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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

This issue is going to be the first for our 43rd volume. We would like to start our new volume with two systematic reviews and a retrospective cohort. If you want to know the new treatment for head lice. I strongly suggest the first article in this issue. You will also find the answer regarding effects of oxytocin in different solutions on cord plasma bilirubin. Our last article in this issue is about sites of cord insertion and delayed the third stage of labor in spontaneous delivery. Medicine never stops, just like all of us. So keep moving, keep reading. We hope you enjoy reading our journal. Good luck.

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

submission

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For online submission

Our issues of each volume will be published online
IN
February, April, June, August, October, and December

reviewing process

All accepted articles are classified into two main categories;
"***standard submission***" with the approximated processing time of 3-4 months and "***expression submission***" with the approximated processing time of 1-2 months. For the latter category, the author must submit as standard submission with notifying our journal for express submission.

Email: theclinicalacademia@gmail.com
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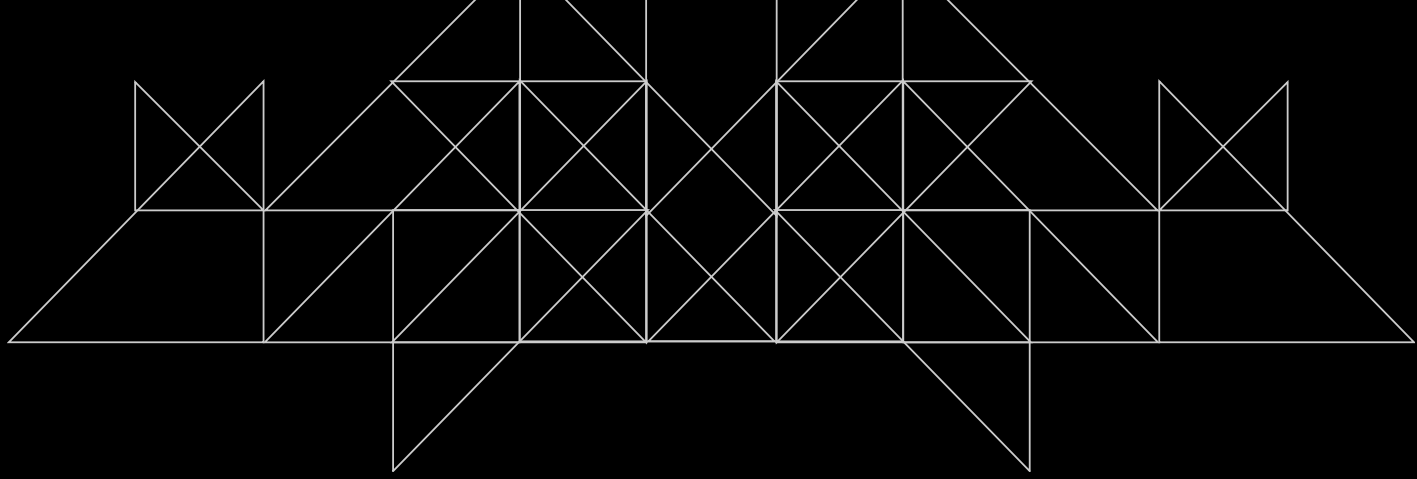
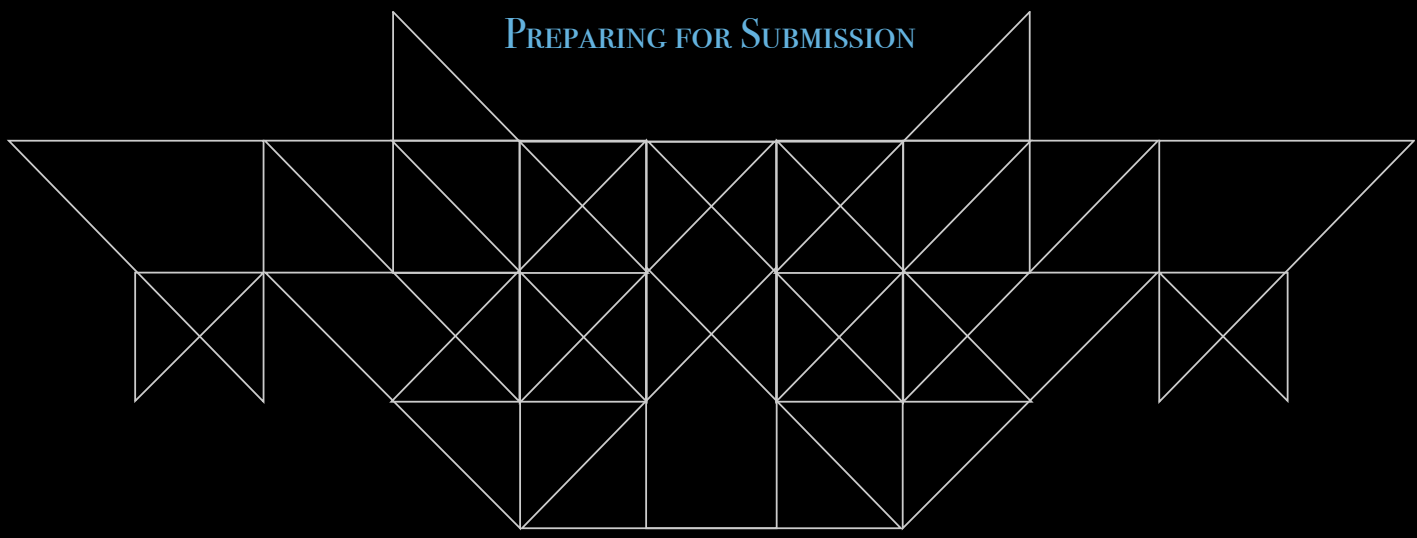
Contents



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.

Conflict of Interest declaration. Conflict of interest information for each author needs to be part of the manuscript; each journal should develop standards with regard to the form the information should take and where it will be posted. The ICMJE has developed a uniform conflict of interest disclosure form for use by ICMJE member journals and the ICMJE encourages other journals to adopt it. Despite availability of the form, editors may require conflict of interest declarations on the manuscript title page to save the work of collecting forms from each author prior to making an editorial decision or to save reviewers and readers the work of reading each author's form.

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.

If you use data from another published or unpublished source, obtain permission and acknowledge that source fully.

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.

i. Illustrations (Figures)

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.

Amylmetacresol and 2,4-dichlorobenzyl alcohol (AMC/DCBA) lozenge for postoperative sore throat: systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

Kittiya Jitpreeda[1], M.D.; Kiattida Boonasa [2], M.D.; Pijak Sirirattanaku[3], M.D. ; Rattanapa Kesonsombat [4], M.D.

[1]Kalasin Hospital, Thailand; [2]Sakon Nakhon Hospital, Thailand; [3]Chum Phae Hospital, Thailand; [4]Udon Thani Hospital, Thailand.

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Correspondence to: Chutharat Thanchonnang; chuth.pp@gmail.com

ABSTRACT

OBJECTIVE

To assertain the efficacy of amylmetacresol and 2,4-dichlorobenzyl alcohol (AMC/DCBA) or Strepsils® lozenge in those with postoperative sore throat (POST).

METHODS

Four independent reviewers systematically searched through electronic databases including Medline, Cochrane Library, Trip Database, Scopus and ClinicalTrials.gov using the keywords (operative OR extubation OR intubation OR "postoperative sore throat" OR POST) AND "sore throat" AND ("Amylmetacresol and 2,4-dichlorobenzyl alcohol" OR "AMC/DCBA" OR "Strepsils" OR lozenge). The search was confined to human studies without language restrictions. We also sought for additional studies using a hand searching to explore other unidentified studies outside the database to identify all relevant randomized controlled trials. We assessed the quality of the included studies using Jadad score and The Cochrane Collaboration's Tool for Assessing Risk of Bias. Meta-analysis was performed where appropriate.

RESULTS

Two included randomized control trials involving 245 participants compared preoperative administration of AMC/DCBA lozenge (N=123) versus placebo (N=122) in patients with POST. This systematic review showed effect of AMC/DCBA lozenge on POST severity score (severity score grading; 0 to 3) compared to placebo within 30 minutes after operation (mean difference (MD) -0.36, 95% confidence interval (CI) -0.5 to -0.21; I^2=0%) and at 24 hours after operation (MD -0.26, 95% CI -0.52 to -0.01; I^2=79%).

CONCLUSION

Preoperative administration of AMC/DCBA lozenge significantly reduced POST severity score within 30 minutes after operation more than that of placebo. However, its effects at 24 hours after the operation could not be concluded due to high heterogeneity.

INTRODUCTION

Postoperative sore throat (POST) is a minor complication that affects nearly 50% of patients undergoing endotracheal intubation.[1,2] There are multiple risk factors for POST including using endotracheal tube rather than laryngeal mask, younger ages, smoking, female, poor American Society of Anesthesiologists (ASA) physical status, using pressure cuff adjustment only at the beginning of the operation rather than pressure cuff adjustment every hour during the operation, larger number endotracheal tube and using fentanyl rather than pethidine.[1-5] Its symptoms are usually mild and resolve within 24 hours.[6,7] However, it may affect patients' satisfaction with the hospital services.[8] Many substance bases of lozenge are used for pain relieving.[9-13] These include amylmetacresol and 2,4-dichlorobenzyl alcohol (AMC/DCBA) as known as Strepsil®, ambroxol, lidocaine and benzocaine.[9-13] AMC/DCBA is used for relieving sore throat symptoms from upper respiratory tract infection.[9, 12] Although many studies and trials support that it can reduce severity score of POST,[14-16] there is no systematic review with meta-analysis comparing the efficacy of the AMC/DCBA lozenge and placebo in patients with POST. Thus, this study aims to ascertain the efficacy of AMC/DCBA in those with POST.

METHODS

STUDY DESIGN

This is a systematic review and meta-analysis to ascertain the efficacy of AMC/DCBA lozenge in patients with POST.

ELECTRONIC SEARCHING

We independently sought through electronic databases including Medline, Cochrane Library, Trip Database, Scopus and ClinicalTrials.gov using terms (operative OR extubation OR intubation OR "postoperative sore throat" OR POST) AND "sore throat" AND ("Amylmetacresol and 2,4-dichlorobenzyl alcohol" OR "AMC/DCBA" OR "Strepsils" OR lozenge). Searching in Pubmed was undertaken by using MeSH search strategy using the combination of the following term; (operative[MesH] OR extubation[MesH] OR intubation[MesH] OR "postoperative sore throat" OR POST) AND ("Amylmetacresol and 2,4-dichlorobenzyl alcohol" OR "AMC/DCBA" OR "Strepsils"[MeSH] OR lozenge). Searching in Trip Database was undertaken by using PICO search strategy; P: (operative OR extubation OR intubation OR "postoperative sore throat" OR POST) AND "sore throat", I: ("Amylmetacresol and 2,4-dichlorobenzyl alcohol" OR "AMC/DCBA" OR "Strepsils" OR lozenge). Searching in Cochrane Library, Scopus and ClinicalTrials.gov were undertaken by using search strategy; (operative OR extubation OR intubation OR "postoperative sore throat" OR POST) AND "sore throat" AND ("Amylmetacresol and 2,4-dichlorobenzyl alcohol" OR "AMC/DCBA" OR "Strepsils" OR lozenge). The search was confined to human studies without language restrictions.

SEARCHING OTHER RESOURCES

We also performed hand searching by tracking references of the included studies from electronic database searching to identify other relevant studies.

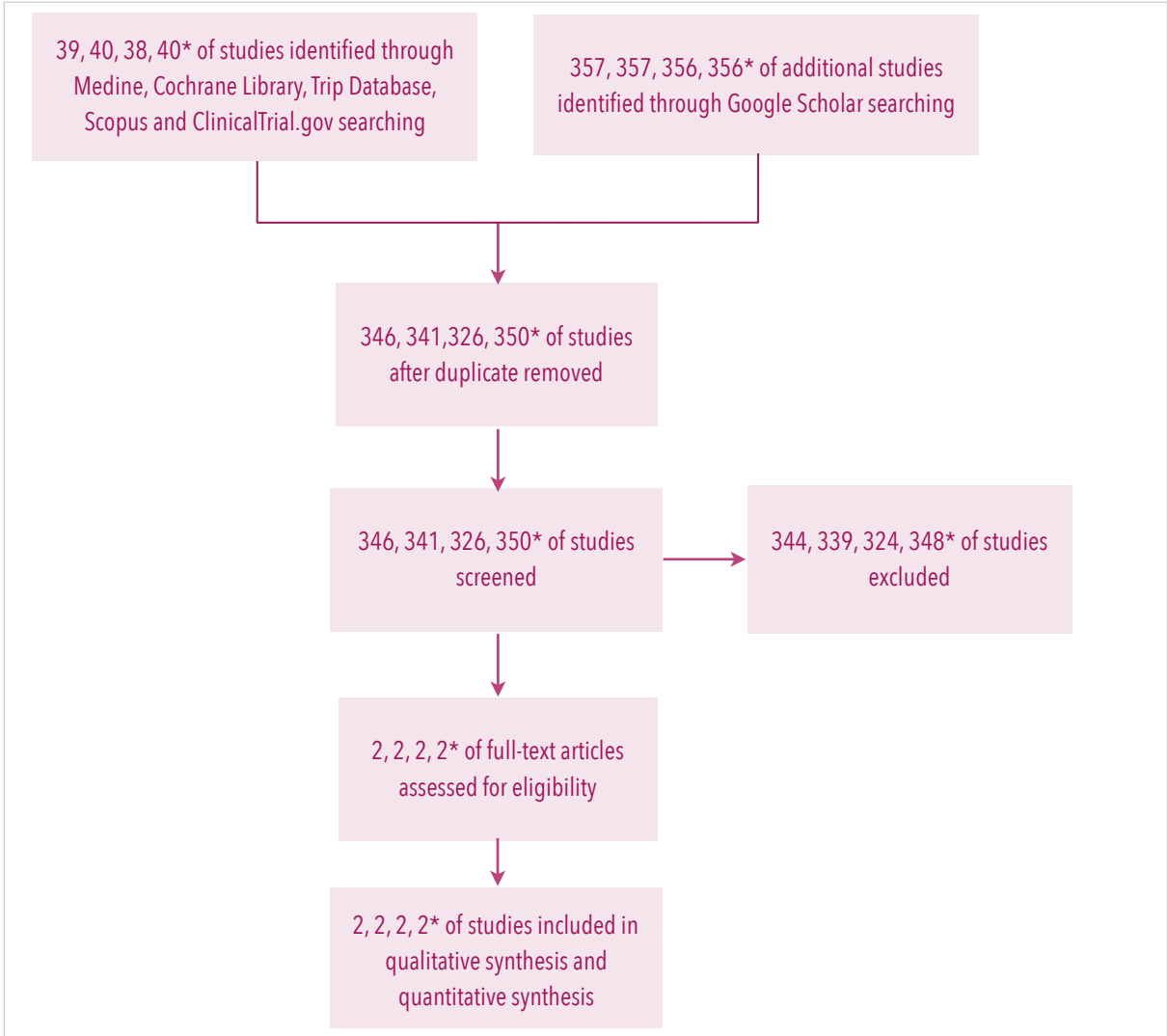

Figure 1. Represents inclusion and exclusion studies in this systematic review
*The numbers of the studies were referred to results of searching by four independent reviewers; Kittiya Jitpreeda, Kiattida Boonasa, Pijak Sirirattanakul, Rattanapa Kesonsombat, respectively.

INCLUSION CRITERIA

We included randomized, controlled clinical trials that evaluated the effect of preoperative administration of AMC/DCBA lozenge in patients with POST. The other studies were excluded. All consensus for including studies was made through discussion or consultation for the fifth reviewers.

SELECTION OF STUDIES

The study selection process was performed independently by the four reviewers. The process is shown in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram. There were two studies included in the quantitative synthesis.

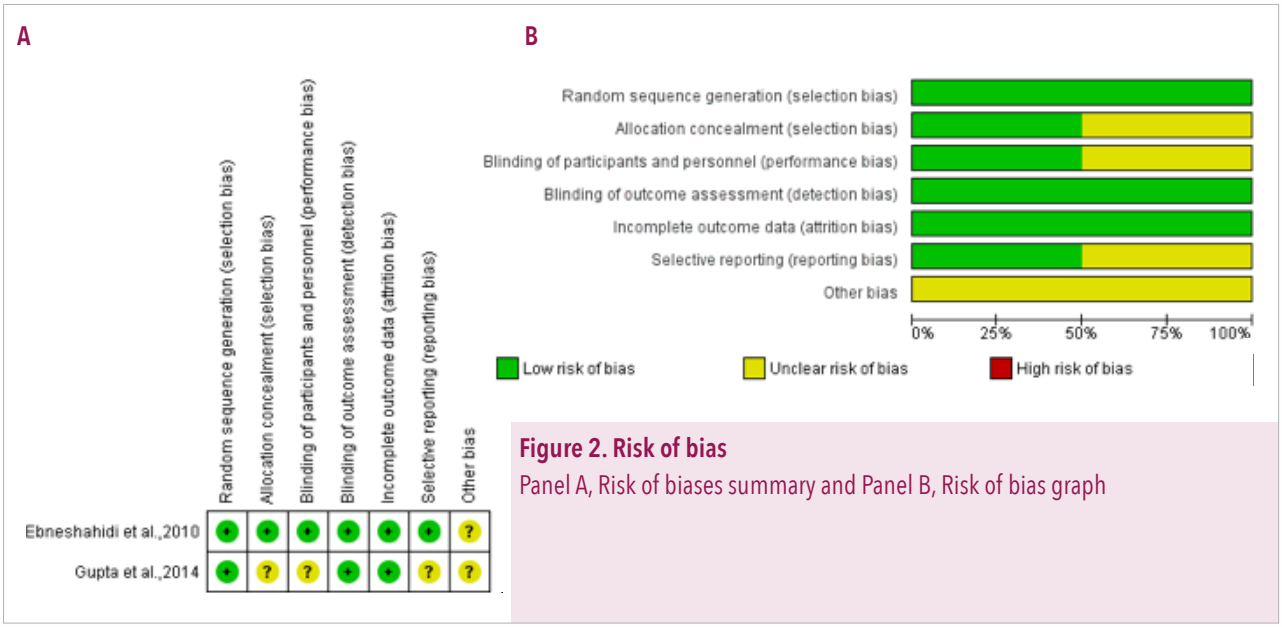

Figure 2. Risk of bias
Panel A, Risk of biases summary and Panel B, Risk of bias graph

DATA EXTRACTION

We independently extracted data from the included trials regarding the first author's name and year of publication, participants' age and sex, numbers of participants in intervention group and control group of each included studies, outcomes and adverse events.

QUALITY OF REPORTING AND RISK OF BIAS

We assessed the quality of the included trials using Jadad score,[17] which included the score for randomization, blinding methods and adequate description of withdrawals or dropouts. In addition, we used The Cochrane Collaboration's Tool for Assessing Risk of Bias.[18] The quality of each trial was categorized into an unclear, low or high risk of bias. All consensus for quality assessment was made through discussion.

DATA ANALYSIS

The combined results were interpreted using forest plot together with a mean difference (MD) and 95% confidence interval (CI). Furthermore, I^2 was calculated to assess the heterogeneity of the studies. We used the fixed-effect model for the combined outcome that $I^2<50\%$ and the random-effect model for the combined outcome that $I^2 \geq 50\%$ in a meta-analysis. We used funnel plots to assess the publication bias. All statistical analyses were done using Review Manager 5.3 statistical software.

RESULTS

RESULTS OF THE SEARCH

From the search methods, 396, 397, 394 and 396 studies were identified independently by reviewers I, II, III and IV, respectively. There were 346, 341, 326 and 350 studies remained after duplication removed. Later, we excluded 344, 339, 324 and 348 studies because they were not eligible for our inclusion criteria based on their titles and abstracts. The remaining two trials were included in the meta-analysis.[14-15] The additional details were shown in the PRISMA flow diagram (Figure 1).

Table 1. Characteristic of the included studies

Trials	Participants	AMC/DCBA lozenge	Placebo	Outcomes
Ebnes-hahidi et al, 2010[14]	n=150 age 19-63 83 male	n=73 45 minutes before anesthesia induction	n=72 placebo tablet 45 minutes before anesthesia induction	The POST severity score at 20 minutes after operation was significantly lower in the AMC/DCBA lozenge group than in the placebo group. (0.2±0.57 vs. 0.52 ±0.85; P<0.05) The POST severity score at 24 hours after operation was significantly lower in the AMC/DCBA lozenge group than in the placebo group. (0.08±0.32 vs. 0.22±0.50; P=0.04)
Gupta et al, 2014[15]	n=100 age 20-65 93 male	n=50 30-45 minutes before anesthesia induction	n=50 sugar candy 30-45 minutes before anesthesia induction	The POST severity score at 30 minutes after operation was significantly lower in the AMC/DCBA lozenge group than in the placebo group. (0.1±0.3 vs. 0.48 ±0.58; P<0.001) The POST severity score at 24 hours after operation was significantly lower in the AMC/DCBA lozenge group than in the placebo group. (0.3±0.51 vs. 0.7±0.46; P<0.001)

Plus-minus value are mean± SD

Table 2. Jadad score of the included trials

Questions regarding		Ebneshahidi 2010	Gupta 2014
Randomized	Mention	1	1
	Appropriate	1	1
	Not appropriate		
Blinding	Mention	1	0
	Appropriate	1	0
	Pot appropriate		
An account of all patients		1	1
Total score		**5**	**3**

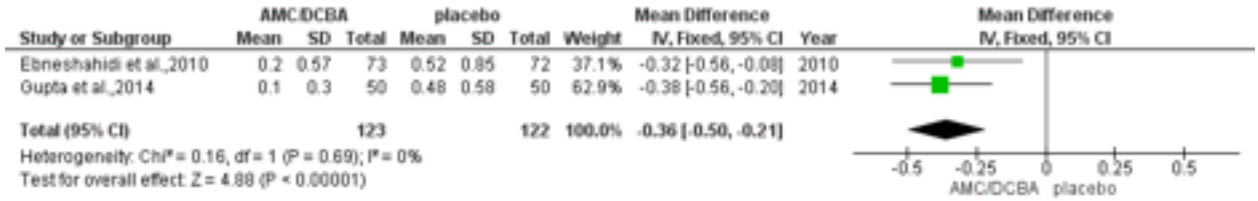

Figure 3. Forest plot, POST severity score at at 30 minutes after operation

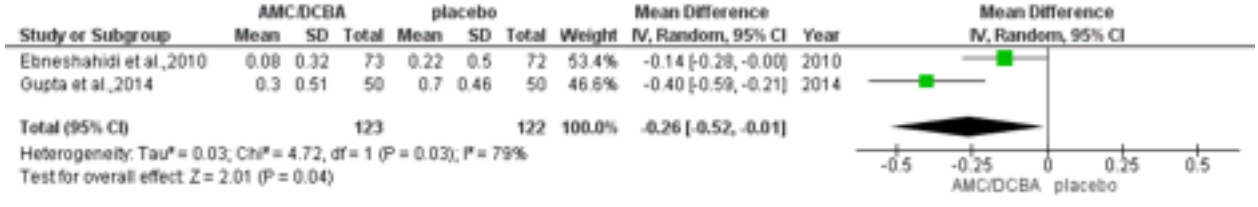

Figure 4. Forest plot, POST severity score at 24 hours after operation

INCLUDED STUDIES

We included two trials which randomized 245 participants to either AMC/DCBA lozenge group (N=123) or placebo group (N=122). These two trials were conducted in Iran[14] and India[15], respectively. The former trial focused on POST severity score, hoarseness and any kind of discomfort symptoms after using either AMC/DCBA lozenge or placebo. The latter focused on POST severity score, postextubation cough (PEC) and hoarseness, however, adverse events were not observed. Ages of all participants were between 19 and 65 years old. All of them underwent surgery under general anesthesia with endotracheal intubation and remaining in hospital over 24 hours; the additional details were summarized in Table 1.

ASSESSING THE QUALITY AND RISK OF BIAS

The quality of the two trials including Ebneshahidi et al. and Gupta et al. was assessed using Jadad score and The Cochrane Collaboration's Tool for Assessing Risk of Bias. The former trial was scored 5 regarding Jadad score as it properly described details of randomization, blinding and complete outcome data. The latter trial was scored 3 as it mentioned that AMC/DCBA lozenge and placebo were identical appearance but lack of mentioning about blinding technique (Table 2). The results of the risk of bias assessment of the study by Ebneshahidi et al. and Gupta et al. using The Cochrane Collaboration's Tool for Assessing Risk of Bias are shown below.

RANDOM SEQUENCE GENERATION

Both trials were described at low risk as they reported methods of random sequence generation; the former trial used table number and the latter trial used drawing chits.

ALLOCATION CONCEALMENT

The former was at low risk of bias as it mentioned that data collectors were blinded and the latter trial was at unclear risk of bias as it did not.

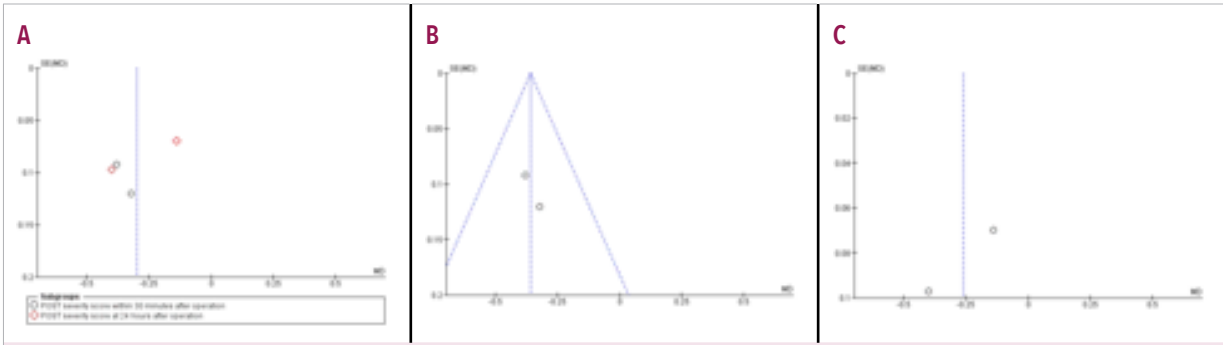

Figure 5. Funnel plot
Panel A, Funnel plot, POST severity score within 30 minutes and at 24 hours after operation; Panel B, Funnel plot, POST severity score within 30 minutes after operation; Panel C, Funnel plot, POST severity score at 24 hours after operation

BLINDING OF PARTICIPANTS AND PERSONAL

The former trial was described as low risk of bias as it mentioned that the participants were blinded. The latter trial was described as unclear risk of bias as it did not.

BLINDING OF PARTICIPANTS AND PERSONAL

Both trials were described as low risk of bias because they evaluated POST severity score by nurses and anesthesiologists, respectively, who were blinded to the study groups.

INCOMPLETE OUTCOME DATA

Both trials were described as low risk of bias due to the absence of incomplete outcome data; the participants were evaluated within the time that they admitted with no drop out.

SELECTIVE REPORTING

The former trial was described as low risk of bias as it reported that none of the patients complained of any discomfort. The latter trial was described as unclear risk of bias because it did not report about adverse effects of intervention or placebo.

OTHER POTENTIAL BIAS

Both trials were described as unclear risk of bias due to lacking mentioning about funding or any conflicts of interests.

OUTCOMES

THE PRIMARY OUTCOME

Comparing between preoperative administration of AMC/DCBA lozenge and placebo within 30 minutes after operation, it showed that using AMC/DCBA lozenge significantly reduced POST severity score more than that of placebo (MD -0.36, 95% CI -0.5 to -0.21; I^2=0%) (Figure 3).

THE SECONDARY OUTCOME

POST SEVERITY SCORE AT 24 HOURS AFTER OPERATION

Comparing between preoperative administration of AMC/DCBA lozenge and placebo at 24 hours after the operation, it showed that using AMC/DCBA lozenge significantly reduced POST severity score more than that of placebo (MD -0.26, 95% CI -0.52 to -0.01; I^2=79%) (Figure 4).

ADVERSE EVENTS

None of the patients from the first study reported any adverse events whereas the second study did not.

PUBLICATION BIAS

We generated the funnel plots of POST severity score within 30 minutes and 24 hours after operation of the two trials (Figure 5). However, the number of studies using in funnel plot were too few to assess for publication bias.

DISCUSSION

PRINCIPAL FINDINGS

In this systematic review and meta-analysis of randomized controlled trials comparing between administered AMC/DCBA lozenge and placebo preoperatively, the results showed that AMC/DCBA lozenge reduced POST severity score more than that of placebo at 30 minutes after the operation with high homogeneity and at 24 hours after the operation with high heterogeneity. No report of adverse effects from one trial and one trial reported no adverse effects during the study period. Publication bias was not assessed due to very few included studies.

STRENGTHS AND LIMITATIONS OF THE STUDY

To our knowledge, this was the first systematic review mentioning the effect of popular AMC/DCBA lozenge or Strepsils® on POST severity score reduction even it has been in the market since 1950.[19] No trials are likely to be missed. The strength of our systematic review is that the conclusion was based on two trials with low to moderate risk of bias. However, our review also has some limitations. The first one was a small number of the included studies. The second one was that our findings showed slightly better of the outcomes in those with the AMC/DCBA comparing with placebo, this might be due to the fact that the assessment of POST severity score was not sensitive for minor differences of the severity outcomes.

COMPARISON WITH OTHER STUDIES

From our literature search, we found no relevant cohorts or case-control studies from electronic databases and other sources. Our review found that AMC/DCBA lozenge for prophylaxis of POST within 30 minutes had a slightly reductive effect. This might be explained by its mechanisms of antibacterial, antiviral and local anesthetic.[20-26] In other words, it reduces the causes of pharyngitis and decreases the perception of pain at throat.[25-27] In one human trial identify clearance of AMC/DCBA in various preparations using radioactivity study, it found that lozenges would stay up in the oropharyngeal area up to 2 hours.[28] Thus, its effects would last no longer than that.[28] This might be the reason why we found the after at 30 minutes but no at 24 hours from both included studies in our review.[14, 15] In relation to its adverse effects, the majority of adverse effects were mild in severity thus they often were not considered to be definitely.[12, 29] However one trials reported mouth ulceration as a severe adverse effect.[9] In brief, AMC/DCBA is relatively safe, however, its efficacy also minimal.

CONCLUSION AND IMPLICATION

AMC/DCBA lozenge significantly reduced POST severity score more than that of placebo within 30 minutes after operation with high homogeneity. It

also significantly reduced POST severity score more than that of placebo at 24 hours after operation with heterogeneity among trials. However, this conclusion was based on a small number of participants, a strong conclusion was unable to deliver. Generalize the findings should be very careful especially in the outcomes with high heterogeneity. However, its adverse effects are trivial. Its harmful uses are then not expected. Further studies should be a randomized controlled trial with greater number of participants. Outcomes should include patient satisfaction and adverse events. The outcomes should also measured using more sensitive scale.

ACKNOWLEDGMENTS & DECLARATION

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COMPETING INTERESTS: This study has no competing on interest.
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Topical sucralfate ointment for postoperative pain reduction after hemorrhoidectomy: systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

Sopanut Akkakraisee[1], M.D.; Rattanawan Mitrapanont[2], M.D.; Anchaleephon Srinathom[3], M.D.

[1]Khon Kaen Hospital, Thailand; [2]Roi Et Hospital, Thailand; [3]Nakhon Phanom, Thailand.

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Correspondence to: Chutharat Thanchonnang; chuth.pp@gmail.com

ABSTRACT

OBJECTIVE

To assess the efficacy of topical sucralfate ointment for postoperative pain reduction after hemorrhoidectomy.

METHODS

Three independent reviewers systematically searched through electronic databases including Cochrane library, Pubmed, Trip Database and Scopus using the term "hemorrhoidectomy" or "post hemorrhoidectomy pain" together with "topical sucralfate ointment". Furthermore, we also sought for additional studies using a hand searching to identify all relevant randomized controlled trials (RCT) that comparing effect of topical sucralfate ointment and other topical treatments for postoperative pain reduction after hemorrhoidectomy. We included RCT with patients undergoing hemorrhoidectomy and using topical sucralfate ointment. We performed risk of bias assessment of the included RCTs, and we later performed the meta-analysis.

RESULTS

Two RCTs were included in the meta-analysis with 138 patients undergoing hemorrhoidectomy; topical sucralfate ointment (N=69) and placebo (N=69). Topical sucralfate ointment had similar effect for pain score reduction to that of placebo at day 7 after hemorrhoidectomy (mean difference (MD) -0.47; 95% confidence interval (CI), -2.01 to 1.07; I^2 =88%) and at day 14 after hemorrhoidectomy (MD -0.16; 95% CI, -1.98 to 1.67; I^2=92%). Furthermore, patients in sucralfate group requested less daily amount of diclofenac than in placebo group at day 7 after hemorrhoidectomy (MD -64.58; 95% CI, -110.61 to -18.56; I^2=92%), but not at day 14 after hemorrhoidectomy (MD -54.25; 95% CI, -113.51 to 5.01; I^2=96%).

CONCLUSION

In patients undergoing hemorrhoidectomy, comparing efficacy between using topical sucralfate ointment and placebo for postoperative pain reduction after hemorrhoidectomy at day 7 cannot be concluded as our review had low volume of studies and participants as well as high heterogeneity.

INTRODUCTION

Hemorrhoids are abnormal dilatation and distortion of the veins of the internal hemorrhoidal venous plexus in the anal canal.[1] It presents when patients have increased abdominal pressure such as straining and chronic constipation.[1] Approximately 40% of patients with hemorrhoids are asymptomatic.[2] Symptomatic hemorrhoids usually present with painless rectal bleeding at the end of defecation or may drip into the toilet, perianal itching and pain due to thrombosis.[2] However, the exact prevalence worldwide of symptomatic hemorrhoids is very difficult to establish as only symptomatic patients will seek for treatment.[3] Its treatments depend on its grading, for instance, hemorrhoidectomy is used in those with grade III or IV hemorrhoids.[4,5] The most common complication of hemorrhoidectomy is postoperative pain due to external wounds cut through a nerve that innervated perianal skin or might be due to bacterial wound infection.[6,7] Conventional analgesics for pain control e.g., nonsteroidal anti-inflammatory drugs (NSAIDs) are often used for short term due to their side effects.[8,9]

Sucralfate is a compound of sucrose sulfate and aluminum hydroxide typically used in oral form for treatment dyspepsia or peptic ulcer.[10,11] It is poorly absorbed in the gastrointestinal tract and it becomes gel-like substance when contacts with water.[10,11] Its action is to release prostaglandin from the gastric mucosa that plays a role in gastric mucosal protection and it also has an antibacterial effect.[12,13] There were prior trials stated that topical sucralfate can stimulate epithelialization and angiogenesis, and it is effective in various condition e.g., second and third-degree burn, perineal excoriation and prevented acute radiation dermatitis.[14-16] Two RCTs from Iran with 48 patients and from Egypt with 90 patients with hemorrhoidectomy showed that using topical sucralfate ointment reduced postoperative pain and usage of analgesia.[17,18] However, there is no evidence of its efficacy for postoperative pain reduction in a patient undergoing hemorrhoidectomy from a systematic review. Thus, we conducted a systematic review to compare the efficacy between topical sucralfate ointment and other topical treatments for postoperative pain reduction after hemorrhoidectomy.

METHODS

SEARCH STRATEGIES

Three independent reviewers systematically searched through electronic databases including Cochrane library, Pubmed, Trip Database, Scopus and other sources e.g., Google Scholar using the combined search terms of "hemorrhoidectomy" or "post hemorrhoidectomy pain" together with "topical sucralfate ointment". We also applied Medical Subject Headings (MeSH) searching using the terms of "hemorrhoidectomy"[MeSH] AND "sucralfate"[MeSH] to identify studies on Pubmed and Cochrane library and applied PICO searching using the terms of P: hemorrhoidectomy with I: topical sucralfate on Trip Database. Furthermore, we also sought for additional studies using hand searching to explore other unidentified studies on the databases to identify all relevant RCTs comparing the efficacy of topical sucralfate ointment and other topical treatments for

Table 1. Characteristics of two studies

Studies	Number of patients (intervention/ control)	Patients' age (years)	Intervention and control	Postoperative analgesic drug	Outcomes
Ala et al 2013	24/24	20-70	10% topical sucralfate ointment 1 g versus topical placebo 1 g	Pethidine for first 24 hours then diclofenac tablets for 14 days	Using topical sucralfate ointment reduced postoperative pain after hemorrhoidectomy more than that of placebo at day 7 and day 14 (P<0.01). Using topical sucralfate ointment reduced daily amount of diclofenac usage at day 7 and day 14 (P<0.001).
Albatanony et al 2016	45/45	21-60	10% topical sucralfate ointment 1 g versus topical placebo 1 g	Pethidine for first 24 hours then diclofenac tablets for 14 days	Using topical sucralfate ointment and placebo had similar efficacy in relation to postoperative pain reduction after hemorrhoidectomy at day 7 (P=0.35) but placebo reduced more at day 14 (P=0.02). Using topical sucralfate ointment reduced daily amount of diclofenac usage at day 7 and day 14 (P<0.001).

postoperative pain reduction after hemorrhoidectomy.

INCLUSION CRITERIA

We included only randomized controlled trial (RCT) with patients undergoing hemorrhoidectomy using topical sucralfate ointment compare with other topical treatments. The outcome of our interest was pain intensity. We excluded the studies that used other topical forms of sucralfate e.g., cream, gel.

QUALITY OF REPORTING AND RISK OF BIAS

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

DATA EXTRACTION

We extracted the data from the included studies regarding the first author, year of publication,

Table 2. Jadad score

	Ala et al	Albatanony et al
Was the study described as randomized ?	1	1
Was the method used to generate the sequence of randomization described and was it appropriate?	1	0
Was the study described as double blind ?	1	1
Was the method of double blind described and was it appropriate ?	1	1
Was there a description of withdrawals and dropouts ?	1	1
Score	5	4

numbers of participants, patients' age, outcomes of visual analog scale (VAS) of pain score and daily amount of diclofenac usage in each study.

DATA ANALYSES

The primary and secondary outcomes from the two trials were meta-analyzed and interpreted using the mean difference (MD) and 95% confidence interval (CI) and were shown as a forest plot. Later we calculated I^2 to evaluate the heterogeneity among the studies. We used the fixed-effect model if $I^2<50\%$ and random-effect model if $I^2\geq50\%$. The publication bias was evaluated as funnel plots. All statistical analyses were done using Review Manager 5.3 statistical software.

RESULTS

STUDY CHARACTERISTICS

Initially, there were 30, 22 and 33 records identified by reviewer I, II and III, respectively, which 9, 7, and 11 of them were duplicated. There were 21, 15 and 22 remained after duplicate removed and excluded 19, 13, 20 from screening articles and abstracts. The remaining two trials were included in the meta-analysis by the consensus of the three reviewers (Figure 1). Both studies compared topical sucralfate ointment and placebo for post hemorrhoidectomy pain reduction. Their characteristics are shown in Table 1.

ASSESSING THE QUALITY AND RISK OF BIAS

The quality of the two studies, Ala et al and Albatanony et al, were assessed using Jadad score to assess the risk of bias.19 They were score 5 and 4, respectively (Table 2). The risk of bias using The Cochrane Collaboration's tool for assessing the risk of bias for both studies was summarized in Figure 2 and Figure 2 and descriptive results are shown below.

RANDOM SEQUENCE GENERATION

The former study was described as low risk of bias as it used a computer-generated table but the later

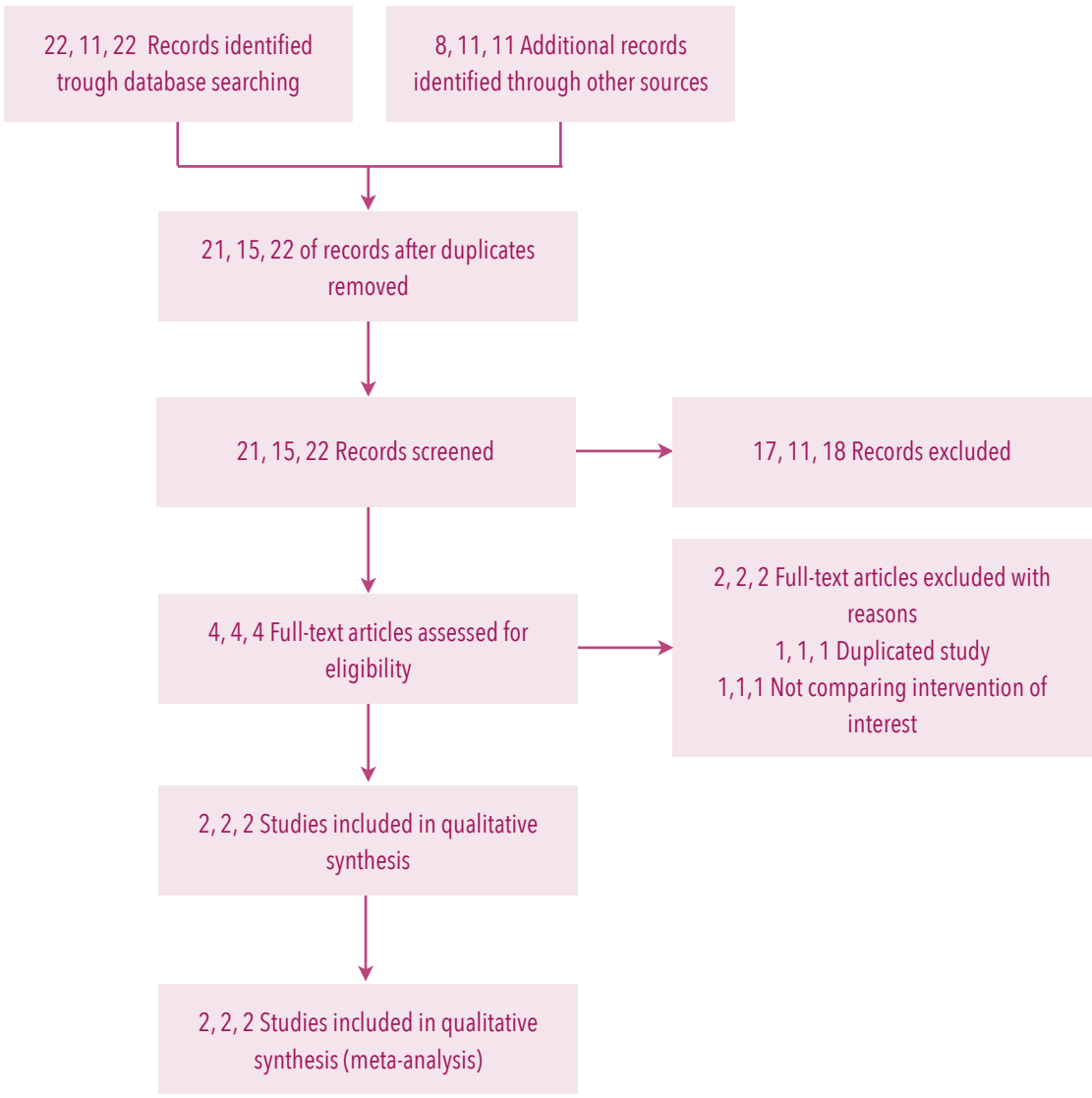

Figure 1. Study flow diagram

study was an unclear risk of bias as it lacked randomization methods description.

ALLOCATION CONCEALMENT

The former study was described as low risk of bias as it blinded data collector and used the identical appearance of containers. The later study also had a low risk of bias as it used closed envelope methods.

BLINDING OF PARTICIPANT AND PERSONAL

Both studies had a low risk of bias as they were double-blind trials with a description of blinding.

BLINDING OF OUTCOME ASSESSMENT

Both studies were described as unclear risk of bias as it did not address this information regarding this process in their studies.

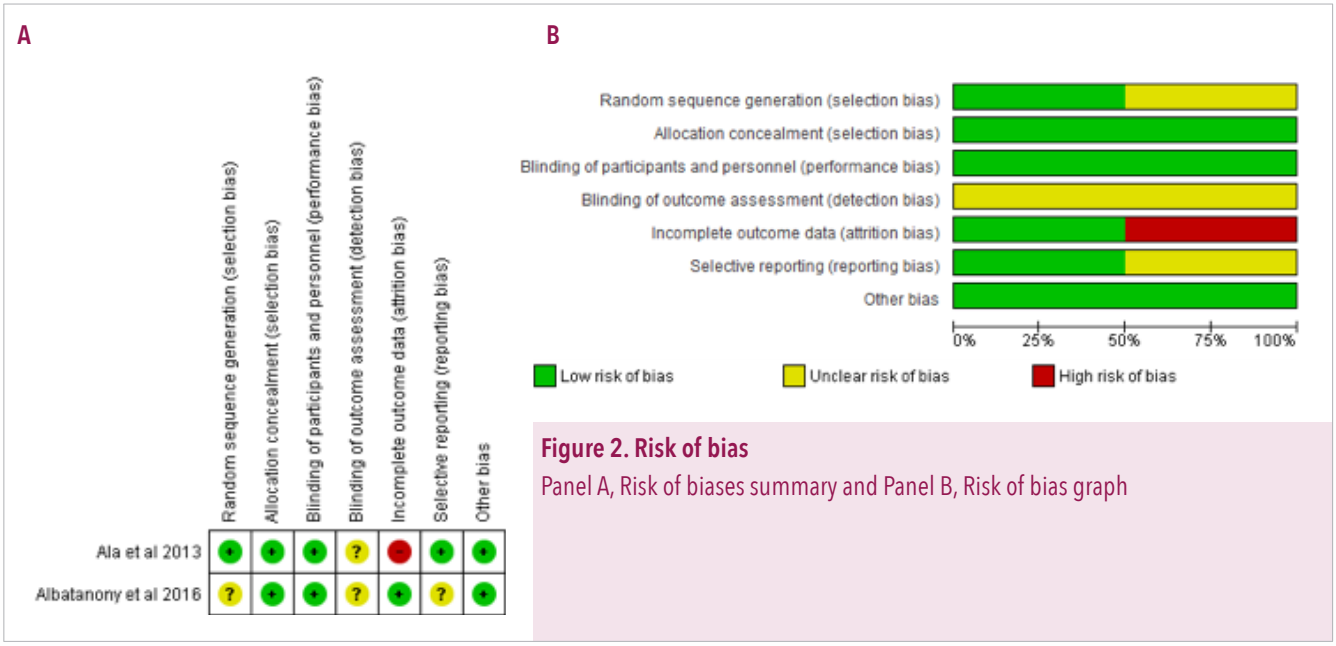

Figure 2. Risk of bias
Panel A, Risk of biases summary and Panel B, Risk of bias graph

INCOMPLETE OUTCOME DATA

The former study had a high risk of bias as it had dropouts. The latter study was a low risk of bias as it had no dropout.

SELECTIVE REPORTING

The former study was described as low risk of bias as all of the outcome data were reported while the later study had an unclear risk of bias as all of the pre-specified primary outcomes was not reported in the study.

OTHER POTENTIAL SOURCES OF BIAS

Both studies had a low risk of bias as they were free from any funding source.

THE PRIMARY OUTCOME

Using topical sucralfate ointment had similar efficacy for post hemorrhoidectomy pain reduction at day 7 after hemorrhoidectomy compared with that of using a placebo (MD -0.47; 95% CI, -2.01 to 1.07; I^2 =88%) (Figure 3).

THE SECONDARY OUTCOME

PAIN SCORE REDUCTION AT DAY 14 AFTER HEMORRHOIDECTOMY

There was no statistically significant difference for post hemorrhoidectomy pain reduction at day 14 between using topical sucralfate ointment and placebo (MD -0.16; 95% CI, -1.98 to 1.67; I^2 =92%) (Figure 4).

DAILY AMOUNT OF DICLOFENAC USAGE

Patients in sucralfate group requested less daily amount of diclofenac than in placebo group at day 7 after hemorrhoidectomy (MD -64.58; 95% CI, -110.61 to -18.56; I^2 =92%) but not at day 14 (MD -54.25; 95% CI, -113.51 to 5.01; I^2 =96%) (Figure 5).

AMOUNT OF PETHIDINE USAGE WITHIN FIRST 24 HOURS

For Ala et al., patients in sucralfate group requested similar amount of pethidine to that in placebo group at 0 to 6 hours after hemorrhoidectomy (MD

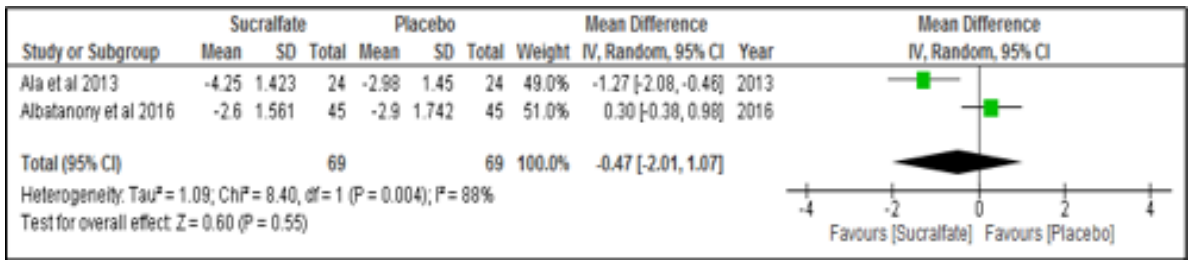

Figure 3. Forest plot: 10% topical sucralfate ointment versus placebo, outcome: Pain score reduction at day 7

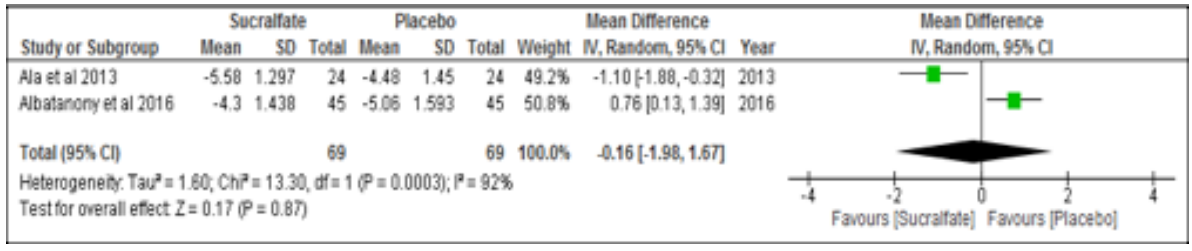

Figure 4. Forest plot: 10% topical sucralfate ointment versus placebo, outcome: Pain score reduction at day 14

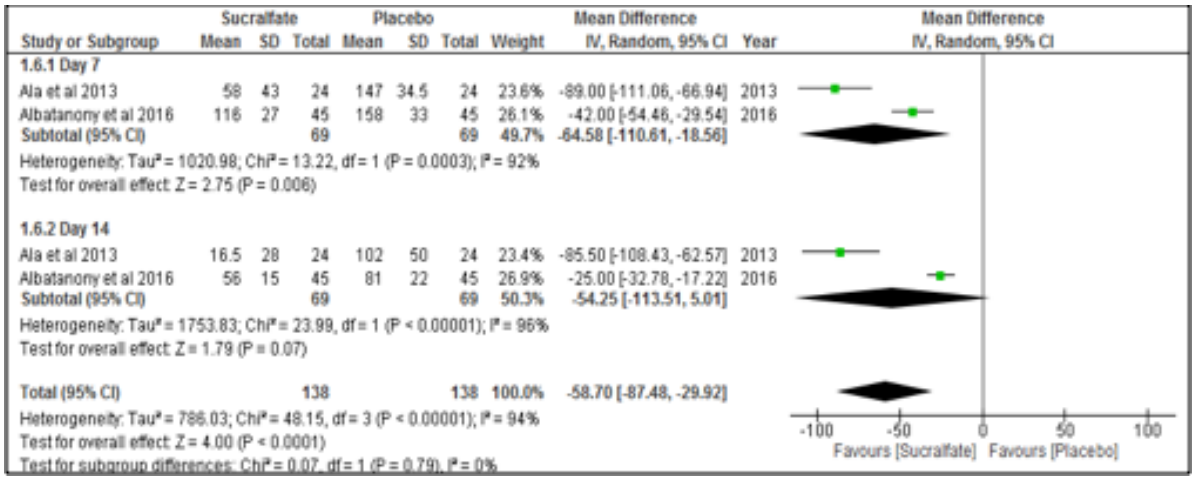

Figure 5. Forest plot: 10% topical sucralfate ointment versus placebo, outcome: Daily amount of diclofenac usage (mg).

-1.04; 95% CI, -14.76 to 12.68) and at 6 to 12 hours after hemorrhoidectomy (MD -4.17; 95% CI, -14.72 to 6.38). However, patients in the sucralfate group requested less amount of pethidine than those in the placebo group at 12 to 24 hours after hemorrhoidectomy (MD -9.37; 95% CI, -18.37 to -0.37). For Albatanony study, patients in sucralfate group requested less amount of pethidine within 24 hours after the operation than placebo group (MD -15.00; 95% CI, -26.45 to -3.55).

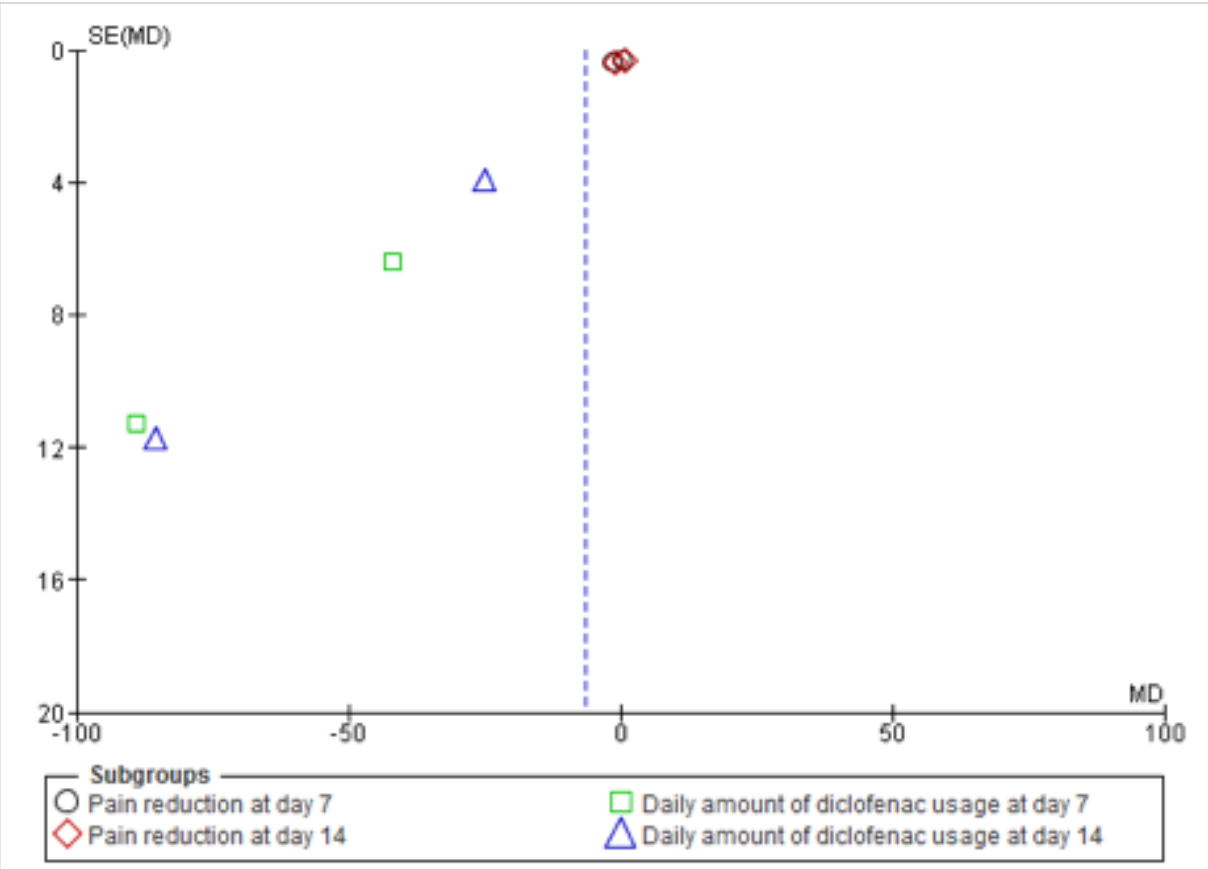

Figure 6. Funnel plot

PUBLICATION BIAS

In our review, the funnel plots of the outcomes were summarized (Figure 6). However, we did not assess publication bias because of too few numbers of the included studies.

DISCUSSION

SUMMARY OF EVIDENCE

In our systematic review, two RCTs were included with 138 patients undergoing hemorrhoidectomy in the analysis, we found that using topical sucralfate ointment had similar efficacy to that of placebo for post hemorrhoidectomy pain reduction at day 7 and day 14. Patients in topical sucralfate ointment group requested a less daily amount of diclofenac than that in the placebo group at day 7. All trials had a low risk of bias but this conclusion was based on high heterogeneity and small numbers of patients. The studies did not describe the adverse effect.

STRENGTH AND LIMITATIONS OF THE REVIEW

Our review is the first systematic review comparing the efficacy of using topical sucralfate ointment and placebo for postoperative hemorrhoidectomy pain reduction. We systematically searched from databases and other sources for published and

unpublished trials. We applied a comprehensive search with no language restrictions. We tended to identify all relevant trials. We conducted this review with the Cochrane handbook and meta-analyses checklist. Our search was comprehensive, our included studies had a low risk of bias.

Our systematic review has several limitations. The first limitation was the small numbers of participants as we found only two RCTs that met our inclusion and exclusion criteria. The second limitation is that an equal amount of topical form of the interventions for each patient was not easily ascertained, this might be a source of high heterogeneity in our review. The third limitation is the included trials did not report adverse effects, implementation of the findings should be careful.

COMPARISON WITH OTHER STUDIES

The use of sucralfate has been started since the animal trial.[16,20] It has been shown that it increased epidermal growth factor (EGF), basic fibroblast growth factor (bFGF) concentration, angiogenesis and granulation tissue in subcutaneous of rats.[16,20] Its use was later applied to those with second-degree burn patients showed that using sucralfate cream increased rate of epithelialization.16 It did not show any allergy or systemic toxicity and soothing on local application.[15] However, the participants in that study were very few.

In our review, we found that using topical sucralfate ointment had a similar effect to that of placebo for pain reduction after hemorrhoidectomy. Our findings contradicted with the previous trials, for instance, the previous two trials by Gupta et al using topical sucralfate in both forms of ointment and cream in those undergoing hemorrhoidectomy and fistulotomy. They stated that using the drug reduced pain after hemorrhoidectomy and fistulotomy more than that of placebo.[21,22] Nonetheless, their outcome measures might not be reliable as it did not have baseline pain. With the gel-like property of sucralfate when contacts with water, it has been used locally as in a study by Miura et al showed that using topical sucralfate reduced post adenotonsillectomy pain more than that of placebo.[23] Again, this trial also did not have baseline pain measure for efficacy evaluation. From all latest available literature, topical sucralfate does not seem to have enough reliable evidence to support the efficacy for postoperative pain reduction.

CONCLUSION AND PRACTICAL IMPLICATION

In patients undergoing hemorrhoidectomy, comparing the efficacy between using topical sucralfate ointment and placebo for postoperative pain reduction after hemorrhoidectomy at day 7 cannot be concluded as our review had a low volume of studies and participants as well as high heterogeneity. For the further study, we suggest an RCT with larger numbers of participants for better estimation of the effect with the proper evaluation of adverse effects evaluating the efficacy for pain reduction after hemorrhoidectomy between topical sucralfate ointment and placebo.

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Adjunction of oral tranexamic acid to topical hydroquinone for melasma: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

Chanon Gettong [1], M.D.; Khuanchanok Buahong [2], M.D.; Panida Tapaneeyakorn [3], M.D.

[1]Sakon Nakhon Hospital, Thailand; [2]Sakon Nakhon Hospital, Thailand; [3]Roi Et, Thailand.

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Correspondence to: Chutharat Thanchonnang; chuth.pp@gmail.com

ABSTRACT

OBJECTIVE

To identify the efficacy of adjunction of oral tranexamic acid to standard topical agents for melasma treatment.

METHODS

Three independently reviewers systematically searched through electronic databases including Cochrane Library, PubMed, Trip Database and Scopus and performed additional hand searching to identify all relevant trials that adjunction of oral tranexamic acid to topical hydroquinone in patients with melasma. We used the Cochrane Collaboration Risk of Bias Tool for assessing the risk of bias. We extracted the data from the included and later performed the meta-analysis.

RESULTS

Two RCTs were included in the systematic review with 360 patients with melasma; 180 in the adjunction of oral tranexamic acid to topical hydroquinone group and 180 in the topical hydroquinone alone group. One was conducted in Nepal, 2012 and another one was in Iran, 2016. MASI score reduction from baseline was similar between the two interventions at week 12 of their treatment (mean difference -2.32, 95% confidence interval -5.25 to 0.62; I^2=84%).

CONCLUSION

We found similar efficacy of using adjunction oral TA to topical HQ and that of using topical HQ alone in patients with melasma at week 12 of their treatment.

INTRODUCTION

Melasma is an acquired hyperpigmentation of the skin.[1] It is a chronic condition usually appearing on the sun-exposed area, especially on the face, which negatively impacts the quality of life.[2,3] The worldwide prevalence of melasma remains unknown.[4,5] However, it has been reported from some specific populations; for instance, it is considered to be the third most common pigmentary disorder in African-Americans.[4,5] Melasma is generally seen more commonly in Asian, Hispanic and African-American descent.[5] Its treatments include topical depigmenting agents, laser therapy and dermabrasion.[6–10] Topical hydroquinone (topical HQ) is considered as one of the standard treatments.[7,9,11–14] In addition, some oral agents such as oral tranexamic acid (oral TA) has a new role in the treatment of melasma.[15–20]

Tranexamic acid is an antifibrinolytic agent.[15,21,22] It is recently found that tranexamic acid inhibits plasminogen-keratinocyte interaction which decreases tyrosinase activity and reduces melanin synthesis in the melanocyte.[7,15,23] Adjunction of oral TA for melasma treatment is a novel concept[17,18] and its efficacy is not established adequately due to the small sample size of the previous randomized controlled trials (RCTs).[17,18] We conducted a systematic review identifying all relevant RCTs and estimate the effect size of the efficacies of adjunction of oral TA to topical HQ in patients with melasma.

METHODS

SEARCH STRATEGIES

Without language restrictions, three independent reviewers systematically searched through electronic databases including Cochrane Library, PubMed, Trip Database and Scopus using the term "melasma" OR "chloasma" AND "oral tranexamic acid" OR "oral transamin". We looked in MeSH database on PubMed using the term ("melasma"[MeSH]) AND "tranexamic acid"[MeSH] and Cochrane Library using the term "melasma" AND "oral tranexamic acid". We searched through Trip Database using PICO search strategy with the term "melasma" for P and "oral tranexamic acid" for I with no specific C and O to identify all relevant trials. Moreover, we performed hand searching for other relevant trials using search terms of "melasma" AND "oral tranexamic acid" in ClinicalTrials.gov, Web of Science and WorldCat. All searches were done on March 1, 2017.

INCLUSION CRITERIA AND EXCLUSION CRITERIA

We included RCTs of adjunction of oral TA to topical HQ in patients with melasma. Trials were excluded using the following criteria (i) trials which were ongoing; (ii) trials which the control group was not topical HQ; (iii) trials which outcome was not melasma area and severity index (MASI)24 score.

ASSESSMENT IF REPORTING BIAS

We used the Cochrane Collaboration Risk of Bias Tool (CCRBT)[25] to present the risk of bias demonstrated as random sequence generation, allocation concealment, blinding of participant and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias by classifying as low risk, high risk and unclear risk of bias.

DATA EXTRACTION

We extracted the characteristics from the included trials regarding author, year of publication, a

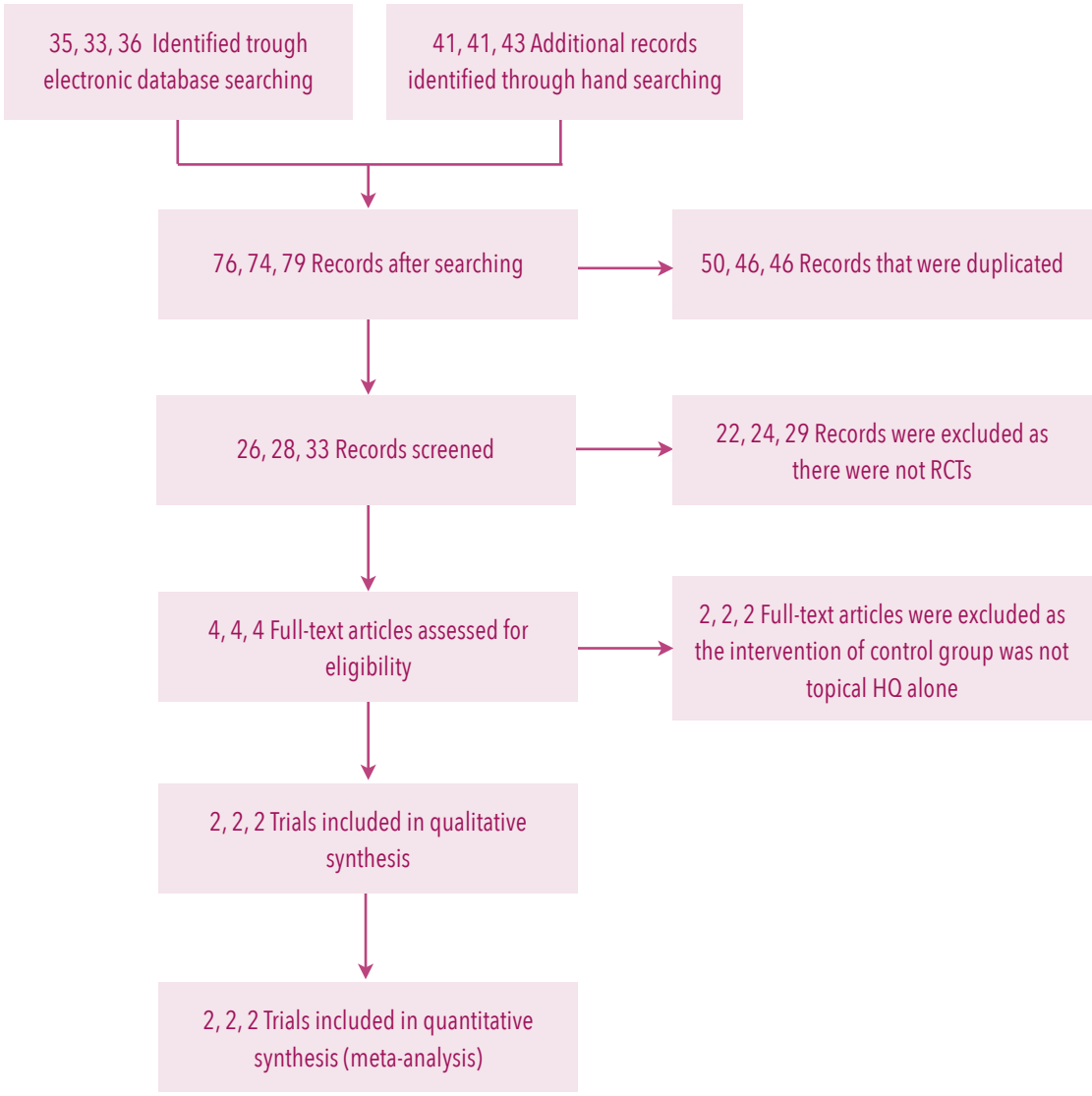

Figure 1. Study flow diagram

number of participants, patient's age, duration of both treatments, duration of trials, interventions described as adjunction of oral TA to topical HQ compared with topical HQ alone and outcome in the term of MASI score reduction from each trial. We extracted sample means, standard deviations (SD) and sample sizes for our outcome measures.

DATA ANALYSES

We used Review Manager 5.3 statistical software to calculate mean difference (MD) for MASI score reduction and pooled relative risk together with their 95% confidence intervals (CIs) between using adjunction of oral TA to topical HQ and topical HQ alone. We calculated I^2 to indicated the trials

Table 1. Characteristics of included RCTs.

Trials	Number of patients (intervention/ control)	Patients' age (years)	Intervention	Control	Outcomes
Karn et al, 2012	130/130	17-55	Oral TA 250 mg twice daily plus topical HQ	Topical HQ alone	MASI score reduction from baseline was no significantly difference between adjunction of oral TA to topical HQ group and topical HQ alone group at week 12 of treatment.
Lajevardi et al, 2016	50/50	18-65	Oral TA 250 mg thrice daily plus topical HQ 4% ointment	Topical HQ 4% ointment alone	MASI score reduction from baseline was significantly greater in adjunction of oral TA to topical HQ group than topical HQ alone group at week 12 of treatment (P<0.001).

heterogeneity. In addition, the results were represented by forest plot. The publication bias was demonstrated in funnel plot.

RESULTS

The search results were 76, 74, and 79 records by reviewers PT, KB and CG, respectively. There were 26, 28 and 33 trials remained after duplicates removed. We later excluded 22, 24 and 29 trials because of being related to our exclusion criteria. The remaining two trials were included in the systematic review.[17,18] Both trials were adjunction of oral TA to topical HQ in patients with melasma. The characteristics of 360 patients with melasma in two RCTs were shown in Table 1.

CHARACTERISTICS OF THE INCLUDED STUDIES

Two RCTs with 360 patients were included in our systematic review comparing between using adjunction of oral TA to topical HQ and topical HQ in patients with melasma. There were 180 patients using adjunction of oral TA to topical HQ and 180 patients using topical HQ alone. In one trial, Karn et al, the intervention was oral TA 250 mg twice daily plus topical HQ and the intervention of another trial, Lajevardi et al, was oral TA 250 mg thrice daily plus topical HQ 4% ointment and the controlled group of both trials was topical HQ 4% ointment alone.

Both RCTs presented the main outcome as MASI score reduction from baseline at week 12 of treatment. In the former trial, the MASI score reduction from baseline was not statistically significant between using adjunction of oral TA to topical HQ and topical HQ alone. But in the latter trial, MASI score reduction from baseline was significantly greater in those with adjunction of oral TA to topical HQ than that of topical HQ alone.

ASSESSMENT OF REPORTING BIAS

RANDOM SEQUENCE GENERATION

Both trials reported the methods of random sequence which we considered as low risks of bias.

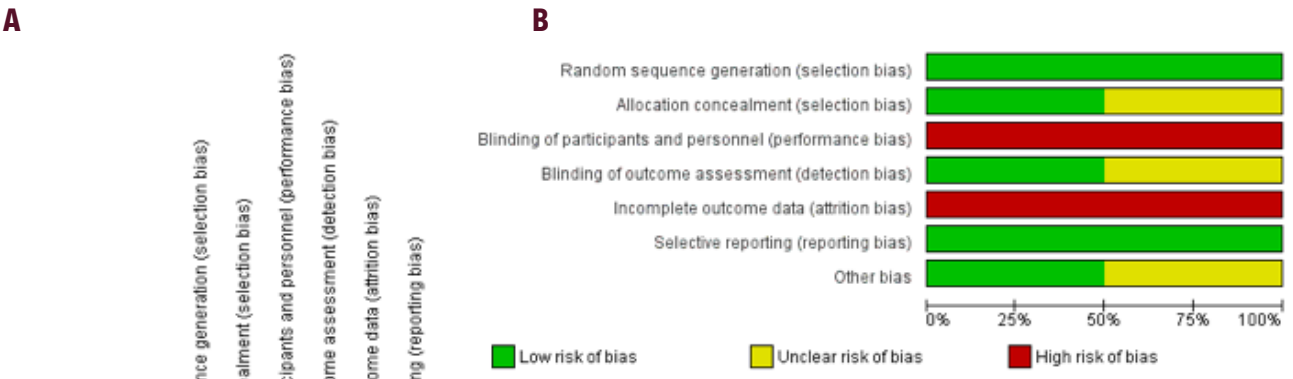

Figure 2. Risk of bias
Panel A, Risk of biases summary and Panel B, Risk of bias graph

ALLOCATION CONCEALMENT

A former trial did not report the allocation process which we considered as unclear risks of bias. A trial was described as low risks of bias as it used closed envelope methods.

BLINDING OF PARTICIPANT AND PERSONAL

Both trials were described as high risks of bias because of their open trial design.

BLINDING OF OUTCOME ASSESSMENT

A former trial was considered unclear risks of bias because they did not describe the outcome assessment process. A latter trial was described as low risks of bias as it blinded the assessor.

INCOMPLETE OUTCOME DATA

Both trials were described as high risks of bias because of missing data and improper described.

SELECTIVE REPORTING

Both trials were described as having low risks of bias because of all of the outcome data were reported.

OTHER POTENTIAL SOURCES OF BIAS

A former trial was described as low risks of bias because it did not have a sponsor. A latter trial was described as unclear risks of bias because it did not mention about sponsor but agency company was noticed.

THE PRIMARY OUTCOME

MASI SCORE AT WEEK 12 OF TREATMENT

MASI score reduction from baseline was not significantly difference between using adjunction of oral TA to topical HQ and topical HQ alone at week 12 of their treatment (MD -2.32, 95% CI -5.25 to 0.62; I2 =84%) (Figure 3).

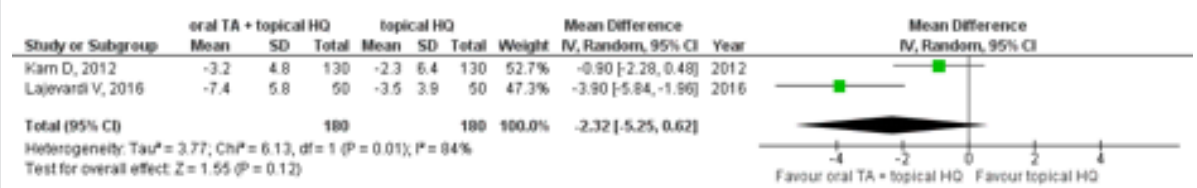

Figure 3. Forest plot: Mean difference MASI score reduction comparing between adjunction of oral tranexamic acid to topical hydroquinone and topical hydroquinone alone for melasma treatment.

PUBLICATION BIAS

In our review, the funnel plot of the outcomes is shown in Figure 4. However, we did not assess publication bias due to too few numbers of the included trials.

DISCUSSION

PRINCIPAL FINDINGS

In this systematic review of two RCTs with 360 patients with melasma, we found that using adjunction of oral TA to topical HQ and topical HQ alone had similar efficacy as MASI scores reduction from the baselines of the two interventions at 12 weeks were not significantly different. However, this conclusion was based on high heterogeneity and small numbers of patients.

STRENGTH AND LIMITATIONS OF THE REVIEW

This is the first systematic review assessing the efficacy of adjunction of oral TA to topical HQ compared with topical HQ alone in patients with melasma. All potential relevant trials were identified. Our systematic review, however, had some limitations. The first limitation was small numbers of participants as we were able to include only two RCTs that met our inclusion and exclusion criteria. The second limitation was the nature of study topical cream which using dosage was difficult to standardize for each patient. This might be a source of high heterogeneity of our pooled effect size. The third limitation was that the patients in each included study were not blinded and the control group did not receive oral placebo as the open trial nature, thus, exaggerate findings was inevitable. The fourth limitation was that adverse reactions were reported only in patients using adjunction of oral TA to topical HQ in both trials. Thus, adverse reactions comparing the two interventions were not possible to be pooled.

COMPARISON WITH OTHER STUDIES

In our review, we found that MASI score reduction from baseline of those using adjunction of oral TA to topical HQ and topical HQ alone in patients with melasma was not significantly different. There were some previous retrospective cohort studies showed the effectiveness of using adjunction oral TA in melasma treatment, for example; Tan AWM et al, 2016, showed that adjunction of low dose oral TA 250 mg twice daily was useful to refractory melasma according to its results; average MASI score was significantly lower from baseline after 3 months of treatment ($P < 0.01$),[26] Lee HC, 2016,

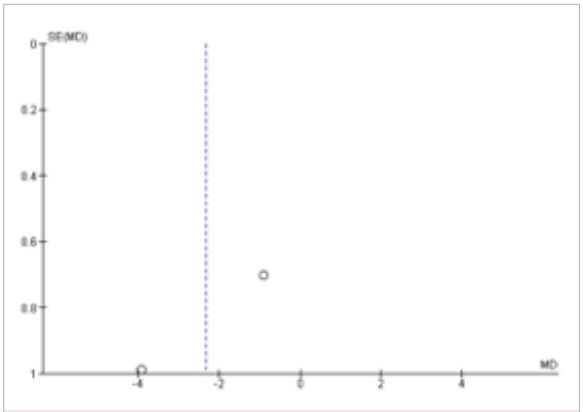

Figure 4. Funnel plot: Melasma area and severity index (MASI) score at week 12

presented that adjunction of oral TA might be an effective treatment for refractory melasma as 561 patients who received oral TA 250 mg twice daily for melasma reported that 89.7% were improved, 10.0% were not improved and 0.4% were worsened.[27] Nevertheless, our outcome showed a difference in the results compared with the mentioned studies. It might be because of a small number of the patient. From all latest available literature, adjunction of oral TA to topical HQ does not seem to have enough reliable evidence to support the efficacy for melasma treatment.

CONCLUSION AND IMPLICATION

We found similar efficacy of using adjunction oral TA to topical HQ and that of using topical HQ alone in patients with melasma at week 12 of their treatment. We suggest large prospective RCT for better estimation of the effect size of both efficacy and adverse reactions.

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The authors would like to thank Dr. Thammasorn Jeeraaumponwat for his supervision, guidance, and all of his support to help us complete the present study. We also would like to thank Khon Kaen Medical Education Center for all resources offered to us and Department of Medical Information System, Khon Kaen Hospital for data accessing.

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Abnormal versus normal neuroimaging in acute infectious encephalitis and mortality

ORIGINAL ARTICLE

ORIGINAL ARTICLE BY

Thanapon Poontong [1], M.D.; Suphaphit Somsri [2], M.D.; Thanayong Seeyo [3], M.D.

[1]Khon Kaen Hospital, Thailand; [2]Nongbualamphu Hospital, Thailand; [3]Nakhon Phanom Hospital, Thailand.

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Correspondence to: Chutharat Thanchonnang; chuth.pp@gmail.com

ABSTRACT

OBJECTIVE

To identify the association between neuroimaging findings and the risk of acute infectious encephalitis and death

METHODS

We conducted the retrospective cohort study by using International Classification of Diseases (ICD) 10 A80-A89 and G04 from Khon Kaen Hospital database, including medical record of patients that was preliminarily diagnosed as acute infectious encephalitis and hospitalized at Khon Kaen Hospital from January 2011 to May 2017 to compare abnormal neuroimaging and normal neuroimaging from CT scan or MRI. The primary outcome was death. The secondary outcomes were seizures, status epilepticus, mechanical ventilation usage, nosocomial infection, intensive care unit (ICU) admission, length of ICU admission and cardiac arrest.

RESULTS

In a total of 376 patients with acute infectious encephalitis were included and divided into 2 groups; 158 patients with abnormal neuroimaging and 218 patients with normal neuroimaging. Characteristics of the two groups were similar. Risk of mortality of those with or without abnormal neuroimaging from CT scan or MRI was not significantly different (hazard ratio (HR), 0.97; 95% confidence interval (CI), 0.67 to 1.40).

CONCLUSION

In current retrospective cohort showed no significantly different risk of mortality between abnormal and normal neuroimaging from CT scan or MRI in patients with acute infectious encephalitis.

INTRODUCTION

Encephalitis is one of the central nervous system infections, and it can be caused by various etiologies and pathogens; viral encephalitis, autoimmune encephalitis, bacterial encephalitis, fungal encephalitis and encephalitis of the unknown cause.[1,2,3] The most common identified cause is from the viral infection.[3,4] Its annual worldwide incidence is 3.5 to 7.4 in 100,000 population.[5-9] Its case-fatality can be as high as 13 to 33%.[2,3,10-12]

Areas of brain involvement depend on types of the pathogen, for instance, herpes simplex encephalitis mostly involves temporal and frontal lobes of the brain while Japanese encephalitis mostly involves thalamus and basal ganglion.[13-18] Moreover, the areas of involvement also determine complications in those with encephalitis. In 2007; there was a case-control study in Taiwan in 330 children with postencephalitic epilepsy (PEE) stated that cortical involvement with or without subcortical lesion increased the risk for PEE.[19] However, a later retrospective cohort study in 2013 from the US in 103 patients with acute encephalitis stated that cerebral edema was associated with the higher mortality regardless of the areas of brain involvement.[2]

Until now, there is no evidence regarding the relationship between other types of abnormal neuroimaging of the brain and mortality. Thus, we aim to determine the relationship between abnormal neuroimaging of the brain in various forms in patients with acute infectious encephalitis, and the mortality in a larger study sample.

METHODS

STUDY DESIGN AND PATIENTS

We conducted a retrospective cohort study of the patients with acute infectious encephalitis hospitalized at Khon Kaen Hospital between January 2011 and May 2017 and preliminary diagnosed as acute encephalitis by using International Classification of Diseases (ICD) 10 A80-A89 and G04 from Khon Kaen Hospital database. Their medical records were reviewed and verified. Those without neuroimaging record approved by a radiologist were excluded.

EXPOSURE

Abnormal neuroimaging from computed tomography (CT) scan or magnetic resonance imaging (MRI) in various forms was exposure in the present study. This included brain edema, frontal lobe involvement, temporal lobe involvement, parietal lobe involvement, occipital lobe involvement, frontoparietal involvement, frontotemporal involvement, temporoparietal involvement, parieto-occipital involvement, basal ganglia involvement, thalamic involvement, cerebellar involvement, midbrain involvement.

STUDY OUTCOMES

Our primary outcome was death within 30 days. Death was ascertained from the medical records. The secondary outcomes included seizure, status epilepticus i.e., evidence of seizure more than five minutes or recurrence of seizure within five minutes with no fully recovered, mechanical ventilation usage, nosocomial infection i.e., present with hospital-acquired pneumonia, ventilator-

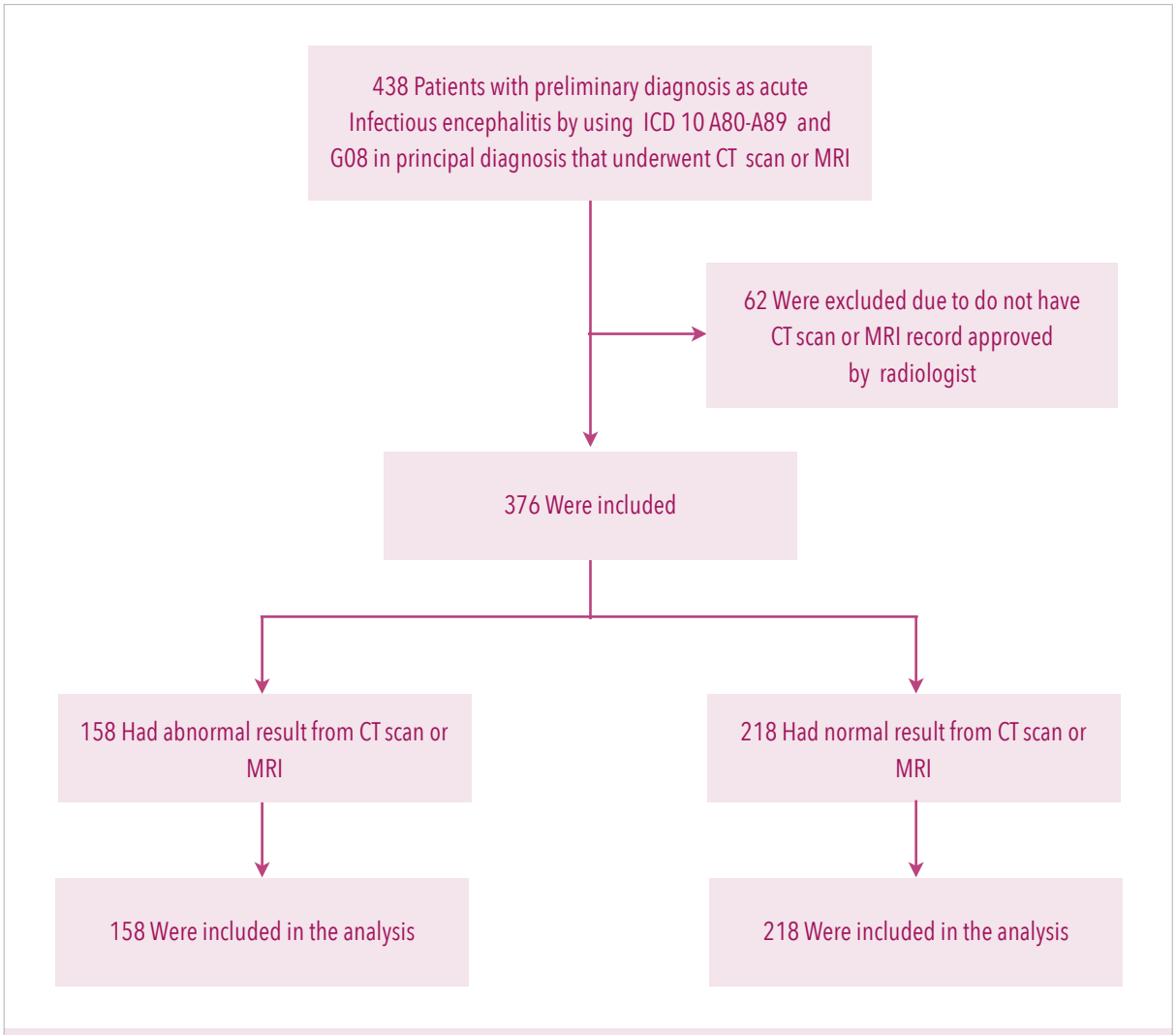

Figure 1. Study flow in the analysis

associated pneumonia, urinary tract infection and thrombophlebitis, intensive care unit (ICU) admission, length of ICU admission and cardiac arrest defined by evidence of cardiopulmonary resuscitation.

DATA COLLECTION

Aside from the exposure and the study outcomes. We also collected sex, age, presence of comorbidities (hypertension, diabetes mellitus, stroke, hematologic disease, cirrhosis, Human Immunodeficiency Virus (HIV) infection, tuberculosis (TB) infection, vital signs i.e., body temperature, systolic blood pressure, diastolic blood pressure and pulse rate, Glasgow coma scale (GCS), cranial nerve defect, focal neurological deficit i.e., hemiparesis, paraparesis and quadriparesis, vomiting, new onset of seizures, status epilepticus, alteration of consciousness, stiff neck, laboratory investigation i.e., blood leukocyte

count, thrombocytopenia and serum sodium level, mechanical ventilation on admission, acyclovir therapy, antibiotic use, type of antibiotic including penicillin group, cephalosporin group, polymyxin group, glycopeptide group, macrolide group, fluoroquinolone group, aminoglycoside group, metronidazole, carbapenems group and anti-tuberculosis drug, length of antibiotic use, steroid use, mannitol and cerebrospinal fluid (CSF) profile including leukocyte count, lymphocyte proportion, polymorphonuclear leukocytes (PMN) proportion, protein level, glucose CSF:blood ratio and open pressure.

STATISTICAL ANALYSIS

We used descriptive statistics to summarize the patient characteristics; we used frequencies and percentage for categorical variables, mean and standard deviation (SD) for normally distributed data and median and interquartile range (IQR) for non-normally distributed data.

For inferential statistics, either Pearson's chi-squared or Fisher exact test was used for categorical variables where appropriate. Mann–Whitney U test was used in continuous variables comparison. We used relative risk (RR) to describe the ratio of the probability of an event rate of the outcomes. Binary logistic regression analysis was used to examine how exposure related to the outcome as crude odds ratio (COR) and adjusted odds ratio (AOR). Moreover, we used the Cox proportional hazard model analysis to describe the risk of mortality as a hazard ratio (HR). For all inferential statistics, 95% confidence interval (CI) was used to describe statistical significance. Kaplan-Meier survival was also used to show the cumulative survival.

RESUILTS

PATIENTS

From January 2011 through May 2017, we included 438 patients with preliminary diagnosis as acute infectious encephalitis by using ICD 0 A80-A89 and G04 in principle diagnosis that underwent CT scan or MRI. Then we excluded 62 patients without CT scan or MRI record approved by radiologist. A total of 376 patients were included and divided into 2 groups; 158 patients with abnormal neuroimaging and 218 patients with normal neuroimaging from CT scan or MRI (Figure 1). Characteristics at the admission of the two groups were relatively similar (Table 1). Most of them were male with an average age of 50 years old. Very few of them had underlying diseases. Moreover, signs and symptoms on admission in the two groups were similar.

Treatment after the admission of the two groups including acyclovir therapy, Antibiotic use and therapy of cerebral edema was similar but in the former group received polymyxin group, metronidazole and mannitol more than the latter group. Besides, the former group had a longer length of antibiotic use (Table 2). CSF parameter in two groups was not significantly different and an average open pressure from the first lumbar puncture was 20 cmH_2O (Table 3).

OUTCOME

Mortality rates as our primary outcome of those with or without abnormal neuroimaging from CT scan or MRI were relatively similar (42.4% vs. 40.4%; RR, 1.05; 95% CI, 0.82 to 1.34). Furthermore, secondary outcomes were not significantly different (Table 4).

Table 1. Baseline characteristics of patients on admission (continued)

Characteristic	Abnormal neuroimaging (n=158)	Normal neuroimaging (n=218)	P Value
Male sex-no. (%)	93 (58.9)	131 (60.1)	0.81
Age-yr			0.15
Median	51	53	
Interquartile range	34.2-63.9	35.1-68	
Comorbidity-no. (%)			
Hypertension	32 (20.3)	53 (24.8)	0.31
Diabetes mellitus	25 (15.8)	51 (23.8)	0.06
Stroke	7 (4.4)	8 (3.7)	0.74
Hematologic disease	6 (3.8)	4 (1.9)	0.34
Cirrhosis	6 (3.8)	8 (3.7)	0.98
HIV infection	7 (4.4)	7 (3.3)	0.56
TB infection	7 (4.4)	6 (2.8)	0.40
Cranial nerve defect-no. (%)	10 (6.6)	22 (10.3)	0.22
New onset of seizures-no. (%)	50 (31.6)	60 (27.5)	0.39
Body temperature (degree celsius)			0.22
Median	37.7	37.5	
Interquartile range	37-38.4	36.7-38.5	
Systolic blood pressure (mmHg)			0.72
Median	130	129	
Interquartile range	113-152.3	111-150.3	
Diastolic blood pressure (mmHg)			0.47
Median	74.5	76	
Interquartile range	66-87	66.8-88	

Table 1. Baseline characteristics of patients on admission (continued)

Characteristic	Abnormal neuroimaging (n=158)	Normal neuroimaging (n=218)	P Value
Median	100	100	
Interquartile range	84.8-118	85.5-114	
Glasgow coma score			0.13
Median	11	10	
Interquartile range	7.8-14	7-13	
Focal neurological deficit-no. (%)			
Hemiparesis	10 (6.6)	9 (4.4)	0.36
Paraparesis	3 (2.0)	3 (1.5)	0.70
Quadriparesis	19 (12.6)	20 (9.8)	0.41
Vomiting-no. (%)	40 (25.3)	41 (18.8)	0.13
Status epilepticus-no. (%)	13 (8.2)	12 (5.5)	0.30
Alteration of conscious-no. (%)	135 (85.4)	191 (87.6)	0.54
Stiff neck-no. (%)	60 (39.2)	99 (46.7)	0.16
Blood leukocyte count, x 1000 cell/mL			0.84
Median	11.7	10.9	
Interquartile range	7.8-16	7.7-16.8	
Thrombocytopenia-no. (%)	15 (10.3)	27 (13.3)	0.40
Serum sodium, mmol/dL			0.23
Median	137	136	
Interquartile range	133-141	132-140	
Mechanical ventilation on admission-no. (%)[2,3,17]	55 (34.8)	78 (35.8)	0.85

* Thrombocytopenia defined as platelet count <100,000/mm3

Table 2. Treatment on admission

Treatment	Abnormal neuroimaging (n=158)	Normal neuroimaging (n=218)	P Value
Acyclovir therapy-no. (%)	48 (30.4)	76 (34.9)	0.36
Antibiotic use-no. (%)	149 (94.3)	211 (96.8)	0.24
Penicillin group	72 (45.6)	109 (50.0)	0.40
Cephalosporin group	136 (86.1)	197 (90.4)	0.20
Polymyxin group	17 (10.8)	11 (5.0)	0.04
Glycopeptide group	29 (18.4)	29 (13.3)	0.18
Macrolide group	11 (7.0)	14 (6.4)	0.84
Fluoroquinolone group	6 (3.8)	7 (3.2)	0.76
Aminoglycoside group	2 (1.3)	1 (0.5)	0.58
Metronidazole	17 (10.8)	10 (4.6)	0.02
Carbapenems group	37 (23.4)	60 (27.5)	0.37
Anti-tuberculosis drug	7 (4.4)	5 (2.3)	0.25
Length of antibiotic use (day)			0.01
Median	10	7	
Interquartile range	3-16.3	3-14	
Therapy of cerebral edema-no. (%)			
None	97 (61.4)	151 (69.3)	0.11
Steroid	52 (32.9)	61 (28.0)	0.30
Mannitol	22 (13.9)	15 (6.9)	0.02

FACTORS DETERMINING OUTCOME

From the crude analysis of the odds ratio, the mortality was relatively similar between abnormal and normal neuroimaging. The mortality was increased in higher age, female and lower GCS (Table 5). From logistic regression analysis of adjusted odds ratio, the mortality was slightly increased in higher age but was decreased in male with higher GCS who had a stiff neck on admission. In other factors, mortality was similar (Table 5). From Cox proportional hazard regression analysis, Risk of mortality was similar in abnormal and

Table 3. CSF profile

CSF Profile	Abnormal neuroimaging (n=158)	Normal neuroimaging (n=218)	P Value
CSF parameter			
Leukocyte count, cells/μL			0.74
Median	30	40	
Interquartile range	2-496.5	0-546	
Lymphocyte proportion %			0.87
Median	5	5	
Interquartile range	0-20	0-32	
PMN proportion %			0.58
Median	75.5	48	
Interquartile range	0-93.3	0-93	
Protein level, mg/dL			0.71
Median	94.2	116.2	
Interquartile range	43.8-352	51.9-289.2	
Glucose CSF:blood ratio			0.97
Median	0.47	0.47	
Interquartile range	0.34-0.62	0.28-0.61	
Open pressure (cmH2O)			0.53
Median	20	20	
Interquartile range	15-29.3	14-27	

normal neuroimaging (HR, 0.97; 95% CI, 0.67 to 1.40). Even though, it was increased 1.01 times in higher age (HR, 1.01; 95% 1.01 to 1.02) and was decreased 0.67 times in male (HR, 0.67; 95% CI, 0.47 to 0.96) and 0.9 times in higher GCS (HR, 0.9; 95% CI 0.86 to 0.95) (Table 5).

SUBGROUP ANALYSIS

In our subgroup analysis, we found that risk of mortality was relatively similar in the patients with or without brain edema in various areas involvement in brain parenchyma from the neuroimagings (Table 6).

Table 4. Outcomes

Outcome	Abnormal neuroimaging (n=158)	Normal neuroimaging (n=218)	Relative risk (95 % CI)	Mean difference (95 % CI)
Primary outcome				
Death-no. (%)	67 (42.4)	88 (40.4)	1.05 (0.82-1.34)	
Secondary outcome				
Seizure-no. (%)	27 (17.1)	38 (17.4)	0.98 (0.63-1.54)	
Status epilepticus-no. (%)	16 (10.1)	12 (5.5)	1.84 (0.90-3.78)	
Mechanical ventilation usage-no. (%)	97 (61.4)	131 (60.1)	1.02 (0.87-1.20)	
Nosocomial infection-no. (%)	46 (29.1)	74 (33.9)	0.86 (0.63-1.16)	
ICU admission-no. (%)	21 (13.3)	25 (11.5)	1.16 (0.67-1.99)	
Length of ICU admission (day)				-8.51 (-22.38 to 5.37)
Median	4.2	4.9		
Interquartile range	1.5-19	1.8-5.8		
Cardiac arrest-no. (%)	24 (15.2)	35 (16.1)	0.95 (0.59-1.53)	

DISCUSSION

In the current study, from 376 patients with acute infectious encephalitis, we found mortality rates were not significantly different between abnormal and normal neuroimaging from CT scan or MRI. The other outcomes also include seizure, status epilepticus, mechanical ventilation usage, nosocomial infection, ICU admission, length of ICU admission and cardiac arrest. Moreover, a result of binary logistic regression and Cox proportional hazard model analysis are still shown not significantly associated with risk for mortality.

COMPARISONS WITH OTHER STUDIES

We divided patients into two groups, comparing mortality outcomes in patients with or without abnormal neuroimaging. The result showed no significance between the two groups. The current study is the first study about abnormal neuroimaging of the brain in various forms and the mortality. However, there was a previous study in 103 patients with acute encephalitis receiving care in ICU stated that patients with cerebral edema had mortality 18.06 times higher than those without it (OR, 18.06; 95% CI, 3.14 to 103.92).[2] In contrast, our subgroup analysis of cerebral edema shown no

Table 5. Factors determine outcome

Factor	Odds ratio (95% CI)		Hazard ratio (95% CI)
	Crude analysis	Adjusted analysis	
Abnormal neuroimaging	1.09 (0.72-1.65)	1.19 (0.73-1.97)	0.97 (0.67-1.40)
Male sex	0.60 (0.39-0.91)	0.58 (0.36-0.95)	0.67 (0.47-0.96)
Age-yr	1.02 (1.01-1.03)	1.02 (1.01-1.04)	1.014 (1.005-1.023)
Systolic blood pressure (mmHg)	1.01 (1.001-1.017)	0.996 (0.98-1.01)	0.999 (0.99-1.01)
Diastolic blood pressure (mmHg)	1.01 (0.999-1.024)	1.01 (0.99-1.03)	1.01 (0.99-1.02)
Glasgow coma score	0.85 (0.80-0.91)	0.85 (0.79-0.91)	0.88 (0.84-0.92)
Body temperature (degree celsius)	1.12 (0.93-1.33)	1.19 (0.96-1.48)	1.07 (0.91-1.25)
Alteration of consciousness	1.43 (0.76-2.66)	0.94 (0.41-2.13)	1.02 (0.54-1.91)
Stiff neck	0.73 (0.48-1.11)	0.56 (0.33-0.94)	0.75 (0.51-1.09)
Serum sodium, mequiv/L	0.995 (0.97-1.02)	0.99 (0.96-1.02)	0.99 (0.96-1.01)
Blood leukocyte count, cell/mL	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)

significant difference in mortality between patients with or without cerebral edema. In our aspect, because they have a small sample size and included just only patients receiving ICU care that can affect the result of mortality. Moreover, our result was defined by the hazard ratio that has higher reliability and larger sample size. Thus, the result of the previous study may not precisely enough to present the relationship between cerebral edema and mortality in patients with encephalitis generally.

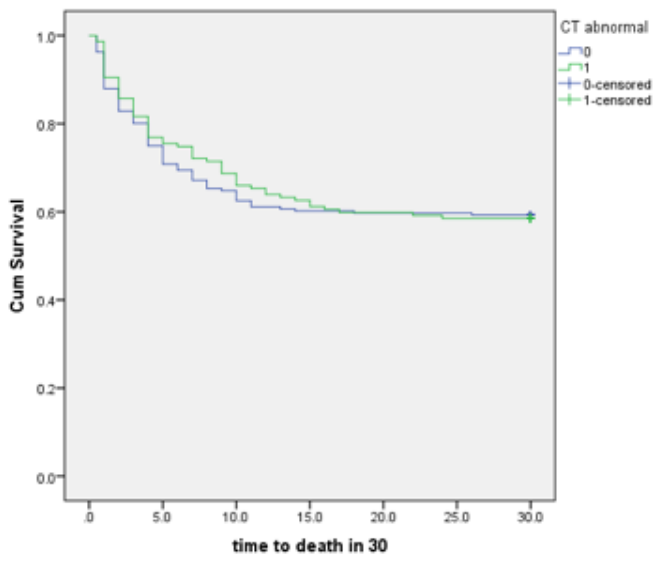

Figure 2. Probability of survival patients with or without abnormal neuroimaging in 30 day

STRENGTHS AND LIMITATIONS OF STUDY

Besides the fact that our findings were from the largest database of patients with acute encephalitis in the world, we still have some limitations in our study. First, missing data were

Table 6. Subgroup analysis

Abnormal neuroimaging	Number of patients death	Cumulative mortality (%)	Hazard ratio (95% CI)
Brain edema (n=45)	21	47	0.92 (0.50-1.67)
Frontal lobe involvement (n=72)	29	40	0.84 (0.52-1.36)
Temporal lobe involvement (n=33)	13	39	0.86 (0.45-1.66)
Parietal lobe involvement (n=39)	18	46	1.07 (0.60-1.93)
Occipital lobe involvement (n=21)	9	43	0.92 (0.40-2.11)
Frontoparietal region involvement (n=14)	6	43	1.07 (0.43-2.71)
Frontotemporal region involvement (n=14)	5	36	0.67 (0.25-1.84)
Temporoparietal region involvement (n=7)	3	43	1.03 (0.25-4.31)
Parieto occipital region involvement (n=11)	5	46	0.78 (0.24-2.50)
Basal ganglia involvement (n=13)	6	46	1.06 (0.45-2.50)
Thalamic involvement (n=10)	4	40	0.83 (0.25-2.69)
Cerebellar involvement (n=6)	3	50	1.96 (0.61-6.30)
Midbrain involvement (n=4)	2	50	0.80 (0.19-3.42)

inevitable due to the retrospective nature of the study. Second, a different time interval for undergoing the CT scan or MRI might affect the stages of the disease and our findings might not be correctly concluded. Third, the results of the CT scan or MRI was approved by only one radiologist.

CONCLUSIONS AND IMPLICATIONS

In our study, we found that risk for mortality of patients with acute infectious encephalitis with or without abnormal neuroimaging was not significantly different. Findings from CT scan or MRI in patients with acute infectious encephalitis might not be useful for predicting the mortality. For further research, three dimensional CT scan is our suggestion. It can show not only areas of brain involvement but also the volume of the lesion. The relationship between the neuroimaging findings and outcome in these patients might be clearer and more precise.

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"I shall either find a way or make one"

-Hannibal Barca

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