154.29±19.40*	0.48
Weight (kg)	46.07±16.33*	46.39±17.29*	0.9
BMI (kg/m^2)	19.57±4.10*	18.80±3.49*	0.4
SBP (mmHg)	110.91±10.02*	111.39±9.52*	0.94
DBP (mmHg)	62.27±7.95*	63.71±7.73*	0.13

* Mean±standard deviation, BMI: Body mass index=weight(kg)/height(meter)^2. SBP: Systolic blood pressure. DBP: Diastolic blood pressure.

Sports Characteristics

Among the athlete group, the average duration of sports participation was 2.6±1.1 years. Most participants (60.8%) engaged in sports with moderate cardiovascular demand such as soccer, swimming, and gymnastics. The median training frequency was 3 sessions per week, with each session lasting approximately 90 minutes.

Electrocardiographic Findings

- Sinus bradycardia was the most prevalent finding in athletes (26.4% vs. 1.2% in controls, p<0.001). In other words, heart rate was significantly lower in the athlete group (p<0.001).
- Other physiologic ECG variants observed in athletes included early repolarization (19%), incomplete right bundle branch block (15.2%), and first-degree AV block (6.3%).
- When comparing parameters of ventriculer repolarization and iCEB between groups, the following significant differences were noted (**Table 2**):

Table 2. Comparison of Ventricular Repolarization Parameters and iCEB Between Groups

	Athlete (n=79)	Control (n=81)	p
Heart rate(bpm)	75.13±16.41	82.70±14.36	0.001
PR(msn)	136.34±19.67	129.87±17.48	0.046
QRS(msn)	79.87±9.72	75.82±11.03	0.025
QT(msn)	367.18±32.09	351.08±28.25	0.001
QTc(Bazett)***	405.20±21.87	408.11±18.82	0.426
Tp-e(msn)	73.41±8.72*	70.11±10.56*	0.038
iCEB	4.65±0.68*	4.70±0.68*	0.663
iCEBc	5.08±0.82*	5.49±0.87*	0.019
Tp-e/QT	0.19(0.14-0.28)**	0.19(0.11-0.26)**	0.982
Tp-e/QTc	0.18(0.13-0.26)**	0.16(0.11-0.24)**	0.012

*mean±standard deviation **median(minimum-maximum), ***Bazett: (QTc=QT/√RR)

- PR interval, QRS duration, QT interval, and Tp-e interval were all significantly longer in athletes ($p<0.05$ for each).
- The QTc interval did not differ significantly between groups ($p=0.08$).
- The Tp-e/QT and Tp-e/QTc ratios were slightly higher in athletes but did not reach statistical significance.
- iCEBc was significantly lower in the athlete group (p:0.02). Although the iCEB value was lower in the athlete group, the difference did not reach statistical significance.
- According to the correlation analysis (**Table 3**),
  - a positive, statistically significant correlation was found between the number frequency of training and age, body mass index (BMI).
  - Among the electrophysiological parameters, a positive and significant correlation was found between Tp-e duration and age.
  - A positive significant correlation was found between Tp-e/QTc ratio and age, and the Tp-e/QTc ratio was found to be higher in males.
  - A negative statistically significant correlation was found between iCEB and BMI, Tp-e, Tp-e/QT and Tp-e/QTc ratios.
  - A negative significant correlation was found between iCEBc value and age, BMI, Tp-e, Tp-e/QT and Tp-e/QTc ratios.

Sex-Based Differences

Subgroup analysis by sex revealed no statistically significant differences in repolarization parameters or iCEB values within the same group. However, male athletes exhibited a trend toward longer QT and Tp-e intervals than female athletes, though not statistically significant.

DISCUSSION

This study investigated the impact of regular sports activity on cardiac electrophysiology in a pediatric population by analyzing ventricular repolarization parameters and the index of cardiac electrophysiological balance (iCEB). Our findings demonstrate that children engaged in structured physical training exhibit significant electrocardiographic changes, most of which are consistent with physiological adaptations. However, the observed alterations in repolarization dynamics also highlight the potential utility of ECG screening tools in identifying latent arrhythmogenic substrates.

The most common finding among the athlete group was sinus bradycardia, detected in over one-quarter of participants. This is a well-documented adaptation to aerobic training and reflects enhanced parasympathetic tone and decreased sympathetic drive (3,7). Previous studies have shown that bradycardia in athletes is typically benign and does not imply sinoatrial node dysfunction unless accompanied by symptoms such as syncope or fatigue (12).

We also observed significantly prolonged PR, QRS, QT, and Tp-e intervals in athletes. These results suggest altered electrophysiological balance, likely reflecting adaptive myocardial remodeling.

Table 3. Correlation between demographic characteristics, training characteristics, and specific ECG findings

	Age (year)	Gender	BMI	Sports time (year)	Number of trainings (session per week)	Training duration (minutes per session)	Tp-e	Tp-e/QT	Tp-e/QTc	iCEB	iCEBc
Age (year)	1										
Gender	r:0.07 p:0.33	1									
BMI	r:0.5 p:0.00	r:-0.07 p:0.36	1								
Sports time (year)	r:0.17 p:0.12	r:0.21 p:0.06	r:-0.04 p:0.72	1							
Number of trainings (session/week)	r:0.27 p:0.01	r:0.06 p:0.60	r:0.24 p:0.03	r:0.18 p:0.11	1						
Training duration (minutes/ session)	r:0.37 p:0.00	r:0.04 p:0.7	r:0.04 p:0.7	r:0.08 p:0.45	r:0.53 p:0.00	1					
Tp-e	r:0.2 p:0.01	r:0.13 p:0.09	r:0.04 p:0.61	r:0.07 p:0.54	r:-0.13 p:0.23	r:-0.07 p:0.50	1				
Tp-e/QT	r:-0.04 p:0.61	r:-0.02 p:0.77	r:0.04 p:0.58	r:0.04 p:0.67	r:-0.11 p:0.31	r:-0.02 p:0.83	r:0.77 p:0.00	1			
Tp-e/QTc	r:0.25 p:0.00	r:0.19 p:0.01	r:0.07 p:0.35	r:0.05 p:0.66	r:-0.04 p:0.73	r:0.06 p:0.57	r:0.91 p:0.00	r:0.71 p:0.00	1		
iCEB	r:-0.13 p:0.08	r:-0.08 p:0.29	r:-0.18 p:0.02	r:-0.12 p:0.29	r:0.01 p:0.88	r:0.02 p:0.84	r:-0.24 p:0.00	r:-0.48 p:0.00	r:-0.23 p:0.00	1	
iCEBc	r:-0.38 p:0.00	r:-0.28 p:0.00	r:-0.20 p:0.01	r:-0.06 p:0.57	r:-0.03 p:0.75	r:-0.07 p:0.51	r:-0.35 p:0.00	r:-0.24 p:0.00	r:-0.45 p:0.00	r:0.74 p:0.00	1

While QTc was not significantly prolonged, the absolute QT and Tp-e durations reflect modifications in repolarization and myocardial refractoriness. These findings are consistent with studies in adult and adolescent athletes, indicating increased repolarization heterogeneity due to structural and functional myocardial adaptations (13,14).

The Tp-e interval and derived ratios (Tp-e/QT and Tp-e/QTc) have been proposed as non-invasive markers of transmural dispersion of repolarization. Elevated Tp-e values have been associated with ventricular arrhythmias, including Torsades de Pointes and sudden cardiac death (SCD), particularly in individuals with long QT syndrome and cardiomyopathies (15-17). Although Tp-e was significantly longer in athletes, the Tp-e/QT ratio remained within normal limits, suggesting physiological rather than pathological remodeling.

More novel is the application of the index of cardiac electrophysiological balance (iCEB), which correlates with the cardiac wavelength (λ=ERP × CV), a crucial determinant of reentrant arrhythmia risk (7,18). Our finding of reduced iCEB and iCEBc in athletes may suggest enhanced myocardial conduction velocity or increased repolarization duration relative to depolarization, both of which reflect efficient physiological adaptation in the absence of disease. Notably, none of the participants in our study demonstrated iCEB values indicative of high arrhythmic risk.

The American Heart Association (AHA) and European Society of Cardiology (ESC) recommend history-taking and physical examination as first-line tools in preparticipation cardiovascular evaluation. However, studies have shown that these methods alone miss up to 80% of conditions associated with SCD in athletes (19,20). In this context, resting ECG—particularly when interpreted with athlete-specific criteria—has emerged as a valuable adjunct.

Our findings support the inclusion of ECG-based parameters, including iCEB, as part of the screening process. This is especially relevant for pediatric populations, where arrhythmogenic conditions may remain silent and undiagnosed. To our knowledge, this is the first study in Türkiye, and one of the few internationally, to assess iCEB in a pediatric athlete cohort, marking an important step toward more evidence-based screening protocols.

This study has several limitations. First, it is a single-center study with a relatively limited sample size. Second, follow-up data were not available to determine the prognostic value of the ECG findings. Third, we did not perform echocardiography or cardiac MRI in all participants, which may have provided additional insights into structural remodeling. Finally, while iCEB is a promising marker, further validation in large, multicenter cohorts with clinical outcomes is needed.

CONCLUSION

In conclusion, this study demonstrates that regular sports participation in children induces measurable changes in cardiac electrophysiology, most notably sinus bradycardia, prolonged repolarization intervals, and alterations in electrophysiological balance indices such as iCEBc. These changes are largely consistent with physiological adaptation; however, they may obscure or mimic pathological conditions, emphasizing the importance of careful preparticipation cardiovascular evaluation.

Ventricular repolarization parameters, particularly the Tp-e interval, and the index of cardiac electrophysiological balance (iCEB) offer promising, non-invasive methods for assessing arrhythmic risk in pediatric populations. Incorporating such indices into routine ECG interpretation could enhance the detection of latent cardiovascular abnormalities, ultimately contributing to the prevention of exercise-related sudden cardiac events.

Further multicenter studies with long-term follow-up are needed to establish normative pediatric values for iCEB and Tp-e parameters, define high-risk thresholds, and validate their prognostic significance. Nonetheless, our findings support the broader implementation of ECG-based risk stratification in the pediatric sports medicine setting.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Atatürk Sanatorium Training and Research Hospital Scientific Studies Ethics Committee (Date: 17.07.2024, Decision No: 120).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

5% $NaHCO_3$ for Skin Antisepsis In Peripheral Intravenous Catheterization In Children: A Randomized Controlled Study

Çocuklarda Periferik İntravenöz Kateterizasyonda Cilt Antisepsisi için %5 $NaHCO_3$: Randomize Kontrollü Bir Çalışma

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ABSTRACT

Aim: In peripheral intravenous catheterization applications, procedural problems may cause local or systemic infections. The aim of this study was to determine the antimicrobial effect of 5% Sodium Bicarbonate in skin antisepsis before catheterization.

Material and Method: The study was randomized, single blind and experimental. In the study, skin antisepsis was used with 5% sodium bicarbonate before peripheral intravenous catheterization. Chlorhexidine gluconate 2% and alcohol 70% were used as a comparison group. The catheter was inserted after antisepsis was applied. One and 24 hours after catheterization, skin swabs were taken and analyzed. Local and systemic infection findings and vital signs were measured every 12 hours.

Results: 5% Sodium Bicarbonate showed antimicrobial effect in skin antisepsis. There was no evidence of systemic infection and vital signs were within normal limits. The most common bacterial subtype was *Staphylococcus hominis*, which was found in skin swabs of 8.1% of the children.

Conclusions: The 5% sodium bicarbonate may be an effective and cost-effective agent for skin antisepsis in children. It can be used for skin antisepsis before peripheral intravenous catheterization. The efficacy of different concentrations of sodium bicarbonate solutions should be investigated.

Keywords: Antiseptic, catheter-related infection, chlorhexidine gluconate, nursing care, peripheral intravenous catheterization, sodium bicarbonate.

ÖZ

Amaç: Periferik intravenöz kateterizasyon uygulamalarında, prosedürel sorunlar lokal veya sistemik enfeksiyonlara neden olabilir. Bu çalışmanın amacı kateterizasyon öncesi cilt antisepsisinde %5 Sodyum Bikarbonat'ın antimikrobiyal etkisini belirlemektir.

Gereç ve Yöntem: Çalışma randomize, tek kör ve deneysel olarak yapıldı. Çalışmada periferik intravenöz kateterizasyon öncesi %5 Sodyum Bikarbonat ile cilt antisepsisi uygulandı. Karşılaştırma grubu olarak %2 Klorheksidin Glukonat ve %70 Alkol kullanıldı. Kateter antisepsi uygulandıktan sonra yerleştirildi. Kateterizasyondan bir ve 24 saat sonra deri sürüntüleri alındı ve analiz edildi. Lokal ve sistemik enfeksiyon bulguları ve vital bulgular 12 saatte bir ölçüldü.

Bulgular: 5 Sodyum Bikarbonat cilt antisepsisinde antimikrobiyal etki gösterdi. Sistemik enfeksiyon bulgusu yoktu ve vital bulgular normal sınırlardaydı. En yaygın bakteriyel alt tip *Staphylococcus hominis* olup, çocukların %8,1'inin deri sürüntülerinde bulunmuştur.

Sonuç: %5 sodyum bikarbonat çocuklarda cilt antisepsisi için etkili ve uygun maliyetli bir ajan olabilir. Periferik intravenöz kateterizasyondan önce cilt antisepsisi için kullanılabilir. Farklı konsantrasyonlardaki sodyum bikarbonat solüsyonlarının etkinliği araştırılmalıdır.

Anahtar Kelimeler: Antiseptik, kateter ilişkili enfeksiyon, klorheksidin glukonat, hemşirelik bakımı, periferik intravenöz kateterizasyon, sodyum bikarbonat.

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INTRODUCTION

Intravenous (IV) therapy is one of the primary elements of modern health care. For pediatric patients, IV routes provided by catheters are necessary to sustain primary and secondary health. However, the risk of mortality and morbidity increases depending on the catheter used, the treatment applied, and the characteristics of the patient (1,2). As in any invasive procedure, there are complications related to the use of catheters, particularly catheter-related infection (CRI). CRIs are defined as the coexistence of findings of local and systemic infection in patients (3). As well as among patients, the increase in incidence of CRIs differs between cities and countries, and it ranks in the top three among hospital-associated infections (4). The incidence reported to be between 0.7-17% (5,6). Although there are many studies about infections related to the use of peripheral intravenous catheters (PIC) in adult patients, there are not as many studies in children about this subject (7,8). When the studies were evaluated, it was seen that various methods have been used for PIC in children (9-11). Since the risk factors for infections in pediatric patients, the characteristics of the catheter used, the drug administered, and the presence of connectors differs from adults, CRI in the pediatric age group requires a separate discussion (4)

It is undeniable that the main steps in the prevention of CRI are the management of PIC and the determination of an appropriate skin antiseptic. Although 70% Alcohol, 2% Chlorhexidine Gluconate (CHG), 1% Octenidine, and 10% povidone-iodine type antiseptics are options for skin antisepsis of children, 2% CHG is the most recommended and the most effective antiseptic recently (12,13). The trials that evaluated CHG usage in children, especially infants, reported that CHG bound keenly to skin proteins and had long-lasting antimicrobial effects on skin (48 hours). It was also seen that there was an inadequacy of studies in children and infants (12,13). Another research examined the efficacy of alcohol and bicarbonate and reported that the bicarbonate group had higher patient satisfaction despite the amount of germs on the skin remained same (14). It is known that 70% Alcohol dries the skin and causes skin lesions (1,15-17). Likewise, it has been reported that the absorption of povidone-iodine through the skin in children may cause many problems, particularly thyroid dysfunctions and skin problems (12,17). In line with this information, the need for a safe antiseptic solution for pediatric age group is emphasized (15-17).

In the world and in our country, sodium bicarbonate ($NaHCO_3$) solutions are used in various areas, such as oral hygiene and dental care, and $NaHCO_3$ as a skin antiseptic has not been associated with any unfavorable side effects (18,19). It has a bactericidal effect by neutralizing pH in the environment of bacteria (20). There is limited information in the literature regarding $NaHCO_3$ as a skin antiseptic, and this information seems to belong to the adult age group (14,19,21). No data were presented regarding the child age group. The aim of this study was to determine the efficacy of 5% $NaHCO_3$ in skin antisepsis before PIC in pediatric patients.

MATERIAL AND METHOD

Ethical aspect of the study

Ethics committee approval was obtained from the Istanbul University-Cerrahpaşa, Clinical Research Ethics Committee (10/07/2018/347) and the coordinating center of the hospital where the study conducted (01/10/2019/A-28), and institutional permission (05/08/2018) from the hospital chief physician and related units. Before the initiation of the study, the written and verbal consents of all children and their parents were obtained. The Helsinki Declaration was complied with in the study.

Aims and Design

The aim of this study was to determine the antimicrobial effects of 5% $NaHCO_3$ in PIC and to compare these effects with 2% Chlorhexidine Gluconate+70% Alcohol and 70% Alcohol. This single-blind, randomized controlled, experimental study was registered with ClinicalTrials.gov (ClinicalTrials number NCT04821193). The CONSORT flowchart was used to conduct the study (**Figure 1**).

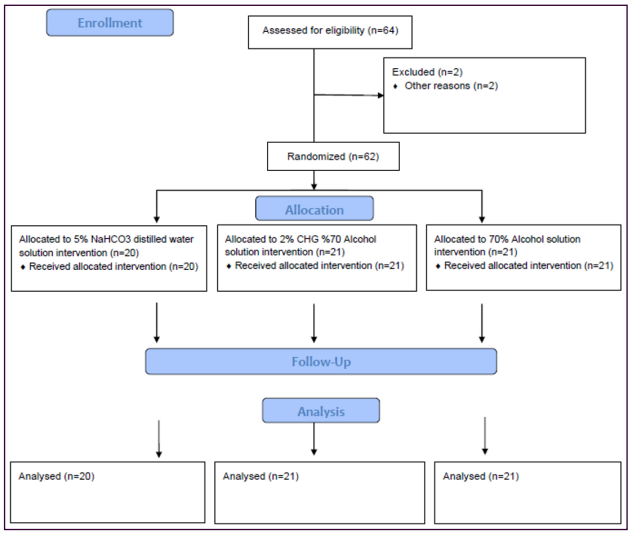

Figure 1. Study flow chart CONSORT

Participants

Children hospitalized in the pediatrics (general pediatrics and pediatric surgery) clinics of a university hospital between August 2018 and January 2019 participated in this study. The population of the study consisted of children who were in the hospital on the specified dates, and the sample size was calculated with the power analysis program. Since there was no literature for a pediatric sample, infection findings in similar studies conducted in adult patients were used to calculate the

sample (14,22). According to this calculation, a total of 57 patients were needed in the three groups, with at least 19 patients for each group (df=54; F=4.020). The groups were defined as Group 1 (% $NaHCO_3$ distilled water solution), Group 2 (2% CHG solution), and Group 3 (70% Alcohol solution). Participants were assigned to the groups through randomization using program (via Randomizer.org).

Patients in the age group of 1-18 years who were treated in inpatient clinics and required IV therapy were included in the study, while patients with a history of skin disease, immunologic disease and allergy were excluded. One patient was excluded at the second hour and one patient was excluded at the twelfth hour due to deterioration in their medical condition. Significance was accepted as $p<0.05$ at 95% confidence interval. At the end of the study, a total of 62 patients were enrolled.

Data collection tools

Data collection form and catheter infection follow-up form were used for data collection. The data collection form included questions about the children such as age, gender and medical diagnosis. It also includes catheter-related information such as the number of the catheter inserted, the site of catheter insertion and the duration of catheter stay. The catheter follow-up form consists of four sections.

The first part includes observation of the appearance of local signs of infection (pain, temperature increase, discoloration, discharge/drainage, tenderness, swelling and edema were observed) at the catheter insertion site. In the second part, systemic infection symptoms were evaluated (White blood cell count (WBC), C-reactive protein (CRP)). The data in this section were obtained from the patient's medical records. In the third section, vital signs were evaluated. In the fourth section, the results of skin swab analysis were recorded. Skin swabs taken at the first and twenty-fourth hours after catheterization were analyzed. The presence of growth and the type of bacteria grown were included.

Protocols

Protocols were designed in line with the literature, for preparation and application of the solutions (23-26). The procedures for PIC and sampling of post-catheterization skin swabs were designed in similar way (25,27).

Data Collection

The solutions used in the study were tested in the laboratory on the most common microorganisms on the skin and 5% $NaHCO_3$ distilled water was found to be effective.

Before the clinical study, skin antiseptics were prepared weekly according to antiseptic preparation protocols. After preparation, these solutions were analyzed in-vitro. Necessary data were collected from the patient file, health care provider and parents. As part of their routine care, PICs were applied to the patients after skin antisepsis with the prepared solutions. Vital signs, local (pain, temperature rise, discoloration, discharge/drainage, tenderness, swelling and edema) and systemic infection (WBC, CRP) findings were observed and recorded at the first, twelfth and twenty-fourth hours. Skin swabs were taken from the catheter insertion site at the first and twenty-fourth hours of catheterization and analyzed. All findings were recorded in the data collection and daily case forms. These procedures were continued until the required number of patients was reached.

Data analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 25 package program (IBM Company, USA). After the normality distribution of the data was determined by Kolmogorov-Smirnov test, descriptive values appropriate to the distribution were given as mean, standard deviation, median and min-max. Categorical variables were given as n (%). Chi-Square, Fisher Exact Chi-Square and Kruskal Wallis tests were used for intra- and intergroup comparisons. Significance was determined as $p<0.05$.

RESULTS

The results of this study to determine the effect of 5% $NaHCO_3$ as skin antisepsis in peripheral intravenous catheterization in children are included in this section. The study was completed with 62 PICs placed in 62 pediatric patients with a mean age of 9.4 years. **Table 1** shows the descriptive characteristics of the children and **Table 2** shows the distribution and comparison of the characteristics related to catheterization according to the groups.

The results of skin swab analysis of the solutions used are presented in **Table 3**, while the results of infection findings are presented in **Table 4**. Since blood culture analysis was not routinely performed in all patients and was completed in only three patients due to the necessity of treatment, no evidence of systemic infection was observed. Bacterial growth was observed in skin swabs in all groups except group 2. As a result, 8.1% (n=5) of all patients had growth in skin swab. In group 1, no additional local infection findings other than pain were observed. There was no statistically significant difference between the groups when systemic and local infection findings were compared ($p>0.05$; **Table 4**). When vital signs were measured at the first, twelfth and twenty-fourth hours after catheter insertion in the groups, it was observed that all vital signs were within normal limits. There was no statistically significant difference between vital signs and the solutions used in all three groups ($p>0.05$).

Table 1: Distribution and comparison of descriptive features by groups (N=62)

Features	Groups			Total (n=62)	p
	Group 1 (n=20)	Group 2 (n=21)	Group 3 (n=21)		
Age (years) Mean±Sd	8.75±5.83	9.28±3.92	10.33±3.70	9.46±4.54	*0.536
	n (%)	n (%)	n (%)	n (%)	
Gender					**0.123
Girl	9 (45)	6 (28.6)	10 (47.6)	25 (40.3)	
Boy	11 (55)	15 (71.4)	11 (52.4)	37 (59.7)	
Clinics					***0.001
Child surgery	6 (30)	0 (0)	0 (0)	6 (9.7)	
General paediatrics	14 (70)	21 (100)	21 (100)	56 (90.3)	
Diagnosis					**0.660
Acute diseases	10 (50)	8 (38.1)	6 (28.6)	24 (38.7)	
Chronic diseases	8 (40)	9 (42.9)	10 (47.6)	27 (43.5)	
Infection diseases	2 (10)	4 (19)	5 (23.8)	11 (17.8)	
Length of hospital stay (days)					**0.107
1	0 (0)	1 (4.8)	3 (14.3)	4 (6.5)	
2	4 (20)	4 (19)	0 (0)	8 (12,9)	
3	3 (15)	2 (9.5)	5 (23.8)	10 (16.1)	
4 and above	13 (65)	14 (66.7)	13 (61.9)	40 (64.5)	

*Kruskal Wallis Test; **Chi Square test; ***Fisher exact Chi Square test; p>0.05, Group 1: % $NaHCO_3$ distilled water solution; Group 2: 2% CHG solution; Group 3: 70% Alcohol solution

Table 2: Distribution and comparison of characteristics related to catheterization according to groups

Features	Groups			Total (n=62)	p
	Group 1 (n=20)	Group 2 (n=21)	Group 3 (n=21)		
At which attempt the catheter was inserted Mean±Sd	1.45±1.14	1.52±1.24	1.00±0.00	1.32±0.98	0.076
Drying time of the used antiseptic Mean±Sd	[a]9.65±2.43	[b]4.80±2.11	[c]5.95±2.65	6.75±3.14	*p<0.001 +a<c<b
Length of stay of the catheter Mean±Sd	3.75±2.12	2.61±2.24	3.09±1.94	3.14±1.83	*0.214
	n (%)	n (%)	n (%)	n (%)	
Catheter number					**0.858
22 gauge	5 (25)	4 (19)	4 (19)	13 (21)	
24 gauge	15 (75)	17 (81)	17 (81)	49 (79)	
Catheter insertion site					**0.362
Hand and wrist	7 (35)	10 (47.6)	14 (66.7)	31 (50)	
Foot and ankle	0 (0)	1 (4.8)	1 (4.8)	2 (3.2)	
Arm	10 (50)	7 (33.3)	5 (23.7)	22 (35.5)	
Leg	0 (0)	1 (4.8)	0 (0)	1 (1.6)	
Joints (knee and elbow)	3 (15)	2 (9.5)	1 (4.8)	6 (9.7)	
Connector status					**0.605
Yes	19 (95)	20 (95.2)	18 (85.7)	57 (91.9)	
No	1 (5)	1 (4.8)	3 (14.3)	5 (8.1)	
Fixation status					***0.943
Yes	6 (30)	8 (38.1)	7 (33.3)	21 (33.9)	
No	14 (70)	13 (61.9)	14 (66.7)	41 (66.1)	
Used patch stick					*** p<0.001
Silk	7 (35)	1 (4.8)	17 (81)	25 (40.3)	
Transparent	13 (65)	20 (95.2)	4 (19)	37 (59.7)	
Type of drug					***0.408
Fluid	10 (50)	7 (33.3)	6 (28.6)	23 (37.1)	
Fluid and drug	9 (45)	9 (42.9)	11 (52.4)	29 (46.8)	
Drug	1 (5)	5 (23.8)	4 (19)	10 (16.1)	
Frequency of administration of the drug					***0.134
1x1	17 (85)	12 (57.1)	15 (71.5)	44 (71)	
2x1	3 (15)	4 (19)	2 (9.5)	9 (14.5)	
3x1	0 (0)	5 (23.9)	4 (19)	9 (14.5)	
Reason for catheter removal					***0.094
Infiltration/Extravasation	3 (15)	10 (47.6)	8 (38.1)	21 (33.9)	
End of treatment	17 (85)	11 (52.4)	13 (61.9)	41 (66.1)	

*Kruskal Wallis Test; **Fisher's Exact Chi Square test; ***Chi Square test; +Bonferroni test; p<0.05, Group 1: %5 $NaHCO_3$ distilled water solution; Group 2: 2% CHG solution; Group 3: 70% Alcohol solution

Table 3: Distribution of in-vivo analysis results of used solutions

Microorganisms	Groups					
	Group 1		Group 2		Group 3	
	1st hours	24th hours	1st hours	24th hours	1st hours	24th hours
*In-vivo analysis						
Citrobacter freundii and *Klebsiella pneumoniae*	-	-	-	-	✓	-
Moraxella catarrhalis and *Streptococcus pneumoniae*	-	-	-	-	✓	-
Staphylococcus auricularis and *Enterobacter Cloacae*	-	-	-	-	✓	✓
Staphylococcus hominis	✓	✓	-	-	-	✓
Staphylococcus warneri	-	-	-	-	-	✓

Group 1: %5 $NaHCO_3$ distilled water solution; Group 2: 2% CHG solution; Group 3: 70% Alcohol solution, *At the 1st and 24th hours, the isolates are different.

Table 4. Distribution of systemic and local infection findings by groups

Features	Solution groups		
	Group 1	Group 2	Group 3
Systemic signs			
Positivity in the skin swap (/patients)	2	0	3
WBC increase	2	6	2
CRP increase	10	10	11
Local signs			
Pain	-	3	4
Temperature increase	2	-	5
Colour change	2	-	3
Drain /drainage	2	-	5
Sensitivity	2	-	3
Swelling	2	-	3
Oedema	2	-	3

Group 1: %5 $NaHCO_3$ distilled water solution; Group 2: 2% CHG solution; Group 3: 70% Alcohol solution; WBC: White blood cell; CRP: C reactive protein; CRP Reference range: <5 mg/dl; WBC Reference Range: 3,6-10,2 µl

DISCUSSION

The aim of this study was to determine the antimicrobial effect of 5% Sodium Bicarbonate in skin antisepsis before catheterization. According to the findings of the study, all three solutions were found to have antiseptic effects. However, two of the solutions (Group 2 and Group 3) were already in clinical use. The 5% Sodium Bicarbonate solution used in Group 1 was applied to children for the first time, and despite being diluted with distilled water, its antiseptic effect in skin cleansing prior to peripheral intravenous catheterization was demonstrated in this study.

Skin swab analysis on catheter inserted in 62 children were performed. Local and systemic signs of infection were not observed in Group 1, and the vital signs of the children were normal. The most effective antiseptic was determined to be 2% CHG+70% Alcohol, and the effects of 5% $NaHCO_3$ and 70% Alcohol were close to each other. As the prevalence of PICs used for examination and treatment in hospitalized patients increases, the incidence of complications such as CRI also increases (14,22). Individual factors, diagnosis, the features of the catheter, and the features of the treatments applied are the risk factors in CRI seen in children (28). In the present study, there was no statistically significant difference between the groups in terms of the individual characteristics of the children, the features for catheterization, and the characteristics of the treatment applied ($p>0.05$), and it was determined that the groups formed within the scope of the study were homogeneous (**Tables 1** and **2**). When the literature was investigated, it was seen that the descriptive characteristics and catheterization features of the children in this present study were similar (3,24,28,29), and they had no effect on the occurrence of complications.

Effective skin antisepsis should be performed before PIC, and the administered antiseptic should dry as rapidly as feasible (2,5,25,27). The antiseptic penetrates under the skin from the catheter entry point if the catheters are inserted without waiting for them to dry, and causes pain in children (29). In this study, the average drying time was 9.6 seconds for Group 1. The average antiseptic drying time was less than 10 seconds, and it was even shorter in Groups 2 and 3, in which alcohol-containing solutions used. This finding can be attributed to the volatile nature of the alcohol used and the fact that Group 1 does not include alcohol.

It can be said with all these findings that 2% CHG+70% Alcohol solution is the most effective skin antiseptic, and this might be a result of its long-lasting antimicrobial activity on the skin, broad effect, and strengthened with another antiseptic agent like 70% Alcohol (15). It is reported that there is not enough evidence for its use in children under the age of two and that the hesitancy continues because it may cause allergic reactions (3,24,27). Although there is little scientific documentation about the activity of the distilled water solution with 5% $NaHCO_3$ which is recommended as an alternative antiseptic in this study, the studies have shown that it actively cleans the oil on the catheter insertion site before PIC in adult patients, that is a more effective solution compared to alcohol, provides usage satisfaction in nurses, reduces pain in patients, and that has an effect in-vitro studies (14,29,30).

Although it is known that efficacy and safety are important criteria in skin antisepsis, the skin antiseptic included in PIC management and care packages in children should

also have these properties (27,28). In the in-vivo analysis of the antiseptics used in this study, bacterial growth was detected in 8.1% of the study population and in only two patients in Group 1, where 5% $NaHCO_3$ distilled water solution was used. When the studies are examined, it is seen that CHG solution enriched with alcohol at different concentrations (0.5%, 2%) is an effective antiseptic agent compared to other antiseptics available in the market (most commonly alcohol/povidone-iodine solutions) (3,12,13). No previous study was found on the use of 5% $NaHCO_3$ distilled water solution as an antiseptic agent in children. Considering these findings, it is clear that more studies including 5% $NaHCO_3$ are needed.

When the most common microorganisms in CRI are examined, *Staphylococcus aureus* and Coagulase Positive Staphylococcus (CoPS) bacteria, especially *Staphylococcus aureus*, are frequently found in human skin, which harbors many beneficial and harmful microorganisms (3,14,31). In case of disruption of skin integrity, CoPS causes many diseases such as sepsis and soft tissue infections (30). In this study, only *Staphylococcus hominis* grew in the group using distilled water solution containing 5% $NaHCO_3$ and *Staphylococcus hominis* was the most commonly grown bacterium in all groups. *Staphylococcus hominis* is considered a potential opportunistic pathogenic microorganism present in normal human skin flora and causes infection by entering the body through weak defense barriers and entry points of invasive devices (30). To prevent microorganisms from causing infection, it is important to provide effective skin antisepsis, monitor catheter entry sites for signs of local infection, and monitor the patient for signs of systemic infection. This also requires retesting by increasing the concentration of the skin antiseptic used or adding a booster to the same concentration.

Catheter-related infection most commonly originates from the catheter insertion site, and systemic and local infection signs and symptoms guide the detection of these infections (3,11,28). A local infection passes through the layers of the skin (epidermis or dermis), and enters the internal environment, and can cause systemic infection (23). In the present study, local infection symptoms were not observed in the distilled water with 5% $NaHCO_3$ group. Symptoms such as oedema, tenderness, and swelling were observed in the groups where 2% CHG+70%Alcohol and 70% Alcohol, and the most common symptom was a color change. No signs of systemic infection (increased CRP and WBC values, positive blood culture) were found in study groups. In another study that 251 catheters were analyzed, it was reported that skin antisepsis was provided with 70% Alcohol, and no signs of CRI were found.29 In other studies, CHG solution use for skin antisepsis and routine monitoring of the catheter site for signs of local infection were recommended. It is reported that CRI could be prevented by providing optimal asepsis and antisepsis conditions in addition to observation (12,27,28). The absence of local infection signs may be an indicator for progression of infection and causing systemic infection. It is thought that the long incubation period of the microorganism is the reason the infectious microorganism is not detected in the swab sample taken from the catheter insertion site in patients with local infection signs. It may also be the effect of the patient immune system or the drugs that the patient used.

Based on the literature review and the results of the present study, 2% CHG solution seems to be an effective skin antiseptic although a safer and more effective antiseptic is needed for children. No signs of systemic and local infection were encountered in the study Group 1 with 5% $NaHCO_3$ distilled water solution, which the effectiveness tested. In light of these findings, 70% Alcohol and 2% CHG+70% Alcohol is commonly used as antiseptics in PIC. In addition, the search for alternative antiseptics for the skin continues.

Limitations

The most important limitations of this study are its single-center design. Another limitation is the absence of similar studies that can be compared and discussed with this study. The availability of powdered $NaHCO_3$ in the form of industry and the lack of 5% $NaHCO_3$ distilled water concentration is also a limitation of this study.

CONCLUSION

In this study, it was found that the groups were similar in terms of the effectiveness of the three antiseptics used in the prevention of CRI, and the most effective antiseptic was 2% CHG+70% Alcohol. The 5% $NaHCO_3$ solution, which was used for the first time in skin antisepsis in children, was found to be an effective antiseptic agent. Sodium bicarbonate may also be a cost-effective (economic) agent for skin antisepsis before PIC use in children. It is thought that the efficacy of different concentrations of sodium bicarbonate solution can be investigated in future studies. Because this study had a single-center design and consisted a small sample size, the effect of 5% $NaHCO_3$ solution should be studied in larger populations in the future.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul University Cerrahpaşa Faculty of Medicine Clinical Researches Ethics Committee (Date: 01.10.2019, Decision No: A-28).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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ORİJİNAL ARAŞTIRMA
ORIGINAL ARTICLE

Monosemptomatik Nokturnal Enürezisli Çocuklarda Desmopressin ve Oksibutinin Kombine Tedavi Etkinliğinin Değerlendirilmesi

Evaluation of Effectiveness of Combined Treatment with Desmopressin and Oxybutynine in Children with Monosymptomatic Nocturnal Enuresis

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Öz

Amaç: Bu çalışma, primer monosemptomatik nokturnal enürezis (MNE) tanılı, desmopressin tedavisine yanıtsız veya kısmi yanıtlı çocuklarda antikolinerjik eklenerek yapılan kombine tedavinin etkinliğini ve etkileyen faktörleri araştırmayı amaçlamaktadır.

Gereç ve Yöntem: Ocak 2022-Aralık 2024 arasında Çocuk Nefroloji polikliniğinde takip edilen, 5-16 yaş arası desmopressine yanıtsız veya kısmi yanıtlı MNE'li çocuklar retrospektif incelendi. Demografik veriler, alt ıslatma durumu ve tedavi yanıtları kaydedildi. Desmopressin tedavisinden en az 1 ay sonra yanıt alınamazsa tedaviye oksibutinin eklendi.

Bulgular: Çalışmaya yaş ortalaması 9,27±2,34 yıl olan 77 çocuktan (31 kız, 46 erkek) dahil edildi. Hastaların %93,5'i her gün, %28,6'sı gecede birden fazla idrar kaçırıyordu. 'Antikolinerjik eklenen 77 hastadan 48'inin kombine tedavi sonrası takibi mevcuttu ve %52'si desmopressine kısmi yanıtlı, %48'i yanıtsızdı. Kombine tedavi ile takibi yapılan 48 hastada; %62,5 tam yanıt, %14,6 kısmi yanıt, %22,9 yanıtsızlık gözlendi. Tam yanıt ile yaş arasında pozitif korelasyon bulundu (r=0,332, p=0,021).

Sonuç: Desmopressine tam yanıt alınamayan MNE olgularında antikolinerjik eklenmesi kombine tedavinin etkin ve güvenilir bir seçenek olduğunu göstermektedir.

Anahtar Kelimeler: Çocuk, desmopressin, nokturnal enürezis, oksibutinin

Abstract

Aim: This study aims to investigate the efficacy and influencing factors of combined treatment with an anticholinergic in children with primary monosymptomatic nocturnal enuresis (MNE) who were unresponsive or partially responsive to desmopressin treatment.

Material and Method: A retrospective review was conducted on children aged 5 to 16 years with MNE who were unresponsive or partially responsive to desmopressin and followed in the Pediatric Nephrology Outpatient Clinic between January 2022 and December 2024. Demographic data, bedwetting status, and treatment responses were recorded. If no response was observed after at least 1 month of desmopressin treatment, oxybutynin was added to the treatment.

Results: The study included 77 children (31 girls, 46 boys) with a mean age of 9.27±2.34 years. Ninety-three percent of the patients had daily urine leakage, and 28.6% had more than one urine leakage per night. Forty-eight of the 77 patients who received anticholinergic therapy were followed up after combination therapy, and 52% showed a partial response to desmopressin and 48% no response. Of the 48 patients who received combination therapy, 62.5% had a complete response, 14.6% a partial response, and 22.9% no response. A positive correlation was found between complete response and age (r=0.332, p=0.021).

Conclusion: In patients with MNE who do not fully respond to desmopressin, the addition of an anticholinergic demonstrates that combination therapy is an effective and reliable option.

Keywords: Child, desmopressin, nocturnal enuresis, oxybutynin

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GİRİŞ

Nokturnal enürezis, 5 yaş üstü çocuklarda uyku sırasında aralıklı idrar tutamama veya yatak ıslatma olarak tanımlanır. Birincil veya ikincil olabilir; ikincil, hastanın en az 6 ay boyunca geceleri başarılı bir şekilde kuru kaldıktan sonra gelişen yatak ıslatma olarak tanımlanır. Monosemptomatik nokturnal enürezis (MNE), gündüz idrar sıklığı, aciliyeti veya idrar tutamama gibi alt üriner sistem semptomlarının eşlik etmediği durumu ifade eder (1). MNE, 5 yaşındaki çocukların yaklaşık %15-20'sini, 10 yaşındakilerin %5'ini, 15 yaşındaki bireylerin %1-2'sini ve genç yetişkinlerin %2'sine kadarını etkiler. MNE'nin etiyolojisinde detrusor aşırı aktivitesine bağlı gece düşük mesane kapasitesi, gece poliüri ve uyarılma bozukluğu rol oynar (2).

Desmopressin, primer MNE'nin onaylı ve kanıta dayalı birinci basamak tıbbi tedavisidir. Desmopressin tedavisinden 3 ay sonra MNE'li vakaların %85'inde kuru geceye yol açtığı bildirilmiştir. Ancak araştırmalar, hastaların yaklaşık %20'sinin 3 aylık ilaç tedavisinden sonra desmopressine dirençli MNE vakaları olduğunu göstermiştir(3). Detrusor aşırı aktivitesi nedeniyle fonksiyonel mesane kapasitesi azaldığı için desmopressin tedavisine ek olarak antikolinerjik ajanlar ile kombine tedavi ile başarılı sonuçlar alınmaktadır (4-6).

Ancak, NE'yi tedavi etmek için desmopressinin antikolinerjik ajanlarla kombinasyonu tartışmalı olmaya devam etmektedir. Azalmış fonksiyonel mesane kapasitesinin yokluğunda, antikolinerjik ajanların PMNE tedavisinde çok az etkiye sahip olduğu düşünülmektedir (7). Ayrıca başlangıç tedavisinin kombine mi yoksa monoterapi ile başlanması konusunda farklı görüşler mevcuttur.

Biz bu çalışmada primer MNE olan ve desmopressin tedavisine yanıtsız veya kısmi yanıtlı hastalarda antikolinerjik eklenerek kombine tedavinin etkinliğini ve bu tedaviye etki eden faktörleri araştırdık.

GEREÇ VE YÖNTEM

Bu çalışmada Ocak 2022-Aralık 2024 yılları arasında Çocuk Nefroloji polikliniğinde takip edilen ve başlangıç olarak desmopressin tedavisine yanıtsız veya kısmi yanıtlı primer MNE'li 5-16 yaş arası çocukların dosyaları retrospektif olarak analiz edildi. Bu çalışma için Karamanoğlu Mehmetbey Üniversitesi Etik Kurulu onayı alındı (Tarih: 26.09.2024, Sayı: 217045). Etik kurul onayı sonrasında, dosyalardan hastaların demografik özellikleri, alt ıslatma sıklığı ve sayısı, aile öyküsü, uyku özelliği ve kombine tedaviye yanıtı kaydedildi. Alt üriner sistem semptomları, kronik böbrek hastalığı, doğumsal üriner sistem anomalileri, üriner sistem taşı ve tekrarlayan idrar yolu enfeksiyonu olan çocuklar çalışma dışı bırakıldı. Hastaların tedavisinde desmopressin 120 microgram/gün olarak başlandı. En az 1 ay tedavi sonrası değerlendirilen hasta, tedaviye yanıtsız veya kısmi yanıtlı ise oksibutin 0,25 mg/kg/gün eklendi. Bir sonraki kontrolde değerlendirilen hasta da tedaviye tam yanıt veya kısmi yanıt varsa mevcut tedaviye devam edildi. Tedaviye yanıtsız vakalarda ilaç tedavisi sonlandırıldı. Tedaviye yanıt Uluslararası Çocuk Kontinans Derneği tarafından tanımlanan kriterlere göre; ıslak gece sayısında %100 azalma tam yanıt; %50-89 azalma kısmi yanıt; %0-49 azalma yanıtsızlık olarak kategorize edildi (8).

Veri girişi ve istatistiksel analizler SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA) paket programı kullanılarak gerçekleştirildi. Verilerin normal dağılıma uygunluğu görsel yöntemler(histogram ve olasılık grafikleri) ile ve analitik yöntemler olan Shapiro-Wilk testi ile değerlendirildi. Sayısal veriler, dağılıma göre ortalama±standart sapma olarak özetlendi. Kategorik veriler ise sayı (n) ve yüzde (%) olarak sunuldu. Sayısal veriler arasındaki ilişki Pearson korelasyon katsayısı ile analiz edildi. İstatistiksel anlamlılık düzeyi $p<0,05$ olarak kabul edildi.

BULGULAR

Çalışmaya nokturnal enürezis tanılı yaş ortalaması 9,27±2,34 yıl olan 77 hasta dahil edilmiş olup 31'i (%40) kız ve 46'sı (%60) erkekti. Hastaların 72'si (%93,5) her gün idrar kaçırıyorken 22'si (%28,6) gecede birden fazla kez idrar kaçırıyordu. Derin uyku hastaların %44,2'sinde (n: 34) saptandı ve %20,8'inde (n: 16) pozitif aile öyküsü mevcuttu (**Tablo 1**).

Tablo 1: Hastarın Demografik ve Klinik Özellikleri

Parametre	Tüm katılımcılar (n: 77)
Cinsiyet	31 kız (%40), 46 erkek (%60)
Yaş ortalaması (yıl)	9,27 ± 2,34
Her gün idrar kaçırma	72 hasta (%93,5)
Gecede birden fazla kaçırma	22 hasta (%28,6)
Derin uyku	34 hasta (%44,2)
Aile öyküsü	16 hasta (%20,8)

Desmopressin tedavisine yanıt alınamayan ve antikolinerjik tedavi eklenen 77 hastadan 48'nin (%62) takibi mevcuttu ve sonuçları değerlendirildi, 32'si erkekti (%67). Bunların 45'inde (%93,8) her gün alt ıslatma, 13'ünde (%27,1) birden fazla kaçırma mevcuttu. Derin uyku 29 hastada değerlendirilmiş ve 22'sinde derin uyku, aile öyküsü 14 hastada değerlendirilmiş 12'sin de mevcuttu.

Kombine tedavi başlanan hastalardan 25'inde (%52) desmopressine kısmi yanıt, 23'ünde (%48) yanıtsızlık vardı.

Desmopressin ve oksibutin kullanan grupta tedaviye 30 hastada (%62,5) tam yanıt, 7 hastada (%14,6) kısmi yanıt, 11 hastada (%22,9) yanıtsızlık saptandı. Kızların 8'inde (%50), erkeklerin 22'sinde (%69) tam yanıt vardı (**Tablo 2**).

Tablo 2: Takibi Değerlendirilen Hastaların Klinik Özellikleri

Parametre	Tüm katılımcılar (n:48)
Cinsiyet	32 erkek (%67), 16 kız (%33)
Her gün kaçırma	45 hasta (%93,8)
Gecede birden fazla kaçırma	13 hasta (%27,1)
Derin uyku (n=29)	22 hasta (%75,9)
Aile öyküsü (n=14)	12 hasta (%85,7)
Desmopressin kulananlar	
Kısmi yanıt	25 hasta (%52)
Yanıtsız	23 hasta (%48)
Desmopressin + Oksibutin kullananlar	
Tam yanıt	30 hasta (%62,5)
Kısmi yanıt	7 hasta (%14,6)
Yanıtsız	11 hasta (%22,9)
Antikolinerjik yan etki nedeniyle tedavisi sonlandırılan	2 hasta (%2,6)

Tedaviye etki eden faktörler araştırıldığında kombine tedaviye tam yanıt ile yaş arasında pozitif korelasyon mevcuttu (r=0,332, p=0,021). Cinsiyet, idrar kaçırma sıklığı, sayısı, derin uyku ve aile öyküsü arasında herhangi bir korelasyon saptanmadı. Kombine tedavi verilen İki hastada (%2,6), antikolinerjik tedaviye bağlı ateş ve ciltte kızarıklık gözlendi ve tedavi sonlandırıldı.

TARTIŞMA

Monosemptomatik nokturnal enürezis çocuklarda yaygın bir sorundur ve hastalığın etiyolojisi heterojendir. Genetik özellikler, MNE'ye neden olan önemli mekanizmalardan biridir. Ebeveynlerinden biri veya her ikisi MNE'den muzdaripse çocuklarda hastalığa yakalanma riski sırasıyla %44 ve %77 oranında artmıştır. Erkeklerdeki insidans oranı kızlara göre daha yüksektir (2). Benzer şekilde vakalarımızın %60'ı erkeklerden oluşmaktadır.

Monosemptomatik nokturnal enürezis önemsiz bir durum değildir. Tedavi edilmezse düşük öz saygıya, sosyal aktivitelerden kaçınmaya ve ebeveyn stresine neden olabilir. Sık idrar kaçırmada tedavi olmaksızın kuru kalma şansının daha düşük olduğu, yıllık %15'lik kendiliğinden remisyon oranı tanımlanmıştır (4). Desmopressin MNE'yi tedavi etmek için ilk tercihtir ve etki mekanizması gece idrar üretimini düşürmesiyle açıklanabilir. Enüretik çocukların yaklaşık üçte biri ilacı aldıkları sürece güvenilir bir şekilde kuru olacakken, üçte biri hiçbir fayda görmeyecek ve üçte biri orta düzeyde bir yanıt verecektir (9). Gece fonksiyonel mesane kapasitesindeki azalmaya bağlı desmopressine yanıtsız enüretik çocuklarda oksibutinin, tolterodin veya propiverin gibi antikolinerjik ajanlar hastalarda semptomları iyileştirmek için kullanılmaktadır (10). Bir meta-analiz, desmopressin monoterapisine kıyasla, desmopressin+antikolinerjik kombine ajan kullanımının MNE tedavisinde daha etkili olduğunu ve güvenlik açısından desmopressin monoterapisine bir antikolinerjik ajan eklenmesinin daha fazla olumsuz olaya neden olmadığını göstermiştir (11).

Primer MNE'li 98 çocuğun değerlendirildiği bir çalışmada desmopressin+ propiverin tedavisi alan çocuklarda tedaviye tam yanıt, sadece desmopressin alan gruba göre istatistiksel olarak anlamlı oranda yüksek bulundu (1). Desmopressin ve oksibutin etkinliğinin değerlendirildiği başka bir çalışmada, 183 çocuk tedavinin 1., 3., ve 6. ayındaki takibine göre değerlendirildi (6). Kombine tedavinin 6. ayında 90 hastadan 83'ü tam yanıt (%92,2), 6 hasta ise kısmi yanıt (%6,6) verdi. Capalbo ve arkadaşlarının yaptığı çalışmada desmopressin tedavisine kısmi yanıtlı veya yanıtsız 78 çocuğun 0,3 mg/kg/gün oksibutinin eklenmesi sonrasında, 38 hasta (%48,7) tam, 8 hasta (%10,2) kısmi ve 32 hasta (%41) yanıt vermedi. Kısmi ve yanıt vermeyen 40 hastaya desmopresin ve 0,5 mg/kg/gün oksibutinin ile kombine tedavi uygulandı ve 16 hastada (%20,5) tam yanıt, 5 hastada (%6,4) kısmi yanıt ve 19 hastada (%24,3) yanıt alınamadı (4). Çalışmamızda literatüre uygun şekilde kombine tedaviye %62,5 oranında tam yanıt, %14,6 oranında kısmi yanıt vardı.

Kombine tedavi etkinliğini veya rekürrensi öngören faktörler arasında nokturnal poliüri, bakım veren olarak annenin olması, kabızlığın yokluğu ve artmış mesane kapasitesi bazı çalışmalarda ortaya konulmuştur (4,5). Desmopressine yanıt oranlarının değerlendirildiği 471 çocuğu içeren bir çalışmada, daha büyük yaş ve gece poliürisi olan çocuklarda daha yüksek yanıt olduğu gösterildi (12). Çalışmamızda tedaviye etki eden faktör olarak daha büyük yaş ile korelasyon saptandı.

SONUÇ

Sonuç olarak desmopressine yanıtsız veya kısmi yanıtlı vakalarda antikolinerjik ile kombine tedavi etkili ve güvenilir bir yöntemdir.

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Aydınlatılmış Onam: Çalışma retrospektif olarak dizayn edildiği için hastalardan aydınlatılmış onam alınmamıştır.

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CASE REPORT
OLGU SUNUMU

The Laboratory's Hidden Trap : Pseudothrombositopenia

Laboratuvarın Gizli Tuzağı: Psödotrombositopeni

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ABSTRACT

Ethylenediaminetetraacetic acid (EDTA)-induced pseudothrombocytopenia is an uncommon but clinically significant laboratory artifact resulting in falsely low platelet counts due to platelet aggregation in vitro. This condition, often misdiagnosed as true thrombocytopenia, can lead to unnecessary investigations or inappropriate treatment if not properly identified. We present the case of a 13-year-old asymptomatic female referred for isolated thrombocytopenia, which was ultimately diagnosed as EDTA-dependent pseudothrombocytopenia through comparative analysis using citrate-anticoagulated samples and peripheral smear evaluation. The case underscores the importance of peripheral blood smear review and awareness of anticoagulant-induced artifacts in the accurate diagnosis of hematologic abnormalities (1).

Keywords: Pseudothrombocytopenia, EDTA, Platelet aggregation, Peripheral smear, Misdiagnosis, Pediatric hematology

ÖZ

Etilendiamintetraasetik asit (EDTA) kaynaklı psödotrombositopeni, nadir görülen ancak klinik açıdan önemli bir laboratuvar artefaktıdır ve in vitro trombosit agregasyonu nedeniyle trombosit sayısının yanlış bir şekilde düşük çıkmasına neden olur. Bu durum, sıklıkla gerçek trombositopeni ile karıştırılır ve doğru şekilde teşhis edilmezse gereksiz tetkiklere veya uygun olmayan tedavilere yol açabilir. Bu makalede, izole trombositopeni nedeniyle sevk edilen 13 yaşındaki asemptomatik bir kadın hastanın vakası sunulmaktadır. Bu hasta, sitrat antikoagülanlı numuneler ve periferik smear değerlendirmesi kullanılarak yapılan karşılaştırmalı analiz sonucunda EDTA bağımlı psödotrombositopeni tanısı almıştır. Bu vaka, hematolojik anormalliklerin doğru tanısında periferik kan smear incelemesinin ve antikoagülan kaynaklı artefaktların farkında olmanın önemini vurgulamaktadır (1).

Anahtar Kelimeler: Psödotrombositopeni, EDTA, Trombosit agregasyonu, Periferik yayma, Yanlış tanı, Pediatrik hematoloji

INTRODUCTION

Pseudothrombocytopenia is a laboratory artifact characterized by a falsely low platelet count in automated complete blood count (CBC) tests, despite the patient's true platelet count being within the normal range. This discrepancy arises due to platelet clumping observed in peripheral blood smears, typically caused by in vitro platelet aggregation. Importantly, pseudothrombocytopenia does not carry any risk of bleeding or clinical thrombocytopenia (2,3). However, it holds significant clinical relevance because patients often present with various symptoms that may prompt unnecessary investigations or inappropriate treatments if misdiagnosed as true thrombocytopenia. Such misdiagnosis can delay the identification and management of the patient's actual underlying condition.

Pseudothrombocytopenia can be induced by several anticoagulants used in blood sample collection, including citrate and oxalate, but the most frequently encountered form is induced by ethylenediaminetetraacetic acid (EDTA). In EDTA-induced pseudothrombocytopenia, conformational changes occur in platelet membrane glycoproteins, exposing epitopes that lead to the binding of naturally occurring antiplatelet autoantibodies, which in turn causes platelet aggregation in vitro (2,3).

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CASE

A 13-year-old female patient was referred to our pediatric hematology clinic from an external center due to persistently low platelet values reported in routine blood tests. The initial referral was prompted by incidental thrombocytopenia detected during a preoperative evaluation for a minor elective surgery, in which the patient was otherwise asymptomatic.

Patient History

The patient was born via normal spontaneous vaginal delivery at term without perinatal complications. She had no history of neonatal jaundice, bleeding diathesis, recent infections, or medication use except for Apicobal (vitamin B12 supplement. Apicobal (vitamin B12 supplement) had been started recently due to mild anemia diagnosed at a local pediatric outpatient clinic. She was attending 7th grade and had an active lifestyle, participating in school sports without any episodes of easy bruising or bleeding, which made clinical thrombocytopenia less likely.

There was no history of autoimmune disorders or hematological diseases in the family. The mother reported four previous miscarriages but no other relevant medical conditions. The father and sibling are healthy. There was no consanguinity or history of inherited platelet disorders. The patient had no recent illnesses, no upper respiratory tract infections, fever, or recent vaccinations within the past 6 weeks , eliminating post-infectious or vaccine-related immune thrombocytopenia from the differential.

Current Clinical Status

On physical examination, the patient was in good general condition. Vital signs were normal. No petechiae, purpura, ecchymoses, or mucosal bleeding were observed. There was no lymphadenopathy or hepatosplenomegaly. The spleen was not palpable even with deep inspiration, and abdominal ultrasound later confirmed normal organ size and echotexture.

Skin inspection was performed under bright light to detect any microbleeds or petechial rash, but none were found. Oral mucosa, conjunctivae, and nailbeds showed no signs of bleeding or pallor. Joint examination was normal.

The absence of clinical bleeding signs despite low platelet counts raised suspicion for pseudothrombocytopenia. However, initial differential diagnosis included immune thrombocytopenic purpura (ITP) due to isolated thrombocytopenia.

Laboratory Findings

Initial complete blood count (CBC) performed at the external center using EDTA-anticoagulated blood showed platelet counts ranging between 80,000 and 95,000/mm^3 over repeated tests. Other hematologic parameters including hemoglobin, white blood cell count, and differential were within normal limits. Coagulation profile (PT, aPTT, INR) and liver function tests were normal.

Reticulocyte count, lactate dehydrogenase (LDH), haptoglobin, and peripheral smear did not show any signs of hemolysis. Antinuclear antibody (ANA) and direct Coombs test were negative, and viral serologies for CMV, EBV, hepatitis B and C were unremarkable.

To clarify the diagnosis, we performed a CBC using both EDTA and sodium citrate anticoagulants simultaneously. Platelet count was 90,000/mm^3 in the EDTA tube but normalized to 225,000/mm^3 in the citrate tube. Peripheral blood smear from the EDTA sample showed marked platelet clumping, while the citrate sample showed normal platelet morphology and distribution without clumping.

Based on these findings, the diagnosis of EDTA-dependent pseudothrombocytopenia was established, a well-documented in vitro phenomenon caused by EDTA-induced exposure of cryptic platelet glycoprotein epitopes that lead to platelet agglutination via autoantibodies.(1,4)

Peripheral Blood Smear Findings

Peripheral blood smear examination was performed on samples collected in both EDTA and citrate anticoagulant tubes to differentiate true thrombocytopenia from pseudothrombocytopenia. Wright-Giemsa-stained smears were evaluated by two independent hematologists blinded to the tube type to ensure diagnostic accuracy. Microscopic evaluation of the EDTA sample revealed large platelet aggregates, including a visible 16-platelet cluster, explaining the falsely low automated count (**Figure 1**). leading to an erroneously low automated platelet count (93,000/mm^3). In contrast, the smear from the citrate tube showed no platelet aggregation, with a platelet count within normal limits (220,000/mm^3), confirming EDTA-induced pseudothrombocytopenia. No significant morphological abnormalities were observed in other blood cell lines. Red cell morphology was normocytic-normochromic, and white cell differential was within normal range with no left shift or dysplasia. These findings were crucial in excluding true thrombocytopenia and guiding appropriate clinical management.

Management and Follow-up

No treatment was initiated as the condition is benign and not associated with bleeding risk. The patient and family were counseled about the laboratory artifact and advised that future platelet counts should be interpreted cautiously and preferably obtained using citrate or heparin tubes.

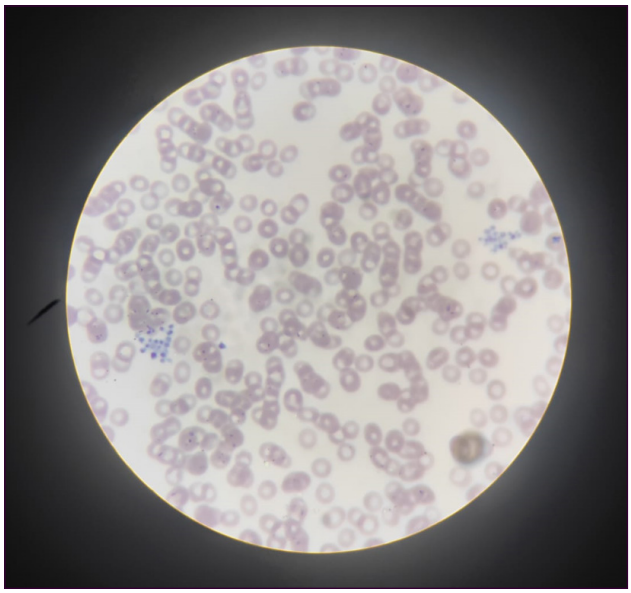

Figure 1. Peripheral smear image of a patient with pseudothrombocytopenia

We issued a formal advisory report to be kept in the patient's medical file to prevent unnecessary interventions such as hematology consultations or even bone marrow biopsies in future healthcare encounters. A laminated card noting the diagnosis and instructions for future blood testing was also given to the family for presentation in emergency situations or hospital admissions.

Six-month follow-up included repeat CBC from a citrate tube, which confirmed persistently normal platelet counts (230,000/mm^3), and the patient remained asymptomatic with no bleeding diathesis. She continued to participate in regular school and sports activities without any restrictions.

DISCUSSION

Pseudothrombocytopenia is a laboratory artifact characterized by a falsely low platelet count despite the patient having a normal platelet number in vivo. The most frequent form, EDTA-induced pseudothrombocytopenia (EDTA-PTCP), results from in vitro platelet clumping due to autoantibodies that interact with glycoprotein IIb/IIIa when conformational changes are induced by calcium chelation. Although clinically insignificant in terms of bleeding risk, failure to recognize this phenomenon can lead to unnecessary anxiety, diagnostic procedures, and potentially harmful treatments such as corticosteroids or intravenous immunoglobulin (IVIG), especially when immune thrombocytopenia (ITP) is misdiagnosed (4,6,7).

In our case, an 13-year-old previously healthy female patient was referred to our pediatric hematology clinic with an isolated low platelet count reported by an external center. Notably, she had no signs or symptoms of bleeding, bruising, or petechiae, and her physical examination was entirely unremarkable. There was no significant history of recent infections, medications, autoimmune conditions, or familial hematologic disorders.

The initial complete blood count performed in the referring center showed thrombocytopenia with a platelet count of 36,000/mm^3. However, when the peripheral smear was reviewed in our center, abundant platelet aggregates and clumps were noted without any signs of platelet morphology abnormalities or other cytopenias. No schistocytes or blasts were identified, and red and white blood cell morphology was normal (4,5).

To further evaluate the suspected pseudothrombocytopenia, repeat samples were drawn using both EDTA and sodium citrate tubes. While the EDTA sample again showed thrombocytopenia and clumping, the citrate sample revealed a normal platelet count of 258,000/mm^3 and no clumping on smear examination. These findings confirmed the diagnosis of EDTA-induced pseudothrombocytopenia.

EDTA-PTCP is estimated to occur in approximately 0.1–2% of routine blood tests. The mechanism involves autoantibodies (most commonly of the IgG, IgA, or IgM class) that bind to the glycoprotein IIb/IIIa complex, whose epitope becomes accessible only when calcium is chelated by EDTA. These antibodies are cold-reactive and do not cause platelet aggregation in vivo, explaining the absence of clinical symptoms despite markedly low platelet counts in laboratory reports (4,8).

Another potential cause of pseudothrombocytopenia—platelet satellitism, where platelets adhere around neutrophils—was excluded in this patient, as no such morphology was observed in the smear. Furthermore, sample mishandling such as inadequate mixing or delayed analysis was also ruled out.

The key to accurate diagnosis in such cases lies in the meticulous review of peripheral blood smear findings and thoughtful consideration of the patient's clinical presentation. Automated hematology analyzers are unable to detect platelet clumps as individual units, leading to spuriously low counts unless manually confirmed. EDTA-PTCP does not require any treatment and has no clinical consequences; however, failure to recognize it may lead to repeated testing, invasive procedures such as bone marrow aspiration, or inappropriate therapies.

CONCLUSION

This case underscores the importance of integrating clinical assessment with careful laboratory evaluation in the diagnosis of thrombocytopenia. EDTA-induced pseudothrombocytopenia, though rare and benign, can

mimic serious hematological conditions like immune thrombocytopenia. Recognizing its features—especially platelet clumping on peripheral smear and normal counts in citrate or heparinized samples—can prevent unnecessary treatments, hospitalizations, and anxiety for both physicians and families. Strong communication between clinicians and laboratory personnel is essential for timely identification and management. Our case highlights the value of clinical vigilance and emphasizes that not all low platelet counts signify true thrombocytopenia.

ETHICAL DECLARATIONS

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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REVIEW
DERLEME

Pharmacokinetic Variability of Antiepileptic Drugs in Neonates: A Narrative Review

Yenidoğanlarda Antiepileptik İlaçların Farmakokinetik Değişkenliği: Kapsamlı Bir İnceleme

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ABSTRACT

Neonatal seizures represent a significant clinical challenge with marked socioeconomic disparities in prevalence, ranging from 1-3 per 1,000 live births in high-income nations to 36-90 per 1,000 in low- and middle-income countries. Neonates present unique pharmacological challenges due to their rapidly changing physiology, requiring careful consideration in antiseizure drug administration. This paper presents a narrative review of existing literature analysing the pharmacokinetic variability of antiseizure drugs in neonates. This variability increases the risk of dose-related adverse reactions and highlights the critical importance of individualized dosing approaches. A comprehensive review of current literature was conducted across multiple electronic databases including PubMed, Embase, Cochrane Library and Medscape examining the pharmacokinetic properties of antiseizure medications in neonates, impact of physiological factors, therapeutic interventions, and long-term neurological consequences. Special attention was given to the effects of therapeutic hypothermia and other intensive care interventions on drug disposition. A total of 60 articles were included after screening 6331 studies and eliminating 6266 articles based on exclusion criteria. Neonatal physiology creates substantial pharmacokinetic variability in antiseizure drug disposition, with immature enzyme systems, altered protein binding, and developmental changes in clearance mechanisms. Therapeutic interventions, particularly hypothermia in hypoxic-ischemic encephalopathy, can substantially alter pharmacokinetic parameters and drug clearance. Animal studies suggest potential neurodevelopmental impacts of early antiseizure drug exposure, though establishing direct causality remains challenging due to the concurrent effects of seizures on brain development. The unique physiological characteristics of neonates necessitate an individualized approach to antiseizure drug dosing. The complex interplay between developmental factors, therapeutic interventions, and drug disposition highlights the importance of careful monitoring and dose adjustment based on patient-specific factors. Further research is needed to better understand the long-term neurodevelopmental implications of early antiseizure drug exposure.

Keywords: Antiseizure drugs, neonatal seizures, pharmacokinetics, newborn , variability

ÖZ

Yenidoğan nöbetleri, yüksek gelirli ülkelerde 1.000 canlı doğumda 1-3, düşük ve orta gelirli ülkelerde ise 1.000 canlı doğumda 36-90 arasında değişen yaygınlık oranları ile belirgin sosyoekonomik farklılıklar gösteren önemli bir klinik sorundur. Yenidoğanlar, hızla değişen fizyolojileri nedeniyle benzersiz farmakolojik zorluklar ortaya çıkarır ve antiepileptik ilaçların uygulanmasında dikkatli bir değerlendirme gerektirir. Bu makale, yenidoğanlarda antiepileptik ilaçların farmakokinetik değişkenliğini analiz eden mevcut literatürün anlatımsal bir incelemesini sunmaktadır. Bu değişkenlik, dozla ilişkili advers reaksiyon riskini artırır ve bireyselleştirilmiş dozlama yaklaşımlarının kritik önemini vurgular. PubMed, Embase, Cochrane Library ve Medscape gibi birçok elektronik veri tabanında, yenidoğanlarda antiepileptik ilaçların farmakokinetik özellikleri, fizyolojik faktörlerin etkisi, terapötik müdahaleler ve uzun vadeli nörolojik sonuçlar incelenerek mevcut literatürün kapsamlı bir incelemesi yapılmıştır. Terapötik hipotermi ve diğer yoğun bakım müdahalelerinin ilaç dağılımı üzerindeki etkilerine özel dikkat gösterilmiştir. 6331 çalışmayı taradıktan ve dışlama kriterlerine göre 6266 makaleyi eledikten sonra toplam 60 makale dahil edildi. Yenidoğan fizyolojisi, olgunlaşmamış enzim sistemleri, değişmiş protein bağlanması ve klirens mekanizmalarındaki gelişimsel değişiklikler nedeniyle antiepileptik ilaçların dağılımında önemli farmakokinetik değişkenlik yaratır. Terapötik müdahaleler, özellikle hipoksik-iskemik ensefalopatide hipotermi, farmakokinetik parametreleri ve ilaç klirensini önemli ölçüde değiştirebilir. Hayvan çalışmaları, erken antiepileptik ilaç maruziyetinin nörogelişimsel etkileri olabileceğini göstermektedir, ancak nöbetlerin beyin gelişimi üzerindeki eşzamanlı etkileri nedeniyle doğrudan nedensellik kurmak hala zordur. Yenidoğanların benzersiz fizyolojik özellikleri, antiepileptik ilaç dozlamasında bireyselleştirilmiş bir yaklaşım gerektirir. Gelişim faktörleri, terapötik müdahaleler ve ilaç dağılımı arasındaki karmaşık etkileşim, hasta özelinde faktörlere dayalı dikkatli izleme ve doz ayarlamasının önemini vurgulamaktadır. Erken antiepileptik ilaç maruziyetinin uzun vadeli nörogelişimsel etkilerini daha iyi anlamak için daha fazla araştırma gereklidir.

Anahtar Kelimeler: Antiepileptik ilaçlar, yenidoğan nöbetleri, farmakokinetik, yenidoğan, değişkenlik

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INTRODUCTION

Antiseizure medications are crucial for managing neonatal seizures, which can have severe consequences if left untreated. Neonatal seizure exhibits substantial socioeconomic variation in prevalence, ranging from 1-3 per 1,000 live births in high-income nations to 36-90 per 1,000 in low- and middle-income countries (1). Neonates present unique pharmacological challenges due to rapid physiological changes, leading to variability in drug disposition and increased risk of adverse reactions.

As per the recommendations of the Neonatal Task force by International League Against Epilepsy (ILAE). in 2023, phenobarbital is the primary antiseizure medication for neonatal seizures. Alternative options include phenytoin, levetiracetam, midazolam, with levetiracetam preferred for neonates with cardiac conditions. Sodium channel blockers are used for suspected channelopathies. For refractory seizures with unknown aetiology, a pyridoxine trial is warranted for neonates with clinical or EEG features of pyridoxine-dependent epilepsy (2).

Neonatal physiology differs significantly from older individuals, profoundly impacting drug disposition. Key variables include variations in distribution, clearance, protein binding, body composition, gastrointestinal function, and enzyme activity. The heightened total body water and altered protein binding in neonates can influence drug distribution, while immature hepatic and renal function impact metabolism, half-life, and elimination. Considering developmental measures such as gestational age, postnatal age, and weight is crucial when dosing antiseizure medications in this population. Special considerations are required in neonates large for their gestational age, where the weight based dosing ,body size metrics and dose capping can be complicated. Fluctuations in albumin and alpha1- acid glycoprotein levels during the neonatal stage can induce alterations in protein binding, which, in turn, influence the distribution and clearance of low-extraction drugs, including valproic acid (95%albumin bound). and carbamazepine (70-90% AAG bound) (3).

Different formulations of antiseizure medications influence their pharmacokinetic profiles. Extended-release formulations offer advantages including reduced dosing frequency and diminished peak-to- trough fluctuations. However, these formulations may not always be bioequivalent to immediate- release versions, potentially necessitating dosage adjustments.

Specific drug metabolising enzymes exhibit varied developmental trajectories during the fetal and neonatal stages. Enzymes like CYP3A7, SULT1A3/1A4 show peak expression during fetal life with activity diminishing over the first two years. CYP3A5, CYP2C19, SULT1A1 enzymes show a moderate increase postnatally, becoming more active later in pediatric period. CYP2D6, CYP3A4, CYP2C9, CYP1A2 enzymes displays modest ontogeny during the second or third trimester of pregnancy followed by another notable increase in phenotypic activity throughout infancy (61). In addition, Genetic polymorphisms in drug-metabolizing enzymes like CYP450 or UGT can cause significant variation in the rate of drug metabolism, clearance, bioavailability, overall efficacy, and adverse drug reactions (3).

Comorbidities like hepatic or renal impairment can further influence drug clearance and increase the risk of adverse reactions. Additionally, common neonatal intensive care interventions, including extracorporeal membrane oxygenation, hypothermia, and continuous renal replacement therapy, can significantly affect pharmacokinetics (2,4-9). The concurrent administration of multiple antiseizure medications to achieve adequate seizure control may increase the risk of drug-drug interactions. This risk is related to the ability of certain antiseizure drugs to modulate drug-metabolizing enzymes and the fact that many antiseizure drugs are substrates of the cytochrome P450 enzyme family. Valproic acid, phenobarbital, and phenytoin are notable for their high potential for DDIs due to their complex pharmacokinetic and metabolic pathways (3).

Pharmacokinetic variability in neonates presents characterization challenges due to complexities of conducting clinical studies in this population, including limited participant numbers, ethical considerations, and blood volume constraints. Population pharmacokinetics and modelling techniques help address data scarcity (3).

Therapeutic Hypothermia

A common intervention in neonates with hypoxic-ischemic encephalopathy which can significantly impact pharmacokinetic parameters. Hypothermia may decrease drug clearance and alter the volume of distribution by modulating intravascular blood volume, organ perfusion, and enzymatic metabolic processes. Studies have shown that phenobarbital clearance is reduced in cases of severe asphyxia and the application of therapeutic hypothermia, highlighting the importance of considering the underlying disease condition also when dosing medications in this patient population (10).

Long-term Neurological Consequences

Prolonged neonatal seizures can have significant long-term neurological consequences including cognitive deficits and increased epilepsy risk in over 30% of survivors (11). Hence, establishing direct causality between antiseizure drugs and developmental/cognitive problems is challenging, as early- onset epilepsy also contributes (12). Differentiating drug induced vs seizure induced neurological consequences is beyond the scope of this review, but therapeutic drug monitoring might benefit the treating physician in preventing overexposure through suitable dose adjustments.

Animal studies have shown that antiseizure drug exposure, especially phenobarbital, phenytoin and sodium valproate can increase neuron apoptosis and inhibit neurogenesis. Levetiracetam does not induce cell death. It is possible that these proapoptotic actions contribute to adverse outcomes observed in rats and cognitive impairment seen in humans following exposure to certain antiseizure medications during postnatal development (13-15).

A retrospective cohort study comparing phenobarbital to levetiracetam in infants assessed outcomes of cerebral palsy and neurodevelopmental outcomes at 24 months using the Bayley Scales of Infant Development (16). The study revealed a 2.3-fold increase in cerebral palsy exclusively with phenobarbital exposure. Assessment of motor, cognitive, and language performance using the Denver Assessment of Early Childhood at 12 months indicated negative effects of increased phenobarbital and levetiracetam exposure, specifically in motor domains. At 24 months, phenobarbital led to lower cognitive and motor skills (8-point and 9-point decreases on the Bayley Scales of Infant Development & BSID motor score respectively). In contrast, levetiracetam was linked to smaller decreases in cognitive and motor skills (2.2-point and 2.6-point decreases respectively), suggesting it may be a better option than phenobarbital (16). Moreover,A recent study comparing fosphenytoin to phenobarbital indicated that neonates treated with fosphenytoin demonstrated improved neurodevelopmental outcomes at 18-24 months compared to phenobarbital. But the small sample size was a major limitation (17).

The Early intervention and adherence to treatment protocols for neonatal seizures are associated with lower progression to status epilepticus, decreased morbidity, and shorter hospital stays (18). Studies on new antiseizure drugs in paediatric epilepsy have found cognitive functioning is often dose- dependently impaired, particularly with combination therapy. Identifying patients prone to cognitive issues early allows for gradual titration, as rapid titration risks neurological side effects (19).

METHODS - SEARCH STRATEGY

A comprehensive literature search was conducted for this narrative review across multiple electronic databases including PubMed, Embase, Cochrane Library and Medscape. The primary search terms were structured to identify literature on pharmacokinetic variability and antiseizure therapy in neonates. The search strategy combined Medical Subject Headings (MeSH). terms and free-text terms: ("pharmacokinetic" OR "pharmacokinetically" OR "pharmacokinetics"). AND ("variabilities" OR "variability" OR "variable"). AND ("anticonvulsants" OR "antiseizure" OR "antiepileptic drugs"). AND ("infant, newborn" OR "neonate" OR "neonatal").

Search strategy is depicted in **Figure 1**. The combined keyword search identified 65 articles published between 1976 and 2024 Articles were reviewed over a six-month period (January to June 2024), focusing on studies examining pharmacokinetic variability of individual antiseizure drugs in neonates. Additional relevant studies were identified through manual searching of reference lists from selected articles. 60 Relevant pharmacokinetic studies on neonates (0-28days). under antiseizure therapy were included in the final review.

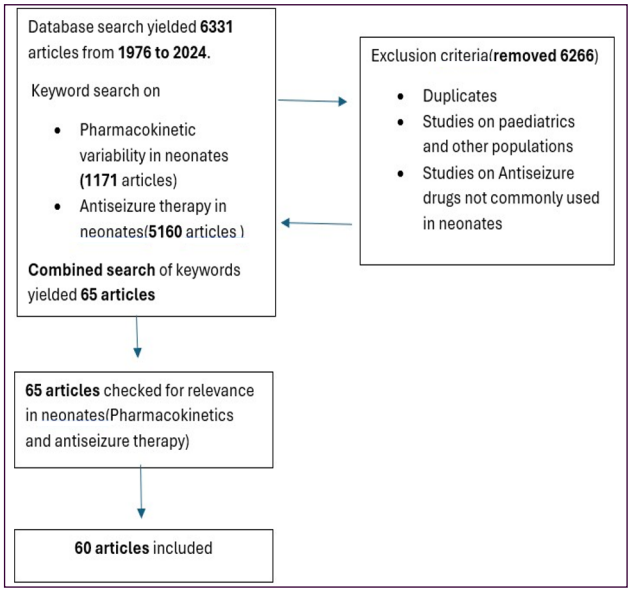

Figure 1. Search strategy for literature review

Phenobarbital Pharmacokinetics

Phenobarbital is a commonly used antiseizure agent in neonates due to its effectiveness and availability in intravenous formulations. Phenobarbital should initially be given at 20 mg/kg intravenously, followed by a maintenance dose of 5 mg/kg/day, either IV or orally. Studies showed a 40% response after the first dose, and giving more IV phenobarbital helped control seizures in both term and preterm neonates (20). It is lipophilic, with a relatively long half-life, which can be advantageous in the treatment of neonatal seizures (9). However, the physicochemical properties of phenobarbital, such as its high protein binding and potential for interactions with other drugs, can also contribute to the variability in its pharmacokinetics and efficacy (9, 21).

In neonates, phenobarbital has reduced oral bioavailability and a longer elimination half-life compared to older children and adults. Therefore, a low dose per kilogram (dose/kg). is recommended during the neonatal period. The dose requirement decreases with increasing age, especially in children also taking valproic acid, which inhibits phenobarbital metabolism (22).

Phenobarbital clearance is reduced in severe asphyxia and therapeutic hypothermia (10). While CYP2C19 metabolism may be suppressed by hypothermia, dose adjustments are typically not required (22-24). However, conflicting recommendations exist regarding second loading doses during therapeutic hypothermia (20). Additionally, factors that may impact renal or hepatic elimination in neonatal encephalopathy could potentially affect phenobarbital metabolism.

In children on renal replacement therapy (RRT), age did not affect phenobarbital dosing recommendations, but higher loading and maintenance doses were needed. In the study by Céline Thibault on neonates undergoing ECMO therapy, phenobarbital clearance was lower but volume of distribution (Vd). estimates was higher. The higher Vd was consistent with a prior study in neonates on extracorporeal membrane oxygenation (ECMO), likely due to factors like fluid resuscitation and inflammation (25).

Recent ILAE guidelines recommend monitoring plasma levels of phenobarbital during maintenance (2). While phenobarbital remains the first-line treatment for neonatal seizures, its use is associated with concerns about potential adverse effects on the developing nervous system (21,26,27). Preclinical studies have shown that early-life exposure to phenobarbital can disrupt synaptic development and induce neuronal apoptosis, which may lead to long-term neurodevelopmental consequences (21,27).

Phenytoin Pharmacokinetics

Phenytoin has a narrow therapeutic index (10±20 mg/l), which becomes even narrower during the neonatal period (6±14 mg/l). Infants and young children often require higher doses of phenytoin per kilogram body weight to achieve therapeutic plasma levels compared to adults, likely due to differences in drug clearance (28,29). An initial loading dose of 20mg/kg phenytoin equivalent is administered over 30 minutes, succeeded by a maintenance regimen of 5 mg/kg/day, administered intravenously or orally in two divided doses (20). The bioavailability of phenytoin in newborns and infants remains controversial (30,31). Additionally, due to non-linear pharmacokinetic elimination, small changes in doses can result in significant variations in serum concentrations. During infancy, impaired protein binding contributes to the pharmacokinetic variability of phenytoin (28,31). At higher concentrations, saturation of protein binding occurs. The protein binding of phenytoin is 90%, and hence in the presence of hypoalbuminemia, concomitant drug administration or renal impairment, lower therapeutic concentrations must be targeted to avoid drug toxicity. Phenytoin clearance may be reduced in patients with decreased activity of CYP2C9 variants, increasing their susceptibility to dose-related side effects (32). Analogous to phenobarbital, experimental evidence suggests that phenytoin may induce apoptotic neurodegeneration (20).

Fosphenytoin is a water-soluble prodrug of phenytoin that can be administered intravenously, providing a more stable and predictable pharmacokinetic profile compared to phenytoin in neonates. However, fosphenytoin still exhibits similar variability in absorption, distribution, and metabolism as phenytoin due to the unique physiology of neonates (5,7,8). Fosphenytoin may be preferred over phenytoin due to a potentially lower risk of adverse effects, easier and safer intravenous administration (33). Fosphenytoin is associated with a lower risk of cardiovascular adverse effects compared to phenytoin, but neonates may still experience complications such as hypotension and arrhythmias.

Levetiracetam Pharmacokinetics

Levetiracetam is safe and effective in paediatric epilepsy, due to its easy titrability and fewer drug interactions. According to the ILAE, levetiracetam should be administered with an initial intravenous loading dose of 40 mg/kg, followed by a subsequent intravenous loading dose of 20 mg/kg if necessary. The maintenance dosage is 40-60 mg/kg/day, administered intravenously or orally in three divided doses. In a study focusing on neonates, the initial cumulative levetiracetam dosage varied between 50 and 100 mg/kg. A separate study on infants with hypoxic-ischemic encephalopathy reported mean total and maintenance levetiracetam doses of 63 and 65 mg/kg/day, respectively (20).

Drug clearance is the most significant parameter to be considered in dosing levetiracetam. Conflicting results on neonatal drug clearance were identified. A study on 18 neonates found that levetiracetam clearance increases significantly during the week of life in neonates with the simultaneous decrease in the mean half-life over the same period (34,35). This means that to maintain therapeutic levels, more frequent dosing may be needed for neonates than in older children and adults.

A population pharmacokinetic model developed for neonates with seizures based on 44 measured concentrations from 20 neonates demonstrated that creatinine clearance (CRCL). and total body weight influence the disposition of levetiracetam, which in turn impacts the dosing strategy required to maintain a target concentration range of 6-20 mg/L when administering this anticonvulsant once daily (36). They also noted that clearance was higher than that predicted based on physiological characteristics. This study did not find any alteration in disposition in infants managed with therapeutic hypothermia (36).

Other studies conclude that neonates have lower clearance, higher volume of distribution, and a longer half-life compared to adults. Small sample sizes and interindividual variability were major limitations (35,37).

The lower clearance and longer half-life in neonates raise concerns about potential toxicity. While we found no reported adverse effects on vital signs, urine output, or hepatic and renal function, even at higher doses, close monitoring for potential toxicity is crucial, especially in neonates with impaired renal function (38). Close monitoring is advised in patients under CRRT therapy (39).

Levetiracetam is not appreciably protein bound and the metabolism is mainly through metabolic pathways such as hydrolysis of acetamide group and not liver CYP 450. Thus, pharmacokinetic interactions with other drugs are unlikely. However, monitoring therapy is recommended when concomitant seizure medications like carbamazepine, phenobarbital are used (40,41).

Overall, neonates require different dosing regimens than adults to maintain therapeutic levels of levetiracetam. A Study by Venkatesan et al suggests that higher loading doses may be necessary (38). and that by Sharpe et al indicates that more frequent dosing is needed (34). Higher cumulative loading doses were reported in neonates undergoing ECMO therapy (42).

Levetiracetam when compared to phenobarbital in neonates had better safety profile. But it requires further investigations in larger sample populations, as other studies comparing the adverse events found no significant differences in both groups (43,44).

Table 1: Pharmacokinetic parameters, variability and special considerations of antiseizure medications in neonates

Drug	Half-Life (hours)	Clearance (mL/min/kg)	Volume of Distribution (L/kg)	Protein Binding (%)	Special Considerations
Phenobarbital	• 45-409 hours (22)	• Reduced in severe asphyxia and therapeutic hypothermia	• 0.85±0.059 L/kg(59) Higher in ECMO therapy	• 36-43% (60)	• Longer elimination half-life vs older children;CYP2C19 metabolism • Higher doses needed in RRT • Dose-dependent side effects: • CNS: drowsiness, ataxia, vertigo, cognitive impairment • Respiratory depression
Phenytoin	• 6.9-194 hours (28,30)	• Reduced in CYP2C9 poor metabolizers • Age-related changes due to enzyme maturation affecting clearance (3)	• GA 27-30 weeks: 1.2±0.11 • L/kg GA 31-36 weeks: 1.17±0.21 L/kg GA • ≥37 weeks: 1.22±0.21 L/kg (30)	• 61-91% (30)	• Narrow therapeutic index in neonates • Non-linear pharmacokinetics • Higher doses/kg needed vs adults • Dose-dependent side effects:Concentration-dependent neurological toxicity • Drug-induced seizures • Pharmacogenetic variability (CYP2C9 & CYP2C19)
Levetiracetam	• Day 1: 18.5 hours • Day 7: 9.1 hours (34)	• Day 1: 0.7 mL/min/kg • Day 7: 1.33 mL/min/kg (34) • Influenced by postnatal age and body weight (3)	• 1.01±0.13 • L/kg(range: 0.81- • 1.24 L/kg) (34) • Higher than adults • Weight-based effect on volume of distribution (3)	• <10% • Not appreciably protein bound (41)	• 50% dose reduction in CRRT • Influenced by creatinine clearance • Dose-dependent ADRs: CNS depression: gait incoordination, fatigue, dizziness • Somnolence, feeding difficulty- Mild apnea and bradycardia
Carbamazepine	• 8.7-24.5 hours (48,51)	• Altered due to immature liver enzymes	• Neonates: 1.52±0.5 L/kg (51)	• Lower binding affinity vs older patients	• Peak levels: 4-16h post- administration • Monitor 10,11-epoxide metabolite • Dose-dependent ADRs:Neurological: ataxia, dizziness, sedation, hypotonia • Respiratory depression • Psychiatric: anxiety, depression • Hematological: leukopenia, thrombocytopenia • Hepatotoxicity, hyponatremia (SIADH) • Sinus tachycardia (in overdose)
Midazolam	• Neonates: 4-12 hours • Average: 6.3 hours (range: 2.6-17.7 • hours) (55) • Seriously ill neonates: 6.5-12 hours	• 1.8 mL/min/kg(range: 0.7-6.7 mL/min/kg) (55)	• 1.1 L/kg(similar to adults) (55)	• Primarily albumin (80% of adult albumin levels)	• Clearance proportional to birth weight • Higher clearance after 39 weeks gestation • CYP3A4/5 metabolism • Dose-dependent ADRs:Gastrointestinal: vomiting • Respiratory depression, hypotension Hypothermia, paradoxical reactions • Neonates: Cognitive/behavioral issues, neuronal injury, seizure-like movements(IV bolus)

*Abbreviations: GA = Gestational Age; CNS = Central Nervous System; ECMO = Extracorporeal Membrane Oxygenation; RRT = Renal Replacement Therapy; CRRT = Continuous Renal Replacement Therapy; ADR = Adverse Drug Reaction; SIADH = Syndrome of Inappropriate Antidiuretic Hormone Secretion

Carbamazepine Pharmacokinetics

Carbamazepine is proposed as the drug of choice in benign familial neonatal seizures (45). Neonatal epilepsy linked to KCNQ2 or SCN2A ion channel disorders demonstrates favourable responses to sodium-channel blockers including carbamazepine.

Autoinduction-related pharmacokinetic variability has been a well-recognized challenge with carbamazepine, potentially leading to suboptimal dosing and toxicity (21,26,46). Oxcarbazepine, an orally administered alternative to carbamazepine, may be safer to use owing to its more favourable characteristics regarding enzyme induction (47).

Carbamazepine exhibits significant pharmacokinetic variability in neonates compared to adults, posing unique challenges in neonatal treatment. Studies like those by Singh et al highlight a considerably shorter elimination half-life in neonates, necessitating different dosing regimens (48,49). This variation is attributed to the immature liver enzyme activity and altered drug clearance mechanisms (50).

A one-compartment pharmacokinetic model by Rey et al in neonates identified peak concentrations ranging from 3.14 to 10 mcg/ml at 2 and 9 hours post-administration, while study by Singh et al showed peak levels attained between 4 to 16 hours post-administration (48,51). Levels declined sharply around 8 to 15 days and then slowly over the subsequent 3 months (48).

Neonates appear to exhibit lower binding affinity for carbamazepine (CBZ). compared to older patients, while the binding of carbamazepine-epoxide (CBZ-E). remains similar. This suggests that the therapeutic range of total CBZ concentrations in neonates may differ from that in adults, but can be confirmed with further clinical studies (52). For infants, children, and adolescents receiving oral carbamazepine, it is recommended to measure serum levels of the 10,11-carbamazepine epoxide metabolite in cases where drug toxicity is suspected, even if the serum carbamazepine concentration is within the therapeutic range (53).

Midazolam Pharmacokinetics

Midazolam, a benzodiazepine, has rapid onset and short duration of action. In healthy neonates, the half-life is 3.3-fold longer and clearance is 3.7-fold smaller, while the volume of distribution is similar compared to adults (54).

Midazolam is metabolized by CYP3A4 and CYP3A5 enzymes, whose activities increase in the liver during the first weeks of life, leading to a lower metabolic rate in neonates. Due to the immaturity of hepatic cytochrome P450 3A4 activity, preterm infants exhibit markedly reduced midazolam clearance compared to older children. Concomitant administration of phenobarbital significantly elevated midazolam clearance. If phenobarbital is replaced by non-CYP3A inducers as the primary anticonvulsant, a 50% reduction in the midazolam maintenance dose may be warranted to prevent excessive exposure during the initial days after birth (56).

Population studies have found that midazolam clearance and volume of distribution are directly proportional to birth weight, with gestational age being a significant factor. Neonates born after 39 weeks gestation demonstrate 1.6 times higher clearance rates (57,58).

Neonatal pharmacokinetics of midazolam are affected by disease states, as multiple organ failure reduces clearance and mechanical ventilation prolongs half-life. Furthermore, extracorporeal membrane oxygenation (ECMO). therapy significantly alters midazolam's half-life, clearance, and volume of distribution (54). In term neonates diagnosed with hypoxic-ischemic encephalopathy receiving therapeutic hypothermia, studies have shown that this intervention does not significantly impact the clearance of phenobarbital or midazolam.

Drug interactions observed included one with indomethacin where exposure to indomethacin and its apparent effects on midazolam clearance suggested that alterations in drug disposition may arise from a patent ductus arteriosus or the direct impacts of indomethacin on hemodynamic or renal function (55).

These findings underscore the complexity of midazolam pharmacokinetics in neonates and the need for individualized dosing strategies based on factors such as gestational age, birth weight, disease state, and treatment modalities.

CONCLUSION

Antiseizure drug therapy in neonates represents one of the most challenging areas in paediatric pharmacotherapy, where the developing brain is uniquely vulnerable to both seizure-related injury and drug-induced neurotoxicity, creating critical needs for precision in therapeutic decision-making.

Substantial pharmacokinetic variability stems from physiological and developmental factors unique to neonates, compounded by distinct drug profiles and under-recognition of adverse reactions in NICUs. This highlights urgent needs for sophisticated drug therapy optimization approaches.

Key clinical implications emerge from this analysis. Firstly, Individualized dosing is essential, as standard weight-based approaches fail to account for profound pharmacokinetic variability. Second, Therapeutic drug monitoring should become routine practice, particularly for phenobarbital and phenytoin with narrow therapeutic windows. Lastly, Intensive care interventions including hypothermia, ECMO, and renal replacement

therapy significantly alter pharmacokinetics and require proactive dose adjustments.

Emerging evidence suggests levetiracetam potentially offers superior long-term safety compared to phenobarbital. However, phenobarbital remains ILAE-recommended first-line therapy due to superior seizure control efficacy, creating tension between immediate management and long-term neurodevelopmental considerations. Distinguishing medication effects from seizure-related injury requires further investigation.

Advanced quantitative methodologies, particularly physiologically-based pharmacokinetic modeling and population analysis, offer promising pathways forward. These approaches capture effects of age, organ development, and concomitant therapies on drug disposition, enabling precise exposure prediction and dosing individualization. Emerging technologies including dried blood spot sampling further enhance intervention precision.

The field must prioritize individualized therapy protocols considering patient characteristics, drug interactions, and long-term outcomes. Success requires a paradigm shift toward precision medicine that recognizes complex interplay between developmental physiology, disease pathology, and drug disposition in this vulnerable population.

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LETTER TO THE EDITOR
EDİTÖRE MEKTUP

Important Health Steps: Newborn Blood Spot Test and Vaccinations

Sağlık İçin Önemli Adımlar: Aşılar ve Yenidoğan Topuk Kanı Testi

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Dear Editor;

Newborn Blood Spot Testing and routine childhood vaccinations represent foundational components of modern preventive healthcare. These interventions are critical for the early identification and prevention of both genetic and infectious diseases that can otherwise lead to lifelong complications or mortality. The blood spot test, typically conducted within the first 48–72 hours after birth, enables the early detection of serious genetic and metabolic disorders such as phenylketonuria, congenital hypothyroidism, and biotinidase deficiency, facilitating timely interventions that can prevent irreversible damage or death (1,2). Similarly, routine immunizations are a proven strategy for controlling and eradicating infectious diseases, significantly reducing child mortality and morbidity worldwide.

According to the 2023 World Health Organization (WHO) and UNICEF (WUENIC) estimates, Türkiye achieved commendable immunization coverage rates among children. Vaccination coverage reached 98% for Bacillus Calmette–Guérin (BCG); 99% for the first and third doses of diphtheria-tetanus-pertussis (DTP1 and DTP3), the third dose of hepatitis B (HepB3), Haemophilus influenzae type b (Hib3), and the first and second doses of inactivated poliovirus vaccine (IPV1 and IPV2); 95% for the first dose of measles-containing vaccine (MCV1) and rubella-containing vaccine (RCV1); 94% for the second dose of MCV; and 95% for the third dose of pneumococcal conjugate vaccine (PCV3) (3).

In 2023, the number of neonates screened through the national newborn blood spot program in Türkiye reached 931,882 (4). This widespread participation underscores the importance attributed to early diagnostic measures in neonatal care and reflects a national commitment to public health prevention strategies. However, the increasing trend of test and vaccine refusal presents a growing challenge that cannot be overlooked.

Vaccine hesitancy, which the WHO identified as one of the top ten threats to global health in 2019, is also reflected in the Turkish context (5). While only 183 families refused childhood vaccinations in 2011, this number sharply rose to over 23,000 by 2017 (6). A similar reluctance is emerging toward newborn screening programs. This growing resistance is often driven by misinformation, disinformation on social media, mistrust in healthcare institutions, and cultural or religious beliefs that discourage medical intervention (7).

These trends have important ramifications. Disease outbreaks, unnecessary disability, and higher public health costs can result from missed or delayed diagnoses of infectious diseases. A multimodal strategy including community-level engagement, education, and communication is needed to reduce these hazards.

The "Vaccinate with Confidence" initiative, administered by the Centers for Disease Control and Prevention (CDC) in the United States, is designed to enhance public confidence in vaccines, mitigate the propagation of misinformation, and fortify the bond of trust between the community and healthcare professionals (8). Furthermore, numerous states mandate that children of school age be fully vaccinated, with only a select few allowing for exemptions for religious or medical reasons (9).

In the context of newborn screening, the Newborn Screening Saves Lives Act in the United States (US) has standardized the scope of screening at the national level and ensured that families are informed (10]. The educational materials prepared by the Health Resources and Services Administration (HRSA) to promote equitable distribution of healthcare resources and increase parental literacy are used during the prenatal and postnatal periods (11). All states in the US mandate

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newborn blood spot screening, yet most states permit parents to decline screening for their infants (12).

In Europe, the public is informed through multilingual and scientific content on digital information platforms such as the European Vaccination Information Portal, which is operated by the European Centre for Disease Prevention and Control (ECDC) (13). In certain countries, such as France and Italy, the administration of childhood vaccinations has been rendered legally mandatory (14).

In the context of newborn screening, the European Reference Network for Rare Diseases is strengthening inter-country coordination with the aim of expanding the scope of screening and promoting the widespread provision of parental counseling services (15).

In the nation of Turkey, newborn blood spot screening is legally protected (16). In instances of refusal, a court-ordered health protection measure may be initiated to ensure the child's right to health is upheld. The current practice requires that when parents decline vaccination or newborn blood spot screening, they must sign an informed refusal form. In addition, counseling is provided by both the family physician and a public health official. These procedures aim to support informed parental decision-making while upholding public health responsibilities.

Promoting trust in preventative health practices is a major responsibility of family doctors. They can address issues, debunk falsehoods, and point families toward trustworthy scientific sources through customized therapy. In order to educate expectant and new parents about the life-saving benefits of these programs, the Ministry of Health and regional health directorates need to step up their efforts. Public awareness and acceptance can be increased through public campaigns, community-based education, and collaborations with educational institutions, the media, and religious authorities.

Strengthening trust in science-based medicine and preventive programs is essential for the health of future generations. The widespread implementation and societal embrace of both newborn screening and vaccination are not only medical necessities but also moral imperatives in the pursuit of sustainable public health.

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