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I don't want you to be only
a doctor but I also want you
to be a man
A quotation by His Royal Highness Prince Mahidol of Songkla

the clinical academia

Aim and Scope

Our journal is an opened access international journal devoted to peer-reviewed contributions dealing with clinical medicine and medical education from experimental to clinical aspects. Our journal publishes only high quality research, review and other types of original articles, technical and clinical reports every two months. Reviews of various global and Asian aspects will be solicited. Innovation or epidemiological aspects as well as health system research will be addressed. Rigorous systematic review and neglected tropical diseases are our priority

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message from the editor

Dear readers,

We hope you enjoy reading articles from our journal as usual. In this issue, we have very informative four articles. You will learn about the benefit of using systemic corticosteroids on mortality in patients with acute infectious encephalitis. You will also get information about factors associated with postoperative pain after cesarean in pregnant mothers as well as risk factors for acute perforation of the appendix. We also have a very interesting systematic review regarding the use of peritubal bupivacaine infiltration for postoperative pain reduction after percutaneous nephrolithotomy. I hope you get something news as usual.

Enjoy!

Thammasorn Jeeraaumponwat, M.D., Ph.D.
Editor-in-Chief of The Clinical Academia

submission

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All accepted articles are classified into two main categories;
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Contents

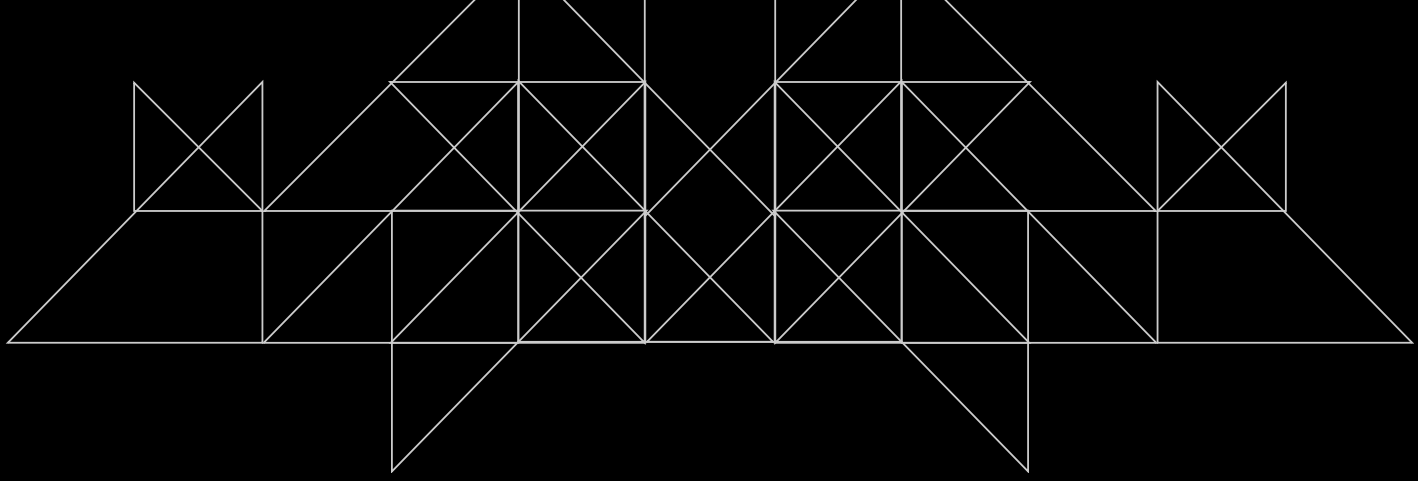
International Committee of Medical Journal Editors (ICMJE) Recommendation for Preparing for Submission *viii*

Original Articles

- *Systemic corticosteroids and mortality in acute infectious encephalitis* *151*
- *Factors associated with post-cesarean pain* *163*
- *Risk factors for acute perforation of the appendix* *171*

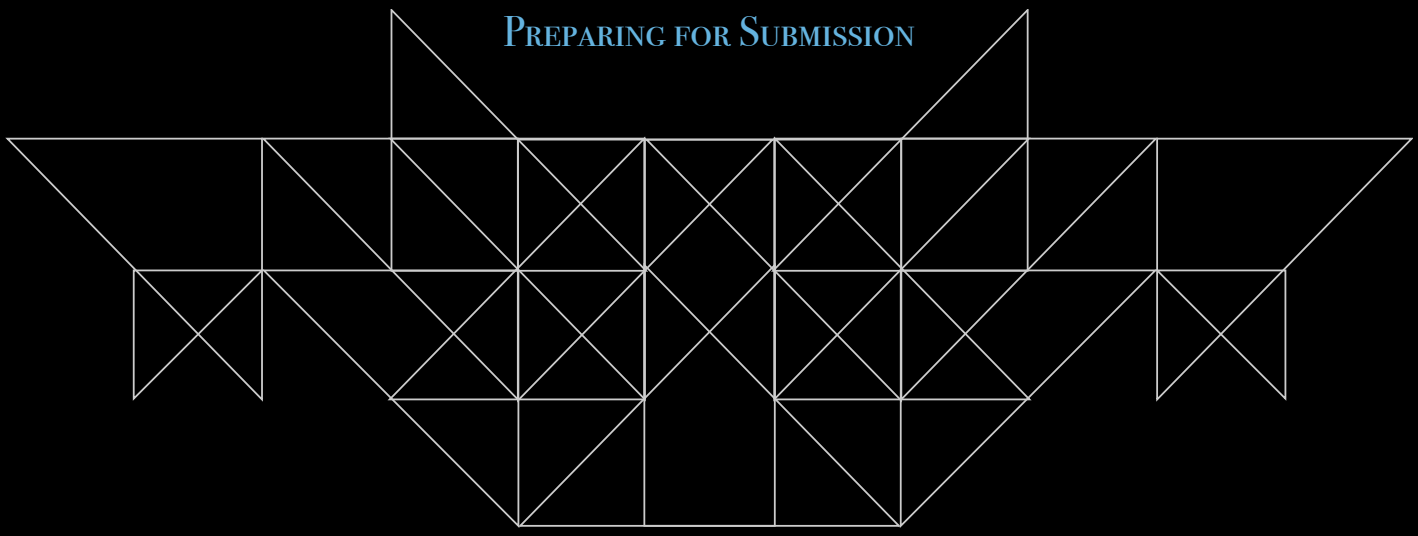
Systematic Review

- *Peritubal bupivacaine infiltration for postoperative pain reduction after percutaneous nephrolithotomy* *179*



International Committee of Medical Journal Editors (ICMJE)

Recommendation for Preparing for Submission



1. General Principles

The text of articles reporting original research is usually divided into Introduction, Methods, Results, and Discussion sections. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection of the process of scientific discovery. Articles often need subheadings within these sections to further organize their content. Other types of articles, such as meta-analyses, may require different formats, while case reports, narrative reviews, and editorials may have less structured or unstructured formats.

Electronic formats have created opportunities for adding details or sections, layering information, cross-linking, or extracting portions of articles in electronic versions. Supplementary electronic-only material should be submitted and sent for peer review simultaneously with the primary manuscript.

2. Reporting Guidelines

Reporting guidelines have been developed for different study designs; examples include CONSORT for randomized trials, STROBE for observational studies, PRISMA for systematic reviews and meta-analyses, and STARD for studies of diagnostic accuracy. Journals are encouraged to ask authors to follow these guidelines because they help authors describe the study in enough detail for it to be evaluated by editors, reviewers, readers, and other researchers evaluating the medical literature. Authors of review manuscripts are encouraged to describe the methods used for locating, select¬ing, extracting, and synthesizing data; this is mandatory for systematic reviews. Good sources for reporting guidelines are the EQUATOR Network and the NLM's Research Reporting Guidelines and Initiatives.

3. Manuscript Sections

The following are general requirements for reporting within sections of all study designs and manuscript formats.

a. Title Page

General information about an article and its authors is presented on a manuscript title page and usually includes the article title, author information, any disclaimers, sources of support, word count, and sometimes the number of tables and figures.

Article title. The title provides a distilled description of the complete article and should include information that, along with the Abstract, will make electronic retrieval of the article sensitive and specific. Reporting guidelines recommend and some journals require that information about the study design be a part of the title (particularly important for randomized trials and systematic reviews and meta-analyses). Some journals require a short title, usually no more than 40 characters (including letters and spaces) on the title page or as a separate entry in an electronic submission system. Electronic submission systems may restrict the number of characters in the title.

Author information: Each author's highest academic degrees should be listed, although some journals do not publish these. The name of the department(s) and institution(s) or organizations where the work should be attributed should be specified. Most electronic submission systems require that authors provide full contact information, including land mail and e-mail addresses, but the title page should list the corresponding authors' telephone and fax numbers and e-mail address. ICMJE encourages the listing of authors' Open Researcher and Contributor Identification (ORCID).

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Source(s) of support. These include grants, equipment, drugs, and/or other support that facilitated conduct of the work described in the article or the writing of the article itself.

Word count. A word count for the paper's text, excluding its abstract, acknowledgments, tables, figure legends, and references, allows editors and reviewers to assess whether the information contained in the paper warrants the paper's length, and whether the submitted manuscript fits within the journal's formats and word limits. A separate word count for the Abstract is useful for the same reason.

Number of figures and tables. Some submission systems require specification of the number of Figures and Tables before uploading the relevant files. These numbers allow editorial staff and reviewers to confirm that all figures and tables were actually included with the manuscript and, because Tables and Figures occupy space, to assess if the information provided by the figures and tables warrants the paper's length and if the manuscript fits within the journal's space limits.

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b. Abstract

Original research, systematic reviews, and meta-analyses require structured abstracts. The abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study participants, settings, measurements, analytical methods), main findings (giving specific effect sizes and their statistical and clinical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations, note important limitations, and not over-interpret findings. Clinical trial abstracts should include items that the CONSORT group has identified as essential. Funding sources should be listed separately after the Abstract to facilitate proper display and indexing for search retrieval by MEDLINE.

Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to ensure that they accurately reflect the content of the article. Unfortunately, information in abstracts often differs from that in the text. Authors and editors should work in the process of revision and review to ensure that information is consistent in both places. The format required for structured abstracts differs from journal to journal, and some journals use more than one format; authors need to prepare their abstracts in the format specified by the journal they have chosen.

The ICMJE recommends that journals publish the clinical trial registration number at the end of the abstract. The ICMJE also recommends that, when a

registration number is available, authors list that number the first time they use a trial acronym to refer to the trial they are reporting or to other trials that they mention in the manuscript. If the data have been deposited in a public repository, authors should state at the end of the abstract the data set name, repository name and number.

c. Introduction

Provide a context or background for the study (that is, the nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

d. Methods

The guiding principle of the Methods section should be clarity about how and why a study was done in a particular way. Methods section should aim to be sufficiently detailed such that others with access to the data would be able to reproduce the results. In general, the section should include only information that was available at the time the plan or protocol for the study was being written; all information obtained during the study belongs in the Results section. If an organization was paid or otherwise contracted to help conduct the research (examples include data collection and management), then this should be detailed in the methods.

The Methods section should include a statement indicating that the research was approved or exempted from the need for review by the responsible review committee (institutional or national). If no formal ethics committee is available, a statement indicating that the research was conducted according to the principles of the Declaration of Helsinki should be included.

i. Selection and Description of Participants

Clearly describe the selection of observational or experimental participants (healthy individuals or patients, including controls), including eligibility and exclusion criteria and a description of the source population. Because the relevance of such variables as age, sex, or ethnicity is not always known at the time of study design, researchers should aim for inclusion of representative populations into all study types and at a minimum provide descriptive data for these and other relevant demographic variables. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer)." Authors should define how they measured race or ethnicity and justify their relevance.

ii. Technical Information

Specify the study's main and secondary objectives–usually identified as primary and secondary outcomes. Identify methods, equipment (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow others to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well-known; describe new or substantially modified methods, give the reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration. Identify appropriate scientific names and gene names.

iii. Statistics

Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to judge its appropriateness for the study and to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as P values, which fail to convey important information about effect size and precision of estimates. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the statistical software package(s) and versions used. Distinguish prespecified from exploratory analyses, including subgroup analyses.

e. Results

Present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Methods Section. Extra or supplementary materials and technical details can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

Give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them, if any. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample."

Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

f. Discussion

It is useful to begin the discussion by briefly summarizing the main findings, and explore possible mechanisms or explanations for these findings. Emphasize the new and important aspects of your study and put your finings in the context of the totality of the relevant evidence. State the limitations of your study, and explore the implications of your findings for future research and for clinical practice or policy. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section.

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted, but label them clearly.

g. References

i. General Considerations Related to References

Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests.Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. On the other hand, extensive lists of references to original work on a topic can use excessive space. Fewer references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently.

Do not use conference abstracts as references: they can be cited in the text, in parentheses, but not as page footnotes. References to papers accepted but not yet published should be designated as "in press" or "forthcoming." Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

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References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses.

References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used for MEDLINE (www.ncbi.nlm.nih.gov/nlmcatalog/journals). Journals vary on whether they ask authors to cite electronic references within parentheses in the text or in numbered references following the text. Authors should consult with the journal to which they plan to submit their work.

ii. Reference Style and Format

References should follow the standards summarized in the NLM's International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Sample References webpage and detailed in the

NLM's Citing Medicine, 2nd edition. These resources are regularly updated as new media develop, and currently include guidance for print documents; unpublished material; audio and visual media; material on CD-ROM, DVD, or disk; and material on the Internet.

h. Tables

Tables capture information concisely and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text.

Prepare tables according to the specific journal's requirements; to avoid errors it is best if tables can be directly imported into the journal's publication software. Number tables consecutively in the order of their first citation in the text and supply a title for each. Titles in tables should be short but self-explanatory, containing information that allows readers to understand the table's content without having to go back to the text. Be sure that each table is cited in the text.

Give each column a short or an abbreviated heading. Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes, and use symbols to explain information if needed. Symbols may vary from journal to journal (alphabet letter or such symbols as *, †, ‡, §), so check each journal's instructions for authors for required practice. Identify statistical measures of variations, such as standard deviation and standard error of the mean.

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Additional tables containing backup data too extensive to publish in print may be appropriate for publication in the electronic version of the journal, deposited with an archival service, or made available to readers directly by the authors. An appropriate statement should be added to the text to inform readers that this additional information is available and where it is located. Submit such tables for consideration with the paper so that they will be available to the peer reviewers.

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Digital images of manuscript illustrations should be submitted in a suitable format for print publication. Most submission systems have detailed instructions on the quality of images and check them after manuscript upload. For print submissions, figures should be either professionally drawn and photographed, or submitted as photographic-quality digital prints.

For X-ray films, scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, send high-resolution photographic image files. Since blots are used as primary evidence in many scientific articles, editors may require deposition of the original photographs of blots on the journal's website.

Although some journals redraw figures, many do not. Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication. Figures should be made as self-explanatory as possible, since many will be used directly in slide presentations. Titles and detailed explanations belong in the legends—not on the illustrations themselves.

Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background. Explain the internal scale and identify the method of staining in photomicrographs.

Figures should be numbered consecutively according to the order in which they have been cited in the text. If a figure has been published previously, acknowledge the original source and submit written permission from the copyright holder to reproduce it. Permission is required irrespective of authorship or publisher except for documents in the public domain.

In the manuscript, legends for illustrations should be on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend.

j. Units of Measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples.

Temperatures should be in degrees Celsius. Blood pressures should be in millimeters of mercury, unless other units are specifically required by the journal.

Journals vary in the units they use for reporting hematologic, clinical chemistry, and other measurements. Authors must consult the Information for Authors of the particular journal and should report laboratory information in both local and International System of Units (SI).

Editors may request that authors add alternative or non-SI units, since SI units are not universally used. Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

k. Abbreviations and Symbols

Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

Systemic corticosteroids and mortality in acute infectious encephalitis

ORIGINAL ARTICLE

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ABSTRACT

OBJECTIVE

To evaluate the association between systemic corticosteroids and mortality in patients with acute infectious encephalitis.

METHODS

We performed a retrospective cohort study in patients with preliminary diagnosed as acute infectious encephalitis admitted in Khon Kaen Hospital, Thailand. We identified the patients through the hospital database using the international classification of disease, 10th revision (ICD-10) matching the disease. We divided the patients into two groups; with systemic corticosteroids administration and without administration. The primary outcome was death.

RESULTS

From January 2011 through May 2017, a total of 533 patients was included; 158 received systemic corticosteroid, 375 did not. The mortality rate was significantly higher in the group with the systemic corticosteroid administration group than that without (relative rate [RR], 1.34; 95% confidence interval [CI], 1.08 to 1.66). The former group also had poorer outcomes; cardiac arrest (RR 1.68; 95% CI, 1.13 to 2.50), on mechanical ventilation (RR 1.44; 95% CI, 1.26 to 1.65). From the former analysis, the factors that found to be associated with death within 30 days after admission included being male (AOR, 0.38; 95% CI, 0.17 to 0.87) and open pressure (AOR, 1.04; 95% CI,1.002 to 1.09). However, from the Cox proportional hazard regression, the factors that found to be associated with 30 days mortality after admission included age (AHR, 1.02; 95% CI, 1.01 to 1.026) and GCS score at admission (AHR, 0.88; 95% CI, 0.84 to 0.91).

CONCLUSION

The systemic corticosteroids had no statistically significant benefit on the mortality rate in acute infectious encephalitis.

INTRODUCTION

Incidence of acute encephalitis varies across the world, 7.4 per 100,000 per year in Western countries and 6.3 per 100,000 per year in tropical countries is 6.34 per 100,000 per year.[1] Acute encephalitis has 5.6% case fatality mortality rate and can be caused by various etiologies.[2] About half of the cases, the etiologic agent is unidentified while the most common identified causes are virus, followed by bacteria and autoimmune disease.[2,3] Moreover, the disease can also cause persistent physical and mental impairment.[4] Acute encephalitis was preliminarily diagnosed by clinical signs and cerebrospinal fluid (CSF) analysis without necessary confirmed by polymerase chain reaction (PCR).[5-7] Specific treatments of acute encephalitis can be antivirals, antibiotics, antituberculosis or antifungals depend on the causative agents, while other treatments are supportive and adjunctive such as systemic corticosteroids.[8,9] However, the benefit of adjunctive corticosteroids has never been clearly identified in acute encephalitis. A retrospective cohort study in 1992 showed no benefit of dexamethasone administration in 55 Thai patients with Japanese encephalitis (JE).[10] However, a later study in 2005 in 45 Japanese patients with herpes simplex viral (HSV) encephalitis stated that adjunctive systemic corticosteroids therapy to acyclovir significantly reduced neurological outcomes and mortality rate.[11] Based on this scarce evidence with small sample sizes and very specific benefit of systemic corticosteroids on JE and HSV encephalitis without information in other encephalitis etiologies, we thus aimed to identify the possible benefit of the medication in those with a preliminary diagnosis with acute infectious encephalitis in a larger study population.

METHODS

STUDY DESIGN AND PATIENTS

We performed a retrospective cohort study of the patients with acute infectious encephalitis that were admitted in Khon Kaen Hospital, Thailand, from January 2011 through May 2017. We identified them through Khon Kaen Hospital Database. We included the medical records of those with a preliminary diagnosis of acute infectious encephalitis, defined by the international classification of disease, 10th revision (ICD-10) code A80-A89, and G04.

EXPOSURE

The systemic corticosteroids administration was identified as the exposure in our study. The systemic corticosteroids including dexamethasone, methylprednisolone, prednisolone, and hydrocortisone. We converted all to dexamethasone dose (mg/day) by collecting total dose and duration of systemic corticosteroid administration.

STUDY OUTCOMES

The primary outcome was death within 30 days after admission. We ascertained the death outcomes either from the medical records or from the Civil Registration Database where appropriate. The secondary outcomes were cardiac arrest, i.e., presented in evidence of cardiopulmonary resuscitation, seizure, status epilepticus i.e., continued seizure more than 5 minutes or recurrent seizure with not recovered of

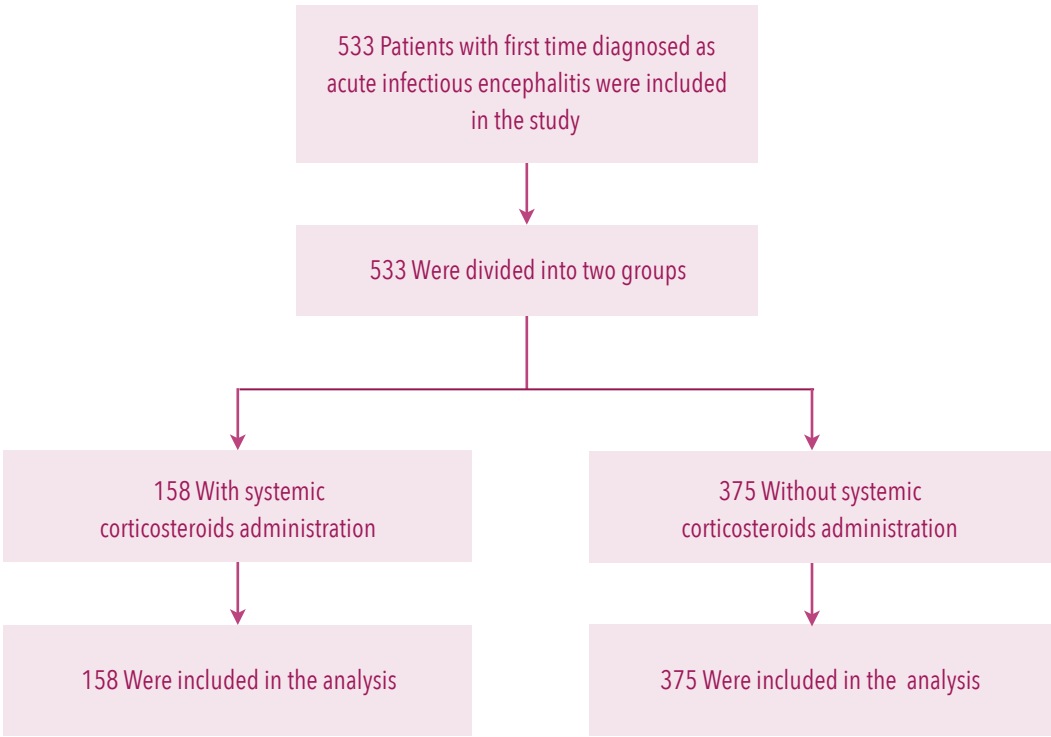

Figure 1. Study flow

consciousness between seizure more than 5 minutes, duration in hospital, duration of intensive care unit (ICU) admission, on mechanical ventilator, nosocomial infection i.e., presented evidence of hospital-acquired pneumonia, ventilator-associated pneumonia, urinary tract infection and phlebitis which occurred during the admission.

DATA COLLECTION

We reviewed and verified all the medical records of the included patients. The collected data included characteristic of patients at admission i.e., sex, age, diabetes mellitus, hypertension, cerebrovascular disease, fever, nausea and vomiting, stiff neck, hemiparesis, paraparesis, quadriparesis, seizure, status epilepticus, Glasgow Coma Scale (GCS) score, respiratory intubation and mechanical ventilation, thrombocytopenia is data collected from serum platelet count and select patient with platelet counts less than 100,000 cells/mm^3, hyponatremia is data collected from serum sodium and selected patient with serum sodium less than 135 mEq/L, abnormal brain imaging defined with an abnormal brain lesion on computerized tomography (CT) or magnetic resonance imaging (MRI) approved by a radiologist, open pressure from first lumbar puncture on admission, CSF profile; leukocyte count, protein, CSF glucose and blood glucose ratio, treatment after admission included acyclovir administration, antibiotic

administration i.e., penicillin group, cephalosporin group, polymyxin group, glycopeptide group,macrolide group, fluoroquinolone group, aminoglycoside group, carbapenems group, metronidazole, and mannitol administration.

STATISTICAL ANALYSIS

Of all patients, we divided them into two groups; systemic corticosteroids administration group and no systemic corticosteroids administration. We used descriptive statistics to summarize the characteristics of the patients in each group; categorical data were presented using numbers and percentage, normally distributed continuous data were presented using mean and standard deviation (SD), and non-normally distributed continuous data were presented using median and interquartile range (IQR). Pearson's chi-squared was used for categorical variable. Mann-Whitney U test was used in continuous variables comparison. Event rate of the primary and secondary outcomes between the two groups was compared using relative ratio (RR). Crude and adjusted odds ratios were derived from binary logistic regression while a hazard ratio (HR) was calculated using Cox regression, All of the inferential statistical analyses of the outcomes were presented together with 95% confidence interval (CI). Kaplan-Meier survival was also used to show the number of surviving patients after the treatment between two groups.

RESULTS

PATIENTS

From January 2011 through May 2017, we included 533 patients with the first episode preliminary diagnosis of acute infectious encephalitis at the Khon Kaen Hospital. We divided the patients into two groups; 158 with systemic corticosteroids administration and 375 without administration (Figure 1). Comparisons between those with and without systemic corticosteroids administration, the former group tended to have higher proportion of patients with quadriparesis (16.3% vs. 9.8%; P=0.04), higher proportion of patients on mechanical ventilation at admission (41.1% vs. 30.4%; P=0.02), lower proportion of patients with cerebrovascular disease (0.6% vs. 4.9%; P=0.02) (Table 1). The former also had lower CSF glucose/blood glucose ratio (0.4, 0.3 to 0.6 vs. 0.5, 0.4 to 0.6; P=0.01) (Table 2). For the treatment after the hospital admission, the former group tended to have higher proportion of patients on acyclovir (39.9% vs. 29.9%; P=0.03), higher proportion of patients on antibiotic; penicillin group (54.4% vs. 43.5%; P=0.02), polymyxin group (14.6% vs. 5.1%; P<0.001), glycopeptide group (27.8% vs. 10.4%; P<0.001), carbapenems group (39.9% vs. 19.2%; P<0.001) and mannitol (20.3% vs. 6.4%; P<0.001) (Table 3). However, the other characteristics were relatively similar.

OUTCOMES

The mortality rate was higher in the group with systemic corticosteroids administration compared with that without (RR, 1.34; 95% CI, 1.08 to 1.66). The secondary outcomes showed that cardiac arrest, status epilepticus, on a mechanical ventilator, the nosocomial infection significantly increased in the group with systemic corticosteroids administration compared with that without. Moreover, the former group had longer hospitalization and ICU admission time shown in Table 4.

Table 1. Characteristics of patients with acute infectious encephalitis

Characteristic	Systemic corticosteroids administration	No systemic corticosteroids administration	P Value
Male sex–no. (%)	86 (54.4)	228 (60.8)	0.17
Age–yr			0.27
Median	51.2	51.3	
Interquartile range	27.9–66.9	28.1–67.6	
Comorbidities–no. (%)			
Diabetes mellitus	25 (15.9)	75 (20.2)	0.25
Hypertension	33 (21.0)	75 (20.2)	0.83
Cerebrovascular disease	1 (0.6)	18 (4.9)	0.02
Signs and symptoms–no. (%)			
Fever*	69 (43.7)	144 (38.4)	0.26
Nausea and vomiting	34 (21.5)	79 (21.1)	0.91
Stiff neck	67 (44.4)	169 (45.7)	0.79
Quadriparesis	24 (16.3)	35 (9.8)	0.04
Hemiparesis	8 (5.4)	17 (4.8)	0.75
Paraparesis	1 (0.7)	7 (2.0)	0.45
Seizure	43 (27.2)	115 (30.7)	0.43
Status epilepticus	16 (10.1)	25 (6.7)	0.17
GCS score at admission †			0.12
Median	10	10	
Interquartile range	8–13.5	8–14	
Respiratory intubation/mechanical ventilation at admission–no. (%)	65 (41.1)	114 (30.4)	0.02
Thrombocytopenia–no. (%) ‡	17 (12.0)	39 (11.7)	0.93
Hyponatremia–no. (%) §	68 (44.7)	149 (41.5)	0.50
Abnormal brain imaging–no (%) ¶	31 (29.2)	79 (32.9)	0.50

* Fever= Body temperature >38.0 degree Celcius[14]
† GCS=Glasgow Coma Scale
‡ Thrombocytopenia=platelet count <100,000 cell/mm^3 [18]
§ Hyponatremia=serum sodium <135 mEq/L[14]
¶ Abnormal brain imaging=detection of brain lesion by CT or MRI[11]

Table 2. CSF profile of patient with acute infectious encephalitis

Profile	Systemic corticosteroids administration	No systemic corticosteroids administration	P Value
Open pressure of lumbar puncture–cmH_2O			0.29
Median	20	20	
Interquartile range	15–28	14–27	
CSF profile			
Leukocyte count–cells/μl			0.78
Median	40	40	
Interquartile range	0–552	2–660	
CSF glucose/blood glucose ratio			0.01
Median	0.4	0.5	
Interquartile range	0.3–0.6	0.4–0.6	
Protein–mg/dl			0.72
Median	110	102.1	
Interquartile range	48.4–292.2	49.0–289.1	

Table 3. Treatment after admission

Treatment	Systemic corticosteroids administration	No systemic corticosteroids administration	P Value
Acyclovir administration–no. (%)	63 (39.9)	112 (29.9)	0.03
Antibiotic administration–no. (%)	152 (96.2)	357 (95.2)	0.61
Penicillin group	86 (54.4)	163 (43.5)	0.02
Cephalosporin group	135 (85.4)	330 (88.0)	0.42
Polymyxin group	23 (14.6)	19 (5.1)	<0.001
Glycopeptide group	44 (27.8)	39 (10.4)	<0.001
Macrolide group	12 (7.6)	23 (6.1)	0.53
Fluoroquinolone group	10 (6.3)	13 (3.5)	0.14
Aminoglycoside group	3 (1.9)	4 (1.1)	0.43
Carbapenems group	63 (39.9)	72 (19.2)	<0.001
Metronidazole	17 (10.8)	20 (5.3)	0.02
Mannitol administration–no. (%)	32 (20.3)	24 (6.4)	<0.001

Table 4. Outcomes of the treatment

Outcome	Systemic corticosteroids	No systemic corticosteroids	Relative Risk (95% CI)	Mean difference
Primary				
Death–no. (%)	75 (47.5)	133 (35.5)	1.34 (1.08–1.66)	
Secondary				
Cardiac arrest–no. (%)	34 (21.5)	48 (12.8)	1.68 (1.13–2.50)	
Seizure–no. (%)	34 (21.5)	58 (15.5)	1.39 (0.95–2.04)	
Status epilepticus–no. (%)	18 (11.4)	18 (4.8)	2.37 (1.27–4.44)	
Intubation/on ventilator–no. (%)	118 (74.7)	194 (51.7)	1.44 (1.26–1.65)	
Nosocomial infection–no. (%)	77 (48.7)	83 (22.1)	2.20 (1.72–2.82)	
Duration in hospital–days				5.78 (3.07–8.48)
Median	4.8	4		
Interquartile range	2.2–10.6	1.9–9.4		
Duration of admission in ICU–day				3.28 (1.18–5.37)
Median	7.1	3.0		
Interquartile range	3.8–18.3	1.2–5.9		

FACTOR DETERMINE OUTCOMES

The result of the binary logistic regression analysis and the Cox regression analysis of the outcomes were summarized in Table 5. From the former analysis, the factors that found to be associated with death within 30 days after admission included being male (AOR, 0.38; 95% CI, 0.17 to 0.87) and open pressure (AOR, 1.04; 95% CI, 1.002 to 1.09). However, from the Cox proportional hazard regression, the factors that found to be associated with 30 days mortality after admission included age (AHR, 1.02; 95% CI, 1.01 to 1.026) and GCS score at admission (AHR, 0.88; 95% CI, 0.84 to 0.91).

SUBGROUP ANALYSIS

The result of the subgroup analysis of systemic corticosteroid administration was shown in Table 6. The systemic corticosteroid administration in any age, time of the first dose, duration and dose of systemic corticosteroid had no significant effects on the mortality.

DISCUSSION

PRINCIPAL FINDINGS

The study showed that the systemic corticosteroids administration was no associated with mortality. The factors that found to be associated with a higher death rate within 30 days after admission

Table 5. Predictors of death

Predictor	Odds ratio (95% confidence interval)		Adjusted hazard ratio (95% confidence interval)
	Crude analysis	Adjusted analysis	
Age–yr	1.02 (1.02–1.03)	1.02 (0.995–1.05)	1.02 (1.01–1.026)
Male sex	0.69 (0.48–0.98)	0.38 (0.17–0.87)	0.75 (0.55–1.01)
Diabetes mellitus	2.59 (1.66–4.03)	1.19 (0.40–3.57)	1.25 (0.85–1.84)
Hypertension	2.68 (1.74–4.14)	2.16 (0.69–6.79)	0.95 (0.65–1.41)
Stiff neck	0.82 (0.58–1.17)	0.77 (0.32–1.84)	
New onset of seizure	0.75 (0.51–1.10)	0.39 (0.13–1.13)	
GCS score at admission	0.85 (0.81–0.90)	0.91 (0.81–1.03)	0.88 (0.84–0.91)
Open pressure–cmH_2O	1.03 (1.01–1.05)	1.04 (1.002–1.09)	
CSF glucose/blood glucose ratio	0.28 (0.11–0.72)	0.14 (0.02–1.03)	
Hyponatremia	1.28 (0.89–1.84)	1.60 (0.72–3.52)	1.18 (0.89–1.58)
Abnormal brain imaging	1.12 (0.73–1.73)	1.26 (0.56–2.85)	
Systemic steroid administration	1.64 (1.13–2.40)	0.84 (0.34–2.09)	1.33 (0.98–1.81)
Acyclovir administration	0.66 (0.45–0.97)	1.35 (0.51–3.58)	0.91 (0.63–1.30)
Mannitol administration	1.10 (0.63–1.93)	0.51 (0.09–2.85)	1.16 (0.70–1.94)

included older age and low GCS score at admission. Various initially time and dosages of the corticosteroids administration also showed no association with death.

COMPARISON WITH OTHER STUDIES

Our findings showed the administration of systemic corticosteroid had no significant benefit on mortality rate in acute infectious encephalitis, similar to the first study on JE patients.[10] and both studies also showed that higher CSF opening pressure resulted in a higher mortality rate. In contrast, a previous study in 45 HSV encephalitis patients showed adjunctive corticosteroid with acyclovir group had significantly improved the neurological outcome and survival rate after three months of treatment, while older age and lower GCS score were associated with a poorer outcome similar to our study.[11] Another study on 25 patients with encephalitis also showed that low GCS score was associated with poor outcome.[27] These could be explained that systemic corticosteroids might have the benefit of only a specific type of infectious encephalitis.

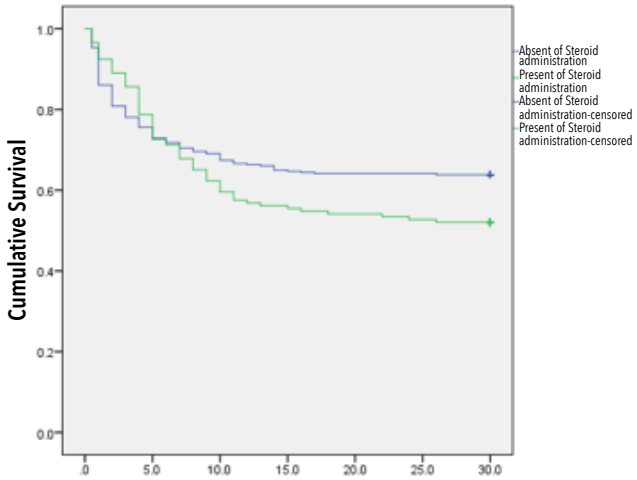

Figure 2. Kaplan-Meier estimates of the probability of survival in 30 days

Table 6. Subgroup analysis of systemic corticosteroids administration

Variable	Adjusted hazard ratio (95% CI)
Age–yr	
<18	0.25 (0.05–1.31)
>60	1.37 (0.88–2.13)
Time to the first dose–hr	
<24	1.49 (0.999–2.22)
≥24	1.16 (0.78–1.72)
Dose–mg/day	
<20	1.37 (0.98–1.91)
>20	1.13 (0.64–1.99)
Duration–day	
<7	1.36 (0.99–1.86)
>7	0.80 (0.29–2.20)

STRENGTHS AND LIMITATIONS OF STUDY

The strength of our study is that, to our knowledge, it is the largest cohort mentioning the use of systemic corticosteroids on acute infectious encephalitis. Aside from that, we also included the dosage and time of corticosteroids administration in our analyses. However, there are also limitations, for instance, missing data were inevitable due to the incomplete medical records. Moreover, the data were from the database of the tertiary medical facility, the patients were often referred from the other hospitals with the previous treament that can affect the treatment outcomes. Fail to acknowledge this information might lead to an erroneous conclusion. Additionally, due to the limitation of our resources, we cannot afford to categorize the types of virus infection causing encephalitis, generalizability is then limited.

CONCLUSION AND POLICY IMPLICATION

In conclusion, we found that systemic corticosteroid administration was not associated with mortality. Due to our limitations, further study with a larger sample size should be conducted for a more precise estimation of the effects of corticosteroids on mortality in patients with a confirmed subtype of acute encephalitis.

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REFERENCES

1. Jmor F, Emsley HCA, Fischer M, Solomon T, Lewthwaite P. The incidence of acute encephalitis syndrome in Western industrialised and tropical countries. Virol J. 2008 Oct 30;5:134.
2. George BP, Schneider EB, Venkatesan A. Encephalitis hospitalization rates and inpatient mortality in the United States, 2000-2010. PloS One. 2014;9(9):e104169.
3. Khetsuriani N, Holman RC, Anderson LJ. Burden of encephalitis-associated hospitalizations in the United States, 1988-1997. Clin Infect Dis Off Publ Infect Dis Soc Am. 2002 Jul 15;35(2):175–82.
4. Mailles A, De Broucker T, Costanzo P, Martinez-Almoyna L, Vaillant V, Stahl J-P, et al. Long-term outcome of patients presenting with acute infectious encephalitis of various causes in France. Clin Infect Dis Off Publ Infect Dis Soc Am. 2012 May;54(10):1455–64.
5. Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis. 2010 Dec;10(12):835–44.
6. McGrath N, Anderson NE, Croxson MC, Powell KF. Herpes simplex encephalitis treated with acyclovir: diagnosis and long term outcome. J Neurol Neurosurg Psychiatry. 1997 Sep;63(3):321–6.
7. Sili U, Kaya A, Mert A, HSV Encephalitis Study Group. Herpes simplex virus encephalitis: clinical manifestations, diagnosis and outcome in 106 adult patients. J Clin Virol Off Publ Pan Am Soc Clin Virol. 2014 Jun;60(2):112–8.
8. Chaudhuri A, Kennedy PGE. Diagnosis and treatment of viral encephalitis. Postgrad Med J. 2002 Oct;78(924):575–83.
9. Whitley RJ, Alford CA, Hirsch MS, Schooley RT, Luby JP, Aoki FY, et al. Vidarabine versus acyclovir therapy in herpes simplex encephalitis. N Engl J Med. 1986 Jan 16;314(3):144–9.
10. Hoke CH, Vaughn DW, Nisalak A, Intralawan P, Poolsuppasit S, Jongsawas V, et al. Effect of high-dose dexamethasone on the outcome of acute encephalitis due to Japanese encephalitis virus. J Infect Dis. 1992 Apr;165(4):631–7.
11. Kamei S, Sekizawa T, Shiota H, Mizutani T, Itoyama Y, Takasu T, et al. Evaluation of combination therapy using aciclovir and corticosteroid in adult patients with herpes simplex virus encephalitis. J Neurol Neurosurg Psychiatry. 2005 Nov;76(11):1544–9.
12. Martinez-Torres F, Menon S, Pritsch M, Victor N, Jenetzky E, Jensen K, et al. Protocol for German trial of Acyclovir and corticosteroids in Herpes-simplex-virus-encephalitis (GACHE): a multicenter, multinational, randomized, double-blind, placebo-controlled German, Austrian and Dutch trial [ISRCTN45122933]. BMC Neurol. 2008 Oct 29;8:40.
13. McGrath N, Anderson NE, Croxson MC, Powell KF. Herpes simplex encephalitis treated with acyclovir: diagnosis and long term outcome. J Neurol Neurosurg Psychiatry. 1997 Sep;63(3):321–6.
14. Riancho J, Delgado-Alvarado M, Sedano MJ, Polo JM, Berciano J. Herpes simplex encephalitis: clinical presentation, neurological sequelae and new prognostic factors. Ten years of experience. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. 2013 Oct;34(10):1879–81.
15. Lahat E, Barr J, Barkai G, Paret G, Brand N, Barzilai A. Long term neurological outcome of herpes encephalitis. Arch Dis Child. 1999 Jan;80(1):69–71.
16. Solomon T, Michael BD, Smith PE, Sanderson F, Davies NWS, Hart IJ, et al. Management of suspected viral encephalitis in adults--Association of British Neurologists and British Infection Association National Guidelines. J Infect. 2012 Apr;64(4):347–73.
17. Granerod J, Cousens S, Davies NWS, Crowcroft NS, Thomas SL. New estimates of incidence of encephalitis in England. Emerg Infect Dis. 2013;19(9).
18. Thakur KT, Motta M, Asemota AO, Kirsch HL, Benavides DR, Schneider EB, et al. Predictors of outcome in acute encephalitis. Neurology. 2013 Aug 27;81(9):793–800.
19. Singh TD, Fugate JE, Hocker S, Wijdicks EFM, Aksamit AJ, Rabinstein AA. Predictors of outcome in HSV encephalitis. J Neurol. 2016 Feb;263(2):277–89.
20. Modi S, Mahajan A, Dharaiya D, Varelas P, Mitsias P. Burden of herpes simplex virus encephalitis in the United States. J Neurol. 2017 Jun;264(6):1204–8.
21. Misra UK, Kalita J. Seizures in encephalitis: predictors and outcome. Seizure. 2009 Oct;18(8):583–7.
22. Badri S, Chen J, Barber J, Temkin NR, Dikmen SS, Chesnut RM, et al. Mortality and long-term functional outcome associated with intracranial pressure after traumatic brain injury. Intensive Care Med. 2012 Nov;38(11):1800–9.
23. Barnett GH, Ropper AH, Romeo J. Intracranial pressure and outcome in adult encephalitis. J Neurosurg. 1988 Apr;68(4):585–8.
24. Rebaud P, Berthier JC, Hartemann E, Floret D. Intracranial pressure in childhood central nervous system infections. Intensive Care Med. 1988;14(5):522–5.
25. Glaser CA, Honarmand S, Anderson LJ, Schnurr DP, Forghani B, Cossen CK, et al. Beyond viruses: clinical profiles and etiologies associated with encephalitis. Clin Infect Dis Off Publ Infect Dis Soc Am. 2006 Dec 15;43(12):1565–77.
26. Raschilas F, Wolff M, Delatour F, Chaffaut C, De Broucker T, Chevret S, et al. Outcome of and prognostic factors for herpes simplex encephalitis in adult patients: results of a multicenter study. Clin Infect Dis Off Publ Infect Dis Soc Am. 2002 Aug 1;35(3):254–60.
27. Granerod J, Cousens S, Davies NWS, Crowcroft NS, Thomas SL. New Estimates of Incidence of Encephalitis in England. Emerg Infect Dis. 2013 Sep;19(9):1455–62.

Factors associated with moderate to severe pain after cesarean delivery under spinal anesthesia

ORIGINAL ARTICLE

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ABSTRACT

OBJECTIVE

To identify factors associated with moderate to severe pain after cesarean delivery under spinal anesthesia.

METHODS

A nested cohort in the randomized controlled trial (RCT) was conducted using the secondary information of term pregnant women undergoing cesarean delivery under spinal anesthesia from a previous RCT. All patients received postoperative intravenous opioids using patient-controlled anesthesia (PCA). The pain scores were assessed at 12, 20 and 24 hours. The time and amount of opioid use by PCA were recorded. The participants who had a pain score $\geq$4, or who needed additional PCA opioid in the first 24 hours were defined as moderate to severe pain.

RESULTS

A total of 100 participants were included in this study. Of these, the intravenous morphine by PCA was used in 8%, 38% and 54% in the first 2, 12 and 24 hours after cesarean delivery, respectively. The mean of intravenous morphine used was 4.4 mg. The mean pain score at 12, 20 and 24 hours were 2.7, 2.5 and 2.3, respectively. Moderate to severe pain occurred in 66 patients and 57 had a pain score $\geq$4 within 24 hours. An associated factor of less pain was the use of an oral analgesic drug (adjusted odds ratio, 0.29; 95% confidence interval, 0.10 to 0.80; $P<0.05$).

CONCLUSION

Nearly two-thirds of patients had moderate to severe pain after cesarean delivery under spinal anesthesia using bupivacaine and intrathecal morphine. The use of oral analgesic drugs was an associated factor with less pain after cesarean delivery.

INTRODUCTION

Cesarean delivery is one of the most common operations in women and accounts for more than 30% of all births.[1] Spinal anesthesia with bupivacaine is the most widely used regional anesthesia for this operation because of its speed of onset and reliability.[1] Postoperative pain is one of the greatest concerns of all mothers.[2] Indeed, evidence suggests that more than half of patients undergoing major surgery report inadequate pain relief.[3] This significantly detracts from the sense of well-being and joy by limiting maternity activities such as baby care and breastfeeding.[4,5] In many centers, opioids are commonly used for pain control after surgery in various forms such as intrathecal, intravenous, intramuscular or patient-controlled anesthesia (PCA). However, the side effects, such as dizziness, nausea, vomiting are commonly found and severe side effect i.e., respiratory depression was also reported.[6] Many non-opioid drugs such as acetaminophen or nonsteroidal anti-inflammatory drug (NSAID) are also commonly used for post-operative pain relief.[7] The use of these analgesics for appropriate pain control after cesarean delivery should depend on the understanding of pain pattern and severity of postoperative pain, however, this understanding is still limited. Therefore, the purpose of this study is to investigate patterns and severity of the pain including factors to be associated with the pain after cesarean delivery.

METHODS

STUDY DESIGN AND OVERSIGHT

This study is a nested cohort study using secondary data from a randomized study that evaluated the effectiveness of oral diclofenac and paracetamol for pain control after cesarean delivery.[8] The study was conducted in a tertiary care regional hospital. The study protocol was approved by the Udonthani Hospital Research Ethics Committee (number 58/2560).

PATIENTS

The patients were pregnant women who underwent a low transverse cesarean section under spinal anesthesia from January through June 2018. They were counseled and invited to participate in this study. The inclusion criteria were singleton term pregnant women who indicated for a low transverse cesarean section. The exclusion criteria were patients who had medical diseases such as hypertension, diabetes, received general anesthesia for this operation or unwilling to participate in this study. Written informed consent was obtained after the explanation of the study methods to the participants.

PROCEDURES

All participants underwent a low transverse cesarean section under spinal anesthesia which was performed by an anesthesiologist in the operating room using 0.5% bupivacaine plus 0.1 to 0.2 mg of morphine. All patients received standard care for a low transverse cesarean section in the operating room, recovery room and were transferred to the postpartum ward after 2 hours post-operation. After the operation, all participants received intravenous morphine by patient-controlled anesthesia (IV–PCA) for pain control. The setting of intravenous morphine by IV–PCA protocol was 1 mg/ml by IV–PCA only mode without loading, the delayed time for each morphine dose was 5 minutes and the maximum

Table 1. Characteristics of the participants

Characteristic	Total (N=100)
Median age (IQR)–yr	29 (24–33)
20–34	83
≥35	17
Median body mass index (IQR)–kg/m^2	29.6 (4.8)
Median gestational age (IQR)–wk	38 (38–39)
37–41	98
≥42	2
Primipara	23
Median operation time (IQR)–minutes	45 (37.0–56.5)
<60	78
≥60	22
Tubal resection	57
Adhesion	15
Previous surgery	51
Indication	
Previous cesarean section	47
Cephalopelvic disproportion	53
Fetal distress	10
Type of incision	
Pfannenstiel	24
Low midline	76
Median blood loss (IQR)–ml	300 (200–300)
≥500	91
>500	9
Oral analgesic used	50

IQR=interquartile range

Table 2. Associated factors for moderate to severe pain after cesarean delivery

Factor	Moderate to severe pain (N=66)	Mild Pain (N=34)	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)	P Value
Advanced maternal age ≥35 yr–no. (%)	12 (18.2)	5 (14.7)	1.29 (0.41–4.02)	1.17 (0.31–4.40)	0.82
Maternal body mass Index–kg/m^2	30.0±4.99	28.8±4.32	1.05 (0.97–1.15)	1.08 (0.98–1.19)	0.14
Primipara–no. (%)	16 (24.2)	7 (20.6)	0.94 (0.51–1.72)	0.67 (0.17–2.66)	0.57
Operation time ≥60 minutes	18 (27.3)	4 (11.8)	2.81 (0.87–9.11)	3.22 (0.89–11.7)	0.08
Tubal resection–no. (%)	37 (56.1)	20 (58.8)	0.89 (0.39–2.07)	1.16 (0.34–3.99)	0.38
Adhesion–no. (%)	12 (18.2)	3 (8.8)	2.30 (0.60–8.77)	3.12 (0.51–19.0)	0.22
Previous surgery–no. (%)	35 (53.0)	16 (47.1)	1.27 (0.55–2.91)	2.81 (0.47–17.0)	0.26
Indication–no. (%)					
Previous cesarean section	30 (45.5)	17 (50.0)			
Cephalopelvic disproportion	30 (45.5)	13 (38.2)	0.85 (0.21–3.44)	1.44 (0.12–17.4)	0.78
Fetal distress	6 (9.1)	4 (11.8)	1.31 (0.54–3.16)	2.37 (0.33–17.0)	0.39
Type of incision–no. (%)					
Pfannenstiel	14 (21.2)	10 (29.4)			
Low midline	52 (78.8)	24 (70.6)	1.54 (0.60–3.98)	1.67 (0.53–5.22)	0.38
Blood loss ≥500 ml	7 (10.6)	2 (5.88)	1.90 (0.37–9.68)	1.41 (0.10–11.2)	0.75
Oral analgesic used	28 (42.4)	22 (64.7)	0.40 (0.17–0.95)	0.29 (0.10–0.80)	0.02

CI=confidence interval

* Plus–minus values are means ±SD.

morphine dose was 30 mg in 4 hours. The pain scores were recorded using a numerical rating scale by trained ward nurses at 12, 20 and 24 hours post–operation. The numerical pain rating scale composed of 11 scores (0 to 10). The 0 score was no pain, 1 to 3 was mild pain, 4 to 6 was moderate pain, 7 to 10 was severe pain.[9] The possible associated factors of pain, such as age, duration of operation, previous surgery, were recorded. The participants who had a pain score of more than or equal to 4 or needed additional opioids by IV–PCA at 12, 20 or 24 hours were defined as a moderate to severe pain group. The participants who had a pain score within 24 hours post–operation of less than 4 and had no need for additional IV–PCA opioids were defined as a mild pain group.

STATISTICAL ANALYSIS

The baseline characteristics of both groups were presented as number and percentage for

categorical data and mean with standard deviation or median with interquartile range for the continuous data. The normality test was done by skewness and kurtosis test for normality. Both groups were compared for possible associated factors for moderate to severe pain using an unpaired t-test for continuous variables, Pearson's Chi-square and Fisher exact tests for categorical variables. The crude and adjusted odds ratio with a 95% confidence interval (CI) was calculated by bivariate and binary logistic regression analyses for the magnitude of the effect. Statistical analysis was performed using Stata version 13. $P<0.05$ was considered statistically significant. The sample size calculation using the formula for estimating the prevalence of moderate to severe post-operative pain[10]. The estimated proportion is 0.5 with an acceptable error of 0.1, an alpha error of 0.05 and the power is 80%. The number of participants by calculation was 97 participants and the total sample size was 100.

RESULTS

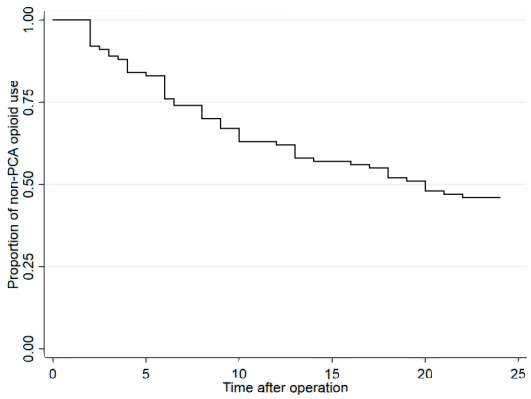
A total of 100 participants were included in this study. The participants' characteristics are shown in Table 1. All participants received low transverse cesarean delivery under spinal anesthesia using 0.5% bupivacaine plus 0.1-0.2 mg of morphine. Fifty participants received diclofenac 50 mg plus paracetamol 500 mg single dose at 12 hours post-operation. All participants were followed until 24 hours post–operation and were included in the analysis. Of these, the addition of morphine by IV–PCA was used in the first 2 hours in 8 participants, within the first 12 hours in 38 participants. After 24 hours post-operation, 54% of them used additional opioids by IV–PCA (Figure 1).

The mean of additional morphine used was 4.4 mg. The mean pain score at 12 hours post-operation was 2.7. At 12 hours post-operation, 12 participants had no pain. Sixty five participants had mild pain, 20 participants had moderate pain and three participants had severe pain (Figure 2A). The mean pain score at 20 hours post-operation was 2.5. At 20 hours post-operation, 14 participants had no pain, 63 participants had mild pain, 22 participants had moderate pain and one had severe pain. (Figure 2B) The mean pain score at 24 hours post-operation was 2.3. At 24 hours post-operation, 19 participants had no pain, 64 participants had mild pain,17 participants had moderate pain and no participant had severe pain. (Figure 2C)

There were 66 participants in moderate to severe pain group. The possible associated factors including; advanced maternal age, maternal body mass index, parity, operative time, tubal resection, adhesion, previous surgery, indication for cesarean delivery, type of incision, amount of blood loss and oral analgesic drug used were compared between moderate to severe pain and mild pain group. An oral analgesic drug used had an adjusted Odd ratio of 0.29 (95% confidence interval 0.10 to 0.80) with a statistically significant difference. No statistically significant difference was demonstrated in other factors between both groups (Table 2).

DISCUSSION

From this study, although intrathecal morphine was used in post–cesarean delivery, about two-thirds of the patients reported moderate to severe pain or



Median=20 hours after operation

Figure 1. Proportion of non-PCA opioid user presented as Kaplan-Meier graph

needed additional morphine. The pain was not related to types of incision, tubal resection and operative time. Additional oral analgesic drugs, however, were associated with reduced postoperative pain significantly.

The mean pain score in this study was similar to that of Nilyam et al. study which reported pain scores 2.9 at both 12 hours and 24 hours after cesarean delivery using both general and spinal anesthesia with intrathecal morphine[11] and Howel et al. study[12] using general anesthesia with postoperative IV–PCA opioids, but more than that of Girgin et al. study which reported pain score at 24 hours 0.1 using spinal anesthesia with intrathecal morphine with postoperative IV–PCA.[13]

Our center is the same as many hospitals, the availability of IV–PCA is limited due to the lack of equipment. Most postoperative pain has been managed by intravenous or intramuscular opioids or NSAIDS when patients request. The limitation of ward staff and the patient's knowledge can cause ineffective pain control which made suffering to the patients.[14] Woldehaimenot et al. reported that only

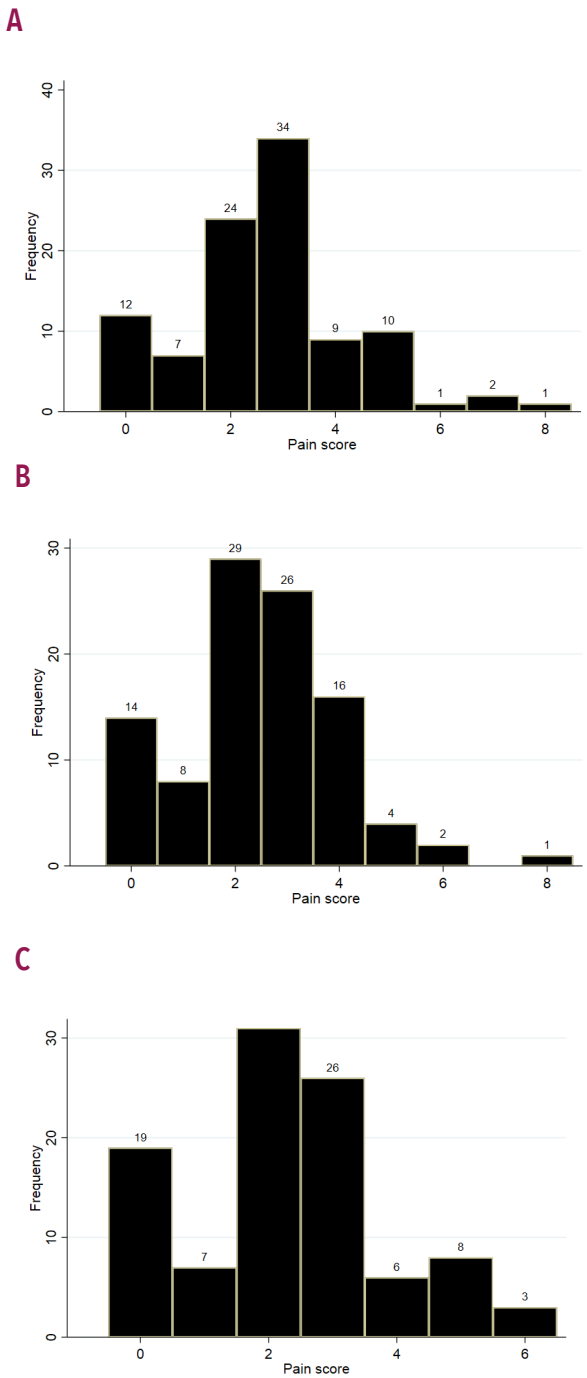


Figure 2. Pain score after operation
Panel A, at 12 hours; Panel B, at 20 hours; Panel C, at 24 hours

a few postoperative patients (2.5%) received pain medication within 15 minutes after complaining of pain and a large number of patients never asked for pain medication during hospitalization.[14] Surgeon and ward staff should be concerned about this fact and postoperative pain management should be based on this limitation.

The clinical implications of this study are first, although intrathecal morphine has been reported for postoperative pain relief at about 16.3 to 17.5 hours,[13] 8.0% of patients needed additional analgesia within 2 hours post-operation, one-fourth of patients within 6 hours and half of the patients within 20 hours. Oral analgesic drugs have been proven for their effectiveness for reducing pain in this study. The starting time however in this study was at 12 hours post-operation which was too late. Therefore, additional analgesic drugs such as paracetamol and NSAIDS especially by the oral route should be offered to patients within 2 hours post-operation. The intravenous or intramuscular analgesic drugs such as NSAIDS or morphine should be added in cases of moderate to severe pain when the oral form of the analgesic drug is insufficient for pain control. This multimodality treatment has been recommended.[1] However, pain control should be managed individually. This is dependent on the level of pain and the patient's satisfaction because nearly half of all patients do not need additional analgesia.

The limitation of this study is the secondary data analysis of a randomized controlled trial, so the pain scores were measured only at 12, 20 and 24 hours post–operation. The pain scores were affected by the intervention (paracetamol plus diclofenac). The post-operative pain in this study was based on pain control by intrathecal morphine with post-operative IV–PCA which is different from general anesthesia or post-operative intravenous or intramuscular opioids. Further research about the result of multimodality pain control with different conditions, such as lack of IV–PCA should be conducted.

In summary, nearly two-thirds of the patients had moderate to severe pain after cesarean delivery under spinal anesthesia using 0.5% bupivacaine with 0.1 to 0.2 mg intrathecal morphine. Pain can happen as early as within two hours after the operation. The use of oral analgesic drugs was associated with pain reduction after cesarean delivery.

REFERENCES

1. Choi J GL, Santos AC. . Obstetric Regional Anesthesia. In: A. H, editor. Hadzic's textbook of Regional Anesthesia and acute pain management. second ed. NewYork: McGraw-Hill; 2017.
2. Carvalho B, Cohen SE, Lipman SS, Fuller A, Mathusamy AD, Macario A. Patient preferences for anesthesia outcomes associated with cesarean delivery. Anesthesia & Analgesia. 2005;101(4):1182-7.
3. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg. 2003;97(2):534-40, table of contents.
4. Leung AY. Postoperative pain management in obstetric anesthesia–new challenges and solutions. Journal of clinical anesthesia. 2004;16(1):57-65.
5. Cunningham F LK, Bloom S, Dashe J, Hoffman B, Casey B,Spong CY. Williams Obstetrics. 25 ed: Mcgraw-hill; 2018.
6. Lacy CF, Armstrong LL, Goldman MP, Lance LL. Drug information handbook with international trade names index: Lexi-Comp Inc; 2007.
7. Moote C. Efficacy of nonsteroidal anti-inflammatory drugs in the management of postoperative pain. Drugs. 1992;44(5):14-30.
8. Norsuwan S NP, Songthamwat S, Songthamwat M. . Effectiveness of diclofenac plus paracetamol for postoperative pain control after caesarean delivery: a randomized trial. . Journal of clinical and diagnostic research : JCDR. 2019;13(3):1-3.

9. Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH, et al. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manage. 2011;41(6):1073-93.
10. Bernard R. Fundamentals of biostatistics. Boston, PWS Publishers. 2000;2:140-246.
11. Nilyam P PL, Apidechahul P, Rungjindamai C. A comparison of pain assessment following cesarean section between ward nurse and pain management team in Siriraj Hospital. Thai J Anesthesiol. 2016;42(4):291-99.
12. Howell PR, Gambling DR, Pavy T, McMorland G, Douglas MJ. Patient-controlled analgesia following caesarean section under general anaesthesia: a comparison of fentanyl with morphine. Can J Anaesth. 1995;42(1):41-5.
13. Girgin NK, Gurbet A, Turker G, Aksu H, Gulhan N. Intrathecal morphine in anesthesia for cesarean delivery: dose-response relationship for combinations of low-dose intrathecal morphine and spinal bupivacaine. J Clin Anesth. 2008;20(3):180-5.
14. Woldehaimanot TE, Eshetie TC, Kerie MW. Postoperative pain management among surgically treated patients in an Ethiopian hospital. PLoS One. 2014;9(7):e102835.

Risk factors for acute perforation of the appendix

ORIGINAL ARTICLE

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ABSTRACT

OBJECTIVE

To identify factors related to acute perforation of the appendix.

METHODS

This study was a retrospective cohort study including patients with acute appendicitis admitted to Khon Kaen Hospital between October 2018 and September 2019. The questionnaires were distributed to the patients on the day following their operation to identify their characteristics. Some information was extracted from medical records. The outcome of our interest was the acute perforation of the appendix.

RESULTS

Three hundred thirty-nine patients with acute appendicitis were admitted during the study period; 74 with acute perforation of the appendix and 265 without. The significant factors related to acute perforation of the appendix were having diabetes, hypertension, cardiovascular diseases, Asia pacific BMI>23 kg/m^2, (or WHO BMI >25 kg/m^2), duration of abdominal pain longer than 12 hours, white blood cell count more than 15,000 cell/mm^3. Symptoms suggested acute perforation of the appendix included fever, nausea, anorexia, vomiting, and diarrhea. Using the Alvarado score and waiting times were not related as a risk.

CONCLUSION

Factor related to acute perforation were having diabetes, hypertension, cardiovascular diseases, high BMI, long duration of abdominal pain and increased white blood cell count.

INTRODUCTION

Acute appendicitis is the most common cause of abdominal pain requiring emergency operations worldwide.[1,2] The incidence of appendicitis is approximately 233 per 100,000 population and is highest in those aged between 10 to 19 years old.[3] Lifetime risk for male and female are 8.6% and 6.9%, respectively.[4] It is sometimes complicated by perforation or rupture.[5] The rate of acute perforation in adults varies from 13.2 to 41.9 %.[6,7] In Thailand, most of the cases are transferred to higher facility hospitals where a higher rate of acute perforation appendix is observed.[8] Risks for the perforation of the appendix have been identified previously e.g., older age, received antibiotics before diagnosis, insurance scheme, however, the information might be out of date as it was based on data from 1987 to 1996 and studied in the context of no universal coverage health scheme.[9] Therefore we aimed to evaluate factors related to perforated appendicitis in a place where access to care is relatively high.

METHODS

STUDY DESIGN

This is a retrospective cohort study determining factors related to acute perforation of the appendix. The study protocol was approved by the Khon Kaen Hospital Institute Review Board in Human Research (KE 61088).

PATIENTS

Patients were all diagnosed as acute appendicitis admitted in Khon Kaen Hospital between October 2018 and September 2019. To accomplish 95% confidence interval (CI) with 1% desired precision, we collected data from at least 192 appendicitis patients. Those with incomplete data were excluded. The informed consent was waived due to this study was a retrospective study.

DATA COLLECTION

During the hospital after the operation, medical records of the included patients were reviewed and verified regarding their characteristics, i.e., nationality, date of birth, underlying diseases, referral status, prior antibiotics usage, the character of the abdominal pain and associated symptoms, time from the onset of abdominal pain to hospital arrival, timing of the hospital arrival, the timing of the operation, pre and postoperative diagnosis, investigations results and length of the hospital stay were extracted from the medical records.

STATISTICAL ANALYSIS

All data were entered into a spreadsheet and statistical analysis was performed with statistical software; STATA 11.0; StataCorp LP, College Station, TX, USA. For descriptive statistics, categorical variables were summarized using numbers and percentages. Continuous data were described with median and interquartile range (IQR) for non-normally distributed variables or mean and standard deviation for normally distributed variables. The univariable analysis was done by Fisher's exact test for categorical data and Student's t-test or Mann–Whitney U-test for continuous data. Risk factors for acute perforation of the appendix were identified using the binary logistic regression analysis and interpreted in term of adjusted odds ratio (AOR) together with 95% confidence interval (CI).

Table 1. Characteristics of the Patients

Characteristics	With acute perforation of the appendix (N=74)	Without acute perforation of the appendix (N=265)	P Value
Age–yr			
Median	15	14	0.066
Interquartile range	(9.0–56.0)	(11.0–26.0)	
Paediatric–no. (%)	35 (47.3)	143 (54.0)	0.31
Adults–no. (%)	39 (52.7)	122 (46.0)	
Thai nationality–no. (%)	74 (100)	263 (99.3)	0.454
Male–no. (%)	44 (59.5)	136 (51.3)	0.215
Body-mass index			
Median	20.8	19.8	0.138
Interquartile range	(16.4–25.4)	(16.4–22.5)	
Underlying disease–no. (%)			
Anemia	1 (1.4)	6 (2.3)	0.625
Diabetic Mellitus	9 (12.2)	5 (1.9)	<0.001
Hypertension	9 (12.2)	10 (3.8)	0.006
Cardiovascular disease	4 (5.4)	0	<0.001
Transferred from other hospitals	58 (78.4)	197 (74.6)	0.507
Antibiotics administration prior to admission–no. (%)	31 (42.5)	66 (25.1)	0.004
Duration of abdominal pain–hr–no. (%)			<0.001
<12	12 (16.2)	110 (41.5)	
≥12	62 (83.8)	155 (58.5)	
Median	24	13	
Interquartile range	(24.0–48.0)	(8.0–24.0)	
System time–minutes			0.520
Median	281.5	270	
Interquartile range	(182–581)	(162–509)	

Table 1. (continued.)

Characteristics	With acute perforation of the appendix (N=74)	Without acute perforation of the appendix (N=265)	P value
Timing from arrival to timing of surgery in Acute appendicitis diagnosed at Emergency room–hr			0.158
Median	5.23	4.48	
Interquartile range	(3.7–10)	(2.52–8.48)	
White blood cell count–cell/mm^3			0.006
Median	16,900	14,900	
Interquartile range	(13,300–20,700)	(11,900–18,200)	
White blood cell count >15,000 cell/mm^3–no. (%)	129 (48.7)	47 (63.5)	0.024
Similar diagnosis with preoperative diagnosis–no. (%)	259 (97.7)	31 (41.9)	<0.001
Length of staying in another hospital prior to KKH	0	0	0.671
Length of the hospital stay–days			<0.001
Median	3	7	
Interquartile range	(2–3)	(6–7)	
Using Alvarado scoring system for diagnosis–no. (%)	93 (35.1)	22 (9.7)	0.389

System time=duration from Khon Kaen Hospital arrival to timing of the operation, pediatric=patient age less than 15 years old, adult patients=patient older than 14 years old.

RESULTS

There were 347 patients with acute appendicitis included in the present study, 8 were excluded due to incomplete data. Finally, there were 339 patients with 74 having a perforation of the appendix. Their characteristics are shown in Table 1. Nearly all were Thai. Comparing those with and without acute perforation of the appendix, the former tended to have a higher proportion of patients with diabetes (P<0.001) and cardiovascular disease (P<0.001) longer duration of abdominal pain (P<0.001), higher white blood cell count (P=0.006) (Table 1). Moreover, the former also had a higher proportion of patients with fever (P<0.001) and nausea (P<0.001) (Table 2). We categorized patients' body mass index (BMI) using both WHO and Asia Pacific criteria and found that higher BMI of both criteria was observed in those with acute perforation of the appendix (P=0.017 and P=0.005, respectively) (Table 3).

From the binary logistic regression analysis, factors found to be associated with higher of risk for acute perforation of the appendix were diabetes (AOR, 5.845; 95% CI, 1.351 to 25.292), longer duration of the abdominal pain (AOR, 1.018; 95% CI, 1.008 to 1.028), fever (AOR, 2.869; 95% CI, 1.532 to 5.374) (Table 4)

Table 2. Symptoms of the patients

Symptom	With acute perforation of the appendix (N = 74)	Without acute perforation of the appendix (N=265)	P Value
	no. (%)		
Abdominal pain	73 (98.7)	264 (99.6)	0.333
Fever	52 (70.3)	111 (41.9)	<0.001
Nausea	48 (64.9)	135 (50.9)	0.034
Anorexia	44 (59.5)	95 (35.9)	<0.001
Vomiting	43 (58.1)	118 (44.5)	0.039
diarrhea	29 (39.2)	69 (26.0)	0.027

After subgroup analysis for those aged 15 years or older, we found factors found to be associated with higher of risk for acute perforation of the appendix were diabetes (AOR, 4.946; 95% CI, 1.035 to 23.647), higher body mass index (AOR,1.163; 95% CI, 1.035 to 1.038), longer duration of abdominal pain (AOR, 1.018; 95% CI, 1.005 to 1.032) and prior treated with antibiotics (AOR, 2.630; 95% CI, 1.031 to 6.712) (Table 4). For those aged younger than 15 years old, we found factors associated with higher of risk for acute perforation of the appendix were the longer

Table 3. Body mass index of the patients

BMI	With acute perforation of the appendix (N = 74)	Without acute perforation of the appendix (N=265)	P Value
WHO			0.017
Underweight (BMI<18.5)	29 (39.2)	104 (39.3)	
Normal (BMI 18.5-24.9)	24 (32.4)	122 (46.0)	
Overweight (BMI 25-29.9)	19 (25.7)	31 (11.7)	
Obese (BMI ≥30)	2 (2.7)	8 (3.0)	
Asia Pacific			0.005
Under weight (BMI<18.5)	29 (39.2)	104 (39.3)	
Normal (BMI18.5–22.9)	15 (20.3)	101 (38.1)	
Over weight (BMI 23–24.9)	9 (12.2)	21 (7.9)	
Obese (BMI≥25)	21 (28.4)	39 (14.7)	

BMI=body mass index.

Table 4. Factors associated with acute perforation of the appendix using binary logistic regression analysis

Factors	Adjusted odds ratio (95% confidence interval)		
	All cases	Age≥15	Age<15
Diabetes	5.845 (1.351–25.292)	4.946 (1.035–23.647)	-
Hypertension	1.233 (0.315 –4.829)	0.867 (0.203–3.703)	-
Body mass index–kg/m^2	1.003 (0.969 – 1.037)	1.163 (1.035–1.308)	0.983 (0.931–1.038)
Duration of abdominal pain–hr	1.018 (1.008 –1.028)	1.018 (1.005-1.032)	1.027 (1.010–1.044)
White blood cell count–cell/mm^3	1.000 (1.000 –1.000)	1.000 (1.000–1.000)	1.000 (1.000-1.000)
Fever	2.869 (1.532 –5.374)	1.872 (0.757–4.626)	6.193 (2.089–18.363)
Nausea	1.909 (0.870 – 4.192)	2.095 (0.634–6.930)	1.728 (0.560–5.327)
Anorexia	1.364 (0.715 – 2.602)	0.944 (0.342–2.603)	2.056 (0.801–5.280)
Vomiting	1.122 (0.535 –2.351)	2.365 (0.734–7.617)	0.903 (0.290–2.809)
Diarrhea	1.439 (0.760 –2.723)	2.362 (0.955–5.841)	0.925 (0.342–2.501)
Prior treated with antibiotics	1.819 (0.973–3.400)	2.630 (1.031–6.712)	1.576 (0.634–3.915)

duration of abdominal pain (AOR, 1.027; 95% CI, 1.010 to 1.044) and fever (AOR, 6.193; 95% CI 2.089 to 18.363).

DISCUSSION

PRINCIPAL FINDINGS

In the present study, acute perforation of the appendix was found in approximately nearly a quarter of our cases. Factors found to be associated with acute perforation of the appendix were diabetes, longer duration of abdominal pain and fever. In our subgroup analysis for those aged 15 years or older, diabetes and higher BMI and longer duration of abdominal pain and prior treated with antibiotics were associated with acute perforation of the appendix. However, longer duration of abdominal pain and fever were the only two factors found to be associated with acute perforation of the appendix.

COMPARISON WITH OTHER STUDIES

Alvarado scoring system usually is used to diagnose acute appendicitis. However, not many were evaluated with Alvarado scores. Still, the rates of acute perforation of the appendix with perforation were similar between those using and not using the score,[16] even there was a study reporting that the score of six or greater was associated with more advanced stages of acute appendicitis.[17] We found a similar duration of timing between hospital arrival and surgery. of those with and without acute perforation of the appendix. This was supported by a previous study in which stating that delay operation overnight with preoperative antibiotics did not increase post appendectomy, complication.[14] Stevenson et al. also reported the median time from emergency department physician evaluation to operation in 955 patients was 7.2 hours and the duration less than 24 hours did not increase the odds of acute

perforation of the appendix.[15] The length of hospital stay in perforated appendicitis is statistical significant longer than acute appendicitis. The shorten the length of hospital stay, the lower the cost of overall treatment.

STRENGTH AND LIMITATION OF THE STUDY

To our knowledge, this study is one of the very first studies examining factors related to acute perforation of the appendix in the setting of universal coverage with adequate power to identify those factors. However, there are also some limitations. First, our findings were from a referral center hospital, the degree of generalizability might be limited. Second, this was a retrospective cohort study. Missing data are inevitable. However, they were kept very low due to the completeness of the original data source.

CONCLUSION AND IMPLICATION

Factors found to be associated with acute perforation of the appendix were diabetes, longer duration of abdominal pain and fever. From our findings, a prehospital factor related to acute perforation of the appendix was the longer duration of abdominal pain since its onset to the hospital arrival. Providing knowledge for better self-awareness to shorter the duration might reduce the possibility of complicated appendicitis. Those with comorbidity such as diabetes might also require close evaluation of possible complications.

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REFERENCES

1. Williams GR. Presidential address: a history of appendicitis. with anecdotes illustrating its importance. Ann Surg 1983;197:495.
2. Fitz RH. Perforating inflammation of the vermiform appendix with special reference to its early diagnosis and treatment. Am J Med Sci 1886;92:321.
3. Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol 1990; 132:910.
4. Körner H, Söndenaa K, Söreide JA, et al. Incidence of acute nonperforated and perforated appendicitis: age-specific and sex-specific analysis. World J Surg 1997;21:313.
5. Douglas Smink, MD, MPH,David I Soybel, MD. Management of acute appendicitis in adults [internet]. Waltham, MA.; 2019 [cited 2019 Apr 1]. Available from: https://www.uptodate.com/contents/management-of-acute-appendicitis-in-adults?search=appendicitis%20adult&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
6. Gadomski A, Jenkins P. Ruptured appendicitis among children as an indicator of access to care. Health Serv Res 2001;36:129–142.
7. Buckley RG, Distefan J, Gubler KD, Slymen D. The risk of appendiceal rupture based on hospital admission source. Acad Emerg Med 1999;6:596–601.
8. Sasithorn Mongkholsawas, Sompong Thepsri. Clinical tracer of appendicitis from surgical patients care team in Khon Kaen Hospital; 2017 April 27; Khon Kaen. Khon Kaen: Khon Kaen Hospital Thailand, 2017.
9. Bratton SL, Haberken CM, Waldhausen JH. Acute appendicitis, risk of complications: age and medicaid insurance. Pediatrics. 2000;106:75–8.
10. N. Sicard, Non–patient factors related to rates of ruptured appendicitis, BJS 2007;94(2): 214-221.
11. Temple CL, Huchcroft SA, Temple WJ. The natural history of appendicitis in adults. A prospective study. Ann Surg 1995;221:278.
12. Pogorelić Z, Rak S, Mrklić I, Jurić I., Prospective validation of alvarado score and pediatric appendicitis score for the diagnosis of acute appendicitis in children., Pediatr Emerg Care 2015;31(3):164-8.
13. Peyvasteh M, Askarpour S, Javaherizadeh H, Besharati S. Modified alvarado score in children with diagnosis of appendicitis. Arq Bras Cir Dig. 2017;30(1):51-52.

14. Burjonrappa S, Rachel D., Pediatric appendectomy: optimal surgical timing and risk assessment. Am Surg. 2014 May; 80(5): 496-9.
15. Stevenson MD, Dayan PS, Dudley NC, Bajaj L, Macias CG, Bachur RG, Sinclair K, Bennett J, Mittal MK, Donneyong MM, Kharbanda AB. Time from emergency department evaluation to operation and appendiceal perforation. Pediatrics 2017;139(6).
16. Taweesuk P, Sithtichok L, Sasithorn M, Outcomes of treatment for appendicitis by using alvarado score in Khon Kaen Hospital, Thailand. Udonthani Hospital Medical Journal 2018;26(2).
17. Nascimento RR, Souza JCG, Alexandre VB, Kock KS, Kestering DM. Association between the Alvarado score and surgical and histopathological findings in acute appendicitis. Rev Col Bras Cir 2018;45(5):e1901. doi: 10.1590/0100-6991e-20181901
18. Obladen M. Necrotizing enterocolitis–150 years of fruitless search for the cause. Neonatology 2009;96:203-210.
19. Holman RC, Stoll BJ, Curns AT, Yorita KL, Steiner CA, Schonberger LB. Necrotising enterocolitis hospitalisations among neonates in the United States. Paediatr Perinat Epidemiol 2006;20:498-506.
20. Guillet R, Stoll BJ, Cotten CM, et al. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. Pediatrics 2006;117(2):e137-e142.
21. Horbar JD, Badger GJ, Carpenter JH, et al. Trends in mortality and morbidity for very low birth weight infants, 1991-1999. Pediatrics 2002;110:143-151.
22. Erasmus HD, Ludwig-Auser HM, Paterson PG, Sun D, Sankaran K. Enhanced weight gain in preterm infants receiving lactase-treated feeds: a randomized, double-blind, controlled trial. J Pediatr 2002;141:532-537.
23. Fitzgibbons SC, Ching Y, Yu D, et al. Mortality of necrotizing enterocolitis expressed by birth weight categories. J Pediatr Surg 2009;44:1072-1075.
24. Ballance WA, Dahms BB, Shenker N, Kliegman RM. Pathology of neonatal necrotizing enterocolitis: a ten-year experience. J Pediatr 1990;117:S6-13.

Peritubal bupivacaine infiltration for postoperative pain reduction after percutaneous nephrolithotomy

SYSTEMATIC REVIEW

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ABSTRACT

OBJECTIVE

To compare the effect of peritubal bupivacaine infiltration to conventional pain management for postoperative pain reduction after percutaneous nephrolithotomy.

METHODS

Two independent reviewers systematically searched through electronic databases including the Cochrane Library, PubMed, Trip Database and Scopus using the term "percutaneous nephrolithotomy" or "PCNL" or "PNL" together with "bupivacaine". We also sought for additional studies using a hand searching to identify all relevant randomized controlled trials (RCTs). We used the Cochrane Collaboration Tool for assessing the risk of bias. Criteria for inclusion in our meta-analysis included participants with percutaneous nephrolithotomy who were assigned randomly to peritubal bupivacaine infiltration or no local anesthetic infiltration and the outcomes were postoperative pain and time to first demand analgesia.

RESULTS

Eight RCTs were included in the meta-analysis with 652 patients undergoing percutaneous nephrolithotomy; peritubal bupivacaine infiltration (N=327) and no local anesthetic infiltration (N=325). The mean visual analog scale (VAS) at 6 hours postoperative care in peritubal bupivacaine infiltration was significantly lower than that of no local anesthetic infiltration (mean difference (MD), -1.36; 95% confidence interval (CI), -1.54 to -1.19). Five RCTs were included in the meta-analysis for time to first demand analgesia evaluation with 415 patients; peritubal bupivacaine infiltration (N=209) and no anesthetic infiltration (N=206). The mean time to first demand analgesia was longer than no local anesthetic infiltration group (MD, 170.4 minutes; 95% confidence interval,161.3 to 179.5 minutes).

CONCLUSION

This meta-analysis found that the peritubal bupivacaine infiltration was significant in alleviating immediate postoperative pain and delaying the time to first demand for analgesia after percutaneous nephrolithotomy.

INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is considered the standard treatment of large renal calculi, that has been described since the late 1970s.[1] However, the placement of a nephrostomy tube results in distressing peritubal pain requiring the administration of analgesia. Inadequate analgesia can result in delayed mobilization, impaired ventilation, and prolong hospitalization.[2] All structures, including renal capsule, muscle, subcutaneous tissue, and skin contribute to the pain during puncture and dilatation at the time of PCNL.[3,4] Infiltration local bupivacaine at peritubal, including skin, subcutaneous tissue, nephrostomy tract, and renal capsule can reduce postoperative pain, prolong the time to first demand analgesia and reduce consumption of rescue analgesia after PCNL.[2,5] Bupivacaine is a long-acting amide local anesthetic, its mechanism is based on their ability to increase the threshold of electrical excitation of nerve fibers.[6] Peritubal infiltration with bupivacaine is increasing interest in recent years as it is simple, safe, inexpensive and provide postoperative analgesia after PCNL.[2,3,5,7,8] However, prior to this study, there has not yet been a systematic review of the effect of postoperative pain reduction in patients undergoing PCNL. This study, thus, aims to compare the efficacy between peritubal bupivacaine infiltration and no local anesthetic infiltration for pain reduction after PCNL.

METHODS

SEARCHING STRATEGIES

Two independent reviewers systematically searched through electronic databases including the Cochrane Library, PubMed, Trip Database and Scopus using the term "percutaneous nephrolithotomy" or "PCNL" or "PNL" together with "bupivacaine". We also sought for additional studies using a hand searching to identify all relevant randomized controlled trials (RCTs). We used the Cochrane Collaboration Tool for assessing the risk of bias. Criteria for inclusion in our meta-analysis included participants with percutaneous nephrolithotomy who were assigned randomly to peritubal bupivacaine infiltration or no local anesthetic infiltration and the outcomes were postoperative pain and time to first demand analgesia.

INCLUSION CRITERIA

STUDY DESIGN

We included only RCTs

PARTICIPANTS

We included RCTs with patients undergoing percutaneous nephrolithotomy under general anesthesia assigning randomly to peritubal bupivacaine infiltration or no local anesthetia.

INTERVENTIONS AND COMPARISONS

Local analgesic pain control with peritubal bupivacaine infiltration after percutaneous nephrolithotomy compared to no local anesthetic infiltration either saline or no infiltration.

OUTCOMES

Outcomes of studies included postoperative pain in visual analog scale at 6 hours and the time to first demand for analgesia.

EXCLUSION CRITERIA

We removed studies that were duplicated and studies that did not perform general anesthesia

during the operation. The studies with any spinal or epidural anesthesia in adjunct postoperative care were excluded. We excluded intervention groups including usage of other local anesthetic drugs than bupivacaine for peritubular infiltration.

QUALITY OF REPORTING AND RISK OF BIAS

We used Jadad score to assess the quality of the included RCTs comprising the evaluation of randomization, blinding methods and adequate description of withdrawals or dropouts.[9] In addition, we used the Cochrane Collaboration's Tool for demonstration the risk of bias in relation to random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias by classifying them to be three degrees which are low risk, high risk, and unclear risk of bias.[10]

DATA EXTRACTION

We extracted the data from the included studies regarding the first author, year of publication, numbers of participants, outcomes of visual analog scale (VAS) of pain score at 6 hours and time to first demand analgesia after PCNL in each study.

DATA ANALYSES

The outcomes VAS pain score at 6 hours from the eight trials were meta-analyzed and interpreted using the mean difference (MD) and 95% confidence interval (CI). The outcomes time for first demand analgesia after PCNL from the five trials were meta-analyzed and interpreted using MD and 95% CI, too. Both outcomes were shown as the Forest plot. Later we calculate I^2 to evaluate the heterogeneity among the studies, if I^2 was higher than 50%, the heterogeneity was considered significant. We used a fixed effect and random effect model for meta-analysis. The publication bias was evaluated as Funnel plots. All statistical analyses were using Review Manager 5.3 statistical software.

RESULTS

STUDY CHARACTERISTICS

Initially, there were 97 citations identified by two independent reviewers. Of these, after duplication removed 26 citations were identified. All studies were RCTs. After screened the titles and abstracts, 59 citations were excluded and then twelve full-text articles assessed for eligibility according to inclusion and exclusion criteria. Finally, eighth studies were included in the meta-analysis by the consensus of two reviewers (Figure 1). Eight studies compared between peritubal bupivacaine infiltration and no anesthetic infiltration for VAS at 6 hours and five studies compared between peritubal bupivacaine infiltration and no local anesthetic infiltration for time to first demand analgesia. The characteristics of the included studies are shown in Table 1.

ASSESSING THE QUALITY AND RISK OF BIAS

The quality of the eight studies was assessed using the Jadad score to assess the risk of bias (Table 2). The risk of bias was assessed using The Cochrane Collaboration's tool for risk of bias assessment and summarized in Figure 2A and Figure 2B. All studies were randomized and used the double-blind method. Six studies did not describe the randomization method and concealment. The

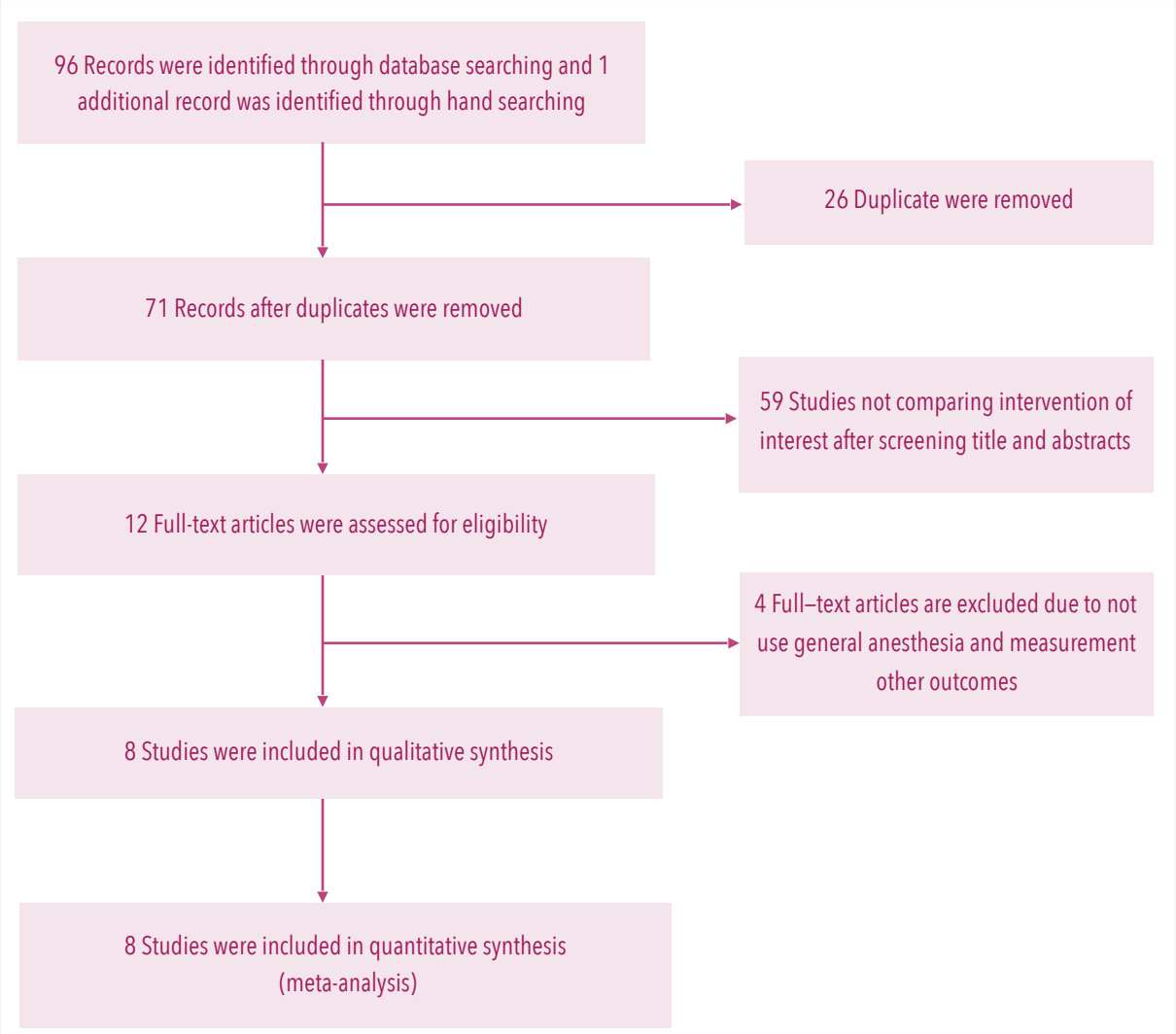

Figure 1. Process of study selection

method of double-blinding did not describe in four studies. One study reported incomplete outcome data.

OUTCOMES

Eight RCTs were included in the meta-analysis with 652 patients undergoing percutaneous nephrolithotomy; peritubal bupivacaine infiltration (N=327) and no local anesthetic infiltration (N=325). The mean VAS at 6 hours postoperative care in peritubal bupivacaine infiltration were significantly lower than no local anesthetic infiltration group (MD, -1.36; 95% CI, -1.54 to -1.19; I^2= 97%) (Figure 3).

Five RCTs were included in the meta-analysis for time to first demand analgesia evaluation with 415 patients; peritubal bupivacaine infiltration (N=209) and no local anesthetic infiltration (N=206). The mean time to first demand analgesia was longer than no local

Table 1. Characteristics of the eight included studies

Study	Year	No. of patients (intervention/control)	Intervention	Control	Outcomes
George E. Haleblian	2007	10/12	0.25% bupivacaine infiltration	Saline infiltration	No significant differences in pain score.
Nirmala Jonnavithula	2008	20/20	0.25% bupivacaine infiltration	No infiltration	Intervention significantly reduced pain score and prolonged time to first demand analgesia.
Geeta P Parikh	2011	30/30	0.25% bupivacaine infiltration	Saline infiltration	Intervention significantly reduced pain score, prolonged time to first demand analgesia and reduced total analgesic requirement.
Mustafa Kirac	2013	61/60	0.25% bupivacaine infiltration	No infiltration	Intervention significantly reduced pain score.
Bannakij Lojanapiwat	2015	53/52	0.25% bupivacaine infiltration	No infiltration	Intervention significantly reduced pain score and prolonged time to first demand analgesia.
Shariq Anis Khan	2017	47/47	0.25% bupivacaine infiltration	Normal saline infiltration	Intervention significantly reduced pain score.
Isra Karaduman	2017	66/64	0.25% bupivacaine 20 mL + 5mg morphine 0.5 mL infiltration	No infiltration	Intervention significantly reduced pain score and prolonged time to first demand analgesia.
Gokce Dundar	2017	20/20	0.25% bupivacaine infiltration	Saline infiltration	Intervention significantly reduced pain score and prolonged time to first demand analgesia.

anesthetic infiltration (MD, 170.4 minutes; 95% CI, 161.3 to 179.5 minutes; I^2=99%) (Figure 4).

In the studies subgroup of each comparison, the mean VAS in peritubal bupivacaine infiltration were significantly lower than saline infiltration (MD, -2.82; 95% CI, -3.15 to -2.48; I^2=97%) (Figure 5) and the mean time to first demand analgesia in the intervention group were longer than saline infiltration group (MD, 340.1 minutes; 95% CI, 322.8 to 357.5 minutes; I^2=100%) (Figure 6). There was a significantly lower VAS in the intervention group than no infiltration group (MD, -0.83; 95% CI, -1.05 to -0.60; I^2=90%) (Figure 7). The time to first

Table 2. Jadad score

Questions	George E. Haleblian 2007	Nirmala Jonnavithula 2008	Geeta P Parikh 2011	Mustafa Kirac 2013	Bannakij Lojanapiwat 2015	Shariq Anis Khan 2017	Isra Karaduman 2017	Gokce Dundar 2017
1. Was the study described as randomized?	1	1	1	1	1	1	1	1
2. Was the method used to generate the sequence of randomization describe and appropriate?	0	1	0	1	0	0	0	0
3. Was the study described as double blind?	1	0	1	0	0	1	0	1
4. Was the method of double blinding described and appropriate?	1	0	1	0	0	1	0	1
5. Was there a description of withdrawals and dropouts?	0	1	1	1	1	1	1	1
Total	3	3	4	3	2	4	2	4

analgesic demand in the intervention group longer than no infiltration group (MD, 60.2 minutes; 95% CI, 34.5 to 85.9 minutes; I^2=89%) (Figure 8).

PUBLICATION BIAS

According to our funnel plot which constructed from the eight trials included in the analysis appeared to be asymmetrical and suggested potential publication bias in this review (Figure 9).

DISCUSSION

SUMMARY OF EVIDENCE

The meta-analysis results indicated that peritubal bupivacaine infiltration reduced the immediate postoperative pain in patients undergoing PCNL and prolonged the time to first demand analgesia when compared to conventional pain management. The data showed high heterogeneity suggesting that there were variations among studies. One of the possible causes of variations among studies was the use of subjective evaluation and measurements to assess the VAS and the time to first demand analgesia. Because pain is both subjective and multidimensional, but postoperative pain measurement most are based on self-reporting of a unidimensional scale aiming to represent subjective pain intensity.[11] The multidimensional evaluation of postoperative status such as a postoperative quality of recovery score would be a useful end-point in perioperative clinical studies.[12]

STRENGTH AND LIMITATIONS OF THE REVIEW

The strength in this systematic review is two independent authors searched for eligible RCTs by screening all titles and abstracts and reading the full-text articles to assess relevant studies, so we

Figure 2. Risk of bias

Panel A, Risk of biases summary and Panel B, Risk of bias graph

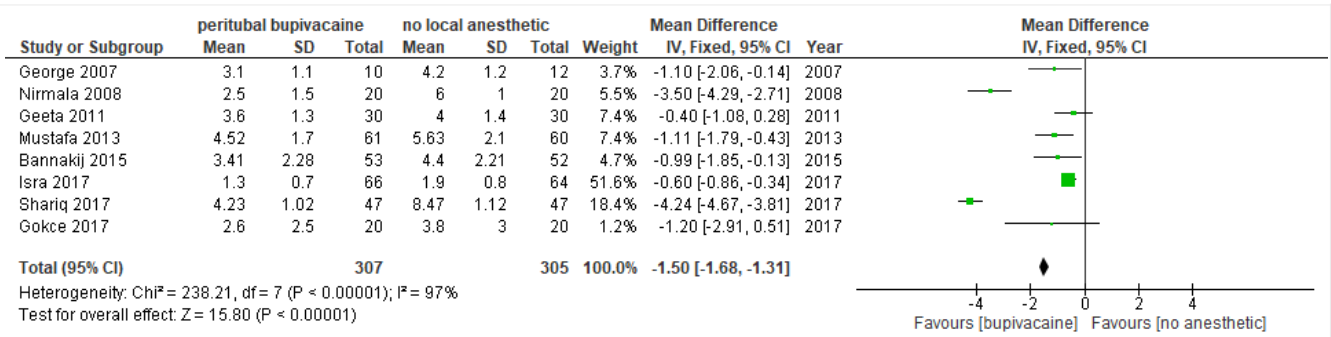

Figure 3. Forest plot: peritubal bupivacaine infiltration versus no local anesthetic infiltration, outcome: VAS in 6 hours postoperative percutaneous nephrolithotomy

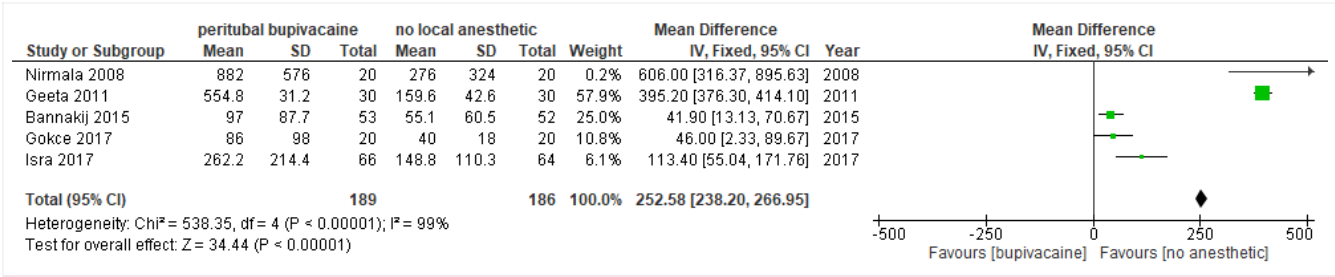

Figure 4. Forest plot: peritubal bupivacaine infiltration versus no local anesthetic infiltration, outcome: time to first demand of analgesia

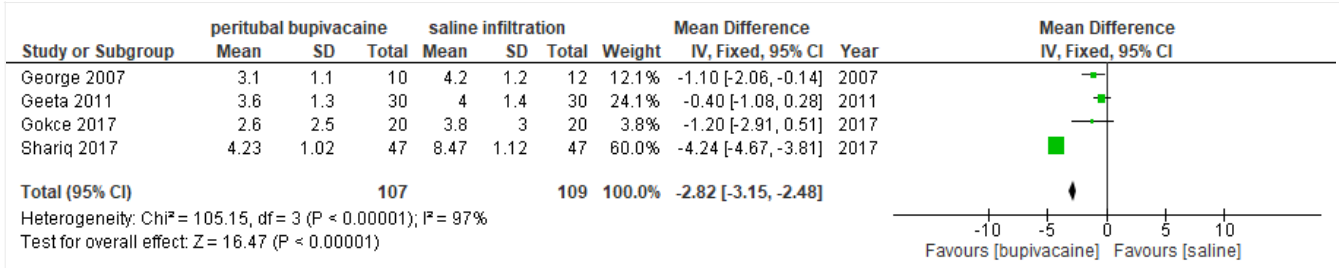

Figure 5. Forest plot: peritubal bupivacaine versus saline infiltration, outcome: VAS in 6 hours postoperative percutaneous nephrolithotomy

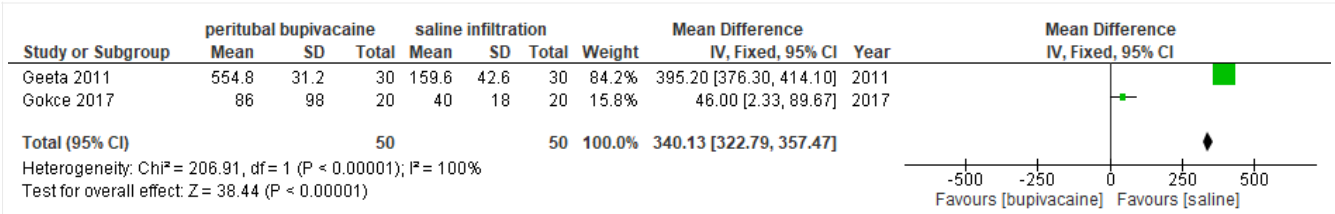

Figure 6. Forest plot: peritubal bupivacaine versus saline infiltration, outcome: time to first demand of analgesia

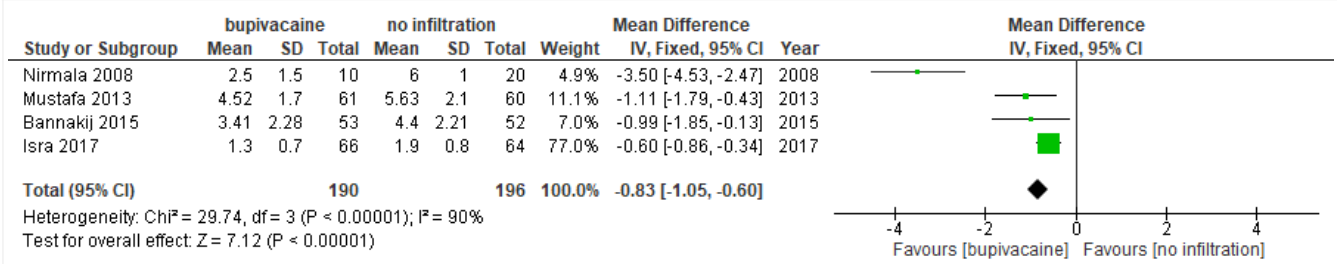

Figure 7. Forest plot: peritubal bupivacaine versus no infiltration, outcome: VAS in 6 hours postoperative percutaneous nephrolithotomy

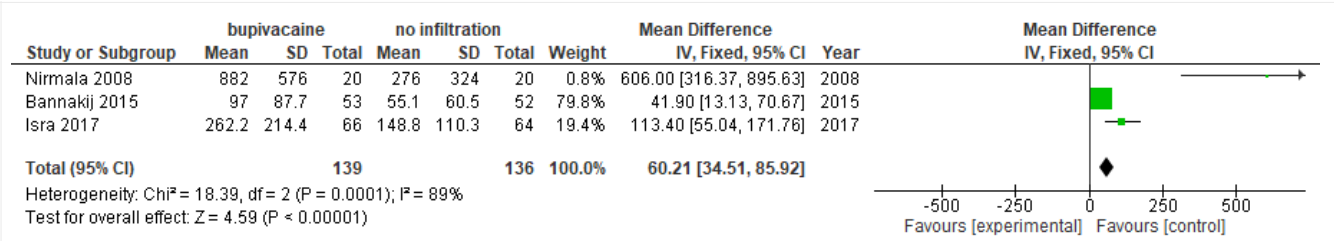

Figure 8. Forest plot: peritubal bupivacaine versus no infiltration, outcome: time to first demand analgesia

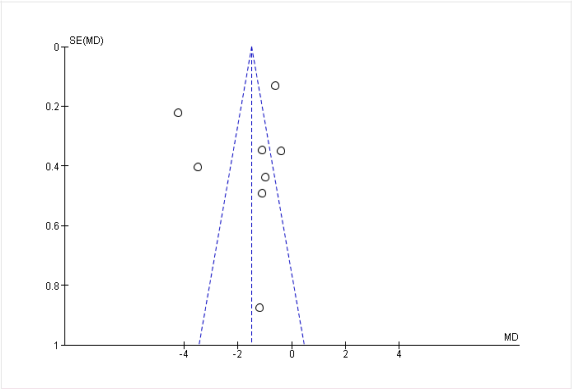

Figure 9. Funnel plot of overall postoperative pain reduction outcomes.

got eligible studies and assured not to miss the important data.

The limitation of this systematic review is the risk of bias. The selection bias, random sequence generation, and allocation concealment were not identified in many studies. The performance bias was presented in half of the included studies due to a lack of blinding of participants and personnel in comparison groups. Baseline preoperative data of VAS did not reveal in all of the included studies. This is a limitation because pain is both subjective and multidimensional and so the VAS cannot capture the complete pain experience. But clinical decisions are made based on existing pain scales, and so it is important to know how much reduction in a VAS score is likely to be clinically meaningful from the patient's perspective.[11]

COMPARISON WITH OTHER STUDIES

PCNL is accepted to be the minimally invasive procedure for large renal stones with less morbidity and mortality, but PCNL still causes significant postoperative pain especially nephrostomy tube placement for tamponade of bleeding along the tract and adequate drainage.[5] Jonnavithola et al. studied the effectiveness of peritubal bupivacaine infiltration of the renal capsule. This technique consisted of the use of a 23 gauge spinal needle along nephrostomy tube at 6 and 12 o'clock and each infiltrated 10 mL of 0.25% bupivacaine into peritubal nephrostomy tract, including skin, subcutaneous tissue, muscle, and renal capsule. That was developed under the rational to relief the pain that might be originated in the renal capsule after PCNL surgery.[3] Munkongsrisuk et al. demonstrated that no significant difference postoperative pain reduction and time to first analgesic demand between only subcutaneous bupivacaine infiltration after PCNL and control group.[13] Recent studies were evaluated the efficacy of peritubal bupivacaine infiltration but there were shown the various results and some studies had few numbers of the participants.[2–5,7,8,14,15] Nonetheless, their outcome

measures might not be reliable as they did not have baseline pain. It is important to know how much reduction in a VAS score is likely to be clinically meaningful from the patient's perspective.[11]

CONCLUSION AND IMPLICATION

This meta-analysis found that the peritubal bupivacaine infiltration was significant in alleviating immediate postoperative pain and delaying the time to first demand for analgesia after PCNL when compared with the no anesthetic infiltration group. However, this study has three key limitations that may limit the implementation of clinical practice. First, the included studies in the meta-analysis lacked a procedure to blind the participants. Second, there was an incomplete baseline VAS pain score. Third, the data showed high heterogeneity. For further study, we suggest having the new RCT that clear study design in allocation concealment, blinding procedure, and well-defined pain score reduction assessment.

REFERENCES

1. Fernström I, Johansson B. Percutaneous pyelolithotomy. A new extraction technique. Scand J Urol Nephrol. 1976;10(3):257–9.
2. Khan SA, Khalid SE, Effendi FN, Mithani MH, Awan AS, Mugal T. Postoperative Pain Score of Bupivacaine versus Placebo in Patients Undergoing Percutaneous Nephrolithotomy. J Coll Physicians Surg--Pak JCPSP. 2018 Nov;28(11):858–61.
3. Jonnavithula N, Pisapati MVLN, Durga P, Krishnamurthy V, Chilumu R, Reddy B. Efficacy of peritubal local anesthetic infiltration in alleviating postoperative pain in percutaneous nephrolithotomy. J Endourol. 2009 May;23(5):857–60.
4. Dalela D, Goel A, Singh P, Shankhwar SN. Renal capsular block: a novel method for performing percutaneous nephrolithotomy under local anesthesia. J Endourol. 2004 Aug;18(6):544–6.
5. Lojanapiwat B, Chureemas T, Kittirattarakarn P. The efficacy of peritubal analgesic infiltration in postoperative pain following percutaneous nephrolithotomy - A prospective randomized controlled study. Int Braz J Urol Off J Braz Soc Urol. 2015 Oct;41(5):945–52.
6. Shafiei FT, Lopez J. Bupivacaine. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 [cited 2019 Jun 25]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK532883/
7. Kirac M, Tepeler A, Bozkurt OF, Elbir F, Ozluk C, Armagan A, et al. The efficacy of bupivacaine infiltration on the nephrostomy tract in tubeless and standard percutaneous nephrolithotomy: a prospective, randomized, multicenter study. Urology. 2013 Sep;82(3):526–31.
8. Parikh GP, Shah VR, Modi MP, Chauhan NC. The analgesic efficacy of peritubal infiltration of 0.25% bupivacaine in percutaneous nephrolithotomy - A prospective randomized study. J Anaesthesiol Clin Pharmacol. 2011 Oct;27(4):481–4.
9. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996 Feb;17(1):1–12.
10. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. The BMJ [Internet]. 2011 Oct 18 [cited 2019 Jul 6];343. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3196245/
11. Myles PS, Myles DB, Galagher W, Boyd D, Chew C, MacDonald N, et al. Measuring acute postoperative pain using the visual analog scale: the minimal clinically important difference and patient acceptable symptom state. Br J Anaesth. 2017 Mar 1;118(3):424–9.
12. Myles PS, Weitkamp B, Jones K, Melick J, Hensen S. Validity and reliability of a postoperative quality of recovery score: the QoR-40. Br J Anaesth. 2000 Jan;84(1):11–5.
13. Mankongsrisuk T, Nualyong C, Tantiwong A, Taweemonkongsap T, Amornvesukit T, Chotikawanich E. Efficacy of Nephrostomy Tract Infiltration with Bupivacaine Before and After Tubeless Percutaneous Nephrolithotomy: A Randomized Control Study. 2017;100:6.
14. Haleblian GE, Sur RL, Albala DM, Preminger GM. Subcutaneous bupivacaine infiltration and postoperative pain perception after percutaneous nephrolithotomy. J Urol. 2007 Sep;178(3 Pt 1):925–8.
15. Karaduman I, Karasu D, Yilmaz C, Oner S, Erdem Solak H, Korfali G. The Effect of Peritubal Infiltration with Bupivacaine and Morphine on Postoperative Analgesia in Patients Undergoing Percutaneous Nephrolithotomy. Pain Res Manag. 2017;2017:2454267.

"I shall either find a way or make one"

-Hannibal Barca

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