VOLUME 43 ISSUE 4
JULY-AUGUST

THE CLINICAL ACADEMIA

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www.kkh.go.th/tca
PRINTED IN THE USA
ISSN:2465-4027


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

the clinical academia

Aim and Scope

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

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message from the editor

Dear readers,

It is my pleasure to welcome you to our TCA volume 43, issue 4 for July-August 2019. In this issue, we would like to present you with three interesting and practical systematic reviews; the first review is about comparing systemic corticosteroids versus nonsteroidal anti-inflammatory drugs for acute gout. The second is about using oral acyclovir for treating of pityriasis rosea and the last one is about the treatment of aphthous stomatitis using silver nitrate cauterization for. Hope you all gain somethings reading our articles.

Enjoy!

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.

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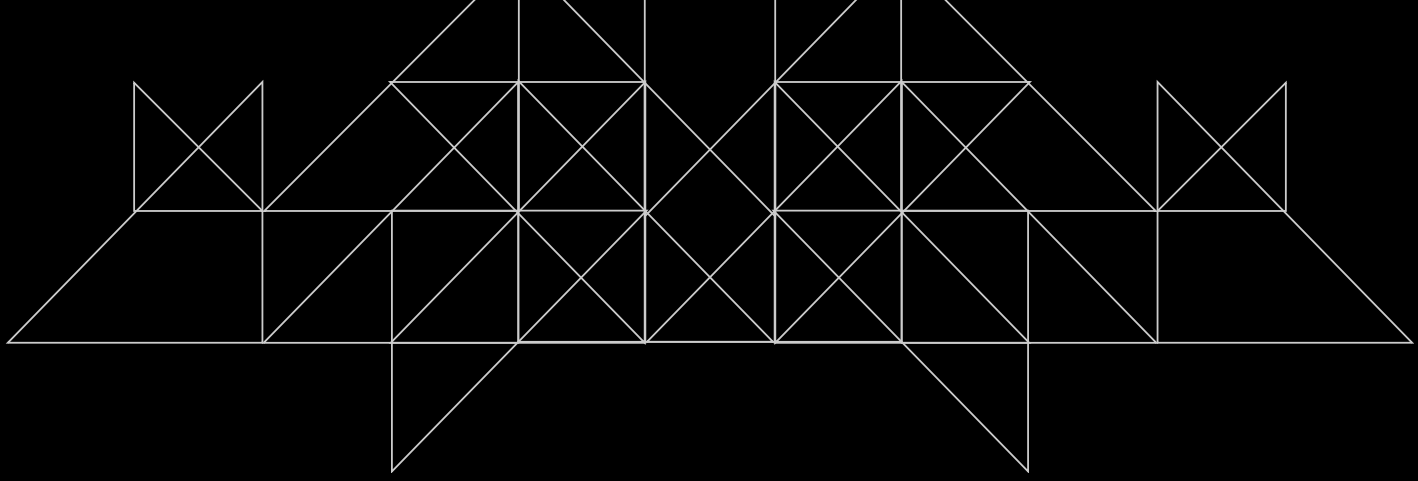
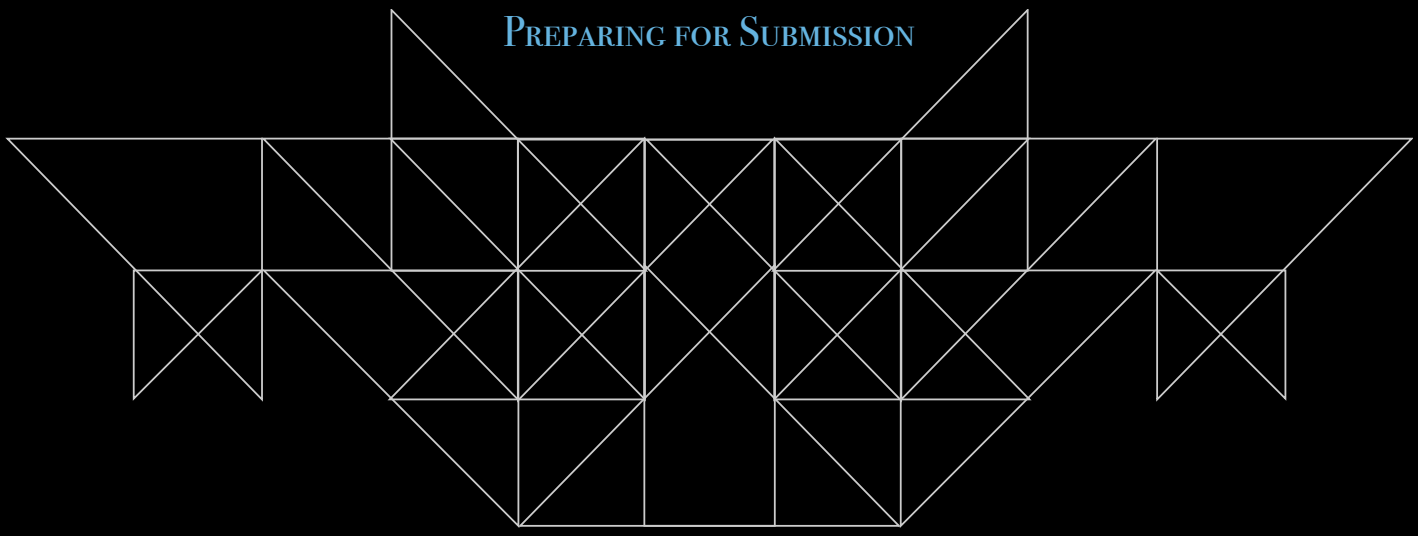
Contents



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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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.

Avoid citing a "personal communication" unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text. For scientific articles, obtain written permission and confirmation of accuracy from the source of a personal communication.

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

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

ii. Reference Style and Format

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

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

h. Tables

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

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

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

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

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.

Systemic corticosteroids versus non-steroidal anti-inflammatory drugs for acute gout: a systematic review

ORIGINAL ARTICLE BY

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Accepted: AUGUST 2019
Latest revision: SEPTEMBER 2019
Printed: SEPTEMBER 2019

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ABSTRACT

OBJECTIVE

to compare pain reduction and adverse events between systemic corticosteroids and NSAIDs in patients with acute gout.

METHODS

Four reviewers systematically and independently searched and evaluated from 4 databases including PubMed, the Cochrane Library, Trip database and Scopus. We included all relevant randomized controlled trials (RCTs) comparing efficacy regarding pain reduction and adverse events of systemic corticosteroids and NSAIDs in patients with acute gout by robust inclusion and exclusion criteria. We assessed the methodological quality using validated tools. Then, continuous and dichotomous data were statistically analysed.

RESULTS

We include 5 RCTs, involving 834 participants with acute gout in this systematic review. Three RCTs with 624 patients indicated that systemic corticosteroids and NSAIDs were similar efficacy in term of pain reduction at rest using a 100 mm-visual analogue scale (VAS) in the first 6 hours (mean difference [MD] 0.64; 95% confidence interval [CI] -2.26 to 3.54, I^2=50%, random-effect model). Two RCTs with 506 participants, systemic corticosteroids were not significantly different from NSAIDs for efficacy in term of pain reduction at activity using a 100 mm-VAS in the first 6 hours (MD -0.28; 95% CI -2.09 to 1.53, I^2=0%, fixed-effect model). Three minor adverse events including nausea, vomiting and indigestion were found significantly higher in those using NSAIDs, (relative risk [RR] 0.23; 95% CI 0.11 to 0.51; RR 0.1; 95% CI 0.02 to 0.54 and RR 0.49; 95% CI 0.28 to 0.84, respectively) while rash was more common in those using systemic corticosteroids (RR 4.61; 95% CI 1.34 to 15.81).

CONCLUSION

Our study found robust evidence that systemic corticosteroids and NSAIDs have similar efficacy for pain reduction but have lesser adverse events in systemic corticosteroids users. Thus, short-term systemic corticosteroids treatment should be considered as first-line alternative to NSAIDs in patients with acute gout.

INTRODUCTION

Global prevalence of gout was 0.8 per 1,000 people in 2010[1] and incidence of acute gout in the United Stated was nearly 180,000 patients in 2008.[2] Those with the attack were commonly treated with non-steroidal anti-inflammatory drugs (NSAIDs) followed by colchicine for relieving symptoms of pain, swelling and redness.[3-7] NSAIDs user often present with gastroduodenal adverse effects such as dyspepsia, nausea, vomiting, abdominal pain, bleeding and heartburn as well as increasing cardiovascular and renal complication[8-12] while gastrointestinal intolerance including nausea, vomiting and diarrhea are also found in those using colchicine.[13,14] Systemic corticosteroid is an alternative treatment for those who cannot tolerate with the adverse effects of NSAIDs or colchicine.[15-17]

A previous systematic review in 2008 with 148 participants stated that adverse events were found less common in those using systemic corticosteroids than that of NSAIDs, however, their comparative efficacies were inconclusive without combined effect sizes of the treatments.[18] There were at least four additional trials since 2008 reported that systemic corticosteroids and NSAIDs had similar efficacy on pain reduction, but they still had limitation regarding small sample size.[19-22] The aim of this systematic review is to compare efficacies and adverse events between systemic corticosteroid and NSAIDs in acute gout.

METHODS

This study is a systematic review to compare pain reduction and adverse events between systemic corticosteroids and NSAIDs in patients with acute gout. It is conducted according to Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0.[23] and followed Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) checklist.[24]

SEARCH STRATEGIES

Four independent reviewers systematically searched for articles through PubMed, the Cochrane Library, Trip Database and Scopus. Searching in Pubmed and Cochrane library were undertaken using MeSH terms; "gout" OR "gouty arthritis" AND "steroids" OR "corticosteroids" AND "NSAIDs" OR "anti-inflammatory agents, non-steroidal". We used PICO search in Trip Database and various combinations of following keywords in Scopus; "gout", "acute gout", "acute gout attack", "acute gouty arthritis", "steroid", "corticosteroids" and "NSAIDs".

INCLUSION CRITERIA

STUDY DESIGN

Randomized controlled trials (RCTs).

PARTICIPANTS

Patients with acute gout.

INTERVENTIONS

Systemic corticosteroids.

CONTROLS

NSAIDs.

OUTCOMES

Pain reduction and the adverse events after using the interventions and controls.

Table 1. Characteristics of the included studies.

Author (year), country	Methods	Participants	Interventions	Control	Outcomes
Man (2007), Hong Kong, China	Controlled randomized trial; double blinded	90 patients	44 patients (male 35) received oral prednisolone 30 mg od 5 days with oral paracetamol 1000 mg prn q. 4 hours	46 (male 39) patients received oral indomethacin 50 mg tid for 2 days and 25 mg tid for 3 days after 1 initial intramuscular injection with 75 mg diclofenac -paracetamol 1000 mg prn q. 4 hours	Primary outcomes: pain reduction at rest and activity (using a 100 mm-VAS); secondary outcome: adverse events
Janssens (2008), the Netherlands	Controlled randomized trial; double blinded	120 patients	60 patients received oral prednisolone 35 mg od and oral placebo naproxen bid	60 patients received oral naproxen 500 mg bid and oral placebo prednisolone od	Primary outcomes: pain reduction at res t (using a 100 mm-VAS); secondary outcomes: adverse events, general disability, walking disability
Zhang (2014), China	Parallel-group randomized trial	60 patients	30 patients received oral compound betamethasone (diprospan) 7mg i.m. only once during the study	30 patients received oral diclofenac sodium 75 mg bid for 7 days	Primary outcomes: pain reduction (using a 5 point Likert scale); secondary outcomes: adverse events, joint tenderness/swelling (using a 5 point Likert scale)
Timothy (2016), Hong Kong, China	Two recent double-blind, randomized, controlled trials	416 patients	208 patients received oral prednisolone 10 mg 3 tabs od and placebo 2 tabs tid for 2 days followed by oral prednisolone 10 mg 3 tabs od and placebo 1 tab tid for 3 days with oral paracetamol 1 gm prn q. 6 hr.	208 patients received oral indomethacin 25 mg 2 tabs tid and placebo 6 tabs od for 2 days, followed by oral indomethacin 25 mg 1 tab tid and placebo 6 tabs once a day for 3 days with oral paracetamol 1 gm prn q. 6 hr.	Primary outcomes: pain reduction at rest and activity (using a 100 mm-VAS); secondary outcomes: adverse events, joint swelling, joint redness, uses of paracetamol, return visits
Lingling (2016), China	Opened-label, randomized, controlled, parallel-group trial	150 patients	41 patients received oral prednisolone 35 mg qid	45 patients received oral indomethacin 50 mg tid	Primary outcomes: pain reduction (using a 5 point Likert scale); secondary outcomes: adverse events, joint tenderness, erythema, swelling and joint activity

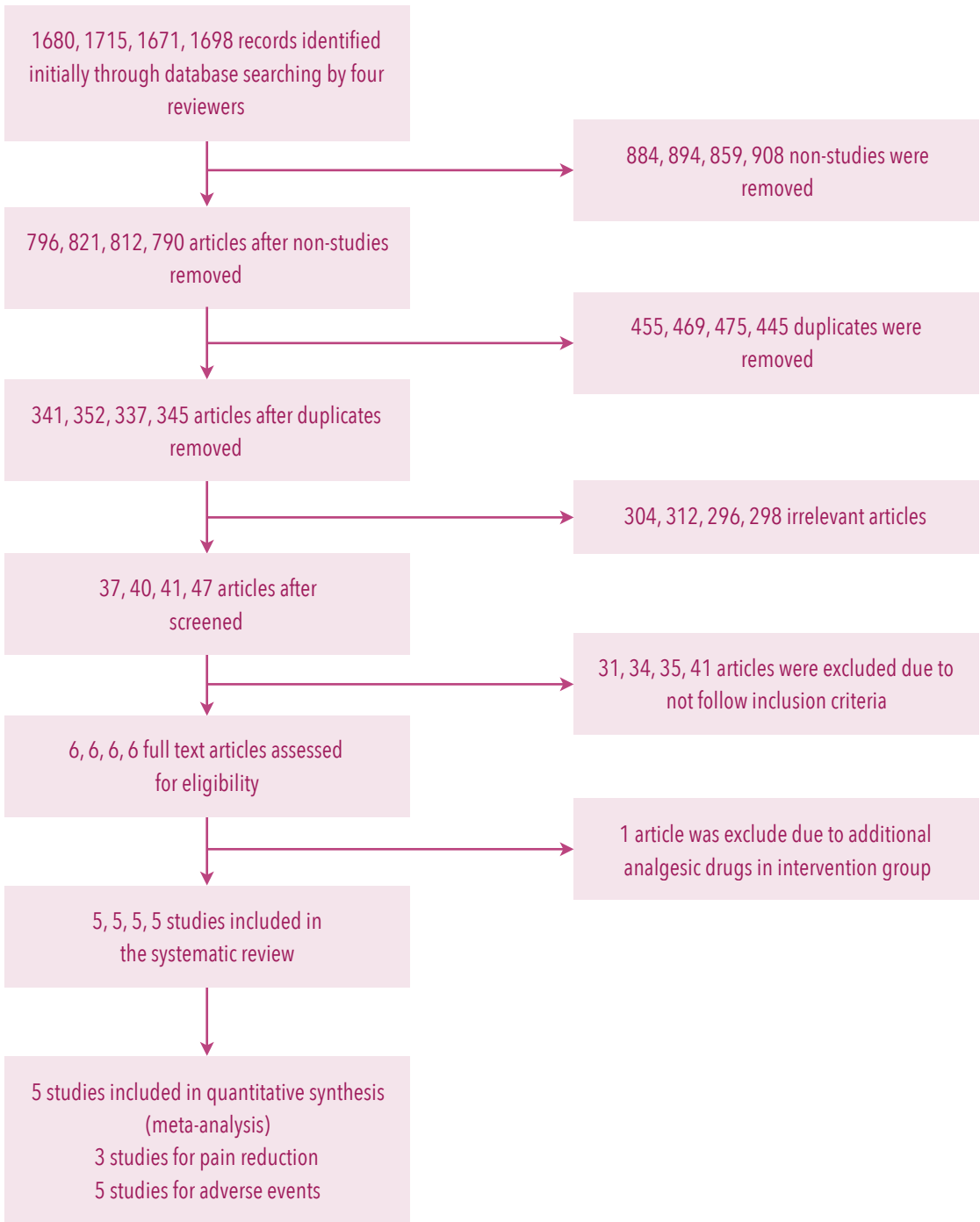

Figure 1. Study flow diagram

Table 2. Quality assessment of the included study based on Jadad score

Item	Man (2007), Hong Kong	Janssens (2008), The	Zhang (2014), China	Timothy (2016), China	Lingling (2016), China
Was the study described as randomized?	1	1	1	1	1
Was the method used to generate the sequence of randomization described and appropriate?	1	1	1	1	1
Was the study described as double blind?	1	1	0	1	0
Was the method of double blind described and was it appropriate?	1	1	0	1	0
Was there a describe of withdrawals and dropouts?	1	1	1	1	1
Score	5	5	3	5	3

Table 3. Summary of results comparing pain reduction of acute gout patients between systemic corticosteroids and NSAIDs

Outcomes	Number of studies	Participants	Number of patients		Mean difference	95%CI
			steroids	NSAIDs		
Primary outcome: pain reduction at rest in the first 6 hours using a VAS 100 mm	3	624	311	313	0.64	-2.26 to 3.45
pain reduction with activity at 2 hours using a VAS scale 100 mm	2	506	252	254	-0.28	-2.09 to 1.53
pain reduction at rest using a 5-Likert scale	1 [Lingling Xu (2016)]	86	41	45	0.11	-0.16 to 0.39
	1 [Zhang (2014)]	60	Number of patients had severe or extreme pain in each group (%)		Difference of number of patients on severe or extreme pain reduction between the two groups: preferable systemic corticosteroids (no statistical data reporting)	
		-baseline	27 (90.0%)	28 (93.3%)		
		-4 hours	17 (56.7%)	22 (73.3%)		

Table 4. Adverse events between systemic corticosteroids and NSAIDs at the end of studies.

Adverse events	Man(2007), Hong Kong		Janssens (2008), The Netherlands		Zhang (2014), China		Timothy (2016), China		Lingling (2016), China		RR (95%CI)
	Steroids (N=46)	NSAIDs (N=44)	Steroids (N=60)	NSAIDs (N=60)	Steroids (N=30)	NSAIDs (N=30)	Steroids (N=208)	NSAIDs (N=208)	Steroids (N=33)	NSAIDs (N=36)	
Major adverse events											
Require hospitalization	0	7	-	-	-	-	-	-	-	-	0.06 (0.00,1.09)
Minor adverse events											
Abdominal pain	0	17	9	9	0	3	12	23	2	3	0.47 (0.19, 1.18)
Dizziness	2	9	4	4	0	1	24	31	0	4	0.61 (0.34, 1.10)
Nausea	3	12	-	-	0	4	4	15	-	-	0.24 (0.11, 0.52)
Dry mouth	9	11	-	-	-	-	35	22	0	1	1.16 (0.64, 2.11)
Drowsiness or fatigue	7	9	-	-	-	-	26	27	0	2	0.88 (0.57, 1.36)
Indigestion or flatulence	4	14	-	-	0	2	13	19	-	-	0.47 (0.23, 0.94)
Vomiting	0	4	-	-	-	-	1	10	-	-	0.10 (0.02, 0.54)
Dyspnea	0	1	3	3	-	-	-	-	-	-	0.80 (0.20, 3.25)
Rash	3	1	-	-	-	-	11	2	-	-	4.49 (1.30, 15.53)

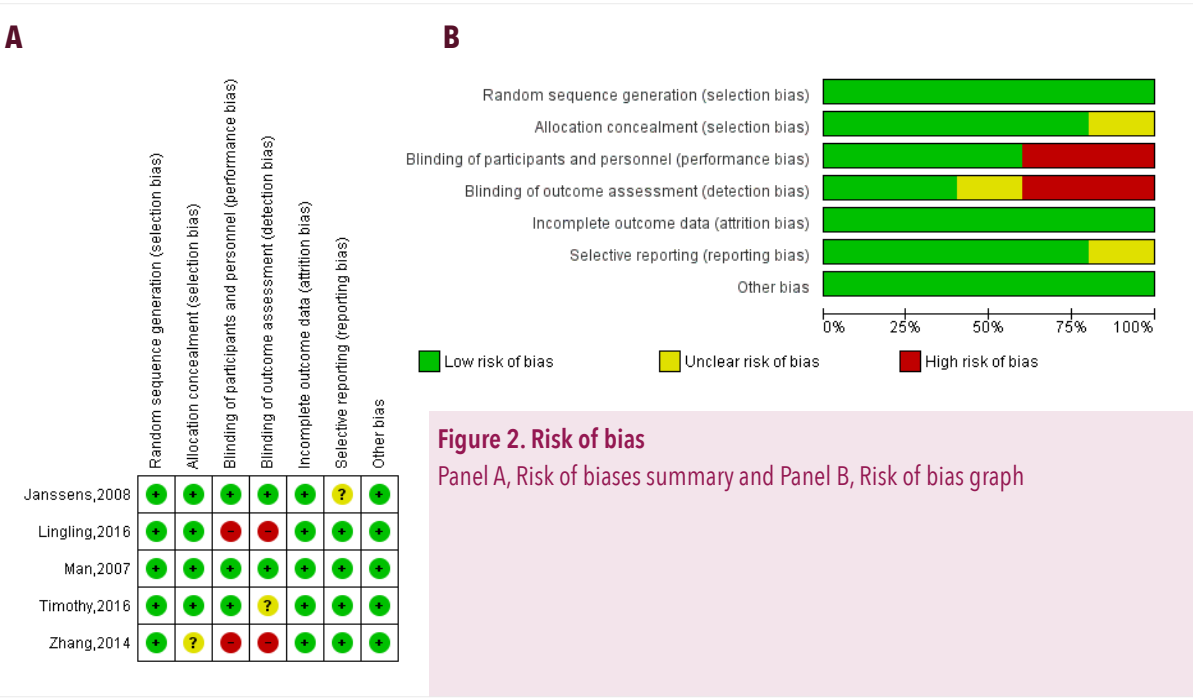

Figure 2. Risk of bias
Panel A, Risk of biases summary and Panel B, Risk of bias graph

EXCLUSION CRITERIA

We excluded articles that used additionally paracetamol or codeine in only intervention or control group and inadequate therapeutic dosage of systemic corticosteroids or NSAIDs.

QUALITY OF REPORTING AND RISK OF BIAS

We evaluated quality and risk of bias of the included studies using Jadad score[25] and the Cochrane Collaboration's tool, recommended by Cochrane Handbook for Systematic Reviews of interventions. The Cochrane Collaboration's tool classifies the study's biases into three groups (low risk, high risk and unclear risk) and regards the following evaluation: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other biases.

DATA EXTRACTION

We extracted data regarding the first author's name, year of publication, country where the study was conducted, method of study, a number of participants, interventions as systemic corticosteroids as well as NSAIDs and outcomes in term of pain reduction and adverse events. Disagreeable data were determined by discussion between the four reviewers.

DATA ANALYSES

We identified different type of outcome data which pain reduction is continuous data and adverse events are dichotomous data. We calculated mean difference (MD) and 95% confidence interval (CI) for pain reduction at rest and activity while calculated relative risk (RR) and 95%CI for adverse events between systemic corticosteroids and NSAIDs in the patients with acute gout. All data were analysed by Review Manager 5.3 statistical software (RevMan 5.3) and shown the result in

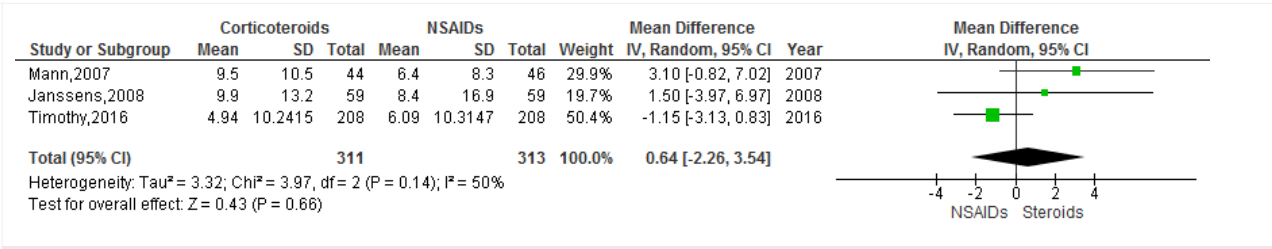

Figure 3. Forest plot of comparison: systemic corticosteroids versus NSAIDs, outcome: 1.1 pain reduction at rest in the first 6

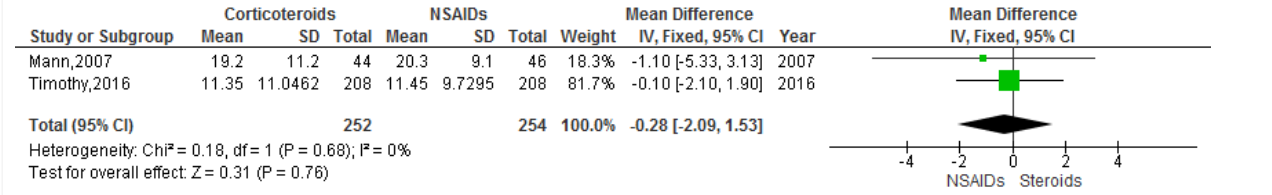

Figure 4. Forest plot of comparison: systemic corticosteroids versus NSAIDs, outcome: 1.2 Pain reduction at activity at 2 hours.

form of forest plots. Publication bias was shown in form of funnel plot. Statistical significance was described as $P<0.05$. If I^2 more than 40%, heterogeneity will be observed and we will use random-effects model for the meta-analysis. If I^2 less than 40%, we will use fixed-effects model.

RESULTS

STUDY CHARACTERISTIC

We initially identified 1680, 1715, 1671 and 1698 records by four reviewers, respectively, 884, 894, 859 and 908 records were removed due to non-studies, out of which 341, 352, 337 and 345 remaining after removed their duplicates. After screening for relevant studies, there were 37, 40, 41 and 47 articles remaining. Then, 31, 34, 35 and 41 articles were excluded mainly because of no acute gout patients and no systemic corticosteroids or NSAIDs using. We retrieved full-text studies for assessment which we included 6 studies and a study was excluded due to adding paracetamol or codeine in the only intervention group. The remaining 5 studies[19-22,26] with 834 participants were included in the analysis (Table 1). Three of them with 624 participants and two of them with 506 participants were included in the meta-analysis for pain reduction at rest and activity, respectively, and all trials were included in the meta-analysis for estimate adverse events (Figure 1).

ASSESSING RISK OF BIAS

The five studies were assessed using Jadad score and the Cochrane Collaboration's tool for assessing risks of bias. Three studies scored 5 points from Jadad score while two studies scored 3 points (Table 2). Risks of bias using the Cochrane Collaboration's tool is shown in Figure 2.

RANDOM SEQUENCE GENERATION

All studies reported the methods of random sequence.

ALLOCATION CONCEALMENT

All studies reported the methods of random sequence excepts the study by Zhang et al did not report details on concealing patient allocation.

Figure 5. Forest plot: comparison systemic corticosteroids versus NSAIDs, outcome: 1.3 nausea.

Figure 6. Forest plot: comparison systemic corticosteroids versus NSAIDs, outcome: 1.4 vomiting.

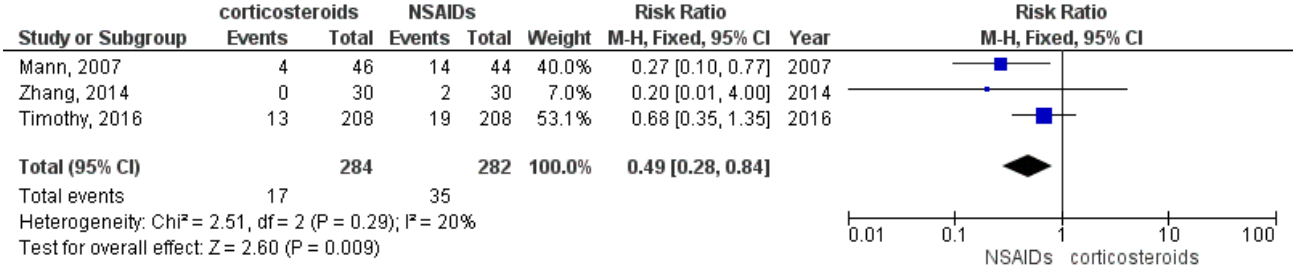

Figure 7. Forest plot: comparison systemic corticosteroids versus NSAIDs, outcome: 1.5 indigestion.

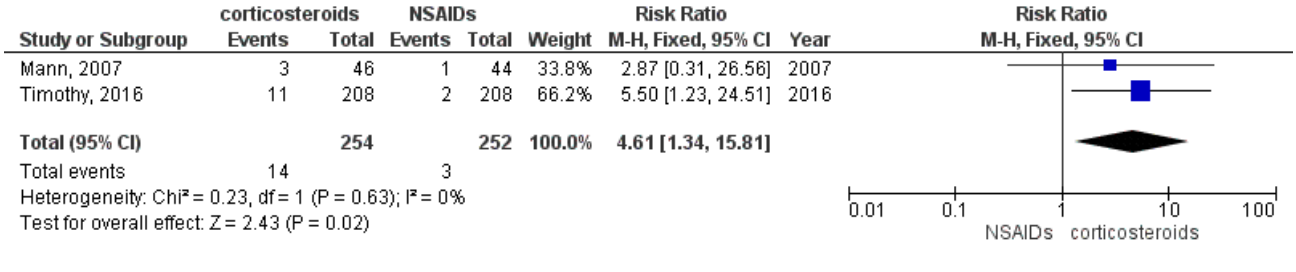

Figure 8. Forest plot: comparison systemic corticosteroids versus NSAIDs, outcome: 1.6 rash.

BLINDING OF PARTICIPANTS AND PERSONNEL

All studies reported that participants were blinded excepts the study by Zhang et al and Lingling et al were not blinded.

BLINDING OF OUTCOME ASSESSMENT

Two studies by Zhang et al and Lingling et al did not blind of outcome assessors and a study by Timothy et al did not describe on blinding of outcome assessors.

INCOMPLETE OUTCOME DATA

All studies were at low risk of bias in this category.

SELECTIVE REPORTING

All studies reported properly describe except the study by Janssens et al did not report adverse effects clearly.

OTHER BIAS

All studies had no potential conflict of interest.

PRIMARY OUTCOMES

PAIN REDUCTION AT REST

Pain reduction at rest was not significantly different between those using systemic corticosteroids and that of NSAIDs, measured by 100 mm-visual analog scale (VAS) in the first 6 hours (MD 0.64; 95% CI -2.26 to 3.54, I^2=50%, random-effect model) (Figure 3).

PAIN REDUCTION AT ACTIVITY

Pain reduction at activity was not significantly different between those using systemic corticosteroids and that of NSAIDs, measured by 100 mm-VAS in the first 2 hours (MD, -0.28; 95% CI, 2.09 to 1.53; I^2=0%, fixed-effect model) (Figure 4).

ADVERSE EVENTS

Adverse events rate were concluded from five studies. Major adverse events including death, life-threatening condition, hospitalization, disability or permanent damage, congenital anomaly and required intervention[27] were reported in the study by Man et al that those using systemic corticosteroids had lesser hospitalization requirement than that of NSAIDs (RR 0.06; 95% CI 0.00 to 1.09) while minor adverse events were reported in all included studies. Comparing systemic corticosteroids to NSAIDs, minor adverse events including nausea, vomiting and indigestion were found significant lower in those using systemic corticosteroids, (RR 0.23; 95% CI 0.11 to 0.51; RR 0.1; 95% CI, 0.02 to 0.54 and RR 0.49; 95% CI, 0.28 to 0.84, respectively) while rash was more common in those using systemic corticosteroids (RR 4.61; 95% CI 1.34 to 15.81) (Figure 5-8). Others adverse events including drowsiness, abdominal pain, dizziness, dyspnea and dry mouth were not significantly different between using systemic corticosteroids and NSAIDs (RR 0.86; 95% CI 0.56 to 1.33; RR 0.47; 95% CI 0.19 to 1.18; RR 0.62; 95% CI 0.41 to 0.95; RR 0.77; 95% CI 0.20 to 3.01; RR 1.28; 95% CI 0.85 to 1.92, respectively) (Table 4) (Figure 9-13).

PUBLICATION BIAS

We present funnel plots of the outcomes (Figure 14). However, we did not interpret due to small number of studies.

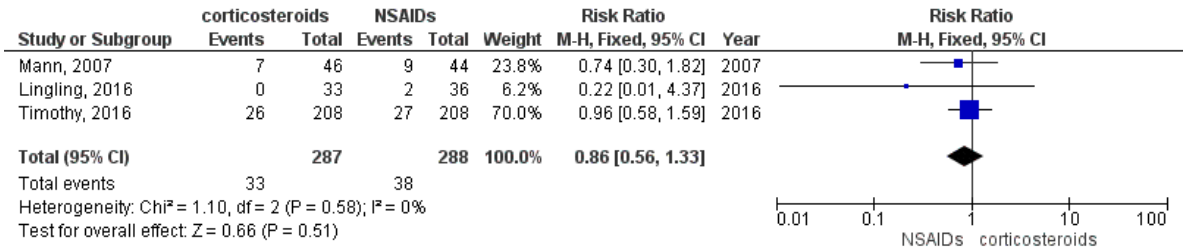

Figure 9. Forest plot: comparison systemic corticosteroids versus NSAIDs, outcome: 1.7 drowsiness or fatigue.

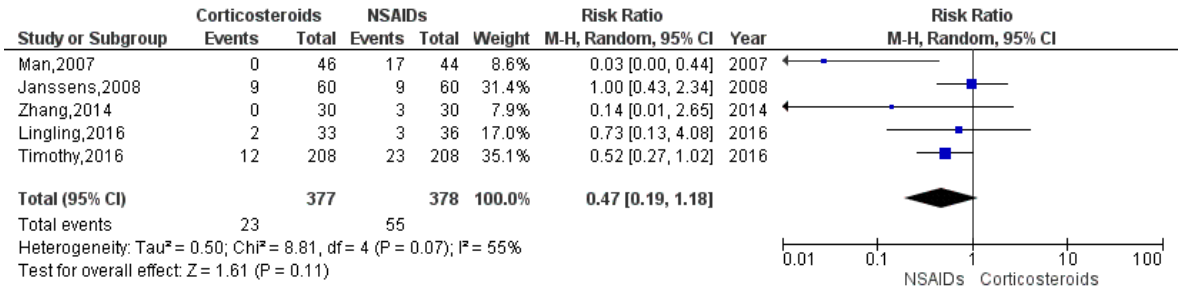

Figure 10. Forest plot: comparison systemic corticosteroids versus NSAIDs, outcome: 1.8 abdominal pain.

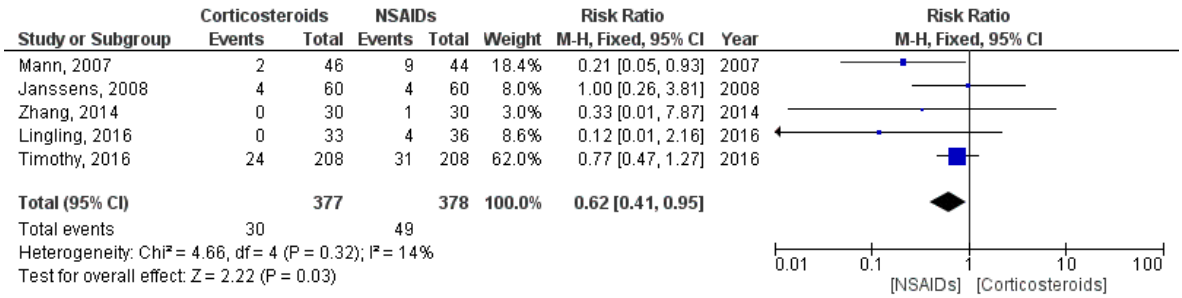

Figure 11. Forest plot: comparison systemic corticosteroids versus NSAIDs, outcome: 1.9 dizziness.

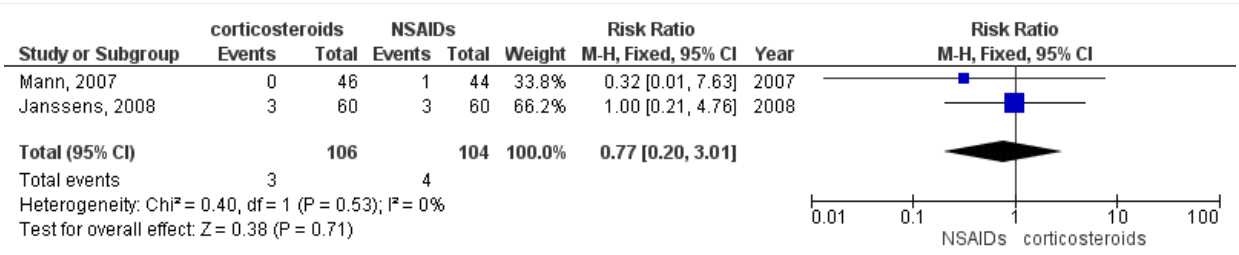

Figure 12. Forest plot: comparison systemic corticosteroids versus NSAIDs, outcome: 1.10 dyspnea.

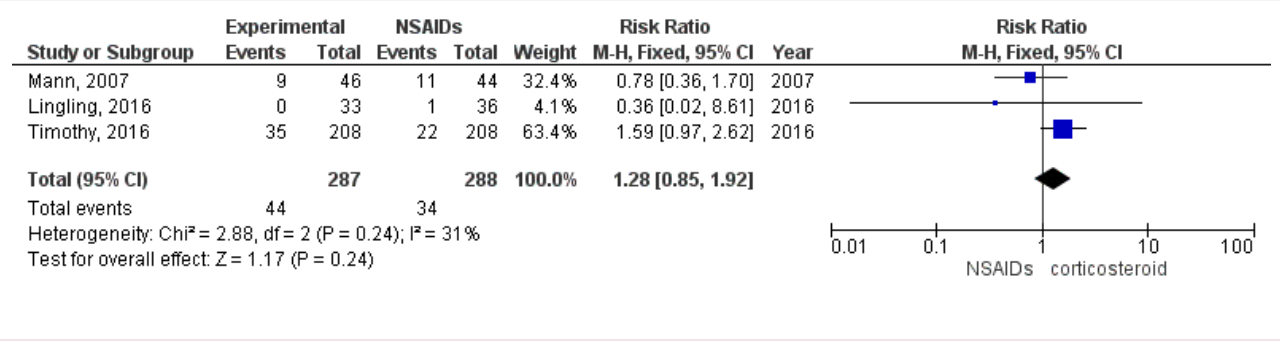

Figure 13. Forest plot: comparison systemic corticosteroids versus NSAIDs, outcome: 1.11 dry mouth.

DISCUSSION

SUMMARY OF EVIDENCE

We have assessed 5 RCTs involving 834 participants in this systematic review. All of the included articles compared capability in pain reduction and adverse events between systemic corticosteroids and NSAIDs. From three studies with 624 participants, we found that using systemic corticosteroids were not significantly different in pain reduction comparing to NSAIDs with moderate heterogeneity that may be due to difference in dosages of interventions, measurement scales, durations of assessment and methodology quality.

In all of the included studies, we found that there was higher incidence of minor adverse events including nausea, vomiting and indigestion in those using NSAIDs while rash has more events in those using systemic corticosteroids. Major adverse events were reported in one study that NSAIDs users required hospitalization more than systemic corticosteroids user. Thus, systemic corticosteroids was found superior to NSAIDs in pain reduction and adverse events.

STRENGTH AND LIMITATIONS

This review contains the largest number of acute gout patients comparing systemic corticosteroids to NSAIDs in pain reduction and adverse events. We searched through available and reliable databases. Results of this meta-analysis arose from combining data across included studies that were different in methodology quality regarding Jaded score and Cochrane Collaboration's tool. However, most of them were high quality, hence, the combined outcomes were reliable. The methodological limitations of our study are different duration of assessment, pain measurement, poor available data and incomplete reporting of statistical data thus they did not be combined with outcome analysis for pain reduction. We did not receive additional data from the authors of two included studies.[20,22] We did not conduct subgroup analyses for addressing heterogeneity due to data limitation.

COMPARISON TO OTHER STUDIES

Our review based on five trials shows robust evidence that no significant difference in pain reduction between using systemic corticosteroids and NSAIDs in acute gout. This result was

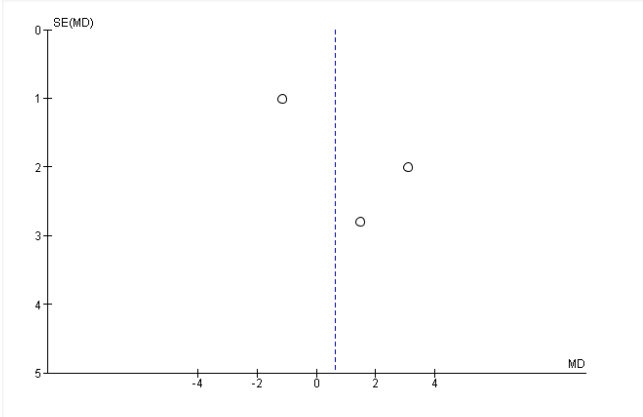

Figure 14. Funnel plot: systemic corticosteroids versus NSAIDs, outcome: 1.1 pain reduction at rest at in the first 6 hours.

supported by previous review which included 2 RCTs overlapping with ours.[28] Another review identifying 3 RCTs stated that the efficacy of systemic corticosteroids in acute gout were inconclusive with no meta-analysis as various types of systemic corticosteroids were used in the primary studies, administered in different routes and different kinds of comparator drugs.[18] However, the current review was able to conclude the treatment outcomes regarding to pain reduction as we included additional four RCTs with larger sample sizes in which NSAIDs were the comparator drugs.

The present review shows that efficacies on pain reduction of systemic corticosteroids and NSAIDs are similar with lower rate of adverse events and there are also two systematic reviews which state that short course of these drugs were safe.[29,30] Moreover, there is a study reported that oral prednisolone is more cost-effective than indomethacin for treatment in patients with acute gout.[31] However, many guidelines for acute gout management recommend that NSAIDs are the first line drugs for pain reduction.[16,32] Those recommendation, nonetheless, based on RCTs without comparing NSAIDS with systemic corticosteroids.

CONCLUSION AND IMPLICATION

Our systematic review including five RCTs showed that efficacy of systemic corticosteroids and NSAIDs in pain reduction was similar in patient with acute gout, but three minor adverse events including nausea, vomiting and indigestion were found more often in those using NSAIDs. Therefore, we prefer short-term systemic corticosteroids to NSAIDs especially in those with contraindications for NSAIDs.

ACKNOWLEDGMENTS & DECLARATION

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.

COMPETING INTERESTS: This study has no competing on interest.
FUNDING:None

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Oral acyclovir in treatment of pityriasis rosea: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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Accepted: AUGUST 2019
Latest revision: SEPTEMBER 2019
Printed: SEPTEMBER 2019

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ABSTRACT

OBJECTIVE

To identify the efficacy of oral acyclovir in treatment of pityriasis rosea (PR).

METHODS

Four independent reviewers systematically searched through electronic databases without language restriction, included Pubmed, Cochrane library, Scopus, and Trip Database. We also performed hand searching to find all relevant studies outside the databases. We assessed quality and risk of bias of the included studies using Jadad score and The Cochrane Collaboration's Tool for Assessing Risk of Bias. We extracted data from the included studies. The meta-analysis was performed where appropriate.

RESULTS

There were four randomized controlled trials identified, involving 251 patients with PR. Using oral acyclovir comparing with placebo or no treatment was associated with 2.76 times higher response rate to treatment (95% confidence interval (CI), 1.86 to 4.09; $P<0.001$; $I^2=11\%$), 2.19 times higher response rate to treatment (95% CI, 1.73 to 2.78; $P<0.001$; $I^2=18\%$) at the first week and the second week, respectively, and 44% relative risk reduction (RR 0.56, 95% CI, 0.41 to 0.77; $P=0.004$; $I^2=21\%$) in occurrence rate of new skin lesion after following in the first week.

CONCLUSION

Oral acyclovir was superior to placebo or no treatment for treating patients with PR regarding response rate to treatment at the first and the second week as well as occurrence rate reduction of the new skin lesion in the first week after starting the treatment.

INTRODUCTION

Pityriasis rosea (PR) is an acute papulosquamous skin disease characterized by pink macules or papules usually appear on trunk with christmas-tree distribution pattern.[1,2] An estimated incidence of PR is 170 per 100,000 with 75% of cases are reported in patients age 10 to 35 years.[3-6] Etiology of PR is remaining incomplete understood, several existing evidences show association between PR and viral infection or endogenous reactivation of human herpesvirus (HHV)-6 and HHV-7.[7-11] Thus, antiviral agents may have a role for treating PR. Although acyclovir is effective against viral infection by its mechanism of deoxyribonucleic acid (DNA) polymerase inhibition,[12] there are studies reporting that it has little or no action against HHV-7 in laboratory condition because its action depends on thymidine kinase and HHV-7 does not possess the gene coding for this enzyme.[13,14] According to the controversy between its mechanism of action and the results from previous studies, we conducted a systematic review to evaluate efficacy of oral acyclovir in treating patients with PR.

METHODS

SEARCH METHODS FOR IDENTIFYING OF STUDIES

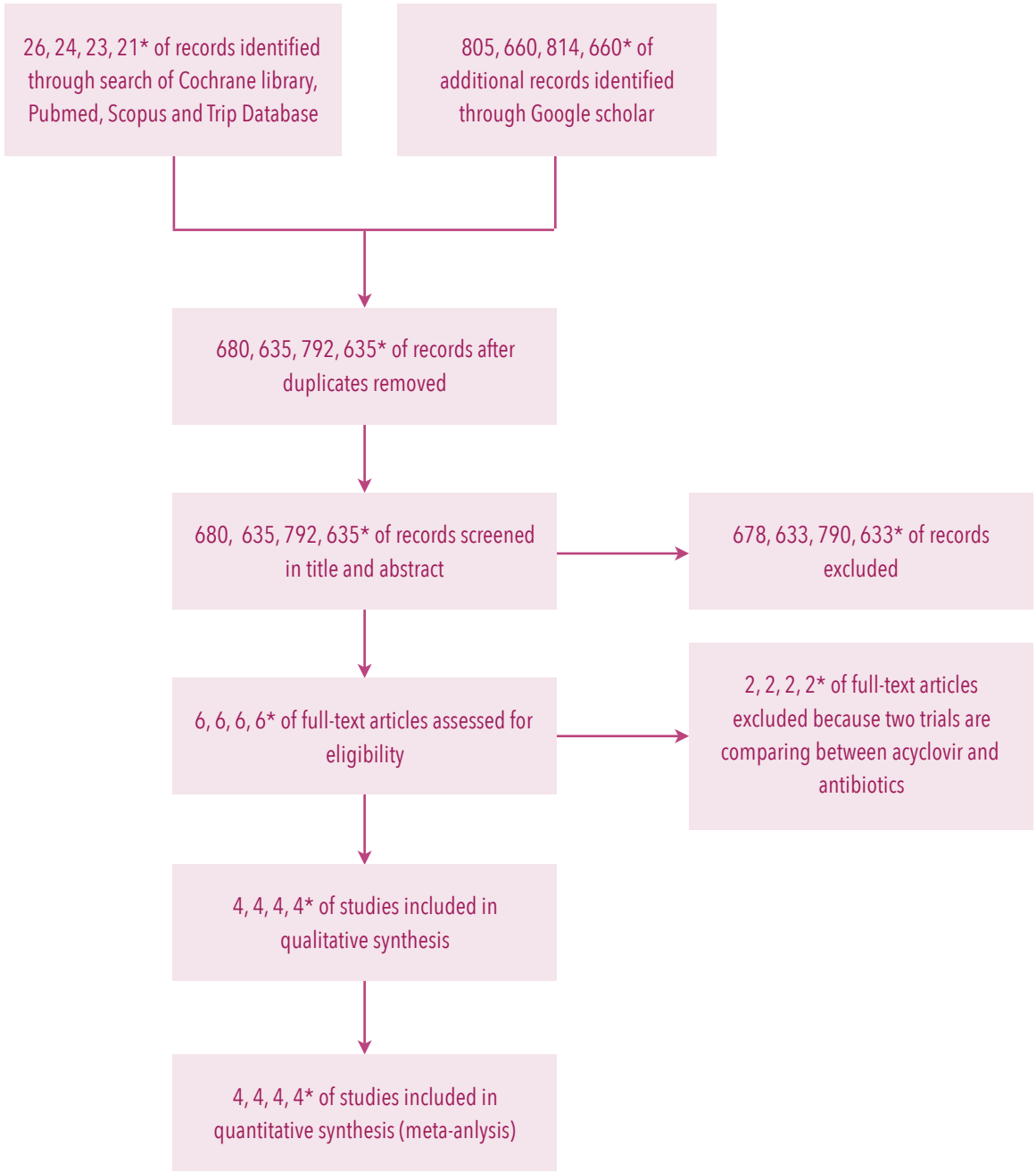
Four independent reviewers systematically searched through electronic databases, included Pubmed, Cochrane library, Scopus and Trip Database using the combination search terms of "pityriasis rosea" and "acyclovir". We also applied Medical Subject Headings (MeSH) searching strategy in term of "Pityriasis Rosea"[Mesh] AND "Acyclovir"[Mesh] to identify studies in Pubmed and Cochrane library. We used PICO searching strategy to identify studies in Trip Database using P: "pityriasis rosea" and I: acyclovir. No restriction of language was assigned and translation was sought when necessary. We also tracked for articles in references of each included study. Moreover, we performed hand searching to find other relevant studies outside the databases.

INCLUSION AND EXCLUSION CRITERIA

Our inclusion criteria were randomized controlled trials (RCTs) that patients with PR were diagnosed by dermatologists, were treated with oral acyclovir and reported outcomes at least on response to treatment at the first and the second week and occurrence rate of new skin lesion after initiating the treatment for one week. To focus on the efficacy of oral acyclovir in treating patients with PR, studies were excluded if they met these following criteria; studies which compared combination therapy of oral acyclovir and other antiviral agents or antibiotics; and studies which compared oral acyclovir with other antiviral agents or antibiotics.

QUALITY OF REPORTING AND RISK OF BIAS

We used Jadad score to assess quality of included trials consist of the evaluations of randomization, blinding methods and adequate description of withdrawals or dropouts.[15] In addition, we used The Cochrane Collaboration's tool for Assessing Risk of Bias to present the risk of bias as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias by categorizing them as high risk, low risk, or unclear risk.[16]



*The 4 numbers refer to the quantity of results searched by Nut Laorueangwatthana, Santhita Pimonbut, Sirinat Suriyachai and Papichaya Songtuntarax, respectively

Figure 1. Flow of Studies by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Table 1. Description of Included Studies.

Trial	No. of patients in intervention/ controlled group	Interventions	Controlled	Outcomes
Daliri, 2008	65/64	Oral acyclovir 800 mg five times daily for 1 week	Vitamin E 100 mg twice daily	Response rate to treatment was higher in acyclovir group than that of placebo group at 1st week (63.2% vs. 28.5%; P=0.014). Response rate to treatment was higher in acyclovir group comparing to that of placebo group at 2nd week (88.1% vs. 47.4%; P=0.014). Formation of new lesion at 1st week was less common in acyclovir group than that of placebo group (47.4% vs. 73.2%; P=0.014).
Rassai et al, 2011	28/26	Oral acyclovir 400 mg five times daily for 1 week	No treatment	Erythema reduction at the 1st week was higher in a acyclovir group than that of placebo group (46.4% vs. 15.4%; P=0.014). Erythema reduction at the 2nd week was higher in acyclovir group comparing to that of placebo group (78.5% vs. 27% P<0.001).
Ganguly, 2014	38/35	Oral acyclovir 800 mg five times daily in adult and 20 mg/kg/ day four times daily in children for 1 week	Vitamin C 100 mg five times daily for adults, 50 mg four times daily for children for 1 week	Response rate to treatment was higher in acyclovir group than that of placebo group (16 vs. 3 out of 30; P=o.oo3 in 1st week and 26 vs. 10 out of 30; P= 0.001 in 2nd week). New skin lesion at the first week was less common in acyclovir group than that of placebo group (o vs. 3 out of 30).
Das et al, 2015	12/12	Oral acyclovir 400 mg thrice daily for 1 week with cetirizine 10 mg once a day at bedtime plus calamine lotion	Cetirizine 10 mg once daily at bedtime plus calamine lotion	New skin lesion at 1st week was less common in acyclovir group than that of placebo group; (2 vs. 7 out of 12; P=0.046).

DATA EXTRACTION

We extracted the data from the included studies regarding the first author, year of publication, number of participants of intervention and controlled groups, dose and duration of study drugs, and outcomes in terms of response rate to treatment at the first and the second week and occurrence rate of new skin lesion after following in the first week.

STATISTICAL ANALYSIS

The meta-analysis was done and reported as relative risk (RR) and 95% confidence interval (CI). We presented the meta-analysis as forest plot. We

calculated I^2 to assess the heterogeneity of the included studies. We used the fixed-effect model if $I^2<50\%$ and the random-effect model if $I^2\geq50\%$. We used funnel plot for assessing publication bias. All statistical analyses were done using Review Manager 5.3 statistical software.

SENSITIVITY AND SUBGROUP ANALYSES

We carried out sensitivity analysis by removing each trial one by one from overall analysis to evaluate the influence of single trial on the pooled analysis. We also restricted the meta-analysis to subgroup of trials that have low risk of bias (Jaded score≥3 and The Cochrane Collaboration's Tool for Assessing Risk of Bias categorized to low risk≥50%).

RESULTS

Initially, there were 831, 684, 837 and 681 studies identified by each of four reviewers as potentially relevant studies from the electronic databases and other sources. Of these, 680, 635, 792 and 635 studies remained after duplicate removed and were screened in title and abstract. Of these, six studies fulfilled the predefined inclusion criteria and were screened in details. We excluded two studies because the studies compared oral acyclovir to oral erythromycin for treating patients with PR.[17,18] Four reviewers finally assent to have four related studies to be included in the quantitative analysis. (Figure 1)

CHARACTERISTICS OF THE INCLUDED STUDIES

We found four trials with 251 patients, met our inclusion criteria. All of them were RCT comparing the use of oral acyclovir with placebo or no treatment for treating patients with PR. A total of 127 patients received oral acyclovir and 124 patients received placebo or no treatment. In two of these trials, patients in the intervention group were prescribed oral acyclovir 800 mg five times daily; in another two studies, patients in intervention group were prescribed oral acyclovir 400 mg five times daily and 400 mg three times daily, respectively. For the two placebo-controlled studies, patients in the controlled group were prescribed one of these following agents as placebo; vitamin E or vitamin C (Table 1).

RISK OF BIAS OF THE INCLUDED STUDIES

Four reviewers assess the quality of the four studies using Jadad score and The Cochrane Collaboration's Tool for Assessing Risk of Bias. Their Jadad scores and the risk of bias summary with graph following The Cochrane Collaboration's tool for Assessing Risk of Bias are summarized in Table 2, Figure 2, respectively.

SUMMARY OF OUTCOMES

RESPONSE RATE TO TREATMENT AT THE FIRST WEEK

For this outcome, there were three trials included with 227 patients. The response rate was significantly higher in the acyclovir group than that of placebo group (RR 2.76; 95% CI, 1.86 to 4.09; $P<0.001$; $I^2=11\%$) (Figure 3).

RESPONSE RATE TO TREATMENT AT THE SECOND WEEK

For this outcome, there were three trials included with 232 patients. The response rate was significantly higher in the acyclovir group than

Table 2. Review Authors' Judgement About Each Risk of Bias for Each Included Study Using Jadad score.

	Daliri, 2008	Rassai et al, 2011	Ganguly, 2014	Das et al, 2015
Was the study described as randomized ?	1	1	1	1
Was the method used to generate the sequence of randomization described and was it appropriate?	0	1	1	1
Was the study described as double blind ?	1	0	1	0
Was the method of double blind described and was it appropriate ?	0	0	1	0
Was there a description of withdrawals and dropouts ?	0	0	0	1
Total score	2	2	4	3

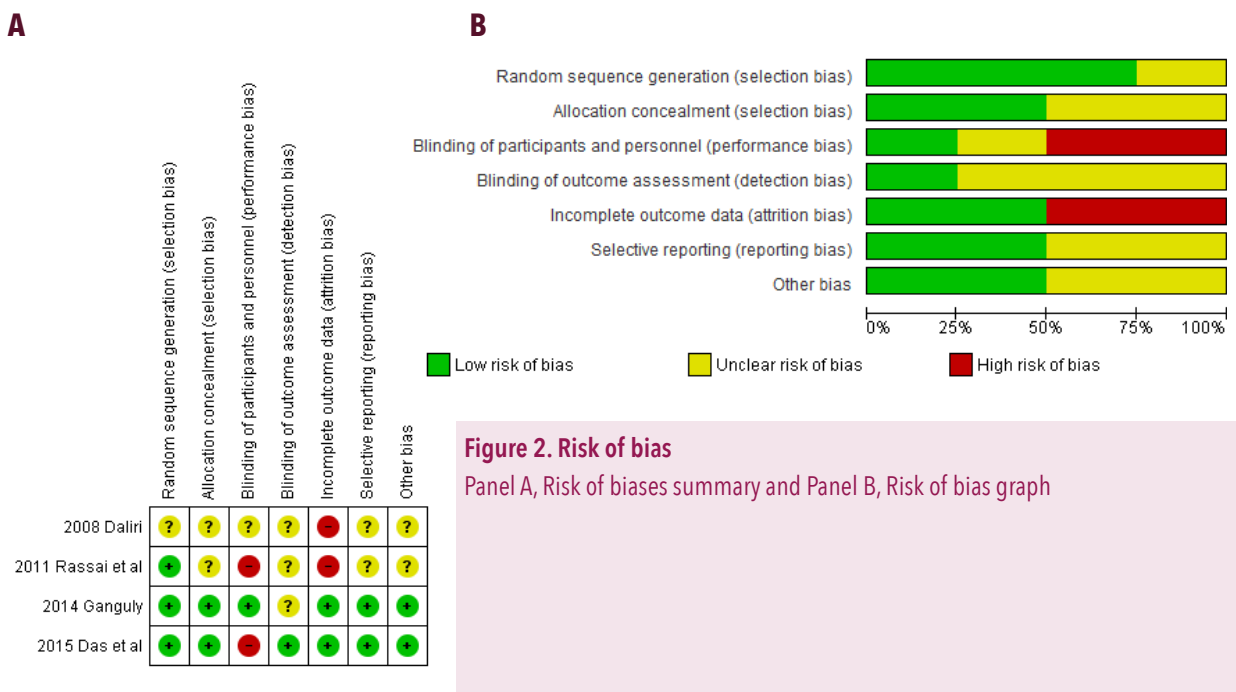


Figure 2. Risk of bias
Panel A, Risk of biases summary and Panel B, Risk of bias graph

that of placebo group (RR 2.19; 95% CI, 1.73 to 2.78; P<0.001; I^2=18%) (Figure 4).

OCCURRENCE RATE OF NEW SKIN LESION AFTER INITIATING THE TREATMENT FOR ONE WEEK

For this outcome, there were three trials included with 197 patients. The occurrence rate of new skin lesion was significantly lower in the acyclovir group than that of placebo group (RR 0.56; 95% CI, 0.41 to 0.77; P=0.004; I^2=21%) (Figure 5).

ADVERSE EFFECTS

Das et al, 2015 reported adverse effects that occurred in both acyclovir and placebo group. Of 12 patients received oral acyclovir, two patients

experienced increased sleep, three patients had headache, two patients had nausea and vomiting and one patient had metallic taste sensation. Of 12 patients in placebo group, only one patient experienced increased sleep.

NUMBER OF DAYS TAKEN TO CURE

Ganguly, 2014 reported time taken for clearance of skin lesion in acyclovir group. The study reported that if treatment started less than 7 days after the onset of the lesions, it took 5.3 days to clear. But if treatment started more than 7 days after the onset of lesions, it took 6.7 days to clear. However, the difference of results between the two groups were not significant (P=0.287).

SENSITIVITY AND SUBGROUP ANALYSIS

None of the studies individually affected the overall results either response rate to treatment at the first or the second week or occurrence rate of new skin lesion after initiating the treatment for one week. The subgroup analysis of low risk of bias trials comprising two RCTs. With 84 patients, occurrence rate of new skin lesion after initiating the treatment for one week was significantly lower in the acyclovir group than that of placebo group (RR 0.24; 95% CI, 0.07 to 0.83; P=0.02; I^2=0%) (Figure 6).

PUBLICATION BIAS

We generated the funnel plots of the treatment outcomes at the first and the second week as well as occurrence rate of new skin lesion after initiating the treatment for one week comparing oral acyclovir and placebo. However, the number of the studies using in the funnel plot were too few to assess for publication bias (Figure 7).

DISCUSSION

SUMMARY OF THE RESULTS

In this meta-analysis, of four trials involving 251 patients, oral acyclovir was superior to placebo or no treatment regarding response rate to treatment as well as reducing the occurrence rate of new skin lesion in treating patients with PR. Adverse events were reported from one trials including increased sleep, headache, nausea and vomiting and metallic taste sensation.

STRENGTH AND LIMITATIONS OF THE REVIEW

From our results, this is the first systematic review comparing oral acyclovir to placebo or no treatment in treating patients with PR. Our review complied to the Cochrane handbook and Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (PRISMA). We comprehensively searched through four electronic databases and also performed hand searching, no study seemed to be missed. In addition, the heterogeneity between the included trials was low.

Our study had several limitations. Firstly, our systematic review consisted of a small number of participants, since only four trials met our predefined inclusion and exclusion criteria. Secondly, the quality and risk of bias of each included trial were varied, there were two trials that have high risk of bias; Daliri and Rassai et al, because of their unclear description about methods of randomization and blinding.[19,20] Finally, each trial prescribed different dosage of acyclovir which may affect the results and cause heterogeneity among studies. Due to the mentioned limitations, implementation of our findings should be done with cautions.

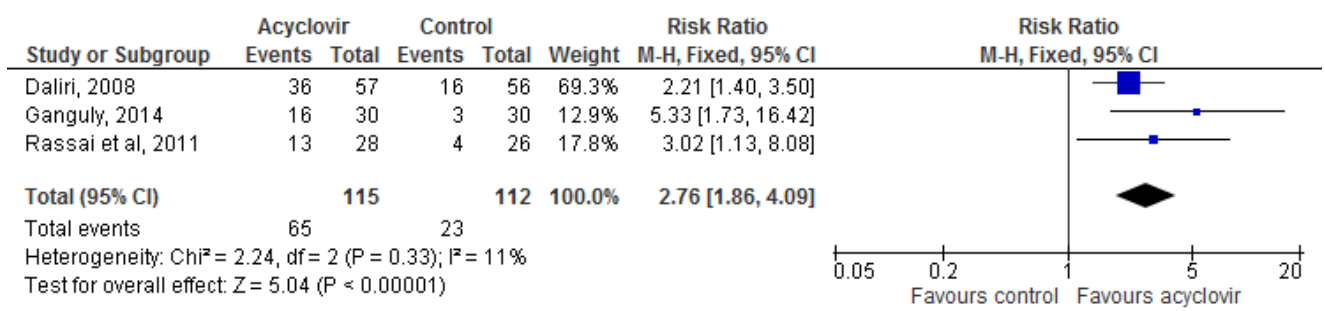


Figure 3. Response Rate to Treatment at the First Week

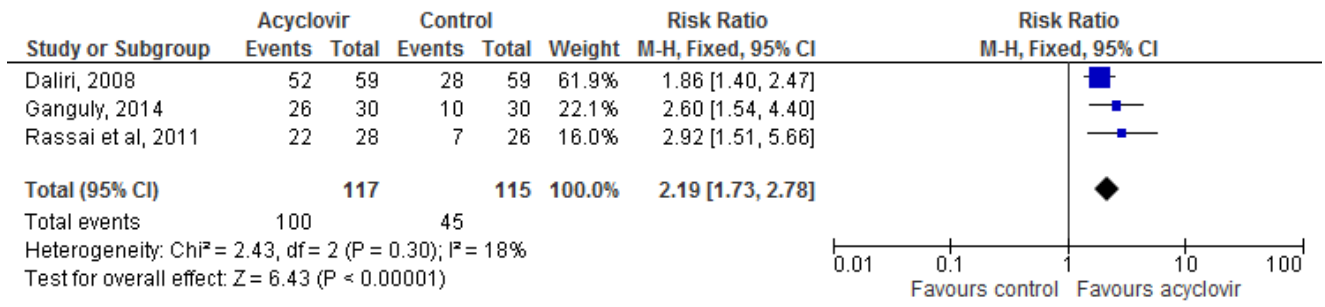


Figure 4. Response Rate to Treatment at the Second Week

COMPARISON TO OTHER STUDIES

We found that using oral acyclovir had superior effect to that of placebo or no treatment for response rate to treatment at the first and the second week as well as reducing occurrence rate of new skin lesion after initiating the treatment for one week. In addition, there were other two relevant studies; a cohort study and an RCT. A former study by Drago et al stated that oral acyclovir might be effective in patients with PR, which consorted with our results.[23] However, the latter study by Singh et al, concluded that oral acyclovir was not effective for PR.[24] The reason of this controversy might be due to a smaller number of patients (N=27) in the study by Singh et al which was also mentioned as its limitations in the study.

Aside from PR, there are several studies reported that oral acyclovir is effective in treatment of various diseases that are caused by virus, such as mucocutaneous herpes simplex, herpes zoster and varicella zoster. However, those studies also reported adverse effects of oral acyclovir comprising of the following systems; (i) central nervous system including headache, dizziness, delirium, ataxia and meningoencephalitis, (ii) respiratory and otolaryngeal system including pneumonia, otitis media, bronchitis, coryza and pharyngitis, (iii) digestive system including dyspepsia, diarrhea and nausea and vomiting and

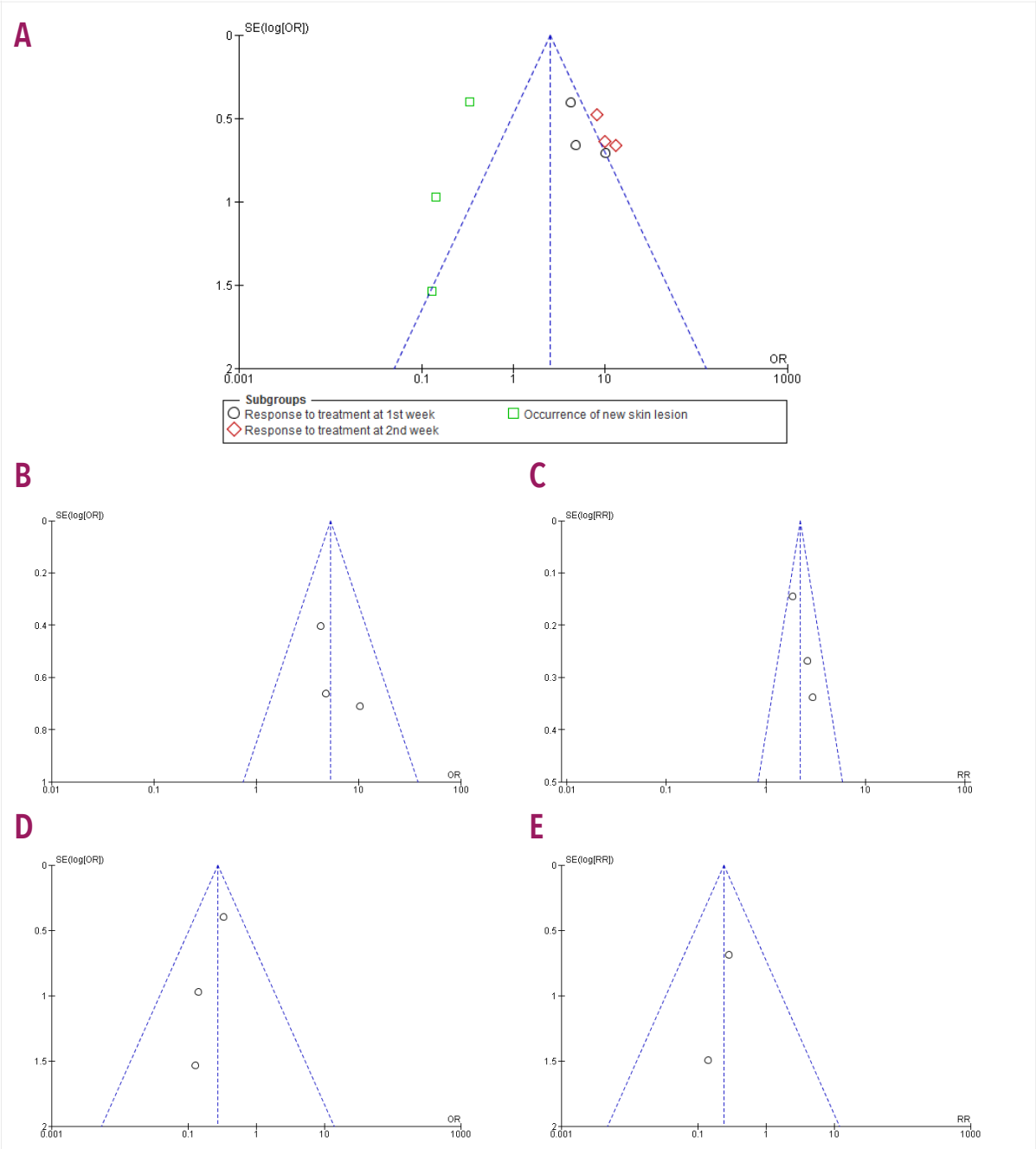


Figure 7. Publication bias

Panel A, Funnel plot comparison: main results

Panel B, Funnel Plot Comparison: Response Rate at the First Week

Panel C, Funnel Plot Comparison: Response Rate at the Second Week

Panel D, Funnel Plot Comparison: Occurrence rate of New Skin Lesion After Following in the First Week

Panel E, Funnel Plot Comparison for Subgroup Analysis: Occurrence rate of New Skin Lesion After Following in the First Week

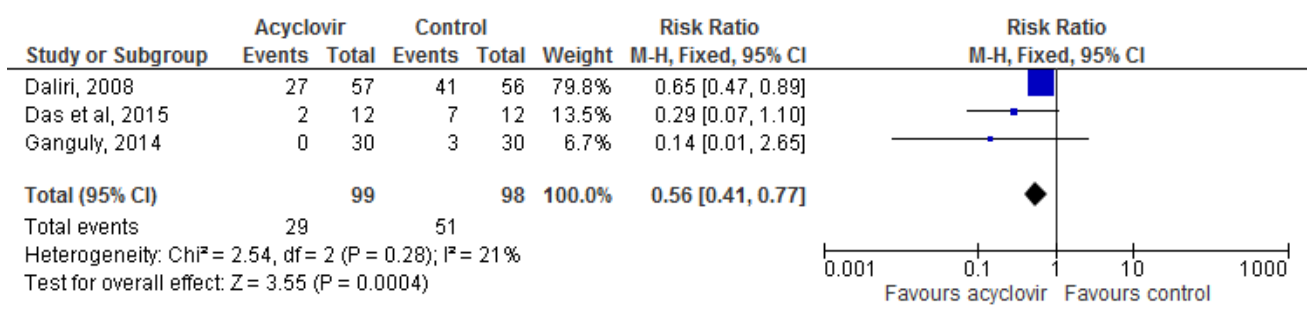


Figure 5. Occurrence Rate of New Skin Lesion After Following in the First Week

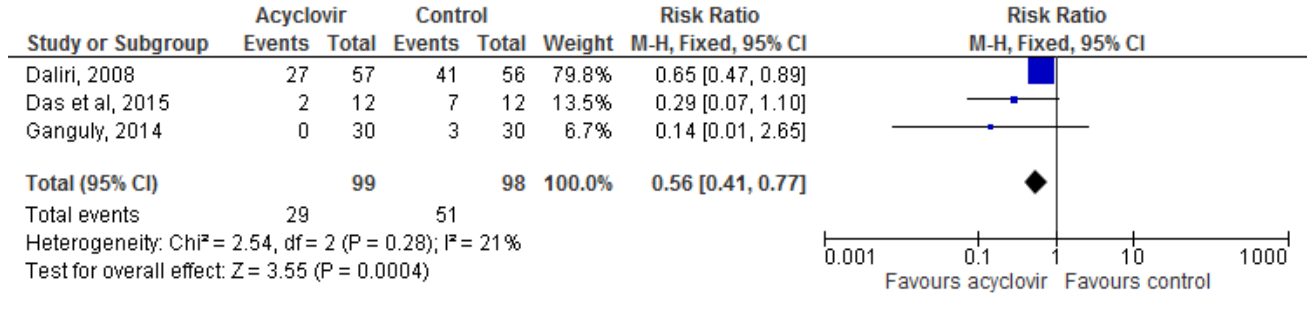


Figure 6. Subgroup Analysis of Trials That Have Low Risk of Bias: Occurrence Rate of New Skin Lesion After Following In the First Week

(iv) urinary system including renal colic, renal polyp, acute kidney injury and acute glomerulonephritis.[25-29] In our review, adverse effects were relatively less common than that of previous studies.

CONCLUSION AND IMPLICATION OF THE RESULTS

Oral acyclovir was superior to placebo in treating patients with PR in terms of response rate to treatment in the first and the second week and reducing occurrence rate of new skin lesion in the first week after the treatment started. PR can cure itself with no sequelae, acyclovir is still not a first-line therapy for treatment of PR.[30] Patient's education and reassurance that the lesion will resolve were all needed in general practice.[30,31] Thus, the use of acyclovir might depend on individual opinion of each physician and each patient's status at that moment.

Efficacy of acyclovir in the treatment of PR is likely to be related to its mechanism of DNA polymerase inhibition.[12] Early administration of high-dose acyclovir before 7 days after onset of lesions could shorten duration of the disease.[24] Nevertheless, there are complexities of using acyclovir, for instance, there are multiple kinetics of acyclovir including high protein binding ratio and poor oral bioavailability that interfere its effect in human body.[12] Multiple doses daily is

recommended due to its short half-life.[12] Moreover, one trial included in our meta-analysis showed that patients who received oral acyclovir had more adverse events than that of placebo group.[22] We also suggested that further RCT should perform subgroup analyses in different patient's status, such as immunosuppression. As well as a network meta-analysis that compared efficacy and safety of various interventions, including acyclovir, in treating patients with PR.

ACKNOWLEDGMENTS & DECLARATION

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.

COMPETING INTERESTS: This study has no competing on interest.
FUNDING:None

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Silver nitrate cauterization for aphthous stomatitis: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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Accepted: AUGUST 2019
Latest revision: SEPTEMBER 2019
Printed: SEPTEMBER 2019

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ABSTRACT

OBJECTIVE

To identify the efficacy of silver nitrate cauterization in shortening healing time of aphthous stomatitis.

METHODS

Three independent reviewers systematically searched through electronic databases including the Cochrane Library, PubMed, Trip Database and Scopus. We also performed hand searching to find all relevant studies outside the databases. We assessed quality and risk of bias of the included studies using The Cochrane Collaboration's Tool for Assessing Risk of Bias. We extracted data from the included studies. The meta-analysis was performed where appropriate.

RESULTS

There were two randomized controlled trials identified, involving 150 patients with aphthous stomatitis. Rate of complete re-epithelialization on the seventh day after the procedure was interpreted that using silver nitrate cauterization was no statistically significant difference from using placebo stick. (relative risk, 1.24; 95% confidence interval, 0.55 to 2.80; P=0.60; I^2=87%)

CONCLUSION

Rate of complete re-epithelialization of aphthous stomatitis was not different between using silver nitrate cauterization and placebo on the seventh day after the procedure.

INTRODUCTION

Aphthous stomatitis is an oral disease characterized by painful oral ulcers that appear multiple small erythematous lesion with circumscribed margins.[1] Its prevalence rate can be as high as 80%.[2–9] Its treatments comprised the uses of steroids, analgesics, topical anesthetic agents, anti-inflammatory agents, antiseptics, tetracycline suspension, sucralfate, carbon dioxide laser and silver nitrate cauterization.[10–22]

Regarding silver nitrate cauterization, in 2005 a randomized controlled trial study (RCT) in 85 patients with aphthous stomatitis concluded that the healing time of those undergoing silver nitrate cauterization was not shorter than that of placebo group.[21] However, the latter study in 2014 in 65 patients with aphthous stomatitis stated that the healing time of silver nitrate cauterization group was shorter than that of placebo group.[22] Due to this controversy, we conducted a systematic review in order to summarized all available evidences to identify the efficacy of silver nitrate cauterization in treatment of aphthous stomatitis.

METHODS

SEARCH METHODS FOR IDENTIFYING OF STUDIES

Three independent reviewers systematically searched through electronic databases including the Cochrane Library, PubMed, Trip Database and Scopus using the term "aphthous stomatitis" or "aphthous ulcer" and "silver nitrate". We also applied Medical Subject Headings (MeSH) searching strategy in term of "Stomatitis, Aphthous"[Mesh] AND "Silver Nitrate"[Mesh] to identify studies in the Cochrane Library and PubMed. We used PICO search strategy to identify studies in Trip Database using P: "aphthous stomatitis" and I: "silver nitrate" with no specific C and O. No restriction of language was assigned and translation was sought when necessary. We also tracked for articles in references of each included study. Moreover, we performed hand searching to find other relevant studies outside the databases such as Google Scholar, ClinicalTrials.gov, Web of Science and WorldCat using the term "aphthous stomatitis" or "aphthous ulcer" and "silver nitrate". All searches were done on February 11, 2017.

INCLUSION AND EXCLUSION CRITERIA

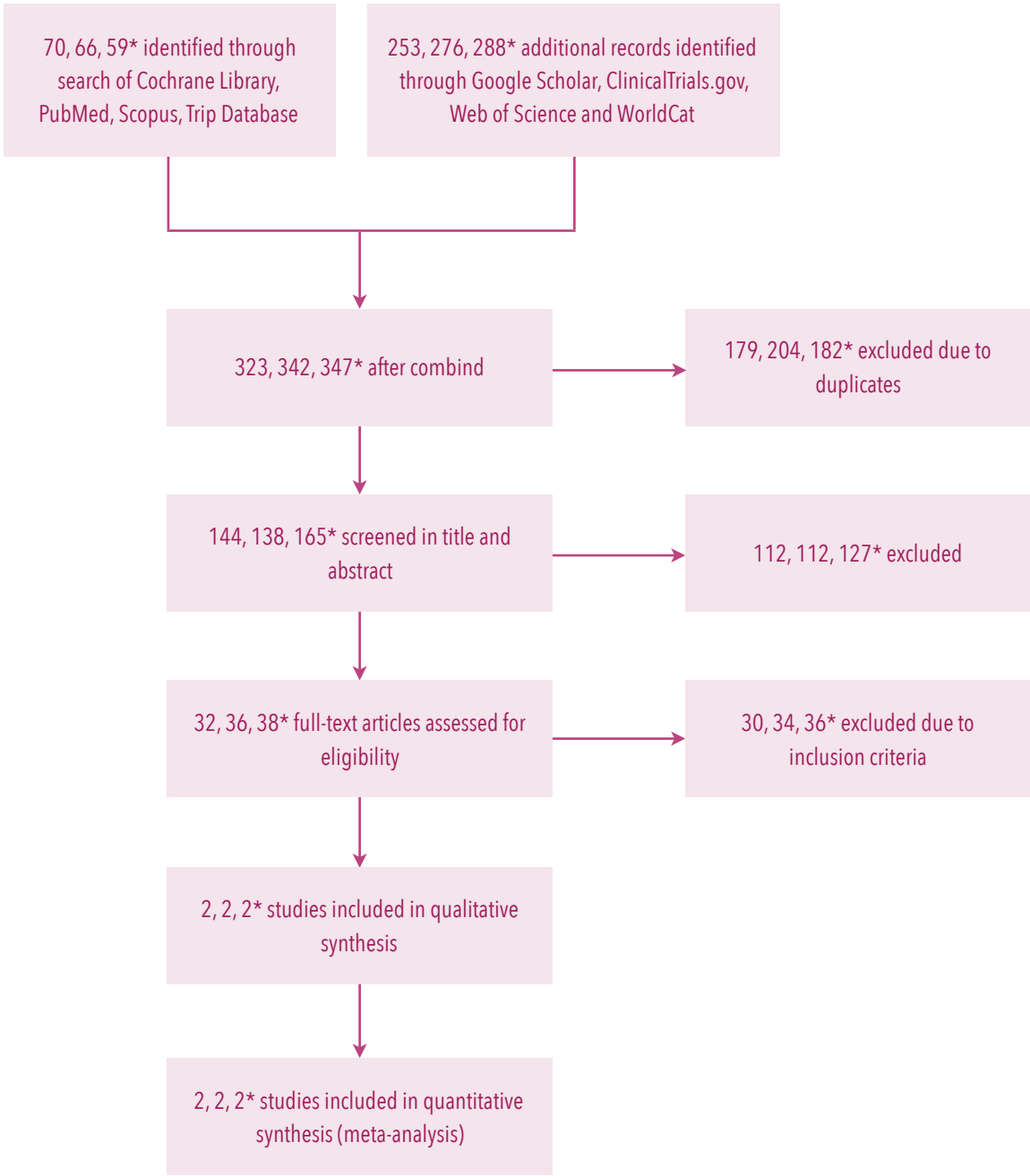
We included only RCTs that patients with aphthous stomatitis were treated with silver nitrate cauterization regardless any outcomes. To focus on the efficacy of silver nitrate cauterization in treating patients with aphthous stomatitis, studies were excluded if they met following this criteria; studies which compared combination therapy of silver nitrate cauterization and other agents.

ASSESSMENT OF REPORTING BIASES

We used The Cochrane Collaboration's tool for Assessing Risk of Bias to present the risk of bias as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias by categorizing them as high risk, low risk, or unclear risk.[23]

DATA EXTRACTION

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



*The three numbers refer to the quantity of results searched by the three reviewers; WL, NW and PJ, respectively.

Figure 1. Flow of Studies by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Table 1. Description of included studies.

Studies	No. of patients in intervention/ controlled group	Interventions	Control	Outcomes
Alidaee et al, 2005	47/38	Silver nitrate cauterization (99.8% purity; Merck, Darmstadt, Germany)	Placebo stick (sugar stick)	Rate of complete re-epithelialization on the seventh day after the procedure (83% vs. 89% ;P=0.39).
Gül Soylu Özler, 2014	35/30	Silver nitrate cauterization	Placebo stick (empty stick)	Rate of complete re-epithelialization on the seventh day after the procedure (60% vs 32% ;P<0.01).

number of participants of intervention and controlled groups, duration of studies, and outcomes in terms of rate of complete re-epithelialization on the seventh day.

STATISTICAL ANALYSIS

The meta-analysis was done and reported as relative risk (RR) and 95% confidence interval (CI). We presented the meta-analysis as forest plot. We calculated I^2 to assess the heterogeneity of the included studies. We used the fixed-effect model if $I^2<50\%$ and the random-effect model if $I^2\geq50\%$. We used funnel plot for assessing publication bias. All statistical analyses were done using Review Manager 5.3 statistical software.

RESULTS

Initially, there were 298, 327 and 325 studies identified by each of the three reviewers (by WL, NW and PJ, respectively) as potentially relevant studies from the electronic databases and other sources (Figure 1). Of these, 144, 138 and 165 studies remained after duplicate removed and were screened for their titles and abstracts. Of these 2, 2, 2 studies fulfilled the predefined inclusion criteria and were screened in details. We finally assented to have two related studies to be included in the quantitative analysis.

CHARACTERISTICS OF THE INCLUDED STUDIES

We found two studies with 150 patients with aphthous stomatitis. All of them were RCT comparing the use of silver nitrate cauterization to placebo for treating patients with aphthous stomatitis; 82 patients in silver nitrate cauterization group and 68 patients in placebo group. For the two placebo-controlled studies, patients in the control group were prescribed with either sugar stick or empty stick (Table 1).

RISK OF BIAS OF THE INCLUDED STUDIES

We assessed the quality of the two included studies by Alidaee et al and Gül Soylu Özler using The Cochrane Collaboration's Tool for Assessing Risk of Bias. Their risk of bias summaries with graphs are summarized in Figure 2, respectively.

RANDOM SEQUENCE GENERATION

A former study did not reported the methods of random sequence, it was described as unclear risk of bias. A latter study reported the methods of

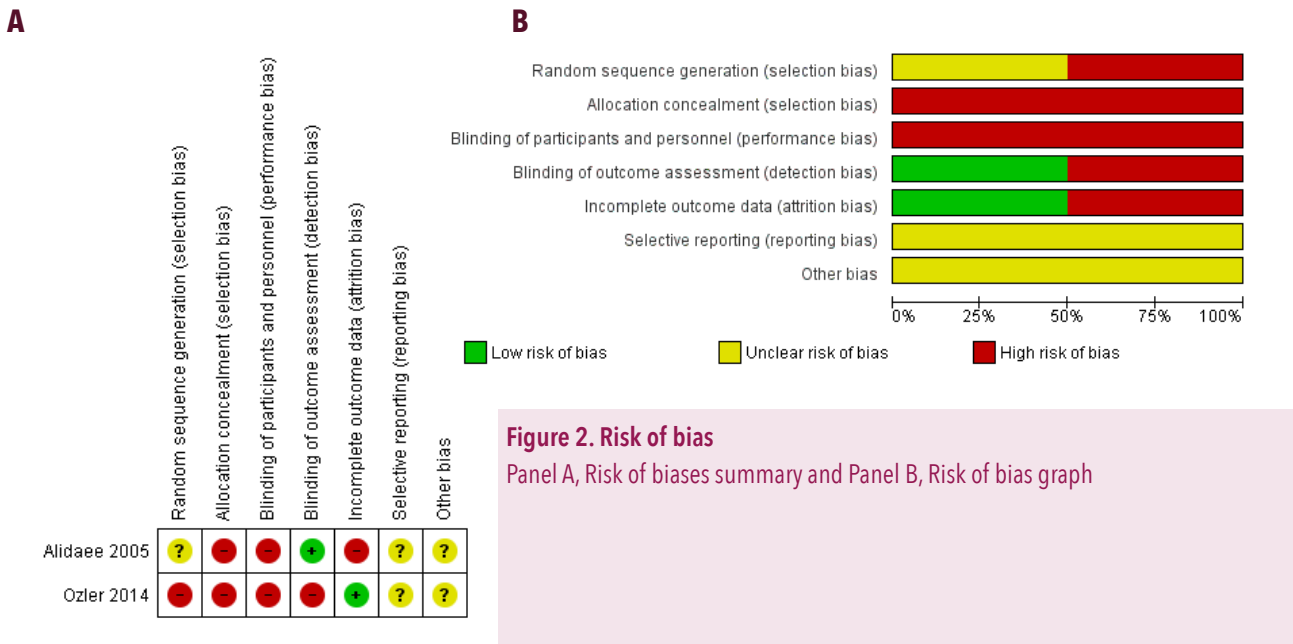


Figure 2. Risk of bias
Panel A, Risk of biases summary and Panel B, Risk of bias graph

random sequence by attendance to the ear nose throat clinic, it was described as high risk of bias.

ALLOCATION CONCEALMENT

A former study reported treatment allocation processed by sealed envelopes but the researcher was not blinded. It was described as high risk of bias. A latter study reported the methods of random sequence by attendance to the ear nose throat clinic with no allocation concealment. The study was described as high risk of bias.

BLINDING OF PARTICIPANT AND PERSONAL

Both studies were described as high risk of bias. A former study blinded only assessor and a latter study blinded only participant.

BLINDING OF OUTCOME ASSESSMENT

A former study evaluated the complete re-epithelialization using by another assessor. The study was described as low risk of bias. Evaluation of complete re-epithelialization of a latter study was described as a high risk of bias as assessor could know the intervention group.

INCOMPLEATE OUTCOME DATA

A former study was described as a high risk of bias as there were no description regarding missing patients on the seventh day of evaluation. A latter study had no missing patient, it was described as a low risk of bias.

SELECTIVE REPORTING

Both studies were rated as unclear risk of bias as they did not record adverse effects of the interventions.

OTHER POTENTIAL SOURCES OF BIAS

No other sources of bias were mentioned in both included studies. Thus, we described them as unclear risk of bias.

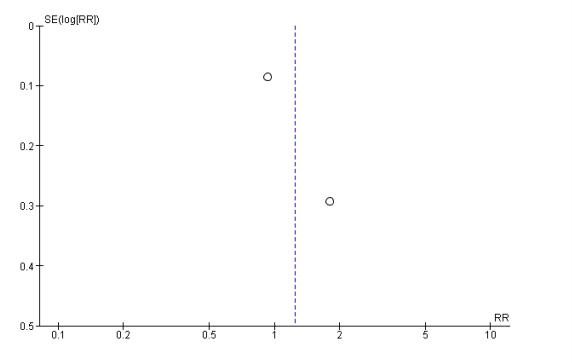


Figure 4. Publication
Funnel plot: Rate of complete re-epithelialization

RATE OF COMPLETE RE-EPITHELIALIZATION OF ULCERS ON THE 7th DAY AFTER THE PROCEDURE

There were two studies included with 150 patients with aphthous stomatitis. Comparing silver nitrate cauterization to placebo stick, rate of complete re-epithelialization on the seventh day after the procedure was not significantly different between the two interventions (RR, 1.24; 95% CI, 0.55 to 2.80; I^2=87%) (Figure 4).

PUBLICATION BIAS

We generated the funnel plot of reported outcomes at rate of complete re-epithelialization on the seventh day comparing silver nitrate and placebo. However, the number of the studies using in the funnel plot were too few to assess for publication bias (Figure 5).

DISCUSSION

SUMMARY OF THE RESULTS

In our systematic review, two RCTs were identified with 150 patients with aphthous stomatitis and included in the analysis. We found no statistically significant difference in rate of complete re-epithelialization between using silver nitrate cauterization and placebo on the seventh day after the procedure. High heterogeneity was observed. In our review, the funnel plots of the outcomes were summarized. However, we did not analyze publication bias as the number of the included studies was too few.

STRENGTH AND LIMITATIONS OF THE REVIEW

Strength and limitations of the review

From our results, this is the first systematic review comparing silver nitrate to placebo in treating patients with aphthous stomatitis. Our study had several limitations. Firstly, our systematic review consisted of a small number of participants, since only two studies met our predefined inclusion and exclusion criteria. Secondly, one of them had high risk of bias because there was selection bias, performance bias, detection bias and reporting bias.22 This can lead to imprecise estimation of the pooled effect size. Thirdly, The included studies did not report adverse effects.21, 22 Finally, that study also did not describe type and concentration of silver nitrate cauterization which can directly affect the effect size and cause the heterogeneity. Due to the mentioned limitations, implementation of our findings should be done with cautions.

COMPARISON TO OTHER STUDIES

In our systematic review, there was no statistically significant difference in rate of complete re-epithelialization between silver nitrate cauterization and placebo on the seventh day after the procedure but there is no study to compare outcomes. This might be due to the fact that aphthous stomatitis is a self-limited disease. [20] Aside from this outcome, pain reduction was

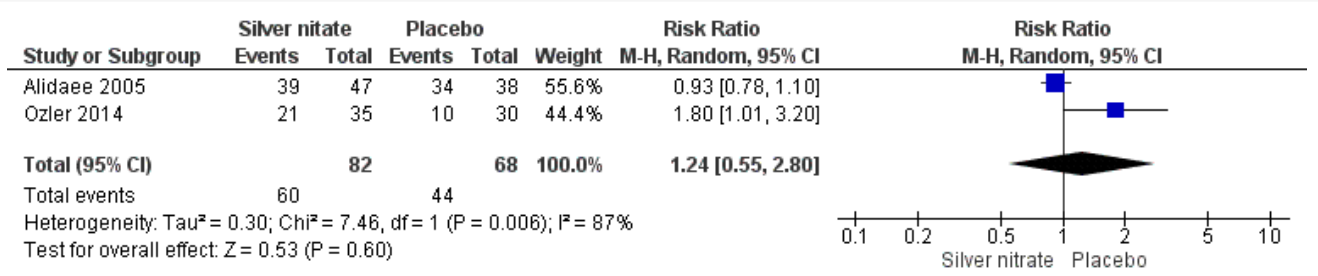


Figure 3. Rate of complete re-epithelialization on the seventh day after the procedure

also described in both of our included studies, however, we did not combine the effect size in term of pain reduction as they reported pain in different scales. However, both included studies suggested that silver nitrate cauterization was able to reduce pain.[21,22] Still, pain in patients with aphthous stomatitis can be ameliorated by topical steroid which found to have similar efficacy to silver nitrate cauterization in term of pain reduction.[10] Adverse effects were not recorded in both included RCTs but they were recorded where else. For instance, aphthous stomatitis diameter was enlarged from 5 mm to 3 cm in 6 days[24] in one case report and silver nitrate caused bisphosphonate-related osteonecrosis of the jaw in another case report.[25]

CONCLUSION AND IMPLICATION OF THE RESULTS

There was no statistically significant difference between using silver nitrate cauterization and placebo stick in rate of complete re-epithelialization on the seventh day after the procedure. For the further upcoming studies, we suggest a large number of participants in the study of RCT in order to evaluate the differences in

ACKNOWLEDGMENTS & DECLARATION

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.

COMPETING INTERESTS: This study has no competing on interest.

FUNDING:None

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"I shall either find a way or make one"

-Hannibal Barca

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