EPAT
Emergency Physicians Association of Turkey

EAJEM

Eurasian Journal of Emergency Medicine

Citation abbreviation: Eurasian J Emerg Med

ISSN 2149-5807 • EISSN 2149-6048

Volume: 19
Issue: 3

www.eajem.com

September
2020

galenos yayinevi

Official Journal of Emergency Physicians Association of Turkey

EAJEM
Eurasian Journal of Emergency Medicine
Citation abbreviation: Eurasian J Emerg Med

galenos yayınevi

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Turkey **Phone:** +90 (212) 621 99 25 **Fax:** +90 (212) 621 99 27
E-mail: info@galenos.com.tr/yayin@galenos.com.tr **Web:** www.galenos.com.tr **Publisher Certificate Number:** 14521

Printing at: Özgün Basım Tanıtım San. Tic. Ltd. Şti. Yeşilce Mah. Aytekin Sok. Oto Sanayi Sitesi No: 21 Kat: 2 Seyrantepe Sanayi, Kağıthane, İstanbul, Türkiye
Telefon/Phone: +90 (212) 280 00 09 **Sertifika No:** 48150
Printing Date: September 2020 **ISSN:** 2149-5807 **E-ISSN:** 2149-6048
International scientific journal published quarterly.

EAJEM
Eurasian Journal of Emergency Medicine
Citation abbreviation: Eurasian J Emerg Med

EAJEM
Eurasian Journal of Emergency Medicine
Citation abbreviation: Eurasian J Emerg Med

Past editors

Erden Erol Ünlüer
Department of Emergency Medicine, Uşak University School of Medicine, Uşak, Turkey
erolerdenun@yahoo.com
ORCID ID: 0000-0003-0334-7440
İsa Kılıçaslan
Department of Emergency Medicine, Gazi University School of Medicine, Ankara, Turkey
isakilicaslan@hotmail.com
ORCID ID: orcid.org/0000-0002-0330-2595

List of the reviewers who reviewed papers for Eurasian Journal of Emergency Medicine between September 2019-December 2019.

Abdulhadi Tashkandi
Arif Karagöz
Celal Katı
Fatih Ozan Kahveci
Elif Çelikel
Ethem Acar
Eylem Kuday Kaykısız
Gülşah Çikrikçi Işik
İsmail Altıntop
Luis Garcia Castrillo Riesgo
Mehmet Altuntaş
Naci Murat
Eylem Kuday Kaykısız
Afşin Emre Kayıpmaz
Nurşah Başol
Ökkeş Taha Küçükdağlı
Fatih Çalışkan
Özgür Söğüt
Kıvanç Karaman
Sadiye Yolcu
A Cüneyt Hocagil
Yunsur Çevik
Yücel Yüzbaşıoğlu

EAJEM
Eurasian Journal of Emergency Medicine
Citation abbreviation: Eurasian J Emerg Med

AIMS AND SCOPE

Eurasian Journal of Emergency Medicine (Eurasian J Emerg Med) is the open access, scientific publication organ of the Emergency Medicine Physicians' Association of Turkey that is published in accordance with independent, unbiased, double blind peer review principles. The journal is published 4 times in a year in March, June, September and December.

The journal aims to publish scientifically high quality articles which can contribute to the literature and written in the emergency medicine field and other related fields. Review articles, case reports, editorial comments, letters to the editor, scientific letters, education articles, original images and articles on history and publication ethics which can contribute to readers and medical education are also published.

The journal's target audience includes Emergency Medicine experts, School members who conduct scientific studies and work in the Emergency Medicine field, researchers, experts, assistants, practicing physicians and other health sector professionals.

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

Eurasian Journal of Emergency Medicine is indexed in Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, EBSCO, EuroPub, ROOT INDEXING, Directory of Research Journals Indexing, J-Gate, Türk Medline, Türkiye Atıf Dizini and ProQuest, CABI.

Processing and publication are free of charge with Eurasian Journal of Emergency Medicine. No fees are requested from the authors at any point throughout the evaluation and publication process. All manuscripts must be submitted via the online submission system which is available through the journal's web page at www.eajem.com. Journal's guidelines, technical information and the required forms are available on the journal's web page.

All expenses of the journal are covered by the Emergency Medicine Physicians' Association of Turkey. Pharmaceutical advertisements may be published in the printed copies of the journal. Potential advertisers should get in contact with the Editorial Office. Advertisement images are only published upon Editor in Chief's approval.

Statements or opinions expressed in the manuscripts published in the journal reflect the views of the author(s) and not the opinions of the Eurasian Journal of Emergency Medicine, the editors, the editorial board and/or the publisher, GALENOS; the editors, the editorial board and the publisher disclaim any responsibility or liability for such materials.

All published content is available online free of charge at www.eajem.com.

Eurasian Journal of Emergency Medicine is distributed internationally and free of charge to its target audience. Archive of the journal is available online at www.eajem.com, free of charge.

The journal is printed on an acid-free paper.

Editorial Office

Prof. Salvatore Di Somma, MD PhD

Emergency Medicine

Department of Medical-Surgery Sciences and Translational Mediicne

Chairman Postgraduate School of Emergency Medicine

Faculty of Medicine and Psychology

University of Rome Sapienza

Rome, Italy

E-mail: salvatore.disomma@uniroma1.it

Phone: +39348.3316131

Open Access Policy

This journal provides immediate open access to its content on the principle that making research freely available to the public supports a greater global exchange of knowledge.

Open Access Policy is based on the rules of the Budapest Open Access Initiative (BOAI) http://www.budapestopenaccessinitiative.org/. By "open access" to peer-reviewed research literature, we mean its free availability on the public internet, permitting any users to read, download, copy, distribute, print, search, or link to the full texts of these articles, crawl them for indexing, pass them as data to software, or use them for any other lawful purpose, without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. The only constraint on reproduction and distribution, and the only role for copyright in this domain, should be to give authors control over the integrity of their work and the right to be properly acknowledged and cited.

OPEN ACCESS

EAJEM
Eurasian Journal of Emergency Medicine
Citation abbreviation: Eurasian J Emerg Med

INSTRUCTIONS TO AUTHORS

Eurasian Journal of Emergency Medicine (Eurasian J Emerg Med), as a double-blind peer reviewed journal published by the Emergency Medicine Physicians' Association of Turkey, publishes original articles on clinical, experimental and basic sciences in the Emergency Medicine field, review articles covering basic and up-to-date subjects, case reports, short editorial manuscripts and manuscripts covering medicine history and publication and research ethics.

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

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

Manuscripts submitted to Eurasian Journal of Emergency Medicine will go through a double blind peer review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in the field in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or the editorial board members of the journal. The Editor in Chief is the final authority in the decision making process of all submissions.

An approval of research protocols by Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", amended in October 2013, www.wma.net) is required for experimental, clinical and drug studies and some case reports. If required, ethics committee reports or an equivalent official document may be requested from the authors. For manuscripts concerning experimental research on humans, a statement should be included that shows informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information on patient consent, name of the ethics committee and the ethics committee approval number should also be stated in the materials and methods section of the manuscript. It is the authors' responsibility to carefully protect the patients' anonymity. For photographs that may reveal the identity of the patients, releases signed by the patient or their legal representative should be enclosed.

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

In the event of an alleged or suspected research misconduct, including plagiarism, citation manipulation, and data falsification/fabrication, among others, the Editorial Board will follow and act in accordance with COPE guidelines.

Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE - www.icmje.org). The ICMJE recommends that authorship be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

2. Drafting the work or revising it critically for important intellectual content; AND

3. Final approval of the version to be published; AND

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he or she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their coauthors.

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

Eurasian Journal of Emergency Medicine requires corresponding authors to submit a signed and scanned version of the authorship contribution form (available for download through www.eajem.com) during the initial submission process in order to act appropriately to authorship rights and prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship", the submission will be rejected without further review. As part of submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all the responsibility for authorship during the submission and review stages of the manuscript.

Eurasian Journal of Emergency Medicine requires and encourages the authors and the individuals involved in the evaluation process of submitted manuscripts to disclose any existing or potential conflicts of interests including financial, consultant, institutional and other relationships that might lead to bias or a conflict of interest.

EAJEM
Eurasian Journal of Emergency Medicine
Citation abbreviation: Eurasian J Emerg Med

INSTRUCTIONS TO AUTHORS

Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board and to disclose potential conflicts of interest ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors. Cases of potential conflicts of interest of editors, authors and reviewers are resolved by the journal's Editorial Board within the scope of COPE and ICMJE guidelines.

Editorial Board of the journal handles appeal and complaint cases within the scope of COPE guidelines. Authors should get in direct contact with the editorial office regarding their appeals and complaints.

When needed, an ombudsperson can be assigned to resolve cases that cannot be resolved internally. The Editor in Chief is the final authority in the decision making process of appeals and complaints. When submitting a manuscript to the Eurasian Journal of Emergency Medicine, authors accept to assign the copyright of their manuscript to Emergency Medicine Physicians' Association of Turkey. If rejected for publication, the copyright of the manuscript will be assigned back to the authors. Eurasian Journal of Emergency Medicine requires each submission to be accompanied by a Copyright Transfer Form (available for download at www.eajem.com). When using previously published content, including figures, tables, or any other material in both print and electronic formats, authors must obtain permission from the copyright holder.

Statements or opinions expressed in the manuscripts published in Eurasian Journal of Emergency Medicine reflect the views of the author(s) and not the opinions of the editors, the editorial board or the publisher; the editors, the editorial board and the publisher disclaim any responsibility or liability for such materials. The final responsibility in regard to the published content rests with the authors.

Manuscript Preparation

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (updated in December 2017 -http://www.icmje. org/icmje-recommendations.pdf). Authors are required to prepare manuscripts in accordance with CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.eajem.com. Manuscripts submitted via any other medium will not be evaluated. Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript is prepared and submitted in accordance with the journal's guidelines. Submissions that don't conform the journal's guidelines will be returned to the submitting author with technical correction requests.

Authors are required to submit the;

- Copyright Transfer Form,

- Author Contributions Form,

- and ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors) during the initial submission. These forms are available for download at www.eajem.com

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

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,

- Name(s), affiliations and major degree(s) of the author(s)

- Grant information and detailed information on the other sources of support,

- The name, address, telephone (including the mobile phone number) and fax numbers and e-mail address of the corresponding author,

- Acknowledgement of the individuals who contributed to the preparation of the manuscript but do not fulfil the authorship criteria.

Abstract: An abstract should be submitted with all submissions except for letters to the editor. The abstract of Original Articles should be structured with subheadings (Aim, Materials and Methods, Results and Conclusion).

Keywords: Each submission must be accompanied by a minimum of three and a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations.

Manuscript Types

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

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with the international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and statistical software that was used during the process must certainly be specified. Data must be expressed as mean±standard deviation when parametric tests are used to compare continuous variables. Data must be expressed as median (minimum-maximum) and percentiles (25th and 75th percentiles) when non-parametric tests are used. In advanced and complicated statistical analyses, relative risk (RR), odds ratio (OR) and hazard ratio (HR) must be supported by confidence intervals (CI) and p values.

EAJEM
Eurasian Journal of Emergency Medicine
Citation abbreviation: Eurasian J Emerg Med

INSTRUCTIONS TO AUTHORS

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

Review Articles: Reviews which are prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into high volume of publication and higher citation potential are taken under review. The authors may be invited by the journal. Reviews should be describing, discussing and evaluating the current level of knowledge or topic used in the clinical practice and should guide future studies. Please check Table 1 for limitations for Review Articles.

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

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

Scientific letter: Manuscripts with prior notification characteristics, announcing new, clinically important scientific developments or information are accepted as Scientific Letters. Scientific Letters should not include sub-headings and should not exceed 900 words. Number of references should be limited to 10 and number of tables and figures should be limited to 2.

Clinical Imaging / Visual Diagnosis: Images must be typical for diagnosis, and should facilitate rapid diagnosis for emergency medicine and / or should be educational. Except for the header and references, it must consist of maximum 400 words. A maximum of three authors name, six images and five refecences should be included.

History: This type of manuscript explains events related to emergency and general medicine and presents information on the history of diagnosis and treatment of diseases. Historical findings should be a result of relevant research studies. Manuscript should not include sub-headings, should not exceed 900 words and total number of references should be limited to 10.

Publication ethics: This type of manuscript includes current information on research and publication ethics and presents cases of ethics infringement. Main text should not exceed 900 words and total number or references should be limited to 10.

Tables

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

Table 1. Limitations for each manuscript type.

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	5000 (Structured)	200	50	6	7 or total of 15 images
Review Article	5000	200	50	6	10 or total of 20 images
Case Report	1500	200	10	No tables	10 or total of 20 images
Letter to the Editor	500	N/A	5	No tables	No media
Scientific letter	900	N/A	10	No tables	2 or total of 4 images
Clinical Imaging/ Visual Diagnosis	400	N/A	5	No tables	3 or total of 6 images
History	900	N/A	10	No tables	3 or total of 6 images
Publication ethics	900	N/A	10	No tables	No media

Figures and Figure Legends

Figures, graphics and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labelled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks and similar marks can be used on the images to support figure legends. Like the rest of

EAJEM
Eurasian Journal of Emergency Medicine
Citation abbreviation: Eurasian J Emerg Med

INSTRUCTIONS TO AUTHORS

the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300DPI. To prevent delays in the evaluation process all submitted figures should be clear in resolution and large in size (minimum dimensions 100x100 mm). Figure legends should be listed at the end of the main document.

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

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

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

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

References

While citing publications, preference should be given to the latest, most up to date publications. If an ahead of print publication is being cited the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ Medline/PubMed (for journal abbreviations consult the List of Journals indexed for MEDLINE, published annually by NLM). When there are 6 or fewer authors, all authors should be listed. If there are 7 or more authors the first 6 authors should be listed followed by "et al". In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples:

Journal article: Lewin MR, Stein J, Wang R, Lee MM, Kernberg M, Boukhman M, et al. Humming is as effective as Valsalva's maneuver and Trendelenburg's position for ultrasonographic visualization of the jugular venous system and common femoral veins. Ann Emerg Med. 2007;50:73-7.

Book Section: Sherry S. Detection of thrombi. In: Strauss HE, Pitt B, James AE, editors. Cardiovascular Medicine. St Louis: Mosby; 1974.p.273-85.

Books with Single Author: Cohn PF. Silent myocardial ischemia and infarction. 3rd ed. New York: Marcel Dekker; 1993.

Editor(s) as author: Norman IJ, Redfern SJ, editors. Mental health care for elderly people. New York: Churchill Livingstone; 1996.

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

Scientific or Technical Report: Smith P. Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX) Dept. of Health and Human Services (US). Office of Evaluation and Inspections: 1994 Oct. Report No: HHSIGOE 169200860.

Thesis: Kaplan SI. Post-hospital home health care: the elderly access and utilization (dissertation). St. Louis (MO): Washington Univ. 1995.

Manuscripts accepted for publication, not published yet: Leshner AI. Molecular mechanisms of cocaine addiction. N Engl J Med In press 1997.

Epub ahead of print Articles: Sarıtaş A, Güneş H, Kandiş H, Çıkman M, Çandar M, Korkut S, et al. A Retrospective Analysis of Patients Admitted to our Clinic with Aortic Dissection. Eurasian J Emerg Med 2011 Dec 10. doi:10.5152/jaem.2011.035. [Epub ahead of print]

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

REVISIONS

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

PROOFS AND DOI NUMBER

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

PERMISSIONS AND REPRINTS

Permission requests for reproduction of published content and reprint orders should be directed to the Editorial Office.

Please get in direct contact with the Editorial Office if you have any questions or comments regarding the journal.

EAJEM
Eurasian Journal of Emergency Medicine
Citation abbreviation: Eurasian J Emerg Med

Review

Original Articles

Letter to the Editor

EURASIAN JOURNAL OF EMERGENCY MEDICINE
Review
DOI: 10.4274/eajem.galenos.2020.71473
Eurasian J Emerg Med. 2020;19(3): 127-35

Characteristics of Patients with Tramadol Use or Abuse: A Systematic Review and Meta-Analysis

Paria Habibollahi[1], Alireza Garjani[2], Samad Shams Vahdati[3], Seyyed-Reza Saadat Ebrahimi[4], Neda Parnianfard[5], Raana Zakeri[6]

[1]Pharmaceutical Analysis Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Department of Pharmacology and Toxicology, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Emergency Medicine Research Team, Tabriz University of Medical Sciences, Tabriz, Iran
[4]Research Center for Evidence-Based Medicine, Iranian Evidence-Based Medicine Center: A Joanna Briggs Institute Affiliated Group, Health Management and Safety Promotion Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran
[5]Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[6]Department of Health Services Management, School of Management and Medical Informatics, Iranian International Safe Community Support Center, Tabriz University of Medical Sciences, Tabriz, Iran

Abstract

Recently, an increasing number of studies have reported an association between the incidence of seizures and the use or abuse of tramadol. The aim of this study was to review articles involving patients with tramadol-induced seizures that reported their characteristics and the consumed tramadol dosage.

The following databases were searched from their inception until October 30, 2018: PubMed, EMBASE, the Cochrane Library, Scopus, Ovid, Proquest and Science direct. All cross-sectional studies that reported the tramadol dosage and individual characteristics of patients with tramadol-induced seizure were included. The studies were assessed for any bias risk using the adapted Newcastle-Ottawa scale. The pooled estimates were reported using random-effects meta-analysis.

Our search identified a total of 3,275 articles, and we finally extracted data from 11 studies involving 970 patients. The included studies were all conducted in developing countries. The pooled data resulted in an estimated mean (± standard deviation) of 1,454.5±333.6 mg for tramadol dosage that induces seizures in patients. The mean minimum tramadol dose causing seizure in the pooled data was 169.5±131.2 mg. The mean age of the patients was 25.85±0.86 years. In addition, 83.37±12.6% of the patients were male, and the manner of poisoning in 70.51±29.07% of the patients was suicide or abuse.

Our findings demonstrated that the prevalence of seizures following the consumption of tramadol was higher among males. Therefore, the probability of seizure should be considered by physicians in prescribing tramadol, and the individuals receiving it, especially the ones at a higher risk of exposure, should be properly informed about its complications.

Keywords: Tramadol, overdose, seizure, systematic review, meta-analysis

Introduction

Tramadol is an atypical synthetic opioid analgesic which is administered as a potent treatment for acute (such as postoperative or trauma) and chronic (such as cancer) pain since 1977. Moreover, it has some reinforcing/rewarding effects which are caused by activation of μ-opioid and monoamine receptor systems (1,2).

Because of having similar effects on other opioid receptor agonists, the risk of tramadol abuse exists in certain populations (3) (ambiguous). In 2013, The International Narcotics Control Board ran a survey in 32 countries, and estimated the tramadol abuse accounts as 69 in 1000 person per year (4). The indicated therapeutic range for moderate to severe pain is 25 up to 400 mg/day in form of oral dosage (disintegrating tablets). Also, for chronic

Corresponding Author: Prof. Samad Shams Vahdati, Emergency Medicine Research Team, Tabriz University of Medical Sciences, Tabriz, Iran
Phone: +98 41 3335 2078 **E-mail:** sshamsv@gmail.com ORCID ID: orcid.org/0000-0002-4831-6691

Received: 31.01.2020
Accepted: 23.07.2020

Cite this article as: Habibollahi P, Garjani A, Vahdati SS, Ebrahimi SRS, Parnianfard N, Zakeri R. Characteristics of Patients with Tramadol Use or Abuse: A Systematic Review and Meta-Analysis. Eurasian J Emerg Med. 2020;19(3):127-35

pain, the advised oral dosage form (extended-release capsules) is 100 up to 300 mg/day. Tramadol overdose can bring about acute renal failure, rise in creatinine phosphokinase, hepatic failure, electrocardiographic changes and acute right heart dysfunction (5,6). Also, there are few death reports caused by tramadol abuse (7).

Although a growing number of recent studies has been reported an association between the incidence of seizures and using/abusing tramadol (8-10), still the mechanism of tramadol in the incidence of seizures is poorly understood; It has been assumed that high concentrations of tramadol inhibiting gamma-aminobutyric acid receptors are associated with the incidence of seizures in animal models (11). In addition, the characteristics of patients with tramadol induced seizure and the consumed tramadol dosage in them varies greatly among different studies (12-21). Since no previous review study has intended to collect this discrete data and put forward reliable and coherent information of tramadol to help physicians and patients to use it safely, the current study aimed to review the articles over the patients with tramadol induced seizure which reported their characteristics and consumed tramadol dosage.

Study Method

A systematic review and meta-analysis of cross-sectional studies over tramadol induced seizure was conducted.

Search Strategy

A skilled librarian defined the search strategies for some of the most important bibliographic databases including PubMed, EMBASE, the Cochrane Library, Scopus, Ovid, Proquest, and Science direct until 30 October 2018. All search data were imported to reference manager software, EndNote X8. The keywords for the search strategy for PubMed were as follows: Seizures AND Tramadol/(Seizure or Convulsion or Convulsive) and (Tramadol)/(Seizure or Convulsion or Convulsive) and (Tramadol or Tramundin or Biodalgic or Jutadol or K-315 or K 315 OR K315 or MTW-Tramadol or MTW Tramadol or MTWTramadol or Nobligan or ProntofORt or Zytram or Takadol or Theradol or Tiral or Tramadol Lindo or Topalgic or Tradol or Tradol-Puren or Tradol Puren or TradolPuren or Tradonal or Tralgiol or Trama AbZ or Trama KD or Trama-DORsch or Trama DORsch or TramaDORsch or Biokanol or Tramabeta or Tramadin or Tramadoc or Ranitidin 1A Pharma or Trama 1A Pharma or Trasedal or Ultram or Xymel 50 or Zamudol or Zumalgic or Zydol or TramadolHameln or TramadolOR or Tramadura or Tramagetic or Tramagit or Tramake or Tramal or Tramex or Adolonta or Contramal or Amadol).

Study Selection

At the first screening stage, two reviewers independently screened title and abstract of retrieved documents in order to determine the ones which met the eligibility criteria. Primary selection of studies was based on the inclusion criteria. The duplicated publications were excluded. Full citations of documents that were considered eligible at least by one reviewer were imported into an EndNote database. In the next stage, the full text of the imported papers was provided and reviewed for subject relevancy by the two reviewers individually. A critical appraisal checklist was used to evaluate the validity of the selected studies and to criticize them. Finally, these two researchers made a face-to-face meeting, discussing article selections. If they did not come to a consensus in a case, a third researcher made the final decision on the eligibility of that particular article. Consequently, the studies that considered valid by both researchers, selected for data extraction.

We included the cross-sectional studies (including the studies with retrospective or prospective observational designs) reporting the patients' characteristics and tramadol dosage in adult patients who received tramadol with or without a prescription and admitted with tramadol induced seizure. The full text of studies in English language were reviewed. The following studies were excluded: laboratory or animal studies, studies published only as synopsis or abstract, studies reporting the use/abuse of tramadol in combination with other co-ingestants or having seizure-related comorbidities, the studies which did not specifically reported the patients' data, studies on efficacy or safety of tramadol (e.g. drug half-life), studies on other adverse effects of tramadol, short communications and case reports. (Find the PRISMA checklist in S1).

Risk of Bias Assessment

The quality of studies was evaluated individually by two authors using the Newcastle-Ottawa scale adapted for cross-sectional studies (22), which evaluates the studies in three domains of selection, comparability, and outcome. Each one of the studies received a score ranging from 0 to 11 based on the sum of scores they gained in each domain (The details of quality assessment is available in our electronic supplementary material, S2). Other co-authors were consulted in case of no agreement between the two authors.

Data Extraction

The extraction table of our review included the following variables: characteristics of the patients (age and gender), consumed tramadol dosage, history of tramadol abuse, route of exposure, manner of poisoning, previous drug or substance abuse, history of any attempts for suicide, type of the seizure, number of episodes of seizure were extracted from the included studies (ambiguous). Two reviewers independently abstracted

the mean and standard deviation (SD) of the review variables from their assigned study and extracted them into the extraction table. For the studies, which were the review variables as mean amounts without SDs, the p values were extracted. In addition, the sample size of each included study was added to the extraction table.

Statistical Analysis

The meta-analysis was utilized for combination and calculation of the review variables. The heterogeneities of review variables along the included study were assessed using Cochran's Q and I2 statistic. Negative values of I2 are put equal to 0% so I2 values can range between 0% and 100%. Zero percent indicates no observed heterogeneity; whereas larger values indicate increasing heterogeneity. Subgroup analyses were used to explore the reasons for heterogeneity. For the variables with a high degree of heterogeneity, the Der-Simonian-Laird method for a random-effect model was used to estimate the overall effect, and for the variables with a small degree of heterogeneity, the Mantel-Haenszel fixed-effect model was used. All statistical analyses were performed using CMA v.2.0 software.

Findings

Literature Search

Our comprehensive search strategy resulted in 3,275 preliminary articles that were screened by title and abstract. Lastly, full papers of 30 studies were evaluated for eligibility, of which 19 studies were excluded (studies on the combination of tramadol with other drugs (n=3), discussing other adverse effects of tramadol (n=4), Short communication (n=3), and not specifically related to our scope (n=9)) and the full texts of 11 studies were critically reviewed (Figure 1).

Bias Assessment

After full text screening, risk of bias was assessed for remaining studies (Table 1). The agreement score between two authors in risk of bias assessment was 89 percent; discrepancies were resolved by discussion and consulting other authors. Most of the studies were of high quality and provided appropriate details about their outcomes and comparability; however, few trials presented clear complete details of their selection procedure and adequate information regarding ascertainment of true seizure and ascertainment of the exposure to tramadol. Also, no significant publication bias was demonstrated in our analysis [Kendall's tau with continuity correction=-0.035, p value (two tailed)=0.9015].

Tramadol Dosage in Patients with Tramadol Induced Seizure

Finally, 11 studies were included. The characteristics of included studies are presented in (Tables 2, 3). The studies were mostly conducted in Iran (nine studies) and Egypt (two studies).

Of 11 included studies, eight studies reported the mean and SD of ingested tramadol dosage inducing seizure; however, two studies reported median and range (17,19) and one study only reported the range of ingested tramadol dosage inducing seizure (14). Therefore, the results of those eight studies were used to calculate estimated mean dose. The pooled data of eight studies with 760 patients resulted in an estimated mean of 1,454.5±333.6 mg for tramadol dosage inducing seizure in patients (Figure 2). The heterogeneity between the included study was significant (Q=6160.68, I2=99.88, p<0.001). The average of each of the minimum values for tramadol dosage in patients with tramadol induced seizure were reported in 10 studies with 874 patients and one study did not report the minimum dose (13). The estimation over the minimum values of consumed tramadol dosage yield a

Table 1. Results of the assessments of the included studies by Newcastle-Ottawa Checklist* adopted for cross-sectional studies

Author	Year	Selection (maximum 6 stars)	Comparability (maximum 2 stars)	Outcome (maximum 3 stars)	Quality points total (maximum 11 stars)
Petramfar et al. (20)	2009	3	1	3	7
Talaie et al. (15)	2009	3	2	3	8
Goodarzi et al. (21)	2011	2	2	3	7
Taghaddosinejad et al. (11)	2011	4	2	3	9
Farajidana et al. (9)	2012	4	2	3	9
Rahimi et al. (16)	2014	2	2	3	7
Enaba et al. (17)	2015	4	2	3	9
Asadi et al. (18)	2015	3	2	3	8
Rizk et al. (13)	2016	6	2	3	11
Ahmadimanesh et al. (19)	2018	3	2	3	8
Mohammadpour et al. (14)	2018	4	2	3	9

*Cross-sectional studies: very good studies: 9-11 points, good studies: 7-8 points, satisfactory studies: 5-6 points, unsatisfactory studies: 0 to 4 points

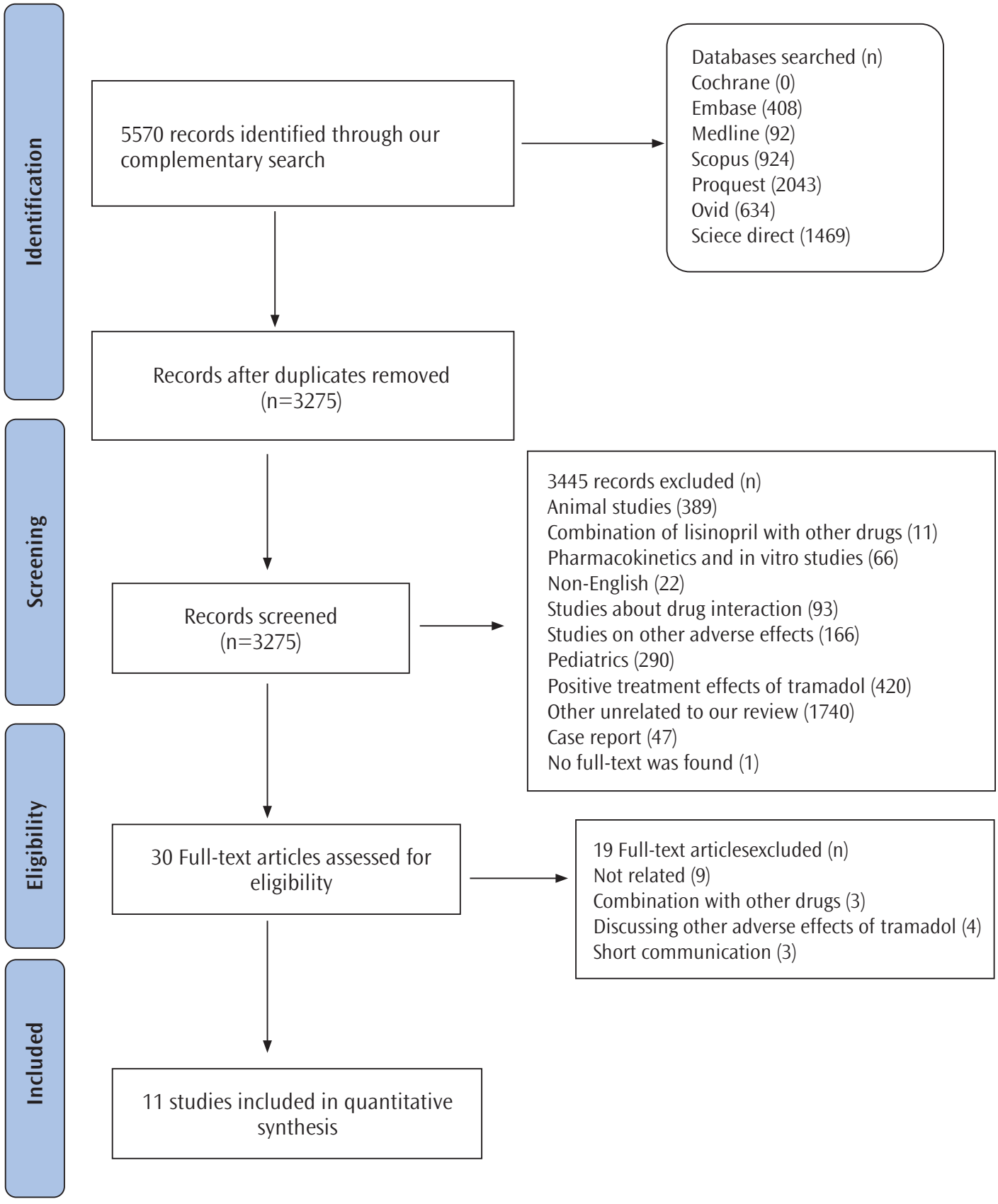

Figure 1. PRISMA flow diagram summarizing retrieved, included, and excluded studies

n: Number, PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

Table 2. Characteristics of studies on seizures due to tramadol use or abuse

Author	Year	Study design	Country	Mean age (range)	Sex male in seizure group number	Sex female in seizure group
Petramfar et al. (20)	2009	Cross-sectional	Iran	26.7±6.9	102	4
Talaie et al. (15)	2009	Cross-sectional	Iran	24.3 (15-69)	51	10
Goodarzi et al. (21)	2011	Cross-sectional	Iran	26.48±7.74 (17-45)	27	27
Taghaddosinejad et al. (11)	2011	Observational prospective	Iran	22.9 (14-50)	101	20
Farajidana et al. (9)	2012	Retrospective	Iran	23±6 (60-3)	197	35
Rahimi et al. (16)	2014	Retrospective	Iran	24.2±7.6 (16-57)	57	12
Enaba et al. (17)	2015	Cross-sectional	Egypt	28.3±6.2	35	2
Asadi et al. (18)	2015	Cross-sectional	Iran	26.44±6.48	69	15
Rizk et al. (13)	2016	Cross-sectional	Egypt	29.7±6.7	51	2
Ahmadimanesh et al. (19)	2018	Observational prospective	Iran	22.8±5.8 (14-37)	47	3
Mohammadpour et al. (14)	2009	Cross-sectional	Iran	25 (14-35)	43	17

Table 3. Characteristics of studies on seizures due to tramadol use or abuse

Author	Ingested dose of tramadol, mean (min-max)	Route of exposure	Type of seizure	Manner of poisoning (%)		Number of seizure episodes
				Prescribed	Abuse or suicide	
Petramfar et al. (20)	363.2±303.1 (50-400)	Oral	Tonic-clonic	18.9%	81.1%	N
Talaie et al. (15)	2059.35±226.04 (500-4000)	Oral	Tonic-clonic	9.7%	65.5%	N
Goodarzi et al. (21)	3248±2515 (200-1100)	Oral	Tonic-clonic	N	24%	1-2 (85%)
Taghaddosinejad et al. (11)	1511±1353 (200-7000)	Oral	Tonic-clonic	6.9%	37%	N
Farajidana et al. (9)	1416±1124 (100-6000)	Oral	Tonic-clonic	2.2%	97%	1-2 (98%)
Rahimi et al. (16)	1395.7±218.3 (100-12000)	Oral	N	0	100%	N
Enaba et al. (17)	1800 (250-6750)	Oral	Tonic-clonic	N	N	Recurrent (81%)
Asadi et al. (18)	140.17±73.53 (50-300±)	Oral	N	N	N	N
Rizk et al. (13)	1726±1049.1	Oral	Tonic-clonic	0	100%	N
Ahmadimanesh et al. (19)	1350 (200-8000)	Oral	N	2%	94%	N
Mohammadpour et al. (14)	491.90±435.54 (45-1850)	Oral	N	N	36%	N

min: Minimum, max: Maximum, N=Not mentioned

mean of 169.5±131.2 mg. The lowest dosage of tramadol dose causing a seizure reported among included studies was 50 mg (18,20).

Sub-group meta-analysis for Iranian studies with an overall number of 727 patients resulted in a mean of 1,416.4±356.0 mg (95% confidence interval: 718.5-2,114.2) for tramadol dosage but still the heterogeneity was significant (Q=6106.52, I2=99.90, p<0.001) (Figure 3).

Characteristics of Patients with Tramadol Induced Seizure

Mean and SD of the age of patients were reported in eight studies and three studies did not report SD (11,14,15). The pooled data for patients' age, which were drawn from eight studies with 665 patients, showed a mean of 25.85±0.86 years old (Figure 4). The average proportion of males among all Data from 11 studies with 907 patients indicated the male gender as the most frequent patients (83.37±12.68 percent of the patients).

In all included studies, the patients used tramadol in oral form. Nine studies (786 patients) reported that the manner of poisoning in 70.51±29.07 percent of the patients was suicide or abuse; however, two studies indicated that 23.2 and 27.2 percent of the patients had a pervious history of suicide. Moreover, data from four studies with 457 patients showed that 50.02±7.17 percent of the patients had an abuse of tramadol.

Discussion

Although the majority of included studies in our review were of high quality, they were considerably lacking adequate information to meticulously describe the policies of the researcher

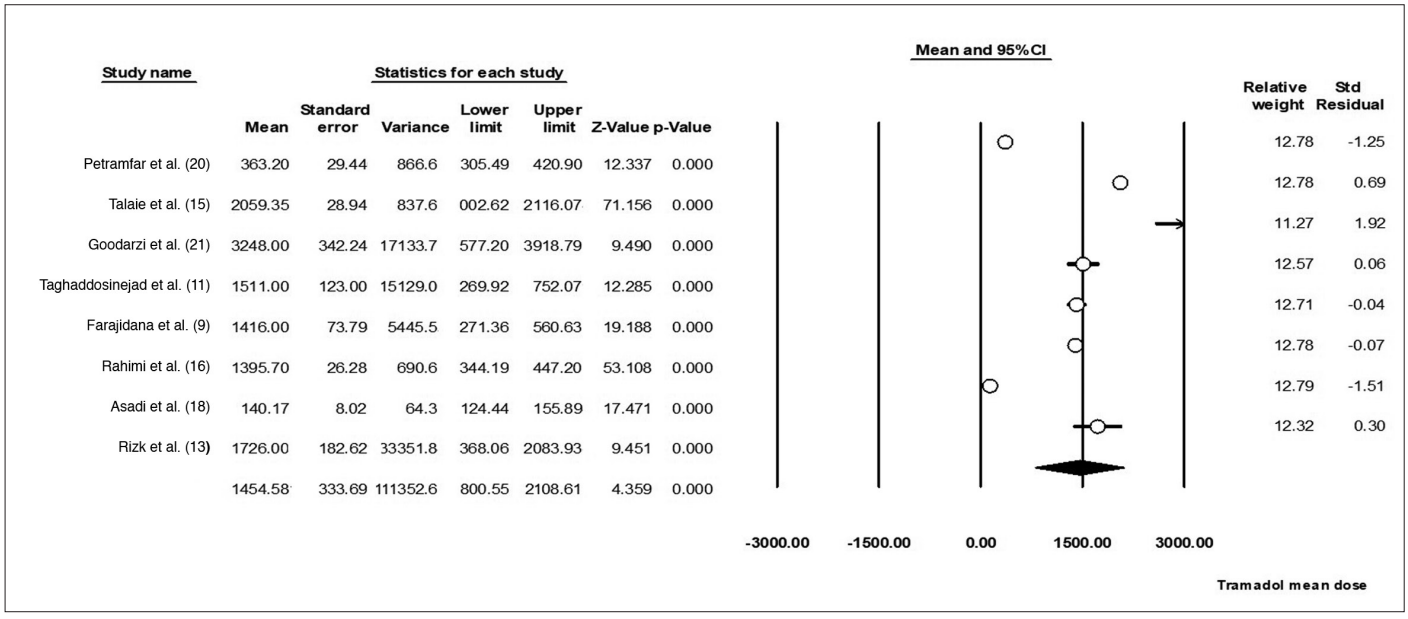

Figure 2. Meta-analysis of the dose of tramadol-induced seizure in all patients

CI: Confidence interval, Std: Standard deviation

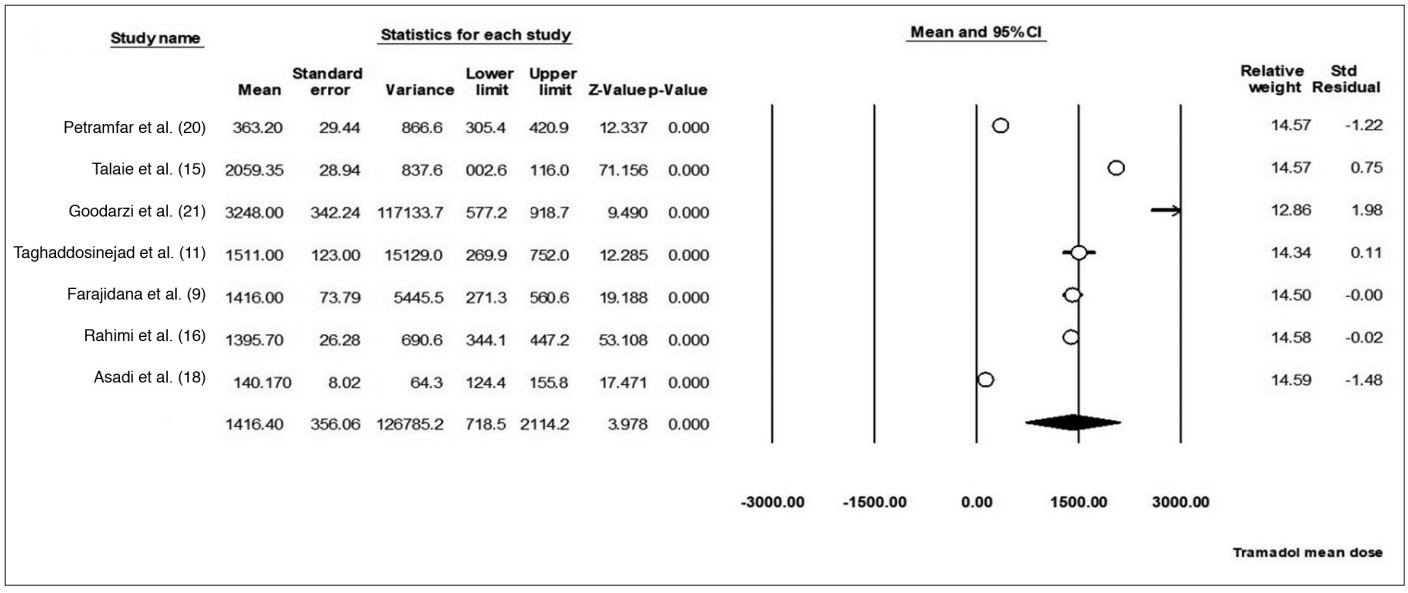

Figure 3. Meta-analysis of the dose of tramadol-induced seizure in the patients in Iran

CI: Confidence interval, Std: Standard deviation

to ascertain a true seizure and consumption of tramadol. Also, the discrepancy between the data of included studies, especially for tramadol dosage, was considerable in majority of included studies (9,11,13-16,19-21) and this discrepancy remained even after sub-group analysis of Iranian studies. Whereas ethnicity was the same, one of the possible reasons for this discrepancy could be inaccurate claims about the number of ingested tablets and their dosages due to the psychological stress of confronting a tonic-clonic seizure or forgetfulness. Three studies did not report the mean and SD or p value of dose of ingested tramadol (14,18,19), therefore they were not included in the meta-analysis of the dose of ingested tramadol (Figures 2 and 3). Also, three studies did not report the mean and SD of age (only the median age was reported), therefore they were not included in the meta-analysis of age (Figure 4) (11,14,15).

The included studies were mostly conducted in Iran and two of them were conducted in Egypt (13,17); which both are developing countries. Therefore, it can be imagined that tramadol is conveniently available within these countries (20,23-25).

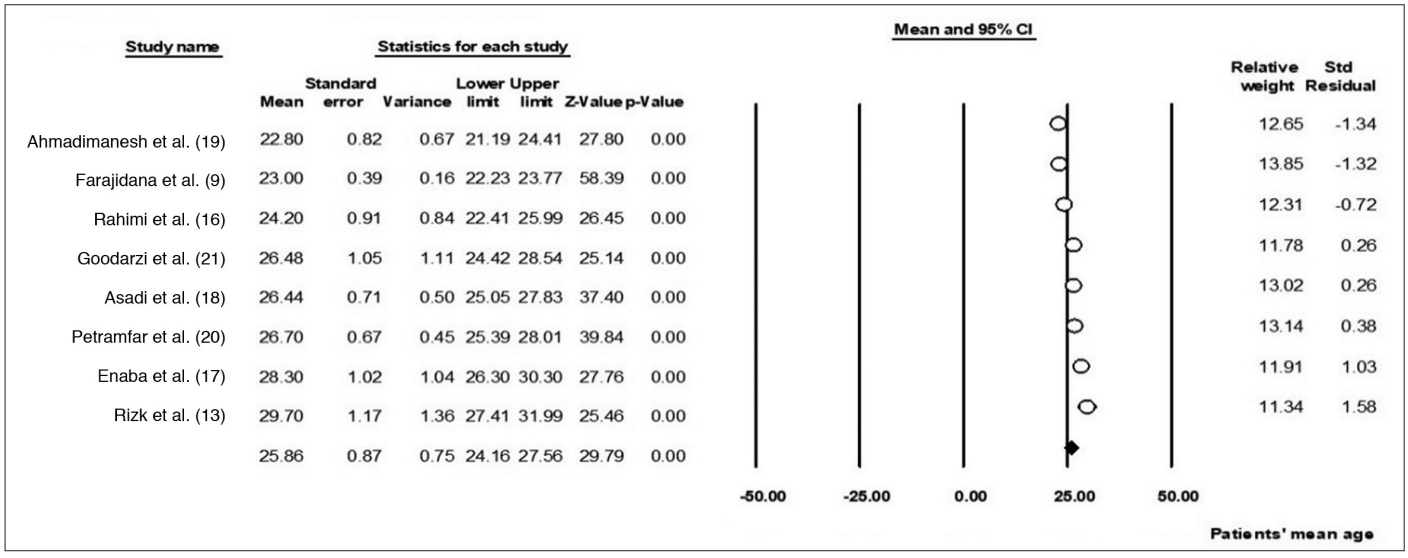

Figure 4. Meta-analysis of the age of patients with seizure due to tramadol

CI: Confidence interval, Std: Standard deviation

A study used two definition of seizure including a broader and more specific definition and indicated that tramadol is not associated with a higher risk of seizure compared to codeine through a broader definition (based on either an outpatient physician claim for seizure disorder or a seizure-related emergency department visit or hospitalization); however, through using a more specific definition of seizure (restricted to a hospital visit with a definite diagnosis of seizure), they showed that tramadol is responsible for an increase of 41% in risk of seizure (26).

In almost all of the included studies, patients were in their early age of 20s and our estimations for their mean of age relieved the similar range. Moreover, in all of the included studies, male patients were more frequent than females. Although most of the patients admitted with tramadol induced seizure indicated that they used tramadol only for suicide or abuse, it is important to note that about one-third of the patients used this drug as a safe medication but still developed seizure. Moreover, about half the patients did not even have a history of tramadol abuse (13,15-18,20). An Australian study indicated that tramadol overdose is associated with a significant risk of seizures in more severe cases, which appear to be related to the ingested dose; They found that seizures are apparently dose dependent and only occur in tramadol dosages of greater than 2000 mg, even in patients without a pre-existing risk of seizures (10).

Our study had some limitations including the considerable heterogeneity between the studies that prevented us to provide more reliable data. Also, this heterogeneity prevented us from drawing a definite conclusion based on the obtained data. Although we tried to reduce the heterogeneity by performing subgroup analysis, it was not that much effective. We included any studies conducted in both developing and developed countries. However, the studies conducted in developed countries were excluded because of our mentioned exclusion criteria. For example, the study of Ryan and Isbister (10) was excluded because they did not exclude the patients receiving co-ingestants or having seizure-related comorbidities when they calculated the mean dose of tramadol which induced seizure. We believe that these co-ingestants or seizure-related comorbidities may affect the dose of tramadol that causes seizure. Thus, we excluded these kinds of studies. Although our study failed to include the reports of the characteristics of patients in developed countries, there is no evidence in literature representing that there could be differences between characteristics of patients in developed and developing countries in terms of susceptibility to seizure due to tramadol. Therefore, this issue could not affect the generalizability of our results. In addition, our review only included the published studies, but we tried our best to contact with researchers and obtain the original data.

Conclusion

The current systematic review and meta-analysis study on tramadol induced seizure indicated that there was a substantial heterogeneity among studies on characteristics of patients with seizure due to tramadol. However, despite the extensive limitations of this study, our results demonstrated the higher prevalence of seizure due to tramadol in young men in developing countries, who mostly used tramadol in a suicide attempt or abuse. Moreover, due to possibility of seizure in patients with prescribed doses of tramadol, this complication should be considered by physicians.

Expert Opinion

Previously tramadol was known as a cheap and safe drug with a low risk of addiction in comparison with other opiates (27), afterwards numerous studies reported severe adverse effects for it, such as seizure, rising the creatinine phosphokinase, acute renal failure, hepatic failure, electrocardiographic changes and acute right heart dysfunction and even death. The current study was mainly designed to review the published works on tramadol induced seizure and investigate the patients' demographics, previous history of drug use and seizure consumed tramadol dosage, and the manner of poisoning with tramadol.

Regarding the patients' demographics with tramadol induced seizure, the ones living in developing countries were the most frequent group of patients with tramadol induced seizure. Low awareness of tramadol side effects among people is another reason for high prevalence of tramadol poisoning and its consequences in developing countries such as Iran and Egypt (13,26). According to an Egyptian study, the increasing violence forms are strictly associated with drug misuse. Low price of tramadol and easy access to it, compared to other abused drugs, and the unplanned and indirect advertisement of social media for tramadol could be other potential risk factors of tramadol poisoning (27,28). Also, our findings indicated that individuals in male sex (83.37±12.6 percent) had higher prevalence of seizure following the consumption of tramadol. The social context, especially in developing countries, provides an easier access of tramadol for young men than the women (26,29-30), consequently, the prevalence of seizure due to tramadol is higher among the male users. Besides, young men have a higher tendency to do risky behaviors than women, so they are more prone to abusing drugs such as tramadol (30).

Our estimations for tramadol dosage inducing seizure in the patients, revealed a mean of 1,454.5±333.6 mg. Also, the minimum dose of tramadol causing seizure was estimated as 169.5±131.2 mg. Thus, if tramadol is being prescribed for therapeutic purposes, the physicians should properly make the patients aware about tramadol's complications; And if there is a high possibility of tramadol abuse in certain environments, more proper prevention programs using media and educational systems, especially in high schools and universities, are required to get administrated by governments against tramadol abuse targeting young population. Therefore, further studies are required to evaluate and introduce the most cost-benefit prevention programs against tramadol abuse, especially in context of developing countries.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.S.V., Concept: P.H., Design: P.H., A.G., Data Collection or Processing: S.R.S.E., Analysis or Interpretation: R.Z., Literature Search: S.S.V., Writing: N.P., R.Z.

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

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

References

1. Abdel-Hamid IA, Andersson KE, Waldinger MD, Anis TH. Tramadol Abuse and Sexual Function. Sexual medicine reviews. 2016;4:235-46.
2. Al-Abri SA, Woodburn C, Olson KR, Kearney TA. Ventricular Dysrhythmias Associated with Poisoning and Drug Overdose: A 10-Year Review of Statewide Poison Control Center Data from California. Am J Cardiovasc Drug. 2015;15:43-50.
3. Duke AN, Bigelow GE, Lanier RK, Strain EC. Discriminative stimulus effects of Tramadol in humans. Journal of Pharmacology and Experimental Therapeutics. 2011;338:255-62. [Epub 2011 Apr 5].
4. Knisely JS, Campbell ED, Dawson KS, Schnoll SH. Tramadol post-marketing surveillance in health care professionals. Drug and Alcohol Depend. 2002;68:15-22.
5. The Statistical Centre of Iran. Iranian Population and Housing Census. Tehran, Iran: The Statistical Centre of Iran. 2016. https://www.unescap.org/sites/default/files/Session6_Iran_Population_and_Housing_Census2016_Census_WS_24-26Jan2018.pdf
6. Tashakori A, Afshari R. Tramadol overdose as a cause of serotonin syndrome: a case series. Clinical Toxicology. 2010;48:337-41.
7. Moore KA, Cina SJ, Jones R, Selby DM, Levine B, Smith ML. Tissue distribution of Tramadol and metabolites in an overdose fatality. Am J Forensic Med Pathol. 1999;20:98-100.
8. Bekjarovski N, Chaparoska D, Radulovikj-Bekjarovska S. Seizures after use and abuse of Tramadol. Contributions (Prilozi). 2012;33:313-8.
9. Farajidana H, Hassanian-Moghaddam H, Zamani N, Sanai-Zadeh H. Tramadol-induced seizures and trauma. European Review for Medical & Pharmacological Sciences. 2012;16(Suppl 1):34-7.
10. Ryan NM, Isbister GK. Tramadol overdose causes seizures and respiratory depression but serotonin toxicity appears unlikely. Clin Toxicol. 2015;53:545-50.
11. Taghaddosinejad F, Mehrpour O, Afshari R, Seghatoleslami A, Abdollahi M, Dart RC. Factors Related to Seizure in Tramadol Poisoning and Its Blood Concentration. J Med Toxicol. 2011;7:183-8.
12. Boostani R, Derakhshan S. Tramadol induced seizure: A 3-year study. Caspian Inton Med. 2012;3:484-7.
13. Rizk MMM, Kamal AM, MA Abdelhameed, Abdefadeel N, Hassan E, Khafagi ATM. Frequency and factors associated with occurrence of seizures in patients with Tramadol abuse: An upper egyptian experience. Addict Disord Treat. 2016;15:42-8.
14. Mohammadpour A, Ashkezari MD, Farahmand B, Shokrzadeh M. Demographic Characteristics and Functional Performance of the Kidneys and Hearts of Patients with Acute Tramadol Toxicity. Drug Research. 2019;69:207-10.
15. Talaie H, Panahandeh R, Fayaznouri MR, Asadi Z, Abdollahi M. Dose-independent occurrence of seizure with Tramadol. J Med Toxicol. 2009;5:63-7.
16. Rahimi HR, Soltaninejad K, Shadnia S. Acute Tramadol poisoning and its clinical and laboratory findings. J Res Med Sci. 2014;19:855-9.

17. Enaba D, Shalaby NM, El-Baz H, Zahra A. The Influence of A118G Single Nucleotide Polymorphism of Human Mu Opioid Receptor Gene and the MDR1 Gene in Egyptian Patients with Tramadol-induced Seizure. Addict Disord Treat. 2015;14:105-12.
18. Asadi P, Kasmaei VM, Ziabari SZ, Zohrevandi B, Manesh AM. Prevalence of Tramadol consumption in first seizure patients; a one-year cross-sectional study. Emerg. 2015;3:159-61.
19. Ahmadimanesh M, Shadnia S, Rouini MR, Sheikholeslami B, Ahsani Nasab S, Ghazi-Khansari M. Correlation between plasma concentrations of Tramadol and its metabolites and the incidence of seizure in Tramadol-intoxicated patients. DMPT. 2018;33:75-83.
20. Petramfar P, Borhani Haghighi A. Tramadol induced seizure: Report of 106 patients. Iranian Red Crescent Med J. 2010;12:49-51.
21. Goodarzi F, Mehrpour O, Eizadi-Mood N. A study to evaluate factors associated with seizure in Tramadol poisoning in Iran. Indian J Forensic Med Toxicol. 2011;5:66-9.
22. Wells G, Shea B, O'connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Department of Epidemiology and Community Medicine, University of Ottawa, Canada. University of Ottawa, Canada. 2012. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
23. Afshari R, Afshar R, Mégarbane B. Tramadol overdose: review of the literature. Réanimation. 2011;20:436.
24. Shadnia S, Soltaninejad K, Heydari K, Sasanian G, Abdollahi M. Tramadol intoxication: a review of 114 cases. J Hum Exp Toxicol. 2008;27:201-5.
25. Gardner JS, Blough D, Drinkard CR, Shatin D, Anderson G, Graham D, et al. Tramadol and seizures: a surveillance study in a managed care population. Journal of Pharmacotherapy: J Hum Pharmacol. 2000;20:1423-31.
26. Morrow RL, Dormuth CR, Paterson M, Mamdani MM, Gomes T, Juurlink DN. Tramadol and the risk of seizure: nested case-control study of US patients with employer-sponsored health benefits. BMJ Open. 2019;9:e026705.
27. Sansone RA, Sansone LA. Tramadol: seizures, serotonin syndrome, and coadministered antidepressants. J Psychiat. 2009;6:17.
28. Fawzi M. Medicolegal aspects concerning Tramadol abuse. the new Middle East youth plague: an Egyptian overview 2010. Journal of forensic research. 2011, https://www.hilarispublisher.com/open-access/medicolegal-aspects-concerning-tramadol-abuse-the-new-middle-east-youth-plague-an-egyptian-overview-2010-2157-7145.1000130.pdf
29. Progler Y. Drug addiction in Gaza and the illicit trafficking of Tramadol. Journal of research in medical sciences: J Res Med Sci. 2010;15:185-8.
30. Cotto JH, Davis E, Dowling GJ, Elcano JC, Staton AB, Weiss SRB. Gender effects on drug use, abuse, and dependence: a special analysis of results from the National Survey on Drug Use and Health. Gender Med. 2010;7:402-13.

EURASIAN JOURNAL OF EMERGENCY MEDICINE
Original Article
DOI: 10.4274/eajem.galenos.2020.16779
Eurasian J Emerg Med. 2020;19(3): 136-41

Evaluation of the Correlation Between Breast Artery Calcification and Coronary Artery Calcium Scores in Predicting the Risk for Cardiovascular Disease

Işıl Yurdaışık[1], Fuad Nurili[2]

[1]Clinic of Radiology, İstinye University Medical Park Gaziosmanpaşa Hospital, İstanbul, Turkey
[2]Department of Radiology and Interventional Radiology, Memorial Sloan Kettering Cancer Center, Avenue, New York, USA

Abstract

Aim: Coronary artery calcium (CAC) score is a scoring system used in the stratification of coronary risks. Breast artery calcification (BAC) is a type of medial artery calcification that can be visualized using mammography and is also known as arteriosclerosis. It has been reported that a significant correlation exists between BAC and CAC and that the presence of BAC improves the ability of detecting women with CAC. This study aimed to evaluate the relationship between mammographically-detected BAC and CAC.

Materials and Methods: A total of 31 patients who presented to our hospital for diagnostic or screening mammography and who underwent CAC scoring between 2015 and 2018 were included in the study. Agatston method was used to determine the CAC score. Total BAC, which varies from 0 to 12, was measured based on the number and length of calcified vessels and the severity of mammographically-visualized calcification.

Results: The mean BAC scores were found to be 0 in 1 patient, 1-3 in nine patients and 4-12 in 21 patients. The mean CAC scores were found to be 0 in eight patients, 11-100 in 12 patients, 101-400 in eight patients and >400 in three patients. There was a statistically significant positive correlation between the BAC and CAC scores.

Conclusion: This study revealed a positive correlation between the BAC and CAC scores. It was found that mammographic calcification scoring, which is already commonly used as a screening tool and is more advantageous than tomography, can be used for the early determination of intermediate risk groups for cardiovascular diseases.

Keywords: Breast artery calcification, coronary artery calcium score, mammography, cardiovascular disease, screening

Introduction

Cardiovascular diseases (CVDs) are the leading cause of death worldwide with approximately 17.9 persons died from CVD in 2016 (1). Similarly, in our country also CVDs rank first among the causes of death. According to the data of the Turkish Statistical Institute, deaths due to CVDs are the leading among all causes of death by 39.8% (2). In the Western countries, yearly rate of CVD mortality has been reported as 2-8/1000 in men and 0.6-3/1000 in women aged between 45 and 74 years. In our country, this rate has been reported as 7.6/1000 in men and 3.8/1000 in women in the same age group (3). Identification of asymptomatic persons who are at a higher risk for future cardiovascular events is the basis of implementing preventive strategies. Coronary artery calcium (CAC), score which is a scoring system based on the measurement of the amount of calcium in the arterial walls that supply heart muscle is used for the stratification of cardiovascular risk. Several studies have shown that CAC score is significantly associated with major cardiovascular events (all causes mortality, cardiac mortality, and nonfatal myocardial infarction) in middle and long term follow up (4). However, currently CAC score is not used in routine screening. The use of CAC is based on clinical findings and a history of genetic predisposition. Nevertheless, CAC occurs in the intima of the vessels, and is closely associated

Corresponding Author: Asst. Prof. Işıl Yurdaışık, Clinic of Radiology, İstinye University Medical Park Gaziosmanpaşa Hospital, İstanbul, Turkey

E-mail: mdisilyurdaisik@gmail.com **ORCID ID:** orcid.org/0000-0001-8316-1229

Received: 25.01.2020
Accepted: 19.06.2020

Cite this article as: Yurdaışık I, Nurili F. Evaluation of the Correlation Between Breast Artery Calcification and Coronary Artery Calcium Scores in Predicting the Risk for Cardiovascular Disease. Eurasian J Emerg Med. 2020;19(3):136-41

with aterosclerotic plaque burden. Therefore, the presence of CAC is in fact a diagnostic factor for cardiovascular disease (5).

Breast cancer is the most common type of cancer in women in the developed and developing countries, and is among the most important global healthcare problems (6). It ranks second following lung cancer worldwide (7), accounting for nearly 30% of all cancers seen in women (8). On the other hand, it is stated that the chance for healing is high when breast cancer is recognized in an early period.

Breast Cancer Screening Program National Standards prepared by the Ministry of Health Public Health Institution recommend screening every 2 years with mammography in women aged between 40 and 69 years (9). Breast Cancer Screening Guidelines by the Turkish Radiology Association accept the age of starting mammographic screening as 40 years, and recommend yearly follow up (10). According to these guidelines, it is advisable to discontinue screening between 70 and 74 years old if life expectancy is under 5 years depending on the age and presence of other comorbidities.

Breast artery calcification (BAC) is a type of medial artery calcification, which can be seen on mammography, and is also named as arteriosclerosis that is known as Monckeberg arteriosclerosis (11,12). Recently, BAC has been shown to be a potential women specific risk factor for both coronary artery disease and cardiovascular disease (13). However, unfortunately the presence or absence of BAC is often neglected in mammographic evaluation. Studies have shown that subclinical atherosclerosis and cardiovascular disease can be assessed with mammography (14,15). It has been reported that there is a significant relationship between BAC and CAC, and the presence of BAC improves the ability for detection of women with CAC (16).

Mammography provides an important alternative screening technique to determine the risk of coronary artery disease in women. Given that millions of women over 40 years old have mammography, a significant correlation between BAC and CVD will provide improvement in risk stratification without additional costs and radiation exposure (17). The objective of this study was to evaluate the relationship between BACs on mammography and CAC score.

Materials and Methods

Among the women who presented to our hospital for screening or diagnosis with mammographic evaluation, a total of 31 women aged between 40-74 years who recently presented for coronary calcium scoring between October 2015 and June 2018 were included in this study. Women aged under or over the specified age range, those with a history of stroke, transient ischemic or coronary artery disease, patients with coronary stents, advanced coronary calcification, those undergone breast surgery, and patients with chronic inflammatory diseases such as infection or autoimmune diseases, hepatic and/or renal failure were excluded from the study. All BAC and CAC evaluations were performed by a radiologist specialized on this topic.

Before the beginning of the study, the necessary approval was received from the local ethics committee with 2/2019.K-018 numbered decision. Patients included in the study were informed about the objective of the study and given written and verbal consents. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Coronary Artery Calcium Scoring

CAC is a pathognomonic finding of atherosclerosis (18). CAC may be observed in any stage of atherosclerosis. Therefore, determination of CAC level is not only a measurement of calcified plaque burden, but it is also an indicator of the non-calcified plaque burden of the existing atherosclerotic disease. The most common method in the measurement of CAC is Agatston score. This score was described by Agatston et al. (19) in 1990 as the first practically applicable quantitative CAC protocol. In this method, any structure with a density of 130 HU or higher and an area of 1 mm^2 or higher is considered as a calcified focus, and the foci found in the anatomic regions of coronary arteries as calcified plaques. Each calcified focus is scored between 1-4 points based on the peak density. Total Agatston score of each person is calculated with summation of the scores of each focus (Table 1).

Coronary artery calcium examinations were performed with visualization between tracheal bifurcation and heart vessel at early mid-diastole, using a 120-sections computed tomography device (Siemens Somatom 2015).

Table 1. Risk stratification according to Agatston score

CAC score	Plaque burden	Cardiovascular risk	Likelihood of obstructive disease
0	No detectable plaque	Very low	Very low <5%
1-10	Minimal plaque	Low	Low <10%
11-100	Mild plaque	Moderate	Mild stenosis
101-400	Moderate plaque	Moderate-to-high	Likelihood of both non-obstructive and obstructive disease
>400	Diffuse atherosclerotic plaque	High	Likelihood of at least one significant stenosis (≥90%)

CAC: Coronary artery calcium

Breast Artery Calcification

Arterial calcification in the breast is a type of medial calcification, which can be easily detected on mammography, and is seen as parallel lines and railways on mammography. Calcification of the arterial intima is considered as coronary calcification and is usually accompanied by plaques consisting of lipid deposits. Whereas BAC occurs in the middle layer of the artery, and known as Mönckeberg medial calcific sclerosis. BAC is a novel potential risk stratification tool for CVD.

Total BAC score differs between 0-12 points, and is produced based on three elements on mammography: the number of calcified vessels (0-6 points), the severity of artery calcification (0-3 points) and the length of calcified vessels (0-3 points). Accordingly, the total scores are divided into three categories with 0 point indicates the absence of BAC, 1-3 points mild calcification, and 4-12 points significant calcifications (Table 2).

Mammography was performed by acquiring mediolateral oblique and craniocaudal images including tomosynthesis (Siemens Mammomat Inspiration 2015).

Statistical Analysis

Data obtained in the study were analysed using SPSS Version 20.0 (SPSS 20.0 for Windows IBM, Virginia, USA) statistical software. Normality of the data was tested and normal distribution value was calculated with Skewness-Kurtosis test. Continuous numerical variables are expressed median (minimum-maximum) values as appropriate, and categorical variables as percentage (%). Paired Student's t-test was used in the comparison of continuous variables. The correlation between continuous variables was studied with Pearson's correlation analysis. P<0.05 values were considered statistically significant.

Table 2. BAC scoring system

Number of vessels		Length of vessels		Severity of calcification	
1	1	1/3 involvement	1	Spot calcification	1
2	2	1/3 - 2/3 involvement	2	Spot calcification in the lumen	2
3	3	>2/3 involvement	3	Intense calcification in the vessel including tangential walls and lumen	3

BAC: Breast artery calcification

Table 3. Correlation between BAC and CAC scores

	No BAC	Mild calcification	Significant calcification	Total	p value
No CAC	1	7	-	8	0.001
Minimal plaque	-	-	-	-	
Mild plaque	-	2	10	12	
Moderate plaque	-	-	8	8	
Diffuse atherosclerotic plaque	-	-	3	3	
Total	1	9	21	31	

BAC: Breast artery calcification, CAC: Coronary artery calcification

Results

A total of 31 women were included in the study. The median age of the participants was 57 (40-74) years. BAC scores were found as 0 in one (3.2%) patient, 1-3 in nine (29.0%) patients, and 4-12 (67.7%) in 21 patients. Both BAC and CAC scores were increased as the age of the patients increased.

CAC scores were found as 0 in eight (25.8%) patients, 11-100 in 12 (38.7%) patients, 101-400 in eight (25.8%) patients and >400 in three (9.2%) patients. Sample of the study mostly consisted of the patients with a CAC score between 11-100 and a BAC score between 4-12.

CAC score was 0 in a patient with a BAC score of 0, while seven (77.8%) of patients with BAC scores of 1-3 were in CAC 0 group, and the remaining two patients were in CAC 11-100 group. Of the 21 patients in BAC 4-12 group, 10 (47.6%) were in CAC 11-100 group, eight (38.1%) in CAC 101-400 group and 3 (9.68%) in CAC >400 group. Accordingly, the highest rate of patients was found in BAC 4-12 and CAC 11-100 groups by 47.6% (Chart 1).

When the results of t-test and mean values of the groups were evaluated together, CAC scores were found to be more effective. Effect of BAC scores on CAC scores was found as 63%. The correlation between BAC and CAC scores was statistically significant (r=0.796 p<0.005) (Table 3). When cardiovascular risk factors related to BAC were examined; Diabetes mellitus was found in 19 (61.29%), hypertension in 17 (54.83%), hyperlipidemia

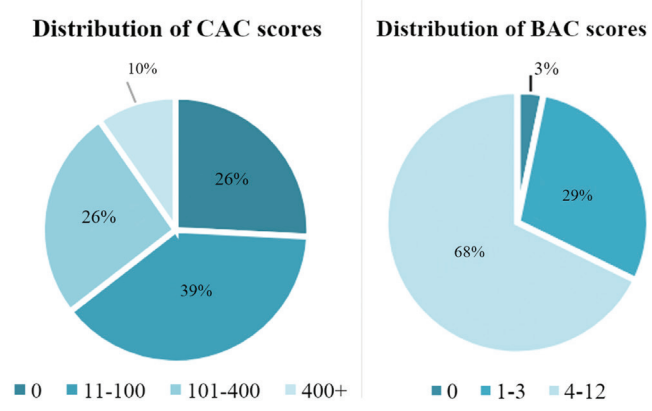

Chart 1. Distribution of CAC and BAC scores

BAC: Breast artery calcification, CAC: Coronary artery calcification

in 16 (51.61%), smoking in four (12.90%), chronic kidney disease in two (6.45%) patients and family history in one (3.22%) patient. The relationship between the presence of BAC and cardiovascular risk factors was given in Table 4.

Samples of moderate and moderate-advanced stage coronary artery and breast vascular calcifications are given in Figures 1 and 2.

Discussion

CAC scoring has been a risk estimation tool for coronary artery calcification as an indicator of subclinical heart disease (19). Higher CAC scores are associated with a higher risk of coronary events. In addition, the presence of CAC has been used to justify modification treatments with a more aggressive CAD risk factor such as aspirin, statins and lifestyle changes (20). Studies have shown that the extent of CAC is strongly associated with the rate of future cardiac events, and that high prevalence of CAC in patients with coronary heart disease make percutaneous coronary intervention difficult (4).

Table 4. Relationships between the presence of BAC and cardiovascular risk factors

	BAC scores	
	BAC -	BAC +
Number of patients (n)	1	30
Age at mammography (mean ± SD)	54 (7.5)	59 (8)
Presence of BAC	1	30
Diabetes mellitus	12	19
Hypertension	14	17
Smoking	4	4
Hyperlipidemia	15	16
Chronic kidney disease	0	2
Family history	0	1

BAC: Breast artery calcification, SD: Standard deviation

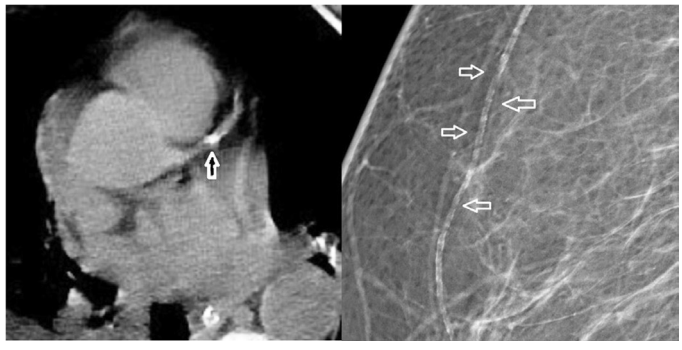

Figure 1. Mild calcification in the left anterior descending coronary artery of a 56-year-old woman with BAC score 4

BAC: Breast artery calcification

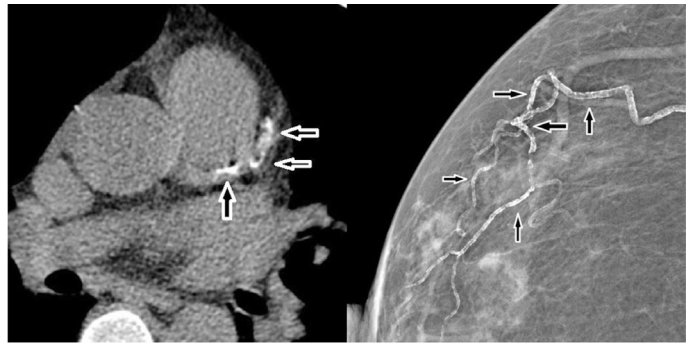

Figure 2. Moderate calcification in the left anterior descending coronary artery of a 74-year-old woman with BAC score 9

BAC: Breast artery calcification

Mammography screening has been widely used in early detection of breast cancer. BAC is a benign finding on mammography especially in elderly women. It has been proposed that this incidental finding can be used as an indicator of vascular disease (21). Therefore, relationships between BAC and cardiovascular disease markers and potential risk factors and CAC scores (22,23).

In the present study the relationship between BAC and CAC was evaluated. As a result of the evaluations and analyses, a strong correlation was found between BAC and CAC. In a study by Pecchi et al. (16) in 2003, a strong correlation was found between BAC and CAC. In 2007, Maas et al. (24) reported a strong correlation between BAC and CAC in 499 women at the end of 9-year follow up. More recently, in a retrospective study by Chadashvili et al. (25) with 145 women who were referred for coronary computed tomography within one year after mammography screening; a significant association was found between the presence of CAC>11 and BAC.

BAC rates increase in patients as CAC scores increase. In our study, BAC scores were found in the range of 4-12 in three patients with a CAC score >400. In a study by Matsumura et al. (26) in 2013, BAC scores were significantly increased in women with a CAC score >400. However, there is currently no exact consensus on this issue in the literature. In a cross-sectional study by Moradi et al. (27), the relationship between BAC and CAC was investigated in 150 Iranian women aged >40 years, and no significant correlation could be found. The authors stated that BAC and the presence of significant coronary stenosis might be independently associated with age, and therefore older women were more susceptible for both BAC and CAC. In our study also, both BAC and CAC scores were increased as the age of the patients increased.

Several factors might have affected these contradictory results. Different study designs might be the major factor affecting the differences between these results. The effect of cardiac risk factors on coronary arteries should be kept in mind.

In a study by Wendling (28) in 2016, CAC was found by 47.6% among 292 women. The authors reported a significant correlation between CAC and BAC. In our study, moderate cardiovascular risk was found by 47.6% among the participants. In addition, we found a strong correlation between CAC and the elements of BAC (number of calcified vessels, length of calcified vessels, and severity of calcification). In a study by Fathala et al. (29), similar results were reported. In addition, in another prospective study by Dale et al. (30) including 1000 women, the likelihood of CAC was found as 6.2 times higher in women with BAC compared to those without BAC in all age groups. The results of that study which has a high number of participants and those of the other studies indicate that mammography could be a helpful tool for the screening of coronary vascular disease. Likewise, previous studies except for the study by Moradi et al. (27), in our study also a significant correlation was found between BAC and CAC scores. However, the reported results should be cautiously interpreted. Because there is difference between sample sizes of the studies, and participants have already presented for computed tomography screening in most of these studies. In addition, different methods and threshold values were used for the measurement of CAC scores among the studies. Sensitivity of BAC in prediction of CAC on mammography is variable and is reported between 17% and 91%. Again, specificity of BAC score is reported between 54% and 94% in different studies. Therefore, further studies with larger cohorts are needed for establishing a definitive consensus on the relationship between these two scores in the literature and introduction of BAC score in routine clinical practice for the prediction of CAC.

Study Limitations

This study has several limitations. First, the number of patients was relatively small. Second, we included only the women who presented for CAC score evaluation. Finally, the study has no long term follow up data. However, we believe that our results would provide contribution to the future consensus on this issue in the literature.

Conclusion

We found a positive correlation between BAC and CAC scores in the studied sample. This correlation between BAC and CAC scores could be used as a diagnostic tool in asymptomatic women. Criteria of this diagnostic method could be determined with further studies including a larger series of patients and longer follow-up.

Ethics

Ethics Committee Approval: Before the beginning of the study, the necessary approval was received from the local ethics committee with 2/2019.K-018 numbered decision.

Informed Consent: Patients included in the study were informed about the objective of the study and given written and verbal consents. The study was conducted in accordance with the principles of the Declaration of Helsinki

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: I.Y., Concept: I.Y., Design: F.N., Data Collection or Processing: F.N., Analysis or Interpretation: F.N., Literature Search: F.N., Writing: I.Y.

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

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

References

1. World Health Organization 2017, cardiovascular disease, viewed 21 January 2019. <https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)>
2. TÜİK Haber Bülteni, Ankara Sayı:24572, 27 Nisan 2017 http://www.tuik.gov.tr/HbPrint.do?id=24572 (Accessed on: 25/03/2019).
3. TÜİK Haber Bülteni, Ankara Sayı:16050, 30 Nisan 2014, http://www.tuik.gov.tr/PreHaberBultenleri.do%3Fid%3D16050
4. Greenland P, Bonow RO, Brundage BH, Matthew J Budoff, Mark J Eisenberg, Scott M Grundy, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol. 2007;49:378-402.
5. Nasir K, Bittencourt MS, Blaha MJ, Blank-stein R, Agatson AS, Rivera JJ, et al. Implications of Coronary Artery Calcium Testing Among Statin Candidates According to American College of Cardiology/American Heart Association Cholesterol Management Guidelines: MESA (Multi-Ethnic Study of Ath. erosclerosis). Journal of the American College of Cardiology. 2015;66:1657-68.
6. Yiğit A. Mamografi Sağlık Teknolojisi ile Meme Kanseri Tarama Programının Klinik Etkililiğinin Meta Analiz Yöntemiyle Değerlendirilmesi. SBE Dergisi. 2017;28:401-30.https://sbedergi.sdu.edu.tr/assets/uploads/sites/343/files/28-sayi-yazi22-20112017.pdf
7. Topuz, E. Meme Kanseri. Tanı-Tedavi-Takip. In: Nobel Tıp Kitapevleri, İstanbul, Aydıner A, İğci A, editors, 2006.
8. Aslan FE, Gürkan A. Kadınlarda Meme Kanseri Risk Düzeyi. Meme Sağlığı Dergisi. 2007;3:63-8.
9. Meme Kanseri Tarama Programı Ulusal Standartları. https://hsgm.saglik.gov.tr/tr/kanser-tarama-standartlari/listesi/meme-kanseri-tarama-program%C4%B1-ulusal-standartlar%C4%B1.html
10. TRD Yeterlilik Kurulu, Rehber ve Standartlar Komitesi-Meme Kanseri Tarama Rehberi, 2011. https://www.turkrad.org.tr/assets/standartlar/meme-tarama-rehberi.pdf
11. Everhart JE, Pettitt DJ, Knowler WC, Rose FA, Bennett PH. Medial arterial calcification and its association with mortality and complications of diabetes. Diabetologia. 1988;31:16-23.

12. Shanahan CM, Cary NR, Salisbury JR, Proudfoot D, Weissberg PL, Edmonds ME. Medial localization of mineralization-regulating proteins in association with Monckeberg's sclerosis: evidence for smooth muscle cell-mediated vascular calcification. Circulation. 1999;100:2168-76.
13. Jiang X, Clark M, Singh RK, Juhn A, Schnatz PF. Association of breast arterial calcification with stroke and angiographically proven coronary artery disease: a metaanalysis. Menopause. 2015;22:136-43.
14. Hendriks EJ, de Jong PA, van der Graaf Y, Mali WP, van der Schouw YT, Beulens JWJ. Breast arterial calcifications: a systematic review and meta-analysis of their determinants and their association with cardiovascular events. Atherosclerosis. 2015;239:11-20.
15. Shah N, Chainani V, Delafontaine P, Abdo A, Lafferty J, Abi Rafeh N. Mammographically detectable breast arterial calcification and atherosclerosis. Cardiol Rev. 2014;22:69-78.
16. Pecchi A, Rossi R, Coppi F, Ligabue G, Modena MG, Romagnoli R. Association of breast arterial calcifications detected by mammography and coronary artery calcifications quantified by multislice CT in a population of postmenopausal women. Radiol Med. 2003;106:305-12.
17. Yoon YE, Kim KM, Han JS, Khang SH, Chun EJ, Ahn S, et al. Prediction of subclinical coronary artery disease with breast arterial calcification and low bone mass in asymptomatic women: Registry for the Women Health Cohort for Breast, Bone, and Coronary Artery Disease Study. Jacc Cardiovasc Imaging. 2018;12:1202-11.
18. Budoff MJ, Gul KM. Expert Review on Coronary Calcium. Vasc Health Risk Manag. 2000;4:315-24.
19. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte Jr M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Colle Cardiol. 1990;15:827-32.
20. Taylor AJ, Bindeman J, Feuerstein I, Le T, Bauer K, Byrd C, et al. Community-based provision of statin and aspirin after the detection of coronary artery calcium within a community-based screening cohort. J Am Coll Cardiol. 2008;51:1337-41.
21. Markopoulos C, Mantas D, Revenas K, Kouskos E, Tzonou A, Liapis C, et al. Breast arterial calcifications as an indicator of systemic vascular disease. Acta Radiol. 2004;45:726-9.
22. Pidal D, Sánchez Vidal MT, Rodríguez JC, Corte MD, Pravia P, Guinea O, et al. Relationship between arterial vascular calcifications seen on screening mammograms and biochemical markers of endothelial injury. Eur J Radiol. 2009;69:87-92.
23. Sedighi N, Radmard AR, Radmehr A, Hashemi P, Hajizadeh A, Taheri AP. Breast arterial calcification and risk of carotid atherosclerosis: focusing on the prefentially affected layer of vessel wall. Eur J Radiol. 2011;79:250-6.
24. Maas AH, van der Schouw YT, Atsma F, Beijerinck D, Deurenberg J, Mali W, et al. Breast arterial calcifications are correlated with subsequent development of coronary artery calcifications, but their aetiology is predominantly different Eur J Radiol. 2007;63:396-400.
25. Chadashvili T, Litmanovich D, Hall F, Slanetz PJ. Do breast arterial calcifications on mammography predict elevated risk of coronary artery disease? Eur J Radiol. 2016;85:1121-4.
26. Matsumura ME, Maksimik C, Martinez MW, Weiss M, Newcomb J, Harris K, et al. Breast artery calcium noted on screening mammography is predictive of high risk coronary calcium in asymptomatic women: a case control study. GefaÃàsskrankheiten J Vas Dis. 2013;42:429-33.
27. Moradi M, Atoosa A, Abedi M. Relationship between breast arterial calcification on mammography with CT Calcium scoring and coronary CT angiography results. Adv Biomed Res. 2014;3:79.
28. Wendling P. Breast Arterial Calcification on Mammography IDs Atherosclerotic CVD Risk. https://www.medscape.com/viewarticle/861029
29. Fathala AL, Alabdulkarim FM, Shoukri M, Alanazic M. Association between breast arterial calcifications found on mammography and coronary artery calcifications in asymptomatic Saudi women. Ann Saudi Med. 2018;38:433-8.
30. Dale PS, Mascarhenas C, Richards M, Mackie G. Mammography as a screening tool for coronary artery disease. J Surg Res. 2008;148:1-6.

EURASIAN JOURNAL OF EMERGENCY MEDICINE
Original Article
DOI: 10.4274/eajem.galenos.2020.93446
Eurasian J Emerg Med. 2020;19(3): 142-8

Time-to-use of Intravenous Antibiotics in Patients with Sepsis in whom Activation of the Sepsis Fast Track Protocol was Facilitated by the National Early Warning Score

Pannika Thuakta[1], Borwon Wittayachamnankul[1], Titisuda Chounjai[2], Theerapon Tangsuwanaruk[1]

[1]Department of Emergency Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand
[2]Maharaj Nakorn Chiang Mai Hospital, Chiang Mai, Thailand

Abstract

Aim: To examine changes in door-to-antibiotic time in pre- and post-intervention groups.

Materials and Methods: A quasi-experimental study was conducted in the Emergency Department involving adult patients who were diagnosed with sepsis or septic shock in a university-based hospital. The patients were distributed into one of two groups: a pre-intervention or post-intervention group. In the post-intervention group, among patients with a suspected infection and a National Early Warning Score (NEWS) of ≥5, the sepsis fast track protocol was used in the normotensive group and the sepsis with shock fast track protocol was used in the hypotensive group. Our primary outcome was the difference in the door-to-antibiotic time in the pre- and post-intervention groups.

Results: Overall, 117 patients were included in the pre-intervention group and 102 patients in the post-intervention group. The median door-to-antibiotic time in the pre-intervention group was 45 min [interquartile range (IQR): 30-65], and the median door-to-antibiotic time in the post-intervention group was 30 min (IQR: 20-55, p=0.009). However, there was no significant difference in the mortality rate (p=0.194).

Conclusion: Using an activated system with NEWS for screening patients suspected with sepsis helped reduce the door-to-antibiotic time.

Keywords: Antibiotic, emergency department, National Early Warning Score, protocol, sepsis

Introduction

Sepsis is associated with high mortality and morbidity (1). In 2017 the World Health Organization reported more than 30 million cases of sepsis worldwide, and more than six million deaths per year had been attributed to sepsis (2). The mortality rate reached 35.09%, making sepsis the fourth leading cause of death worldwide (3,4). To improve survival in cases of sepsis the Surviving Sepsis Campaign Bundle 2018, guidelines recommend administering empirical intravenous antibiotics within one hour and adequate fluid resuscitation in sepsis cases with hypotension or with serum lactate levels ≥4 millimoles per liter (mmol/L) (1,5-7).

An important factor in prompt management has been the introduction of an accurate and rapid detection tool (8). In a recent study it was found that the quick Sequential Organ Failure Assessment (qSOFA) predicted hospital mortality rates and intensive care unit (ICU) length of stay more accurately than the Systemic Inflammatory Response Syndrome (SIRS) (9). However very recent studies have found the National Early Warning Score (NEWS) to be as effective in the prediction of hospital mortality rate and ICU admission as qSOFA and more accurate in comparison to SIRS (9-12). Somehow, NEWS has been found to have more accuracy in predicting mortality and ICU admission when compared to qSOFA (12-14). However, no previous studies have reported the use of NEWS for early activation of the sepsis code to lessen the time to goal of therapeutic intervention including the administration of empirical antibiotics, fluid resuscitation, or to reduce mortality in the emergency department (ED).

Corresponding Author: Theerapon Tangsuwanaruk, MD, Department of Emergency Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand
E-mail: theerapon.t@cmu.ac.th ORCID ID: orcid.org/0000-0003-1783-3095
Cite this article as: Thuakta P, Wittayachamnankul B, Chounjai T, Tangsuwanaruk T. Time-to-use of Intravenous Antibiotics in Patients with Sepsis in whom Activation of the Sepsis Fast Track Protocol was Facilitated by the National Early Warning Score. Eurasian J Emerg Med. 2020;19(3):142-8

Received: 11.05.2020
Accepted: 15.06.2020

This study aimed to compare door-to-antibiotic time before and after implementation of NEWS as a sepsis screening tool, where a NEWS ≥5 and suspected infection were used to trigger the activation of the sepsis fast track protocol.

Materials and Methods

Study Design

This study was a retrospective and prospective, quasi-experimental study which was approved by the Research Ethics Committee of Faculty of Medicine of Chiang Mai University (no: 377/2018, date: 03.10.2018). Written informed consent was obtained from patients who were enrolled on the prospective study. This study was registered in the Thai Clinical Trials Registry (www.clinicaltrials.in.th, TCTR20191002001).

Study Setting and Population

Patients who visited the ED from June 1, 2018 to August 31, 2018, prior to the implementation of NEWS as a sepsis trigger tool, were recruited onto the study. The qSOFA criteria had been used for the screening of these patients who were suspected sepsis and action had been taken as for a general patient without the sepsis fast track protocol. These patients were classified as the pre-intervention group. ED patients from October 1, 2018 to December 31, 2018, after the implementation of NEWS as a sepsis screening tool, were included in the post-intervention group. The inclusion criteria were as follows: patients aged 18 years or over with a suspected infection from a medical condition with NEWS ≥5. The exclusion criteria included patients referred from another hospital without available medical records, patients requiring emergency surgery, patients discharged from the ED, patients with a misdiagnosis, patients who had received antibiotics within the last 30 days, or refusal by patient and/or guardian refusal or were not able to consent to participation in the research.

Data collection occurred at two time points: three months pre-intervention and three months post-intervention, intervention being the implementation of the sepsis fast track protocol. Patients in the pre-intervention group were recruited from June 1, 2018 to August 31, 2018, and included those diagnosed with sepsis or septic shock, according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems, with a NEWS ≥5. From September 1 to September 30, 2018, triage and screening personnel were briefed on the use of NEWS as a screening tool in patients with suspected sepsis (run in phase). If NEWS ≥5, screening personnel were to alert the emergency physician, who would be the one to decide on the activation of the sepsis fast track protocol. The protocol was divided into two sections: a normotensive and a hypotensive group. The normotensive group included patients with a systolic blood pressure (SBP) ≥90 millimeters of mercury (mm Hg) or a mean arterial pressure (MAP) ≥65 mm Hg, and appropriate antibiotics were given during treatment. The hypotensive group included patients with SBP <90 mm Hg or MAP <65 mm Hg. In this group, in addition to appropriate antibiotics, adequate fluid resuscitation would be administered. Data for analysis of the post-intervention group was collected from October 1 to December 1, 2018 by both nurses and physicians. The emergency physicians and the nurses are the same team, no increase population, no have any benefit or punish in pre- and post-intervention group.

Outcome Measures

The primary outcome was the door-to-antibiotic time in patients when NEWS was used as a trigger tool to activate sepsis fast track protocol, in comparison to the door-to-antibiotic time in patients where such a tool was not used. The secondary outcomes examined the door-to-intravenous bolus time (door-to-IV bolus time), door-to-laboratory time (door-to-lab time) taken, lactate clearance, time to admission decision, average hospital length of stay (LOS), and average number of days ICU free, average ventilator free days, and 28-day mortality rate. The door-to-IV bolus time was defined as time between patient arriving at ED to IV bolus being achieved. The door-to-lab time taken was defined as time between patient arriving at ED to blood test taken. The lactate clearance was defined as percentage of blood lactate at arrival minus blood lactate concentration at follow up 2 hours after resuscitation. For lactate clearance, patients in whom there was no follow up of blood lactate, or blood lactate at visit <2 mmol/L or missed data were not included in this outcome. The time to admission decision was defined as time between patient arriving at ED to the nurse receiving the admission order.

Sample Size Calculation

To ensure the number of patients in this study was adequate, the sample size was calculated by independent mean (15). A previous study had reported a mean of door to antibiotics time in the pre-intervention group as 139 minutes [standard deviation (SD)=74] and in the post-intervention group as 81 minutes (SD=39) with an alpha error of 0.05 and a beta error of 0.1, required a sample size of 22 patients in each group (8).

Statistical Analysis

Descriptive statistics were used for categorical data and mean values, standard deviation, medians, and interquartile ranges for continuous data. The Shapiro-Wilk test was used to test a normal distribution. Variables that approximated to a normal distribution were summarized as mean ± SD, and groups were compared using t-tests. Other continuous or ordinary scaled variables were summarized as median, interquartile range, and groups and compared using Mann-Whitney U tests. All statistical

analyses were performed using SPSS® Statistics version 22 (IBM®, Armonk, New York, USA). Statistical significance was designated as $p<0.05$ unless stated otherwise.

Results

There was a total of 539 patients over 18 years of age with sepsis or septic shock, with a NEWS ≥5 and following application of the exclusion criteria, 275 patients were eligible for inclusion in this study. One hundred and seventeen patients were included in the pre-intervention group and 102 in the post-intervention group as shown in Figure 1. Baseline characteristics, including underlying diseases, hospital readmission within three months, vital signs, NEWS, lymphocyte count, and serum lactate did not significantly differ between the pre-and post-intervention groups (Table 1).

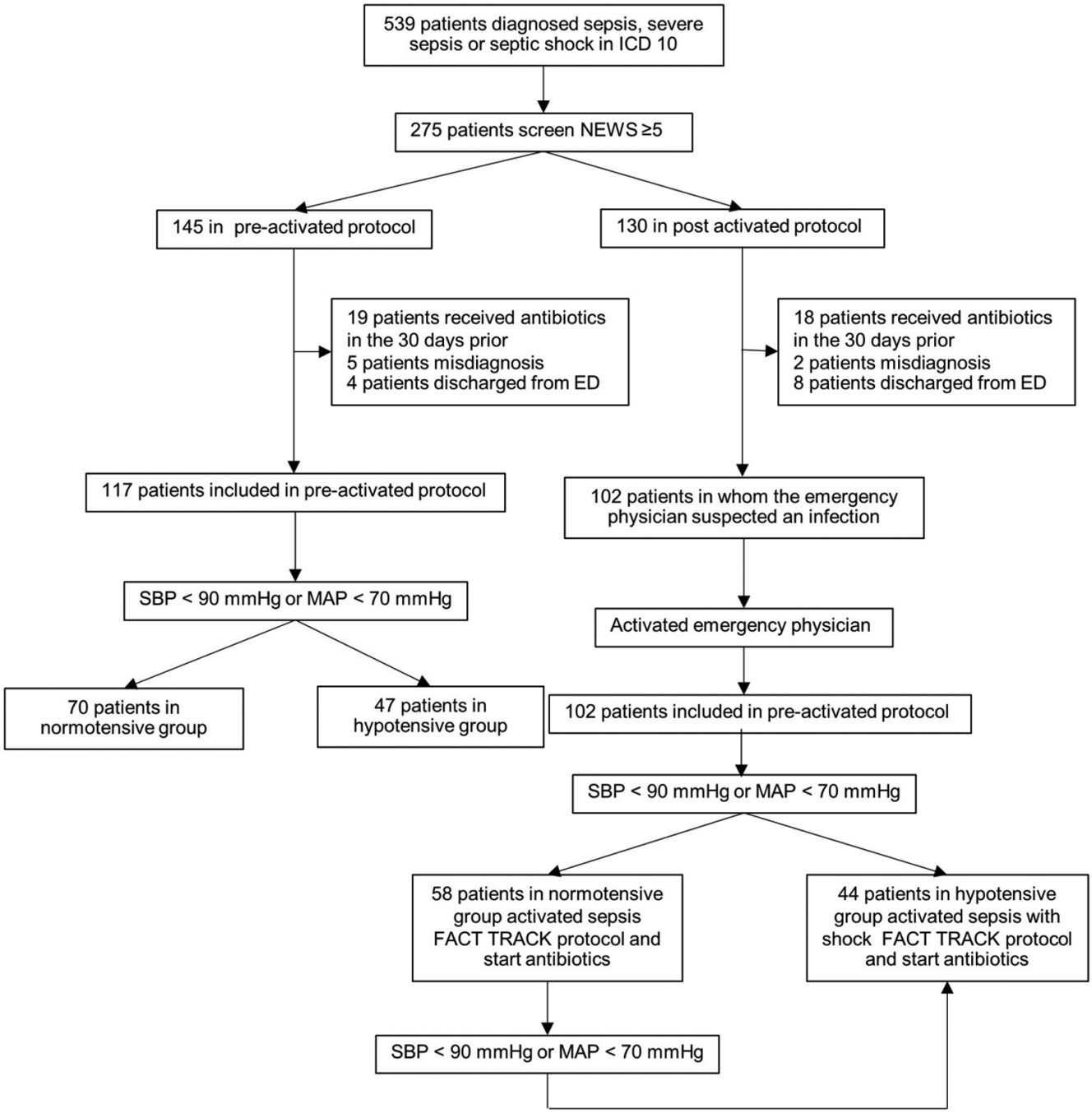

Figure 1. Study flow chart

ED: Emergency department, ICD 10: 10th revision of the International Statistical Classification of Diseases and Related Health Problems, MAP: Mean arterial pressure, mmHg: Millimeters of mercury, NEWS: National Early Warning Score, SBP: Systolic blood pressure

Table 1. Baseline characteristics			
	Pre-intervention (n=117)	**Post-intervention (n=102)**	**p value**
Group - n (%)			
Normotensive group	47 (42.0)	44 (43.14)	0.657
Hypotensive group	70 (59.8)	58 (56.9)	0.657
Male - n (%)	66 (56.4)	48 (47.1)	0.213
Age - years	64.4±18.7	65.5±18.2	0.643
Medical condition - n (%)			
Diabetes mellitus	19 (16.2)	22 (21.6)	0.404
Hypertension	42 (35.9)	45 (44.1)	0.271
Dyslipidemia	23 (19.7)	26 (25.5)	0.384
Cancer	33 (25.2)	30 (29.4)	0.962
Chronic kidney disease	17 (14.5)	18 (17.6)	0.658
Cerebrovascular disease	17 (14.5)	24 (23.5)	0.126
Readmission within 3 months-n (%)	39 (33.3)	32 (31.4)	0.869
Temperature - degrees Celsius	37.9±1.5	38.0±1.3	0.579
Heart rate - beats per min	107.1±24.2	111.5±25.9	0.197
Respiratory rate - times per min	29±16.9	25±8.9	0.102
SBP - mmHg (IQR)	105.5 (83.0-130.5)	91.5 (77.5-131.0)	0.248
MAP - mmHg (IQR)	72.5 (61.0-90.5)	67.5 (58.0-100.5)	0.072
Oxygen saturation - % (IQR)	90.0 (84.0-96.0)	93.5 (89.0-97.0)	0.693
NEWS - score (IQR)	9.0 (7.0-10.5)	8.5 (7.0-11.0)	0.679
White blood cell count - $x10^3$ cell/cu.mm (IQR)	12.0 (5.6-21.2)	11.6 (6.3-16.0)	0.843
Serum lactate - mmol/L (IQR)	3.05 (1.8-4.6)	2.5 (1.9-3.8)	0.297

Data presented as mean ± SD or median (interquartile range), depending on distribution.
cell/cu.mm: Cell per cubic millimeter, IQR: Interquartile range, lab: Laboratory, MAP: Mean arterial pressure, min: Minute, mmHg: Millimeters of mercury, NEWS: National Early Warning Score, mmol/L: millimole per liter, SBP: Systolic blood pressure, SD: Standard deviation, n: Number

After implementing the sepsis fast track protocol, the median door-to-antibiotic time was 34 minutes (20 to 55); this was statistically significantly lower from the pre-intervention median time of 45 minutes (30 to 65; p=0.009). Median door-to-lab time taken in the post-intervention group was lower than the pre-intervention group [18 (8-40) vs 11 (5-20); p=0.003]. However, there were no difference in door-to-IV bolus time, time to an admission decision, average hospital LOS, average ICU free days, average ventilator free days, and 28-day mortality rate (Table 2).

Hypotensive patients and Normotensive patients were separated in a subgroup analysis, baseline characteristics of patients (Tables 3 and 4), including treatment received, did not significantly differ, apart from one exception, in the normotensive group there was a lower prevalence of cerebrovascular disease in the pre-group than in the post-group (12.9 vs 39.8; p=0.013). In the post-intervention normotensive group, door-to-antibiotic time was found to be statistically significantly reduced, median pre-intervention 44.5 (30.0 to 64.3) minutes and post-intervention 25.0 (20.5 to 51.5) minutes; p=0.003, but there was no significant difference in the hypotensive group. Likewise, in the post-intervention group, door-to-lab time taken was also found to be reduced, again with statistical significance, median pre-intervention 16.5 (6.8 to 27.3) minutes, post-intervention 11.5 (5.5 to 20.0) minutes; p=0.005. There were no other significant differences found. With regards to the hypotensive group, time to admission decision increased, with statistical significance, median pre-intervention being 213.0 (173.0 to 300.0) minutes, and post-intervention 273.0 (196.3 to 327.5) minutes; p=0.025.

Discussion

This study found activation of code sepsis using NEWS to detect sepsis patients earlier significantly reduced time to antibiotic administration. Several studies have been conducted to compare different sepsis screening tools. Usman et al. (16) and Thodphetch et al. (17) found that NEWS as a sepsis screening tool had higher sensitivity in comparison to qSOFA, SIRS, and Search Out Severity Score. Screening tools with a higher sensitivity are believed to result in more rapid detection of sepsis and thus more prompt management. Seymour et al. (6) found that the administration of antibiotics prior to 0.95 hours can reduce the mortality rate

Table 2. Primary and secondary outcomes			
	Pre-intervention (n=117)	**Post-intervention (n=102)**	**p value**
Door-to-antibiotic time - min (IQR)	45.0 (30.0-65.0)	30.0 (20.0-55.0)	0.009
Door-to-IV bolus time - min (IQR)	12.0 (6.0-32.0)	8.5 (5.0-20.0)	0.150
Door-to-lab time taken - min (IQR)	18.0 (8.0-40.0)	11.0 (5.0-20.0)	0.003
Lactate clearance - %	23.1±28.7	17.0±37.3	0.339
Time to admission decision - min (IQR)	225.0 (175.0-297.0)	223.0 (180.5-297.0)	0.919
Average hospital LOS - day (IQR)	8.0 (4.0-17.0)	7.0 (5.0-13.0)	0.603
Average ICU free days - day (IQR)	6.0 (3.0-12.0)	7.0 (3.0-10.0)	0.885
Average ventilator free days - day (IQR)	6.0 (2.5-10.0)	7.0 (3.0-10.0)	0.773
28-day mortality rate-n (%)	35 (29.9)	31 (30.4)	0.194

Data presented as mean ± SD or median (interquartile range), depending on distribution.
ICU: Intensive care unit, IQR: Interquartile range, IV: Intravenous, lab: Laboratory, LOS: Length of stay, min: Minute, SD: Standard deviation, n: Number

Table 3. Baseline characteristics in subgroup analysis by normotensive group and hypotensive group						
	Pre-intervention normotensive (n=70)	**Post-intervention normotensive (n=58)**	**p value**	**Pre-intervention hypotensive (n=47)**	**Post-intervention hypotensive (n=44)**	**p value**
Male sex - n (%)	42 (60.0)	31 (53.5)	0.571	23 (48.9)	17 (38.6)	0.437
Age - year	63.0±17.7	67.3±17.8	0.181	71.0 (54.0-89.0)	66.0 (59.8-78.8)	0.950
Medical condition - n (%)						
Diabetes mellitus	11 (15.7)	13 (22.4)	0.709	8 (17.0)	9 (20.5)	0.880
Hypertension	22 (31.4)	28 (48.8)	0.078	20 (42.6)	17 (38.6)	0.868
Dyslipidemia	14 (20.0)	16 (27.6)	0.424	9 (19.2)	10 (22.7)	0.872
Cancer	19 (27.1)	13 (22.4)	0.682	14 (29.8)	17 (38.6)	0.504
CKD	13 (18.6)	14 (24.1)	0.582	4 (8.5)	4 (9.1)	1.000
Cerebrovascular disease	9 (12.9)	19 (32.8)	0.013	8 (17.0)	5 (11.4)	0.638
Readmission within 3 months - n (%)	24 (34.3)	19 (32.8)	1.000	15 (31.9)	13 (29.6)	0.986
Temperature - degree Celsius (IQR)	38.60 (37.8-39.7)	38.50 (37.8-39.1)	0.992	37.3±1.37	337.5±1.38	0.508
Heart rate - beats per min	108.7±19.7	113.6±27.3	0.235	104.8±29.9	109.5±25.2	0.417
Respiratory rate - times per min (IQR)	29.0 (24.0-37.0)	28 (22.5-35.0)	0.218	28.0 (22.0-40.0)	24.0 (20.5-32.0)	0.583
SBP - mmHg	129.1±28.9	138.9±28.5	0.184	81.0 (70.0-91.0)	81.0 (72.3-95.5)	0.381
MAP - mmHg	88.0 (78.5-97.8)	93.0 (112.0-141.8)	0.004	61.0 (56.0-69.0)	59.5 (56.3-76.0)	0.862
Oxygen saturation - % (IQR)	91.0 (87.3-94.0)	92.0 (89.3-95.0)	0.530	88.0 (78.0 -97.0)	95.0 (86.8-98.0)	0.199
NEWS - score (IQR)	8.0 (7.0-9.0)	8.0 (7.0-10.0)	0.325	9.5±3.3	9.0±2.8	0.416
White blood cell count x10^3 cell/cu.mm (IQR)	13.4 (4.5-20.8)	10.3 (5.2-17.0)	0.553	8.9 (5.8-21.9)	12.2 (7.7-16.7)	0.715
Serum lactate - mmol/L (%)	3.8 (3.0-4.9)	3.9 (2.8-5.5)	0.820	4.7 (3.7-6.3)	3.6 (2.8-6.3)	0.091

Data presented as mean ± SD or median (interquartile range), depending on distribution.
cell/cu.mm: Cell per cubic millimeter, IQR: Interquartile range, MAP: Mean arterial pressure, min: Minute, mmHg: Millimeter of mercury, NEWS: National Early Warning Score, mmol/L: Millimole per liter, SBP: Systolic blood pressure, SD: Standard deviation, n: Number, CKD: Chronic kidney disease

in sepsis (6). The findings from these studies led to the surviving sepsis campaign in 2018 the outcomes of which recommended the administration of adequate empirical intravenous antibiotics within the first hour of treatment. In addition, it was found that the activation of the sepsis care system in the ED causes faster intervention than conventional treatment (18-20). Furthermore, activation of the system was found to reduce door-to-lab time significantly. Such findings were in agreement with a study by Hayden et al. (8) which concluded that faster lab results resulted in a faster diagnosis, using the SOFA score, according to the Third International Consensus Definitions for Sepsis and Septic Shock (SEPSIS-3) definition. However, in our study there were no differences with regard to time to fluid resuscitation. This resulted from patients with a lower MAP score in our study being triaged

Table 4. Primary and secondary outcomes in subgroup analysis by normotensive group and hypotensive group						
	Normotensive group			Hypotensive group		
	Pre-intervention (n=71)	Post-intervention (n=58)	p value	Pre-intervention (n=47)	Post-intervention (n=44)	p value
Door-to-antibiotic time - min (IQR)	44.5 (30.0-64.3)	25.0 (20.5-51.5)	0.003	41.0 (23.0-58.0)	37.5 (19.0-83.5)	0.617
Door-to-IV bolus time - min (IQR)	-	-	-	12.0 (6.0-32.0)	10.00 (5.0-24.8)	0.143
Door-to-lab time taken - min (IQR)	16.5 (6.8-27.3)	11.50 (5.5-20.0)	0.005	9.0 (3.0-15.0)	9.0 (5.0-18.3)	0.299
Lactate clearance - % (IQR)	35.2 (9.2-45.3)	35.0 (7.5-47.2)	0.890	22.0 (13.3-38.2)	13.3 (-1.3-31.4)	0.335
Time to admission decision - min	260.4±104.9	229.8±108.1	0.109	213.0 (173.0-300.0)	273.0 (196.3-327.5)	0.025
Average hospital LOS - day (IQR)	8.0 (6.0-21.5)	14.5 (8.3-17.8)	0.863	9.0 (4.0-32.0)	7.0 (5.0-12.0)	0.633
ICU free days - day (IQR)	7.0 (4.0-13.0)	7.0 (4.0-10.5)	0.435	4.0 (0.0-9.0)	6.0 (2.0-9.0)	0.296
Ventilator free days - day (IQR)	7.0 (4.0-12.3)	7.0 (3.0-10.5)	0.642	4.0 (0.0-9.0)	6.0 (2.0-9.0)	0.279
28-day mortality rate - n (%)	11 (15.7)	15 (25.9)	0.230	24 (51.0)	16 (36.4)	0.230

Data presented as mean ± SD or median (interquartile range), depending on distribution.
ICU: Intensive care unit, IQR: Interquartile range, IV: Intravenous, lab: Laboratory, LOS: Length of stay, min: Minute, SD: Standard deviation, n: Number

as a resuscitation case, and thus most patients would receive rapid fluid administration regardless of sepsis fast track use. This study shows no statistical difference in the 28-day mortality rate, possibly due to insufficient numbers of patients, or possibly that the door-to-antibiotic time in the pre-intervention group was less than other studies (18). Future studies with larger number of patients are needed to verify this.

In our subgroup analysis, we found that the activation of sepsis fast track reduced door-to-antibiotic time and door-to-lab time. However, for the hypotensive group, there were no significant differences in door-to-antibiotic time, door-to-lab time, and time to fluid administration between the pre- and post-intervention groups. An explanation for this is probably because patients in the hypotensive group were triaged as resuscitation cases, thus would receive prompt intervention regardless of protocol activation. However, this study does highlight how the protocol helps personnel to have an increased focus on sepsis as regards normotensive patients. Time to admission decision was increased in the study, a finding which was in line with those published by both Hayden et al. (8) and Permpikul et al. (21). Both studies found that rapid diagnosis and management in the "golden hour", including administering norepinephrine in septic shock patients reduced the duration of shock, pulmonary edema, and new-onset arrhythmia, another field of septic shock which needs further investigation.

Study Limitations

As this study was a quasi-experimental study, some information obtained retrospectively may be missing. As for the post-intervention group, using NEWS as a screening tool screens by the severity of the case; thus, this may not be inclusive of instances where the infection was not initially suspected. In addition, the numbers of patients with sepsis according to the SEPSIS-3 definition were not analyzed in this study as a diagnostic study; nonetheless, the ED uses the SEPSIS-3 definition to guide diagnosis (1). Additionally, if at any time the physician does not suspect sepsis after activation of the protocol, the physician will indicate in the records that sepsis was not suspected and re-designate the case as an infectious or non-infectious case instead.

Conclusion

Using NEWS as a trigger tool to activate the sepsis fast track protocol helps to reduce the door-to-antibiotic time in patients suspected of sepsis in the ED.

Ethics

Ethics Committee Approval: This study was a retrospective and prospective, quasi-experimental study which was approved by the Research Ethics Committee of Faculty of Medicine of Chiang Mai University (no: 377/2018, date: 03.10.2018).

Informed Consent: Written informed consent was obtained from patients who were enrolled on the prospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: P.T., B.W., T.C., T.T., Concept: P.T., B.W., T.C., T.T., Design: P.T., B.W., T.C., T.T., Data Collection or Processing: P.T., B.W., T.C., T.T., Analysis or Interpretation: P.T., B.W., T.C., T.T., Literature Search: P.T., B.W., T.C., T.T., Writing: P.T., B.W., T.C., T.T.

Conflict of Interest: The authors declare they have no competing interest.

Financial Disclosure: Financial Disclosure: This study received Faculty of Medicine Research Fund of Chiang Mai University (grant no. 068-2562).

References

1. Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. Intensive Care Med. 2018;44:925-8.
2. Rhee C, Dantes R, Epstein L, Murphy DJ, Seymour CW, Iwashyna TJ, et al. Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009-2014. JAMA. 2017;318:1241-9.
3. Ministry of Public Health of Thailand. Mortality rate in patients with community-acquired severe sepsis or septic shock [Internet]. Bangkok: Ministry of Public Health of Thailand; 2018 [cited 2019 Oct 1]. Available from: http://healthkpi.moph.go.th/kpi/kpi-list/view/?id=964
4. Hatfield KM, Dantes RB, Baggs J, Sapiano MRP, Fiore AE, Jernigan JA, et al. Assessing Variability in Hospital-Level Mortality Among U.S. Medicare Beneficiaries with Hospitalizations for Severe Sepsis and Septic Shock. Crit Care Med. 2018;46:1753-60.
5. de Groot B, Ansems A, Gerling DH, Rijpsma D, van Amstel P, Linzel D, et al. The association between time to antibiotics and relevant clinical outcomes in emergency department patients with various stages of sepsis: a prospective multi-center study. Crit Care. 2015;19:194.
6. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, et al. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. N Engl J Med. 2017;376:2235-44.
7. Zasowski EJ, Claeys KC, Lagnf AM, Davis SL, Rybak MJ. Time Is of the Essence: The Impact of Delayed Antibiotic Therapy on Patient Outcomes in Hospital-Onset Enterococcal Bloodstream Infections. Clin Infect Dis. 2016;62:1242-50.
8. Hayden GE, Tuuri RE, Scott R, Losek JD, Blackshaw AM, Schoenling AJ, et al. Triage sepsis alert and sepsis protocol lower times to fluids and antibiotics in the ED. Am J Emerg Med. 2016;34:1-9.
9. Amland RC, Sutariya BB. Quick Sequential [Sepsis-Related] Organ Failure Assessment (qSOFA) and St. John Sepsis Surveillance Agent to Detect Patients at Risk of Sepsis: An Observational Cohort Study. Am J Med Qual. 2018;33:50-7.
10. Askim A, Moser F, Gustad LT, Stene H, Gundersen M, Asvold BO, et al. Poor performance of quick-SOFA (qSOFA) score in predicting severe sepsis and mortality – a prospective study of patients admitted with infection to the emergency department. Scand J Trauma Resusc Emerg Med. 2017;25:56.
11. Finkelsztein EJ, Jones DS, Ma KC, Pabon MA, Delgado T, Nakahira K, et al. Comparison of qSOFA and SIRS for predicting adverse outcomes of patients with suspicion of sepsis outside the intensive care unit. Crit Care. 2017;21:73.
12. Goulden R, Hoyle MC, Monis J, Railton D, Riley V, Martin P, et al. qSOFA, SIRS and NEWS for predicting inhospital mortality and ICU admission in emergency admissions treated as sepsis. Emerg Med J. 2018;35:345-9.
13. Smith GB, Prytherch DR, Meredith P, Schmidt PE, Featherstone PI. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. Resuscitation. 2013;84:465-70.
14. Churpek MM, Snyder A, Han X, Sokol S, Pettit N, Howell MD, et al. Quick Sepsis-related Organ Failure Assessment, Systemic Inflammatory Response Syndrome, and Early Warning Scores for Detecting Clinical Deterioration in Infected Patients outside the Intensive Care Unit. Am J Respir Crit Care Med. 2017;195:906-11.
15. Rosner B. Fundamentals of Biostatistics, 8th ed. Boston, MA: Cengage Learning; 2016. http://galaxy.ustc.edu.cn:30803/zhangwen/Biostatistics/Fundamentals+of+Biostatistics+8th+edition.pdf
16. Usman OA, Usman AA, Ward MA. Comparison of SIRS, qSOFA, and NEWS for the early identification of sepsis in the Emergency Department. Am J Emerg Med. 2019;37:1490-7.
17. Thodphetch M, Chenthanakij B, Wittayachamnankul B, Tangsuwanaruk T. Comparison of modified Systemic Inflammatory Response Syndrome (mSIRS), quick Sequential Organ Failure Assessment (qSOFA), modified National Early Warning Score (mNEWS) and modified Search Out Severity (mSOS) score for Predicting in-hospital Mortality among Patients with Suspected Infection Presenting to the Emergency Department. Thai J Emerg Med. 2019;1:120-1.
18. Robert Boter N, Modol Deltell JM, Casas Garcia I, Rocamora Blanch G, Llados Beltran G, Carreres Molas A. Activation of a code sepsis in the emergency department is associated with a decrease in mortality. Med Clin (Barc). 2019;152:255-60.
19. Ferreras Amez JM, Arribas Entrala B, Sarrat Torres MA, Garcia Noain A, Caudevilla Martinez A, Colas Oros C, et al. Before-after study of the effect of implementing a sepsis code for emergency departments in the community of Aragon. Emergencias. 2017;29:154-60.
20. Bruce HR, Maiden J, Fedullo PF, Kim SC. Impact of nurse-initiated ED sepsis protocol on compliance with sepsis bundles, time to initial antibiotic administration, and in-hospital mortality. J Emerg Nurs. 2015;41:130-7.
21. Permpikul C, Tongyoo S, Viarasilpa T, Trainarongsakul T, Chakorn T, Udompanturak S. Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER). A Randomized Trial. Am J Respir Crit Care Med. 2019;199:1097-105.

EURASIAN JOURNAL OF EMERGENCY MEDICINE
DOI: 10.4274/eajem.galenos.2020.51423
Original Article
Eurasian J Emerg Med. 2020;19(3): 149-53

Evaluation of the Impact of a 2-Day Point-of-care Ultrasonography Course on the Theoretical Knowledge and Practical Skills of Physicians

Arif Karagöz

İzmir Çiğli Training and Research Hospital, Clinic of Emergency Medicine, İzmir, Turkey

Abstract

Aim: This study aimed to evaluate the impact of Turkey's first European accredited 2-day point-of-care ultrasonography (POCUS) course on the theoretical knowledge and practical skills of physicians.

Materials and Methods: Forty physicians and five lecturers attended the course. All the lectures were arranged as per the POCUS Curriculum Guidelines given by the International Federation of Emergency Medicine. At the beginning and the end of the course, a theoretical exam was conducted with the same set of questions. Practical skills were evaluated at the hands-on training stations using checklists. Pre-test and post-test results were statistically compared.

Results: All the attendants of the course were included in the study. The numbers of the correct pre-test and post-test answers were 1.23±0.89 and 1.95±0.64 for abdominal aorta ultrasound (USG), 3.23±1.27 and 5.08±1.07 for cardiac USG, 0.95±0.68 and 1.78±0.42 for USG physics, 3.03±1.42 and 4.48±1.11 for expanded-focussed assessment with sonography in trauma, 1.75±0.74 and 2.35±0.62 for hepatobiliary USG, 1.4±0.71 and 1.85±0.36 for inferior vena cava USG, 1.18±0.55 and 1.48±0.51 for renal USG and 1.88±1.04 and 2.7±0.82 for lung USG, respectively. All the differences were statistically significant.

Conclusion: The study shows that our 2-day basic course has effectively conveyed the fundamental POCUS knowledge and skills.

Keywords: Point-of-care testing, ultrasonography, medical education

Introduction

Point-of-care ultrasonography (POCUS) is a rapidly growing area in medicine and used in nearly all kinds of medical practise, especially in primary care, emergency medicine and critical care departments (1). The most widely used POCUS applications are focused assessment with sonography in trauma (FAST) and expanded-FAST (E-FAST), bedside cardiac ultrasound (USG), aorta and vena cava inferior USG, bedside lung USG, renal USG and bedside hepatobiliary USG. The American College of Emergency Physicians (ACEP) has categorised POCUS into five functional clinical categories: resuscitative, diagnostic, symptom or sign-based, procedure guidance, therapeutic and monitoring (1). Different POCUS applications can be used solely or in a combined manner at the bedside for answering single or multiple queries about the patient's clinical status.

Although it is internationally acknowledged that POCUS is one of the essential skills for clinicians working in all fields of medicine and especially in emergency departments, there is no standardised method of POCUS education for resident physicians or medical students (2-6). The first curriculum study regarding USG training in emergency medicine was conducted by Mateer et al. (7) in 1994. In Turkey, there are efforts to standardise POCUS education, which is provided by senior clinicians in the field and by physician associations.

The Emergency Medicine Physicians Association of Turkey is one of the leading associations in Turkish Medicine and tries to spread

Corresponding Author: Arif Karagöz, MD, İzmir Çiğli Training and Research Hospital, Clinic of Emergency Medicine, İzmir, Turkey
E-mail: dr.akaragoz@hotmail.com ORCID ID: orcid.org/0000-0002-4568-1247

Received: 26.11.2019
Accepted: 11.06.2020

Cite this article as: Karagöz A. Evaluation of the Impact of a 2-Day Point-of-care Ultrasonography Course on the Theoretical Knowledge and Practical Skills of Physicians. Eurasian J Emerg Med. 2020;19(3):149-53

the POCUS skills among emergency physicians by its branch of the bedside USG education program "SonoSchool". Since its foundation in 2016, Sonoschool has been organising POCUS courses both inside and outside of Turkey. The first basic POCUS course that was internationally accredited by the European Accreditation Council for Continuing Medical Education (EACCME) in Turkey was organised by SonoSchool in Istanbul in December 2018.

In this study, we evaluated the impacts of this accredited 2-day course on the theoretical knowledge and practical skills of physicians.

Materials and Methods

This was a prospective observational study examining the effect of a 2-day basic POCUS course. In total, 40 physicians attended the course, of which 20 were EPs, 15 were anaesthesiologists working in intensive care units, two were paediatric EPs, two were general practitioners and one was a paediatrician. Thirty-six attendants were from Turkey, two were from Jordan, one was from Greece and one was from the United Kingdom. There were five lecturers, all of which were EPs who were experienced in POCUS and had previously taught it. Two of the lecturers were from Turkey, two were from Egypt and one was from India. Two EPs were placed to monitor the course and to make all arrangements during the course, allowing the lectures to focus on the course and the hands-on trainings. The lectures included diagnostic POCUS applications; any POCUS applications for procedural guidance were not included since this was a basic course. The topics of the theoretical lectures and the targets of the hands-on stations were arranged in the guidance of the International Federation of Emergency Medicine (IFEM) POCUS Curriculum Guidelines (2). The topics were as follows: USG physics, E-FAST, cardiac axes, limited bedside echocardiography, abdominal aorta USG, vena cava inferior USG, bedside renal USG, bedside hepatobiliary USG and lung USG (Table 1). There were four theoretical lectures and two hands-on training parts on the first day and four theoretical lectures, two hands-on training parts and one interactive session on the second day (Table 1). Pre-testing was performed at the start of the course, and a post-test was done at the end of the course with the same questions. The test contained 25 questions regarding the course topics; all questions covered the course material. Nineteen questions covered only one topic of the course, and six questions combined the knowledge about two topics of the course. Four stations were arranged for the hands-on training parts, with each station containing one healthy volunteer and a USG device equipped with three probes: curved array, phased array and linear probes. Attendants were divided into four groups, and the groups changed the stations for each hands-on training. Each attendant had a checklist to be completed at the hands-on training station and to be signed by the lecturer. After one of the lecturers had provided some information and practised the USG application, all attendants practised the application on the volunteer and completed all skills on the checklist. This ensured that each attendant gained the targeted skills in the hands-on trainings. At the end of the course, a post-test was performed with the same questions as in the pre-test. After the post-test, attendants were asked to fill a feedback form to evaluate the lecturers for both the theoretical lectures, the hands-on training and the overall course format, using a four-score evaluation form: 1=poor, 2=average, 3=good and 4=excellent.

Statistical Analysis

After the course, pre-test and post-test answers were statistically compared to evaluate the theoretical knowledge of the physicians. The Wilcoxon signed rank test was used to compare the results. Each correct answer was ranked as 2.5 points and each incorrect answer as 0 points for both tests. The results

Table 1. The course program

	Hours	Topic
First day	08.30-09.00	Introduction and pre-test
	09.00-09.40	Ultrasound physics
	09.40-09.50	*Coffee break*
	09.50-10.30	E-FAST
	10.30-12.00	Hands-on training
	12.00-13.00	*Lunch*
	13.00-13.40	Cardiac axes
	13.40-13.50	*Coffee break*
	13.50-14.30	Bedside cardiac ultrasound
	14.30-16.00	Hands-on training
Second day	08.30-09.00	Abdominal aorta and vena cava inferior ultrasound
	09.00-09.40	Lung ultrasound
	09.40-09.50	*Coffee break*
	09.50-10.30	Renal ultrasound
	10.30-12.00	Hands-on training
	12.00-13.00	*Lunch*
	13.00-13.40	Hepatobiliary ultrasound
	13.40-13.50	*Coffee break*
	13.50-14.30	Interactive session
	14.30-16.00	Hands-on training
	16.00-16.30	Post-test
	16.30-17.00	Feedback forms

E-FAST: Expanded focused assessment with sonography in trauma

were compared both as gained points and percentage of correct results; statistical significance was set at $p<0.05$. The feedback forms were evaluated, and the mean values of the points obtained from the forms were calculated for each lecturer. This study protocol has been approved by local ethics committee (2018-186).

Results

All of the 40 physicians who attended the course were included in the study. The numbers of the correct answers for the pre-test and the post-test were as follows: 1.23±0.89 and 1.95±0.64 for abdominal aorta USG, 3.23±1.27 and 5.08±1.07 for cardiac USG, 0.95±0.68 and 1.78±0.42 for USG physics, 3.03±1.42 and 4.48±1.11 for EFAST, 1.75±0.74 and 2.35±0.62 for hepatobiliary USG, 1.40±0.71 and 1.85±0.36 for vena cava inferior USG, 1.18±0.55 and 1.48±0.51 for renal USG and 1.88±1.04 and 2.70±0.82 for lung USG, respectively (Table 2). All differences were statistically significant. The percentages of correct answers for the pre-test and the post-test were as follows: 40.83±29.72% and 65.01±21.30% for abdominal aorta USG, 40.31±15.88% and 63.44±13.39% for cardiac USG, 47.50±33.87% and 88.75±21.15% for USG physics, 43.22±20.31% and 63.90±15.84% for E-FAST, 70.00±35.45% and 92.50±18.08% for hepatobiliary USG, 58.75±27.47% and 73.75±25.29% for renal USG and 46.88±26.06% and 67.50±20.57% for lung USG, respectively (Table 2 and Figure 1). The mean test results were 45.40±11.73% for the pre-test and 68.90±8.23% for the post-test (Table 2). All differences were statistically significant.

All attendants completed the checklists for the hands-on training and therefore gained the ability to perform USG scanning on a healthy subject. However, unfortunately, we have no information about their scanning abilities on real patients and in real clinical cases.

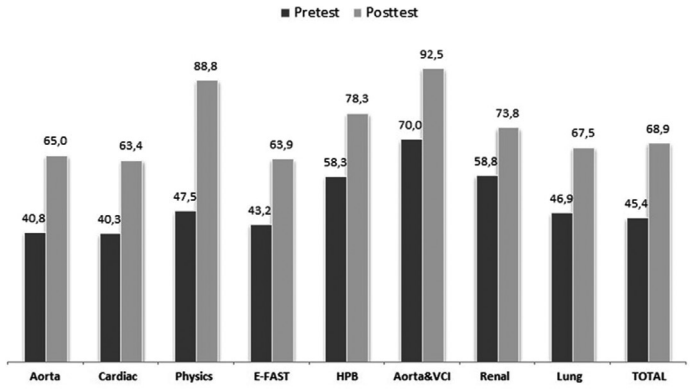

Figure 1. Graphic of the correct answers by percentages for pre-test and post-test

E-FAST: Expanded focused assessment with sonography in trauma, HPB: Hepatobiliary, VCI: Vena cava inferior

Table 3. Mean scores for the instructors obtained from feedback forms (0: worst, 4: best)

Mean points		
Instructor	**Theoretical lessons**	**Hands-on training**
Instructor-1	4.00	4.00
Instructor-2	4.00	4.00
Instructor-3	4.00	4.00
Instructor-4	4.00	3.75
Instructor-5	3.90	4.00

Table 4. Mean scores for the overall course format obtained from feedback forms (0: worst, 4: best)

Category	Mean score (0 to 4 points)
Quality of the event	3.95
Relevance of the event	4.00
Suitability of formats used during the event	3.82
Ways the event affected the participants´ practice	3.95
Commercial bias	4.00

Table 2. Correct answers by numbers and percentages for pre-test and post-test

	Correct answers by number			Correct answers by percentage		
Topic	**Pre-test (Avg ± SD)**	**Post-test (Avg ± SD)**	**p**	**Pre-test (Avg ± SD)**	**Post-test (Avg ± SD)**	**p**
Aorta	1.23±0.89	1.95±0.64	0.000	40.83±29.72	65.01±21.30	0.000
Cardiac	3.23±1.27	5.08±1.07	0.000	40.31±15.88	63.44±13.39	0.000
Physics	0.95±0.68	1.78±0.42	0.000	47.50±33.87	88.75±21.15	0.000
E-FAST	3.03±1.42	4.48±1.11	0.000	43.22±20.31	63.90±15.84	0.000
HPB USG	1.75±0.74	2.35±0.62	0.000	58.33±24.75	78.33±20.74	0.000
Aorta & VCI USG	1.40±0.71	1.85±0.36	0.000	70.00±35.45	92.50±18.08	0.000
Renal	1.18±0.55	1.48±0.51	0.005	58.75±27.47	73.75±25.29	0.005
Lung	1.88±1.04	2.70±0.82	0.000	46.88±26.06	67.50±20.57	0.000
Total	-	-	-	45.40±11.73	68.90±8.23	0.000

E-FAST: Expanded focused assessment with sonography in trauma, HPB: Hepatobiliary, USG: Ultrasonography, VCI: Vena cava inferior, Avg: Average, SD: Standard deviaton,

The feedback forms were also evaluated, and the mean points for the lecturers and for the overall course format were calculated. Three of the lecturers achieved a score of 4.00 for both theoretical lectures and hands-on training. One lecturer achieved a score of 4.00 for theoretical lectures and a score of 3.75 for hands-on training, while one lecturer obtained 3.90 for theoretical lectures and 4.00 for hands-on training (Table 3). The mean points of the overall course ratings were as follows: 3.95 for the quality of the event, 4.00 for the relevance of the event, 3.82 for the suitability of formats used during the event, 3.95 for the ways the event affected the participant's practice and 4.00 for commercial bias (Table 4). These results show that the attendants were pleased both by the lecturers and the overall course format.

Discussion

Our study consisted of the evaluation of a basic POCUS course given by five expert instructors. We implemented a formal 2-day POCUS course for physicians practising in different areas. Our course format was approved and accredited by EACCME. This accreditation improves our course program's validity for different areas of medicine. Different clinical scenarios require different types of knowledge about POCUS, and we tried to include the complete spectrum of basic POCUS knowledge that can be required at the patient's bedside. We arranged our course topics upon the IFEM POCUS Curriculum Guidelines (2).

The necessity for POCUS instruction is clear, but the best methods of attaining these skills remain poorly defined (8,9). We tried to combine the theoretical lessons with PowerPoint presentations, hands-on training, interactive sessions and pre- and post-tests. Our results showed that such a course could improve skills in USG knowledge, normal image acquisition on healthy volunteers, image interpretation and comfort with USG technique. These improvements were apparent immediately after the course by the difference between pre-test and post-test and hands-on training checklists. There was a statistically significant difference between pre-test and post-test results, suggesting that our approach was highly efficient.

The hands-on training sessions were also effective because all attendants completed a checklist at the hands-on stations and practised each POCUS application on the checklist. The checklists included all of the required basic POCUS practical abilities of the related topics.

The rapidly expanding POCUS literature supports a multisystem approach for the evaluation of the patients, especially critically ill ones (10-12). We organised our course program to meet this need and included major organ systems such as lung USG, bedside cardiac USG, abdominal USG, hepatobiliary USG and aorta and vena cava inferior USG. Established protocols require integrated knowledge about all of these organ systems, and we integrated this knowledge with both interactive sessions and some questions in our pre- and post-tests. In our interactive sessions, we used a web-based simulation program. A case-scenario was introduced to a group of three attendants who then decided to use one of the basic POCUS applications and applied it to a healthy volunteer; the pathologic image based on the scenario was shown to the class. Subsequently, the attendants made a diagnosis or used another POCUS application until they reached a diagnosis. This way, the integration of the acquired knowledge could be improved.

Based on a previous study, students feel that hands-on practise is the best way to learn technical POCUS skills (8). We performed hands-on training sessions for every topic included in our course and asked the attendants to practise every POCUS skill by him- or herself on healthy volunteers. We also used active-learning methods in our interactive sessions.

We asked the students to answer a feedback form about our course structure and about our instructors. Based on the results, the students found our course structure effective and our instructors sufficient. This point is very important because both aspects play a crucial role in the students' interest in the lessons and in their willingness to gain new skills. Unsatisfaction in this regard results in a lower interest and has a negative impact on learning.

Study Limitations

One limitation of our study is that practical hands-on training was performed on healthy subjects. All attendants completed the checklists for the hands-on training sessions and therefore gained the ability to perform USG scanning on a healthy subject. However, unfortunately, we have no information about their scanning abilities on real patients and in clinical settings.

Conclusion

Our study shows that our 2-day basic POCUS course integrating theoretical lessons, hands-on training on healthy volunteers, interactive sessions, pre- and post-tests and feedback forms is effective to provide basic POCUS knowledge to a range of multidisciplinary physicians.

Ethics

Ethics Committee Approval: The study protocol has been approved by local ethics committee (approval number: 2018-186).

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

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

References

1. Policy Statement. Ultrasound Guidelines: Emergency, Point-of-care, and Clinical Ultrasound Guidelines in Medicine. Ann Emerg Med. 2017;69:e27-54.
2. International Federation for Emergency Medicine, Emergency Ultrasound Special Interest Group. Point-of-Care Ultrasound Curriculum Guidelines. International Federation for Emergency Medicine, 2014. ISBN: 978-0-9873901-2-7.
3. Lee JB, Tse C, Keown T, Louthan M, Gabriel C, Anshus A, et al. Evaluation of a point of care ultrasound curriculum for Indonesian physicians taught by first-year medical students. World J Emerg Med. 2017;8:281-6.
4. Ma IWY, Arishenkoff S, Wiseman J, Desy J, Ailon J, Martin L, et al. Internal Medicine Point-of-Care Ultrasound Curriculum: Consensus Recommendations from the Canadian Internal Medicine Ultrasound (CIMUS) Group. J Gen Intern Med. 2017;32:1052-7.
5. Bornemann P. Assessment of a Novel Point-of-Care Ultrasound Curriculum's Effect on Competency Measures in Family Medicine Graduate Medical Education. J Ultrasound Med. 2017;36:1205-11.
6. Wilson SP, Mefford JM, Lahham S, Lotfipour S, Subeh M, Maldonado G, et al. Implementation of a 4-Year Point-of-Care Ultrasound Curriculum in a Liaison Committee on Medical Education-Accredited US Medical School. J Ultrasound Med. 2017;36:321-5.
7. Mateer J, Plummer D, Heller M, Olson D, Jehle D, Overton D, et al. Model curriculum for physician training in emergency ultrasonography. Ann Emerg Med. 1994;23:95-102.
8. Cartier RA 3rd, Skinner C, Laselle B. Perceived effectiveness of teaching methods for point of care ultrasound. J Emerg Med. 2014;47:86-91.
9. American College of Emergency Physicians. Emergency Ultrasound Guidelines. Ann Emerg Med. 2009;53:550-70.
10. Abbasi S, Farsi D, Hafezimoghadam P, Fathi M, Zare MA. Accuracy of emergency physician-performed ultrasound in detecting traumatic pneumothorax after a 2-h training course. Eur J Emerg Med. 2013;20:173-7.
11. Gracias V, Frankel HL, Gupta R, Malcynski J, Gandhi R, Collazzo L, et al. Defining the learning curve for the focused abdominal sonogram for trauma (FAST) examination: implications for credentialing. Am Surg. 2001;67:364-8.
12. Elmer J, Noble VE. An Evidence-Based Approach for Integrating Bedside Ultrasound into Routine Practice in the Assessment of Undifferentiated Shock. ICU Director. 2010;1:163-74.

EURASIAN JOURNAL OF EMERGENCY MEDICINE
Original Article
DOI: 10.4274/eajem.galenos.2020.26817
Eurasian J Emerg Med. 2020;19(3): 154-8

Retrospective Analysis of the Treatment of Patients with Acute Stroke in a Training and Research Hospital

Cemile Haki

Bursa Yüksek İhtisas Training and Research Hospital, Department of Neurology, Bursa, Turkey

Abstract

Aim: This study aimed to evaluate the indications for intravenous recombinant tissue plasminogen activator (IV r-tPA) and/or mechanical thrombectomy in patients with acute stroke and the research intended to determine why these treatments were not applied in some cases.

Materials and Methods: This study included 300 stroke patients treated between January 2018 and June 2019 for whom the data were accessible. The patients with acute stroke were retrospectively examined with regards to demographic and clinical information.

Results: Of the 300 patients, 142 (47%) were females and 158 (52%) were males and 214 patients (71%) were admitted to the hospital within the first 4.5 hours. The mean age of the patients was 68.11±13.15 years (34-94 years). Moreover, 58 (19%) patients did not receive IV r-tPA and/or undergo mechanical thrombectomy owing to contraindications.

Conclusion: In this study, we determined that the most common reason for not applying IV r-tPA and/or mechanical thrombectomy was the inability of some patients to reach the hospital within the treatment window. Multi-centre studies are needed to investigate the various factors contributing to the delay in accessing treatment for patients with acute ischaemic stroke. Addressing these issues may increase the proportion of patients receiving thrombolytic therapy and/or undergoing mechanical thrombectomy.

Keywords: Acute stroke, thrombolytic therapy, mechanical thrombectomy

Introduction

Acute ischemic stroke is the third most common cause of mortality after coronary artery diseases and cancer (1). It is a severe neurological problem that ranks first worldwide in terms of morbidity. Approximately 6 million people die due to a stroke and 17 million people have a stroke each year (2,3). Ischemic strokes constitute more than 85% of all strokes (4). In our country, this rate was reported to be 71% (5).

In the treatment of acute ischemic stroke, intravenous recombinant tissue plasminogen activator (iv r-tPA) is the only approved medical treatment option for patients admitted in the treatment window (6,7). Endovascular treatment is recommended in patients with major vascular occlusion (8). Unfortunately, the most important obstacle to these treatments is the limited duration. 1.9 million neurons are lost in every minute of the brain until reperfusion is achieved (9).

However, despite the efficacy of iv r-tPA in acute ischemic stroke patients iv r-tPA, due to numerous limiting factors, it has been reported that only 3.0-8.5% of patients with ischemic stroke were applied iv r-tPA (10-12). The aim of this study was to evaluate the iv r-tPA and/or mechanical thrombectomy indications in the patients with acute stroke admitted to our emergency department and/or hospitalized at the neurology department and in case these treatments were not applied, to determine reasons why these treatments were not applied in our patients and to correct these issues.

Materials and Methods

Bursa Yüksek İhtisas Training and Research Hospital is a tertiary care hospital. In our hospital, periodic training on stroke is being provided to healthcare personnel since 4 years. A number of awareness programs have been organized to increase public awareness about stroke.

This study was presented as an oral presentation at the 15th International Emergency Medicine Congress (April 25-28, 2019).
Corresponding Author: Cemile Haki, Bursa Yüksek İhtisas Training and Research Hospital, Department of Neurology, Bursa, Turkey
Phone: +90 224 294 40 00 **E-mail:** cemilehaki@gmail.com **ORCID:** orcid.org/0000-0002-9679-8007
Cite this article as: Haki C. Retrospective Analysis of the Treatment of Patients with Acute Stroke in a Training and Research Hospital. Eurasian J Emerg Med. 2020;19(3):154-8
Received: 06.12.2019
Accepted: 15.06.2020

In our stroke centre, iv r-tPA was first administered to patients with acute ischemic stroke in 2016. Since 2017, mechanical thrombectomy is being performed in our hospital.

The study included 300 patients with accessible data who had been admitted to the emergency department of our hospital for the diagnosis of stroke and/or hospitalized in the neurology department due to stroke between January 2018 and June 2019. The study was approved by the ethics committee of Bursa Yüksek İhtisas Training and Research Hospital, decision numbered and dated: 2011-KAEK-25, 2019/06-28, and the requirement of informed consent was waived off because of the retrospective nature of the study. The patients with acute stroke were retrospectively examined with regards to demographic (age, sex) and clinical information (the time of stroke, admission time, risk factors for stroke, neurological examination findings, stroke severity, and radiological findings), whether iv r-tPA and/or mechanical thrombectomy treatment was applied, and the reasons why these treatments were not applied. Stroke severity at admission was determined using the National Institutes of Health Stroke Scale (NIHSS). In the case of wake-up strokes, the onset of the symptom was accepted as the last point in time when the patient appeared normal.

Statistical Analysis

The consistency of continuous variables to normal distribution was examined with the Kolmogorov-Smirnov test. According to the normality test result, continuous variables are expressed with mean, standard deviation, minimum and maximum values. Categorical variables were given as n (%) values as indicative statistics. SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) program was used for statistical analysis.

Results

Of the 300 patients, 142 (47%) were females and 158 (52%) were males; all the patients had been admitted between January 2018 and June 2019 to the emergency department of our hospital with the diagnosis of stroke and/or hospitalized in the neurology department due to stroke.

The mean age of the patients was 68.11±13.15 years (34-94 years). The time between the onset of stroke symptoms and admission to the emergency department varied from 15 minutes to 10 days, and the mean time was 5 (0.42:420) hours. NIHSS scores ranged between 0 and 32. Of the 259 (86%) patients diagnosed with ischemic stroke, 11 (3.6%) and 30 (10%) were diagnosed with intracerebral haemorrhage and transient cerebral ischemic attack, respectively.

Total 137 (45%) patients had been admitted to the hospital in the first 1.5 hours; 53 (17%), between 1.5 and 3 hours; 24 (8%), between 3 and 4.5 hours; 54 (18%), between 4.5 and 24 hours; and 32 (10.6%), after 24 hours. A total of 214 (71%) patients had been admitted to the hospital within the first 4.5 hours; 58 (19%) of the patients admitted to the hospital during the window period had contraindications for iv r-tPA.

When the patients were evaluated in terms of risk factors of stroke, it was found that 191 (63%), 64 (21%), 86 (28%), 104 (34%), 78 (26%), 86 (28%), and 57 (19%) of the patients had hypertension, hyperlipidemia, coronary artery disease, Diabetes mellitus, were smokers, history of stroke, and history of atrial fibrillation, respectively.

There were 64 (21%) patients with NIHSS of ≥6 who could not reach the hospital within the treatment window.

Ninety-seven (32%) patients with NIHSS of ≥6 who had been admitted to the hospital in the first 4.5 hours (treatment window) were examined, and it was found that 27 of these patients underwent iv r-tPA, three underwent iv r-tPA and mechanical thrombectomy, and nine underwent only mechanical thrombectomy. Fifty-eight (19%) of the patients did not undergo iv r-tPA and/or mechanical thrombectomy due to contraindications (Table 1).

Table 1. Reasons for non-treatment in patients with NIHSS of ≥6 who had been admitted to the hospital within the first 4.5 hours

Reason	Number	Percentage
Blood pressure could not be lowered	5	8.6%
Hypodensity >1/3 of the cerebral hemisphere	4	6.8%
Wake-up stroke	6	10.3%
Due to advanced age and other concomitant diseases	9	15.5%
Use of NOAC in the last 48 hours	1	1.7%
Thrombocytopenia	1	1.7%
Previous stroke in last 3 months	1	1.7%
Disability that prevents mobility	4	6.8%
Lack of consent	2	3.4%
Intracerebral giant aneurysm	1	1.7%
Major surgery performed within the previous 14 days	1	1.7%
Rapid recovering stroke	6	10.3%
Oral anticoagulant use and INR >1.7	2	3.4%
Suitable time window had passed before the examinations were completed	6	10.3%
Intracerebral haemorrhage	9	15.5%
Total	58	100%

NIHSS: National Institutes of Health Stroke Scale, NOAC: Non-vitamin K antagonist oral anticoagulant, INR: International normalized ratio

Of the 27 patients over the age of 80 years who had been admitted within the first 4.5 hours, eight underwent iv r-tPA, one underwent iv r-tPA and mechanical thrombectomy, and one underwent only mechanical thrombectomy.

Discussion

The license for the use of iv r-tPA in acute ischemic stroke was obtained in Turkey in 2006. Although the application of iv r-tPA in Turkey is not yet at the desired level, its use is gradually increasing (13). It has been shown that in the case of acute ischemic stroke, 15-minute decrease in the door-to-needle time leads to 5% decrease in mortality in iv r-tPA application (14).

It has been determined that the annual rate of stroke-related deaths has decreased by 34% in the 10-year period between 1997 and 2007 owing to the efforts conducted to combat stroke and the fact that treatments applied in the acute period are becoming increasingly common (15).

Unfortunately, previous studies have found the rates of patients treated with iv r-tPA to be far below the desired level owing to many factors (10-12), this is caused by different reasons in different countries (11,16).

Many patients are unable to reach the hospital within the treatment window. One of the most important reasons for the inability of patients to reach the hospital within the treatment window may be society's low level of knowledge on this subject (17).

In terms of treatment window, in this study, 63% and 71% of the patients were admitted to the hospital within the first 3 hours and 4.5 hours, respectively. This ratio was found to be higher compared with that in previous studies (18-23). This may be the result of the training and awareness-raising efforts regarding acute stroke that have been conducted over the past 3 years for healthcare professionals and the public.

In our study, there were 64 (21%) patients with NIHSS of ≥6 who could not reach the hospital within the treatment window, missing the opportunity for acute stroke treatment. In other words, had these patients arrived within the appropriate timeframe, these treatments could have been applied. A significant portion of these delays was due to the prolonged examination times within the hospital. There were six (2%) patients who reached the hospital within the treatment window, but they could not receive treatment as the treatment period was exceeded by the time their tests were completed.

There were 97 (32%) patients with NIHSS of ≥6 who admitted to our hospital within the treatment window. Of these patients, 27 received iv r-tPA, three received iv r-tPA and mechanical thrombectomy, and nine received mechanical thrombectomy. Fifty-eight (19%) of the patients could not be treated due to contraindications.

iv r-tPA and/or mechanical thrombectomy were not considered for six of the patients who arrived at the appropriate time, because these patients had rapid recovery and no significant deficits remained. The administration of iv r-tPA is recommended for patients who improve noticeably but continue to have significant deficits (24,25).

It has been reported that iv r-tPA can be administered in aneurysms with a diameter of <10 mm (26). Thrombolytic therapy was not performed in one of our patients due to a giant aneurysm with a diameter of >10 mm in the intracerebral artery.

Although the risk of intracerebral haemorrhage is higher in elderly patients, the use of iv r-tPA is recommended in patients over 80 years old unless there are other exclusion criteria (27,28). In nine patients, iv r-tPA was not administered due to the increased risk of intracerebral haemorrhage associated with advanced age and other accompanying risk factors. Of the 27 patients who were ≥80 years old and arrived at the hospital in the first 4.5 hours, eight received iv r-tPA, one received iv r-tPA + mechanical thrombectomy, and one received only mechanical thrombectomy.

Patients do not benefit adequately from iv r-tPA when they have a mobility-preventing disability that develops before the stroke. However, iv r-tPA is still recommended moderate disability or in patients who can remain standing with assistance (27-30). In our study, four bed-ridden patients were not treated due to their mobility-preventing disability.

Before initiating iv r-tPA treatment, blood pressure must be below 185/110 mmHg to reduce the risk of intracerebral haemorrhage (27,31). In five of our patients, iv rt-PA was not administered due to blood pressure that could not be reduced below 185/110 mmHg despite antihypertensive treatment.

Two patients did not receive iv r-tPA treatment due to warfarin use and an international normalized ratio (INR) value of >1.7. IV r-tPA is administered in patients using oral anticoagulants if their INR is <1.7 (31).

Study Limitations

The limitations of the present study include the limited number of patients, the inclusion of a single centre, and the lack of access to certain data owing to the retrospective nature of the study. This study investigated and presented the reasons why current treatment modalities for acute stroke treatment, such

as thrombolytic treatment and mechanical thrombectomy, were not applied in some of our patients.

Conclusion

In our study, we determined that the most common reason for not applying iv r-tPA and mechanical thrombectomy treatments out of contraindications to patients was the fact that these patients could not reach the hospital within the treatment window and loss of time that occurred during the examinations and tests performed in the hospital.

To ensure the application of treatments, such as r-tPA and mechanical thrombectomy, which are life-saving and prevent disabilities, it is necessary to prepare algorithms in the hospital so that the processes after a patient is admitted to the emergency department can be managed rapidly. Addressing these factors may increase the ratio of patients who can receive thrombolytic therapy or undergo mechanical thrombectomy.

Ethics

Ethics Committee Approval: The study was approved by the ethics committee of Bursa Yüksek İhtisas Training and Research Hospital, decision numbered and dated: 2011-KAEK-25, 2019/06-28.

Informed Consent: The requirement of informed consent was waived off because of the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42:517-84.
2. Blackham KA, Meyers PM, Abruzzo TA, Albuquerque FC, Fiorella D, Fraser J, et al. Society for NeuroInterventional Surgery. Endovascular therapy of acute ischemic stroke: report of the standards of practice committee of the society of neurointerventional surgey. J Neurointerv Surg. 2012;4:87-93.
3. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet. 2014;383:245-54.
4. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee Heart disease and stroke statistics—2008 update: a report from the American Heart Associations Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2008;117:e25-146.
5. Özdemir G, Özkan S, Uzuner N, Özdemir Ö, Gücüyener D. Türkiye'de beyin damar hastalıkları için major risk faktörleri. Türk çok merkezli stroke çalışması. TBDHD. 2000;6:31-5.
6. NINDS rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N. Engl J Med. 1995;333:1581-7.
7. Hache W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. ECASS investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317-29.
8. Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, et al. American Heart Association Stroke Council. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guidelinefor Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2015;46:3020-35.
9. Saver JL. Time is brain–quantified. Stroke. 2006;37:263-6.
10. Reeves MJ, Arora S, Broderick JP, Frankel M, Heinrich JP, Hickenbottom S, et al. Coverdell Prototype Registries Writing Group. Acute stroke care in the US: results from 4 pilot prototypes of the Paul Coverdell National Acute Stroke Registry. Stroke. 2005;36:1232-40. [Epub 2005 May 12].
11. Eissa A, Krass I, Bajorek BV. Barriers to the utilization of thrombolysis for acute ischaemic stroke. Journal of Clinical Pharmacy and Therapeutics. 2012;37:399-409.
12. Hills NK, Johnston SC. Why are eligible thrombolysis candidates left untreated? Am J Prev Med. 2006;31:S210-6.
13. Kutluk K, Kaya D, Afsar N, Arsava EM, Ozturk V, Uzuner N, et al. Turkish Thrombolysis Study Group. Analyses of the Turkish National Intravenous Thromboliysis Registry. J Stroke Cerebrovasc Dis. 2016;25:1041-7.
14. Fonarow GC, Smith EE, Saver JL, Reeves MJ, Bhatt DL, Grau-Sepulveda MV, et al. Timeliness of tissue-type plasminogen activator therapy in acute ischemic stroke: Patient characteristics, hospital factors, and outcomes associated with door-to-needle times within 60 minutes: Circulation. 2011;123:750-8.
15. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. Circulation. 2011;123:e18-e209.
16. Baatiema L, Otim ME, Mnatzaganian G, de-Graft Aikins A, Coombes J, Somerset S. Health professionals' views on the barriers and enablers to evidence-based practice for acute stroke care: a systematic review. Implement Sci. 2017;12:74.
17. Kim YS, Park SS, Bae HJ, Heo JH, Kwon SU, Lee BC, et al. Public awareness of stroke in Korea: a population-based national survey. Stroke. 2012;43:1146-9.
18. Williams LS, Bruno A, Rouch D, Marriott DJ. Stroke patients' knowledge of stroke: influence on time to presentation. Stroke.1997;28:912-5.
19. Lacy CR, Suh DC, Bueno M, Kostis JB. Delay in presentation and evaluation for acute stroke: stroke time registry for outcomes knowledge and epidemiology (S.T.R.O.K.E.). Stroke. 2001;32:63-9.
20. Azzimondi G, Bassein L, Fiorani L, Nonino F, Montaguti U, Celin D, et al. Variables associated with hospital arrival time after stroke: effect of delay on the clinical efficiency of early treatment. Stroke. 1997;28:537-42.
21. Chen CH, Tang SC, Tsai LK, Hsieh MJ, Yeh SJ, Huang KY, et al. Stroke code improves intravenous thrombolysis administration in acute ischemic stroke. PLoSOne. 2014;9:e104862.
22. Tekin B, Yatmazoğlu M, Acar E, Senadim S, Çoban E, Dayan C, et al. Pre-hospital Obstacles in Thrombolytic Therapy and Suggested Solutions. Turk J Cerebrovasc Dis. 2015;21:194-7.
23. Ashraf VV, Maneesh M, Praveenkumar R, Saifudheen K, Girija AS. Factors delaying hospital arrival of patients with acute stroke. Ann Indian Acad Neurol. 2015;18:162-6.
24. Re-examining Acute Eligibility for Thrombolysis Task Force; Levine SR, Khatri P, Broderick JP, Grotta JC, Kasner SE, Kim D, et al. NINDS rt-PA Stroke Trial Investigators. Review, historical context, and clarifications of the NINDS rt-PA stroke trials exclusion criteria: Part 1: rapidly improving stroke symptoms. Stroke. 2013;44:2500-5.
25. Topçuoğlu MA, Arsava EM, Özdemir AÖ, Gürkaş E, Necioğlu Örken D, Öztürk Ş. Intravenous thrombolytic therapy in acute stroke: Problems and solutions. Turk J Neurol. 2017;23:162-75.

26. Kim JT, Park MS, Yoon W, Cho KH. Detection and significance of incidental unruptured cerebral aneurysms in patients undergoing intravenous thrombolysis for acute ischemic stroke. J Neuroimaging. 2012;22:197-200.

27. Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC, et al. Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2016;47:581-641.

28. Topçuoğlu MA, Arsava EM, Özdemir AÖ, Gürkaş E, Necioğlu Örken D, Öztürk Ş. Intravenous Thrombolytic Therapy in Acute Stroke: Frequent Systemic Problems and Solutions. Turk J Neurol. 2018;24:13-25.

29. Foell RB, Silver B, Merino JG, Wong EH, Demaerschalk BM, Poncha F, et al. Effects of thrombolysis for acute stroke in patients with pre-existing disability. CMAJ. 2003;169:193-7.

30. Merlino G, Corazza E, Lorenzut S, Gigli G, Cargnelutti D, Valente M. Efficacy and safety of intravenous thrombolysis in patients with acute ischemic stroke and pre–existing disability. J Clin Med. 2019;8:400.

31. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. American Heart Association Stroke Council. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2018;49:e46-110.

EURASIAN JOURNAL OF EMERGENCY MEDICINE
Original Article
DOI: 10.4274/eajem.galenos.2020.17894
Eurasian J Emerg Med. 2020;19(3): 159-65

Diagnostic Value of Adropin Levels in Acute Pulmonary Embolism Patients

Mustafa Kürşat Ayrancı[1], Mehmet Gül[1], Leyla Öztürk Sönmez[2], Fatma Hümeyra Yerlikaya Aydemir[3], Mohamed Refik Medni[1]

[1]Department of Emergency Medicine, Meram Medical Faculty, Necmettin Erbakan University, Konya, Turkey
[2]Department of Physiology, Selçuklu Medical Faculty, Selçuk University, Konya, Turkey
[3]Department of Biochemistry, Meram Medical Faculty, Necmettin Erbakan University, Konya, Turkey

Abstract

Aim: This study aimed to evaluate the relationship between serum adropin levels in patients with acute pulmonary embolism (PE).

Materials and Methods: Patients pre-diagnosed with PE based on computed tomographic pulmonary angiography findings and not fulfilling any of the exclusion criteria were included in the PE group. An identical number of participants with comorbidities similar to those of the PE group were included in the control group. These patientswere selected from those who had been referred to the emergency department and were not considered to have PE based on clinical symptoms and risk scores.

Results: Serum adropin levels were found to be high in the PE group. Although the adropin values were high in the case of all comorbidities, the values significantly elevated only in patients with hypertension, acute ischaemic stroke, and previous history of PE. The adropin values were quite different among the Wells score categories, and the mean adropin levels varied significantly between the PE and control groups.

Conclusion: In this study, the plasma adropin levels were significantly high in patients with acute PE and exhibited high positive predictivity, sensitivity, and specificity in detecting PE.

Keywords: Adropin, atherothrombosis, endothelial function, pulmonary embolism

Introduction

Currently, pulmonary embolism (PE) is the most common cardiovascular disease following acute ischemic diseases and stroke. The disease was described by Laennec in 1819, and the association between deep vein thrombosis and PE was firstly demostrated by Virchow in 1846 (1).

In 1856, Virchow identified three factors leading to intravascular coagulation. These factors are stasis, hypercoagulability and vascular endothelial damage. The activation of endothelial cells causes thrombus formation by activating the coagulation system or inhibition of the anticoagulant mechanism (2,3).

Vascular obstruction and increase of resistance are insufficient to explain the pathophysiology of PE alone. Hypoxia and ischemia, neurotrophil activation, release of free oxygen radicals and increased pulmonary artery pressure have destructive effects on endothelium (4).

Endothelium plays a significant role in maintaining vascular circulation. It contributes to the development and progression of inflammatory, metabolic and infectious diseases on the basis of atherothrombosis which has developed due to the disrupted endothelium (5).

Endothelial cells play a role in various physiological and pathological events that affect blood flow and blood pressure by regulating coagulation, fibrinolysis and vascular tonus by its mediators (6).

Endothelial dysfunction has been associated with risk factors of acute vascular events such as hypertension (HT), coronary artery disease (CAD), HF, chronic renal failure, diabetes mellitus (DM)

Corresponding Author: Mustafa Kürşat Ayrancı, MD, Department of Emergency Medicine, Meram Medical Faculty, Necmettin Erbakan University, Konya, Turkey
Phone: +90 332 223 64 17 **E-mail:** drmka157@gmail.com **ORCID:** orcid.org/0000-0002-7196-0856

Received: 26.03.2019
Accepted: 15.06.2020

Cite this article as: Ayrancı MK, Gül M, Öztürk Sönmez L, Yerlikaya Aydemir FH, Medni MR. Diagnostic Value of Adropin Levels in Acute Pulmonary Embolism Patients. Eurasian J Emerg Med. 2020;19(3):159-65

and obesity. Endothelial dysfunction is not only the first step of the atherosclerotic process by causing plaque formation, but also causes the plaque to grow, rupture and trigger thrombogenic events (7).

The concentration of adropin in the circulation is regulated by energy intake. Its release is regulated by energy status and dietary nutrient contents (8).

It has been reported that atropine has functions in liver sinusoidal cells, brain vascular cells - neuroglial cells and neurons, cerebellum vascular cells - purkinje cells and neuroglial cells, endocardial - myocardial and epicardial tissue in the heart (9).

PE is a clinical condition which is difficult to diagnose, with high morbidity and mortality rates. Levels of D-dimer, cardiac Troponin T and I (cTnT, I), brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) in blood are traditionally studied in patients suspected to have PE (10-12). Although these parameters may indicate the level of fibrin degradation products and cardiovascular dysfunction, they are not enough to provide a certain diagnosis of PE. Thus, new parameters to make a diagnosis of PE more easily and rapidly are required.

Adropin is a recently discovered protein which is considered to be related to endothelial function regulation, thus it is claimed to be an endothelial dysfunction marker (9,13,14).

According to recent studies, adropin may be related to endothelial dysfunction that indicates atherothrombotic changes, especially in DM, acute coronary sydrome (ACS), heart failure (HF), stable CAD and acute ischemic stroke (AIS). In our study, we investigated the relation between adropin levels and PE that may occur based on the endothelium-related atherothrombosis. Also, when the literature was examined, we could not find a study that analysed the relation between adropin and acute PE.

The aim of this prospective study is to evaluate the relation between serum adropin levels and PE diagnosis in acute PE patients.

Materials and Methods

Consent was taken from Necmettin Erbakan University Meram Faculty of Medicine Ethics Board before the study (decision date/no: 2016/470). This was a prospective study and informed consent was taken from all patients included in the study. Patients who referred to emergency department between February 2016 and October 2016, examined with PE pre-diagnosis, did not have exclusion criteria and received certain diagnosis via computed tomography pulmonary angiography (CTPA) were included as PE group. The same number of participants with comorbidities similar to the PE group, but not considered to have PE diagnosis from their clinical symptom and risk scorings were selected as the control group. The flow chart describing the group content is shown in Figure 1.

Exclusion Criteria

We excluded patients with trauma, those under 18 years of age, the pregnant and those who did not accept to participate in the study.

Study Protocol

Demographic characteristics, comorbidity conditions and PE major risk factors were noted for the patients included in the study across groups. Results of laboratory tests and the examinations used for imaging, demographic data, blood pressure, heart rate, body temperature, respiratory rate and physical examination were also recorded.

Well's and Revised Geneva Risk Scorings were used for clinical probability determination in patients suspected to have acute PE. Transthoracic echocardiography (ECHO) was performed by a cardiologist in all patients suspected to have acute PE. Considering the clinical probability scores, multi-slice CTPA was ordered to make a certain diagnosis in patients who had no contraindication for contrast enhanced CTPA. Patients who were diagnosed as PE via CTPA and did not have exclusion criteria were included in the study as the PE group.

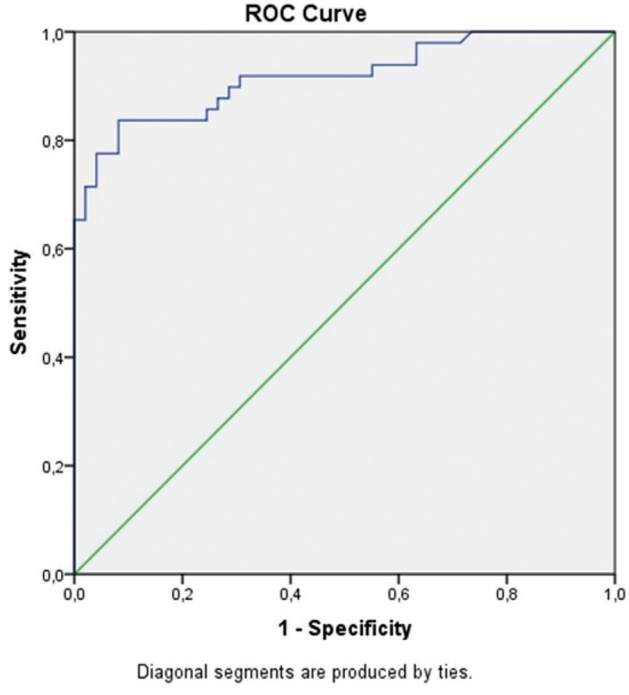

Figure 1. Flow chart describing group contents

ROC: Receiver operating characteristic

Patients randomly selected among individuals with similar age and comorbidities to the PE group and not considered to have PE diagnosis according to the clinical and risk scorings were determined as the control group. Patients were followed-up during hospitalization and any hospital mortalities were registered.

From the blood samples taken for routine blood tests of the patients, routine biochemical, hematological analyses and urine analyses results were obtained. Hematological analyses were performed using XN-1000 Sysmex hematology analyzer. All biochemical parameters were analyzed with kits manufactured for use with Architect c16000 Auto-Analyzer.

From the patients included in the study, intravenous blood samples were also taken to examine adropin levels on referral. Blood serum samples were centrifuged at 4000 rev/min for 10 minutes in a cooling centrifuge device (HR 46R) and the serums were separated. The separated serum samples were secured in a freezer at -80 °C. In serum samples; Human adropin levels were analyzed using human adropin ELISA kit via ELISA method in the biochemistry laboratory by a biochemistry specialist.

Statistical Analysis

Data set analyses were made using SPSS 19.0 program. Continuous variables were presented as median (25-75%). Categorical variables were given as frequencies and percentages. Normality of distribution of constant numeric variables was made using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used for analyzing two independent groups. Spearman's rho correlation was used to detect the relation between numerical variables and Monte Carlo corrected chi-square analysis was used to detect the relation between categorical variables. A p value was accepted as statistically significant ($p<0.05$).

Results

A total of 98 patients including 49 patients in PE group who had a final diagnosis and 49 patients in the control group who were not diagnosed with PE were included. While no difference was observed in age, gender and total comorbidity among PE and control groups included in the study (p=0.96, p=0.54, p=1, respectively), a history of previous PE was found significantly high in PE group (p=0.022). Details on demographic, comorbidity and laboratory variables are given in Table 1.

Serum adropin levels were found notably high in PE group ($p<0.001$). While serum adropin level was 273.2 (214.4-411.0) ng/dL in the PE group, it was measured as 135.6 (91.2-173.6) ng/dL in the control group.

Table 1. Numeric values of demographical, comorbidity and laboratory parameters

	PE group (n=49)	Control group (n=49)	p
Demographical parameters			
Age [median (25-75%)]	67 (47.5-81)	66 (52-77)	0.963
Gender, n (%) (female/male)	26 (53.1)/23 (46.9)	23 (46.9)/26 (53.1)	0.547
Comorbidity, n (%)	35 (71.4)	35 (71.4)	1.000
Malignancy, n (%)	13 (26.5)	8 (16.3)	0.221
Hypertension, n (%)	25 (51)	18 (36.7)	0.156
CAD, n (%)	13 (26.5)	13 (26.5)	1.000
DM, n (%)	12 (24.5)	15 (30.6)	0.500
AIS, n (%)	8 (16.3)	3 (6.1)	0.111
Past History of PE, n (%)	5 (10.2)	0 (0)	**0.022**
Laboratory parameters [median (25-75)]			
Adropin (ng/dL)	273.2 (214.4-411.0)	135.6 (91.2-173.6)	**<0.001**
WBC (10^3/uL)	10.40 (7.95-13.20)	8.80 (7.10-10.35)	**0.030**
Neutrophil (10^3/uL)	7.50 (5.85-10.05)	5.90 (4.25-8.00)	**0.014**
Lymphocyte (10^3/uL)	1.50 (1.10-2.25)	1.60 (1.00-2.30)	0.884
Neutrophil/ Lymphocyte ratio	4.81 (3.37-7.85)	3.40 (2.00-8.73)	0.140
RBC (10^6/uL)	4.60 (3.85-5.05)	4.80 (4.45-5.25)	0.081
Haemoglobin (g/dL)	12.60 (10.80-14.70)	14.10 (11.85-14.95)	0.179
Haemotocrit (%)	37.60 (33.60-43.00)	40.90 (36.70-44.35)	0.076
MCV (fL)	84.20 (81.75-89.30)	84.90 (79.80-87.05)	0.760
RDW (%cv)	14.50 (13.40-16.20)	13.50 (12.60-15.65)	**0.024**
Platelet (10^3/uL)	221 (162-252.5)	244 (218-270)	**0.019**
MPV (fL)	10.50 (9.80-11.25)	9.90 (9.50-10.65)	**0.011**
BUN (mg/dL)	36.2 (27.5-48.6)	34.10 (27.85-47.85)	0.714
Creatine (mg/dL)	0.79 (0.65-0.89)	0.83 (0.74-1.05)	0.077
Sodium (mmol/L)	136.2 (134.8-138.3)	136.6 (134.4-137.5)	0.903
Potassium (mmol/L)	4.40 (4.20-4.75)	4.40 (4.15-4.75)	0.792

CAD: Coronary artery disease, DM: Diabetes mellitus, AIS: Acute ischemic stroke, PE: Pulmonary embolism, WBC: White blood cell, RBC: Red blood cell, MCV: Mean corpuscular volume, RDW: Red cell distribution width, MPV: Mean platelet Volume, BUN: Blood urea nitrogen
Significant values are shown bold, n: Number

In the analyses of the complete blood count (CBC) and biochemical parameters, while white blood cell, neutrophil, red cell distribution width values were significantly higher in PE group compared to the control group (p=0.03, p=0.014, p=0.024, respectively), platelet and mean platelet volume values were detected to be significantly low (p=0.019, p=0.011, respectively). It was detected that there was no difference between other CBC and biochemical parameters between the two groups (Table 1).

Well's and Revised Geneva Average Scorings were also significantly related to PE (p<0.001, p=0.001 respectively). Adropin levels were found to have higher at the intermediate level of clinical probability assessment in both scoring systems. Adropin measurements were compared according to gender, comorbidity parameters and clinical scorings in all PE and control group patients (n=98). Although adropin values were high in the presence of all comorbidity conditions, adropin values were measured significantly higher only in patients who had HT, AIS and previous PE (p=0.032, p=0.032, p=0.05 respectively). Adropin values were also notably different according to Well's Scoring groupings (p<0.001) (Table 2).

In the comorbidity-adropin relation analysis made only in the PE group, this difference was not significant although serum adropin levels were found to be higher in patients with malignancy, HT, DM and AIS and low in patients with CAD (p=0.602, p=0.258, p=0.111, p=0.700, p=0.717, respectively) (Table 3).

As mean adropin levels were found significantly different among PE and control groups, a test of whether adropin had a distinctive diagnosis character or not was done via ROC analysis. The analysis showed that the ROC curve was rather high and significant (p<0.001) (Figure 2). Adropin cut-off values corresponding to the maximum value for the total of sensitivity and specificity were measured as 196.60 ng/dL. It was also detected that serum adropin levels had 83.6% sensitivity, 91.3% specificity in PE diagnosis and false negativity ratio was detected as 16.3%.

Discussion

Although there are many diagnostic methods today, PE still constitutes a significant diagnosis problem for clinicians. The mortality ratio of the disease can be decreased from 30% to 2-10% with early diagnosis and treatment applications (15,16). CTPA and ECHO are diagnosis tools which are not easily accessible for early diagnosis. Studies are being made with many different markers today to reach a faster PE diagnosis. But sensitivity and specificity are not adequate as many markers are disease-related (15-17). Thus, the search for new biomarkers continues.

It is reported that only 30% of all PE cases are diagnosed and treated in USA (18). Thus, new biochemical markers with high diagnostic accuracy are required. Biomarkers with high diagnostic specificity may provide the clinician with the possibility to early risk classification and start the appropriate treatment.

Adropin, which was discovered for the first time in 2008 by Kumar et al. (13), is a product of the *energy homeostasis-associated* (*ENHO*) gene and a peptide-structured hormone containing 42 aminoacid, and is thought to play a role in the regulation of energy homeostasis (19,20). Lower adropin levels are associated with obesity, dyslipidemia, hepatic steatosis, and increased fat mass. Circulating adropin levels were found to be low in DM, gestational DM, metabolic syndrome, non-alcoholic fatty liver disease, polycystic ovary syndrome, and CAD (19-21). In addition, adropin has a protective effect on endothelial functions by enhancing the release of nitric-oxide and activating endothelial nitric oxide (eNOS) (21). Based on the fact that there is endothelium

Table 2. Comparison of adropin levels in PE and control group according to gender, comorbidity and clinical scoring results

		Adropin value (ng/dL) [median (25-75%)]	p
Gender	Female	196.0 (138.4-263.0)	0.394
	Male	168.8 (105.0-314.8)	
Malignancy	Negative	180.8 (120.4-261.8)	0.408
	Positive	220.4 (127.0-387.8)	
HT	Negative	164.8 (112.4-238.0)	**0.032**
	Positive	218.0 (148.8-286.0)	
CAD	Negative	168.4 (112.8-278.5)	0.138
	Positive	209.0 (164.2-268.4)	
DM	Negative	190.4 (128.4-273.2)	0.978
	Positive	178.4 (109.2-279.2)	
AIS	Negative	178.4 (119.6-264.0)	**0.032**
	Positive	259.6 (203.6-411.2)	
PE	Negative	180.8 (120.4-270.0)	**0.05**
	Positive	264.0 (209.6-571.2)	
Well's score	Low	150.0 (103.4-212.5)	**<0.001**
	Mean	268.6 (211.4-400.2)	
	High	212.4 (137.5-643.0)	
Revised Geneva score	Low	151.6 (90.4-215.8)	0.094
	Mean	199.2 (135.9-280.9)	
	High	183.6 (124.4-505.7)	

Significant values are shown bold.
HT: Hypertension, CAD: Coronary artery disease, DM: Diabetes mellitus, AIS: Acute ischemic stroke, PE: Pulmonary embolism

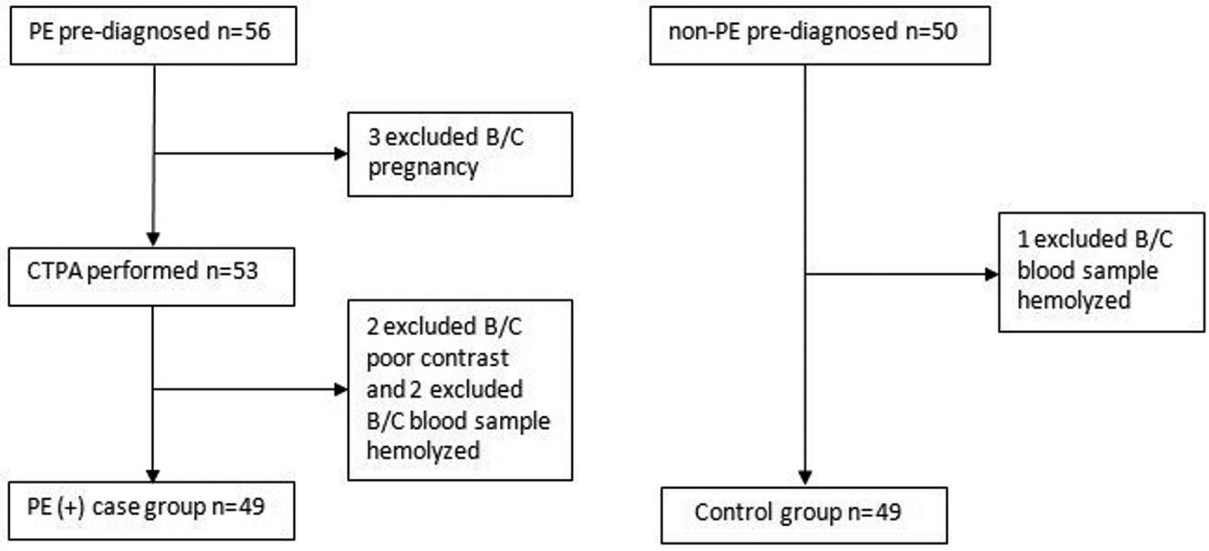

Figure 2. ROC curves of adropin in PE and control group
ROC: Receiver operating characteristic, PE: Pulmonary embolism, CTPA: Computed tomography pulmonary angiography, BUN: Blood urea nitrogen, B/C: BUN/Creatinine ratio, n: Number

Table 3. Adropin levels of PE group according to comorbidities

		Adropin value (ng/dL) [median (25-75%)]	p
Malignancy	Negative (n=36)	265.4 (214.4-411.1)	0.602
	Positive (n=13)	350.4 (210.8-409.6)	
HT	Negative (n=24)	242.6 (169.1-565.2)	0.258
	Positive (n=25)	279.2 (251.4-408.8)	
CAD	Negative (n=36)	277.8 (201.5-411.0)	0.717
	Positive (n=13)	266.8 (234.0-411.0)	
DM	Negative (n=37)	259.6 (201.8-393.2)	0.111
	Positive (n=12)	345.0 (231.3-748.7)	
AIS	Negative (n=41)	266.8 (208.4-408.8)	0.700
	Positive (n=8)	281.2 (225.7-425.9)	

HT: Hypertension, CAD: Coronary artery disease, DM: Diabetes mellitus, AIS: Acute ischemic stroke, PE: Pulmonary embolism

damage in the pathogenesis of PE and the consequent relation between adropin and PE, our study aimed to examine the effect, sensitivity and specificity of adropin as a diagnostic tool for PE.

Marczuk et al. (22) investigated the physiological and pathophysiological role of adropin and stated that release and regulation of adropin was controversial and adropin was detected in brain, cerebellum, liver, kidney, heart, pancreas, small intestine, endothelial cells, colostrum, milk and other different tissues and body fluids. Detection of adropin in endothelial cells makes us consider that adropin would have a significant effect on endothelial function. Adropin is considered to be related to endothelium function regulation (9,13). Topuz et al. (9) claimed that adropin could be a marker for endothelial dysfunction. Lovren et al. (19) claimed that adropin is released from umblical vein and coronary artery endothelial cells and regulated eNOS and adropin is a potential preserver.

Wenlin et al. (20) showed that the adropin levels were directly proportional with HF severity in HF patients. Wu et al. (8) stated that circulating low adropin levels were closely related to coronary atherosclerosis occurrence in diabetic and nondiabetic coronary atherosclerosis patients and could be regarded as an atherosclerosis marker. Aydin et al. (23) claimed that adropin was released in the blood after cardiac muscle cell damage. It has been shown that adropin is released into the bloodstream during myocardial muscle injury caused by myocardial infarction, and serum adropin levels increase as myocytes die.

It was also reported that serum adropin levels could be a potential marker for diagnosis in acute coronary syndrome patients. It has been shown that adropin increases with other cardiac markers and adropin begins to decrease at 4 hours earlier than other markers, in enzyme positive acute coronary syndrome (24). Based on the results of our study, we think that adropin will increase in cases such as atherosclerosis and atherothrombosis in order to protect the endothelium.

For the pathogenesis, an increasing number of proofs state that adropin is a strong regulator for cardiovascular functions (25). Gu et al. (26) stated that adropin is an independent marker for HT and can influence blood pressure by preserving endothelial function. Zhao et al. (27) stated that low serum adropin levels are a significant marker for stable CAD. Supporting the literature,

adropin values in the PE group were found lower in patients who had CAD before.

Serum adropin levels were significantly lower in DM patients compared to non-diabetic patients, and conversely, they were independently associated with angiographic severity of coronary atherosclerosis (8). In our study, when all DM patients in the case and control groups were considered, adropin levels were found to be high in DM patients. In our study, in our control group without PE; Adropin levels were found 125.6 ng/dL (79.6-160.0) and 139.6 ng/dL (92.6-181.5) in DM patients (n=15) and in patients without DM (n=34), respectively. Consistent with literature data, adropin levels were found low in DM patients without PE.

There have been many studies about other biomarkers in PE diagnoses. Kelly et al. (28) and Brown et al. (29) found D-dimer test to have a high sensitivity but a low specifity. Elevated serum troponin levels indicate right ventricle dysfunction (30). High BNP levels are reported to be related with right ventricle dysfunction and early mortality (31,32).

For prognostic purposes, troponin, BNP and NT-proBNP tests may be useful to distinguish massive and submassive PE from non-massive. But, it should be kept in mind that these markers are also high in chronic obstructive pulmonary disease attack, sepsis, acute renal failure, trauma, rhabdomyolysis and congestive HF (33).

Adropin positive predictivity, sensitivity and specificity were detected to be significantly high in the examination. These parameters allow us to note that adropin can be a useful biomarker for PE diagnosis. Based on these measurements, we also think that more attention should be paid to PE pre-diagnosed patients who have adropin values over 196.60 ng/dL cut-off value. Similarly, the cut-off values of adropin in ACS, Cardiac syndrome X and STEMI patients were found to be 412 ng/dL, 273 ng/dL, 275.9 ng/dL, respectively (24,34,35).

Due to all these findings mentioned above and considering the literature studies, we think that adropin levels can be a diagnostic biochemical marker for PE and more comprehensive studies on this subject are required.

Study Limitations

Our study is a cross-sectional study with relatively small sample size. The low number of patients, the low number of isolated PE patients due to additional comorbidities of the patients, lack of adropin tests for post-PE treatment can be counted as the limitations of our study. Since additional diseases of the patients in the study population also affect adropin levels, they may contribute negatively to the results of our study.

Conclusion

Plasma adropin levels were found significantly high in acute PE patients in our study and had high positive predictivity, sensitivity and specificity. Based on these data, adropin can be a significant biochemical marker for the diagnosis of acute PE patients. We believe that a decrease in mortality, morbidity and avoidance of unnecessary health expenses can be achieved if more comprehensive biomarker studies such as adropin are supported to achieverapid diagnosis in acute PE and fast access to treatment. Therefore, our results should be confirmed by multicenter prospective studies and animal experiments in patients with definitive PE diagnosis who do not have concomitant diseases affecting adropin levels such as ACS, CAD, HF, Malignancy, HT, DM, AIS with larger sample size.

In addition, studies on levels of adropin for a single clinical condition should be also performed in cases of hypoxic conditions and endothelial damage.

Ethics

Ethics Committee Approval: Consent was taken from Necmettin Erbakan University Meram Faculty of Medicine Ethics Board before the study (decision date/no: 2016/470).

Informed Consent: This was a prospective study and informed consent was taken from all patients included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.K.A., M.G., F.H.Y.A., Concept: M.K.A., M.G., L.Ö.S., Design: M.K.A., M.G., L.Ö.S., M.R.M., Data Collection or Processing: M.K.A., M.G., Analysis or Interpretation: M.K.A., M.G., F.H.Y.A., Literature Search: M.K.A., L.Ö.S., Writing: M.K.A., L.Ö.S., M.R.M.

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

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

References

1. Smith TP. Pulmonary embolism; what's wrong with this diagnosis? AJR. 2000;174:1489-97.
2. Guyton AC, Hall JE. Tıbbi Fizyoloji. In: Yüce Yayıncılık, İstanbul, Çavuşoğlu HN, Yeğen BC, Aydın Z, Alican İ, editors. 9. Baskı; 1996;463-9.
3. Riedel M. Venous Tromboembolic Disease, Acute Pulmonary Embolism, Pathophysiology, Clinical Presentation and Diagnosis. Heart. 2001;85:229-40.
4. Stratmann G, Gregory GA. Neurogenic and humoral vasoconstriction in acute pulmonary thromboembolism Anesth Analg. 2003;97:341-54.
5. Verma S, Buchanan MR, Anderson TJ. Endothelial function testing as a biomarker of vascular disease. Circulation. 2003;108:2054-9.

6. Endemenn DH, Schriffrin EL. Endothelial dysfunction. J Am Soc Nephrol. 2004;15:1983-92.
7. Roquer J, Segura T, Serena J, Castillo J. Endothelial dysfunction, vascular disease and stroke: the ARTICO study. Cerebrovasc Dis. 2009;27(Suppl 1):25-37.
8. Wu L, Fang J, Chen L, Zhao Z, Luo Y, Lin C, et al. Low serum adropin is associated with coronary atherosclerosis in type 2 diabetic and non-diabetic patients. Clin Chem Lab Med. 2014;52:751-8.
9. Topuz M, Celik A, Aslantas T, Demir AK, Aydin S, Aydin S. Plasma adropin levels predict endothelial dysfunction like flow-mediated dilatation in patients with type 2 diabetes mellitus. J Investig Med. 2013;61:1161-4.
10. Di Nisio M, Squizzato A, Rutjes AWS, Büller HR, Zwinderman AH, Bossuyt PMM. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. J Thromb Haemost 2007;5:296-304.
11. Giannitsis E, Müler-Bardoff M, Kurowski V, Weidtmann B, Wiegand U, Kampmann M, et al. Independent prognostic value of cardiac troponin T in patients with confirmed pulmonary embolism. Circulation. 2000;102;211-7.
12. Stein BC, Levine RI. Natriuretic peptides: Physiology, therapeutic potential, and risk stratification in ishemic heart disease. Am Heart J. 1998;135:914-23.
13. Kumar KG, Trevaskis JL, Lam DD, Sutton GM, Koza RA, Chouljenko VN, et al. Identification of adropin as a secreted factor linking dietary macronutrient intake with energy homeostasis and lipid metabolism. Cell Metab. 2008;8:468-81.
14. Kumar KG, Zhang J, Gao S, Rossi J, Mc Guinness OP, Halem HH, et al. Adropin deficiency is associated with increased adiposity and insulin resistance. Obesity (Silver Spring). 2012;20:1394-402.
15. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC) Endorsed by the European Respiratory Society (ERS). Eur Heart J. 2014;35:3033-69.
16. Merli GJ. Pulmonary Embolism in 2017: How We Got Here and Where Are We Going? Tech Vasc Interv Radiol. 2017;20:128-34.
17. Cohen DM, Winter M, Lindenauer PK, Walkey AJ. Echocardiogram in the Evaluation of Hemodynamically Stable Acute Pulmonary Embolism: National Practices and Clinical Outcomes. Ann Am Thorac Soc. 2018;15:581-8.
18. Morgenthaler TI, Ryu JH. Clinical characteristics of fatal pulmonary embolism in a referral hospital. Mayo Clin Proc. 1995;70:417-24.
19. Lovren F, Pan Y, Quan A, Singh KK, Shukla PC, Gupta M, et al. Adropin is a novel regulator of endothelial function. Circulation. 2010;122(Suppl):S185-92.
20. Wenlin L, Xiaosong G, Yongwen Q, Xing Z. Elevated Plasma Levels of Adropin in Heart Failure Patients. Intern Med. 2011;50:1523-7.
21. Inal ZO, Erdem S, Gederet Y, Duran C, Kucukaydin Z, Kurku H, et al. The impact of serum adropin and ischemia modified albumin levels based on BMI in PCOS. Endokrynol Pol. 2018;69:135-41.
22. Marczuk N, Cecerska-Heryc E, Jesionowska A, Dolegowska B. Adropin physiological and pathophysiological role. Postepy Hig Med Dosw. 2016;70:981-8.
23. Aydin S, Kuloglu T, Aydin S, Kalayci M, Yilmaz M, Çakmak T, et al. Elevated adropin: a candidate diagnostic marker for myocardial infarction in conjunction with troponin-I. Peptides. 2014;58:91-7. [Epub 2014 Jun 14].
24. Aydin S, Eren MN, Yilmaz M, Yardim M, Aydin S, Kalayci M, et al. Adropin as a potential marker of enzyme-positive acute coronary syndrome. Cardiovasc J Afr. 2017;28:40-7.
25. Li L, Xie W, Zheng XL, Yin WD, Tang CK. A novel peptide adropin in cardiovascular diseases. Clinica Chimica Acta. 2016;453:107-13.
26. Gu X, Li H, Zhu X, Gu H, Chen J, Wang L, et al. Inverse Correlation Between Plasma Adropin and ET-1 Levels in Essential Hypertension: A Cross-Sectional Study. Medicine Baltimore. 2015;94:e1712.
27. Zhao LP, Xu WT, Wang L, You T, Chan SP, Zhao X, et al. Serum adropin level in patients with stable coronary artery disease. Heart, Lungand Circulation. 2015;24:975-9.
28. Kelly J, Rudd A, Lewis RR, Hunt BJ. Plasma D-dimers in the diagnosis of venous thromboembolism. Arch Intern Med. 2002;162:747-56.
29. Brown MD, Rowe BH, Reeves MJ, Bermingham JM, Goldhaber SZ. The accuracy of the enzyme-linked immunosorbent assay D-dimer test in the diagnosis of pulmonary embolism: a meta-analysis. Ann Emerg Med. 2002;40:133-44.
30. Pruszczyk P, Bochowicz A, Torbicki A, Szulc M, Kurzyna M, Fijałkowska A, et al. Cardiac troponin T monitoring identifies high-risk group of normotensive patients with acute pulmonary embolism. Chest. 2003;123:1947-52.
31. Kucher N, Printzen G, Goldhaber SZ. Prognostic role of brain natriuretic peptide in acute pulmonary embolism. Circulation. 2003;107:2545-7.
32. Cavallazi R, Nair A, Vasu T, Marik PE. Natriuretic peptides in acute pulmonary embolism: a systematic review. Int Care Med. 2008;34:2147-56.
33. Lazzeri C, Bonizzoli M, Cianchi G, Gensini GF, Peris A. Troponin-I in the intensive care unit setting: from the heart to the heart. Intern Emerg Med. 2008;3:9-16.
34. Celik A, Balin M, Kobat MA, Erdem K, Baydas A, Bulut M, et al. Deficiency of a New Protein Associated with Cardiac Syndrome X; Called Adropin. Adropin as a potential marker of enzyme-positive acute coronary syndrome. Cardiovasc Ther. 2013;31:174-8.
35. Ertem AG, Ünal S, Efe TH, Açar B, Yayla Ç, Kuyumcu MS, et al. Association between serum adropin level and burden of coronary artery disease in patients with non-ST elevation myocardial infarction. Anatol J Cardiol. 2017;17:119-24.

EURASIAN JOURNAL OF EMERGENCY MEDICINE
Original Article
DOI: 10.4274/eajem.galenos.2020.75537
Eurasian J Emerg Med. 2020;19(3): 166-71

Low-Dose Intravenous Ketamine Bolus versus Conventional Technique for the Reduction of Upper and Lower Extremity Fractures in Children: A Randomised Controlled Clinical Trial

Mehdi Nasr Isfahani, Narges Shahverdi, Keihan Golshani

Department of Emergency Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Aim: Ketamine administration in high dosage leads to certain adverse reactions. This study aimed to evaluate the effect of low-dose intravenous ketamine bolus versus conventional injection for the reduction of upper and lower extremity fractures in children.

Materials and Methods: A total of 198 paediatric patients with extremity fractures were enrolled. They were randomly categorized into two groups. In the intervention group, a number of 100 patients participated with a mean age of 8.89±4.37, among them 77 (77%) were male and upper limb fractures were more common (84%). They were assigned to receive 1% ketamine at a dose of 0.5 mg/kg (within 5 s), and in the control group, a number of 98 patients participated with a mean age of 9.08±3.98, among them 73 (74.5%) were male and upper limb fractures were more common (83.7%). They received ketamine at 1.5 mg/kg for 30-60 s. The outcomes were measured, and the satisfaction of patients and physicians was recorded.

Results: Successful sedation rate was significantly lower in the low-dose ketamine group than in the control group (7% vs 100%; $p<0.001$). Moreover, the duration of drug effect and recovery rate were significantly lower in the low-dose ketamine group than in the high-dose ketamine group ($p<0.05$). In addition, the rates of neurological (20.4% vs 5%) and physiological (10.2% vs 2%) side effects were significantly higher in the control group than in the intervention group ($p<0.05$).

Conclusion: The findings of this study did not show that low-dose intravenous ketamine bolus had any beneficial effects in sedating paediatric patients, suggesting that it should not be considered as an accompaniment for standard therapy in short-term pain control.

Keywords: Low-dose intravenous ketamine bolus, fracture, children

Introduction

Fractures constitute 10-25% of all pediatric trauma. The calculated risk for a boy to sustain a fracture before reaching skeletal maturity is between 42% and 60% and for a girls is between 27% and 40%, respectively (1,2). The peak of incidence of fractures in children occurs at the time of peak height velocity: 11.5 and 13.5 years of age in girls and boys, respectively (3).

Ten to twenty-five percentage of trauma in children cause fractures. The risk of fracture before reaching skeletal maturity is about 42% to 60% and for girls is 27% to 40% (1,2). The incidence of fractures in children is 11.5 and 13.5 for girls and boys, respectively (3). Non-operative treatment of fractures in children includes: restoration of length, anatomic alignment and immobilization, which need appropriate sedation in order to reduce patient awareness (4). For this purpose, different sedation methods and drugs have been introduced such as midazolam, propofol, fentanyl, and also ketamine, which recently has been added to the list of sedative drugs for fracture (5).

Recently, ketamine has been introduced as a common drug given to sedate children for different painful procedures in the emergency department (ED) (6-8). Ketamine is one of the phencyclidine derivatives with quick onset and short duration of action (9), which is cost-effective, easily accessible, stable at room temperature and has safe sedation and analgesia recommended by the World Health Organization, as an essential medication for

Corresponding Author: Dr. Narges Shahverdi, Department of Emergency Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
E-mail: narges.shahverdi@gmail.com **ORCID:** orcid.org/0000-0002-8016-523X
Cite this article as: Nasr Isfahani M, Shahverdi N, Golshani K. Low-Dose Intravenous Ketamine Bolus versus Conventional Technique for the Reduction of Upper and Lower Extremity Fractures in Children: A Randomised Controlled Clinical Trial. Eurasian J Emerg Med. 2020;19(3):166-71

Received: 08.10.2019
Accepted: 30.04.2020

sedation procedures (10-16). In the study conducted by McCarty et al. (17), it was shown that ketamine is reliable, safe, and provides quick and adequate sedation in children's fractures in ED. Ketamine at doses more than 1 mg/kg has been routinely used in brief procedures in ED, causing many adverse effects, including neuropsychiatric problems, especially in pediatric patients (18,19), such as hallucinations in the short periods of time (20,21), unpleasant dreams, or acute psychosis (22). To the extent that we know, only a few prospective studies exist regarding the administration of lower doses of ketamine in ED. Moreover, contrary results have been reported for ketamine in sub-anaesthetic doses; therefore, we decided to assess and compare the clinical efficacy of low-dose intravenous ketamine bolus versus usual dosage of ketamine, for reduction of upper and lower extremity fractures in children.

Materials and Methods

Study Design and Participants

This prospective double-blind clinical trial was carried out in the ED of Isfahan Al-Zahra University Hospital, from May 2016 to June 2017 (ClinicalTrials.gov Identifier: NCT03499886). The study was approved by the Ethical Committee of Isfahan University of Medical Sciences in April 2016 (registration number: 395779), and all participants and their parents signed the informed consent form. The sedation levels and different outcomes of patients receiving low-dose intravenous ketamine bolus (intervention group) were compared to patients receiving higher doses of intravenous ketamine (control group), for reduction of upper and lower extremity fractures. Inclusion criteria consisted of parents' desire and consent to participate in the study, body mass index within the normal range, having age of 6 months to 17 years, requiring a reduction of upper and lower limb fractures, not receiving benzodiazepines and other sedative drugs before intervention.

Exclusion criteria consisted of patients' age <3 months with the body temperature of >38 °C, due to upper respiratory tract infection. Patients having any other complications such as cardiovascular, gastrointestinal, psychological and neurological were excluded from the study. We also excluded the patients who have withdrawn from the study.

Participants and Intervention

The study flow diagram is depicted in Figure 1. Two hundred and ten patients with a diagnosis of upper and lower extremity fractures, diagnosed by Emergency Medicine Specialist, were enrolled based on X-ray images and inclusion criteria.

The participants were randomly divided into two groups, using a permuted random allocation program (available at www.graphpad.com/quickcalcs) while maintaining a balance across treatment groups with matching participants in each block based on sex and age. Setting the power of the study at 80% and at 95% confidence limit, the calculated sample size becomes two hundred. One hundred ninety-eight patients, however, completed the study; including one hundred from the intervention group and 98 from the control group.

After informed consent was obtained, eligible patients were enrolled. All patients were monitored by direct observation and continuous cardiovascular monitoring, in order to check the vital signs and also by pulse oximeters to examine the blood oxygen saturation level.

Tools and measures used for each patient during the process were as follows:

1- Recurrent suction and, if necessary, use of atropine to control excessive salivation

2- Laryngospasm and respiratory suppression and, airway management measures, in case of any complications

3- Controlling the heart rate and blood pressure, intracranial pressure and performing sedation and using beta-blocker, if needed

4- Forecasting emergency response and providing a quiet and dark room and administrating midazolam, if needed.

In the intervention group, ketamine 1% was administered rapidly at a dose of 0.5 mg/kg (within 5 seconds), and in the control group, ketamine 1.5 mg/kg was slowly injected for 30 to 60 seconds. Patient assessment was performed before and two minutes after ketamine injection, and then every 5 minutes after the reduction of the fracture, by an anaesthetist blind to the type of intervention.

Finally, after the intervention, the patients were put under close and direct observation in a quiet and dim room. The incidence of any side effects of ketamine injections such as gastrointestinal (nausea, vomiting, increase in salivary secretion), neurological (light-headedness, dizziness, headache, visual disturbance, nystagmus, numbness, drowsiness, or increased skeletal tone), psychological (dysphoria or confusion, hallucination, disorientation, mood change or agitation) and cardiopulmonary (major: hypotension and hypoxia; minor: hypertension and tachycardia) were recorded by a nurse, blinded to the intervention group; if necessary, immediate action was taken.

Aldrete scoring system was used to assess the recovery and to determine the patient readiness for discharge. Wisconsin sedation scale and the Aldrete scoring system were calculated for each patient; if the Wisconsin sedation scale was >5 and the

Aldrete scoring system >10, the patient was ready to discharge from the ED.

Statistical Analysis

Only data from patients with complete information were analysed and reported. Statistical analysis of data was carried out by SPSS version 22 software. To compare qualitative variables between groups chi-square test was used. In order to assess the normal distribution of all quantitative studied parameters, Kolmogorov-Smirnov test was used. We used also Student's t-test and paired t-test for normally distributed variables. In addition, for variables without normal distribution, Mann-Whitney U and Wilcoxon tests were used. The two tailed p value less than 0.05 were considered statistically significant (Figure 1).

Results

Demographic features, in terms of age (p=0.856), sex (p=0.68) were similar in both groups (Table 1). Twelve patients were withdrawn from the study and 198 patients completed the study. Results showed that the successful sedation rate, in the low dose ketamine group was significantly lower as compared to control group (7% vs 100%) (p<0.001). Moreover, in terms of duration of the drug effect and of recovery, the low dose ketamine group were significantly lower compared to the other group, receiving higher doses of ketamine (p<0.05). Furthermore, the sedation depth based on Wisconsin sedation scale was significantly higher in the low dose ketamine group compared to the other group. These data suggest that the sedation level, in patients responded to the drug (n=7), was spontaneous without the stimulus (awake and calm or drowsy with eyes open or closed, easily aroused), while in the control group required sustained painful stimulus (levels: 1-3) (p<0.001). Moreover, patients and Physician satisfaction with control group was significantly higher than low dose ketamine group (p<0.001).

By evaluating different complications, we found that the rate of neurological (20.4% vs 5%) and physiological (10.2% vs 2%) adverse events in the control group was meaningfully higher than low dose ketamine group (p<0.05), while the other complications

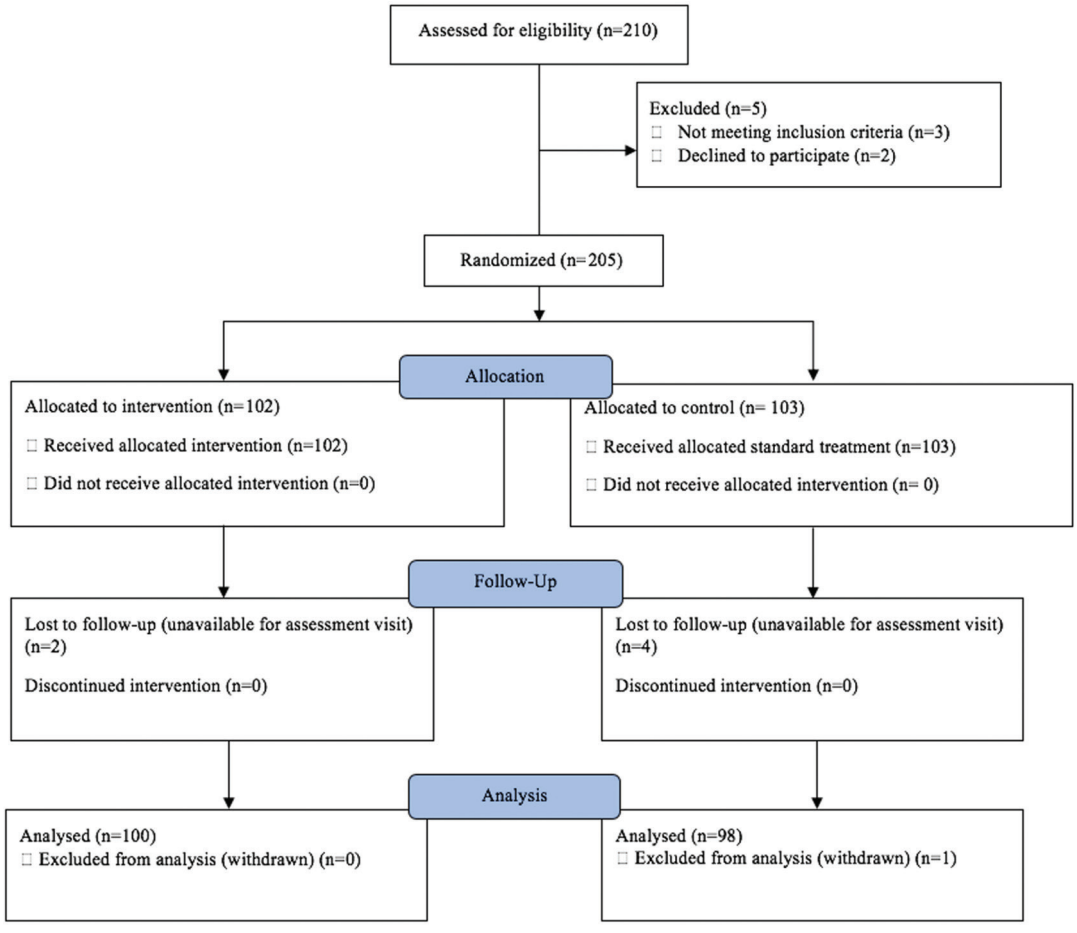

Figure 1. Study flowchart (CONSORT flow diagram)

CONSORT: Consolidated standards of reporting trials, n: Number

Table 1. Studied variables in control and low dose ketamine groups				
Group variables		**Low dose ketamine**	**Control**	**p-value**
Age (years)		8.89±4.37	9.08±3.98	0.856
Sex (male)		77 (77%)	73 (74.5%)	0.68
Type of fracture	Upper extremities	84 (84%)	82 (83.7%)	0.95
	Lower extremities	16 (16%)	16 (16.3%)	
Successful sedation		7 (7%)	98 (100%)	<0.001
Starting the drug effect (s)		54.28±12.72	62.57±8.61	0.048
Duration of the drug effect (min)		13.42±6.13	17.61±4.68	0.034
Duration of recovery (min)		15.28±4.15	65±12.69	<0.001
Wisconsin sedation scale		5.53±0.74	1.95±0.71	<0.001
Patients satisfaction		1.17±0.49	4.58±0.53	<0.001
Physician satisfaction		1.12±0.47	4.85±0.35	<0.001
Complications	Gastrointestinal	5 (5%)	9 (9.2%)	0.251
	Neurological	5 (5%)	20 (20.4%)	0.001
	Physiological	2 (2%)	10 (10.2%)	0.016
	Minor cardiopulmonary	1 (1%)	6 (6.1%)	0.064
	Major cardiopulmonary	0	0	-

min: Minute, s: Second

such as gastrointestinal and cardiopulmonary (minor and major) adverse events did not show any differences among the groups (p>0.05).

Discussion

Sedation with intravenous ketamine in children conventionally involves doses of 1 to 2 mg/kg, administered slowly. The main objective of this study was to demonstrate if lower doses of ketamine, pushed rapidly achieve adequate sedation. Our data show, prescribing low dose ketamine (0.5 mg/kg) for reduction of fractures in children, did not induce proper sedation levels, while by increasing the dosage to 1.5 mg/kg, appropriate sedation was achieved in the ED; however, the side effects especially neurological and physiological complications were increased in the latter dosage.

In 2012, a study arranged by Yazigi et al. (23), found that low-dose ketamine, did not decrease acute pain scores and supplemental morphine was required following thoracotomy, even in combination with a continuous intercostal nerve block. Furthermore, they found that the rate of complications such as psychomimetic adverse effects did not differ as compared to the control group. Edwards et al. (24) reported that a combination of morphine and low-doses ketamine in elderly patients, after upper abdominal surgery did not significantly decrease the pain and did not improve the lung function. Another study performed by Menigaux et al. (25) showed that low-dose ketamine (0.15 mg/kg) had no beneficial effect on pain scores at rest, following orthopaedic surgery. However, in terms of studied population, sample size and chief complaints were different compared to ours, but the results were consistent with our data.

While in 2016, a study performed by Lee and Lee (26) showed that the effect of ketamine on pain reduction differs according to the pain site. Furthermore, they demonstrated that low-dose ketamine may be a key modality for pain management in ED, without causing any side effects. Ahern et al. (27) showed that low-dose ketamine infusion in ED resulted in significant pain control, with generally mild adverse events and with no severe side effects such as major cardiopulmonary complications. Goltser et al. (28) demonstrated that low-dose ketamine infusion may be safe and effective drug in pain reduction for patients with a history of chronic opioid use. Moreover, the results of Ahmadi et al. (29) in 2014, showed that low-dose ketamine in accompany with midazolam has an analgesic effect similar to morphine, on pain relief in closed limb fractures, with less respiratory adverse events. Furthermore, Pandit et al. (30) found that low-dose intravenous ketamine bolus, produced marked sedation for about 20 minutes, followed by moderate sedation during intravenous infusion in patients in ED.

The results of these studies were in contrast to our study, which may be due in part to differences in sample size, race, demographic features (children age groups) and chief complaints. Furthermore, we evaluated seven patients in low-

dose intravenous ketamine group, which in regards to small sample size, it is very small for evaluating the other outcomes such as the sedation levels, satisfaction and complications. Therefore, further studies are required to use higher sample size with different demographic features, in order to find the exact effect of low-dose intravenous ketamine bolus injection. As the rate of adverse events in this group was significantly low, appropriate patient sample size is required in order to examine the response to the indicated dosage.

Conclusion

The findings of this study did not show any beneficial effects of low-dose intravenous ketamine bolus in sedating paediatric patients, for reduction of upper and lower extremity fractures. Our data suggest that the indicated low dose should not be prescribed as a substitute for standard therapy and control of pain in the short term; however, side effects were noted to be significantly lower.

Acknowledgments

This study was financially supported by the Technology and Research Development Department of Isfahan University of Medical Sciences. We gratefully appreciate the dedicated efforts of the researchers, the coordinators and the volunteer patients who contributed to this study, and the Clinical Research and Development Units (CRDU) of Al-Zahra University.

Ethics

Ethics Committee Approval: This article is approved by Ethics Committee of Isfahan University of Medical Sciences. Ethic approval number is 395779.

Informed Consent: All participants and their parents signed the informed consent form after informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.N.I., N.S., K.G., Concept: M.N.I., Design: M.N.I., N.S., Data Collection or Processing: M.N.I., N.S., K.G., Analysis or Interpretation: M.N.I., N.S., K.G., Literature Search: M.N.I., N.S., K.G., Writing: M.N.I., N.S., K.G.

Conflict of Interest: The authors declare no conflicts of interests regarding the content of this article.

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

References

1. Landin LA. Epidemiology of children's fractures. J Pediatr Orthop B. 1997:6:79-83.
2. Karlsson MK, Duan Y, Ahlborg H, Obrant KJ, Johnell O, Seeman E. Age, gender, and fragility fractures are associated with differences in quantitative ultrasound independent of bone mineral density. Bone. 2001;28:118-22.
3. Tanner JM, Davies PS. Clinical longitudinal standards for height and height velocity for North American children. J Pediatr. 1985;107:317-29.
4. Constantine E, Steele DW, Eberson C, Boutis K, Amanullah S, Linakis JG. The use of local anesthetic techniques for closed forearm fracture reduction in children: a survey of academic pediatric emergency departments. Pediatr Emerg Care. 2007;23:209-11.
5. Migita RT, Klein EJ, Garrison MM. Sedation and analgesia for pediatric fracture reduction in the emergency department: a systematic review. Arch Pediatr Adolesc Med. 2006;160:46-51.
6. Godambe SA, Elliot V, Matheny D, Pershad J. Comparison of propofol/fentanyl versus ketamine/midazolam for brief orthopedic procedural sedation in a pediatric emergency department. Pediatrics. 2003;112:116-23.
7. Luhmann JD, Schootman M, Luhmann SJ, Kennedy RM. A randomized comparison of nitrous oxide plus hematoma block versus ketamine plus midazolam for emergency department forearm fracture reduction in children. Pediatrics. 2006;118:e1078-86.
8. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. Ann Emerg Med. 2011;57:449-61.
9. Morrison T, Carender C, Kilbane B, Liu RW. Procedural Sedation with Ketamine Versus Propofol for Closed Reduction of Pediatric Both Bone Forearm Fractures. Orthopedics. 2017;6:1-7. [Epub ahead of print].
10. World Health Organisation. WHO Model List of Essential Medicines for Children, 5 th List (April 2015) WHO Medicines. https://www.who.int/selection_medicines/committees/expert/20/CORRIGENDA_Rev.1_EMLc_BC.pdf?ua=1 (accessed 8 Feb 2016).
11. Donnelly RF. Stability of diluted ketamine packaged in glass vials. Can J Hosp Pharm. 2013;66:198.
12. Walker SE, Law S, DeAngelis C. Stability and compatability of hydromorphone and ketamine in normal saline. CJHP. 2001:193-201.
13. Kohrs R, Durieux ME. Ketamine: teaching an old drug new trick. Anesth Analg. 1998;87:1186-93.
14. Reich DL, Silvay G. Ketamine: an update on the first twenty-five years of clinical experience. Can J Anaesth. 1989;36:186-97.
15. Smith DC, Mader TJ, Smithline HA. Low dose intravenous ketamine as an analgesic: a pilot study using an experimental model of acute pain. Am J Emerg Med. 2001;19:531-2.
16. Nasr A, Alimohammadi N, Isfahani MN, Alijanpour S. Development and Domestication of a Clinical Guideline for Pharmacological Pain Management of Trauma Patients in Prehospital Setting. ATR. 2019;8:111.
17. McCarty EC, Mencio GA, Walker LA, Green NE. Ketamine sedation for the reduction of children's fractures in the emergency department. J Bone Joint Surg Am. 2000;82-A:912-8.
18. Weinbroum AA. A single small dose of postoperative ketamine provides rapid and sustained improvement in morphine analgesia in the presence of morphine-resistant pain. Anesth Analg. 2003;96:789-95.
19. Nesher N, Serovian I, Marouani N, Chazan S, Weinbroum AA. Ketamine spares morphine consumption after transthoracic lung and heart surgery without adverse hemodynamic effects. Pharmacol Res. 2008;58:38-44.
20. Hartvig P, Larsson E, Joachimsson PO. Postoperative analgesia and sedation following pediatric cardiac surgery using a constant infusion of ketamine. J Cardiothorac Vasc Anesth. 1993;7:148-53.
21. Green SM, Nakamura R, Johnson NE. Ketamine sedation for pediatric procedures: Part 1, A prospective series. Ann Emerg Med. 1990;19:1024-32.
22. Malhotra AK, Pinals DA, Weingartner H, Sirocco K, Missar CD, Pickar D, et al. NMDA receptor function and human cognition: The effects of ketamine in healthy volunteers. Neuropsychopharmacol. 1996;14:301-7.

23. Yazigi A, Abou-Zeid H, Srouji T, Madi-Jebara S, Haddad F, Jabbour K. The effect of low-dose intravenous ketamine on continuous intercostal analgesia following thoracotomy. Ann Card Anaesth. 2012;15:32-8.
24. Edwards ND, Fletcher A, Cole JR, Peacock JE. Combined infusions of morphine and ketamine for postoperative pain in elderly patients. Anaesthesia. 1993;48:124-7.
25. Menigaux C, Fletcher D, Dupont X, Guignard B, Guirimand F, Chauvin M. The benefits of intraoperative small-dose ketamine on postoperative pain after anterior cruciate ligament repair. Anesth Analg. 2000;90:129-35.
26. Lee EN, Lee JH. The Effects of Low-Dose Ketamine on Acute Pain in an Emergency Setting: A Systematic Reviewand Meta-Analysis. PLoS One. 2016;11:e0165461.
27. Ahern TL, Herring AA, Miller S, Frazee BW. Low-Dose Ketamine Infusion for Emergency Department Patients with Severe Pain. Pain Med. 2015;16:1402-9. [Epub 2015 Feb 3].
28. Goltser A, Soleyman-Zomalan E, Kresch F, Motov S. Short (low-dose) ketamine infusion for managing acute pain in the ED: case-report series. Am J Emerg Med. 2015;33:601.e5-7. [Epub 2014 Sep 26].
29. Ahmadi O, Isfahani MN, Feizi A. Comparing low-dose intravenous ketamine-midazolam with intravenous morphine with respect to pain control in patients with closed limb fracture. J Res Med Sci. 2014;19:502-8.
30. Pandit SK, Kothary SP, Kumar SM. Low dose intravenous infusion technique with ketamine. Amnesic, analgesic and sedative effects in human volunteers. Anaesthesia. 1980;35:669-75.

EURASIAN JOURNAL OF EMERGENCY MEDICINE
Original Article
DOI: 10.4274/eajem.galenos.2020.53315
Eurasian J Emerg Med. 2020;19(3): 172-7

Thirty-Day Mortality in Septic Shock Patients is Directly Associated with High Disease Severity Score but not with the Length of Stay in the Emergency Department

Gülseren Elay[1], Behçet Al[2]

[1]Department of Medical Intensive Care Unit, Gaziantep University, Gaziantep, Turkey
[2]Department of Emergency Medicine, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey

Abstract

Aim: To determine the factors associated with mortality in septic shock patients who are transferred from the emergency department (ED) to the intensive care unit (ICU).

Materials and Methods: We used the data of 206 patients who were admitted to the ED with infection and were diagnosed with septic shock between December 2016 and January 2020.

Results: The 206 patients had a mean Glasgow Coma score of 11.42 (range: 3-15), mean Acute Physiology and Chronic Health Evaluation (APACHE-II) score of 21.66 (range: 8-49) and mean Sequential Organ Failure Assessment Score (SOFA) of 10.24 (range: 2-22). There were no differences in 30-day mortality and in need for renal replacement therapy (RRT) or mechanical ventilation (MV) between patients transferred to the ICU within 1 hour of ED admission and those transferred to the ICU more than 6 hours after ED admission ($p>0.05$). Patients with an APACHE-II score ≥20 or a SOFA score ≥8 had longer MV duration and ICU and hospital stay, greater RRT and MV need and higher mortality rate than the patients with lower value ($p<0.05$).

Conclusion: Septic shock patients who have high disease severity scores have poor prognosis. The length of time between ED and ICU admission does not affect patient outcomes.

Keywords: Septic shock, emergency department, admission time, mortality

Introduction

Sepsis, an urgent condition, causes life-threatening organ dysfunction due to dysregulated host response to infection (1). According to the World Health Organization, approximately thirty million people suffer from sepsis each year globally, with approximately six million sepsis deaths (2). Despite adequate fluid resuscitation, vasopressor need to maintain a mean arterial pressure ≥65 mmHg, and a serum lactate level >2 mmol/L called septic shock which is a more serious stage of sepsis. Septic shock in-hospital mortality is in excess of 40% (1). The incidence, morbidity, and mortality of septic shock are much higher in developing countries, like Turkey. Most septic shock cases are diagnosed in emergency department (ED), and is inherently difficult to manage due to the advanced hemodynamic monitorization need. Early diagnosis and treatment are key to prevent mortality (3,4). Septic shock patients are normally transferred to an intensive care unit (ICU) after ED diagnosis. The first six hours after shock onset are regarded as the "golden hours" for intervention. We hypothesize that, septic shock patients who are treated in ICU during the first six "golden hours" will have better outcomes. The present study investigates factors contributing to the morbidity and mortality of septic shock patients.

Corresponding Author: Asst. Prof. Gülseren Elay, Department of Medical Intensive Care Unit, Gaziantep University, Gaziantep, Turkey
E-mail: gulserenelay56@gmail.com **ORCID:** orcid.org/0000-0003-2166-0545

Received: 05.04.2020
Accepted: 26.07.2020

Cite this article as: Elay G, Al B. Thirty-day Mortality in Septic Shock Patients is Directly Associated with High Disease Severity Score but not with the Length of Stay in the Emergency Department. Eurasian J Emerg Med. 2020;19(3):172-7.

Materials and Methods

In this retrospective study, participants were recruited from the ED of Gaziantep University Faculty of Medicine Hospital, who all presented between December 2016 and January 2020 and were diagnosed with septic shock based on the Sepsis-3 criteria. A total of 206 patients were included in this study (Figure 1).

In this ED approximately 250,000 patients are treated per year. Study data were retrieved from the hospital's electronic record system. Study participants were diagnosed with septic shock within one hour of admission at the ED, treated shortly after diagnosis, and had to be transferred to the ICU for further treatment; detailed inclusion criteria are described below. Septic shock was diagnosed in sepsis patients who met the following criteria (3): (i) mean arterial pressure be maintained at ≥65mmHg by vasopressor, despite adequate fluid resuscitation, and (ii) serum lactate level >2 mmol/L. The following data were recorded for all included study participants: demographics, disease severity scores, comorbidities, antibiotic administration, blood culture results, length of hospital stay, and 30-day mortality. Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II were calculated at ICU admission. The study was done in tertiary stage medical ICU. Informed consent for the study was taken from patients or their relatives by calling phone.

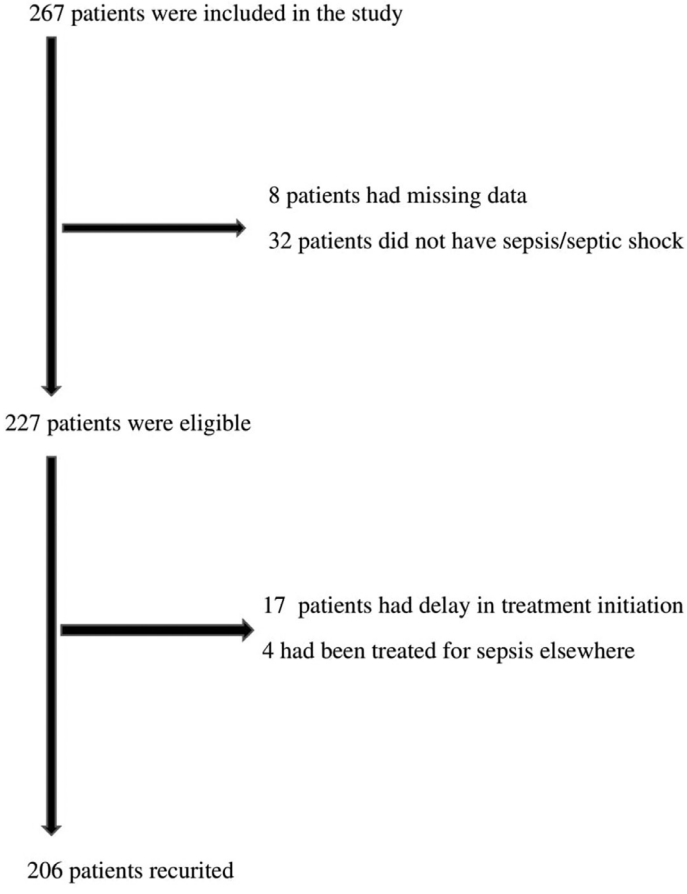

Figure 1. Description of patient enrolment

Inclusion Criteria

Patients were recruited as study participants if they met all the following inclusion criteria: (i) aged 18 years or more, (ii) presented to the study center ED due to infection, (iii) diagnosed with septic shock, according to Sepsis-3 criteria, within one hour of admission in ED, (iv) expected to survive for longer than 24 hours after septic shock diagnosis, (v) consented to receiving septic shock treatment, and (vi) received appropriate antibiotic treatment within one hour, (vii) moved to ICU. All study participants gave informed consent to be included in the study.

Exclusion Criteria

Patients were excluded from the study if they met one or more of the following criteria: (i) not diagnosed with septic shock according to Sepsis-3 criteria, (ii) had been treated for sepsis elsewhere prior to presenting at the study center for further treatment, (iii) contraindication for diagnostic tests, (iv) had suffered delay in treatment initiation, (v) fluid or antibiotic treatment contraindicated for any reason, moribund patients.

Statistical Analysis

Data were analyzed using frequency, percentage, and descriptive statistics using SPSS 22.0 software. Comparisons were made using a chi-square test for categorical variables and a Mann-Whitney U test for continuous variables. Values of $p<0.05$ were accepted as statistically significant.

Ethical Consideration

Ethical approval for this study was obtained from the Clinical Research and Ethical Committee of Gaziantep University (approval no: 2019/472, date: 25.12.2019).

Results

The study had a total of 206 participants, with the following demographics: (i) mean age 65.67 years (20-100), and (ii) 117 (56.8%) were male and 89 (43.2%) were female. Study participants had a mean duration of MV support of 3.22 days (0-42), and they had the following mean clinical scores: Glasgow coma score of 11.42 (3-15), APACHE-II score of 21.66 (8-49), and SOFA score of 10.24 (2-22). Study participants received antibiotic treatment for a mean of 9.01 days (1-45), and antifungal treatment for a mean of 2.76 days (0-46). Ninety-nine study participants (48.0%) had an APACHE-II score ≥20, 144 (69.9%) had a SOFA score ≥8, and

40 (19.42%) had a lactate level ≥4 mmol/L. Eighty-seven study participants (42.23%) were transferred to the ICU within one hour of admission to the ED, while 51 (24.76%) were transferred to the ICU more than six hours after presenting to the ED. MV was required by 109 (52.91%) study participants, and RRT by 27 (13.11%). The median interval between ED admission and ICU admission was two hours (1-5), the median ICU stay length was eight days (3-14.25), and the mean hospital stay length was nine days (1-50) (Table 1).

Table 1. Demographics and baseline characteristics

	Overall patients (n=206)
Age	65.67 (20-100)
Gender n (%)	
Male/female	117 (56.8)/89 (43.2)
Score	
GCS	11.42 (3-15)
APACHE- II	21.66 (8-49)
SOFA	10.24 (2-22)
Lactate ≥4 mmolL^{-1} at admission to ICU	40 (19.42)
APACHE -2≥20 at admission to ICU	99 (48.06)
SOFA ≥8 at admission to ICU	144 (69.90)
Comorbidities n (%)	
Chronic respiratory disease	32 (15.53)
Solid organ malignancy	44 (21.36)
Liver disease	14 (6.80)
Hematological malignancy	51 (24.75)
Immunosupression	49 (23.78)
Diabetus mellitus	26 (12.62)
Therapies, n (%)	
MV	109 (52.91)
Vasopressor	139 (67.48)
RRT	27 (13.11)
Admission to ICU within an hour	87 (42.23)
Admission to ICU after six hours or later	51 (24.76)
ED admission to ICU transfer time	2 (1-5)
Length of stay (days)	
MV	3.32 (0-42)
ICU	8 (3-14.25)
Hospital	9.67 (1-50)
Duration of antibiotic therapy (days)	9.01 (1-45)
Duration of antifungal therapy (days)	2.76 (0-46)
30-day mortality	133 (64.56)

GCS: Glascow coma score, APACHE-II: Acute Physiology and Chronic Health Evaluation II, SOFA: The Sequential Organ Failure Assessment, ED: Emergency department, ICU: Intensive care unit, RRT: Renal replacement therapy, MV: Mechanical ventilation, n: Number, Data are presented as median (minimum-maximum).

A total of 133 (64.56%) study participants died within 30 days of septic shock diagnosis. In our study, 70 (33.98%) of participants had lung infection, 53 (25.73%) had abdominal infection, 25 (12.14%) had central nervous system infection, and 18 (8.73%) had urinary tract infection (Table 2).

Participants who had APACHE-II score ≥20 or a SOFA score ≥8 had statistically significant higher 30-day mortality, greater RRT and MV need, and longer MV, ICU and hospital day compared to participants who had APACHE-II score <20 or a SOFA score <8 ($p<0.05$) (Table 3).

There were no statistically significant differences regarding 30-day mortality, RRT need, or MV need between participants who were transferred from ED to ICU within one hour of admission and those who were transferred after at least six hours of admission ($p>0.05$). Participants with lactate level ≥4 mmol/L had greater RRT and MV need ($p<0.05$) than those whose lactate level was <4 mmol/L (Table 4).

Table 2. Isolated microorganisms and therapies

Source of infection	**n (%)**
Lung	70 (33.98)
Abdomen	53 (25.73)
Urinary tract	18 (8.73)
Central nervous system	25 (12.14)
Soft tissue	7 (3.40)
Isolated microorganisms n (%)	
Culture-negative-infected patients	60 (29.13)
Aspergillus spp.	2 (0.97)
Candida spp.	24 (11.65)
Escherichia coli	41 (19.90)
Pseudomonas spp.	20 (9.71)
Acinetobacter spp.	48 (23.30)
Klebsiella pneumonia	32 (15.53)
Enterococcus spp.	40 (19.42)
Staphylococcus aureus	62 (30.10)
Streptococcus spp.	2 (0.97)
Antimicrobial used	
Quinolone	49 (23.79)
Macrolides	75 (36.41)
Cephalosporin	134 (65.05)
Meronem	130 (63.11)
Vanko	91 (44.17)
Teicoplanin	5 (2.42)
Colistin	27 (13.11)

spp: Species, n: Number

Table 3. Comparison of outcomes among admission time, disease severity scores and lactate level with MV duration, length of hospital stay, length of ICU stay

	MV (day)	Length of ICU stay (day)	Length of hospital stay (day)
ED to ICU admission time in 1 hour			
Yes	1 (1-4)	7 (3-12)	9 (3-17)
No	1 (1-2)	6 (3-12)	8 (4-13)
	p=0.215	p=0.716	p=0.807
ED-ICU admission time ≥6 hours			
Yes	1 (0-6)	7 (4-13)	9 (5-13)
No	1 (0-2)	7 (3-12)	8 (3-16)
	p=0.345	p=0.415	p=0.801
APACHE-II ≥20			
Yes	1 (1-6)	6 (2-12)	6 (2-12)
No	0 (0-1)	7 (4-13)	9 (5-18)
	p=0.000	p=0.036	p=0.001
SOFA ≥8			
Yes	1 (0-4)	6 (2.25-12)	7 (3-13.75)
No	0 (0-2)	9 (5-13.25)	9 (6-17.25)
	p=0.000	p=0.010	p=0.005
Lactate ≥4 mmolL^{-1}			
Yes	1 (0-3)	4.5 (2.25-10)	5 (3-11)
No	0 (0-2.25)	7 (3.75-13)	9 (4-16)
	p=0.127	p=0.070	p=0.064

ED: Emergency department, ICU: Intensive care unit, APACHE-II: Acute Physiology and Chronic Health Evaluation II, SOFA: The Sequential Organ Failure Assessment, MV: Mechanical ventilation unit, n: Number, Data are presented as median (minimum-maximum).

Table 4. Outcomes of early-late ICU admission time, high disease severity scores and lactate level

	30-day mortality n (%)	Vasopressor n (%)	RRT n (%)	MV n (%)
ED to ICU transfer within 1 hour				
Yes	55 (63.2)	60 (69.0)	11 (12.6)	49 (56.3)
No	32 (36.8)	27 (31.0)	76 (87.4)	38 (43.7)
	p=0.730	p=0.696	p=0.866	p=0.402
ED to ICU transfer ≥6 hours passed				
Yes	34 (66.7)	35 (68.6)	3 (5.9)	30 (58.8)
No	17 (33.3)	16 (31.4)	48 (94.1)	21 (41.2)
	p=0.717	p=0.840	p=0.078	p=0.330
APACHE-II ≥20				
Yes	73 (73.7)	73 (73.7)	18 (18.2)	77 (77.8)
No	26 (26.3)	26 (26.3)	81 (81.8)	22 (22.2)
	p=0.008	p=0.065	p=0.038	p=0.001
SOFA ≥8				
Yes	100 (69.4)	102 (70.8)	24 (16.7)	92 (63.9)
No	44 (30.6)	42 (29.2)	120 (83.3)	52 (36.1)
	p=0.026	p=0.117	p=0.021	p=0.001
Lactate ≥4				
Yes	24 (60.0)	28 (70.0)	10 (25)	28 (70)
No	16 (40.0)	12 (30.0)	30 (75)	12 (30)
	p=0.502	p=0.704	p=0.013	p=0.016

ED: Emergency department, ICU: Intensive care unit, APACHE-II: Acute Physiology and Chronic Health Evaluation II, SOFA: The Sequential Organ Failure Assessment, MV: Invasive mechanical ventilation, RRT: Renal replacement therapy, n: Number

Discussion

This study revealed no statistically significant differences in RRT or MV need, or 30-day mortality between study participants who were transferred from the ED to the ICU within one hour of ED admission and those transferred after more than six hours (p>0.05). The first six-hour time-points were chosen because the first six hours have been determined to be the most critical time-window for effective intervention (5). Intervention for septic shock should be fast, with rapid determination of source of infection. Angus (6) reported that the infection side is respiratory tract in half of cases, followed by intra-abdominal infection and urinary tract. Baykara et al. (7) conducted a study in 132 ICUs in Turkey and reported that respiratory tract was the most common (71.60%) side of infection in septic shock. Our study revealed a much lower incidence of respiratory tract infection (33.98%); we hypothesize difference is due to comorbidities and regional/local differences. Because the study by Baykara et al. (7), had been performed mostly on surgical ICU patients, but our study conducted in medical ICU. Our results indicate that participants with higher disease severity scores had poorer prognoses. Nearly half (48%) of the study participants had an APACHE-II score ≥20, while 69% had a SOFA score ≥8. It is important to note that only patients who had not been treated for sepsis anywhere except the study center were included in the study. Our study participants had a mean age of 66 years, and a significant number were already diagnosed with hematological or solid cancers. Septic shock symptoms are often obscure in elderly and immunosuppressed patients, so the disease can go undetected by patients and relatives. Patients with cancer, chronic liver disease, or diabetes, immunsuppression have a greater tendency to develop sepsis, and they have high mortality (6). Previous studies show that a high disease severity score is important and associated with greater mortality (8,9). A study of septic shock patients by Labelle et al. (8) found APACHE-II score to be a key determinant of mortality. In another large-scale retrospective study of 14,788 patients, higher in-hospital mortality was reported among patients who waited more than 2.4 hours for ICU admission; this association strengthened with higher APACHE-IV score (9). The time taken to be admitted to ICU following ED admission varies geographically and even between hospitals in

the same geographic region (10,11). To the best of our knowledge, there is no nationwide study reporting the average time interval between ED and ICU admission of septic shock patients in Turkey. Mahsanlar et al. (12) found the mean length of stay of general patients in EDs to be 6.5 hours. Erkuran et al. (13) conducted study with 2,380 general patients, found a mean length of stay in ED 1.23 hours (10 minutes - 10.02 hours). In our study, the median delay time was two hours (1-5 hours). Since this time was relatively short, we could not find any relationship between delay time and mortality.

Vilella and Seifert (14) reported higher in-hospital mortality; with higher APACHE-II score, also reported mortality being 2.5 times higher in patients whose lactate level was >2.5 mmol/L in sepsis patients. Lactate is a known indicator of tissue hypoperfusion that has developed as a result of circulatory collapse, and it has been reported that increased lactate levels negatively affect prognosis (1). Casserly et al. (15) revealed a linear relationship between lactate level and mortality, and that lactate levels ≥4 mmol/L are associated with significantly increased mortality. Since the current study defined sepsis using the current Sepsis-3 criteria, patients were only recruited to the study if their lactate level ≥2 mmol/L. Consistent with the literature, the current study found that participants whose lactate level ≥4 mmol/L had increased MV and RRT times. In the current study, the ICU mortality rate was 64.56%, while the largest current study of septic shock patients in Turkey reported an ICU mortality rate of 75.9%, based on the Sepsis-3 criteria (7). ICU mortality rates from studies of septic shock patients in other countries include 55.7% in Brazil and 64.6% in India (16,17). The mortality rate found in the current study is much lower than expected considering that all study participants were diagnosed with septic shock at ED admission, and that a significant percentage also had high disease severity scores and serious comorbidities. The results showed that delayed transfer to ICU was not related to mortality; this may be due to prompt and proper medical intervention in the ED. Non-intensivists play a very important role in the timely and appropriate management of sepsis patients, with the pre-hospitalization phase being critical (18,19). Pre-hospital healthcare providers treat more cases of sepsis than of acute myocardial infarction or stroke (20). Studies have shown that pre-hospital care play a key role in the early diagnosis and treatment of sepsis (21). Both the USA and Canada have implemented a pre-hospital diagnosis and treatment initiation protocol for sepsis patients (22); in particular, the USA has initiated the pre-hospital sepsis project and implemented web-based education for physicians (23). To our knowledge, there is no specific pre-hospital diagnosis or treatment initiation protocol for sepsis patients in Turkey. Intense patient and physician education would be effective for initiation of early sepsis interventions and would likely reduce sepsis patient mortality.

Study Limitations

The study took a retrospective, single-centered design, and it included a relatively low number of patients (206 participants) due to the strict study inclusion and exclusion criteria. Study participants had been diagnosed with septic shock according to Sepsis-3 criteria, and were transferred from the ED to the ICU. Furthermore, each participant was administered the most appropriate broad-spectrum antibiotic for their infection focus, with antibiotic selection revised according to tissue culture results. Information was unavailable regarding pre-hospital interventions prior to ED admission.

Conclusions

This study indicates ED patients diagnosed with septic shock; with high APACHE-II score, high SOFA score, and elevated lactate levels have a poor prognosis. However, prognosis is independent from ED to ICU transfer time. We believe that, septic shock patients will have improved outcomes if they present to the ED before developing septic shock, and since signs of sepsis may be obscure in elderly and immunosuppressed patients, patient education is needed to increase awareness of sepsis.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Clinical Research and Ethical Committee of Gaziantep University (approval no: 2019/472, date: 25.12.2019).

Informed Consent: Informed consent for the study was taken from patients or their relatives by calling phone.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.E., Concept: G.E., B.A., Design: G.E., B.A., Data Collection or Processing: G.E., B.A., Analysis or Interpretation: G.E., B.A., Literature Search: G.E., Writing: G.E.

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

Financial Disclosure: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Singer M, Deutschman CS, Seymour C, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) JAMA - J Am Med Assoc. 2016;315:801-10.

2. Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S. Recognizing sepsis as a global health priority — A WHO Resolution. N Engl J Med. 2017;377:414-7.
3. Tupchong K, Koyfman A, Foran M. Sepsis, severe sepsis, and septic shock: A review of the literature. African J Emerg Med. 2015;2:127-35.
4. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Crit Care Med. 2017;45:486-552.
5. Mathieu Jozwiak, Xavier Monnet1, Jean-Louis Teboul. Implementing sepsis bundles. Ann Transl Med. 2016;4:332.
6. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med. 2013;369:840-51.
7. Baykara N, Akalin H, Arslantaş MK, Hanci V, Çağlayan Ç, Kahveci F, et al. Epidemiology of sepsis in intensive care units in Turkey: a multicenter, point-prevalence study. Crit Care. 2018;22:93.
8. Labelle A, Juang P, Reichley R, Micek S, Hoffmann J, Hoban A, et al. The determinants of hospital mortality among patients with septic shock receiving appropriate initial antibiotic treatment. Crit Care Med. 2012;40:2016-21.
9. Groenland CNL, Termorshuizen F, Rietdijk WJR, van den Brule J, Dongelmans DA, de Jonge E, et al. Emergency Department to ICU Time Is Associated with Hospital Mortality: A Registry Analysis of 14,788 Patients From Six University Hospitals in The Netherlands. Crit Care Med. 2019;47:1564-71.
10. Carter AW, Pilcher D, Bailey M, Cameron P, Duke GJ, Cooper J. Is ED length of stay before ICU admission related to patient mortality? Emerg Med Australas. 2010;22:145-50.
11. Thijssen WAMH, Kraaijvanger N, Barten DG, Boerma MLM, Giesen P, Wensing M. Impact of a well-developed primary care system on the length of stay in emergency departments in the Netherlands: a multicenter study. BMC Health Serv Res. 2016;16:149.
12. Mahsanlar Y, Parlak I, Yolcu S, Akay S, Demirtas Y, Eryigit V. Factors Affecting the Length of Stay of Patients in Emergency Department Observation Units at Teaching and Research Hospitals in Turkey. Turk J Emerg Med. 2016;14:3-8.
13. Erkuran MK, Duran A, Ocak T, Citisli V, Kaya H. The impact of the duration of admission to the emergency room on the mortality of intensive care patients. Niger J Clin Pract. 2014;17:320-3.
14. Vilella AL, Seifert CF. Timing and appropriateness of initial antibiotic therapy in newly presenting septic patients. Am J Emerg Med. 2014;32:7-13. [Epub 2013 Oct 17].
15. Casserly B, Phillips GS, Schorr C, Dellinger RP, Townsend SR, Osborn TM, et al. Lactate measurements in sepsis-induced tissue hypoperfusion: results from the Surviving Sepsis Campaign database. Crit Care Med. 2015;43:567-73.
16. Machado F, Cavalcanti A, Bozza F, Angus D, Ferreira E, Carrara F, et al. Epidemiology of sepsis in brazilian icus: a nationwide stratified sample. Intensive Care Medicine Experimental 2015;3:A642.
17. Todi S, Chatterjee S, Bhattacharyya M. Epidemiology of severe sepsis in India. Crit Care 2007. DOI: doi.org/10.1186/cc5225
18. Daniels R. Surviving the first hours in sepsis: Getting the basics right (an intensivist's perspective). J Antimicrob Chemother. 2011;66:11-23.
19. Seymour CW, Rea TD, Kahn JM, Walkey AJ, Yealy DM, Angus DC. Severe sepsis in pre-hospital emergency care: analysis of incidence, care, and outcome. Am J Respir Crit Care Med. 2012;186:1264-71. [Epub 2012 Oct 18].
20. Wang HE, Weaver MD, Shapiro NI, Yealy DM. Opportunities for emergency medical services care of sepsis. Resuscitation. 2010;81:193-7.
21. Nguyen HB, Rivers EP, Abrahamian FM, Moran GJ, Abraham E, Trzeciak S, et al. Severe sepsis and septic shock: review of the literature and emergency department guidelines. Ann Emerg Med. 2006;48:28-54.
22. Sibley AK, Sibley DS. Total infection. Recognizing & treating sepsis in the field. JEMS. 2007;32:64-6.
23. Baez AA, Hanudel P, Wilcox SR. The prehospital sepsis project: Out-of-hospital physiologic predictors of sepsis outcomes. Prehosp Disaster Med. 2013;28:632-5.

EURASIAN JOURNAL OF EMERGENCY MEDICINE
Original Article
DOI: 10.4274/eajem.galenos.2019.52385
Eurasian J Emerg Med. 2020;19(3): 178-83

Diagnostic Value of C-Reactive Protein/Albumin Ratio to Differentiate Simple Versus Complicated Appendicitis

Serkan Doğan[1], Melis Dorter[1], Utku Murat Kalafat[1], Büşra Bildik[1], Ramiz Yazıcı[1], İnanç Şamil Sarıcı[2], Başar Cander[1]

[1]Clinic of Emergency Medicine, Kanuni Sultan Süleyman Training and Research Hospital, University of Health Sciences Turkey, İstanbul, Turkey
[2]Clinic of General Surgery, Kanuni Sultan Süleyman Training and Research Hospital, University of Health Sciences Turkey, İstanbul, Turkey

Abstract

Aim: The C-reactive protein (CRP)/albumin ratio is a new inflammation-based prognostic score that correlates with inflammation severity.

Objective: The present study investigated the diagnostic value of the CRP/albumin ratio to distinguish between patients with simple and complicated acute appendicitis. This retrospective study was conducted at the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, Department of Emergency Medicine, after approval from the ethics committee.

Materials and Methods: A total of 188 patients with acute appendicitis were included. Biochemical parameters, CRP/albumin ratio, ultrasonography (USG) and computed tomography (CT) results, operation findings and length of hospital-stay were compared between patients with simple and complicated appendicitis.

Results: There was no statistically significant difference in terms of leukocyte count, albumin value and diameter of the appendicitis between both USG and CT. The CRP/albumin ratio could specifically differentiate the complicated appendicitis group. The cut-off point of the CRP/albumin ratio for the diagnosis of complicated appendicitis was 4.4.

Conclusion: The CRP/albumin ratio may be used as a valuable biomarker in the clinical diagnostic process and in treatment planning, particularly to differentiate patients with acute complicated appendicitis from those with non-complicated acute appendicitis.

Keywords: Appendicitis, C-reactive protein, albumin, CRP/albumin ratio, complicated appendicitis

Introduction

Acute appendicitis is a common surgical problem and its lifetime prevalence is around 7% (1). The basis of treatment in acute appendicitis is based on early diagnosis and emergency surgery. A delay in treatment may cause perforation in the appendix, which may lead to an increase in morbidity and mortality (2). In current clinical practice; physical examination, ultrasonography (USG) and computed tomography (CT) widely used in the diagnoses of acute appendicitis. However, diagnostic failure is often difficult even for experienced surgeons and the rate of negative laparotomy can be up to 30%. Therefore, in the preoperative diagnosis of acute appendicitis, recently, a number of laboratory parameters for inexpensive, effective and rapid diagnosis have been shown to help in the correct diagnosis (2,3).

It is also important to determine whether appendicitis is non-complicated or complicated by the importance of acute appendicitis diagnosis. Because of the fact that acute appendicitis may be complicated in cases where the diagnosis is delayed, the patient's surgical intervention is difficult and even the rate of post-operative complications increases. Therefore, these patients have high rates of readmission, reintervention, postoperative hospital stay, and postoperative complications (4).

C-reactive protein (CRP) are widely used serum inflammatory markers (5). CRP as a positive acute phase reactant is frequently

Corresponding Author: Asst Büşra Bildik, MD, Clinic of Emergency Medicine, Kanuni Sultan Süleyman Training and Research Hospital, University of Health Sciences Turkey, İstanbul, Turkey
Phone: +90 212 404 15 00 **E-mail:** drbusrabeyoglu@gmail.com **ORCID:** orcid.org/0000-0002-1546-4612

Received: 19.09.2019
Accepted: 29.12.2019

Cite this article as: Doğan S, Dorter M, Kalafat UM, Bildik B, Yazıcı R, Sarıcı İŞ, Cander B. Diagnostic Value of C-Reactive Protein/Albumin Ratio to Differentiate Simple versus Complicated Appendicitis. Eurasian J Emerg Med. 2020;19(3):178-83

used in the diagnosis and follow-up of inflammatory diseases, as well as in the follow-up of postoperative complications and even in the estimation of morbidity and mortality in intensive care setting (6). However, because of its short half-life, CRP alone may not show that acute appendicitis is complicated or non-complicated.

Serum albumin level is a reliable predictor that is widely recommended in critically ill patients with various diseases that can be measured in the laboratory. As albumin is a negative acute phase protein, it is frequently used in the follow-up of patients with frail, malignancy and malnutrition (7). Although there is a relationship between inflammation and albumin value, there is no use of albumin in the diagnosis of acute appendicitis in routine practice.

The CRP/Albumin ratio is a new inflammation-based prognostic score and it is correlated to the inflammation severity and mortality (8). CRP/albumin ratio has recently been shown to be effective in early diagnosis and treatment of acute cholecystitis, acute pancreatitis, cancer diagnosis, polycystic ovary syndrome and critical care patients. However, there is no study on CRP/albumin ratio in the diagnosis of acute appendicitis. The present study investigated the diagnostic value of the CRP/Albumin ratio for acute appendicitis patients with evaluation of simple or complicated.

Materials and Methods

Study Design and Settings

This study was performed in University of Health Sciences Turkey, University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital, Department of Emergency Medicine, it was taken retrospectively with the approval of the ethics committee (no: KAEK/2018.1.21).

Participants

The data of patients diagnosed with acute appendicitis aged 18 years and older who applied to the study between January 2017-2018 were obtained by scanning the "Hospital Information Management System" and patient files with the approval of the ethics committee.

Data Collected

Age, gender, complaints, history, hemogram and biochemistry parameters, CRP/Albumin ratio, USG and CT results, operation findings, length of stay, the onset of the complaint and the operation was taken from the data that was filled by the physician who performed the operation on the date, time to the emergency room and recorded in the case data form. The result of histopathology was recorded according to the results of the pathology expert who examined the operation material.

Statistical Analysis

In the histopathology reports, the results of perforation, abscess, necrosis, gangrene appendicitis were evaluated as complicated appendicitis. Histopathological findings compatible with edematous, inflamed were evaluated as noncomplicated (simple) appendicitis. Patients with hematological, infectious, liver disease and pathology reports indicating a normal appendix or a malignancy were excluded from the study.

All patient data were recorded in the case data form and analyzed in SPSS for Windows 22.0 program. The fit of the parameters to normal distribution was evaluated by Shapiro-Wilks test. Beside of descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum), the Student's t-test was used to compare two groups of variables that showed normal distribution in the comparison of quantitative data. Kruskal-Wallis test and Mann-Whitney U test with Bonferroni correction were used in the comparison of groups with three or more groups not showing normal distribution. Diagnostic scanning tests (sensitivity, specificity, positive predictive value, negative predictive value) and "Receiver Operator Characteristic" (ROC) curve analysis were used for cut-off determination for parameters. Statistically, 95% confidence interval, $p<0.05$ was considered significant.

Results

Total of 188 cases, 135 (71.8%) patients were male and 53 (28.2%) patients were female. The mean age of the patients was 33.73±12 years, and the median age was 30.5 years. While 166 (88.3%) cases were non-complicated (simple) appendicitis, 22 (11.7%) patients were complicated appendicitis. The demographic characteristics of the cases are shown in Table 1.

When we compared the complicated and non-complicated appendicitis groups, there was no statistically significant difference in terms of leukocyte count, albumin value and diameter of the appendicitis in both USG and CT. The time between the onset of the complaint to the operation was found significantly higher in the complicated appendicitis group compared to the non-complicated appendicitis group ($p=0.006$). The median level of CRP is 12.7 (33.75±50.83) in non-complicated group while 52.2 (90.79±89.2) in complicated group ($p=0.000$). Additionally, the median level of CRP/albumin ratio is 2.8 (7.69±12.05) in non-complicated group while 10.8 (19.94±20.05) in complicated group ($p=0.000$) (Table 2).

The ROC curve was drawn for leukocyte and albumin in the diagnosis of complicated appendicitis (Figure 1). Respectively, the area under the curve (AUC) is 0.576, 0.519; the standard error (SE) is 0.07 for both. The area under the ROC curve for both of

Table 1. Demographic characteristics of patients		
	Minimum-maximum (median)	**Mean ± SD**
Age	18-73 (30.5)	33.73±12
Fever	36-37.5 (36.5)	36.41±0.41
CRP	0.1-318.1 (15.6)	40.42±59.26
Albumin	3.5-44 (4.6)	4.82±2.89
CRP/Albumin ratio	0-75.2 (3.4)	9.12±13.75
Leukocyte	3,670-26,140 (15,060)	14,724.57±40,65.2
Diameter of appendix (USG) (mm)	6.4-32 (9)	9.68±2.83
Diameter of appendix (CT) (mm)	6-35 (11)	11.23±3.1
Time between application and operation (hour)	6-40 (13)	14.73±6.34
	n	%
Gender		
Female	53	28.2
Male	135	71.8
Pathology		
Non-complicated	166	88.3
Complicated	22	11.7

CRP: C-reactive protein, USG: Ultrasonography, CT: Computed tomography, SD: Standard deviation, n: Number

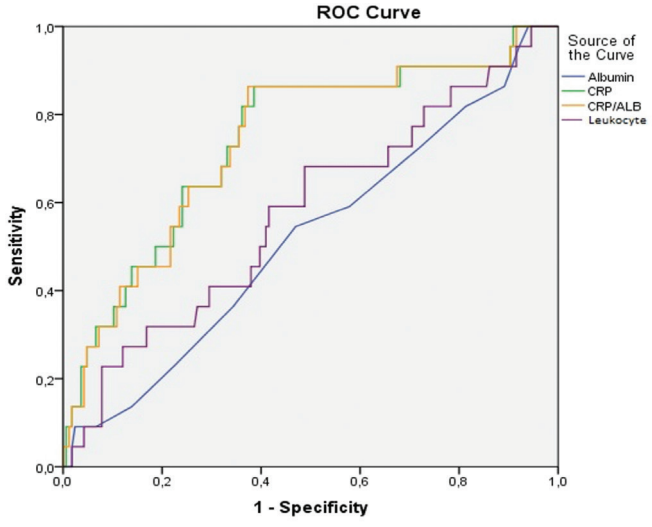

Figure 1. ROC curve to determine the efficacy of albumin, CRP, CRP/albumin ratio, leucocyte levels in the diagnosis of complicated appendicitis

ROC: Receiver operating characteristic, CRP: C-reactive protein, ALB: Albumin

leukocyte and albumin was not significantly higher than 0.5 (p=0.262, p=0.779 respectively; p>0.05). The cut-off point for leukocyte and albumin in the diagnosis of complicated was not able to established (Table 3).

The ROC curve was drawn for the CRP/Albumin ratio in the diagnosis of complicated appendicitis. The AUC is 0.737, the SE is 0.06. The area under the ROC curve was significantly higher than 0.5 (p=0.001). The cut-off point for the CRP/Albumin ratio in the diagnosis of complicated appendicitis is >4.4. The sensitivity of this value was 86.36%, the specificity was 62.65%, the positive predictive value was 23.46% and the negative predictive value was 97.2% (Figure 1, Table 3).

The ROC curve was drawn for CRP in the diagnosis of complicated appendicitis. The AUC is 0.74, the SE is 0.06. The area under the ROC curve was found to be significantly higher than 0.5 (p=0.001). The cut-off point for CRP in the diagnosis of complicated appendicitis was >19.5. The sensitivity of this value was 86.36%, specificity 61.45%, positive predictive value 22.89%, negative predictive value 97.14% (Figure 1, Table 3).

ROC curves were drawn and the areas under the curve were compared in order to determine which parameter as albumin, CRP, CRP/Albumin ratio and Leucocyte were more effective in the diagnosis of complicated appendicitis. The AUC of the albumin (AUC=0.519) was found to be significantly lower than that of CRP (AUC=0.740) and CRP/Albumin ratio (AUC=0.737) (p_1=0.039; p_2=0.043; p<0.05). There was no statistically significant difference between albumin and leukocyte areas under the curve (p=0.484; p>0.05). There was no statistically significant difference between CRP and CRP/Albumin ratio areas under the curve (p=0.339; p>0.05). Although the AUC of the leukocyte (AUC=0.576) was lower than that of CRP (AUC=0.740) and CRP/Albumin ratio (AUC=0.737), this difference was close to significance but not statistically significant (p_1=0.073; p_2=0.080; p<0.05) (Figure 1, Table 3). The level of 4.4 for CRP/Albumin ratio is 10.624 times higher for non-complicated appendicitis [Odds ratio: 10.624 (95% confidence interval: 3.021-37.363)].

Discussion

Acute appendicitis is one of the most common causes of the acute abdomen and one of the most frequent indications for an emergent abdominal surgical procedure worldwide (1). Appendicitis occurs most frequently in the second and third decades of life. The annual incidence is approximately 9.38 per 100,000 population in the United States of America (9). The incidence of negative appendectomy in patients undergoing appendectomy is 13-36%. The possibility of detecting complicated appendicitis during surgery varies between 12-21%.

Clinic of acute appendicitis typically presenting with pain localized to periumbilical region to right lower quadrant. However, the symptoms of the appendicitis vary depending on differences localizations of appendicitis. Although the appendix

Table 2. Evaluation of non-complicated and complicated groups

	Non-complicated (n=166)	Complicated (n=22)	p
	Mean ± SD (median)	Mean ± SD (median)	
Leukocyte*	14,581.69±4,030.61	15,802.73±4,258.36	[1]0.186
CRP	33.75±50.83 (12.7)	90.79±89.2 (52.2)	[2]0.000**
Albumin	4.84±3.07 (4.6)	4.65±0.31 (4.7)	[2]0.774
CRP/Albumin ratio	7.69±12.05 (2.8)	19.94±20.05 (10.8)	[2]0.000**
Diameter of appendix (USG) (mm)	9.46±1.91 (9)	12.11±7.34 (10)	[2]0.281
Diameter of appendix (CT) (mm)	10.98±2.38 (11)	13.06±6.03 (11)	[2]0.193
Time between onset of complaint and operation (hour)	14.17±5.88 (13)	18.95±8.07 (20)	[2]0.006**

CRP: C-reactive protein, USG: Ultrasonography, CT: Computed tomography, SD: Standard deviation, n: Number
[1]Student's t-test, [2]Mann-Whitney U test, *No median value since the leukocyte values showed normal distribution, **p<0.05

Table 3. Cut-off point determination for CRP/Albumin ratio and CRP

						ROC curve		p
	Cut-off	Sensitivity	Specifity	Positive predictive value	Negative predictive value	Area (SE)	95% CI	
CRP/Albumin ratio	>4.4	86.36	62.65	23.46	97.20	0.737 (0.06)	0.668-0.799	0.001*
CRP	>19.5	86.36	61.45	22.89	97.14	0.740 (0.06)	0.671-0.801	0.001*
Leukocyte	-	-	-	-	-	0.576 (0.07)	0.502-0.648	0.262
Albumin	-	-	-	-	-	0.519 (0.07)	0.445-0.592	0.779

CRP: C-reactive protein, ROC: Receiver operating characteristic, SE: Standard error, CI: Confidence interval
*p<0.05

has a retrocecum at a rate of 65-70%, it may also have different localizations, such as subcecum, paracolic and paraileal (10). Because of these differences and change in the acute appendicitis clinic from patient to patient, some findings and scoring methods have been described. McBurney's (11) point tenderness is described as maximal tenderness at 3-5 cm from the anterior superior iliac spine on a straight line to the umbilicus with a 72% sensitivity and 80% specificity. Additionally, Rovsing's sign refers to pain in the right lower quadrant with palpation of the left lower quadrant. This sign is also called indirect tenderness and is indicative of right-sided local peritoneal irritation with a 45% sensitivity an 77% specificity (12). The most popular of the scoring systems and the most commonly used is the modified Alvarado scale. A low Alvarado score (<4) has more diagnostic utility to "rule out" appendicitis than a high score (≥7) does to "rule in" the diagnosis. Unfortunately, a high score (≥7) alone had poor diagnostic utility, as the overall specificity was 81% (13).

Imaging is used mainly to increase the specificity of the diagnostic evaluation for appendicitis and to decrease the negative appendectomy rate. CT demonstrates higher diagnostic accuracy than ultrasound or MRI. An enlarged fluid-filled appendix (>7 mm in diameter) is considered an abnormal finding, while an appendix with a diameter of 6 to 7 mm is considered an inconclusive finding. However, CT is contraindicated in patients with pregnancy, renal insufficiency and hypersensitivity reaction to iodinate contrast (14). On the other hand, tomography and ultrasound are not found in many centers especially in rural areas and night shift conditions. This led the clinician to detect inflammation caused by acute appendicitis by different laboratory parameters.

There are many studies in the literature about laboratory values for the diagnosis of acute appendicitis. It has been emphasized that many parameters such as neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, mean platelet volume, red cell distribution width, D-lactate level, procalcitonin and many interleukins are important in the diagnosis of acute appendicitis (15,16). Another issue as important as the diagnosis of appendicitis is whether appendicitis is complicated or not. As is known, the morbidity and mortality of complicated appendicitis is higher than non-complicated appendicitis. Eddama et al. (17) found CRP values significant in the diagnostic distinctions of non-complicated and complicated appendicitis. Additionally, in previously studies red cell distribution width and eosinopenia accompanied by higher neutrophil and leukocyte counts were defined as useful biomarkers in perforated appendicitis (18,19). Pham et al. (20) found high leukocyte counts in necrosis or perforated appendicitis. In the study performed by Kim et al. (8), CRP and INR levels were estimated in the diagnosis of complicated appendicitis and it

was found to be significantly higher in patients with complicated appendicitis. In the study of Shelton et al. (21), it was seen that the rate of postoperative complications increased in patients with high preoperative CRP levels. In our study, complicated and non-complicated appendicitis groups have no differences in terms of leukocyte count, albumin value and diameter of the appendicitis in both USG and CT. The time between the onset of the complaint to the operation was found significantly higher in the complicated appendicitis group compared to the non-complicated appendicitis group.

CRP is a positive acute phase protein and increases in inflammation; since serum albumin is a negative acute phase protein (7). Therefore, it was thought that CRP/Albumin ratio would show inflammation more specific than CRP alone. In the case of an inflammation, the increase in CRP/Albumin ratio in patients is an expected result in the normal course of the disease. Therefore, CRP/albumin ratio has recently been shown to be effective in early diagnosis and treatment of acute cholecystitis, acute pancreatitis, cancer diagnosis, polycystic ovary syndrome and critical care patients. However, there is no study showing the relationship between this value and acute appendicitis. In our study, we examined the correlation between histopathologically diagnosed acute appendicitis and CRP/albumin ratios in patients with complicated and non-complicated appendicitis. According to our results, the median level of CRP is significantly higher in complicated group. The cut-off point for CRP in the diagnosis of complicated appendicitis was >19.5. Additionally, the median level of CRP/albumin ratio is 2.8 (7.69±12.05) in non-complicated group while 10.8 (19.94±20.05) in complicated group (p=0.000). We also found cut-off point for the CRP/albumin ratio in the diagnosis of complicated appendicitis is >4.4. The level of 4.4 for CRP/albumin ratio is 10.624 times higher for non-complicated appendicitis.

Conclusions

Cut-off values of laboratory tests in acute appendicitis cases can help diagnosis and treatment planning. We think that increased CRP/albumin ratio may be used as a valuable biomarker in clinical diagnostic process and treatment planning, especially to differentiate complicated or non-complicated setting.

Ethics

Ethics Committee Approval: This study was performed in University of Health Sciences Turkey, University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital, Department of Emergency Medicine, it was taken retrospectively with the approval of the ethics committee (no: KAEK/2018.1.21).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.Ş.S., Concept: S.D., M.D., U.M.K., İ.Ş.S., B.C., Design: S.D., U.M.K., İ.Ş.S., B.C., Data Collection or Processing: M.D., R.Y., Analysis or Interpretation: S.D., M.D., B.B., R.Y., Literature Search: M.D., U.M.K., B.B., Writing: S.D., B.B., R.Y., B.C.

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

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

References

1. Shogilev DJ, Duus N, Odom SR, Shapiro NI. Diagnosing appendicitis: evidence-based review of the diagnostic approach in 2014. West J Emerg Med. 2014;15:859-71.
2. Keskek M, Tez M, Yoldas O, Acar A, Akgul O, Gocmen E, et al. Receiver operating characteristic analysis of leukocyte counts in operations for suspected appendicitis. Am J Emerg Med. 2008;26:769-72.
3. Guler K, Tihan DN, Duman U, Dandin Ö, Dilektaşlı E, Erol F, et al. Are Preoperative serum C-reactive Protein and Leucocyte Values Useful to Predict the Perforation in Patients with Acute Appendicitis? Turk J Colorectal Dis. 2016;26:6-12.
4. Nimmagadda N, Matsushima K, Piccinini A, Park C, Strumwasser A, Lam L, et al. Complicated appendicitis: Immediate operation or trial of nonoperative management? Am J Surg. 2019;217:713-7.
5. Devran O, Karakurt Z, Adıguzel N, Güngör G, Yazıcıoğlu Moçin O, Kalamanoğlu Balcı M, et al. C-reactive protein as a predictor of mortality in patients affected with severe sepsis in intensive care unit. Multidiscip Respir Med. 2012;7:47.
6. Soltani F, Pipelzadeh MR, Akhondzadeh R, Rashidi M, Ekrami A. Evaluation of C-reactive Protein, Albumin and the C-reactive Protein/Albumin Ratio as Prognostic Markers in Trauma Patients Admitted to Intensive Care Unit. BJMMR. 2016;12:1-7.
7. Roberts I, Blackhall K, Alderson P, Bunn F, Schierhoutet G. Human albumin solution for resuscitation and volume expansion in critically ill patients. Cochrane Database Syst Rev. 2011;10:CD001208.
8. Kim M, Kim SJ, Cho HJ. International normalized ratio and serum C-reactive protein are feasible markers to predict complicated appendicitis. World J Emerg Surg. 2016;11:31.
9. D'Souza N, Nugent K. Appendicitis. Am Fam Physician. 2016;93:142-3.
10. Jaffe BM, Berger DH. The appendix. In: Schwartz's Principles of Surgery, 8th ed, Schwartz SI, Brunicardi CF editors, McGraw-Hill Companies, New York; 2005.
11. McBurney C. Experience with early operative interference in cases of disease of the vermiform appendix. NY Med J. 1889;50:676.
12. Jahn H, Mathiesen FK, Neckelmann K, Hovendal CP, Bellstrøm T, Gottrup F. Comparison of clinical judgment and diagnostic ultrasonography in the diagnosis of acute appendicitis: experience with a score-aided diagnosis. Eur J Surg. 1997;163:433-43.
13. Ohle R, O'Reilly F, O'Brien KK, Fahey T, Dimitrov BD. The Alvarado score for predicting acute appendicitis: a systematic review. BMC Med. 2011;9:139.
14. Yun SJ, Ryu CW, Choi NY, Kim HC, Oh JY, Yang DM. Comparison of Low- and Standard-Dose CT for the Diagnosis of Acute Appendicitis: A Meta Analysis. AJR Am J Roentgenol. 2017;208:W198-207.

15. Al-Abed YA, Alobaid N, Myint F. Diagnostic markers in acute appendicitis. Am J Surg. 2015;209:1043-7.
16. Aydin OU, Soylu L, Dandin O, Uysal Aydin E, Karademir S. Laboratory in complicated appendicitis prediction and predictive value of monitoring. Bratisl Lek Listy. 2016;117:697-701.
17. Eddama M, Fragkos KC, Renshaw S, Aldridge M, Bough G, Bonthala L, et al. Logistic regression model to predict acute uncomplicated and complicated appendicitis. Ann R Coll Surg Engl. 2019;5:107-18.
18. Ertekin B, Kara H, Erdemir E, Doğan E, Acar T, Demir LS. Efficacy of Use of Red Cell Distribution Width as a Diagnostic Marker in Acute Appendicitis. Eurasian J Emerg Med. 2017;16:29-33.
19. Akay S, Akay H, Vardar E, Erkul Z. Comparison of Eosinophil Values with Other Biomarkers in Predicting Perforation of Acute Appendicitis. Eurasian J Emerg Med. 2017;16:8-11.
20. Pham XD, Sullins VF, Kim DY, Range B, Kaji AH, de Virgillo CM, et al. Factors predictive of complicated appendicitis in children. J Surg Res. 2016;206:62-6.
21. Shelton JA, Brown JJ, Young JA. Preoperative C-reactive protein predicts the severity and likelihood of complications following appendicectomy. Ann R Coll Surg Engl. 2014;96:369-72.

EURASIAN JOURNAL OF EMERGENCY MEDICINE
Letter to the Editor
DOI: 10.4274/eajem.galenos.2020.68095
Eurasian J Emerg Med. 2020;19(3): 184-5

Resuscitation of Patient with Suspected/Confirmed COVID-19: How to Increase Medical Staff Safety

Semih Korkut[1], Togay Evrin[2], Burak Katipoğlu[2], Jacek Smereka[3], Anna Drozd[4], Lukasz Szarpak[5]

[1]Department of Emergency Medicine, Kartal Dr. Lütfi Kırdar Training and Research Hospital, University of Health Sciences Turkey, İstanbul, Turkey
[2]Clinic of Emergency Medicine, Dr. Rıdvan Ege Training and Research Hospital, Ufuk University Faculty of Medicine, Ankara, Turkey
[3]Department of Emergency Medical Service, Wroclaw Medical University, Wroclaw, Poland
[4]Polish Society of Disaster Medicine, Warsaw, Poland
[5]Bialystok Oncology Center, Bialystok, Poland

Dear Editor,

Cardiopulmonary resuscitation (CPR) is a substantial burden for medical personnel, particularly during the 2019 Novel Coronavirus (COVID-19) pandemic. Although the precise transmission mechanisms of the new coronavirus are presently unclear, human-to-human transmission can occur, and the risk of airborne spread during aerosol-generating medical procedures remains a concern in certain circumstances (1).

Medical personnel, including physicians, nurses, and paramedics, as provided by the Center for Disease Control and Prevention, should be in full personal protective equipment (PPE) during aerosol-generating procedures (2,3). CPR exemplifies an aerosol-generating procedure. Notably, as the mortality rate in COVID-19 is 7% because of the occurrence of viral pneumonia and progressive hypoxia occurring in COVID-19, it can be concluded that resuscitation is a frequent and essential lifesaving procedure. In the resuscitation room, patients in the most severe condition are treated; hence a variety of emergency medical equipment is available. Medical personnel of the resuscitation room is emergency physicians, nurses, and paramedics experienced in treating critically severe patients.

Due to the risk of infectious aerosol, a key component of resuscitation should be endotracheal intubation and assisted breathing through a respirator; this fully supports the respiratory system, simultaneously reducing the risk of contamination. Difficulties consequential to wearing a face mask, goggles, protective visor, and double gloves appoint video-laryngoscopy as the preferred method of intubation in comparison to direct laryngoscopy. Non-invasive ventilation for the treatment of COVID-19 patients should be used as early as possible, and in some cases, it may ensure that endotracheal intubation is avoided; however, in the case of resuscitation, endotracheal intubation is the standard procedure.

The use of PPE can increase the discomfort of the rescuer; besides, it hinders the performance of medical procedures, including getting intravascular access. As indicated by research, therefore, the intramedullary injection should be recommended (4), which concerning drug pharmacokinetics and pharmacodynamics, is in no way inferior to peripheral vascular access. Some patients under emergency procedures require rapid sequence intubation with intravenous anesthetics, opioids, and muscle relaxants. The need for endotracheal intubation by the most experienced medical personnel and the use of videolaryngoscopy should be noted, as in severe initial hypoxia, increased hypoxia due to prolonged endotracheal intubation or insertion of the tube into the esophagus may have fatal consequences.

Another important element of resuscitation is high-quality chest compressions. During CPR, however, performing chest compression may cause the rescuer's face protection devices to adhere to exposing the rescuer to viral infection (5) poorly. To prevent such a situation, it is reasonable to use automated chest compression devices (ACCDs) during the resuscitation of COVID-19 patients. Though the European Resuscitation Council guidelines do not recommend routine ACCDs, it should be noted

Corresponding Author: Assoc. Prof. Lukasz Szarpak, Department of Emergency Medicine, Lazarski University, Warsaw, Poland
Phone: +48 50 018 62 25 **E-mail:** lukasz.szarpak@gmail.com **ORCID:** orcid.org/0000-0002-0973-5455

Received: 24.04.2020
Accepted: 15.05.2020

Cite this article as: Korkut S, Togay E, Katipoğlu B, Smereka J, Drozd A, Szarpak L. Resuscitation of Patient with Suspected/Confirmed COVID-19: How to Increase Medical Staff Safety. Eurasian J Emerg Med. 2020;19(3):184-5

that the current extraordinary situation COVID-19 narrates the use of extraordinary solutions such as ACCDs. Application ACCDs beyond chest compressions allows for transport of patients to the hospital while carrying out chest compression with minimal risk of infection to the rescuer.

In summary, it is imperative to exercise extreme caution in aerosol-generating procedures during the COVID-19 pandemic. Furthermore, to reduce the risk of infection of medical personnel, resuscitation should include endotracheal intubation, intramedullary punctures, and ACCDs.

Keywords: Cardiopulmonary resuscitation, COVID-19, SARS-CoV-2, endotracheal intubation, intraosseous access, chest compression, personal protective equipment, safety

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: T.E., L.S., Design: T.E., B.K., A.D., Data Collection or Processing: S.K., T.E., L.S., Analysis or Interpretation: T.E., A.D., LS., Literature Search: S.K., B.K., J.S., Writing: S.K., T.E., B.K., J.S., A.D., L.S.

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

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

References

1. Dzieciatkowski T, Szarpak L, Filipiak KJ, Jaguszewski M, Ladny JR, Smereka J. et al. COVID-19 challenge for modern medicine. Cardiol J. 2020;27:175-83.
2. Ruetzler K, Szarpak L, Filipiak KF, Ladny JR, Smereka J. The COVID-19 pandemic — a view of the current state of the problem. Disaster Emerg Med J. 2020;5:106-7.
3. Smereka J, Szarpak L. The use of personal protective equipment in the COVID-19 pandemic era. Am J Emerg Med. 2020;38:1529-30.
4. Smereka J, Szarpak L, Filipiak KJ, Jaguszewski M, Ladny JR. Which intravascular access should we use in patients with suspected/confirmed COVID-19? Resuscitation. 2020;151:8-9.
5. Hwang SY, Yoon H, Yoon A, Kim T, Lee G, Jung KY, et al. N95 filtering facepiece respirators do not reliably afford respiratory protection during chest compression: A simulation study. Am J Emerg Med. 2020;38:12-7.