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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

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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

From data to information, from information to knowledge. Every medical article is only a piece of knowledge. Production of knowledge is not the privilege to only those with rich capital. Limitation is only a perception. Novice medical student can produce medical information even with the certain limit of time and resources. In this issue, we provide the medical articles by the medical students who by now are medical graduates. Integrating research-based learning is a part of the medical education revolution at Khon Kaen Medical Education Center.

We cannot level up our society by saying nothing and do nothing. Be courage, be yourself, stand out, help each other and start now.

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

submission

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Our issues of each volume will be published online
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All accepted articles are classified into two main categories;
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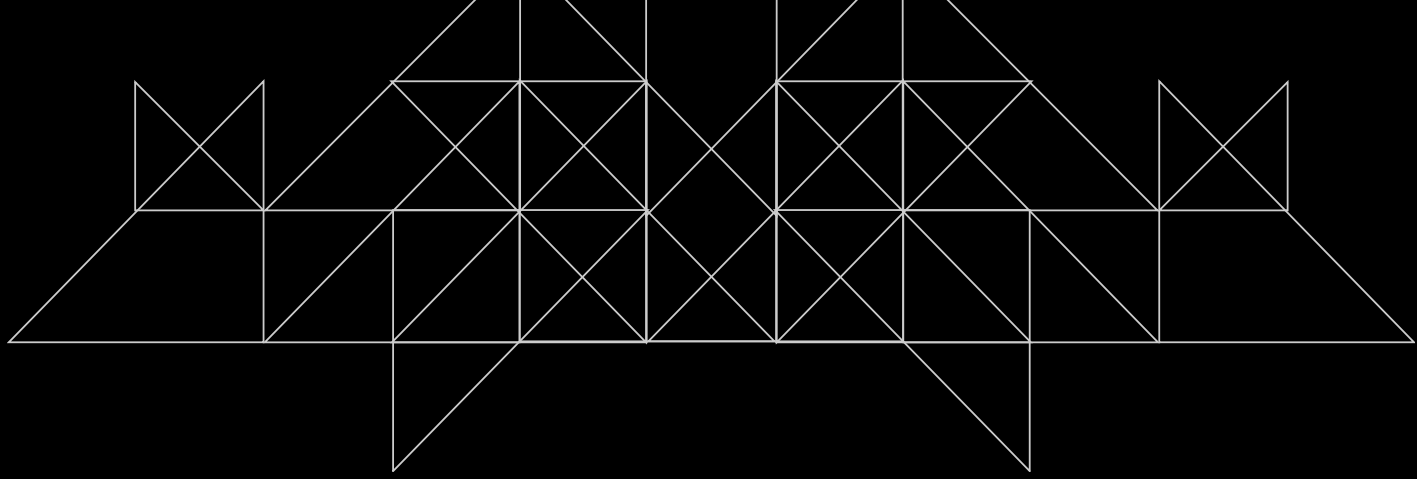
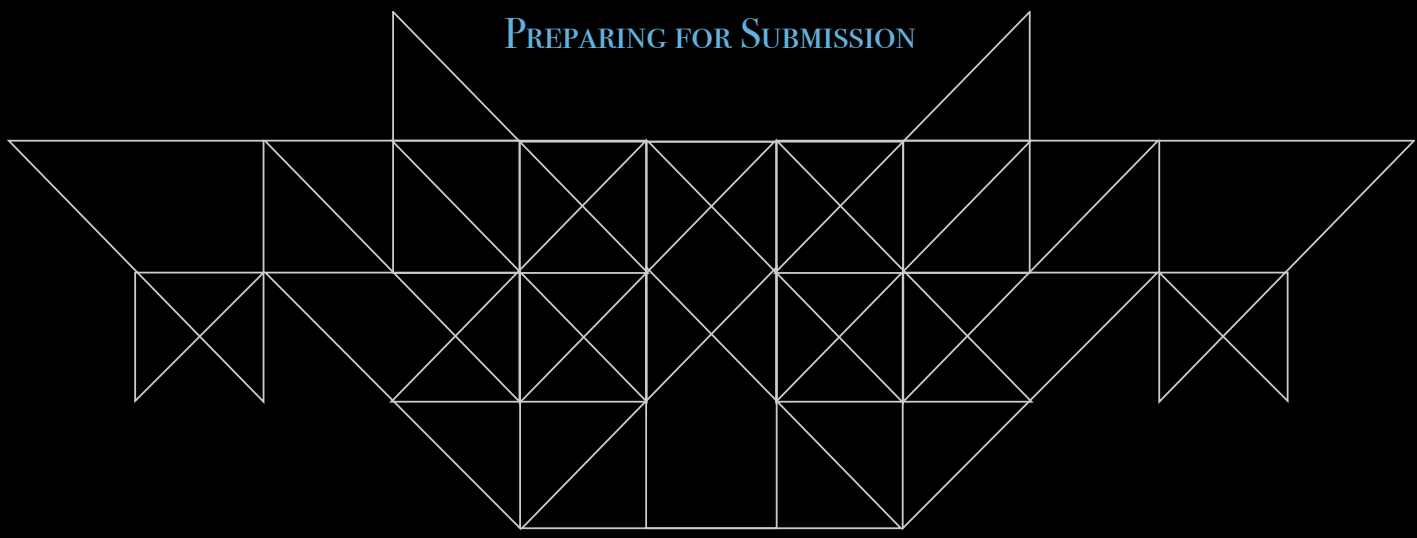


International Committee of Medical Journal Editors (ICMJE) Recommendation for Preparing for Submission



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

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

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

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b. Abstract

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

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

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

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

c. Introduction

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

d. Methods

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

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

i. Selection and Description of Participants

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

ii. Technical Information

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

iii. Statistics

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

e. Results

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

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

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

f. Discussion

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

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

g. References

i. General Considerations Related to References

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

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

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.

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.

Glyburide versus metformin in management of gestational diabetes mellitus: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To identify the efficacy of glyburide and metformin for the management of patients with gestational diabetes mellitus (GDM)

METHODS

We systematically searched through electronic databases including Pubmed, Scopus and The Cochrane Library as well as hand searching of both published and unpublished randomized controlled trials (RCT) and observational studies of acceptable quality to assess the effectiveness of glyburide compared with metformin the in management of gestational diabetes mellitus. The primary outcome was maternal fasting glucose (FBG) level.

RESULTS

We included three RCTs with a total of 421 pregnant women with gestational diabetes mellitus. Most of included trials had a low risk of bias. The meta-analysis showed no difference between glyburide and metformin for controlling maternal FBG (standard mean difference [SMD] 0.10; 95% confidence interval [CI] [-0.46 to 0.66]; I^2=87%). Comparing between glyburide group and metformin group, the former had a significant increase in neonatal birth weight (SMD 0.37; 95% CI [0.18 to 0.57]; I^2=0%), higher rate of infant with large for gestational age (relative risk [RR] 2.32; 95% CI [1.23 to 4.37]; I^2=0%), higher maternal weight gain (SMD 0.32; 95% CI [0.08 to 0.56]; I^2=0%) and lower capillary glycemia (mg/dL) at 1 and 3 hour (SMD -0.34; 95% CI [-0.58 to -0.10]; I^2=0%; SMD -0.46; 95% CI [-0.70 to -0.22]; I^2=0%, respectively).

CONCLUSION

Glyburide comparing with metformin in the management of GDM had no statistical difference in controlling maternal FBG.

INTRODUCTION

Definition of gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with first identified during pregnancy.[1] GDM is associated with an increased risk of maternal and neonatal complications during pregnancy and birth.[2] Treatment for GDM aims to keep maternal FBG levels equal to those of pregnant women who do not have GDM.[3] Insulin is the first recommended for treating women with GDM whose FBG cannot be controlled by diet and exercise.[3-8] There is increasing evidence that metformin and glyburide are safe in women with GDM.[4,6] Randomized controlled trials (RCTs) and a systematic review have reported that glyburide and metformin are as effective as insulin and no significant differences of maternal or neonatal outcome were found with the use of glyburide or metformin compared with the use of insulin.[9-13] One RCT comparing between metformin and glyburide for the treatment of GDM found their equivalent efficacy regarding maternal FBG level or neonatal and maternal complications.[14] However, an RCTs in 2012 evaluating the impact during the perinatal period of the use of metformin and glyburide, suggested that neonatal birth weight was lower while glucose levels at 1 and 3 hours after birth were higher in the newborns of the metformin group.[15] Regarding adverse events from the drugs, maternal hypoglycemia symptoms were more common in the glyburide group.[15] Therefore, we conducted systematic review and meta-analysis to compare the effectiveness and maternal and neonatal outcomes between metformin and glyburide in treating women with GDM with hope to clarify the controversies that mentioned above.

METHODS

SEARCH STRATEGIES

We searched for studies through Pubmed, Scopus and The Cochrane database of systematic review since the commencement of the databases till 2014 without any language restriction. We used a combination of Medical Subject Headings (MeSH) for Pubmed and Cochrane Library searching ("diabetes, gestational" AND "glyburide" AND "metformin") and used keyword "gestational diabetes AND glyburide AND metformin", "gestational diabetes AND glibenclamide AND metformin", "gestational diabetes AND neogluconin AND metformin", "gestational diabetes AND euglucon AND metformin", "gestational diabetes AND diabeta AND metformin","gestational diabetes AND micronase AND metformin","gestational diabetes AND daonil AND metformin","gestational diabetes AND maninil AND metformin", "gestational diabetes AND oral hypoglycemic agents", "pregnancy induced diabetes AND glyburide AND metformin", "pregnancy induced diabetes AND glibenclamide, "pregnancy induced diabetes AND neogluconin AND metformin", "pregnancy induced diabetes AND euglucon AND metformin", "pregnancy induced diabetes AND maninil AND metformin", "pregnancy induced diabetes AND micronase AND metformin", "pregnancy induced diabetes AND daonil AND metformin" in Scopus. We checked the references of included studies and handy searched for

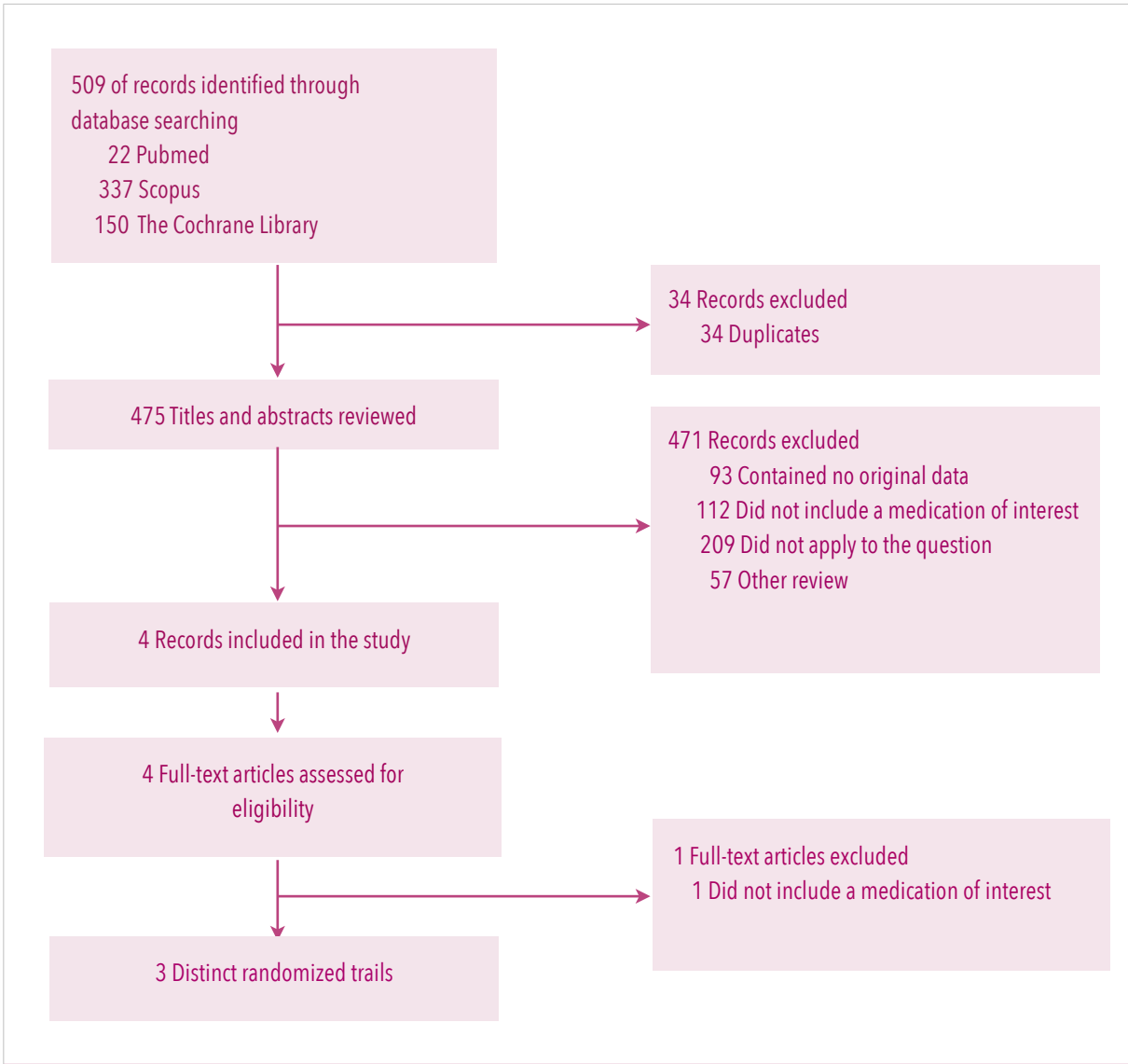

Figure 1. Flow of the study

additional studies which were relevant. Overall, 77 abstracts were reviewed.

INCLUSION AND EXCLUSION

The systematic review is performed by collecting both published and unpublished randomized controlled trials and observational studies of acceptable quality to evaluate the effectiveness of glyburide compared with metformin in achieving maternal fasting blood glucose (FBG) level and to assess the maternal and neonatal outcomes in GDM. The primary outcome was maternal FBG level. Secondary outcomes were maternal outcomes including maternal weight gain,

neonatal birth weight, large for gestational age, capillary glycemia at 1 hour, 3 hour, 2-hour postprandial glucose, rate of cesarean delivery, hypertensive syndrome, participants who change to insulin treatment and neonatal outcomes including incidence of neonatal hypoglycemia, gestational age of delivery, macrosomia, Apgar score at 1 minutes, 5 minutes, capillary glycemia at 6 hour, needed intensive care. We included observational studies and RCTs in which the units of randomization are individuals. We excluded quasi-RCTs, cross-over trials and the studies that include pregnant women with preexisting type 2 diabetes.

STUDY SELECTION AND DATA EXTRACTION

This review was conducted following the recommendations of The Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0.29 Four review authors independently assessed for all titles and abstracts to include and exclude the studies. Then we read full-text of all potentially relevant studies. Disagreements were resolved by discussion. Four review authors individually extracted data are as follows: the language of publication, inclusion and exclusion criteria, interventions, number of participant and baseline data, date and duration of the study and outcomes. We extracted data into simple standard forms.

QUALITY OF REPORTING AND RISK OF BIAS

The four authors evaluated the quality and risk of bias of the included studies with Jadad score to appraise the quality of selected articles. A score of 3 or more is considered as high-quality study. Moreover, we used the domain base-evaluation following The Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0.29 The Domain base-evaluation evaluated in random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting and others bias. They specified the criteria and classified the study into three groups; low risk, high risk and, unclear risk. Potential publication bias was assessed by using a funnel plot.

DAT ANALYSES

To standardize the reporting of our results, we calculated the standard mean difference (SMD) and relative risk (RR) with 95% confidence interval (CI) from continuous or dichotomous data in each group for every trial. All analyses were performed with Revman 5.3 statistical software using fixed-effect model meta-analysis to assess the effectiveness of glyburide compared with metformin in achieving glycemic control and maternal and neonatal outcomes in GDM. The statistical heterogeneity was evaluated by chi-square and I2. The statistical test of heterogeneity was significant if $P<0.05$ and heterogeneity was considered high if the I^2 statistic was more than 50%. We used a random effect model for the meta-analysis when heterogeneity was statistical significance.

RESULTS

Overall 509 records were identified through database searching. Of these, 475 records after duplicates removed were identified. After screened

Table 1. Characteristics of the included study

	Moore, 2010	Silva, 2010	Silva, 2012
Study design	RCT, not blind	RCT, double blind	RCT, double blind
Language of publication	English	English	English
Date and duration	July 2003 to May 2008 4 years 10 months	July 1,2008 to October 30,2009 1 year 4 months	July 1,2008 to September 30, 2010 2 years 3 months
Inclusion criteria	(i) Pregnant women with GDM, and (ii) not maintain fasting blood glucose less than 105 mg/dL or 2-hour postprandial blood glucose less than 120 mg/dL	(i) Pregnant women with GDM, (ii) age≥18 years old, (iii) singleton pregnancy, (iv) GA 11 to 33 weeks, (v) fetal abdominal circumference was within normal percentiles, and (vi) no maternal or fetal conditions likely to affect treatment or neonatal outcome	(i) pregnant women with GDM, (ii) age≥18 years old, (iii) singleton pregnancy, (iv) GA 11 to 33 weeks, (v) fetal abdominal circumference within normal percentile, and (vi) absence of other pathologies that might interfere with perinatal results or hypoglycemic therapy
Exclusion criteria	(i) History of significant renal or hepatic disease, (ii) chronic hypertension necessitating medication, and (iii) substance misuse.	(i) Intolerance of the drugs, (ii) unwillingness to participate; fetal risk , (iii) lack of follow up during pregnancy, and (iv) malformation diagnosed on delivery.	(i) intolerance of the drugs, (ii) unwillingness to participate, fetal risk, (iii) lack of follow-up, and (iv) fetal malformation diagnosed upon delivery.
No of pregnancy in each group	G=74 M=75	G=40 M=32	G=96 M=104
Age-years	G=29.6±7.8 M=31.0±7.1	G=31.5±5.4 M=33.6±5.8	G=31.3±5.4 M=32.6±5.6
Gestational age at inclusion -weeks	G=29.1±5.0 M=27.3±6.8 (Below 24 wk at entry G=8 (11%) M=13 (17%))	G=26.8±6.0 M=25.6±6.4	G=25.4±7.1 M=27.0±6.4
No. of previous pregnancies	Not available	G=2.8±1.5 M=2.9±1.2	G=2.5±1.3 M=2.8±1.3
Pre-pregnancy BMI-kg/m^2	G=32.7±7.0 M=32.8±5.8	G=28.8±5.8 M=30.3±5.7	G=28.6±5.9 M=28.7±5.4
Diagnosis	50g OGTT/ Carpenter and Coustan guidelines	75g OGTT/ WHO criteria	75g OGTT/ WHO criteria
Dose of oral hypoglycemic drugs	G=2.5 mg twice daily Max.=20 mg/d M=500 mg/d Max.=2000 mg/d	G=2.5-5 mg/d Max.=20 mg/d M=500-1000 mg/d Max.=2500 mg/d	G=2.5-5 mg/d Max.=20 mg/d M= 500-1000 mg/d Max.=2500 mg/d

Table 1. (Continued)

FBS-mg/dL	G=90.9±13.0 M=94.3±15.0	G=87.7±12.7 M=78.2±8.9	G=88.23±11.71 M=90.52±11.78
2-hour PPG-mg/dL	G=111.67±19.44 M=109.67±16.43	G=129.1±20.8 M=136.0±23.7	Not available
weight gain-kg	Not available	G=10.3±5.8 M=7.6±8.1	G=9.84±6.42 M=7.78 ± 7.42
Hypertensive syndrome-no. (%)	G=3 (4) M=2 (2.7)	G=1 (2.5) M=0	Not available
Changing to insulin treatment-no.(%)	G=12 (16.22) M=26 (34.67)	G=10 (23.8) M=8 (25)	G=28 (29.17) M=22 (21.15)
Neonatal birth weight-g	G=3,329.6±334 M=3,103±600	G=3.463±535.6 M=3.360±509.5	G=3387.98±512.16 M=3193.87±521.22
Rate of infant with large for gestational age-no.(%)	Not available	G=9 (22.5) M=3 (9.4)	G=19 (19.79) M=9 (8.65)
Capillary glycemia at 1 hour-mg/dL	Not available	G=54.7±15.4 M=57.9±20.3	G=54.08±12.97 M=59.78±15.21
Capillary glycemia at 3 hour-mg/dL	Not available	G=54±12.2 M=65.8±25.5	G=55.89±11.65 M=61.53±15.53
Capillary glycemia at 6 hour-mg/dL	Not available	G=55.4±11.2 M=58.3±12.6	G=57.12±10.77 M=59.14±10.66
Neonatal hypoglycemia-no. (%)	G=0 M=1 (1.3)	G=7 (17.5) M=6 (18.7)	G=13 (13.54) M=11 (10.58)
Gestational age of delivery-weeks	G=38±1 M=38±2	G=38.6±1.1 M=38.6±1.3	G=38.41±1.17 M=38.25±1.41
Macrosomia-no. (%)	G=4 (5.4) M=1 (1.3)	G=6 (15) M=2 (6.2)	Not available
APGAR score at 1 minute	Not available	G=8±1 M=8.1±0.9	G=8.08±1.07 M=8.17±1.18
APGAR score at 5 minutes	Not available	G=9.3±0.6 M=9.1±0.7	G=9.23±0.59 M=9.17±0.69
Needed intensive care-no. (%)	G=1 (1.3) M=4 (5.33)	G=2 (5) M=5 (15)	G=7 (7.29) M=9 (8.65)
Jadad score	3	5	5

G=glyburide, M=metformin,
RCT=randomized controlled trial, GA=gestational age, FBG=fasting blood glucose, 2-h PPG=2 hour postprandial glucose, Max.=maximum, WHO=World Health Organization; Normal percentiles of fetal abdominal circumference=percentile >10% and <75%; Fetal risk=abdominal circumference at percentile >97% or <5%, BMI=body mass index

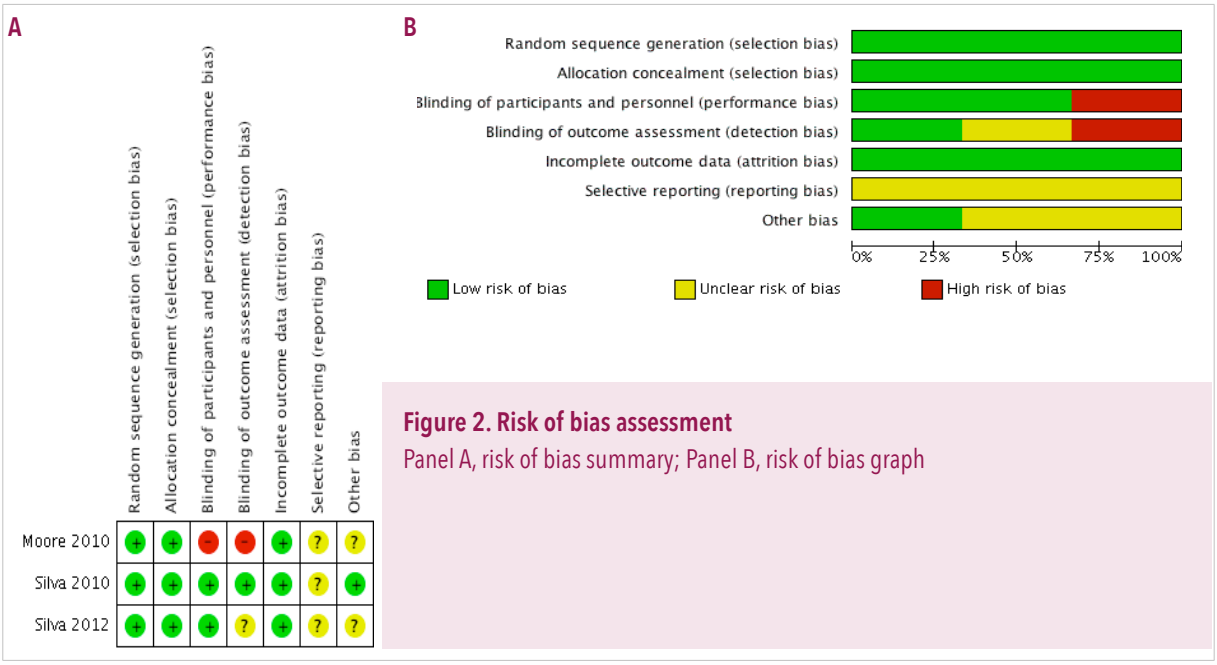

Figure 2. Risk of bias assessment
Panel A, risk of bias summary; Panel B, risk of bias graph

titles, 398 records were excluded and then 73 records after screening the abstract were excluded following the exclusion criteria (Figure 1). Four full-text articles were assessed as eligible. One study was not included the medication of interest. We collected 3 distinct randomized controlled trials and no observational studies. The included studies assigned 421 patients to receive either glyburide (n=202) or metformin (n=219).

STUDY CHARACTERISTICS

All included studies were conducted in Brazil and the United States. Two studies were double-blind and one was open-label trial. Four hundred and twenty-one participants were enrolled in the studies; their means of age were 29.6 to 33.6 years and means of gestational age were 25.4 to 29.1 weeks. The oral hypoglycemic agents; glyburide doses used in eligible studies was 2.5 to 20.0 mg/d and metformin was 500 to 2,500 mg/d. The duration of eligible studies was vary from 1 year 3 months to 4 years 10 months (Table 1).

BIAS RISK ASSESSMENT

Three included trials were assessed using Jadad score (Table 1) and domain base-evaluation (Figure 2). All studies reported low risk of bias in the domain of sequence generation, allocation concealment, and incomplete outcome data. All studies were unclear risk of bias in the domain of selective reporting. Only one study had high risk in the domain of blinding of participant and blinding of outcome assessment.16 We evaluated the potential publication bias by using a funnel plot of intervention effect versus the standard error for the studies. Visually our funnel plot which constructed from the three trials included in the analysis appeared to be symmetrical (Figure 21).

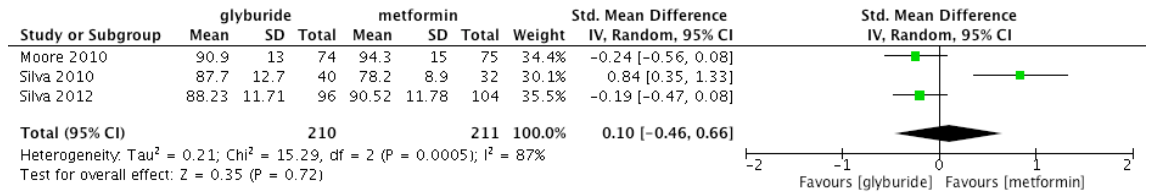

Figure 3. The forest plot showing meta-analysis of maternal FBG level in glyburide comparing with metformin for managing GDM

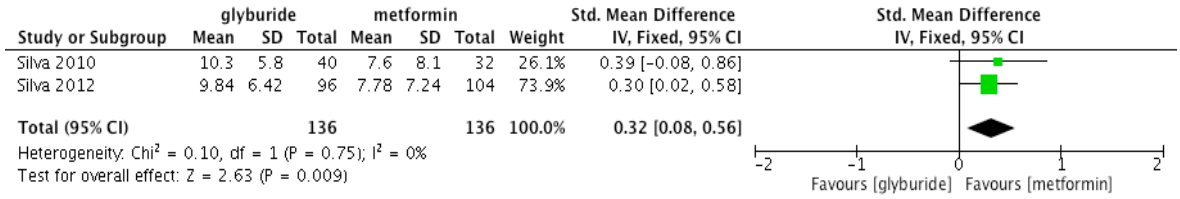

Figure 4. The forest plot showing meta-analysis of maternal weight gain in glyburide comparing with metformin for managing GDM

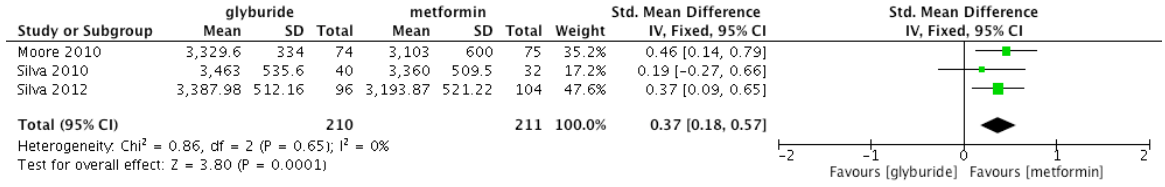

Figure 5. The forest plot showing meta-analysis of neonatal weight gain in glyburide comparing

CLINICAL OUTCOMES

PRIMARY OUTCOME

The primary outcome was maternal FBG. The meta-analysis of three studies showed no statistically significant difference between glyburide and metformin for controlling maternal FBG level (SMD 0.10; 95% CI [-0.46 to 0.66]; chi-square=15.29; I^2=87%) (Figure 4).

SECONDARY OUTCOMES

Comparing between glyburide group and metformin group, the former had a significant

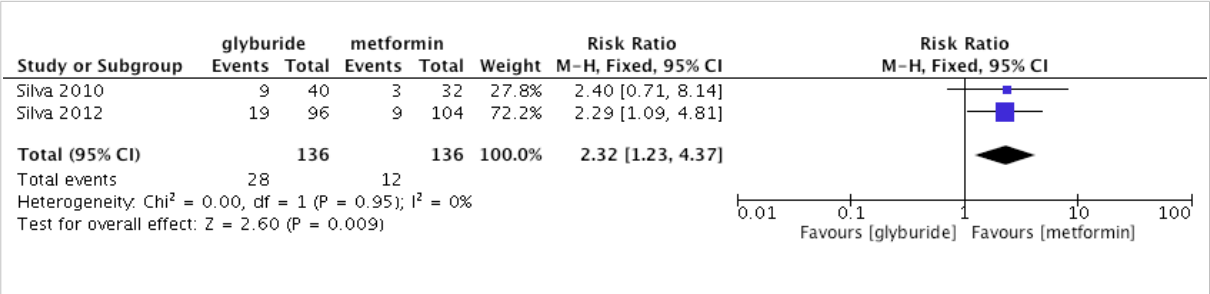

Figure 6. The forest plot showing meta-analysis of gestational age in glyburide comparing with metformin for managing GDM

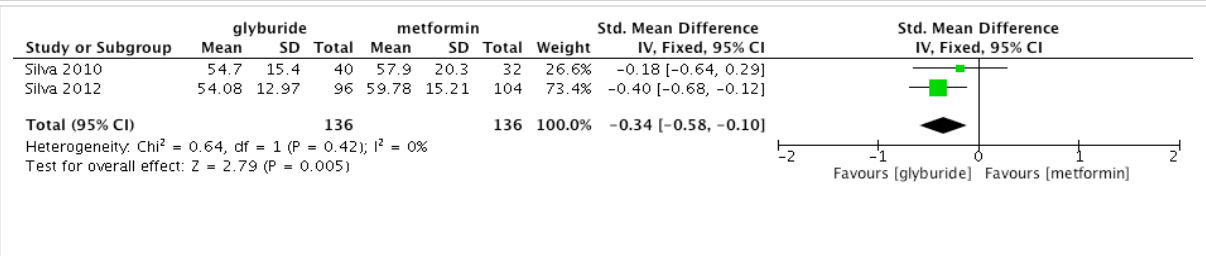

Figure 7. The forest plot showing meta-analysis of capillary glycemia at 1 hr (mg/dL) in glyburide comparing with metformin for managing GDM

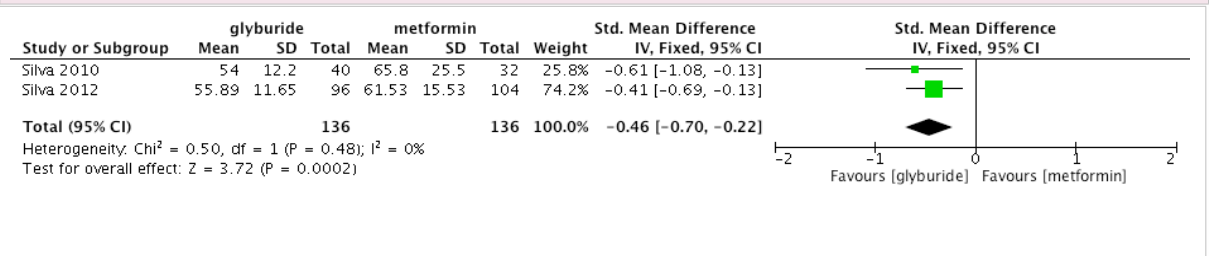

Figure 6. The forest plot showing meta-analysis of gestational age in glyburide comparing with metformin for managing GDM

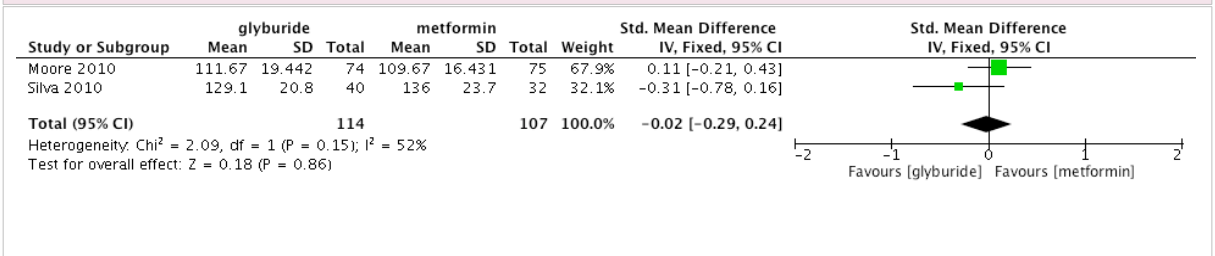

Figure 9. The forest plot showing meta-analysis of 2-hour postprandial glucose in glyburide comparing with metformin for managing GDM

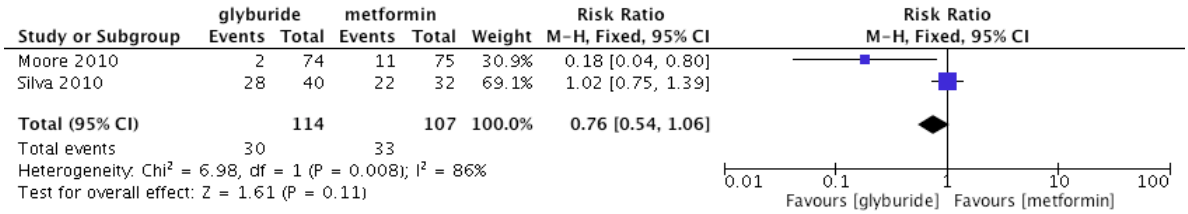

Figure 10. The forest plot showing meta-analysis of rate of cesarean delivery in glyburide comparing with metformin for managing GDM

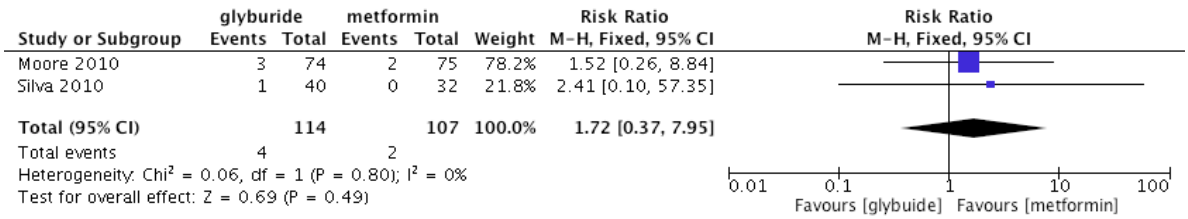

Figure 11. The forest plot showing meta-analysis of hypertensive syndrome in glyburide comparing with metformin for managing GDM

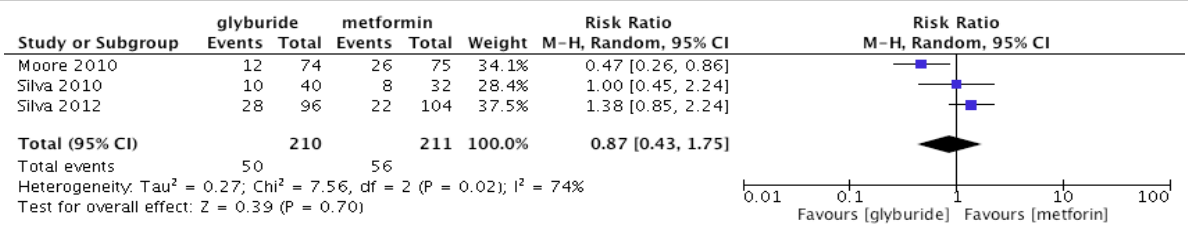

Figure 12. The forest plot showing meta-analysis of participant changed to insulin treatment in glyburide comparing with metformin for managing GDM

increase in maternal weight gain (SMD 0.32; 95% CI [0.08 to 0.56]; chi-square=0.10; I^2=0%), higher in neonatal birth weight (SMD 0.37; 95% CI [0.18 to 0.57]; chi-square=0.86; I^2=0%), higher rate of infant with large for gestational age (relative risk [RR] 2.32; 95% CI [1.23 to 4.37]; chi-square=0.00; I^2=0%) and lower capillary glycemia (mg/dL) at 1 and 3 hour (SMD -0.34; 95% CI [-0.58 to -0.10]; chi-square=0.64; I^2=0%; SMD -0.46; 95% CI [-0.70 to -0.22]; chi-square=0.50; I^2=0%, respectively). However, the other outcomes including 2-hour postprandial glucose, rate of cesarean delivery, hypertensive syndrome, changing to insulin treatment, incidence of neonatal hypoglycemia, gestational age of delivery, macrosomia, apgar score at 1 and 5 minutes, capillary glycemia at 6 hour and needed intensive care were not significantly different between the those with glyburide and metformin (Figure 4-19).

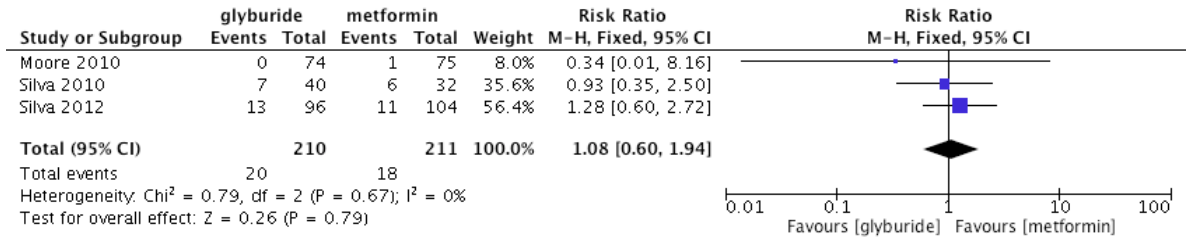

Figure 13. The forest plot showing meta-analysis of neonatal hypoglycemia in glyburide comparing with metformin for managing GDM

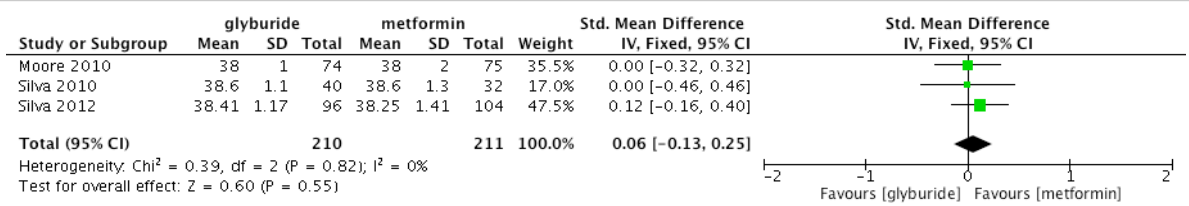

Figure 14. The forest plot showing meta-analysis of gestational age of delivery, weeks in glyburide comparing with metformin for managing GDM

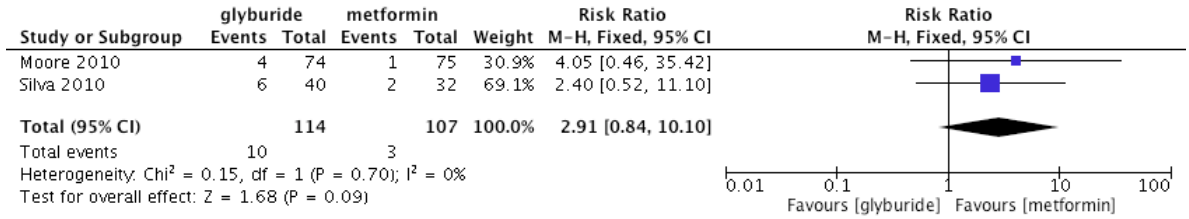

Figure 15. The forest plot showing meta-analysis of macrosomia in glyburide comparing with metformin for managing GDM

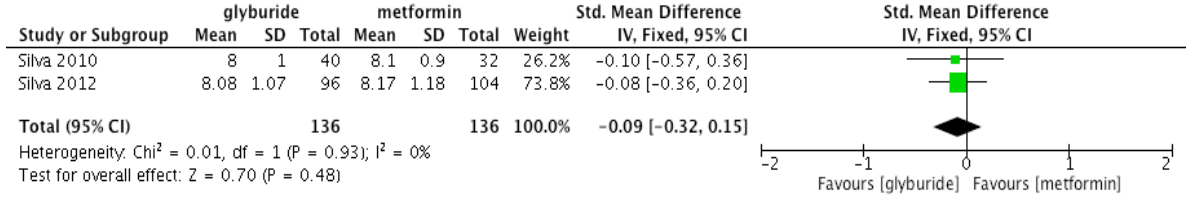

Figure 16. The forest plot showing meta-analysis of apgar score at 1 minute in glyburide comparing with metformin for managing GDM

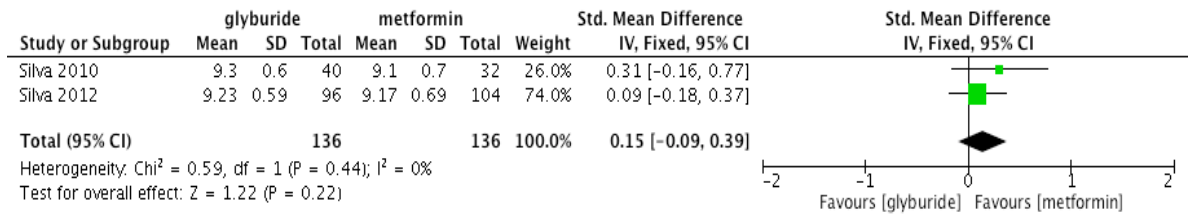

Figure 17. The forest plot showing meta-analysis of apgar score at 5 minute in glyburide comparing with metformin for managing GDM

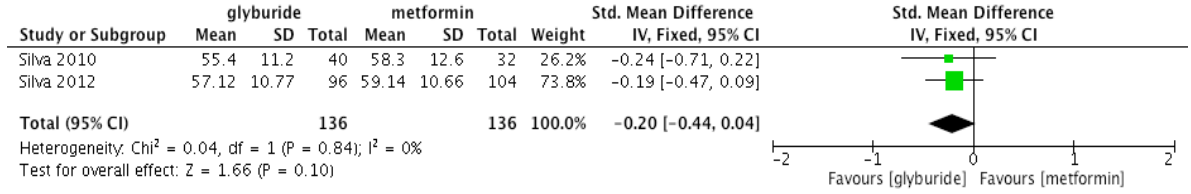

Figure 18. The forest plot showing meta-analysis of capillary glycemia at 6 hr (mg/dL) in glyburide comparing with metformin for managing GDM

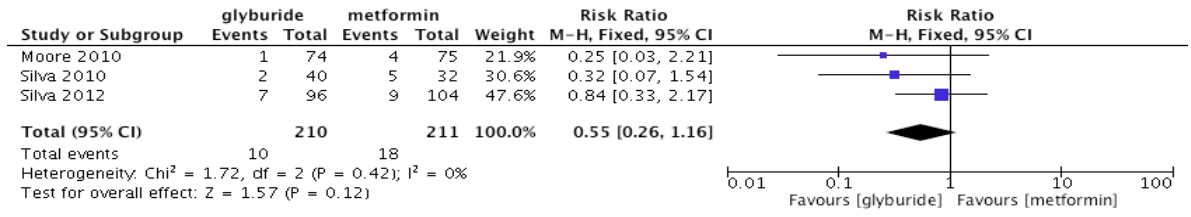

Figure 19. The forest plot showing meta-analysis of needed intensive care in glyburide comparing with metformin for managing GDM

Moreover, we produced the funnel plot to assess the potential of publication bias, however, the included studies were to few to assess the bias.

DISCUSSION

in this meta-analysis, three randomized controlled trials in women with GDM were included. Our study showed that there was no statistically significant difference in maternal FBG. There were the significant increase in maternal weight gain, neonatal birth weight, the rate of infant with large for gestational age and lower capillary glycemia (mg/dL) at 1 and 3 hours in glyburide group. According to secondary outcomes, the result showed that metformin was preferable to

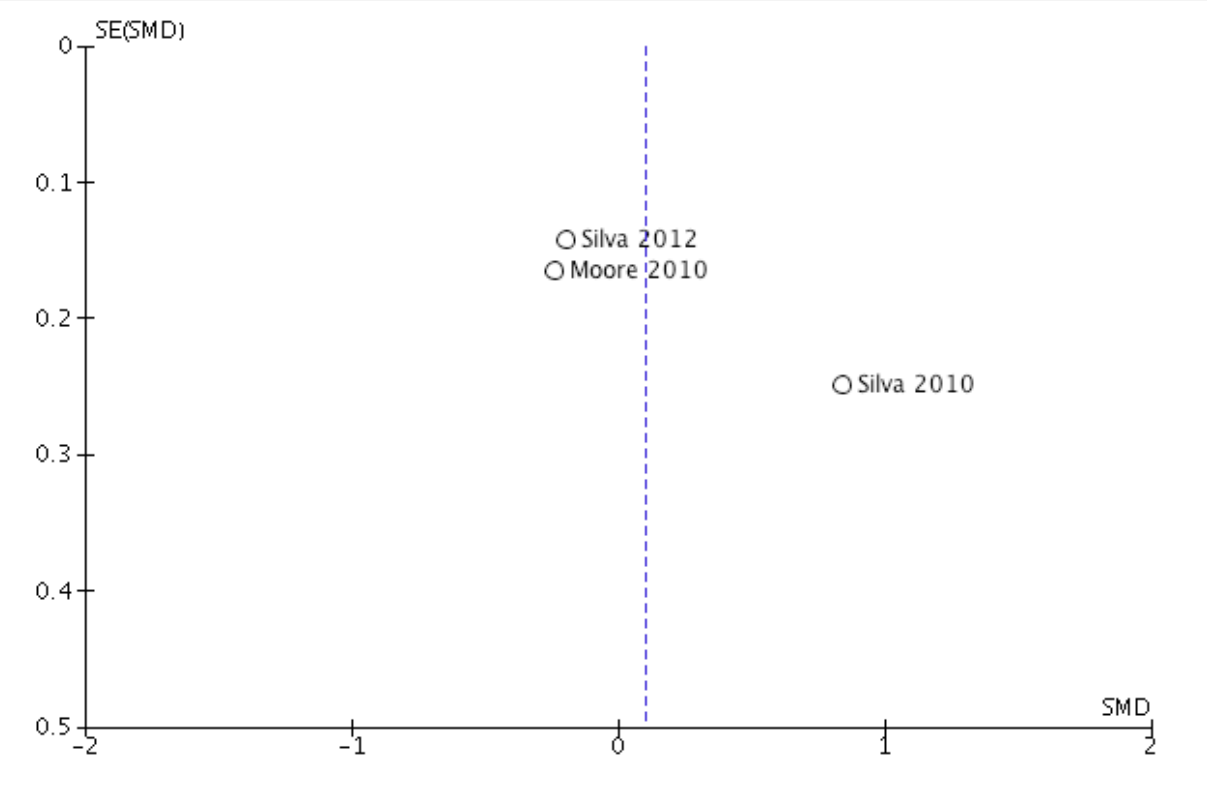

Figure 20. Funnel plot of included studies in meta-analysis

glyburide. In our study, maternal weight gain in women with GDM treated by glyburide was higher than those in the metformin group. This difference between two groups may due to the particular mechanism of drug action. Mechanisms of metformin were hepatic glucose output deduction and gluconeogenesis inhibitor. Moreover, it also seemed to induce weight reduction, principally involving adipose tissue.[23,26]

SSTRENGTH AND LIMITATION OF THE REVIEW

Our systematic review and meta-analysis followed the Guide for developing a Cochrane protocol.[31] Four authors screened all titles and abstracts, extracted data independently. Our study examined the risk of bias of each study carefully using Jadad score and domain base-evaluation. Our included studies were considered as high-quality studies. Moreover, our meta-analysis had high homogeneity that confirmed the potential benefit of the treatment. However, many countries still not used glyburide and metformin as alternative drugs in the treatment of GDM. Thus, the limitations of our review were a few included studies which compared the effectiveness of glyburide and metformin and small sample size (n=421).

Furthermore, one study with potential to be included in our review had to be excluded due to the inability to find full-text article. Therefore, publication bias was unavoidable.

COMPARISON WITH OTHER STUDIES

To our knowledge, this was the first published systematic reviews on the use of glyburide compared to metformin in GDM. We found guidelines of GDM in some countries showed that pregnant women with GDM whose FBG were not controlled by diet and exercise should be treated with insulin injection.[3,5-8] In some guidelines reported that oral hypoglycemic agents (e.g. metformin, glyburide) can be used as a second line of therapy instead of insulin.[24-28] Moreover, we found one narrative review about oral hypoglycemic agents for GDM treatment.[20] The review reported that glyburide and metformin can be used in GDM as same as insulin. Maternal weight gain had the same result as our study but failure rate in control maternal FBG levels occurred twice as often among users of metformin compared to those taking glyburide.[20] Unlike our study, there was not significantly different between the two groups.

CONCLUSION AND IMPLICATION

In summary, this meta-analysis showed that using glyburide and metformin as oral hypoglycemic agents to treat women with GDM was not significantly different in control maternal FBG level. Therefore the limited number of patients included in this meta-analysis, further RCT including more participants with adequate power to assess the effects of glyburide and metformin for pregnant women with GDM are needed not only to confirm the result of our study but also to support the oral hypoglycemic agents to be used as the alternative drug in management of GDM instead of insulin. Complications from using these oral hypoglycemic agents and health service costs should be evaluated in the further study aside from the their efficacies.

ACKNOWLEDGMENTS & DECLARATION

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COMPETING INTERESTS: This study has no competing on interest.
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Combined antiviral agents with corticosteroids versus corticosteroids alone in the treatment of Bell's palsy: a systematic review

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To compare the efficacy between using combined antiviral agents with corticosteroids and corticosteroids alone for treatment of Bell's palsy.

METHODS

We systematically searched through electronic databases including The Cochrane Library, MEDLINE, Scopus, CINAHL, ClinicalTrials.gov as well as other sources than database such as Google scholar and hand searching of published randomized controlled trials (RCTs). We considered of participants were diagnosed with unilateral facial paralysis without any identifiable causes, who started therapy within seven days from the onset of the disease, and who satisfied the author's requirement for eligibility and inclusion. We assessed participants who received any types of corticosteroids therapy alone versus the combination of corticosteroids with acyclovir, valacyclovir or famciclovir, regardless of routes, dosages and duration of administration of the therapies. The primary outcome was the incomplete recovery of facial function.

RESULTS

We included ten RCTs with a total of 1,850 participants, who received combined antiviral agents with corticosteroids (n=922) and corticosteroids (n=928). Our study showed combined antiviral agents with corticosteroids statistically significant reduced incomplete recovery of facial function than corticosteroids alone for Bell's palsy treatment (relative risk (RR), 0.74; 95% confidence interval (CI), 0.61 to 0.90; I^2=38%). Combined famciclovir with corticosteroids showed a significant benefit more than corticosteroids alone (RR, 0.44; 95% CI, 0.27 to 0.71). It also showed combined antiviral agents with the cumulative dose of prednisolone greater than 400 mg but less than 500 mg significantly reduced in incomplete recovery of facial function (RR, 0.73; 95% CI, 0.55 to 0.98) than both cumulative doses that lesser than or equal 400 mg and at least 500 mg of prednisolone (RR, 0.77; 95% CI, 0.55 to 1.07), (RR, 1.04; 95% CI, 0.48 to 2.26) respectively.

CONCLUSION

In conclusion, there was evidence of a benefit of famciclovir in combination with greater than 400 mg but less than 500 mg of prednisolone for Bell's palsy treatment.

INTRODUCTION

Bell's palsy or idiopathic facial paralysis is defined as an acute unilateral paralysis of the facial nerve first recognized by the Scottish surgeon; Sir Charles Bell.[1] The annual incidence of Bell's palsy is 20 per 100,000 populations and the incidence tends to increase with age.[2] The etiology is still unclear but genetic, vascular, infectious and immunological causes have all been hypothesized.[3] In addition, previous studies found that herpes infection as the etiology of the paralysis based on serological evidence.[4,5] Positive serology for herpes simplex virus (HSV) has been reported in 20-79% of participants.[4,5] Concerning that HSV can cause inflammation of the facial nerve in the infected patients.[6] Although most of the participants will completely or near normal recover, the rest will have persistent moderate to severe weakness, facial contracture or synkinesis.[7] the major aims of treatment for Bell's palsy are to recover and prevent the sequelae. Nowadays, the treatment of choices for the Bell's palsy are corticosteroids and a combination of an antiviral agent with corticosteroids (combined therapy).[8] Corticosteroids are recommended for treatment of Bell's palsy by many physicians to reduce facial nerve inflammation.[8]

Bell's palsy suspected to be caused by herpes infection. Therefore, antiviral agents (e.g., acyclovir, valacyclovir and famciclovir) when administered with corticosteroids may be obtained the additional benefit for Bell's palsy treatment. There were three systematic reviews published in 2009 and no consensus was found.[9-11] Even though the therapeutic effects of combined therapies are controversial, some physicians still prescribe combined antiviral agents with corticosteroids for Bell's palsy.

Since those reviews three further studies have been published: three of them were RCTs. Two of studies suggested that greater outcome for Bell's palsy participants occurred if they were treated with antiviral agents and corticosteroids in combination instead of corticosteroids alone.[12,13] The remaining studies showed no significance.[14] Subgroup analysis by type of antiviral agents and cumulative dose of corticosteroids was not analyzed by three recent systematic reviews. Therefore, we included three new RCTs and analyzed subgroups by type of antiviral agents and cumulative dose of corticosteroids in our study.

METHODS

SEARCH STRATEGIES

We searched for studies through The Cochrane Library, MEDLINE, Scopus, CINAHL and ClinicalTrials.gov without any language restriction. We used a combination of Medical Subject Headings (MeSH) for MEDLINE and Cochrane Library searching (("Bell Palsy"[Mesh]) AND "Antiviral Agents"[Mesh]) AND "Steroids"[Mesh] and used keyword "bell's palsy AND antiviral drugs AND steroid", "bell's palsy AND antiviral drugs ", "bell's palsy AND steroid", "bell's palsy AND acyclovir AND steroid", "bell's palsy AND valacyclovir AND steroid" , "bell's palsy AND famciclovir AND steroid", "bell's palsy AND corticosteroids AND antiviral drugs " in Scopus, CINAHL, ClinicalTrials.gov and other database like Google scholar. We checked the references of

included studies and hand searched for additional studies which were relevant. Overall, 132 titles and abstracts were reviewed.

INCLUSION CRITERIA

PARTICIPANTS

Studies in the participants with unilateral facial nerve weakness of no identifiable causes had seen within seven days of the onset.

INTERVENTIONS

Treatment with corticosteroids plus antiviral agents and corticosteroids alone which started within seven days from the onset of the disease, regardless of types, routes, dosages and durations of administration of the therapies.

OUTCOMES

The primary outcome was the incomplete recovery of facial function at the end of the study measured using a validated rating scale. Duration of studies included in this systematic review was at least three months. Secondary outcomes included motor synkinesis and adverse events.

EXCLUSION CRITERIA

Studies in the participants with uncontrolled diabetes mellitus, herpes zoster, peptic ulcer disease, suppurative otitis media, multiple sclerosis, pregnancy, and breastfeeding women were excluded.

STUDY SELECTION

This systematic review is searched and considered the design of each trial; randomized controlled, involving acyclovir, valacyclovir or famciclovir combined with any corticosteroids therapy in the treatment of Bell's palsy. All inclusion and exclusion criteria of RCTs were specified prior to the literature selection. For a study to be eligible, the

DATA EXTRACTION

Data were extracted and recorded from five review authors individually. We extracted data was as follows criteria for diagnosis, inclusion and exclusion criteria, the language of publication, interventions, number of participant, date, and duration of the study and outcomes. We extracted data into simple standard forms.[15]

QUALITY OF REPORTING AND RISK OF BIAS

The five authors evaluated the quality and risk of bias of the included studies with Cochrane risk of bias tool to assess the quality of selected studies. Moreover, we used the domain base-evaluation following The Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0.15 The Domain base-evaluation evaluated in 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) and selective reporting (reporting bias) and others bias. They classified the study into low risk, high risk and unclear risk for each bias tool. Potential publication bias was assessed by using a funnel plot.

DATA ANALYSES

To standardize the reporting of our results, we calculated relative risk (RR) with 95% confidence

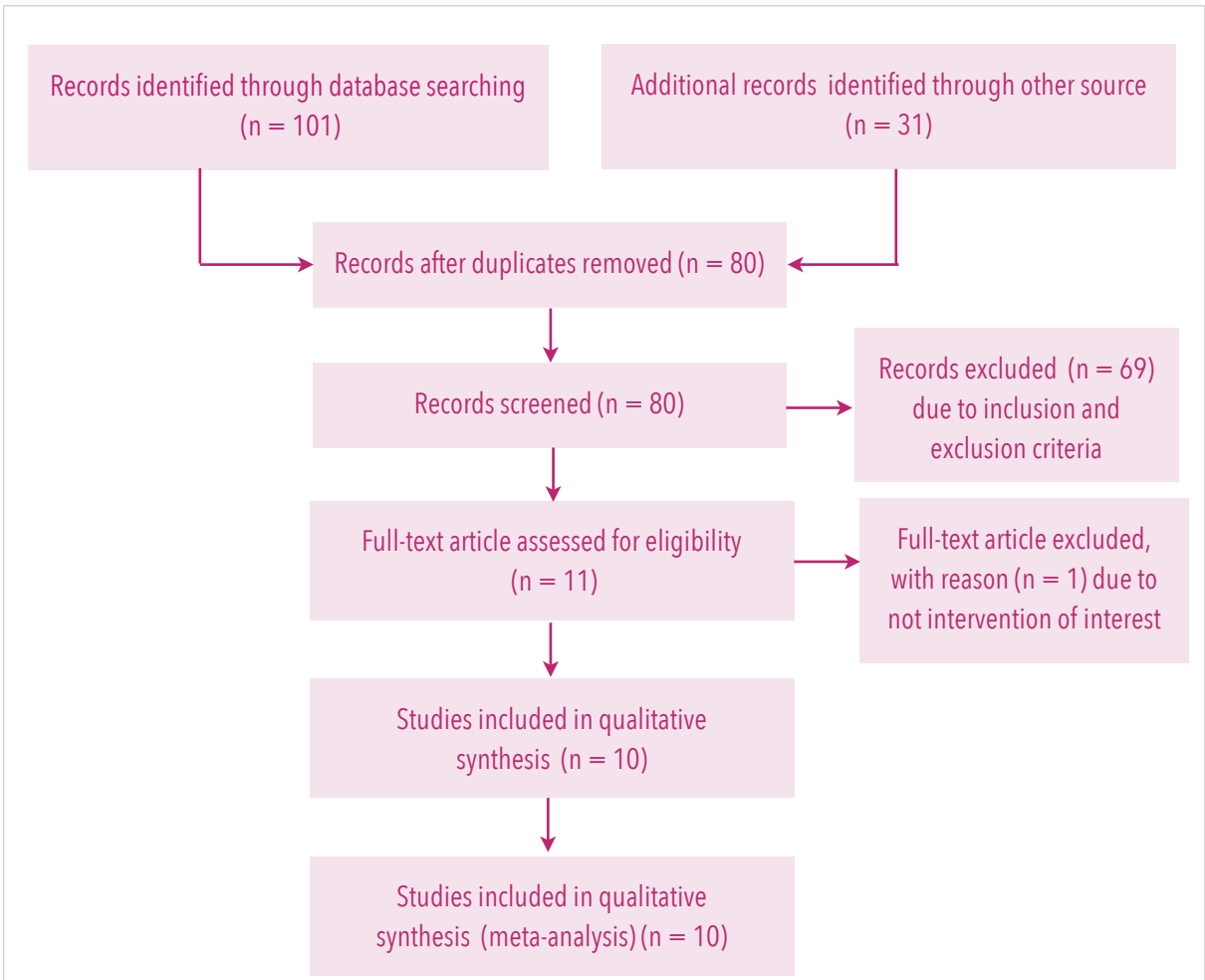

Figure 1. Process of study selection.

interval (CI) from dichotomous data in each group for every trial. All analyses were performed with Revman 5.3.0 (RevMan, the programme provided by the Cochrane Collaboration) statistical software using fixed effect model meta-analyses to assess the effectiveness of combined antiviral agents with corticosteroids compared with corticosteroids alone for Bell's palsy treatment in achieving incomplete recovery of facial function, motor synkinesis occurrence rate and adverse events. The chi-square and I^2 statistics were used to evaluate statistical heterogeneity across trials. The statistical test of heterogeneity was significant if $P<0.05$ and heterogeneity was considered high if the I^2 statistics was more than 50%. We considered to use a random effect model for the meta-analysis when heterogeneity was statistical significance from the I^2 statistics.

Table 1. Characteristics of the included study

Source	Combined group/corticosteroids alone group					Intervention		Outcomes	Duration of Follow-up (Mo)
	N	Age (Y) (Mean±SD)	Sex (% Male)	Initial Severity of Palsy	Therapy Start*	Combined Therapy Group	Corticosteroids Group†		
Ho yun, 2013	99/107	46.7±16.2/ 48.6±15.1	50.5/47.7	HB≥5	First 7 days	Corticosteroids plus famciclovir (750 mg/d) for 7 days	Methylprednisolone, 64 mg/d for 4 days 48 mg/d for 2 days 32 mg/d for 2 days 16 mg/d for 2 days	HB≤II	6
Axelsson, 2012	206/209	NR	NR	SB 0-20, 18.9/18; SB 21-40, 36/34; SB ≥40, 45.1/47.8	First 3 days	Corticosteroids plus valaciclovir two 500-mg tablets 3 times daily for 7 days	Prednisolone, 60 mg/d for 5 days,tapering by 10 mg/ day for 5 days	SB=100 (HB =I)	12
Shahidullah, 2011	34/34	31.1±9.6/ 35.1±1.7	64.7/76.5	HB, 4.4±1.0/ 4.3±1.2	Early treatment group (≤3 day), late treatment group (>3 d)	Corticosteroids plus famciclovir 250 mg, 3 times daily for 5 days.	Prednisolone 60 mg/day for 7 days.	HB=1	3
Engström, 2008	206/210	42/40	61/61	HB, 4/4	First 3 days	Corticosteroids plus valaciclovir 1000 mg 3 times daily for 7 days	Prednisolone 60 mg/day for 5 days	HB=1	12
Vázquez, 2008	22/19	42.5±20.8/ 40.1±18.5	36.4/42.1	FGS, 39.4±12.7/ 33.5±15.6	First 3 days	Corticosteroids plus valacyclovir, 2000 mg/day for 7 days	Prednisone for 1 mg/kg, single dose for first 7 days lowered of a 10 mg every 3 days within 14 days.	FGS>90	6
Yeo, 2008	44/47	42.7±15.7/ 40.2±18.4	47.7/ 42.6	HB, 3.76±1.3/ 3.6±0.9	Early treatment group (≤3 day), late treatment group (>3 d)	Corticosteroids plus acyclovir 2,400 mg/d for 5 days.	Prednisolone 1 mg/kg per day (maximum, 80 mg/d) for 4 days, reduced to 60 mg/day on days 5-6, 40 mg on days 7-8, 20 mg on days 9-10	HB≤II	6
Hato, 2007	114/107	52.3/48.4	52/53	YH, 14.7/15.3	First 7 days	Corticosteroids plus valacyclovir, 500 mg, twice a day for 5 days	Prednisolone, 20 mg, 3 times a day for 5 days;10 mg, 3 times a day on day 6-8;10 mg, once per day on day 9-10	YH>36 (HB=I)	6
Sullivan, 2007	124/127	43.7±16.4/ 42.7±15.9	51.6/55.9	HB,3.4±1.2/ 3.5±1.2	Within 3 days	Corticosteroids plus acyclovir, 400 mg, 5 times a day for 10 days	Prednisolone, 25 mg twice a day for 10 days	HB=I	9

Table 1. (Continued)

Source	N	Combined group/corticosteroid alone group				Intervention		Outcomes	Duration of Follow-up (Mo)
		Age (Y) (Mean±SD)	Sex (% Male)	Initial Severity of Palsy	Therapy Start[a]	Combined Therapy Group	Corticosteroids Group[b]		
Inanli, 2001	20/22	38/42	70/59	NR	First 4 days	Corticosteroids plus acyclovir, 800 mg, 3 times a day for 10 days	Prednisolone 1 mg/kg per day tapering to terminated within12 days	HB ≤2	3
Adour, 1996	53/46	41.9±14.1/ 44.6±15.1	55/ 43	FPRP; 3.0/3.1	First 3 days	Corticosteroids plus acyclovir, 2000 mg/day for 10 days	Prednisolone,30 mg, 2 times a day for 5 days; 5 mg, 2 times a day at day 6-10	FPRI=10 (HB=I)	4

Abbreviation: NR; not reported, HB; House-Brackmann Scale, SB; Sunnybrook score, FPRP; Facial Paralysis Recovery Profile, FPRI; Facial Paralysis Recovery Index, FGS; Facial Grading System

*Time after disease onset that therapy initiated.

† Combined therapy: corticosteroids plus antiviral agents.

RESULTS

The literature search retrieved 101 citations and additional 31 citations were identified through other sources like manual searches reference lists of articles and Google scholar. Of these, 80 citations after duplicates removed were identified. After screened titles and abstracts, 69 citations were excluded and then 11 full-text articles assessed for eligibility according to inclusion and exclusion criteria. Ultimately, ten articles were included as eligible (Fig. 1).

All studies were RCTs regarding study design and performed between 1996 and 2013. The included studies assigned 1,850 participants, who received combined antiviral agents with corticosteroids (n=922) and corticosteroids (n=928).

STUDY CHARACTERISTICS

All ten trials provided a comparison of disease outcome after combined antiviral drugs with corticosteroids treatment and corticosteroids alone. Four trials compared acyclovir combined prednisolone and prednisolone alone, four trials compared valacyclovir combined prednisolone, and two trial compared famciclovir combination to corticosteroids and corticosteroid alone (Table 1).

RISK OF BIAS ASSESSMENT

Ten trials were assessed using Cochrane risk of bias tool. Here are the results of the assessment of the 10 included studies (Fig. 2 and Fig. 3).

SEQUENCE GENERATION, ALLOCATION CONCEALMENT, AND BLINDING

Four studies were randomized, double-blind and placebo-controlled trial.[16-19] Four studies did not adequately describe methods of random sequence generation.[13,14,20,21] Three of these and one more studies did not adequately describe methods of allocation concealment.[12,14,20,21] Two studies did not adequately describe methods of blinding of participants and personnel.[12,21] Two studies did not

adequately describe methods of blinding of outcome assessment.[14,21] Three studies were not blind or placebo use,[13,20,21] two of these studies did not conceal of allocation.[13,21]

INCOMPLETE OUTCOME DATA

All studies reported frequencies and reasons for failure to complete follow up.

SELECTIVE OUTCOME REPORTING

All studies were the low risk of bias in the domain of selective reporting.

OTHER POTENTIAL SOURCE OF BIAS

One study stated participants were diagnosed with Bell's palsy but did not give any further information.[16] And one study reported modified intention to treat.[19] Visually our funnel plot which constructed from the ten trials included in the analysis appeared to be symmetrical (Fig. 8).

CLINICAL OUTCOMES

PRIMARY OUTCOME

The primary outcome was the incomplete recovery of facial function. The meta-analysis of ten studies showed a statistically significant difference between combined antiviral agents with corticosteroids and corticosteroids alone for Bell's palsy treatment, RR 0.74 (95% CI, 0.61 to 0.90; chi-square 14.60; I^2=38%) (Fig. 4).

We analyzed subgroup of these trials by type of antiviral agents. Four trials compared acyclovir plus prednisolone and prednisolone alone, there was no significant reduction in the rate of incomplete recovery, RR 0.79 (95% CI, 0.47 to 1.34).[16,18,20,21] Four trials provided data valacyclovir plus prednisolone versus prednisolone.[14,17,19,22] The relative risk of incomplete recovery was again non-significant, RR 0.83 (95% CI, 0.66 to 1.04). The remaining trials showed comparison of famciclovir plus corticosteroids and corticosteroids alone.[12,13] This analysis showed a significant improvement in facial function, RR 0.44 (95% CI, 0.27 to 0.71) (Fig. 4).

We also analyzed subgroup by cumulative dose of corticosteroids. Two RCTs were not included in this analysis due to limited information of cumulative dose of corticosteroids.[19,20] Therefore, there were eight RCTs were analyzed. Two trials, combined therapies with lesser than or equal 400 mg of prednisolone were no significant association with a reduction in the risk of incomplete recovery (RR, 0.77; 95% CI, 0.55 to 1.07).[16,17] Three trials showed significant RR reduction in incomplete recovery of facial function in participants treated with combined antiviral agents with greater than 400 mg but less than 500 mg of prednisolone (RR, 0.73; 95% CI, 0.55 to 0.98).[13,14,22] And two trials gave data combined therapies with at least 500 mg prednisolone showed no significant improvement of facial function (RR, 1.04; 95% CI, 0.48 to 2.26).[18,21] One trial was no significant difference in rates of incomplete recovery between combined antiviral agents with 448 mg of methylprednisolone and methylprednisolone alone (RR, 0.51; 95% CI, 0.31 to 0.85) (Fig. 5).[12]

SECONDARY OUTCOMES

The secondary outcome was motor synkinesis. Two trials showed a significant reduction in motor

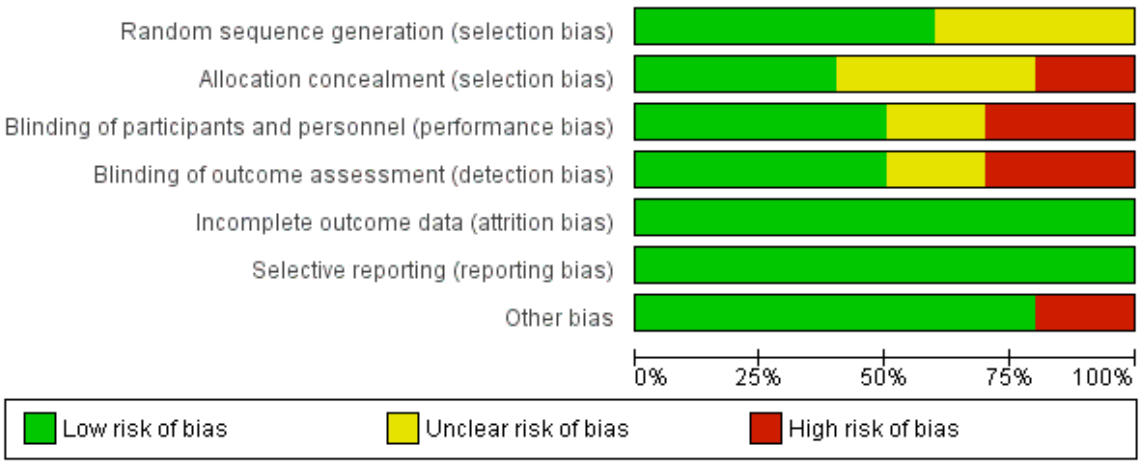

Figure 3. Risk of bias graph

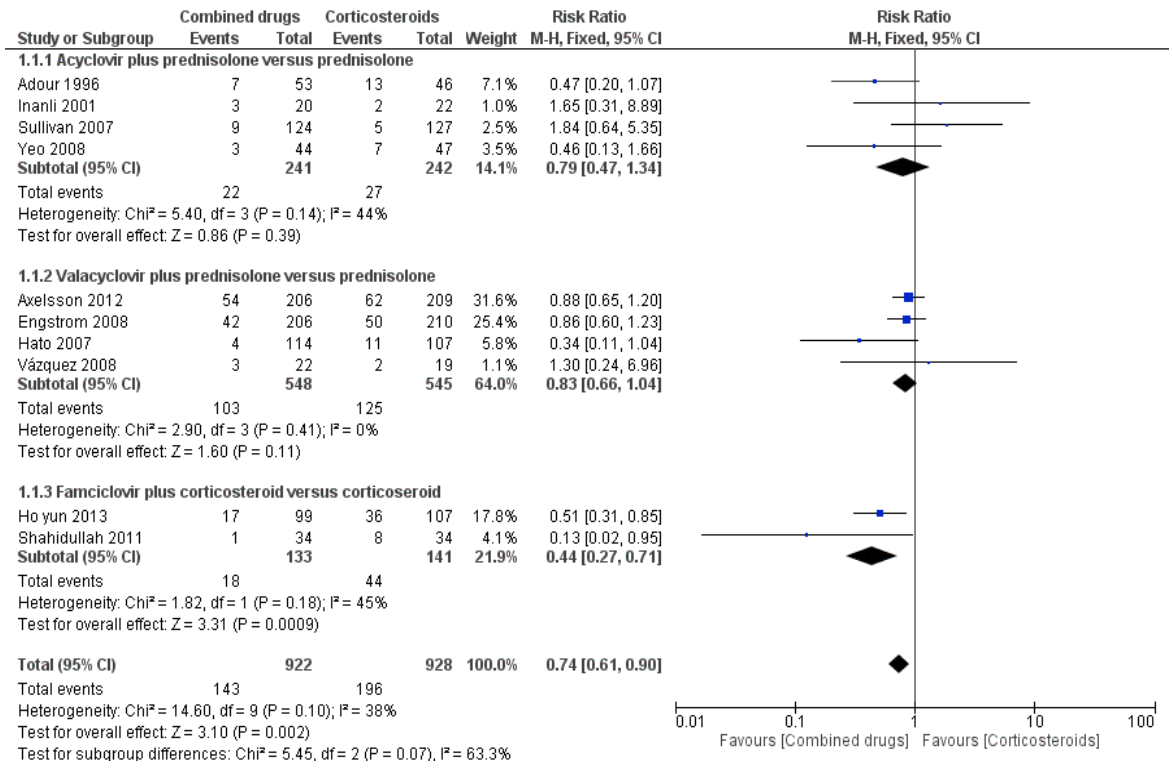

Figure 4. Forest Plot; Combined drugs vs corticosteroids alone; primary outcome, incomplete recovery of facial function

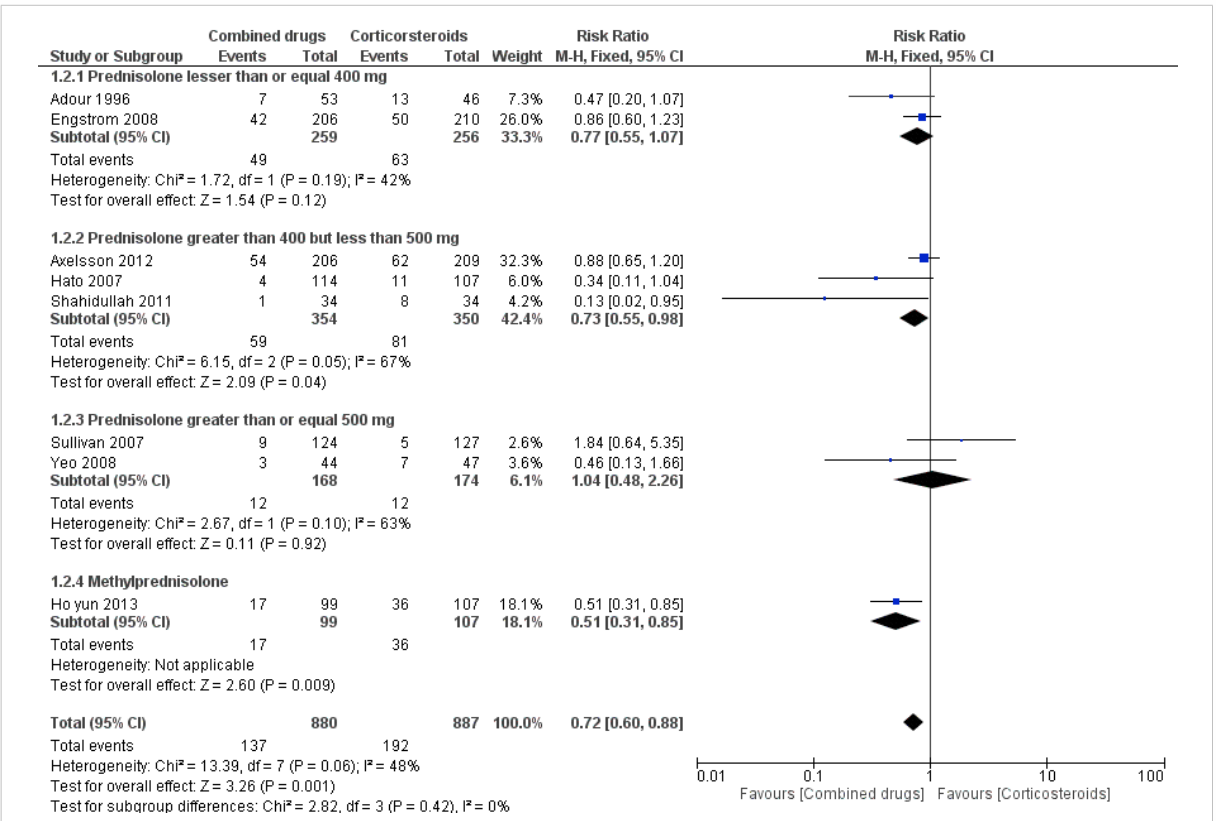

Figure 5. Forest Plot; Combined drugs vs corticosteroids alone; primary outcome, incomplete recovery of facial function with subgroup analysis dosage of corticosteroids

synkinesis occurrence rate, RR 0.56 (95% CI, 0.36 to 0.87; chi-square 0.24; I^2=0%) (Fig. 6).[14-16] Three trials gave data for adverse events, there were not significantly different between two groups, RR 1.18 (95% CI, 0.83 to 1.69; chi-square 0.30; I^2=0%) (Fig. 7).[17,18,22]

DISCUSSION

Our systematic review, a meta-analysis of ten RCTs showed a statistically significant difference between combined antiviral agents with corticosteroids and corticosteroids alone for Bell's palsy treatment. These results were influenced by the two trials suggesting that combined famciclovir with corticosteroids treatment had a significant higher rate of recovery of Bell's palsy.[12,13] There was no significant reduction in the incomplete recovery rate in acyclovir or valacyclovir plus prednisolone versus prednisolone alone. These results may due to mechanisms of the drug. Mechanisms of famciclovir are superior oral bioavailability and longer intracellular half-life than other antiviral agents.[23,24]

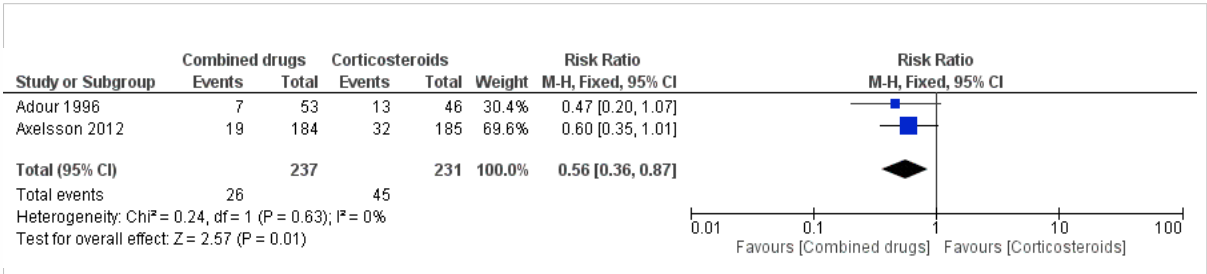

Figure 6. Forest Plot of Comparison

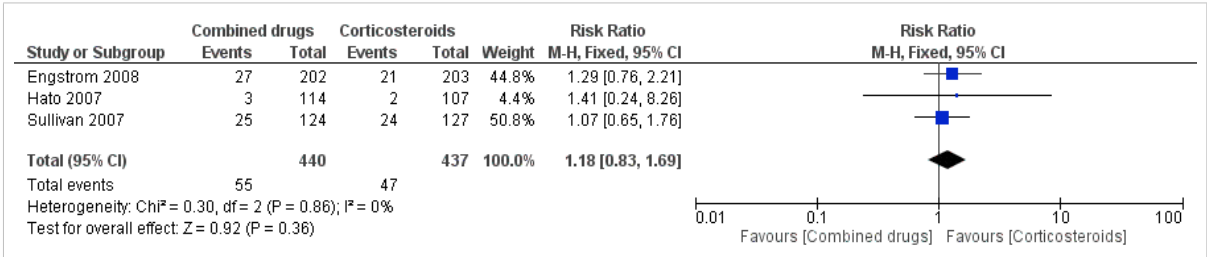

Figure 7. Forest Plot of Comparison

When combined antiviral agents with the different cumulative dose of corticosteroids were subgroup analyzed, the participants receiving greater than 400 mg but less than 500 mg of prednisolone were significantly more likely to recover than those receiving other doses of prednisolone. There was a significant reduction in incomplete recovery in combined antiviral agents with 448 mg of methylprednisolone, but there was only one RCT included in this analysis.[12] Therefore, there was no sufficient data to support using of combined antiviral agents with methylprednisolone for Bell's palsy treatment. From the minimal data for comparison of motor synkinesis, the results of two studies with separate comparisons were significant. Other secondary outcomes including adverse events which were reported by three studies were not significant.

STRENGTH AND LIMITATION OF THE REVIEW

This systematic review has much strength. Five authors searched for eligible RCTs by screening all titles and abstracts and read full-text articles to assess relevant studies, thus, we got eligible studies and can be assured not to missed important data. The data extraction has been performed by individual reviewers and independently. Furthermore, our included studies were considered as high methodological quality with a low risk of bias and the results from these studies can be trusted. This study examined the risk of bias of each study thoroughly using Cochrane risk bias tool.

The limitations of this systematic review are various data of initial severity at the onset of disease and time to start treatment. These factors may affect facial recovery rate. Our study may have

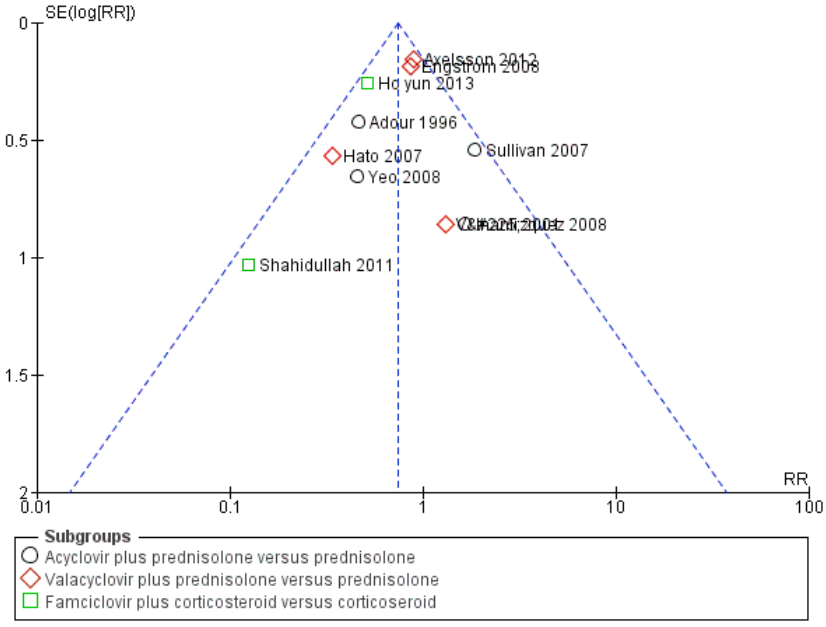

Figure 8. Funnel Plot of Comparison

inadequate power for some outcomes such as adverse events of combined antiviral agents with corticosteroids therapy and reduction rate of motor synkinesis due to few literature.

COMPARISON WITH OTHER STUDIES

There were three systematic reviews studied combined antiviral agents with corticosteroids versus corticosteroids. The Cochrane systematic review included seven RCTs with 1,987 participants. The rate of incomplete recovery was significantly less with the combined treatment than with corticosteroids alone which would suggest a beneficial effect from antiviral agents but this analysis showed moderate heterogeneity.[9] One review suggested a borderline significant risk reduction of borderline superior effect of the combined therapy over corticosteroids alone.[10] The last review included five RCTs with 738 participants and showed no benefit of using antiviral agents with corticosteroid compared with corticosteroid alone.[11] In our study, we included ten RCTs with 1,850 participants. Five RCTs were included in Cochrane systematic review and John R systematic review, two RCTs also included in John R systematic review and three more RCTs were newly added to our systematic review. Two RCTs in Cochrane systematic review.[25,26] and nine RCTs in John R systematic review were excluded from our studies because they did not meet our inclusion criteria.[26-34] In John R systematic review, two RCTs had missing information which published only abstract and no available full-text publication.[35,36] Finally, combined antiviral agents with corticosteroid

showed statistically significant to reduce incomplete recovery of facial function (RR 0.74, 95% CI, 0.61 to 0.90). Our results were similar to John R systematic review which found a benefit of antiviral agents with corticosteroid (RR 0.75, 95% CI, 0.56 to 1.00), but our study slightly more precise (95% CI, 0.61 to 0.90 versus 95% CI, 0.56 to 1.00 respectively). In addition, our study analyzed subgroups of these trials by type of antiviral agents and dosage of corticosteroids which the recent three systematic reviews did not report. In an analysis, famciclovir presented a significant effect on the outcome of incomplete recovery (RR 0.44, 95% CI, 0.27 to 0.71). The cumulative dose of prednisolone greater than 400 mg but less than 500 mg and methylprednisolone 448 mg showed a significant reduction in a risk of incomplete recovery (RR, 0.73; 95% CI,0.55 to 0.98, RR, 0.51; 95% CI, 0.31 to 0.85 respectively).

CONCLUSION AND IMPLICATIONS

In conclusion, this systematic review and meta-analysis of ten RCTs showed a statistically significant increase recovery rate of Bell's palsy in combined famciclovir with greater than 400 mg but less than 500 mg of prednisolone compared to prednisolone alone. Combined therapy with 448 mg of methylprednisolone also showed significant improvement of facial function. Though these results showed significant, only one randomized controlled trial was included in this analysis. Therefore, the data to support using of combined antiviral agents and methylprednisolone for the treatment of Bell's palsy were insufficient.

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Effects of oral and nasal steroids in nasal polyps: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE
To identify the effect of oral and nasal steroids in patients with nasal polyps.

METHODS
We systematically searched through electronic databases including Pubmed, The Cochrane Library, Scopus, Google scholar using keywords related to oral steroids or corticosteroids and nasal polyps. We included studies that used oral plus nasal steroids for treating patients with nasal polyps. The primary outcome was the decrease of nasal polyp size. Other outcomes included hyposmia, nasal obstruction, and nasal nitric oxide. The full texts of the included studies were appraised for risk of bias and their data were extracted for meta-analysis comparing between oral plus nasal steroids and nasal steroids alone or placebo.

RESULTS
Six randomized controlled trials were included in the present review with a total of 490 patients; 335 in oral steroids followed by nasal steroids group, 78 in nasal steroids alone group and 77 in the placebo group. The first comparison is using oral plus nasal steroids compared to nasal steroids alone which the result after 2 weeks of starting oral steroids treatment, oral steroids showed statistically significant decrease nasal polyp size, mean difference (MD) -1.66 (95% confidence interval (CI), -2.54 to -0.78). At the various ends of the studies, oral plus nasal steroids showed statistically significant decrease nasal polyp size, MD -0.43 (95% CI, -0.52 to -0.34). The second comparison is using oral plus nasal steroids compared to placebo which the result after 2 weeks of starting oral steroids treatment, oral steroids showed statistically significant decrease nasal polyp size, MD -0.64 (95% CI, -1.19 to -0.1). After 12 weeks of starting nasal steroids, the patients in treatment group showed the reduction of the nasal polyp size, MD -0.68 (95% CI -1.16 to -0.19).

CONCLUSION
We suggested the possible benefit of oral steroids followed by nasal steroids for decrease nasal polyp size. However, our conclusion was based on 490 patients, the randomized controlled trials with large of participants are suggested.

INTRODUCTION

Nasal polyps are noncancerous multiple masses that growth from paranasal sinus and extend to a nasal cavity. The polyps usually occur bilaterally and maybe the cause of nasal obstruction while the etiology is still unknown with the plausible link to chronic inflammation, allergies, and asthma.[1-6] The global incidence of nasal polyps is 1-4% among adults.[7-9] Nowadays the corticosteroids are the treatment of choice while topical nasal steroid is a preferred route of administration.[10,11] In addition, previous studies have suggested the benefits of oral steroids for nasal polyp treatment.[12,13] According to two previous systematic reviews in 2007 and 2011 comparing between oral steroids followed by nasal steroids and placebo stating that oral steroids had benefit for the relief of nasal symptoms and nasal polyp size reduction.[13,14]

Since those reviews five randomized controlled trials (RCT) further studies have been published Three of these studies suggested that oral steroids followed by nasal steroids had the better outcome for patients with nasal polyps comparing to placebo.[15-18] Another two studies compared oral steroids followed by nasal steroids to nasal steroids alone.[19,20] When using oral steroids followed by nasal steroids, both of them showed significant decrease of nasal polyp size but the improvement of hyposmia was still debatable; one study in 2012 with 67 patients showed significant improvement of hyposmia after the use of oral steroids followed by nasal steroids compared to nasal steroid alone while another one in 2011 with 30 patients did not.[19,20] Thus, we conducted a systematic review to evaluate whether oral steroids followed by nasal steroids had effects for decrease nasal polyp size, improvement of hyposmia, improvement of nasal obstruction and increase nasal nitric oxide compared to nasal steroids alone or placebo in patients with nasal polyps.

METHODS

SEARCH STRATEGIES

We searched for studies through the Cochrane Library, Pubmed, Scopus and Google Scholar. We used a combination of Medical Subject Headings (MeSH) for Pubmed and Cochrane Library searching; ("Nasal Polyps" [Mesh] OR "Rhinopolyps*" [Mesh] OR ("Polyps" [Mesh] OR "Polyp*" [Mesh] AND "NOSE" [Mesh] OR "Nasal" [Mesh] OR "Intranasal" [Mesh] OR "Sinonasal" [Mesh]) AND "Steroids" [Mesh] OR "Corticosteroid" [Mesh] OR "Adrenal cortex hormones" [Mesh] OR "Glucocorticoids"[Mesh] OR "Prednisolone" [Mesh] OR "Budesonide" [Mesh]) and used keywords ; "Polyp*" OR "Papillom*" OR "Rhinopolyp*" AND "Steroid*" OR "Glucocorticoid*" OR "Corticosteroid*" OR "Prednisolone*" in Scopus and Google scholar. We checked every reference of the included studies and manually searched for additional studies which were relevant.

Overall 3,587 titles and abstracts were reviewed. We conducted systematic searches for RCTs. There were no languages, publication years or publication status restrictions. The date of the last search was February 19, 2015.

INCLUSION CRITERIA

PARTICIPANTS

We selected only the studies which included patients with nasal polyps based on nasal endoscope.

INTERVENTIONS

Any dose of oral steroids followed by nasal steroids versus nasal steroids alone as well as any dose of oral steroids followed by nasal steroids versus placebo

OUTCOMES

Our primary outcome was nasal polyp size measured by Lildholdt 's scale for nasal polyp grading.[21] Secondary outcomes were hyposmia, nasal obstruction, and nasal nitric oxide.

EXCLUSION CRITERIA

We excluded studies that patients were given steroids after sinus surgery

DATA EXTRACTION

Five reviewers read full texts of the eligible articles and selected RCTs that involving oral steroids followed by nasal steroids compared with nasal steroids alone or placebo in patients with nasal polyps. All problems were solved by the discussion of five reviewers and data extracted from included studies and recorded by five reviewers. We used the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 to organize the standard forms to extract data.[22]

QUALITY OF REPORTING AND RISK AND BIAS

We used Jadad scale for assessed the risks in term of randomization, blinding and an account of all patients. Potential publication bias was assessed by using a funnel plot. Moreover, We used The Cochrane Handbook for Systematic Reviews of Interventions version 5.3.0 for assessed risk of bias of the included RCTs which risk of bias was weighed regarding random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Then the RCTs were classified into three groups; low risk, high risk and unclear risk by the risk of bias score.

DATA ANALYSES

To standardize the reporting of our results, we calculated mean difference (MD) for continuous data that outcomes were measured in the same manner; nasal polyp size, nasal obstruction, and nasal nitric oxide at week 2, week 12 compared to week 0. And we used standardized mean difference (SMD) for continuous data which outcomes were measured in various methods; hyposmia was the case in the present review. Both MD and SMD of the outcomes were presented together with their 95% confidence interval (CI). All analyses were performed with Revman 5.3.0 (RevMan, the programme provided by the Cochrane Collaboration) statistical software to assess the effectiveness of oral steroids followed by nasal steroids compared with either nasal steroids alone

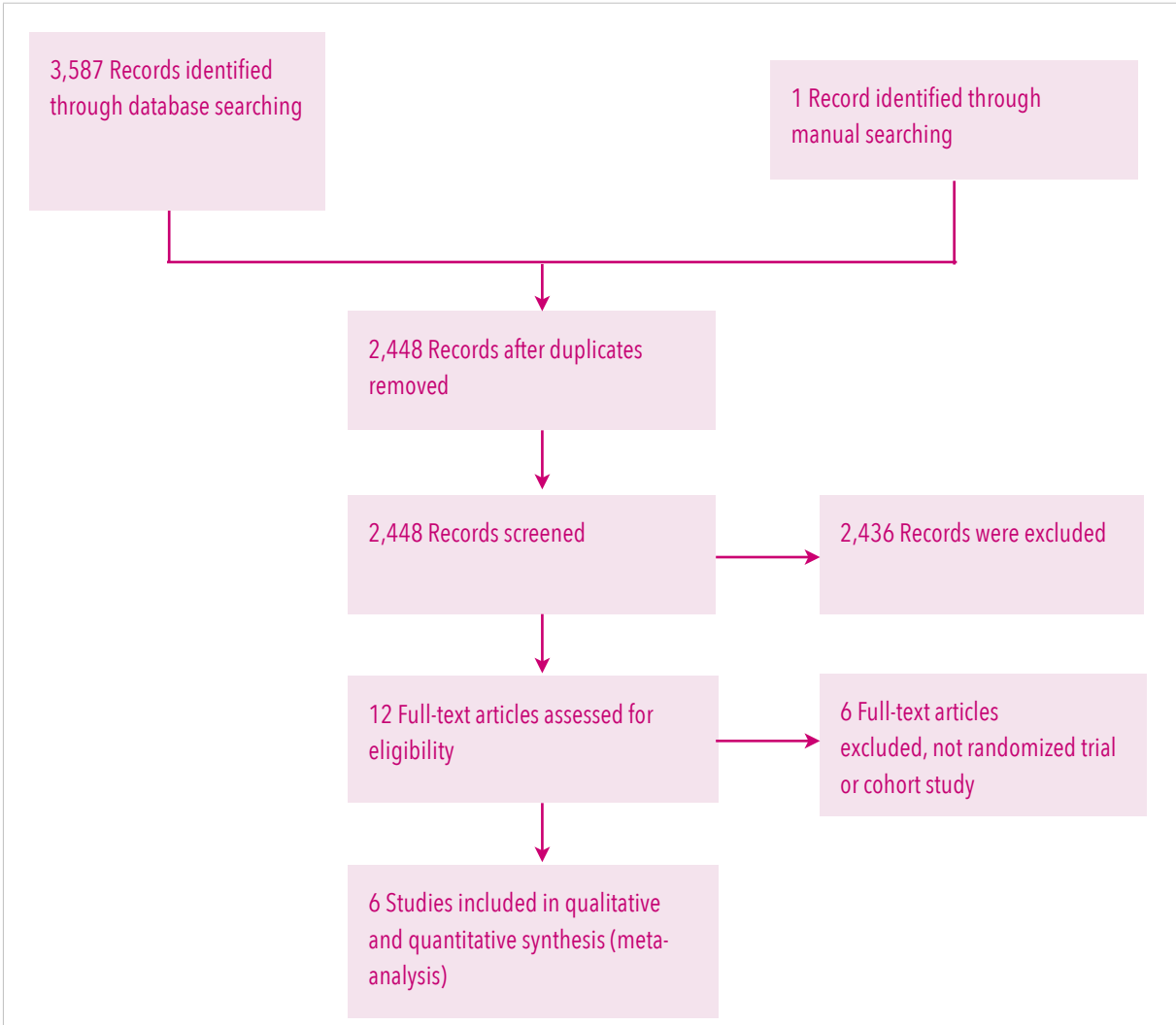

Figure 1. Flowchart presenting the number of articles retrieved, included and excluded in this systematic riew.

or placebo for nasal polyp treatment according to nasal polyp size, hyposmia, nasal obstruction and nasal nitric oxide.[23] The statistical test of heterogeneity was high if $P<0.10$ and I^2 statistic was more than 50%. We used a random effect model for the meta-analysis when heterogeneity was high and used a fixed effect model for the meta-analysis when heterogeneity was low. We did not perform sensitivity analysis due to the small number of trials that could be included in the analysis of the outcomes. This strategy was also applied elsewhere.[23]

Table.1 Characteristics of the included studies

Author	Location	Study design	Population	Duration of study	Sample size (I/C)	Mean age (year)	Duration of treatment (weeks)	Regimen of interventions	Jadad scale
Alobid 2006	Spain	RCTs	Patients with nasal polyps diagnosed endoscopically and radiologically, 22 to 84 yr	Feb 1999 to Jul 2003	78 (60/18)	50	48	Prednisone 30 mg daily for 4 days, followed by a two-days reduction of 5 mg for 2 weeks followed by intranasal budesonide (400 µg/twice a day)for 46 weeks	0
Benitez 2006	Spain	RCTs	Patients with severe NP diagnosis by nasal endoscopic,22 to 84 yr	Feb 1999 to Nov 2003	74 (63/21)	51.7	14	Oral prednisone for 2 weeks (30 mg daily for 4 days followed by a 2-day reduction of 5 mg) followed by 400 g intranasal budesonide twice a day for 12 weeks	2
Vaidyanathan 2011	United Kingdom	RCTs	Patients with moderate and large nasal polyps	-	58 (30/28)	-	28	Prednisolone 25 mg/day for 2 weeks, followed by fluticasone propionate nasal drops, 400 g twice daily, for 8 weeks and then fluticasone propionate nasal spray, 200 g twice daily, for 18 weeks.	4
Kirtsree sakul 2012	Thailand	RCTs	Patients with benign bilateral nasal polyps, 18-65 yr	May 2007 to Sep 2010	117 (69/48)	45.6	12	50 mg of prednisolone for 2 weeks then treated with mometasone furoate nasal spray (MFNS) at 200 microgram twice daily for 10 weeks	2
Alobid 2012	Spain	RCTs	Patients with moderate to severe nasal polyps	-	62 (46/16)	49	14	30 mg/day for 4 day followed by a 2 days Reducing 5 mg, 2 weeks and intranasal steroids 400 micrograms BID 12 weeks	2
Alobid 2014	Spain	RCTs	Patients with moderate to severe nasal polyps	-	89 (67/22)	42	14	30 mg/day for 4 day followed by a 2 days reducing 5 mg, 2 weeks and intranasal steroids 400 micrograms BID 12 week	3

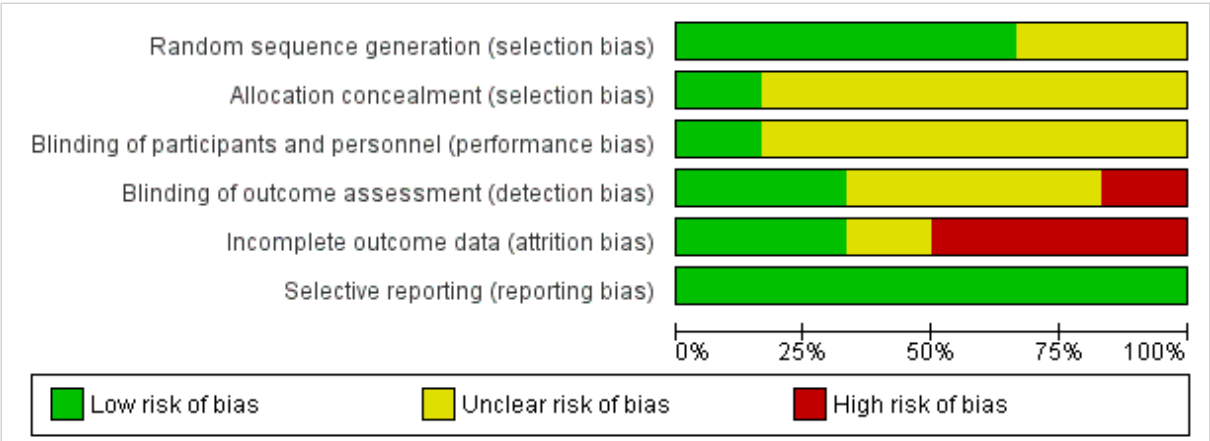

Figure 2. Risk of bias graph.

RESULTS

DESCRIPTION OF STUDIES

The literature search retrieved 3,587 citations and additional 1 citation was identified through manual searches reference lists of relevant articles (Figure 1). Of these, 2,548 citations after duplicates removed were identified. Later we screened for titles and abstracts, 2,536 citations were excluded. In the end, 12 full-text articles were assessed for eligibility according to inclusion and exclusion criteria. Ultimately, six articles were included in the present review.

INCLUDED STUDIES AND EXCLUDED STUDIES

The remaining six RCTs determined the effect of oral steroids to improve nasal symptoms and polyp grading in patients with nasal polyps were all designed and conducted between 2006 and 2014. They assigned 490 patients; 335 patients received oral plus nasal steroids, 78 patients received nasal steroids alone and 77 patients received placebo. 15-18 The characteristics of six included studies were summarized in Table 1.

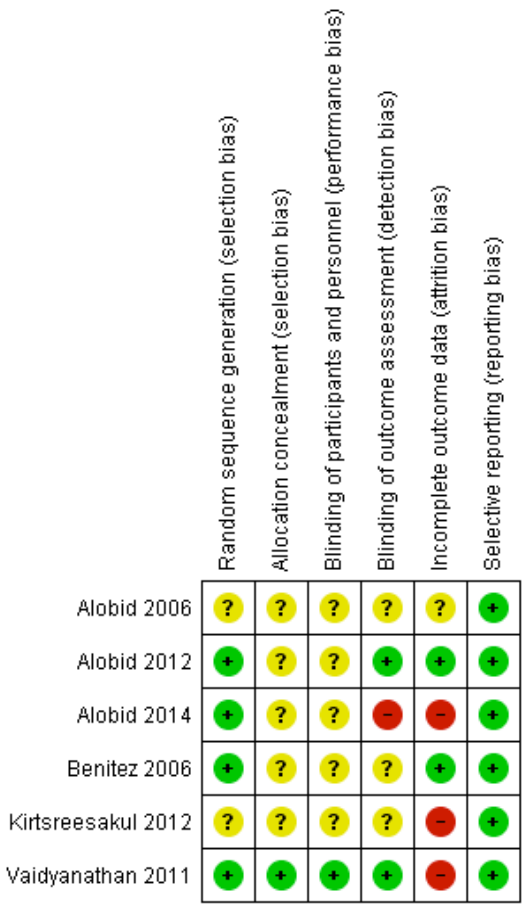

Figure 3. Risk of bias summary

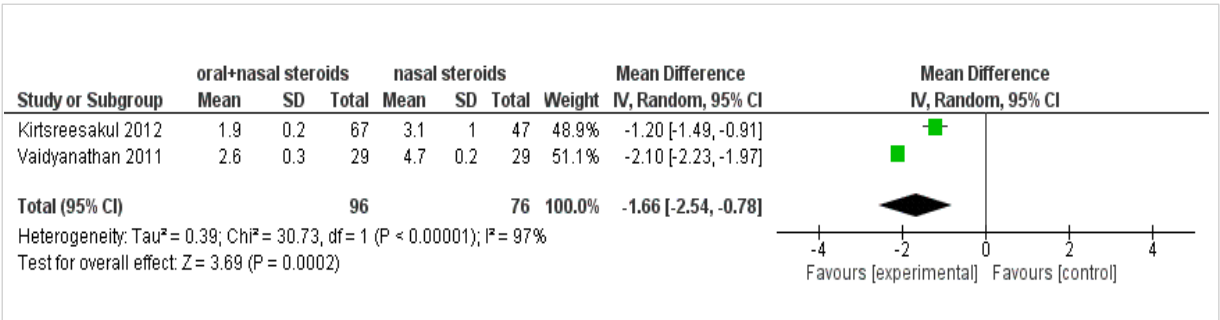

Figure 4. Forest plot of comparison of oral plus nasal steroids versus nasal steroids alone, outcome: polyp size at 2 weeks after oral steroids

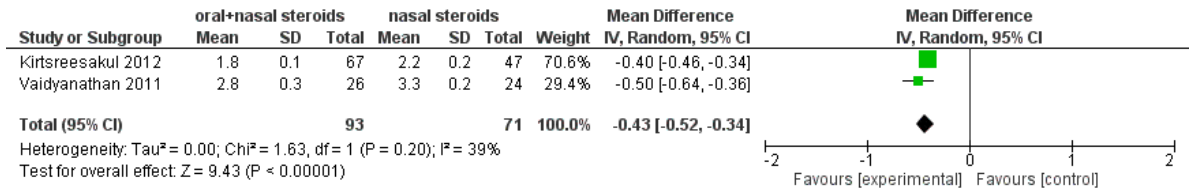

Figure 5. Forest plot of comparison of oral plus nasal steroids versus nasal steroids alone, outcome: polyp size at the end of study

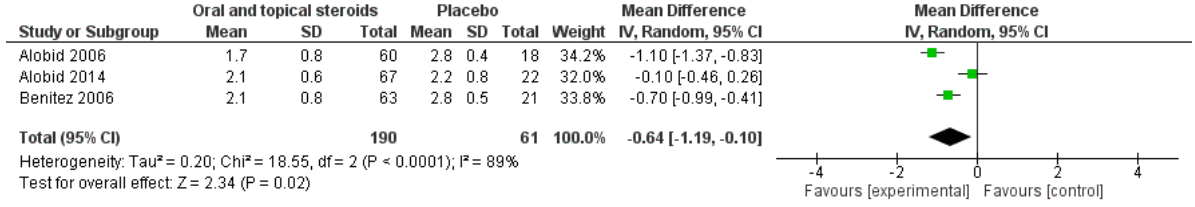

Figure 6. Forest plot of comparison of oral plus nasal steroids versus placebo, outcome: polyp size

RISK OF BIAS OF THE INCLUDED STUDIES

All RCTs were assessed quality using Jadad scale (Table1). The study by Vaidyanathan was scored 4 because of no detail of an account of all patients.[19] The study by Alobid in 2014 was scored 3 because of no detail of methods of blinding. Three studies by Alobid in 2011, Benitez and Kirtsreesakul were scored 2 because of no detail of methods of blinding and no detail of methods of an account of all patients.[16,17,20] The study by Alobid in 2006 was scored 0 because of no detail of methods of randomization, blinding, and account of all patients. Furthermore, the included six RCTs were assessed by The Cochrane Collaboration's tool for

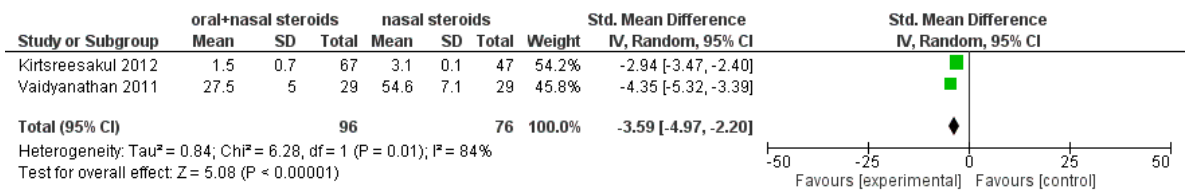

Figure 7. Forest plot of comparison of oral steroids followed by nasal steroids versus nasal steroids alone, outcome: Hyposmia at 2 weeks after oral steroids.

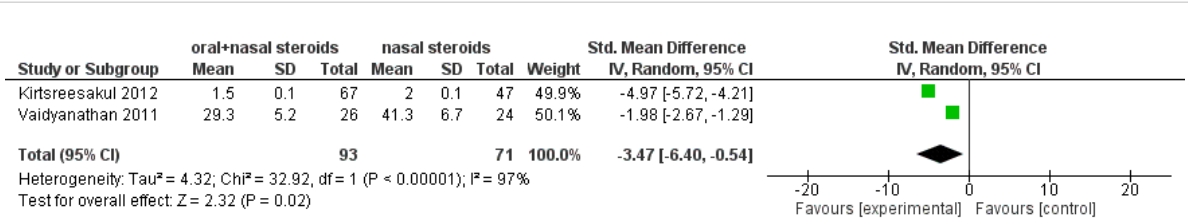

Figure 8. Forest plot of comparison: Oral steroids followed by nasal steroids versus nasal steroids alone , outcome: hyposmia at the end of study

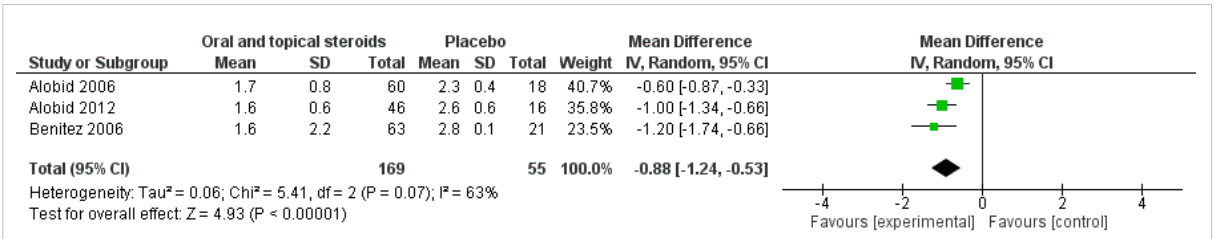

Figure 9. Forest plot of comparison: Oral steroids followed by nasal steroids versus placebo, outcome: hyposmia

assessing risk of bias which a risk of bias graph expressed methodological quality showed in Figure 2 and the risk of bias summary in each included study showed in Figure 3.

PRIMARY OUTCOME

We analyzed two trials which examined the effect of oral steroids followed by nasal steroids compared to nasal steroids alone.[19,20] At 2 weeks after starting oral steroids, the former group showed significant reduction of nasal polyp size, MD -1.66 (95% CI, -2.54 to -0.78, I^2=97%) (Figure 4). At the various ends of the studies, the former group again showed significant reduction of polyp size, MD -0.43 (95% CI, -0.52 to -0.34, I^2=39%). (Figure 5). Three RCTs studied the improvement of

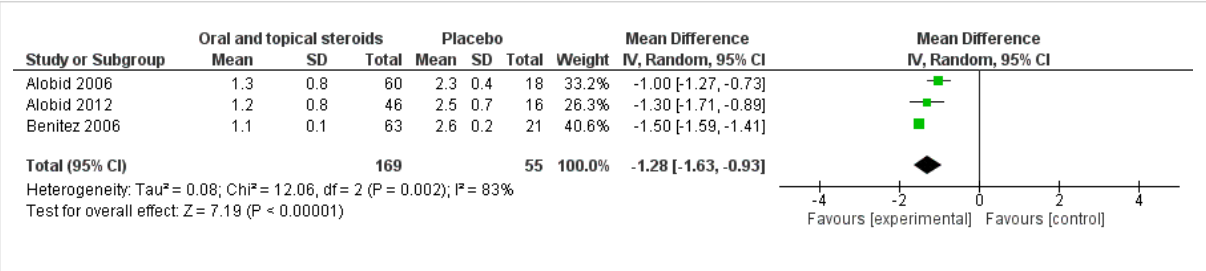

Figure 10. Forest plot of comparison: Oral steroids followed by topical steroids versus placebo, outcome: nasal obstruction

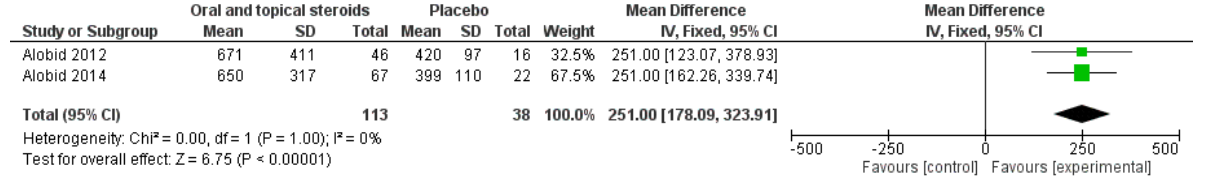

Figure 11. Forest plot of comparison: Oral steroids followed by topical steroids versus placebo, outcome: nasal nitric oxide

nasal polyp size that compared between oral plus nasal steroids and placebo.[15-17] At 2 weeks after starting oral steroids, the former group showed significant improvement of nasal polyp size, MD -0.64 (95% CI, -1.19 to -0.1, I^2=89%).(Figure 6). At 12 weeks after starting nasal steroids, the reduction of nasal polyp size comparing between week 12 and week 0 in treatment group was significant, MD -0.68 (95% CI -1.16 to -0.19) but in control group was not measured due to medical ethics of human researches as it cannot consider offering ineffective treatment to the control group for longer than 6 weeks

HYPOSMIA

Two RCTs studied the improvement of hyposmia that compared between oral plus nasal steroids and nasal steroid alone.[19,20] At 2 weeks after starting oral steroids, the former group showed significant improvement of hyposmia, SMD -3.59 (95% CI -4.97 to -2.20, I^2=84%) (Figure 7). At the various ends of the studies, oral plus nasal steroids showed significant improvement of hyposmia, SMD -3.47 (95% CI -6.40 to -0.54, I^2=97%) (Figure 8).

Three RCTs studied the improvement of hyposmia that compared between oral plus nasal steroids and placebo.[15-17] At 2 weeks after starting oral steroids, the former group showed significant improvement of hyposmia, MD -0.88 (95% CI -1.24 to -0.53, I^2=97%) (Figure 9). At 12 weeks after starting nasal steroids, the improvement of hyposmia was not sustained, MD -0.35 (95% CI -0.10 to 0.29) (Figure 9).

NASAL OBSTRUCTION

Three RCTs studied the improvement of nasal obstruction that compared between oral plus nasal steroids and placebo.[15-17] At 2 weeks after starting oral steroids, the former group showed significant improvement of nasal obstruction, MD -1.28 (95% CI -1.63 to -0.93, I^2=83%)(Figure 10) and after 12 weeks of starting nasal steroids, nasal steroids can maintain the improvement of nasal obstruction, MD -1.06 (95% CI -1.45 to -0.69).

NASAL NITRIC OXIDE

Two RCTs studied the improvement of nasal obstruction that compared between oral plus nasal steroids and placebo.[17-18] At 2 weeks after starting oral steroids, the former group showed a significant increase nasal nitric oxide, MD 251.00 (95% CI 178.09 to 323.91, I^2=0%) (Figure 11) and after 12 weeks of starting nasal steroids, nasal steroids can also maintain the level of nasal nitric oxide, MD 198.50 (95% CI 166.73 to 230.27)

We did not create the funnel plot as our outcomes were derived from the combined findings of only two and three RCTs. The number of the included studies were too few to assess the publication bias.

DISCUSSION

SUMMARY OF MAIN RESULTS

In the present systematic review and meta-analysis, we found that using oral steroids for 2 weeks was effective to decrease polyp size, improve hyposmia, relief nasal obstruction and increase nasal nitric oxide in patients with nasal polyps. When using oral steroids followed by nasal steroids, polyp size and hyposmia were more improved than using nasal steroids alone. Moreover, oral steroids followed by nasal steroids can also maintain improvement of polyp size, nasal obstruction, and nasal nitric oxide level.

OVERALL COMPLETENESS AND APPLICABILITY OF EVIDENCE

Both Vaidyanathan 2011 and Kirtsreesakul 2012 studied the effect of oral steroids followed by nasal steroids compared to nasal steroid only at different doses and forms.[19,20] At 2 weeks, both of them showed the significant improvement of polyp size and hyposmia in the former group when compared with the latter group. After 2 weeks, nasal steroids was given to all of the patients and measured the outcomes at the variant times. At the end of both studies, they still showed significant improvement of polyp size after using oral followed by nasal steroids but hyposmia was different, Kirtsreesakul 2012 showed significant improvement of hyposmia at 12 weeks while Vaidyanathan 2011 did not at 28 weeks. In our meta-analysis of two studies suggested the significant improvement of hyposmia. However, the limitation of these analyses should be reminded that it was measured the final outcomes at the different times.[19,20]

Alobid 2006, Benitez 2006, Alobid 2012 and Alobid 2014 studied the effects of oral steroids followed by nasal steroids in treatment group compared with the patients in control group who received placebo by measuring various outcomes at 2 weeks after patients in treatment group receiving oral steroids and 12 weeks after the treatment group converting to use nasal instead oral steroids for 10 weeks.[15-18] After 2 weeks, the significant improvements of polyp size, hyposmia,

nasal obstruction and nasal nitric oxide were shown in patients with nasal polyps who received oral steroids.[15-18] The end of studies at 12 weeks, they still showed significant improvement of polyp size, nasal obstruction, and nasal nitric oxide but hyposmia was different. Alobid 2006 showed hyposmia can be maintained the improvement while Alobid 2012 and Benitez 2006 found that using oral followed by nasal steroids cannot maintain the improvement of hyposmia.[15-17]

QUALITY OF THE EVIDENCE

This systematic review has much strength. Five authors search RCTs by screening all titles and abstracts and read full-text articles to assess relevant studies. All of include studies were precisely assess quality and bias used the standard assessment such as the Cochrane Collaboration's tool for assessing risk of bias and Jadad scale. The limitation of this systematic review has high heterogeneity of included studies and possible publication bias. The RCTs with a large number of participants is suggested for stronger evidence to support the effect of oral steroids and nasal steroids in patients with nasal polyps.

AGREEMENTS AND DISAGREEMENTS WITH OTHER STUDIES OR REVIEW

Our findings have benefit for receiving oral steroids followed by nasal steroids for nasal polyps treatment which decrease polyp size, improve hyposmia, relief nasal obstruction and increase nasal nitric oxide. A recent systematic review of oral steroids for nasal polyps by Martinez-Devesa P et al, 2011 found three RCTs which moderate to poor quality but they suggested a short-term benefit of oral steroids in those with multiple nasal polyps.[14] Our analysis differs Martinez-Devesa P et al. by being a meta-analysis and we included more studies, more diverse populations, and more comparison.[14] In six RCTs in our study, there are two RCTs: Vaidyanathan and Kirtsreesakul which used oral steroids followed by nasal steroids compared with nasal steroids alone while Martinez-Devesa P et al.'s used oral steroids followed by nasal steroids compared with placebo.[14,19-20]

About the hyposmia outcome, there were different outcomes of following for long-term usage in each RCTs, our results suggested the benefit of the short-term use but the long-term outcome was still unclear. There was a systematic review by Banglawala et al, 2014 reviewed the olfactory outcome in chronic rhinosinusitis with nasal polyposis.[25] The results of their meta-analysis demonstrated that oral and nasal steroids significantly improve olfaction in patients suffering from chronic rhinosinusitis with nasal polyposis.[25]

CONCLUSION AND IMPLICATION

We suggest the possible benefit of oral steroids followed by nasal steroids for decrease nasal polyp size. However, our suggestion was based on 490 patients with relatively high heterogeneity, the further RCT with larger of participants are needed.

ACKNOWLEDGMENTS & DECLARATION

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

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Amniotomy and postpartum endometritis: a case-control study

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To assess the whether amniotomy is the risk for postpartum endometritis.

METHODS

This is a case-control study to identify risk factors for postpartum endometritis in patients underwent vaginal delivery. Cases were patients who had postpartum endometritis after vaginal delivery, including spontaneous vaginal delivery or assisted vaginal delivery between 2010 and 2014 at Khon Kaen Hospital. Each case was matched to four controls for age and parity on consecutive delivery. Controls were patients who had vaginal delivery including spontaneous vaginal delivery or assisted vaginal delivery but were not diagnosed as postpartum endometritis.

RESULTS

We selected 46 cases and 184 age and parity matched controls. There was no association between amniotomy and postpartum endometritis (crude odds ratio [COR], 1.55; 95% confidence interval [CI], 0.81 to 2.96, adjusted odds ratio [AOR], 1.71; 95% CI, 0.61 to 4.76). Retained piece of placenta (COR, 35.86; 95% CI, 7.73 to 166.25; AOR, 19.75; 95% CI 2.10 to 186.12), postpartum hemorrhage (COR, 48.53; 95% CI, 10.62 to 221.88; AOR, 101.03; 95% CI 7.54 to 1353.14) and body mass index (BMI)≥30 (COR, 3.78; 95% CI, 0.796 to 18.13, AOR, 9.18; 95% CI, 1.11 to 76.08) were the three factors that increased the risk for postpartum endometritis.

CONCLUSION

Our study found that amniotomy was not significantly associated with the occurrence of postpartum endometritis but retained piece of placenta, postpartum hemorrhage, and BMI≥30 increased the occurrence of postpartum endometritis were associated with higher risk of postpartum endometritis.

INTRODUCTION

Postpartum endometritis is an infection of endometrium in pregnant women after delivery.[1] This condition is one of the morbidities in patients with postpartum fever.[2] Risk factors for postpartum endometritis include bacterial vaginosis, prolong labor, many vaginal examinations, prolonged rupture of membranes, amniotic membrane infection, operative birth, anal sphincter laceration, meconium staining, and also procedures perform during labor such as amniotomy.[3-6]

Amniotomy, also known as artificial rupture of membranes, is one of the most common induction procedures which breaking of membranes of amniotic sac.[7] Rupture of amniotic membranes lead to be the release of prostaglandin E2 and oxytocin, so it may induce labor and shorten the duration of labor.[8] However, the procedure might be a risk factor for many complications such as intrauterine infection.[9]

Nonetheless, there is no study that shows the association between amniotomy and risk for postpartum endometritis in patients with vaginal delivery. Therefore, we conducted a case-control study to identify the association between amniotomy and postpartum endometritis in patients with vaginal delivery. In addition, we also adjusted for other risk factors that might associate with postpartum endometritis including age, parity, body-mass index, positive HBsAg, pharmacological induction, antibiotics prophylaxis, gestational diabetes mellitus, meconium stain, mode of vaginal delivery, number of vaginal examination, retained piece of placenta, and postpartum hemorrhage.

METHODS

This is a case-control study to identify risk factors for postpartum endometritis in patients with vaginal delivery. This study was conducted in Khon Kaen Hospital, Thailand. Cases were patients who had body temperature≥38.0 degree Celsius and uterine tenderness or foul smell lochia after vaginal delivery, including spontaneous vaginal delivery or assisted vaginal delivery.[10] We defined the date of admission as the index date. We included both early postpartum endometritis (<48 hours after delivery) and late postpartum endometritis (3 days-6 weeks after delivery).[11] Each case was matched to four controls for age and parity on consecutive delivery. Controls were patients who had the vaginal delivery, including spontaneous vaginal delivery or assisted vaginal delivery, but were not diagnosed as postpartum endometritis.

The mother's demographic characteristics were obtained from selected information of labor and delivery records from women who delivered during the period from 2010 and 2014 at Khon Kaen Hospital. The data record included date of birth, estimated gestational age, parity, newborn number, body-mass index, positive HBsAg, reactive HIVAb, reactive VDRL, pharmacological induction, antibiotics prophylaxis for prolonged premature

Table 1. Characteristics of controls and case patients with odds ratios for risk factors for postpartum endometritis

Characteristic	Controls (N=184)	Cases (N=46)	Crude odds ratio	Adjusted odds ratio
	no. (%)		*95% Confidence interval*	
Age-yr				
10–19	56 (30.4)	14 (30.4)	1	1
20–29	84 (45.7)	21 (45.7)	1.00 (0.47-2.13)	0.86 (0.27-2.77)
30–39	44 (23.9)	11 (23.9)	1.00 (0.41-2.42)	0.21 (0.03-1.55)
Estimated gestational age*				
Preterm	31 (16.8)	9 (19.6)	1	NA
Term	151 (82.1)	36 (78.3)	0.82 (0.36-1.88)	NA
Postterm	2 (1.1)	1 (2.2)	1.7 (0.14-21.24)	NA
Parity				
Nulliparous	108 (58.7)	27 (58.6)	1	1
≥1	76 (41.3)	19 (41.3)	1.00 (0.52-1.93)	0.98 (0.28-3.38)
Newborn number				
Singleton	183 (99.5)	45 (97.8)	1	NA
≥2	1 (0.5)	1 (2.2)	4.1 (0.25-66.27)	NA
Body-mass index†				
<18.5	34 (20.7)	9 (22.5)	1	1
18.5 - 22.9	83 (50.6)	18 (45.0)	0.82 (0.34-2.00)	0.90 (0.27-3.06)
23 - 24.9	23 (14.0)	6 (15.0)	0.99 (0.31-3.15)	1.89 (0.39-9.13)
25 - 29.9	20 (12.2)	3 (7.5)	0.57 (0.14-2.34)	0.39 (0.05-3.19)
≥30	4 (2.4)	4 (10.0)	3.78 (0.79-18.13)	9.18 (1.11-76.08)
Positive HBsAg	4 (2.2)	2 (4.3)	2.01 (0.36-11.34)	2.61 (0.23-29.59)
Reactive HIVAb	1 (0.6)	0	NA	NA
Reactive VDRL	1 (0.6)	0	NA	NA
Pharmacological Induction				
Misoprostol	13 (7.1)	6 (13.0)	1.97 (0.68-5.73)	2.31 (0.50-10.56)
Oxytocin	64 (34.8)	14 (30.4)	0.93 (0.45-1.94)	0.51 (0.15-1.75)
Both misoprostol and oxytocin	9 (4.9)	3 (6.5)	1.42 (0.36-5.66)	3.05 (0.46-20.17)
Antibiotics prophylaxis‡	34 (18.5)	6 (13.0)	0.66 (0.26-1.69)	0.26 (0.06-1.25)

Table 1. (Continued)

Characteristic	Controls (N=184)	Cases (N=46)	Crude odds ratio	Adjusted odds ratio
	no. (%)		*95% Confidence interval*	
Amniotomy	80 (43.5)	25 (54.3)	1.55 (0.81-2.96)	1.71 (0.61-4.76)
Gestational diabetes mellitus	7 (3.8)	1 (2.2)	0.56 (0.07-4.69)	0.30 (0.00-255.23)
Premature rupture of membranes¶				
≤24 hr	9 (4.9)	2 (4.3)	0.85 (0.18-4.09)	NA
>24 hr	6 (3.3)	0	NA	NA
Meconium stained amniotic fluid	26 (14.1)	6 (13.0)	0.91 (0.35-2.36)	0.63 (0.14-2.81)
Mode of vaginal delivery				
Spontaneous	176 (95.7)	42 (91.3)	1	1
Vacuum extraction	8 (4.3)	4 (8.7)	2.10 (0.60-7.29)	7.95 (0.96-65.73)
Lacerations				
None	158 (85.9)	36 (78.3)	1	NA
First	14 (7.6)	5 (10.9)	1.57 (0.53-4.63)	NA
Second	8 (4.3)	4 (8.7)	2.19 (0.63-7.69)	NA
Third	3 (1.6)	1 (2.2)	1.46 (0.15-14.48)	NA
Fourth	1 (0.5)	0	NA	NA
Rupture of membranes to delivery time				
≤24 hr	177 (96.2)	46 (100.0)	NA	NA
>24 hr	7 (3.8)	0	NA	NA
Vaginal examination				
<3	52 (28.3)	10 (21.7)	1	1
≥3	132 (71.7)	36 (78.3)	1.42 (0.66-3.07)	1.39 (0.42-4.61)
Retained piece of placenta	2 (1.1)	13 (28.3)	35.86 (7.73-166.25)	19.75 (2.10-186.12)
Postpartum hemorrhage	2 (1.1)	16 (34.8)	48.53 (10.62-221.88)	101.03 (7.54-1353.14)

* By ultrasound or last menstrual period.

† The body-mass index is the weight in kilograms divided by square of height in meter.

‡ Antibiotics prophylaxis for prolonged PROM (PROM > 24hrs.) or third- to fourth- degree perineal laceration included penicillin, cephalosporins, aminoglycosides, metronidazole and macrolides.

¶ Patient who is beyond 37 weeks' gestation and has presented with rupture of membranes (ROM) prior to the onset of labor.

rupture of membranes (PROM)>24 hours or third- to fourth-degree perineal laceration, amniotomy, gestational diabetes mellitus, prolonged rupture of membranes, meconium stain, mode of vaginal delivery, degree of laceration, rupture of membranes to delivery time, number of vaginal examination, retained piece of placenta, and postpartum hemorrhage. We excluded cases and controls with abortion or those with any previous history of endometritis.

We imputed data by double entry and cleaned all data before analysis. Frequency tables for all variable were generated to identify wild value. All statistical analyses were performed using the Statistical Package for the Social Science (SPSS) software. We described variables using number and percentage for categorical variables. For inferential statistics, we used binary logistic regression analysis to identify whether amniotomy was one of the risk factors for postpartum endometritis where the model adjusted for age, parity, body-mass index, positive HBsAg, pharmacological induction, antibiotics prophylaxis, amniotomy, gestational diabetes mellitus, meconium stain, mode of vaginal delivery, number of vaginal examination, retained piece of placenta, as well as postpartum hemorrhage.[12-14] The association between risk and the outcomes was presented in term of crude odds ratio (COR), adjusted odds ratio (AOR) and its 95% confidence Interval (95% CI).

RESULTS

We selected 46 cases and 184 matched controls by age and parity. The average age of patients was 24 years (range,14-37 years). There were 135 nulliparous women and 95 parous women. About 80% of them had term delivery. Almost patients gave birth to a singleton (98.7%). Only two of them gave birth to twins (1.3%). About a half of them had BMI 18.5 to 22.9 kg/m^2 (47.8%). Six patients had positive HBsAg (3.25%). Only one had reactive VDRL and HIVAb (0.6%) each. Less than half gave birth without pharmacological induction (46%), 10% received misoprostol, 32.6% received oxytocin, 11.4% received both misoprostol and oxytocin as pharmacological induction. Nearly half of them underwent amniotomy (49%). Eight patients had gestational DM (3%). Seventeen of them had PROM (6.25%), eleven had PROM less than 24 hours (4.6%), six had PROM more than 24 hours (1.65%). Meconium-stained amniotic fluid was found in 13.6% of the patients. The majority gave birth spontaneously (93.5%). Few patients gave birth using vacuum extraction (6.5%). Nobody had performed forceps extraction. Four-fifths of patients did not have perineal laceration (82.1%). Almost everybody had rupture of membranes to delivery time less than 24 hours (98%). Three-fourths had vaginal examination more than 3 times (75%). About a quarter of them had retained the piece of placenta (14.3%) and postpartum hemorrhage (18.0%).

There was no association between amniotomy and postpartum endometritis (COR, 1.55; 95% CI 0.81 to 2.96; AOR, 1.71; 95% CI, 0.61 to 4.76) (Table 1). Risk for postpartum endometritis was substantially higher in patients who had retained piece of placenta (COR, 35.86; 95% CI, 7.73 to 166.25, AOR, 19.75; 95% CI

2.10-186.12), postpartum hemorrhage (COR, 48.53; 95% CI, 10.62 to 221.88; AOR, 101.03; 95% CI, 7.54 to 1353.14), and BMI≥30 (AOR, 9.18; 95% CI, 1.11 to 76.08). However, gestational diabetes mellitus, prolonged rupture of membranes, meconium-stained amniotic fluid, mode of vaginal delivery (included spontaneous and vacuum extraction), perineal lacerations, vaginal examination were not associated with postpartum endometritis.

DISCUSSION

In this study, we found that amniotomy was not significantly associated with the occurrence of postpartum endometritis but postpartum hemorrhage, retained piece of placenta, and BMI≥30 increased the occurrence of postpartum endometritis after input data into the logistic regression analysis.

In the comparison to other studies: One study supports our finding, the occurrence of postpartum endometritis was not statistically significantly associated with amniotomy and spontaneous rupture of membranes, in low transverse cesarean section.[4] One study support, retained placenta increased the risk factor for postpartum endometritis, in cows.[15] There was a study of retrospectively reviewed on women that supported postpartum hemorrhage increased the risk for postpartum endometritis.[16] There was a randomized trial study shown that early amniotomy increased the rate of intrauterine infection comparing to late amniotomy.[9] In another study, intrauterine infection was no statistically significant between early amniotomy and late amniotomy in nulliparous women.[17] Our study did not analyze for early and late of amniotomy so we were unable to define an association between early or late of amniotomy and postpartum endometritis.

The study has two strengths. Firstly, this is the first study that analyzed about an association between amniotomy and postpartum endometritis in patients with vaginal delivery. Secondly, we reviewed the medical record of cases to make sure that they actually had postpartum endometritis. However, our study has some limitations. Firstly, the case was matched to four controls that sample size smaller than sample size calculation, which reduced the power of the study, increasing the risk for a type II error. Secondly, included cases and controls may have other conditions or diseases without postpartum endometritis that we did not include to analyze. Thus, they may be risks or confounding factors for the occurrence of postpartum endometritis. Third, we included both early and late postpartum endometritis but we did not separate the outcome as early or late postpartum endometritis. Amniotomy may not be a risk for late endometritis. Late endometritis may be caused by other risk factors, such as retained placenta.[16] Last, our study did not separate early and late amniotomy.

From our case-control study, we suggested to increase sample size in control groups for reduction of type II error and separate intervention of the early and late amniotomy to identify the association with risk for postpartum endometritis. In the further study, we recommend studying about the risk factors for early and late postpartum endometritis separately.

In conclusion, our study found that amniotomy was not significantly associated with the occurrence of postpartum endometritis but retained piece of placenta, postpartum hemorrhage and BMI≥30 were found to be associated with the significant increasing the occurrence of postpartum endometritis. Like amniotomy, our study found gestational diabetes mellitus, prolonged rupture of membranes, meconium-stained amniotic fluid, mode of vaginal delivery (included spontaneous and vacuum extraction), perineal lacerations and vaginal examination were not associated with postpartum endometritis.

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No human being is constituted to know the truth, the whole truth, and nothing but the truth; and even the best of men must be content with fragments, with partial glimpses, never the full fruition.

(William Osler)

"I shall either find a way or make one"

-Hannibal Barca

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