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

the clinical academia

Aim and Scope

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

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message from the editor

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

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

submission

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Our issues of each volume will be published online
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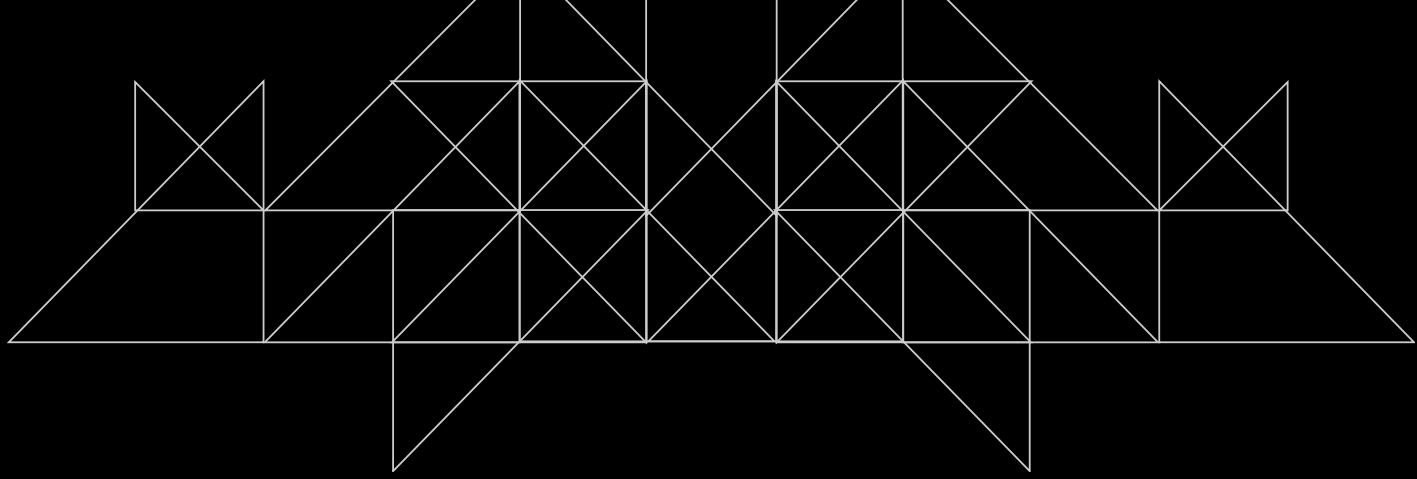
reviewing process

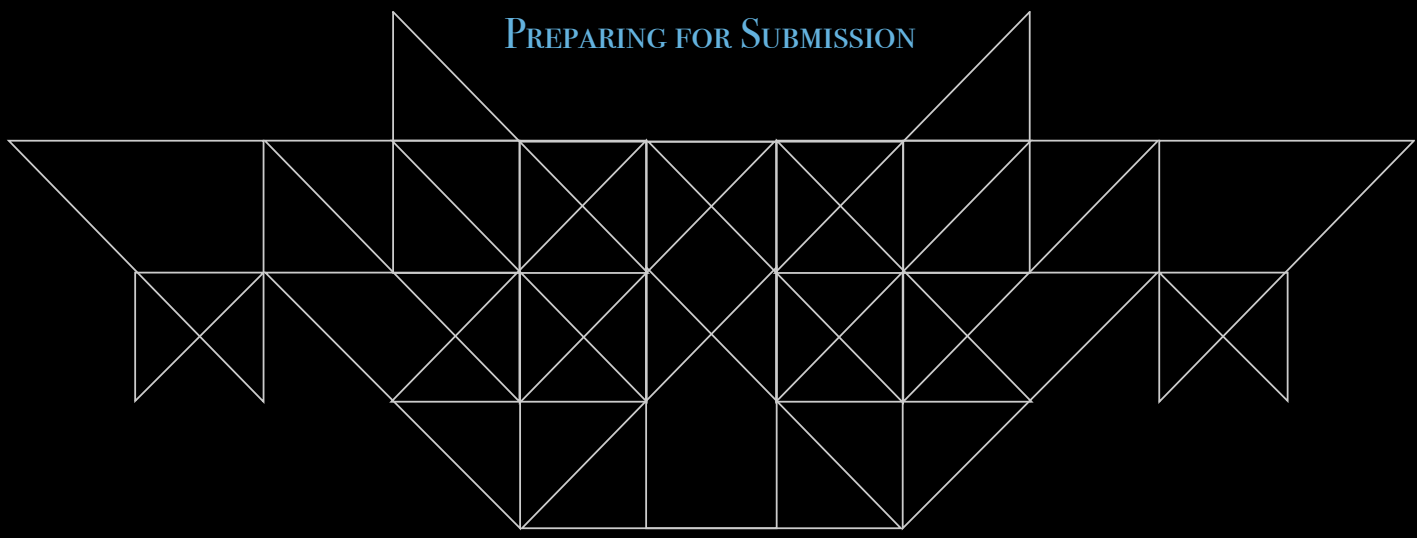
All accepted articles are classified into two main categories;
"***standard submission***" with the approximated processing time of 3-4 months and "***expression submission***" with the approximated processing time of 1-2 months. For the latter category, the author must submit as standard submission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

Email: theclinicalacademia@gmail.com
Telephone: (+66) 086 964 2222
Official LINE: @thaimaf

Contents



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



1. General Principles

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

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

2. Reporting Guidelines

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

3. Manuscript Sections

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

a. Title Page

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

Article title. The title provides a distilled description of the complete article and should include information that, along with the Abstract, will make electronic retrieval of the article sensitive and specific. Reporting guidelines recommend and some journals require that information about the study design be a part of the title (particularly important for randomized trials and systematic reviews and meta-analyses). Some journals require a short title, usually no more than 40 characters (including letters and spaces) on the title page or as a separate entry in an electronic submission system. Electronic submission systems may restrict the number of characters in the title.
Author information: Each author's highest academic degrees should be listed, although some journals do not publish these. The name of the department(s) and institution(s) or organizations where the work should be attributed should be specified. Most electronic submission systems require that authors provide full contact information, including land mail and e-mail addresses, but the title page should list the corresponding authors' telephone and fax numbers and e-mail address. ICMJE encourages the listing of authors' Open Researcher and Contributor Identification (ORCID).

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

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

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

b. Abstract

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

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

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

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

c. Introduction

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

d. Methods

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

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

i. Selection and Description of Participants

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

ii. Technical Information

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

iii. Statistics

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

e. Results

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

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

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

f. Discussion

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

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

g. References

i. General Considerations Related to References

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

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

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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.

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

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

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

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

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

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

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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.

Oral ivermectin versus 0.5% topical malathion lotion in patients with head lice: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

Kasidet Jaroongjittanusonti [1], M.D.; Kasama Polyiam, [2] M.D.; Jirawat Pomchaiya [3], M.D.; Witchuda Siangloet [3], M.D.

[1]Srisaket Hospital, Thailand; [2]Khon Kaen Hospital, Thailand;
[3]Sakon nakhon hospital, Thailand.

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

ABSTRACT

OBJECTIVE
To compare the efficacy between oral ivermectin and 0.5% topical malathion lotion in patients with head lice infestation.

METHODS
We systematically and independently searched and reviewed by four reviewers. We searched seven sources including Trip Database, Pubmed, Google Scholar, UpToDate, the Cochrane Library, ClinicalTrials.gov and Scopus as well as the reference lists preliminary included article from searching. We included all relevant randomized controlled trial comparing efficacy of oral ivermectin and 0.5% topical malathion lotion.

RESULTS
We identified and included two randomized controlled trials with 892 patients with head lice infestation. The absence rate of live head lice on day 8 was not significantly different between using oral ivermectin and malathion lotion (relative risk [RR] 1.18; 95% confidence interval [CI], 0.62 to 2.07; I^2=96%). The absence rate of live head lice on day 15 was not significantly different between using two of them (RR 1.05; 95% CI, 0.92 to 1.21; I^2=80%). The absence rate of live head lice on day 29 was concluded that using oral ivermectin was statistically significant superior to absence rate of head lice using malathion lotion (RR 1.08; 95% CI, -1.04 to -1.13; I^2=0%). Any adverse events was not a statistically significant difference between using the two of them (RR 0.94; 95% CI, 0.74 to 1.20; I^2=0%). The following outcomes of comparing between oral ivermectin and malathion were concluded based on one study; serious adverse effects, adverse events the primary reason for discontinuation and treatment-related adverse events showed (RR 1.04; 95% CI, -0.07 to -16.62), (RR 1.46; 95% CI, 0.47 to -4.56) and (RR 0.70; 95% CI, 0.45 to -1.08), respectively.

CONCLUSION
There was no statistically significant difference in the absence rate of live head lice on day 8 between using oral ivermectin and malathion lotion.

INTRODUCTION

Head lice infestation is a worldwide problem affecting patients.[1–5] It is caused by head louse (Pediculus humanus capitis) that lives on human scalp.[6–10] This parasite is transmitted by direct contact with the hair by head-to-head contact of an infested person.[11–14] The most common hosts of head lice are elementary schoolchildren, pre-school children attending child care and the household members of infested children.[15-16]

Since 1980, oral ivermectin is an anti-parasite drug that applied to medical use for treating many types of parasites which is recommended, dose of 200-400 micrograms per kilogram, by the Centers for Disease Control and Prevention including head lice.[17–20] Other treatments include 1% permethrin lotion, 0.5% topical malathion lotion, 5% benzyl alcohol lotion, 0.9% suspension topical spinosad, 1% lindane shampoo, pyrethrin.[20–22] Each drug varies in effectiveness and side effects.[23] The pyrethroid insecticide, 1% permethrin, is the drug of choice for treating head lice recommended by Sanford Guide.[24-25] However, malathion which is an organophosphate insecticide increased the role of an alternative treatment due to permethrin drug resistance,[26] Still, the increasing of 0.5% malathion resistance has also been reported.[27] Findings regarding comparative effects between oral ivermectin and 0.5% topical malathion lotion are still controversial.[28-29] In this review we aim to compare the effects between oral ivermectin and malathion lotion rusing the systematic review approach.

METHODS

This is a systematic review to compare the efficacy between oral ivermectin and 0.5% topical malathion lotion in patients with head lice infestation.

SEARCH STRATEGIES

We systematically independently searched studies through electronic databases including trip database, pubmed, google scholar, clinicaltrials.gov, cochrane, scorpus and UpToDate using keywords of "head lice" or "pediculosis", "ivermectin", "malathion" as well as their synonyms. Medical subject heading search strategy was used in applicable databases.We also hand searched using the reference lists preliminary included articles.

INCLUSION CRITERIA

STUDY DESIGN

Our inclusion criteria comprised of any randomized controlled trials comparing between oral ivermectin and topical malathion lotion in patients with head lice infestation.

PARTICIPANT

Patients with head lice infestation diagnosed by combining the dry hair with a dedicated fine-toothed comb.

INTERVENTION

The intervention was ivermectin (at a dose of 200-400 micrograms per kilogram) given orally at day 1 and day 8.

Table 1. Characteristics of the included studies

Author (years)	Participants	Age (Years)	Results	Duration of trial (months)
Olivier Chosidow, et al 2010	N=812, all were positive combing hair with a dedicated fine-toothed comb. Male=106 (26.1%)	Median, 10 years; range, 7-14 years	Both single and two doses of oral ivermectin 200-400 micrograms per kilogram were superior to 0.5% malathion lotion in absence rate of live head lice at day 8 and day 15. The adverse effects were not a statistically significant difference between using oral ivermectin and malathion lotion.	6
Ahmad Nofal, et al 2010	N=80, all were positive combing hair with a dedicated fine-toothed comb. Male=24 (60%)	Range 6-14 years	Both single and two doses of oral ivermectin 200-400 micrograms per kilogram were not statistically significant difference to 0.5% malathion lotion in term of absence rate of live head lice at day 8 and day 15.	-

Table 2. Jadad score

Question	Olivier Chosidow, et al 2010	Ahmad Nofal, et al 2010
Was the study described as randomized ?	1	1
Was the method used to generate the sequence of randomization described and was it appropriate?	1	0
Was the study described as double blind ?	1	0
Was the method of double blind described and was it appropriate ?	1	0
Was there a description of withdrawals and dropouts ?	1	1
Score	5	2

COMPARISON

The comparison intervention was 0.5% malathion lotion applied dry hair patients until all the hair and scalp were thoroughly moistened then leave for 10 to 12 hours after that washed the hair with the mild shampoo provided by the investigation team in a treatment kit and to rinse as usual at day 1 and 8.

OUTCOMES

All treatment outcomes including beneficial and adverse effects were included. We did not exclude any outcomes.

EXCLUSION CRITERIA

We excluded those were duplicated, irrelevant titles and abstracts to head lice and guidelines. The remaining studies were included in the analysis.

QUALITY OF REPORTING AND RISK OF BIAS

We evaluated quality and risk of bias of the included studies using Jadad score and the Cochrane risk of bias tool regarding the domain based-evaluation; random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment,

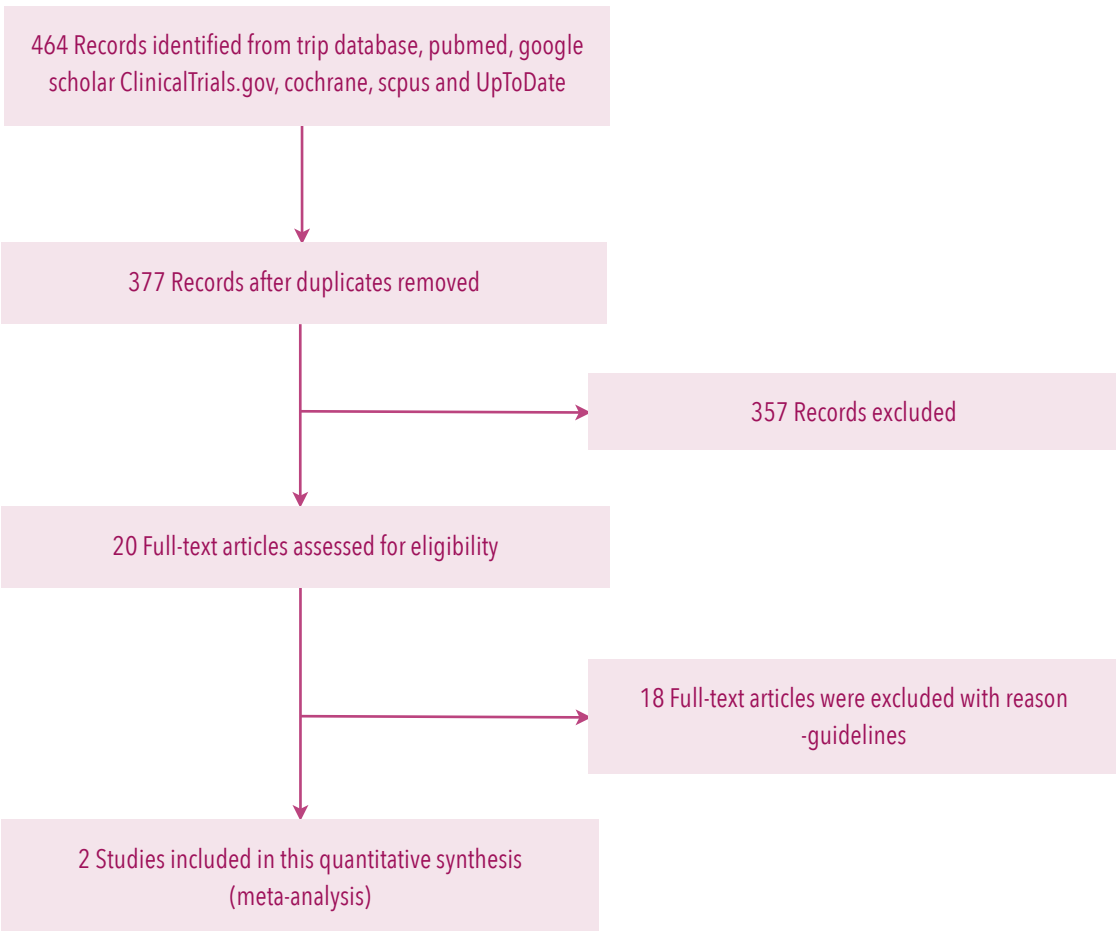

Figure 1. Diagram presents inclusion and exclusion journal in this study

incomplete outcome data, selective reporting and other biases. These presence or absence of these biases were used to classify each study into three groups; low risk, high risk and unclear risk of bias regarding the tool.

DATA EXTRACTION

We extracted data from the included studies regarding authors, number of participants, duration of each study, intervention, comparison and outcomes.

DATA ANALYSES

We calculated relative risk (RR) with 95% confidence interval (CI). All data were analyzed with Review Manager 5.3 statistical software to assess the effects of oral ivermectin and 0.5% malathion lotion at any doses in term of the absence rate of live head lice of patients with head lice infestation at day 1, day 8 and day 29. The chi-square and I^2 were used for evaluating heterogeneity, if $P<0.05$ or I^2 was higher than 50%, the heterogeneity was considered significant. We used a fixed effect and

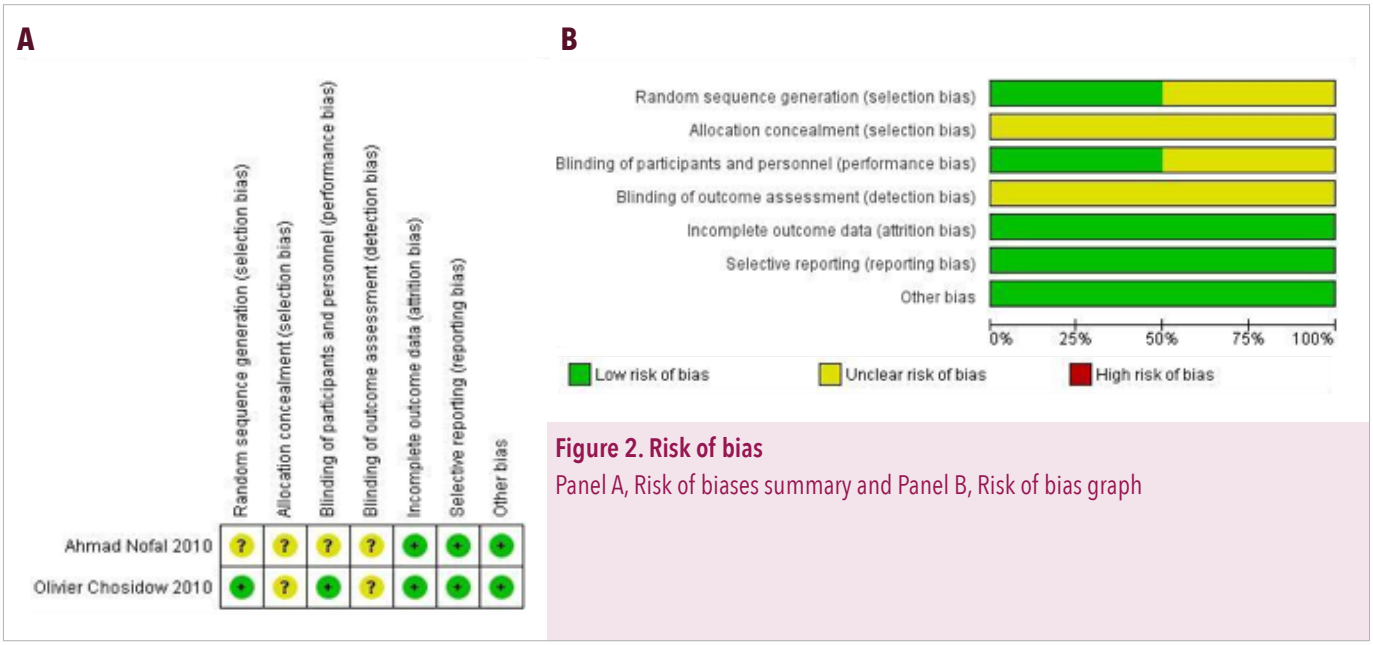

Figure 2. Risk of bias
Panel A, Risk of biases summary and Panel B, Risk of bias graph

random effect model for meta-analysis. We created funnel plot to identify potential of publication bias.

RESULTS

STUDY CHARACTERISTICS

We identified 464 records, out of which 87 were duplicates. Of the remain 377, 357 were excluded because their titles were irrelevant. Of the remaining 30, 18 records were excluded because they were guideline. The remaining two records were included in the meta-analysis (Figure 1). Both trials compared oral ivermectin and topical malathion lotion in those with head lice. Table 1 shows characteristics of the included studies.

ASSESSING RISK OF BIAS

The two studies were assessed using Jadad score and the Cochrane Collaboration's tool for assessing risk of bias. One trial was assessed as having scores of 5 from the Jadad score while another study was scored 2 (Table 2). For the Cochrane Collaboration's tool, risk of bias was summarized in Figure 2 and Figure 2.

RANDOM SEQUENCE GENERATION

Olivier Chosidow, et al 2010's study was reported the methods of random sequence.

ALLOCATION CONCEALMENT

Both studies did not report details on concealing patient allocation.

BLINDING OF PARTICIPANTS AND PERSONNEL

Olivier Chosidow, et al 2010's study was blinded participant but Ahmad Nofal, et al 2010's did not report details on blinding of participants and personnel.

BLINDING OF OUTCOME ASSESSMENT

Both studies did not described on blinding of outcome assessors.

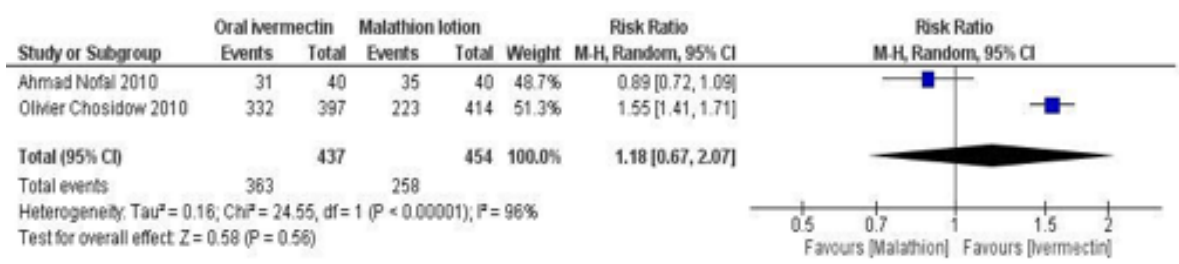

Figure 3. Forest plot: Oral Ivermectin versus 0.5% Topical Malathion Lotion, outcome: 1.1 Absence rate of live head lice at day 8.

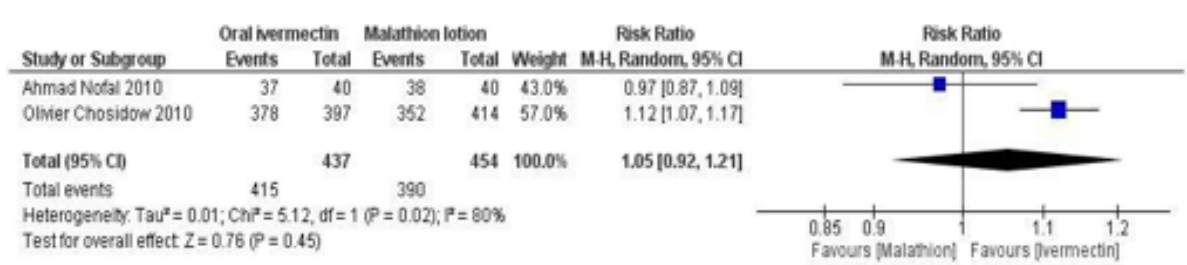

Figure 4. Forest plot: Oral Ivermectin versus 0.5% Topical Malathion Lotion, outcome: 1.2 Absence rate of live head lice at day 15.

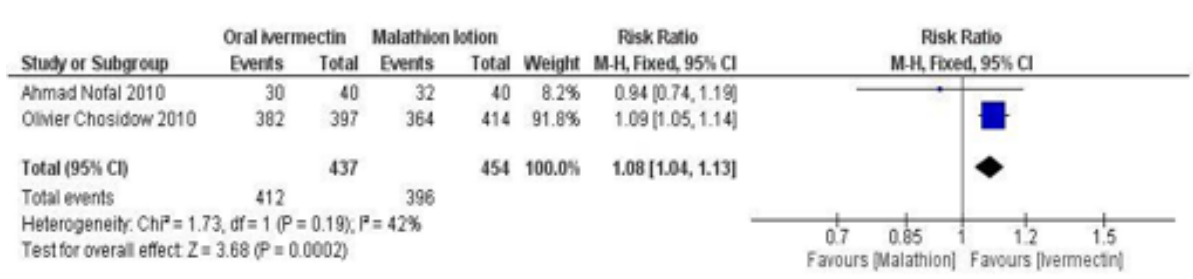

Figure 5. Forest plot: Oral Ivermectin versus 0.5% Topical Malathion Lotion, outcome: 1.3 Absence rate of live head lice at day 29.

INCOMPLETE OUTCOME DATA

Both of the included studies had the low risk of bias.

SELECTIVE REPORTING

Both studies properly described all relevant data and information regarding the interventions and were classified as low risk of bias.

OTHER POTENTIAL

Both studies had no potential conflict of interest were classified as low risk.

THE PRIMARY OUTCOME

THE ABSENCE RATE OF LIVE HEAD LICE ON DAY 8

The absence rate of live head lice on day 8 was concluded based on the two studies and there was

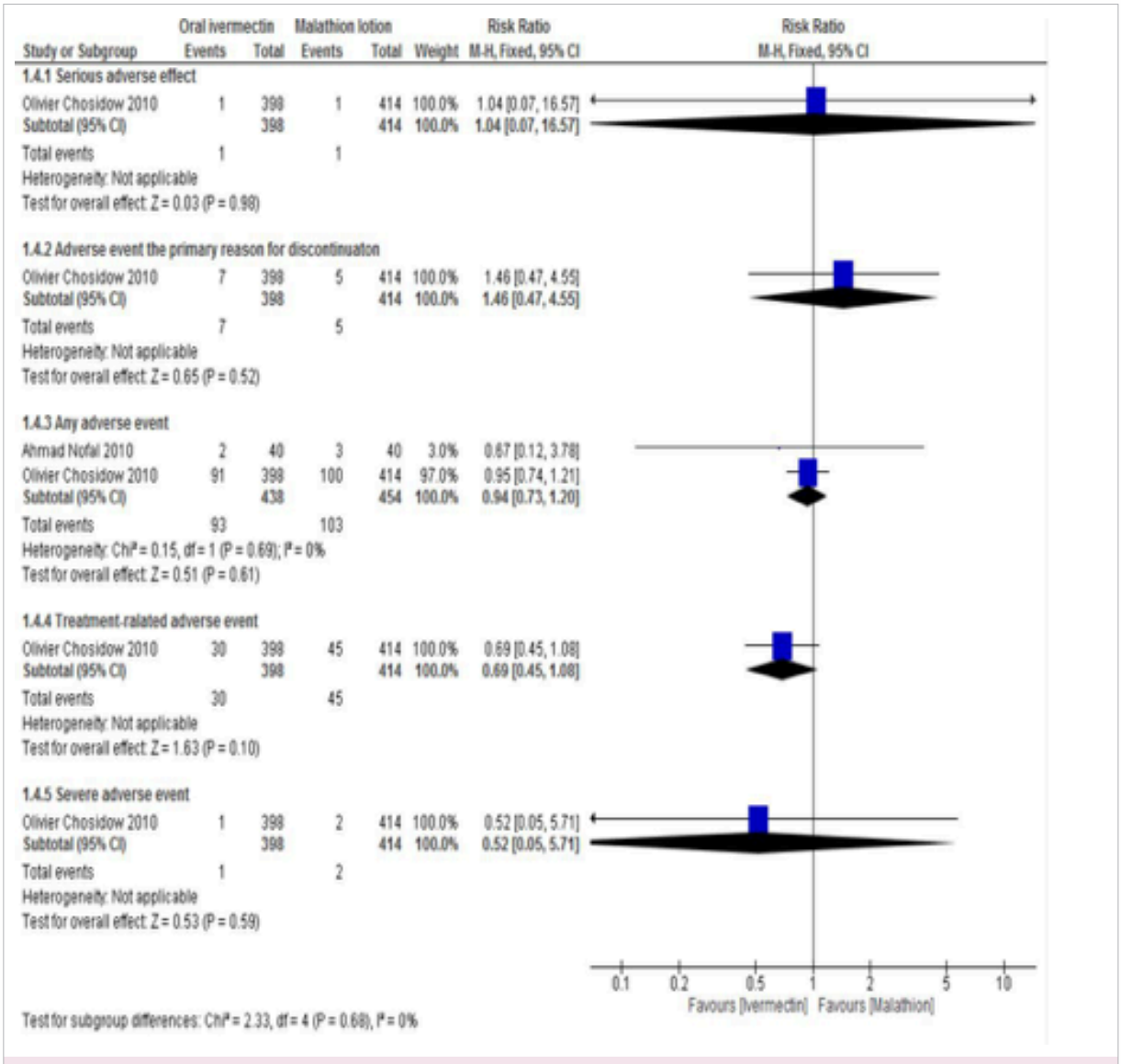

Figure 6. Forest plot: Oral Ivermectin versus 0.5% Topical Malathion Lotion, outcome: 1.4 Adverse effect.

not a significantly different between using oral ivermectin and malathion lotion (RR 1.18; 95% CI, 0.62 to 2.07, random effect model, I^2=96%.) (Figure 3).

THE SECONDARY OUTCOMES

THE ABSENCE OF LIVE HEAD LICE ON DAY 15

The absence rate of live head lice on day 15 was concluded based on the two studies that was not a statistically significant difference between using oral ivermectin and malathion lotion (RR 1.05; 95% CI, 0.92 to 1.21, random effect model, I^2=80%.) (Figure 4).

THE ABSENCE OF LIVE HEAD LICE ON DAY 29

The absence rate of live head lice on day 29 was concluded based on the two studies that using oral ivermectin was superior to using malathion lotion

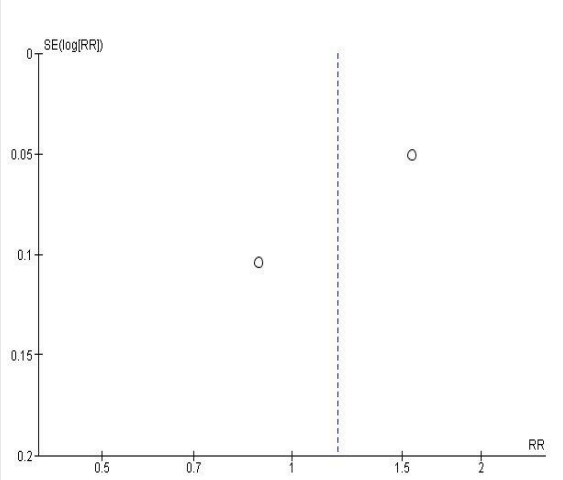

Figure 7. Funnel plot: Oral Ivermectin versus 0.5% Topical Malathion Lotion, outcome: 1.1 Absence rate of live head lice at day 8.

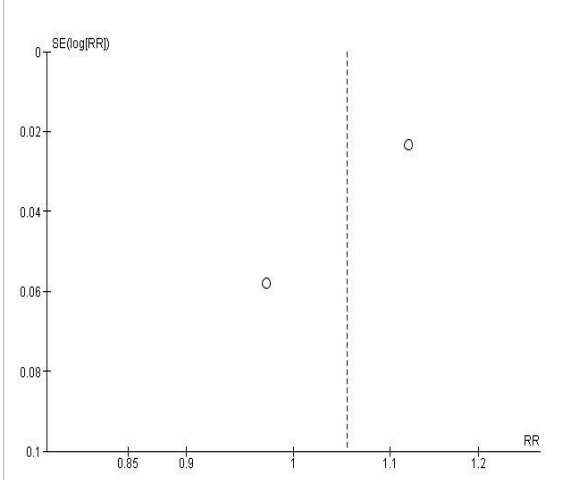

Figure 8. Funnel plot: Oral Ivermectin versus 0.5% Topical Malathion Lotion, outcome: 1.2 Absence rate of live head lice at day 15.

(RR 1.08; 95% CI, -1.04 to -1.13, fixed--effect model, I^2=42%.) (Figure 5).

ANY ADVERSE EVENTS

Any adverse events were concluded based on the two studies that was not a statistically significant difference between using oral ivermectin and malathion lotion (RR 0.94; 95% CI, 0.74 to 1.20, fixed-effect model, I^2=0%) (Figure 6).

SERIOUS ADVERSE EFFECT

Serious adverse effecs were concluded based on one study that there was not a statistically significant difference between using oral ivermectin and malathion lotion (RR 1.04; 95% CI, -0.07 to -16.62) (Figure 6).

ADVERS EVENTS AS THE PRIMARY REASON FOR DISCONTINUATION

Adverse events as the primary reason for discontinuation was concluded based on one study that was not a statistically significant difference between using oral ivermectin and malathion lotion (RR 1.46; 95% CI, 0.47 to -4.56) (Figure 6).

TREATMENT-RELATED ADVERSE EVENTS

Treatment-related adverse events was concluded based on one study that was not a statistically significant difference between using oral ivermectin and malathion lotion (RR 0.70; 95% CI, 0.45 to -1.08) (Figure 6).

DISCUSSION

IMPLICATIONS OF THE FINDINGS

Our systematic review shows that using oral ivermectin and malathion lotion have similar rates of eradicating live head lice on day 8. The outcomes of these two studies also have high heterogeneity (I^2 >50). Therefore, this data should be used carefully in clinical practice. There was not a statistically significant difference in the absence of live head lice on day 15 or adverse events. However, we found that using oral ivermectin was

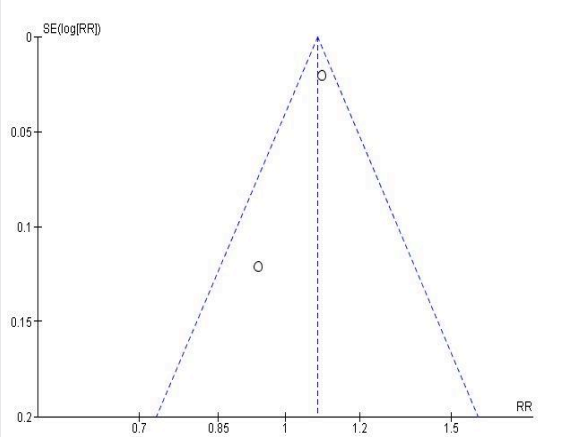

Figure 9. Funnel plot: Oral Ivermectin versus 0.5% Topical Malathion Lotion, outcome: 1.3 Absence rate of live head lice at day 29.

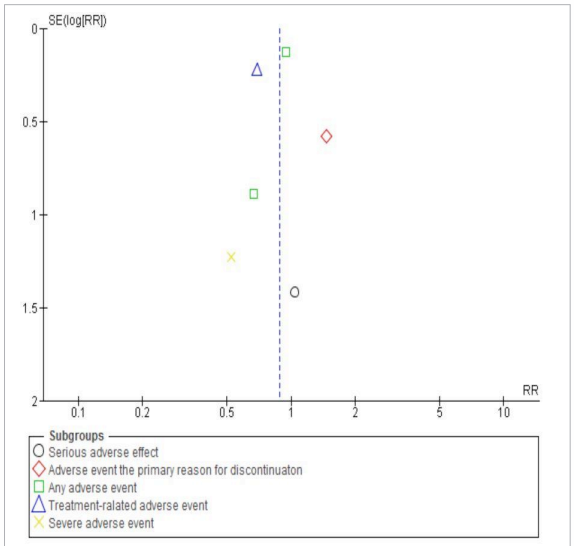

Figure 10. Funnel plot: Oral Ivermectin versus 0.5% Topical Malathion Lotion, outcome: 1.4 Adverse effect.

statistically significant in the removal of live head lice on day 29 compared to malathion lotion. Only one randomized controlled trial assessed serious adverse effects, which are the primary reason for discontinuation of treatment. Treatment-related adverse events showed no statistically significant difference between the two treatments. Therefore, this systematic review should help doctors choose the most appropriate way of treatment regardless of effectiveness and side effects that differentiate oral ivermectin and 0.5% malathion. The following outcomes, absence of live head lice day 8 and day 29 from funnel plots were symmetrical that showed no publication bias. The absence rate of live head lice day 29 displayed an asymmetrical funnel plot showing publication bias that negative data did not report in the studies.

CLINICAL IMPLICATIONS

This systematic review found no difference between efficacies and adverse effect of oral ivermectin and malathion lotion that helped to decide and select appropriate drugs for individual patients. Therefore, compliance, facility to using, avoiding drug resistance, and cost of drugs should be used carefully as decision making tools in clinical practice. Our systematic review shows no statistically significant difference between using oral ivermectin and malathion lotion in absence of live head lice on day 8, day 15, and adverse effects were similar to one RCT (Ahmad Nofal, et al 2010). We found a statistically significant superior to using oral ivermectin in absence of live head lice on day 29 that was similar to another RCT (Olivier Chosidow, et al 2010). We have not found any cohort studies or case control studies in comparing oral ivermectin and 0.5% malathion in eradicating live head lice or adverse effect. We found only one literature review associating with our study. Our systematic review is different from the literature

review, (Health technology assessment 2010) as they had only one RCT (Olivier Chosidow, et al 2010) comparing the efficacy of oral ivermectin and malathion lotion. Moreover, our study includes two randomized controlled trials used to determine the best decisions in treating head lice.

STRENGTHS AND LIMITATIONS OF THE SYSTEMATIC REVIEW

The studies included in our systematic review had different durations of follow up. One study did not describe the time of follow up and another study included sixth months of follow up. Nevertheless, the outcomes of the two studies were similar, in the absence rate of live head lice on day 8, day 15 and day 28. This increases the reliability of our systematic review. Our systematic review assessed the risk of bias using the Jadad Score and the Cochrane Collaboration's Tool. We included studies that were determined to be high quality with low risk of bias, further increasing the validity of our results. In these two studies, there were two unclear risks of bias in allocation concealment and blinding of outcome assessment. One of the studies had an unclear risk of bias in blinding participants and random sequence generation. The other biases of two studies were classified as low risk bias. Our studies had different secondary outcomes; however, both studies were randomized and maintained balanced baseline characteristics of participants in each group. We found a few RCTs that were combined in a systematic review to compare efficacies and adverse effects of oral ivermectin and malathion lotion. The two studies had many difference of sample sizes which result could be either ways, according to the poor quality of the study design or the analysis from the assessors.

CONCLUSION

There was not a statistically significant difference in the absence of live head lice on day 8 and 15, adverse events, serious adverse effects, adverse events as the primary reason for discontinuation, and treatment-related adverse events between using oral ivermectin and malathion lotion. However, using oral ivermectin showed a statistically significant improvement compared to malathion lotion in the absence of live head lice on day 29. In future research, we suggest having RCTs with a clearer study design, methods, and assessment of efficacies and adverse effects.

ACKNOWLEDGMENTS & DECLARATION

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COMPETING INTERESTS: This study has no competing on interest.
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REFERENCES

1. Meinking TL, Serrano L, Hard B, et al. COmparative in vitro pediculicidal efficacy of treatments in a resistant head lice population in the united states. Arch Dermatol. 2002 Feb 1;138(2):220–4.
2. Abdel-Ghaffar F, Al-Quraishy S, Al-Rasheid KAS, Mehlhorn H. Efficacy of a single treatment of head lice with a neem seed extract: an in vivo and in vitro study on nits and motile stages. Parasitol Res. 2011 Jun 11;110(1):277–80.
3. İnanir I, Şahin MT, Gündüz K, Dinç G, Türel A, Öztürkcan S. Prevalence of Skin Conditions in Primary School Children in Turkey: Differences Based on Socioeconomic Factors. Pediatr Dermatol. 2002 Jul 1;19(4): 307–11.
4. Silva L, Alencar R de A, Madeira NG. Survey assessment of parental perceptions regarding head lice. Int J Dermatol. 2008 Mar 1;47(3):249–55.
5. Hunter JA, Barker SC. Susceptibility of head lice (Pediculus humanus capitis). Parasitol Res. 2003 Jun 26;90(6):476–8.
6. Burkhart CG, Burkhart CN, Burkhart KM. An assessment of topical and oral prescription and over-the-counter treatments for head lice. J Am Acad Dermatol. 1998 Jun;38(6):979–82.
7. An assessment of topical and oral prescription and over-the-counter treatments for head lice [Internet]. [cited 2016 Jun 22]. Available from: http://www.sciencedirect.com/science/article/pii/S019096229870163X
8. Head Lice Infestation: Single Drug Versus Combination Therapy With One Percent Permethrin and Trimethoprim/Sulfamethoxazole | ELECTRONIC ARTICLE | Pediatrics [Internet]. [cited 2016 Jun 22]. Available from: http://pediatrics.aappublications.org/content/107/3/e30
9. Mumcuoglu DKY. Prevention and Treatment of Head Lice in Children. Pediatr Drugs. 2012 Nov 27;1(3):211–8.
10. Therapy for Head Lice Based on Life Cycle, Resistance, and Safety Considerations | Review Articles | Pediatrics [Internet]. [cited 2016 Jun 22]. Available from: http://pediatrics.aappublications.org/content/119/5/965
11. Canyon D, Speare R. Do head lice spread in swimming pools? Int J Dermatol. 2007 Nov 1;46(11):1211–3.
12. Jones KN, English JC. Review of Common Therapeutic Options in the United States for the Treatment of Pediculosis Capitis. Clin Infect Dis. 2003 Jun 1;36(11): 1355–61.
13. Takano-Lee M, Edman JD, Mullens BA, Clark JM. Transmission potential of the human head louse, Pediculus capitis (Anoplura: Pediculidae). Int J Dermatol. 2005 Oct 1;44(10):811–6.
14. Wolf R, Davidovici B. Treatment of scabies and pediculosis: Facts and controversies. Clin Dermatol. 2010 Sep; 28(5):511–8.
15. Borges R, Mendes J. Epidemiological Aspects of Head Lice in Children Attending Day Care Centres, Urban and Rural Schools in Uberlândia, Central Brazil. Mem Inst Oswaldo Cruz. 2002 Mar;97(2):189–92.
16. Speare R, Buettner PG. Head lice in pupils of a primary school in Australia and implications for control. Int J Dermatol. 1999 Apr 1;38(4):285–90.
17. Encyclopedia of Parasitology | Heinz Mehlhorn | Springer [Internet]. [cited 2016 Jun 22]. Available from: http://www.springer.com/us/book/9783540489948
18. Children ID in, Bell S 2012Edward A, PharmD, BCPS. Head lice pharmacotherapy update for school year 2012-2013 [Internet]. [cited 2016 Jun 22]. Available from: http://www.healio.com/pediatrics/practice-management/news/print/infectious-diseases-in-children/%7B09d6fca6-5c75-4e36-875d-becf310afa95%7D/head-lice-pharmacotherapy-update-for-school-year-2012-2013
19. The Prevention and Treatment of Head Lice in Children [Internet]. Medscape. [cited 2016 Jun 22]. Available from: http://www.medscape.com/viewarticle/761664
20. Diamantis SA, Morrell DS, Burkhart CN. Treatment of head lice. Dermatol Ther. 2009 Jul 1;22(4):273–8.
21. Villegas SC, Breitzka RL. Head Lice and the Use of Spinosad. Clin Ther. 2012 Jan; 34(1):14–23.
22. Eisenhower C, Farrington EA. Advancements in the Treatment of Head Lice in Pediatrics. J Pediatr Health Care. 2012 Nov;26(6):451–61.
23. Pediculicides and Scabicides Drug Class Review [Internet]. [cited 2016 Jun 22]. Available from: http://webcache.googleusercontent.com/search?q=cache:DAUWlySNnloJ:www.health.utah.gov/pharmacy/ptcommittee/files/Criteria%2520Review%2520Documents/01.14/Pediculicides%2520and%2520Scabicides%2520Drug%2520Class%2520Review.pdf+&cd=1&hl=th&ct=clnk&gl=th
24. Prevention C-C for DC and. CDC - Lice - Head Lice - Treatment [Internet]. [cited 2016 Jun 22]. Available from: http://www.cdc.gov/parasites/lice/head/treatment.html
25. Lice Quyen Vu 03-08-12.doc [Internet]. [cited 2016 Jun 22]. Available from: https://view.officeapps.live.com/op/view.aspx?src=http://web.stanford.edu/group/parasites/ParaSites2012/Ectoparasites%20Lice%20Quyen%20Vu/Lice%20Quyen%20Vu%2003-08-12.doc
26. Kristensen M, Knorr M, Rasmussen A-M, Jespersen JB. Survey of Permethrin and Malathion Resistance in Human Head Lice Populations from Denmark. J Med Entomol. 2006 May 1;43(3):533–8.
27. Meinking TL, Vicaria M, Eyerdam DH, Villar ME, Reyna S, Suarez G. Efficacy of a

Reduced Application Time of Ovide Lotion (0.5% Malathion) Compared to Nix Creme Rinse (1% Permethrin) for the Treatment of Head Lice. Pediatric Dermatology. 2004;21(6):670–4.

28. Chosidow O, Giraudeau B, Cottrell J, Izri A, Hofmann R, Mann SG, et al. Oral Ivermectin versus Malathion Lotion for Difficult-to-Treat Head Lice. N Engl J Med. 2010 Mar 11;362(10):896–905.

29. Nofal A. Oral ivermectin for head lice: a comparison with 0.5 % topical malathion lotion. JDDG: Journal der Deutschen Dermatologischen Gesellschaft. 2010;8(12):985–8.

Effects of oxytocin in different solutions on cord plasma bilirubin levels: systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

Kittiphum Vejsitthangkul[1], M.D.; Pimprapa Muenpirom[2], M.D.; Khakhanang Chantarayotha[3], M.D.; Benjaporn Namyotee[3], M.D.

[1]Udon Thani Hospital, Thailand; [2]Roi Et Hospital, Thailand; [3]Khon Kaen Hospital, Thailand.

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

ABSTRACT

OBJECTIVE

To identify the effects of oxytocin in different solutions on cord plasma bilirubin levels.

METHODS

We searched systematically for studies through PubMed, the Cochrane Library, Scopus, Clinicaltrials.gov, Trip Database and Google Scholar as well as hand-searching to identify relevant randomized controlled trials (RCTs) that compared the cord plasma bilirubin levels of solutions of oxytocin infusion in 5% glucose in water and in 0.9% NaCl solution as the primary outcome. The secondary outcomes included their effects on neonatal plasma bilirubin levels day 2-3 and cord plasma sodium levels.

RESULTS

We identified and included two RCTs with 269 full-term pregnant women with singleton pregnancy. Cord plasma bilirubin levels was not significantly different between using oxytocin in either 5% glucose in water or 0.9% NaCl solution (mean difference (MD), -0.03; 95% confidence interval (CI) [-0.52 to 0.46], I^2=93%). Neonatal plasma bilirubin levels in day 2-3 was also not significantly different between using oxytocin in either 5% glucose in water or 0.9% NaCl solution (MD, 0.27; 95% CI, [-1.59 to 2.13], I^2=97%). Cord plasma sodium levels of using oxytocin in 5% glucose in water was significantly lower than that of in 0.9% NaCl solution group (MD, -2.00; 95% CI, [-3.57 to -0.44], I^2=95%).

CONCLUSION

There was no statistically significant difference in cord plasma bilirubin levels between using oxytocin in 5% glucose in water and in 0.9% NaCl solution.

BACKGROUND

Induction of labor is a procedure that stimulates uterine contractions during pregnancy, then labor begins later and leads to a vaginal childbirth.[1,2] In 2006, It accounted for 22.5% of the total labor in United States.[3] Nowaday, we have many methods used for induction of labor such as breast stimulation, amniotomy, membrane stripping and using synthetic oxytocin.[2,4] Oxytocin is widely used in obstetrics not only to induce labor, but it is also used for augmentation of labor and postpartum hemorrhage prevention.[7-10] In the Southern Sweden, oxytocin was used in 33.2% of pregnant women for induction of labor between 2001 and 2002.[6]

Oxytocin has antidiuretic hormone-like effect that increases the permeability to water of the cell membrane and increases red blood cell fragility.[5,6] Oxytocin-induced labor is associated with increasing adverse effects in neonates such as hyponatremia, neonatal seizures and retinal hemorrhage.[11-13] Using oxytocin for induction of labor was reported as one of the factors that causes neonatal hyperbilirubinemia,[14,15] one of the most common medical problems in 50% term infants that leads to neurotoxicity in severe condition.[16,17]

Oxytocin can be diluted in either 5% glucose in water or 0.9% NaCl solution before administration.[18-20] In 1993, a Nigerian RCT with 164 pregnant women reported that cord plasma bilirubin level was significantly higher in infants of mothers with oxytocin in 5% glucose in water than those with 0.9% NaCl solution and the control group; without any intravenous fluid infusion and oxytocin.[21] However, another Turkish RCT in 2003 reported that cord plasma bilirubin levels in 105 infants was not statistically different among the three groups, oxytocin in 5% glucose in water group, oxytocin in 0.9% NaCl solution group and control group; without any intravenous fluid infusion and oxytocin.[22] Regarding the controversy mentioned above, the aim of this systematic review is to determine the effects of oxytocin in 5% glucose in water and in 0.9% NaCl solution on cord plasma bilirubin levels.

METHODS

This study is a systematic review to determine the effects of oxytocin in different solutions on cord plasma bilirubin levels. It was conducted according to Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 and followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[23,24]

DATA SOURCES

We searched systematically for studies through PubMed, the Cochrane Library, Scopus, Clinicaltrials.gov, Trip Database and Google Scholar to identify the articles. Searching in Pubmed and the Cochrane Library were undertaken using MeSH terms: (i) "jaundice, neonatal" OR "hyperbilirubinemia, neonatal" AND "oxytocin" AND "solution" OR "diluent", (ii) "neonatal" AND "bilirubin" AND "oxytocin" AND "solution" OR "diluent". We used PICO search to identify articles in Trip database ("oxytocin" AND "solution" OR "dilution for I, "neonatal serum bilirubin" OR "neonatal jaundice" OR "neonatal hyperbilirubinemia" for O, no filling for P and C) and we used various combinations of following keywords in the other databases: neonatal,

Table 1. Characteristics of included studies

First author's name	Year	Country	During of trial	Number of participants			Cord blood					
				5% glucose in water	0.9% NaCl solution	Control group	Mean neonatal plasma bilirubin (SD)			Mean neonatal plasma sodium(SD)		
							5% glucose in water	0.9% NaCl solution	Control group	5% glucose in water	0.9% NaCl solution	Control group
A.O. Omigbodun	1993	Nigeria	N/A	40	42	82						
Day 0							1.0 (0.7)	0.8 (0.5)	0.8 (0.5)	130.1 (6.5)	132.9 (4.2)	132.5 (6.3)
Day 2-3							5.8 (3.9)	4.6 (2.7)	4.4 (2.7)	N/A	N/A	N/A
Engin Oral	2003	Turkey	January to December in 1995.	36	29	40						
Day 0							1.6 (0.8)	1.9 (0.9)	1.7 (0.5)	139.8 (5.9)	141.0 (4.7)	140.0 (3.6)
Day 2-3							5.2 (2.0)	5.9 (3.1)	6.82 (3.2)	N/A	N/A	N/A

bilirubin, neonatal jaundice, neonatal hyperbilirubinemia, oxytocin, solution and diluent. We latter performed hand-searching by exploring references of the preliminary included articles from database searching and manually searched for additional relevant studies.

STUDY SELECTION

The selection of identified articles included two steps. For the first step, we screened titles and abstracts by four independent reviewers. The second step, all selected articles were read in full text by four reviewers then we assessed and selected studies by inclusion criteria and exclusion criteria for using data in this systematic review. Controversies among the four reviewers were resolved by consensus of the fifth author.

INCLUSION CRITERIA

STUDY DESIGN

We included all RCTs comparing the cord plasma bilirubin levels of the infants of the mothers using either oxytocin in 5% glucose in water or in 0.9% NaCl solution.

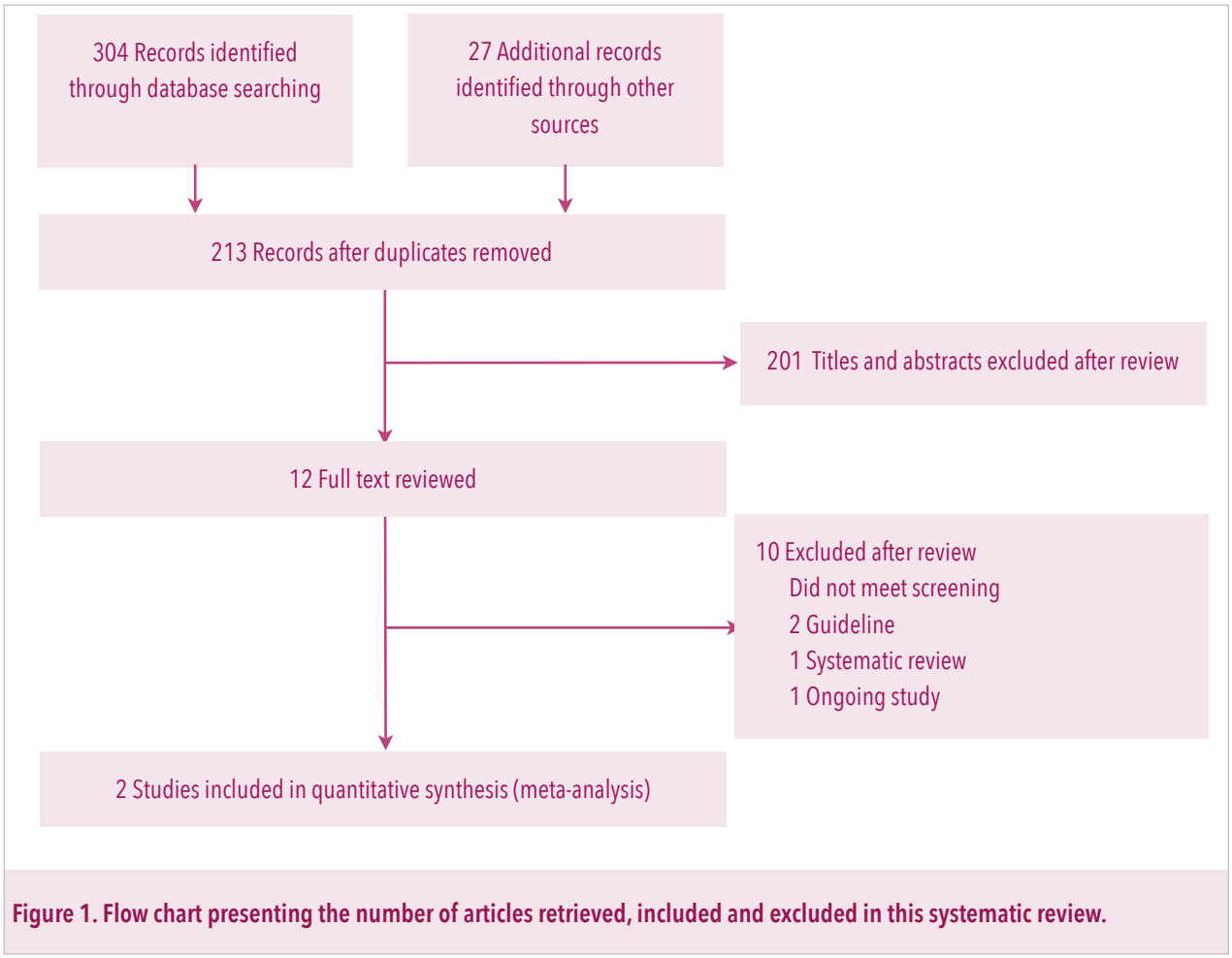

Figure 1. Flow chart presenting the number of articles retrieved, included and excluded in this systematic review.

PARTICIPANTS

The participants were pregnant women with gestational age 37 weeks or greater with singleton pregnancy.

INTERVENTIONS

Oxytocin diluted in either 5% glucose in water or in 0.9% NaCl solution.

CONTROLS

No any intravenous fluid solutions or oxytocin infusion.

OUTCOMES

The primary outcome was cord plasma bilirubin levels of the infants and the secondary outcomes were neonatal plasma bilirubin levels in day 2-3 and cord plasma sodium levels of the infants.

EXCLUSION CRITERIA

We excluded studies with patients with hemolytic disease (e.g., glucose-6-phosphate dehydrogenase deficiency and Rhesus and ABO incompatibility), medical complication of pregnancy (e.g., hypertension, diabetes mellitus, pyrexia, jaundice

Table 2. Jadad Score

	A.O. Omigbodun et al., 1993	Engin Oral et al., 2003
Was the study described as randomized?	1	1
Was the method used to generate the sequence of randomization described and was it appropriate?	1	1
Was the study described as double-blind?	0	0
Was the method of double-blind described and was it appropriate?	0	0
Was there a description of withdrawals and dropouts?	1	1
Score	3	3

and anemia) and fetal problems (e.g., intrauterine growth restriction, macrosomia and fetal anomaly).

DATA EXTRACTION AND QUALITY ASSESSMENT

From each study, we extracted data regarding the first author's name, year of publication, country where the study was done, during of trial, number of participant, and outcome. We extracted data into simple standard forms. Four reviewers independently assessed the quality of the studies by using Jadad score and the Cochrane Collaboration's tool, recommended by Cochrane Handbook for Systematic Reviews of Interventions. [23] The Cochrane Collaboration's tool classifies the study's biases into three groups (low risk, high risk and unclear risk) and regards the following evaluation: random sequence generation, allocation concealment, blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data, selective reporting and other biases.

STATISTICAL ANALYSIS

All analyses were performed with Review Manager 5.3 statistical software to assess the effects of oxytocin in different solutions on cord plasma bilirubin levels. We calculated mean difference (MD) of discrepancies of all outcomes between 5% glucose in water and control group and that of between 0.9% NaCl solution and control group with 95% confidence interval (CI) for continuous data. The I^2 statistics were used to evaluate statistical heterogeneities across the studies. The statistical test of heterogeneity was significant if $P<0.1$ and heterogeneity was high if the I^2 statistics was more than 50%. We used a random-effect model for the meta-analysis when heterogeneity was statistical significance and also used a fixed-effect model when heterogeneity was not statistical significance. We created funnel plots showing the standard error and the effect size to identify the potential of publication bias in our review.

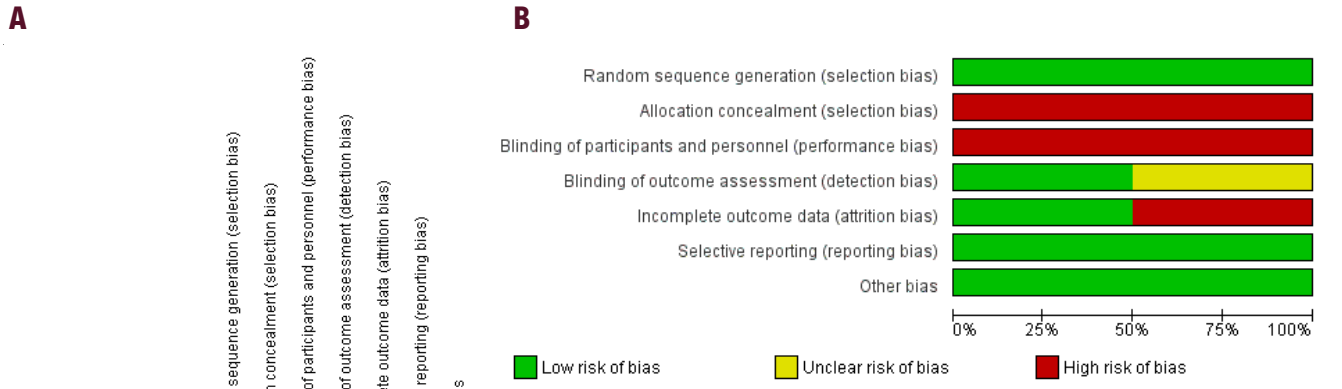

Figure 2. Risk of bias
Panel A, Risk of biases summary and Panel B, Risk of bias graph

RESULTS

STUDY CHARACTERISTICS

We identified 331 studies; 304 from database searching and 27 from hand-searching, 118 were excluded because they were duplicated (Figure 1). Of the remaining 213 studies, 201 were excluded because their titles and abstracts were not relevant to the diluents of oxytocin or neonatal bilirubin levels. Then, we reviewed 12 full texts and excluded ten studies; six did not meet screening criteria, two were guidelines, one was a systematic review and one was an ongoing trial. Finally, two eligible trials were included in our systematic review. The included two trials were set in Nigeria and Turkey and their characteristics were summarized in Table 1.

ASSESSING RISK OF BIAS

The two studies were assessed using Jadad score and the Cochrane Collaboration's tool for assessing risk of bias. One trial was assessed as having scores of 5 from the Jadad score while another study was scored 2 (Table 2). For the Cochrane Collaboration's tool, risk of bias was summarized in Figure 2.

RANDOM SEQUENCE GENERETION

Using the Cochrane Collaboration's tool for assessing risk of bias, both trials showed random sequence processes properly and were classified as "low risk".

ALLOCATION CONCEALMENT

Both trials did not show allocation concealment processes and were assumed to be open-label trials. They were classified as "high risk".

BLINDING OF PARTICIPANT AND PERSONNEL

Both trials were assumed to be open-label trials and were classified as "high risk"

BLINDING OF OUTCOME ASSESSMENT

The study in 1993 did not report details on blinding of the outcome assessment and was classified as "unclear" while another study stated

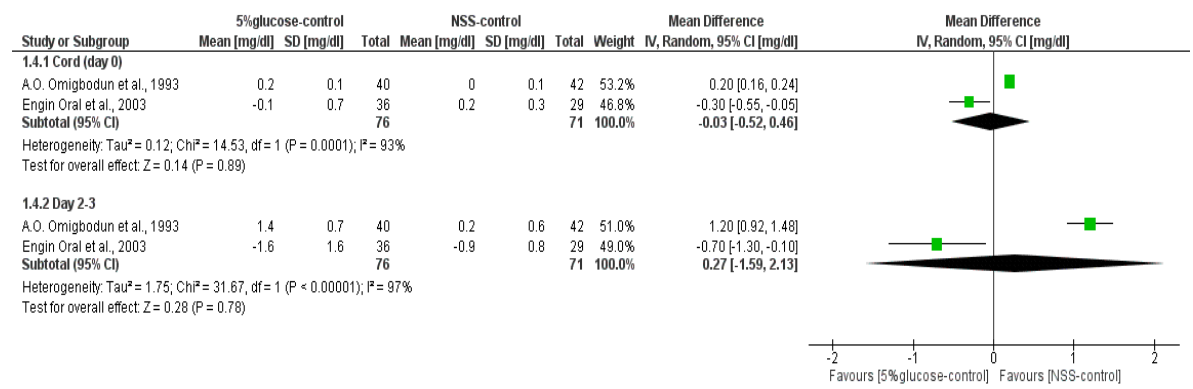

Figure 3. Estimates of mean differences of discrepancies on cord (day 0) and day 2-3 neonatal plasma bilirubin levels in 5% glucose in water and in 0.9% NaCl solution comparing with their controls.

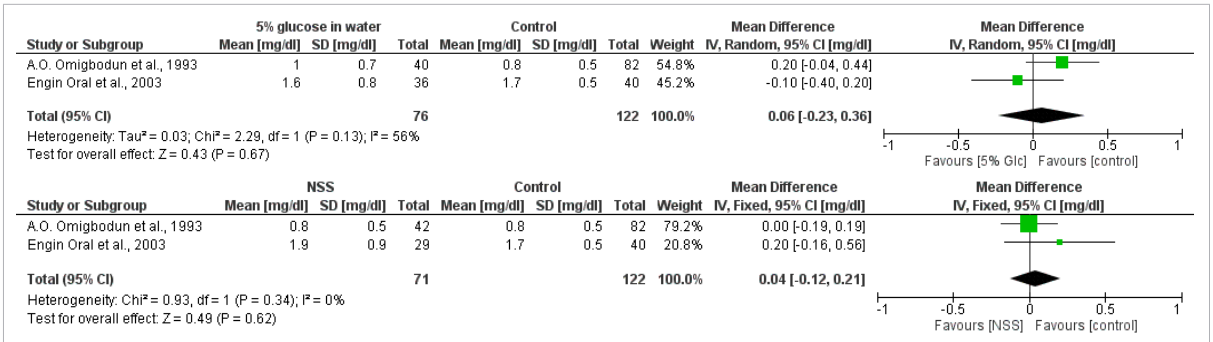

Figure 4. Estimates of discrepancies on cord (day 0) plasma bilirubin levels in 5% glucose in water and in 0.9% NaCl solution comparing with their controls.

the process properly and was classified as "low risk".

INCOMPLETE OUTCOME DATA

Both of the included studies properly described all data of the outcomes and were classified as low risk.

SELECTIVE REPORTING

Both studies described all outcomes properly and were classified as "low risk".

OTHER POTENTIAL SOURCES OF BIAS

Both studies had no potential conflict of interest were classified as "low risk".

PRIMARY OUTCOME

MEAN CORD PLASMA BILIRUBIN LEVELS

The meta-analysis of the two trials showed no statistically significant difference between using oxytocin in 5% glucose in water and oxytocin in 0.9% NaCl solution regarding discrepancies of cord plasma bilirubin levels between both solutions and their controls (MD -0.03; 95% CI [-0.52 to 0.46], random-effect model) (Figure 3). The heterogeneity was measured as having I^2 equal to 93%.

The meta-analysis of the two trials also showed no statistically significant difference between using oxytocin in 5% glucose in water and the control regarding mean difference of cord plasma bilirubin levels (MD 0.06; 95% CI [-0.23 to 0.36], random-

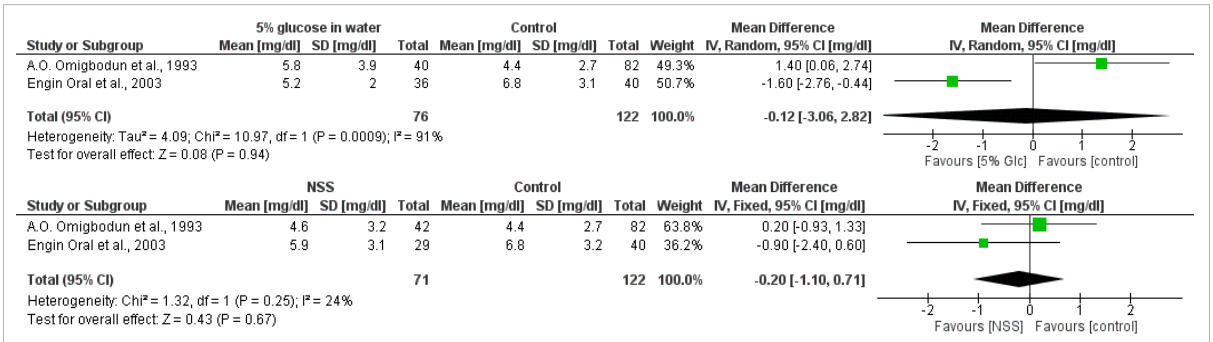

Figure 5. Estimates of discrepancies on day 2-3 neonatal plasma bilirubin levels in 5% glucose in water and in 0.9% NaCl solution comparing with their controls.

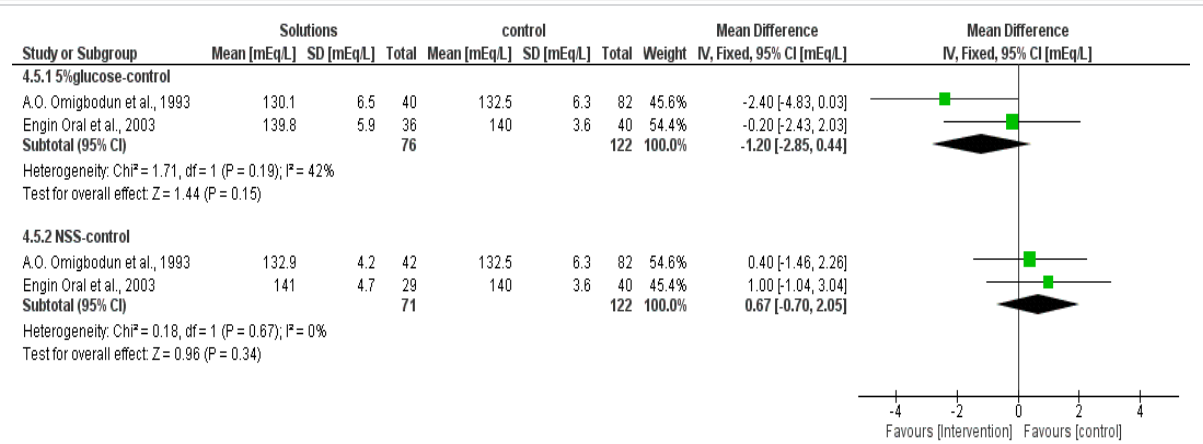

Figure 6. Estimates of mean differences of cord plasma sodium levels in 5% glucose in water and in 0.9% NaCl solution comparing with their controls.

effect model), the heterogeneity was measured as having I^2 equal to 56%, and it also showed that using oxytocin in 0.9% NaCl compared with the control had no statistically significant difference regarding mean difference of cord plasma bilirubin levels (MD 0.04; 95% CI [-0.12 to 0.21], fixed-effect model) (Figure 4), the heterogeneity was measured as having I^2 equal to 0%.

SECONDARY OUTCOMES

MEEN NEONATAL PLASMA BILIRUBIN LEVELS IN DAY 2-3

The meta-analysis of the two trials showed no statistically significant difference between using oxytocin in 5% glucose in water and oxytocin in 0.9% NaCl solution regarding discrepancies of neonatal plasma bilirubin levels in day 2-3 between both solutions and their controls (MD 0.27; 95% CI [-1.59 to 2.13], random-effect model) (Figure 3). The heterogeneity was measured as having I^2 equal to 97%.

The meta-analysis of the two trials also showed no statistically significant difference between using oxytocin in 5% glucose in water and the control regarding mean difference of neonatal plasma bilirubin levels in day 2-3 (MD -0.12; 95% CI [-3.06 to 2.82], random-effect model), the heterogeneity was measured as having I^2 equal to 91%, and it

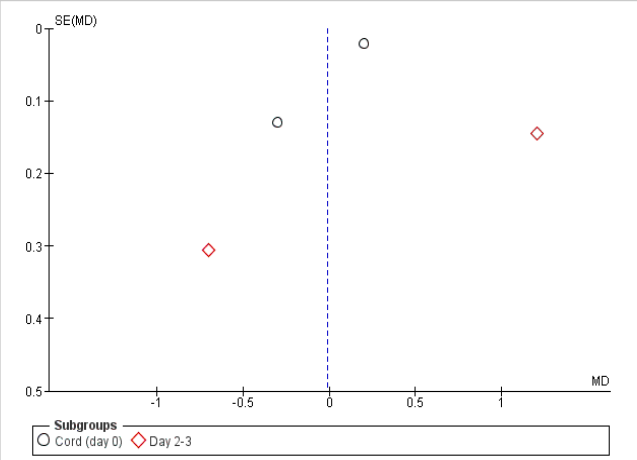

Figure 7. Funnel plot of comparison: mean differences of discrepancies on cord (day 0) and day 2-3 plasma bilirubin levels in both solutions comparing with the controls.

also showed that using oxytocin in 0.9% NaCl compared with the control had no statistically significant difference regarding mean difference of cord plasma bilirubin levels (MD -0.20; 95% CI [-1.10 to 0.71], fixed-effect model) (Figure 5), the heterogeneity was measured as having I^2 equal to 24%.

MEAN CORD PLASMA SODIUM LEVELS

The meta-analysis of the two trials showed that mean cord plasma sodium levels using oxytocin in 5% glucose in water compared with its control was not significantly reduced (MD -1.20; 95% CI [-2.85 to 0.44], fixed-effect model) (Figure 6), the heterogeneity was measured as having I^2 equal to 42%, while mean cord plasma sodium levels using oxytocin in 0.9% NaCl solution compared with its control was also not significantly reduced (MD 0.67; 95% CI [-0.70 to 2.05], fixed-effect model) (Figure 6), the heterogeneity was measured as having I^2 equal to 0%.

DISCUSSION

PRINCIPAL FINDINGS

Our systematic review showed that using oxytocin in 5% glucose in water and in 0.9% NaCl solution had similar effect on cord plasma bilirubin levels and neonatal plasma bilirubin levels in day 2-3. However, high heterogeneities were observed. Oxytocin in 5% glucose in water did not decrease cord plasma sodium levels compared with its control, and oxytocin in 0.9% NaCl solution did not decrease the cord plasma sodium levels compared with its control, either.

COMPARISON WITH OTHER STUDIES

We searched studies in many databases and we did not get cohort studies and case control studies associated with using oxytocin in different solutions and its effect. Our meta-analysis found that oxytocin in 5% glucose in water did not decrease cord plasma sodium levels. These findings contrasted with a previous RCT claimed that using oxytocin in 5% glucose in water decreased the cord plasma sodium levels,[26] the contrary might be due to that this RCT got 0 score from Jadad score (high risk of bias) and our study included two trials that had 3 score from Jadad score (fair risk of bias) and had more amount of participants, this RCT had 140 and our study had 269.

We also found that oxytocin in 0.9% NaCl solution did not decrease cord plasma sodium levels and a 1987's study reported that Hartmann's solution compared with control had no statistically significant difference on cord plasma sodium levels.[27] Thus, we assumed that the solutions had no effect on cord plasma sodium levels.

STRENGTHS AND LIMITATIONS

Our study was a systematic review, a high quality study design. To our knowledge, all relevants articles were identified. All processes of conducting the present review were followed the standard protocol of Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0.[23] Our review, however, had relatively small number of 269 participants from two studies that included in the meta-analysis. Both of the trials had fair quality after assessing for risk of bias using Jadad score, and limited quality using the Cochrane Collaboration's tool. Our outcomes regarding serum bilirubin had high heterogeneities. Thus, our conclusion can be definite.

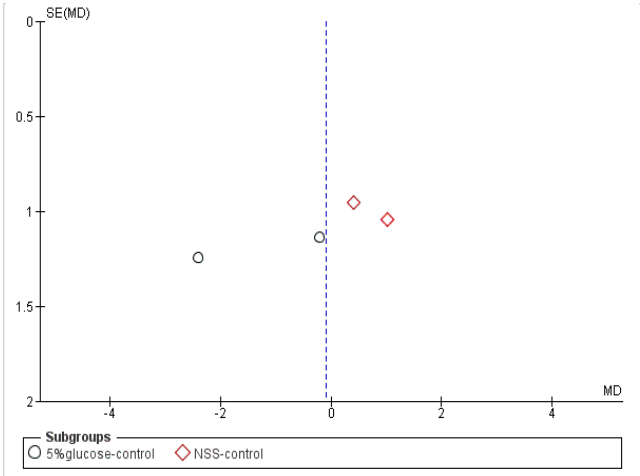

Figure 8. Funnel plot of comparison: mean differences of cord plasma sodium levels in both solutions comparing with the controls.

CONCLUSION

Oxytocin in 5% glucose in water and in 0.9% NaCl had no statistically significant difference in cord plasma bilirubin levels and neonatal plasma bilirubin levels in day 2-3. We also found that using oxytocin in 5% glucose in water and 0.9% NaCl solution had no statistically significant difference on cord plasma sodium levels compared with its own controls. However, our meta-analyses of the outcomes had high heterogeneities. Moreover, our systematic review was based on only two RCTs. Implication of our results should be careful. Further study should be a larger RCT regarding using oxytocin in these solutions for better estimation of their effects.

ACKNOWLEDGMENTS & DECLARATION

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COMPETING INTERESTS: This study has no competing on interest.
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REFERENCES

1. Labor induction - Mayo Clinic [Internet]. [cited 2016 Jul 7]. Available from: http://www.mayoclinic.org/tests-procedures/labor-induction/basics/definition/prc-20019032
2. ACOG Committee on Practice Bulletins -- Obstetrics. ACOG Practice Bulletin No. 107: Induction of labor. Obstet Gynecol 2009; 114:386.
3. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S, et al. Births: final data for 2006. Natl Vital Stat Rep 2009;57:1–102. (Level II-3)
4. Methods for Cervical Ripening and Induction of Labor - American Family Physician [Internet]. [cited 2016 Jul 16]. Available from: http://www.aafp.org/afp/2003/0515/p2123.html
5. V M Buckalew Jr, Gruber and KA. Natriuretic Hormone. Annual Review of Physiology. 1984;46(1):343–58.
6. Oscarsson ME, Amer-Wåhlin I, Rydhstroem H, Källén K. Outcome in obstetric care related to oxytocin use. A population-based study. Acta Obstet Gynecol Scand. 2006;85(9):1094–8.
7. Stanton C, Armbruster D, Knight R, Ariawan I, Gbangbade S, Getachew A, et al. Use of active management of the third stage of labour in seven developing countries. Bull World Health Organ. 2009 Mar;87(3):207–15.
8. Pitocin (oxytocin) dosing, indications, interactions, adverse effects, and more [Internet]. [cited 2016 Jul 16]. Available from: http://reference.medscape.com/drug/pitocin-oxytocin-343132#0
9. Pitocin (Oxytocin Injection) Drug Information: Medication Guide and Patient Information - Prescribing Information at RxList [Internet]. RxList. [cited 2016 Jul 16]. Available from: http://www.rxlist.com/pitocin-drug/medication-guide.htm
10. Postpartum Haemorrhage, Prevention and Management (Green-top Guideline No. 52) [Internet]. Royal College of Obstetricians & Gynaecologists. [cited 2016 Jul 16]. Available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg52/
11. Minchom P, Niswander K, Chalmers I, Dauncey M, Newcombe R, Elbourne D, et al. Antecedents and outcome of very early neonatal seizures in infants born at or after term. BJOG: An International Journal of Obstetrics & Gynaecology. 1987 May 1;94(5):431–9.
12. Schwartz RH, Jones RW. Transplacental hyponatraemia due to oxytocin. Br Med J. 1978 Jan 21;1(6106):152–3.
13. Schoenfeld A, Buckman G, Nissenkorn I, Cohen S, Ben-Sira I, Ovadia J. Retinal hemorrhages in the newborn following labor induced by oxytocin or dinoprostone. Arch Ophthalmol. 1985 Jul;103(7):932–4.
14. Beazley JM, Alderman B. Neonatal hyperbilirubinaemia following the use of oxytocin in labour. Br J Obstet Gynaecol. 1975 Apr;82(4):265–71.
15. Chew WC, Swann IL. Influence of simultaneous low amniotomy and oxytocin infusion and other maternal factors on neonatal jaundice: a prospective study. Br Med J. 1977 Jan 8;1(6053):72–3.
16. Evans D. Neonatal jaundice. BMJ Clin Evid [Internet]. 2007 Jun 1 [cited 2016 Jul 5];2007. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2943774/
17. Hyperbilirubinemia AS on N. Neonatal Jaundice and Kernicterus. Pediatrics. 2001 Sep 1;108(3):763–5.
18. Oxytocin 10 IU/ml Solution for infusion - Summary of Product Characteristics (SPC) - (eMC) [Internet]. [cited 2016 Jul 15]. Available from: https://www.medicines.org.uk/emc/medicine/30427
19. Pitocin - FDA prescribing information, side effects and uses [Internet]. [cited 2016 Jul 15]. Available from: https://www.drugs.com/pro/pitocin.html
20. UCLH Drug Guideline and Policy Documents [Internet]. [cited 2016 Jul 15]. Available from: http://www.uclhguide.com/public/guideline
21. Omigbodun AO, Akindele JA, Osotimehin BO, Fatinikun T, Fajimi JL, Adeleye JA. Effect of saline and glucose infusions of oxytocin on neonatal bilirubin levels. International Journal of Gynecology & Obstetrics. 1993 Mar 1;40(3):235–9.
22. Oral E, Gezer A, Çagdas A, Pakkal N. Oxytocin infusion in labor: the effect different indications and the use of different diluents on neonatal bilirubin levels. Arch Gynecol Obstet. 267(3):117–20.
23. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. [cited 2016 Jul 9]. Available from: http://handbook.cochrane.org/
24. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009 Jul 21;339:b2700.
25. Tylleskär J, Finnström O, Leijon I, Hedenskog S, Rydén G. Spontaneous Labor and Elective Induction—a Prospective Randomized Study. Acta Obstetricia et Gynecologica Scandinavica. 1979 Jan 1;58(6):513–8.
26. Singhi S, Chookang E, Hall JSE, Kalghatgi S. Iatrogenic neonatal and maternal hyponatraemia following oxytocin and aqueous glucose infusion during labour. BJOG: An International Journal of Obstetrics & Gynaecology. 1985 Apr 1;92(4):356–63.
27. Lao TTH, Loong EPL, Chin RKH. Intrapartum fluid administration and sodium concentration in maternal and umbilical cord plasma. European Journal of Obstetrics & Gynecology and Reproductive Biology. 1987 Aug 1;25(4):271–6.

Jul 15]. Available from: https://www.drugs.com/pro/pitocin.html

20. UCLH Drug Guideline and Policy Documents [Internet]. [cited 2016 Jul 15]. Available from: http://www.uclhguide.com/public/guideline

21. Omigbodun AO, Akindele JA, Osotimehin BO, Fatinikun T, Fajimi JL, Adeleye JA. Effect of saline and glucose infusions of oxytocin on neonatal bilirubin levels. International Journal of Gynecology & Obstetrics. 1993 Mar 1;40(3):235–9.

22. Oral E, Gezer A, Çagdas A, Pakkal N. Oxytocin infusion in labor: the effect different indications and the use of different diluents on neonatal bilirubin levels. Arch Gynecol Obstet. 267(3):117–20.

23. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. [cited 2016 Jul 9]. Available from: http://handbook.cochrane.org/

24. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009 Jul 21;339:b2700.

25. Tylleskär J, Finnström O, Leijon I, Hedenskog S, Rydén G. Spontaneous Labor and Elective Induction–a Prospective Randomized Study. Acta Obstetricia et Gynecologica Scandinavica. 1979 Jan 1;58(6):513–8.

26. Singhi S, Chookang E, Hall JSE, Kalghatgi S. Iatrogenic neonatal and maternal hyponatraemia following oxytocin and aqueous glucose infusion during labour. BJOG: An International Journal of Obstetrics & Gynaecology. 1985 Apr 1;92(4):356–63.

27. Lao TTH, Loong EPL, Chin RKH. Intrapartum fluid administration and sodium concentration in maternal and umbilical cord plasma. European Journal of Obstetrics & Gynecology and Reproductive Biology. 1987 Aug 1;25(4):271–6.

Sites of cord insertion and delayed of the third stage of labor in singleton spontaneous delivery: a retrospective cohort study

ORIGINAL ARTICLE

ORIGINAL ARTICLE BY

Thanapon Daroj [1], M.D.; Piyachat Chanidkul [2], M.D.; Weerada Trongtranonth [3], M.D.

[1]Sunpasitthiprasong Hospital, Thailand, [2]Roi Et Hospital, Thailand, [3]Khon Kaen Hospital, Thailand

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

ABSTRACT

OBJECTIVE

To identify the association between sites of cord insertion and delayed of the third stage of labor in spontaneous delivery.

METHODS

We conducted a retrospective cohort study comparing duration of the third stage of labor between central and non-central cord insertion.The medical records of women admitted with singleton spontaneous delivery from July 2014 to December 2015 at Khon Kaen Hospital Thailand were reviewed for site of cord insertion and other variables. The primary outcome was delayed the third stage of labor. The secondary outcomes were postpartum hemorrhage, fetal sex, fetal birth weight, APGAR score, low placental weight, manual removal of the placenta and placental curettage.

RESULTS

A total of 1697 pregnant women with singleton spontaneous delivery were reviewed (296 in the central cord insertion group and 1401 in the non-central cord insertion group). There was no difference between the two groups in relation to delayed the third stage of labor; 23 women (7.4%) in the former group and 76 women (5.4%) in the latter group (adjusted odds ratio [AOR], 1.41; 95% confidence interval [CI], 0.86 to 2.34; P=0.178). There was also no difference between the two groups regarding rate of low birth weight of the infants (5.4% vs. 4.8%;AOR, 1.17; 95% CI, 0.66 to 2.09; P=0.594).

CONCLUSION

In women with singleton spontaneous delivery, we found no significant difference in delayed the third stage of labor between central cord and non-central cord insertion.

INTRODUCTION

Factors affecting delayed the third stage of labor include gestational age less than 36 week, longer latent phase of labor, second stage of labor, previous history of abortions three times or more, amnionitis, delivery not in hospital, augmented labor, preterm labor, parity of four or more and elderly mothers.[1–5] Duration of the third stage of labor especially more than 10 minutes increase risk for postpartum hemorrhage.[5–8] The range of prevalence rate of postpartum hemorrhage are varied from 18 to 21.4 percent, approximately 4 percent in vaginal deliveries. This is an obstetric emergency that can cause of maternal morbidity and mortality [6–11]

Sites of umbilical cord insertion are described as central and non-central insertion (i.e., paracentral or lateral, marginal and velamentous or membranous cord insertion).[13] More than 90% are central and paracentral cord insertion followed by marginal cord insertion, the least frequent of umbilical cord insertion is velamentous type[13] From real-time ultrasonographic technology performed in the third stage of labor, eccentric umbilical cord insertion can thicken placenta as well as increase intensity of uterine contraction that can later shorten the third stage of labor.[14–16] However, no study demonstrates the association between the site of cord insertion and delayed the third stage of labor, hence, the aim of the present study was to identify the relationship between various sites of cord insertion and delayed the third stage of labor in those with singleton spontaneous delivery.

METHODS

We conducted a retrospective cohort study comparing delayed the third stage of labor between those with central and non-central cord insertion in women with the singleton spontaneous delivery.

PATIENTS

We reviewed medical records of women with singleton spontaneous delivery at Khon Kaen Hospital, Thailand from July 2014 to December 2015. We excluded medical records of women with breech presentation, gestational diabetes mellitus, multiple pregnancy, eclampsia and complication of delivery such as who use vacuum or forceps in delivery.

DATA COLLECTION

All medical records of women with singleton spontaneous delivery were identified using the International Classification of Disease (ICD) 10 080.0. Those who admitted at Khon Kaen Hospital were reviewed. Variables including age, gestational age, gestational age, parity, previous abortion, previous cesarean section, preeclampsia, labor onset, rupture of membrane, augmented labor, accoucheur, anesthesia, amnionitis, hypertension and duration of the second stage of labor were recorded.

EXPOSURES

Various sites of cord insertion; central and non-central were considered as exposure in the present study.

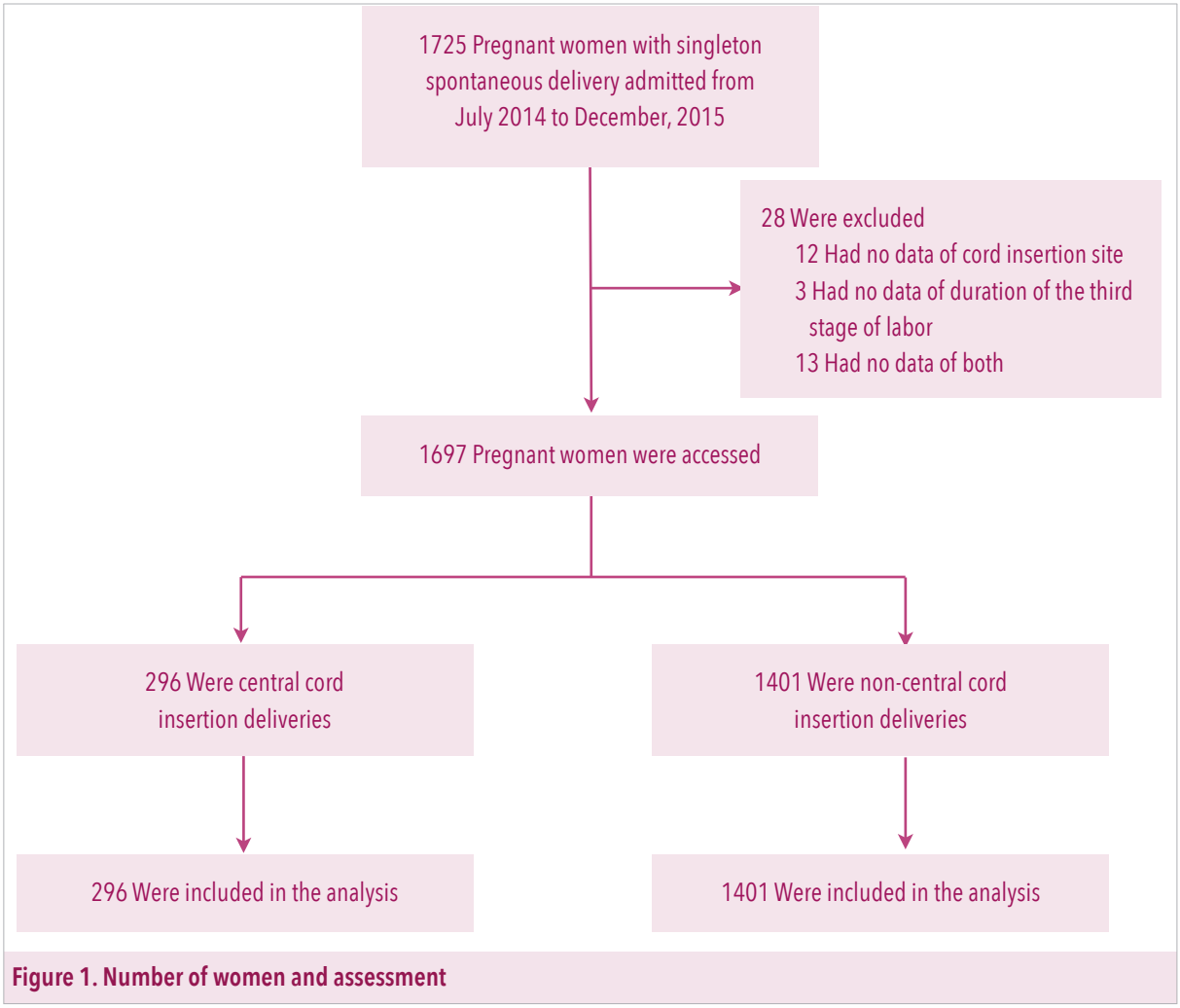

Figure 1. Number of women and assessment

OUTCOMES

The primary outcome was delayed the third stage of labor. The secondary outcomes were postpartum hemorrhage, fetal sex, fetal birth weight, APGAR score, low placental weight, manual removal of the placenta, placental curettage and placental separation.

STATISTICAL ANALYSIS

We used descriptive statistics to summarize baseline characteristics of women in each group; number and percent for categorical variable, mean with standard deviation (SD) for normally distributed continuous variable and median and interquartile range (IQR) for non-normally distributed continuous variable. Event rate of the primary and the secondary outcomes between the two groups was analyzed using relative risk. Later, adjusted odds ratio (AOR) from logistic regression analysis was used to identify the relationship between exposure and outcomes of the study. In additional, hazard ratio (HR) from the Cox model used to identify the associated between the exposures and placental separation.

RESULTS

CHARACTERISTICS OF THE PREGNANT WOMEN

From July 2014 to December 2015, a total of 1725 pregnant women were admitted and underwent singleton spontaneous delivery at Khon Kaen Hospital. Of these patients, 28 were excluded because the data of duration of the third stage of labor or sites of umbilical cord insertion were not available. Therefore the remaining 1697 pregnant women were included in the analysis. (Figure 1.)

The women delivered vaginally with the median age of 24.6 (IQR, 18.9 to 30.4). Most of the women were in their first (46.0%) or second pregnancies (36.8%). Most of them had no history of abortion (82.7%), one-fourth of them had once history of abortion. The median gestational age at the time of delivery was 272.11 (IQR, 261.11 to 283.11). Seventy eight (4.6%) of them were induced labor, 724 (42.7%) were augmented labor as well. One thousand two hundred and forty-seven (26.5%) of vaginal deliveries had done by nurse-accoucheur, 1,483 (87.4%) of deliveries use local anesthesia. The mean length of the second stage of labor was 15.7+16.4, almost were less than 1 hour (98.1%) while the remainder were within 1 to 2 hour. However, baseline demographic characteristics were similar in pregnant women whom central umbilical cord insertion and non-central umbilical cord insertion.

Comparing between central cord insertion and non-central cord insertion, the former tended to have more parity (P=0.03) and have higher proportion of those delivered by physician (P=0.011). However, there were no significant differences between the two groups regarding median age (P=0.052), median gestational age (P=0.583), proportion with induced labor (P=0.624), proportion with augmented labor (P=0.631), proportion of women with hypertension (P=0.225), proportion with local anesthesia (P=0.875), proportion with history of previous abortion (P=0.335) and mean duration of the second stage of labor (P=0.978) (Table 1`.).

STUDY OUTCOME

Delayed the third stage of labor 10 minutes or more was diagnosed in 99 postpartum vaginal deliveries. The median length of the third stage of labor in both groups were 4.0 minutes with IQRs of 3.0 to 6.0 (P=0.327). Comparing between central cord insertion and non-central cord insertion, there was no significant difference between the two groups in relation to delayed the third stage of labor (7.8% vs. 6.4%; RR 1.43, 95% CI, 0.91 to 2.24; P=0.118). There was no significant difference in term of volume of blood loss between the two groups (P=0.853) and no significant difference regarding proportion of male fetus between the two groups (50.0% vs. 51.8%; P=0.569). Low birth weight was diagnosed in 83 feti. The rate of this outcome was not significantly different between the two groups (5.4% vs. 4.8%; RR, 1.13; 95% CI, 0.66 to 1.92; P=0.652). The median of APGAR score at 1 minute in both groups were 9.0 with IQR 9.0 to 10.0 (P=0.535), at 5 minutes were 10.0 with IQR 10.0 to 10.0 (P=0.896), at 10 minutes were 10.0 with IQR 10.0 to 10.0 (P=0.914). Low placental weight was diagnosed in 45 women. The rate of this outcome was not significantly different between the two groups (3% vs. 2.6%) (Table 2).

Table 1. Characteristics of the Pregnant women

Characteristic	Central umbilical cord insertion	Non-central umbilical cord insertion	P Value
Maternal age-yr			0.052
Median	25.1	23.6	
Interquartile range	19.9-29.5	19.9-28.4	
Gestational age-day			0.583
Median	273.0	273.0	
Interquartile range	266.0-278.0	266.0-279.0	
Parity-no. (%)			0.003
0	120 (40.5)	660 (47.1)	
1	112 (37.8)	512 (36.5)	
2	48 (16.2)	185 (13.2)	
3	8 (2.7)	36 (2.6)	
≥4	8 (2.7)	8 (0.6)	
Previous abortion-no. (%)			0.335
0	237 (80.1)	1167 (83.3)	
1	51 (17.2)	211 (15.1)	
2	6 (2.0)	20 (1.4)	
≥3	2 (7.0)	3 (2)	
Induced labor-no. (%)	12 (4.1)	66 (4.7)	0.624
Augmented labor-no. (%)	130 (43.9)	594 (42.4)	0.631
Nurse accoucheur-no. (%)	200 (67.6)	1047 (74.7)	0.011
Local anesthesia-no. (%)	259 (88.7)	1224 (88.4)	0.875
Duration of the second stage of labor-min			0.866
Median	11.0	11.0	
Interquartile range	7.0-19.0	7.0-17.0	
Duration of the second stage of labor-hr-no. (%)			0.735
<1	288 (97.6)	1376 (98.3)	
1-2	6 (2)	20 (1.4)	
>2	1 (0.3)	4 (0.3)	

Table 2. The primary and the secondary outcomes in the third stage of labor according to cord insertion site

Outcome	Cord insertion site		Relative risk (95% confidence interval)	P Value
	Central cord	Non-central cord		
Delayed of the third stage of labor-no. (%)	23 (7.8)	76 (5.4)	1.43 (0.91-2.24)	0.118
Duration of the third stage-min				0.327
Median	4.0	4.0		
Interquartile range	3.0-6.0	3.0-6.0		
Postpartum hemorrhage-ml				
Mean+SD	144.7±25.7	144.3±26.3		
Median	150.0	150.0		0.853
Interquartile range	150.0-150.0	150.0-150.0		
Male fetus-no. (%)	148 (50.0)	726 (51.8)		0.569
Fetal birth weight-kg				0.413
Median	3.1	3.1		
Interquartile range	2.8-3.3	2.8-3.3		
Low birth weight*-no. (%)	16 (5.4)	67 (4.8)	1.13 (0.66-1.92)	0.652
APGAR score				
At 1 min				
Mean±SD	9.1±0.8	9.1±0.8		
Median	9.0	9.0		0.535
Interquartile range	9.0-10.0	9.0-10.0		
At 5 min				
Mean+SD	9.9±0.3	9.9±0.3		
Median	10.0	10.0		0.896
Interquartile range	10.0-10.0	10.0-10.0		
At 10 min				
Mean+SD	10.0±0.1	10.0±0.2		
Median	10.0	10.0		0.914
Interquartile range	10.0-10.0	10.0-10.0		
Low placental weight-no (%)	9 (3.0)	36 (2.6)	1.18 (0.58-2.43)	0.655

Table 3. Multivariable analysis of risk factors associated with delayed the third stage of labor

Factor	Delayed of the third stage of labor			
	Crude odds ratio (95% CI)	P Value	Adjusted odds ratio (95% CI)	P Value
Central cord insertion	1.47 (0.90-2.38)	0.120	1.41 (0.86-2.34)	0.178
Maternal age-yr	1.02 (0.99-1.06)	0.182	1.01 (0.97-1.06)	0.516
Gestational age-day	1.00 (0.98-1.02)	0.847	1.00 (0.98-1.01)	0.636
Parity		0.062		0.884
0	1.00		1.00	
1	1.09 (0.68-1.76)		0.82 (0.47-1.44)	
2	2.04 (1.18-3.52)		1.06 (0.47-2.40)	
3	1.95 (0.66-5.74)		0.79 (0.20-3.13)	
≥4	2.79 (0.61-12.72)		1.20 (0.20-7.22)	
Previous abortion	1.88 (1.18-2.98)	0.007	1.87 (1.00-3.53)	0.052
Induction of labor	2.22 (1.07-4.58)	0.032	2.38 (1.13-5.04)	0.023
Augmentation of labor	1.08 (0.72-1.63)	0.712	1.12 (0.74-1.70)	0.593
Nurse-accoucheur	1.56 (0.93-2.60)	0.091	1.77 (1.03-3.05)	0.040
Non local anesthesia	1.93 (1.14-3.26)	0.014	1.77 (0.96-3.28)	0.067
Duration of the second stage of labor more than 1 hr	1.63 (0.49-5.45)	0.425	1.37 (0.31-6.18)	0.680

ADDITIONAL ANALYSES

From the logistic regression analysis, central cord insertion did not significantly increase rate of delayed the third stage of labor (AOR 1.14; 95% CI, 0.86 to 2.34; P=0.178). The factors significantly increased rate of delayed the third stage of labor were induction of labor (AOR 2.38; 95% CI, 1.13 to 5.04; P=0.023), nurse-accoucheur (AOR 1.77; 95% CI, 1.03 to 3.05; P=0.040). However, maternal age, gestational age, parity, previous abortion, augmented labor, non local anesthesia and duration of the second stage of labor were not associated with delayed the third stage of labor (Table 3.).

Central cord insertion did not significantly increase rate of low birth weight (AOR 1.17; 95% CI, 0.66 to 2.09; P=0.594). However, the gestational age significantly increased rate of low birth weight (AOR 0.98; 95% CI, 0.97 to 0.99; P=0.001) (Table 4.). In additional, rate of low birth weight was related to the number of parity, comparing with the nulliparous, the pregnant

Table 4. Multivariable Analysis of Risk Factors Associated with Low birth weight.

Factor	Low birth weight			
	Crude odds ratio (95% CI)	P Value	Adjusted odds ratio (95% CI)	P Value
Central cord insertion	1.14 (0.65-1.99)	0.652	1.17 (0.66-2.09)	0.594
Maternal age-yr	0.94 (0.90-0.98)	0.006	0.98 (0.93-1.02)	0.302
Gestational age-day	0.98 (0.97-1.00)	0.006	0.98 (0.97-0.99)	0.001
Parity		0.001		0.002
0	1.00		1.00	
1	0.41 (0.24-0.69)		0.40 (0.21-0.75)	
2	0.17 (0.05-0.54)		0.13 (0.03-0.55)	
3	1.29 (0.45-3.74)		1.24 (0.31-4.95)	
≥4	0.86 (0.11-6.65)		0.73 (0.08-7.08)	
Previous abortion	0.64 (0.33-1.26)	0.201	1.38 (0.54-3.51)	0.505

women with parity of one or two tended to have lower rate of low birth weight (AOR, 0.40; 95% CI, 0.21 to 0.75; AOR, 0.13; 95% CI, 0.03 to 0.55; respectively). Nevertheless, maternal age and previous abortion were not associated with rate of low birth weight.

From the Table 5 and Fig. 2, sites of cord insertion was not associated with the incidence density of placental separation (HR, 0.99; 95% CI, 0.87 to 1.12; P=0.850), only nurse-accoucheur was significantly associated with lower of the placental separation (HR, 0.66; 95% CI, 0.59 to 0.74; P<0.001). However, maternal age, gestational age, parity, induced labor, augmented labor, non local anesthesia, duration of the second stage and hypertension were found not to have the association with the placental separation.

DISCUSSION

PRINCIPAL FINDINGS

In this study, we found no significant difference in delayed the third stage of labor between central cord and non-central cord insertion. There were also no significant difference in rate of low birth weight, rate of postpartum hemorrhage, proportion of male fetuses, median fetal birth weight, rate of low placental weight, rate of manual removal of the placenta and rate of placental curettage. However, nurse accoucheur and induced labor significantly increased rate of delayed the third stage of labor. Regarding to the gestational age significantly increase rate of low birth weight, conversely more number of parity tended to have lower rate of low birth weight.

Table 5. Factors associated with placental separation

Factor	Hazard Ratio (95% CI)	P Value
Central cord insertion	0.99 (0.87-1.12)	0.850
Maternal age-yr	0.99 (0.98-1.00)	0.196
Gestational age-day	0.99 (0.99-1.00)	0.440
Parity		0.503
0	1.00	
1	1.10 (0.97-1.24)	
2	1.13 (0.93-1.39)	
3	1.36 (0.92-2.00)	
≥4	1.18 (0.66-2.10)	
Previous abortion		0.125
0	1.00	
1	0.88 (0.75-1.04)	
2	0.63 (0.41-0.98)	
≥3	0.58 (0.22-1.51)	
Induced labor	0.89 (0.71-1.13)	0.335
Augmented labor	0.92 (0.83-1.01)	0.087
Nurse-accoucheur	0.66 (0.59-0.743)	<0.001
Non local anesthesia	0.87 (0.73-1.03)	0.107
Duration of the second stage		0.269
<1 hr	1.00	
1-2 hr	1.08 (0.73-1.61)	
>2 hr	2.04 (0.84-4.93)	
Hypertension	0.50 (0.12-2.07)	

STRENGTHS AND LIMITATIONS OF THE STUDY

Our study has several strengths. Firstly, the design of the study is retrospective cohort, more clearly to clarify the sequence between the exposure and outcomes. Secondly, we include all the women with singleton spontaneous delivery who has the record of sites of cord insertion and duration of the third stage of labor, minimize selection bias. Thirdly, Baseline characteristics between central cord insertion and non central cord insertion were balance, allowed us to decrease confounding bias in interpreting results. Fourthly, we did several statistic analysis leading to increase reliable.

Our study also has some limitations. We used the data from medical records to perform a retrospective cohort. As a result, some data may lose and increase missing bias. Inability to access the large sample size as computed from Winpepi due to the short duration. Our inability to detect significant difference sites of cord insertion and delayed of the third stage of labor may result from inadequate statistical power. Another limitation was the generalizability of these study is singleton pregnancy those excluded breech presentation, vacuum or forceps delivery thus we were unable to adjust these factors.

COMPARISON OF THE OTHER STUDIES

Our study had a cut point of delayed the third stage of labor at 10 minutes, the median of maternal age was 24.6 years old with IQR 18.9 to 30.4, consequently, we found not the association between the maternal age and delayed the third stage of labor. In contrast, the previous study clarified prolonged the third stage of labor as 30 minutes or more, as a result, the pregnant women

whom 30 years old or more tended to have prolonged the third stage of labor[1].In additional, nurse-accoucheur increased rate of prolonged the third stage of labor. In comparison, our study revealed the relation between nurse-accoucheur and delayed the third stage of labor as well. Our study found that delayed the third stage of labor was not associated with augmented labor, parity of one, two, three and four or more, history of previous abortion, in contrast with two studies, increasing rate of prolonged the third stage of labor associated with augmented labor, nulliparous and history of previous abortion[1,2].

Another study, the primiparous and the parity of two were a significantly increased rate of low birth weight[21], our study is similarly to the previous one as well. Maternal age was not associated to low birth weight but the previous one found extremely maternal age significantly increased rate of low birth weight.

CONCLUSION AND IMPLICATION

In summary, our study did not support the association between sites of cord insertion and duration of the third stage of labor. Though our study had a limitation in population size, extensive studies with larger sample size are required to clearly clarify the association between delayed the third stage of labor and sites of umbilical cord insertion. Moreover, we propose that umbilical cord insertion diagnosis during pregnancy should be performed.

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REFERENCES

1. Prolonged Third Stage of Labor: Morbidity and Risk Factors.: Obstetrics & Gynecology [Internet]. LWW. [cited 2016 May 11]. Available from: http://journals.lww.com/greenjournal/Fulltext/1991/06000/Prolonged_Third_Stage_of_Labor__Morbidity_and_Risk.13.aspx
2. The Length of the Third Stage of Labor and the Risk of Postp...: Obstetrics & Gynecology [Internet]. LWW. [cited 2016 May 11]. Available from: http://journals.lww.com/greenjournal/Fulltext/2005/02000/The_Length_of_the_Third_Stage_of_Labor_and_the.13.aspx
3. Magann EF, Doherty DA, Briery CM, Niederhauser A, Chauhan SP, Morrison JC. Obstetric Characteristics for a Prolonged Third Stage of Labor and Risk for Postpartum Hemorrhage. Gynecol Obstet Invest. 2007 Dec 10;65(3):201–5.
4. Diagnosis and Management of Clinical Chorioamnionitis [Internet]. [cited 2016 Jun 2]. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3008318/
5. Diagnosis of preterm labor and overview of preterm birth [Internet]. [cited 2016 May 31]. Available from:http://www.uptodate.com/contents/diagnosis-of-preterm-labor-and-overview-of-preterm-birth?source=search_result&search=preterm+labor&selectedTitle=1~150
6. Taebi M, Kalahroudi MA, Sadat Z, Saberi F. The duration of the third stage of labor and related factors. Iranian Journal of

Nursing and Midwifery Research. 2012 Feb; 17(2 Suppl1):S76.

7. KAREN et al. Preventing Postpartum Hemorrhage: Managing the Third Stage of Labor. American Family Physician. 2006;

8. Combs CA, Murphy EL, Laros RK. Factors associated with postpartum hemorrhage with vaginal birth. Obstet Gynecol. 1991 Jan;77(1):69–76.

9. Sheiner E, Sarid L, Levy A, Seidman DS, Hallak M. Obstetric risk factors and outcome of pregnancies complicated with early postpartum hemorrhage: a population-based study. J Matern Fetal Neonatal Med. 2005 Sep;18(3):149–54.

10. Risk factors for a prolonged third stage of labor and postpartum hemorrhage. - Abstract - Europe PMC [Internet]. [cited 2016 May 11]. Available from: http://europepmc.org/abstract/med/23380748

11. Motanya S. Implementing an Evidence-Based Educational Module on Nurses' Role on Management of Postpartum Hemorrhage [Internet]. Walden University; 2015 [cited 2016 May 11]. Available from: http://scholarworks.waldenu.edu/dissertations/1651

12. WHO | WHO recommendations for the prevention of postpartum haemorrhage [Internet]. WHO. [cited 2016 May 11]. Available from: http://apps.who.int/rhl/archives/guideline_pphprevention_fawoleb/en/

13. Pathak S, Hook E, Hackett G, Murdoch E, Sebire NJ, Jessop F, et al. Cord coiling, umbilical cord insertion and placental shape in an unselected cohort delivering at term: relationship with common obstetric outcomes. Placenta. 2010 Nov;31(11):963–8.

14. Herman A, Weinraub Z, Bukovsky I, Arieli S, Zabow P, Caspi E, et al. Dynamic ultrasonographic imaging of the third stage of labor: New perspectives into third-stage mechanisms. American Journal of Obstetrics and Gynecology. 1993 May 1;168(5):1496–9.

15. Ebbing C, Kiserud T, Johnsen SL, Albrechtsen S, Rasmussen S. Prevalence, Risk Factors and Outcomes of Velamentous and Marginal Cord Insertions: A Population-Based Study of 634,741 Pregnancies. PLoS One [Internet]. 2013 Jul 30 [cited 2016 May 31];8(7). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3728211/

16. Salafia CM, Yampolsky M, Shlakhter A, Mandel DH, Schwartz N. Variety in placental shape: When does it originate? Placenta. 2012 Mar;33(3):164–70.

17. Centrality of the Umbilical Cord Insertion in a Human Placenta Influences the Placental Efficiency - pdf [Internet]. [cited 2016 May 11]. Available from: http://www.placentajournal.org/article/S0143-4004(09)00307-5/pdf

18. Pregnancy outcomes in healthy nulliparas who developed hypertension [Internet]. [cited 2016 May 13]. Available from: http://www.sciencedirect.com/science/article/pii/S0029784499004627

19. Preeclampsia: Clinical features and diagnosis [Internet]. Available from: http://www.uptodate.com/contents/preeclampsia-clinical-features-and-diagnosis?source=search_result&search=preeclampsia&selectedTitle=1%7E150

20. Influence of the Umbilical Cord Insertion Site on the Optimal Individual Birth Weight Achievement [Internet]. [cited 2016 May 13]. Available from: http://www.hindawi.com/journals/bmri/2014/341251/

21. Mavalankar DV, Gray RH, Trivedi CR. Risk Factors for Preterm and Term Low Birthweight in Ahmedabad, India. Int J Epidemiol. 1992 Apr 1;21(2):263–72.

22. Delivery of the preterm low birth weight singleton fetus [Internet]. [cited 2016 May 13]. Available from: http://www.uptodate.com/contents/delivery-of-the-preterm-low-birth-weight-singleton-fetus

23. Newborn AA of PC on FA, Practice AC of O and GC on O. The Apgar Score. Pediatrics. 2015 Oct 1;136(4):819–22.

24. Placental weight and its ratio to birth weight in normal pregnancy at Songkhlanagarind Hospital. - PubMed - NCBI [Internet]. [cited 2016 May 14]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16578997

25. Placenta weight percentile curves for singleton deliveries. - PubMed - NCBI [Internet]. [cited 2016 May 14]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17516963

"I shall either find a way or make one"

-Hannibal Barca

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