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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

The systematic review is now considered as a source of reliable information. It can be large including a lot of trials or very small including no trial. It can be also very rigid to answer a specific clinical question or pragmatic to answer common problems we face in everyday life. In this issue, you will find three systematic reviews answering the common clinical questions; the common medication we used to reduce heart rate before undergoing computed tomography angiography, which one is better; or bladder infusion versus standard catheter removal in those with urinary retention, which one is superior; or flunarizine and betahistine in patients with vertigo, which one is recommended. Moreover, there is also an article exploring the myth of using acetazolamide in children with meningitis with increased intracranial pressue. All the answers can be found in this issue. Find them out yourself. Enjoy!

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

submission

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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.

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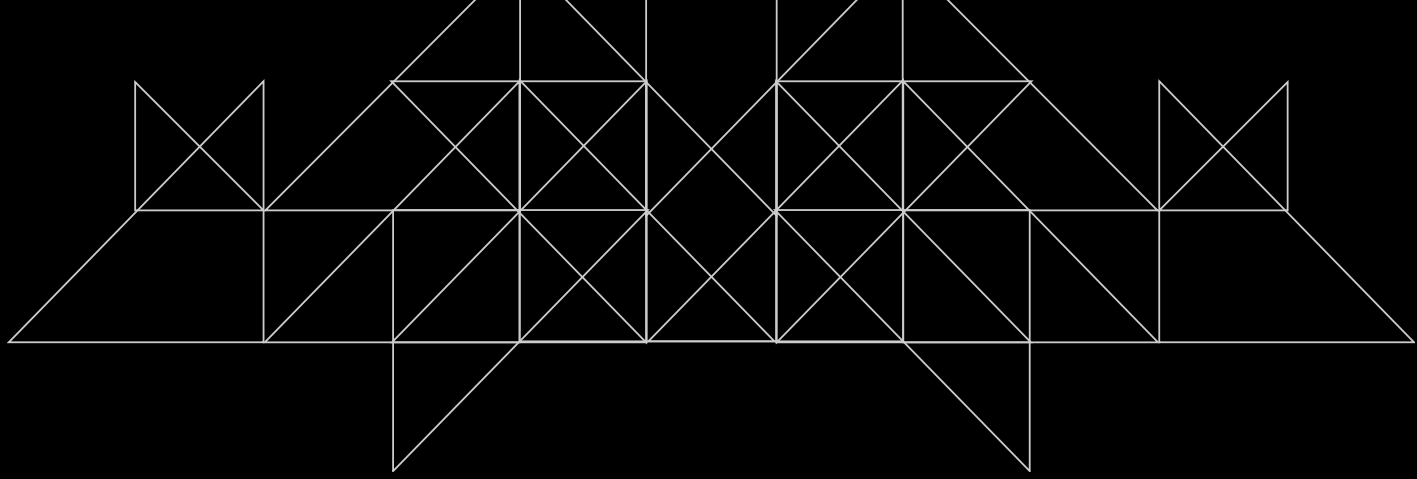
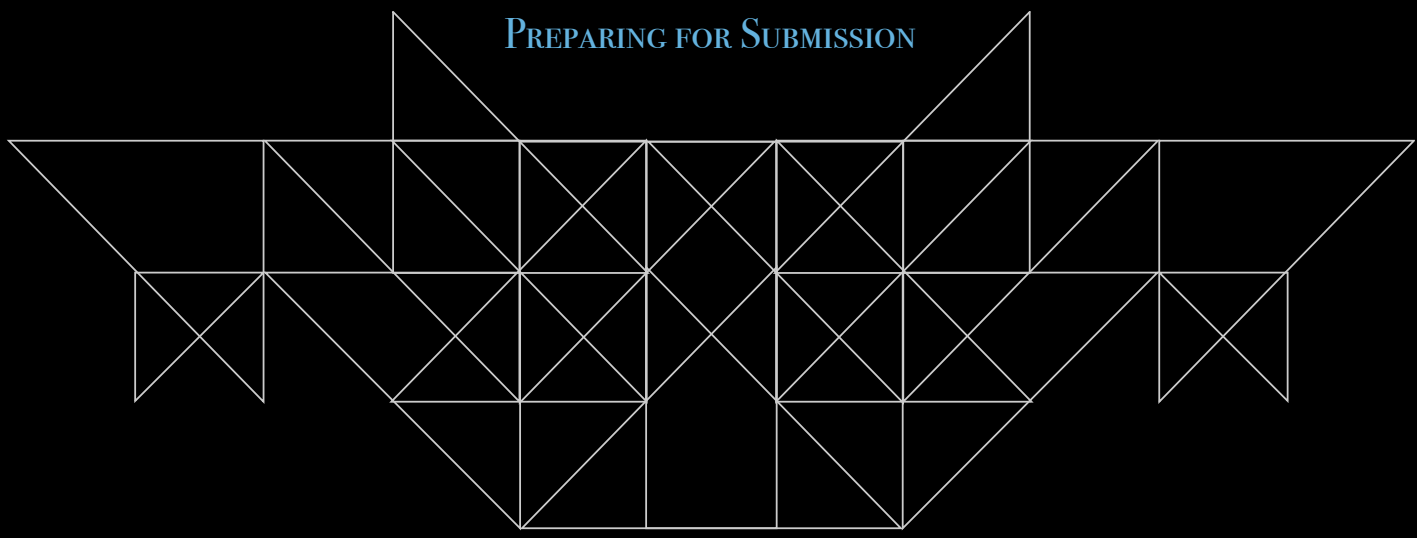


International Committee of Medical Journal Editors (ICMJE) Recommendation for Preparing for Submission



1. General Principles

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

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

2. Reporting Guidelines

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

3. Manuscript Sections

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

a. Title Page

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

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

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b. Abstract

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

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

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

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

c. Introduction

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

d. Methods

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

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

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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.

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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.

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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

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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.

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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.

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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.

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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.

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

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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.

Effects of acetazolamide in children with meningitis with increased intracranial pressure: a retrospective cohort study

ORIGINAL ARTICLE

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To investigate the effects of acetazolamide to reduce cerebrospinal fluid (CSF) pressure in children with meningitis and increased intracranial pressure.

METHODS

We conducted a retrospective cohort study of children (3 to 15 years old) with meningitis and increased intracranial pressure receiving acetazolamide and standard therapy and the children who received standard therapy alone in Khon Kaen Hospital, Thailand between Jan 2009 and December 2015. The primary outcome was the difference of opening CSF pressure change between these two groups.

RESULTS

A total of 85 patients were included in the analysis, 15 were prescribed acetazolamide and 70 were received standard treatment alone. The mean change of opening CSF pressure was similar between the two groups (-13.2±10.9 in acetazolamide group and -7.2±9.7 in the standard treatment group; mean difference, 6.05; 95% confidence interval (CI), -4.83 to 16.93; P=0.26). After adjusting the confounder, adjunct acetazolamide to standard treatment was not related to the opening CSF pressure change (regression coefficients [B], 1.15; 95% CI, -23.20 to 25.50), and the adverse effects included hypokalemia (adjusted odds ratio [AOR], 0.47; 95% CI, 0.06 to 4.06) and metabolic acidosis (AOR, 0.57; 95% CI, 0.07 to 4.76). However, opening CSF pressure at admission was inversely associated with the opening CSF pressure change (B, -0.66; 95% CI, -1.31 to -0.003).

CONCLUSION

In children with meningitis and increased intracranial pressure, adjunct acetazolamide to standard treatment did not have benefit in reduction of CSF pressure.

INTRODUCTION

Meningitis is a meningeal inflammation and is defined by an increased in a number of leukocytes in the cerebrospinal fluid (CSF), and is manifested by fever, generalized headache, nuchal rigidity, and alteration of consciousness.[1] Meningitis can be caused by bacteria, viruses, fungi, physical injury, cancer, systemic illness or certain drugs.[2,3] Meningitis can lead to increased intracranial pressure.[4] CSF pressure is measured by lumbar puncture (LP), normally ≤150 mmH_2O and considers the upper limit of normal CSF pressure to 200 mmH_20.[5-7] CSF is produced by choroid plexus in the ventricles and circulates through the subarachnoid space.[8,9] From an experiment in white rabbits in 1974, it showed that acetazolamide, a carbonic anhydrase inhibitor, decreased CSF production and resulted in a decrease in intracranial pressure.[10] Similarly, the studies in 1966 and 2012, suggested that acetazolamide is the main medical treatment for idiopathic intracranial hypertension.[11-13] From our extensive search, there are a few studies regarding the usage of acetazolamide in addition to standard treatment in patients with meningitis and increased intracranial pressure; a case series in Thailand published in 1979 suggested that repeated LP in 24 children patients with tuberculous meningitis and communicating hydrocephalus and adjunct treatment with acetazolamide could reduce the CSF pressure.[14] Later in 2002, there was an RCT comparing CSF pressure between those using adjunct acetazolamide to standard treatment and those with standard treatment alone in 22 Thai adults with cryptococcal meningitis and elevated intracranial pressure, however, the trial was terminated as patients who were prescribed acetazolamide developed severe metabolic acidosis and hyperchloremia.[15] In 2005, another randomized single-blinded pilot study in 18 adults with AIDS and cryptococcal meningitis and increased intracranial pressure in Uganda had demonstrated that acetazolamide combining with serial LP had no adverse effects and clinical improvement was observed.[16] These studies are mostly in adults with small sample size. Moreover, their conclusions were still controversial and were based on non-RCT studies. In the settings of Thailand, acetazolamide is still prescribed in some children with meningitis and increased intracranial pressure by expert opinions. Regarding reasons given above, our study aims to evaluate the effects of acetazolamide in a reduction of CSF pressure in children with meningitis and increased intracranial pressure.

METHODS

STUDY DESIGN

We conducted a retrospective cohort study to compare the effects of acetazolamide in a reduction of CSF pressure in children with meningitis and increased intracranial pressure admitted at Khon Kaen Hospital, Thailand from January 2009 to December 2015.

PATIENTS AND MEDICAL RECORD

We reviewed medical records of pediatric patients age 3 to 15 years old with diagnosis of any types of

Table 1. Characteristics of the patients

Characteristic	Standard treatment with acetazolamide (n=15)	Standard treatment (n=70)	P Value
Age – yr.	9.5±2.9	8.7±3.3	0.42
Male – no. (%)	11 (73.3)	50 (71.4)	>0.99
Findings on admission – no. (%)			
Headache	11 (73.3)	59 (84.3)	0.45
Fever	9 (60.0)	58 (82.9)	0.08
Neck stiffness	9 (60.0)	51 (72.9)	0.36
Cranial nerve palsy	1 (6.7)	6 (8.6)	>0.99
Hemiparesis	1 (6.7)	9 (12.9)	0.68
Seizure	5 (33.3)	15 (21.4)	0.33
Weight – kg			0.52
Median	26.0	20.5	
IQR	15.0-38.0	16.0-31.3	
Respiratory rate– breaths/min			0.84
Median	22	24	
IQR	22-28	22-24	
Blood pressure – mmHg			
Systolic			0.50
Median	113	110	
IQR	98-120	100-117	
Diastolic			0.03
Median	78	64	
IQR	60-80	60-70	
Score on Glasgow Coma Scale			0.74
Median	15	15	
IQR	14-15	14-15	
Score <8, indicating coma – no. (%)	1 (6.7)	4 (5.7)	>0.99
Peripheral-blood white-cell count–cell per mm3	n=15	n=65	0.78
Median	15,210	12,600	
IQR	6,900-17,600	8,765-19,250	
HIV infection– no. (%)	3 (20.0)	5 (7.1)	0.14
Serum electrolytes– mmol/liter			

Table 1. Characteristics of the patients

Characteristic	Standard treatment with acetazolamide (n=15)	Standard treatment (n=70)	P Value
Sodium	n=15	n=57	0.44
Median	135.0	135.0	
IQR	132.0-137.0	133.0-138.0	
Potassium	3.4±0.4	3.7±0.6	0.02
Chloride	n=15	n=53	0.87
Median	99.0	99.0	
IQR	93.0-104.0	95.0-102.5	
Bicarbonate	22.2±3.1	22.3±4.5	0.89
Serum creatinine – mg/dl	n=13	n=40	0.36
Median	0.5	0.5	
IQR	0.3-0.6	0.4-0.6	
Indexes of CSF inflammation			
Protein – mg/dl	n=15	n=56	0.92
Median	58.8	61.1	
IQR	41.6-143.2	40.5-116.8	
CSF sugar per blood sugar	0.4±0.2	0.5±0.2	0.009
White-cell count – cell per mm3	n=15	n=64	0.20
Median	358.0	53.5	
IQR	20.0-770.0	10.0-352.5	
CSF opening pressure at admission – cm of water	n=15	n=41	<0.001
Median	32.0	20.0	
IQR	27.0-48.0	16.0-26.5	
CSF closing pressure at admission – cm of water	n=15	n=37	0.12
Median	21.0	17.0	
IQR	16.0-26.0	13.6-21.0	
Pathogen from CSF profile or culture – no./total no. (%)			0.02
Bacteria	6/15 (40.0)	35/69 (50.7)	
Fungus	3/15 (20.0)	3/69 (4.3)	
Mycobacterium tuberculosis	4/15 (26.7)	6/69 (8.7)	
Other	2/15 (13.3)	25/69 (36.2)	

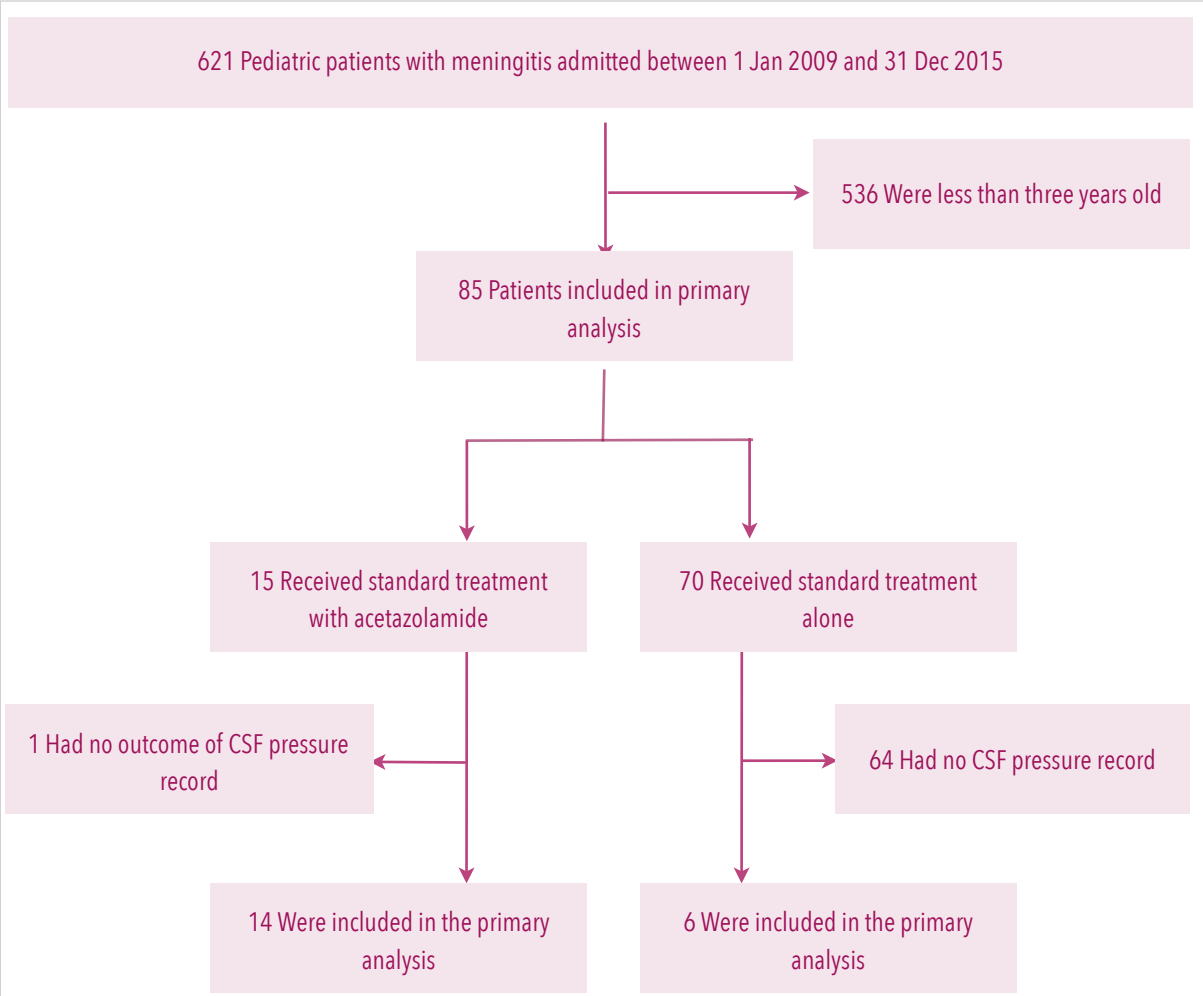

Figure 1. Study flow and assessment of primary outcomes

meningitis and increased intracranial pressure. We had no specific exclusion criteria.

DATA COLLECTION

All databases of patients diagnosed with meningitis using the International Classification of Disease (ICD) 10 and increased intracranial pressure who admitted at Khon Kaen Hospital.[17] For patients with readmission with the same diagnosis, every admission was included. The primary outcome in each patient was recorded into the mean of opening CSF pressure change between the admission date and the terminal date of treatment records. Furthermore, we recorded the characteristics such as age, sex, headache, fever,[18] neck stiffness, cranial nerve palsy, hemiparesis, seizure, weight, vital signs, score on Glasgow Coma Scale (GCS),[19] peripheral-blood white-cell count, HIV infection, serum sodium, serum potassium, serum chloride, serum

bicarbonate, serum creatinine, CSF values (protein, glucose, white-cell count, opening pressure, closing pressure), pathogen from CSF profile or culture.

OUTCOMES

The primary outcome was the difference of opening CSF pressure change before and after the treatment. The secondary outcomes were adverse drug effects included hypokalemia and metabolic acidosis.[22-25]

STATISTICAL ANALYSIS

We used descriptive statistics to summarize baseline characteristics of patients in each group; number and percent for categorical variables, mean with standard deviation (SD) for normally distributed continuous variables, and median and interquartile range (IQR) for non-normally distributed continuous variables. For inferential statistics, categorical variables were compared using the chi-square test; normally distributed continuous variables were compared using student t-test while the Mann-Whitney U test was used for comparing non-normally distributed continuous variables. For the difference of opening CSF pressure change between the two groups, we analyzed by using mean difference and we used linear regression to estimate B and corresponding 95% CIs for the risk factors associated with the outcome.[20,21] Relative risk was reported for the event rate of the secondary outcomes between the two groups and the adjusted odds ratio for the risk factors that associated were analyzed by logistic regression. We considered $P<0.05$ were significant difference.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Initially, the medical records of 621 pediatric patients diagnosed with meningitis from KKH database were reviewed, 536 were excluded due to younger than 3 years old, 85 were met the inclusion criteria and included in this study, 15 were treated with acetazolamide and 70 were treated with standard treatment alone. After excluding 65 patients with no CSF pressure record, one was treated with acetazolamide group and 64 in standard treatment alone group, 20 were included in the analysis of the primary outcome (Figure 1). Their mean (±SD) age was 8.9±3.3 years old. Approximately 70% were male. There were few HIV-infected patients (9.4%). The median weight was 24 kg (IQR 16 to 34). Their median respiratory rate was 24 (IQR 22 to 24). Their median systolic blood pressure was 110 mmHg (IQR 100 to 118) and their mean diastolic blood pressure was 66 mmHg (IQR 60 to 73). Most of the patients had 15 scores in GCS (71.8%). The median peripheral-blood white-cell count was 13,350 cell/mm³ (IQR 8,732.5 to 18,875). Serum electrolytes and serum creatinine often were within normal range. The median CSF protein levels and white-cell counts were 61 mg/dl (IQR 41.6 to 119) and 62.5 cell/mm³ (IQR 10 to 430), respectively. The mean CSF sugar per blood sugar was 0.5±0.2. The median opening pressure and the mean close pressure were 22 cmH_2O (IQR 17.13 to 32) and 19.1±7.7 cmH_2O, respectively. As expected, most of the patients had a headache (82.4%), fever (78.8%), and neck stiffness (70.6%), but, few children had a seizure (23.5%),

Table 2. The primary and the secondary outcomes after treatment

Outcomes	N	Standard Treatment with acetazolamide	Standard treatment	Mean difference (95% CI)	Relative risk (95% CI)	P Value
Opening CSF pressure change*	20	-13.2±10.9	-7.2±9.7	6.05 (-4.83- 16.93)		0.26
Hypokalemia†	44	3 (23.1)	6 (19.4)		1.19 (0.35-4.06)	>0.99
Metabolic acidosis‡	31	7 (63.6)	12 (60)		1.06 (0.60-1.88)	>0.99

Plus–minus values are means ±SD.

*Opening CSF pressure change between the admission date and the terminal date of treatment records

†Serum potassium<3.5 mmol/L

‡Bicarbonate<22 mmol/L

hemiparesis (11.8%), and cranial nerve palsy (8.2%). Nearly half of them were bacterial meningitis.

The characteristics of those receiving acetazolamide and those not receiving acetazolamide were similar in relation to age, sex, weight, HIV infection, respiratory rate, systolic blood pressure, score on GCS, clinical findings on admission, peripheral white blood cell, serum sodium, serum chloride, serum bicarbonate, serum creatinine, CSF protein, white blood cell in CSF, CSF opening and closing pressure at admission (Table 1). However, the former group had higher diastolic blood pressure (P=0.03), lower serum potassium (P=0.02), lower CSF sugar per blood sugar (P=0.009), higher CSF opening pressure at admission (P<0.001), higher proportion of patients with fungus and Mycobacterium tuberculosis meningitis, and lower proportion of bacterial and other meningitis (P=0.02) (Table 1).

OUTCOMES

There was no difference in term of mean change of opening CSF pressure between the two groups (-13.2±10.9 in acetazolamide group and -7.2±9.7 in the standard treatment group; mean difference, 6.05; 95% CI, -4.83 to 16.93; P=0.26) (Table 2). Similarly, the secondary outcomes, there was no difference in hypokalemia between acetazolamide treatment group (23.1%) and standard treatment group (19.4%) (RR, 1.19; 95% CI, 0.35 to 4.06; P>0.99), and metabolic acidosis between acetazolamide treatment group (63.6%) and standard treatment group (60%) (RR, 1.06; 95% CI, 0.60 to 1.88; P>0.99) (Table 2).

FACTORS ASSOCIATED WITH THE OUTCOMES

From the linear regression and logistic regression analysis, acetazolamide was not associated with the opening CSF pressure change, hypokalemia, and metabolic acidosis (B, 1.15; 95% CI, -23.20 to 25.50; AOR, 0.47; 95% CI, 0.06 to 4.06; AOR,

Table 3. Risk factors associated with the outcomes

Factors	Opening CSF pressure change B coefficient (95% Confidence interval)	Hypokalemia Adjusted odds ratio (95% Confidence interval)	Metabolic acidosis Adjusted odds ratio (95% Confidence interval)
Age	-0.84 (-5.00 to 3.32)	0.61 (0.30 to 1.20)	0.89 (0.45 to 1.76)
Weight	0.14 (-0.82 to 1.10)	1.11 (0.96 to 1.27)	1.01 (0.88 to 1.16)
Acetazolamide treatment	1.15 (-23.20 to 25.50)	0.47 (0.06 to 4.06)	0.57 (0.07 to 4.76)
Serum potassium at admission	2.48 (-17.50 to 22.45)	0.18 (0.008 to 3.94)	0.62 (0.03 to 13.94)
Serum bicarbonate at admission	0.18 (-1.46 to 1.82)	0.99 (0.78 to 1.27)	0.95 (0.711 to 1.27)
Opening CSF pressure at admission	-0.66 (-1.31 to -0.003)	1.02 (0.94 to 1.10)	1.03 (0.94 to 1.12)

*The data show the regression coefficients.

0.57; 95% CI, 0.07 to 4.76, respectively) (Table 3). However, opening CSF pressure at admission was inversely associated with the opening CSF pressure change (B, -0.66; 95% CI, -1.31 to -0.003) (Table 3).

DISCUSSION

MAJOR FINDINGS

In our study, we found that acetazolamide was not associated with the opening CSF pressure change, hypokalemia, and metabolic acidosis. However, opening CSF pressure at admission was the only factor associated with the opening CSF pressure change.

STRENGTHS AND LIMITATIONS OF THE STUDY

Our study is the first retrospective cohort design, that did in children and any causes of infectious meningitis. However, several limitations of this study should also be mentioned, firstly the sample size that the study required was 100 patients, but, in fact, ours was 85 patients, it was slightly different. Secondly, the medical records were not complete as some cases had no records of CSF pressure especially the record before discharge because in the case of improved clinical symptoms, the physician would not repeat LP for measuring CSF pressure and the patient would reject the procedure for those reasons the CSF pressure change could not access and it also was the one reason why we excluded some cases. Thirdly, the interval in each LP was varied. In addition, the LP technique, the measurement technique and the experiences of practitioners have affected by the measure of the CSF pressure.

COMPARISON WITH PREVIOUS STUDIES

In our study, we found that adjunct acetazolamide to standard treatment in children with any causes

of infectious meningitis and increased intracranial pressure had no difference in reduction of CSF pressure and adverse effects to standard treatment alone similar to the previous randomized single-blinded pilot study, from Uganda in 2005, the result showed no adverse effects and reduction in intracranial opening pressure.[16] However, the study performed in only 18 adult patients with AIDS and cryptococcal meningitis and increased intracranial pressure, which the intervention also combined with serial LP and the primary outcome was focused on clinical improvement. Only one study that found the adverse effects of acetazolamide was an RCT in 2002, comparing CSF pressure between those using adjunct acetazolamide to standard treatment and those with standard treatment alone in 22 Thai patients, also studied in adults with cryptococcal meningitis and elevated intracranial pressure, was terminated as patients who were prescribed acetazolamide developed severe metabolic acidosis and hyperchloremia.[15] However, there was a case series of 24 children, in 1979, suggested that repeated LP combined with acetazolamide adjunct to standard treatment could reduce the CSF pressure.[14] But there was no comparison group and performed in only children patients with tuberculous meningitis and communicating hydrocephalus.

Acetazolamide, however, is used as the main medical treatment for idiopathic intracranial hypertension (IIH) for reduction of CSF production.[11,13] The evidence supports in this condition are the same as mentioned earlier and no studies can confirm the effectiveness of acetazolamide. Prior case series in children with IIH mentioned the success for improving symptoms of increased intracranial pressure and vision more than half patients.[26,27] Subsequently, the pilot RCT of 50 patients in the United Kingdom, 2010, is difficult to practice due to poor recruitment and compliance.[28] And their limitation is the same as ours in the term of sample size. Later, in 2014, a multi-center, double-blinded, RCT of 86 patients in the United States showed the improvement of visual field function but did not mention of other benefits.[29]

CONCLUSION AND IMPLICATION

Adjunct acetazolamide to standard treatment had no difference in reduction of CSF pressure in children with meningitis and increased intracranial pressure. However, for better estimation effects of acetazolamide, the larger sample size is needed. Multi-center retrospective cohort design should be conducted in settings where acetazolamide is of use for preliminary approximation effects of acetazolamide before conducting an RCT.

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Ivabradine versus metoprolol for heart rate reduction in patient ongoing coronary computed tomography angiography: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To compare the efficacy of ivabradine with that of metoprolol for heart-rate-lowering inpatient ongoing coronary computed tomography angiography (CCTA).

METHODS

We systematically searched the electronic database including PubMed, the Cochrane Library, Scopus, UpToDate and Trip Database with no language restriction. The last search was performed on December 2015. In addition, we hand searched the reference lists and relevant articles of all included studies to identify the further studies. The primary outcome was heart rate (HR) reduction between pre-medication and during CCTA inpatient ongoing CCTA who received either ivabradine or metoprolol. We also compared HR reduction between pre-medication and prior CCTA inpatient ongoing CCTA who received either ivabradine or metoprolol.

RESULTS

We included four randomized controlled trials (RCTs) with a total of 455 patients who suspected coronary artery disease (CAD) and ongoing CCTA. Most of the included trials had a low risk of bias. This meta-analysis we found ivabradine had a statistically significant reduction of HR more than that of metoprolol inpatient ongoing CCTA comparing pre-medication and during CCTA (mean difference (MD) -2.71, 95% CI -3.81 to -1.60, fixed-effect model; I^2=0%). Though comparing pre-medication and prior CCTA, the difference of HR reduction was not statistically significant between ivabradine and metoprolol (MD -2.46, 95% CI -7.34 to 2.41, random-effect model; I^2=93%). For the meta-analysis of the two studies that were high quality, we found that ivabradine had a statistically significant reduction of HR more than that of metoprolol inpatient ongoing CCTA comparing pre-medication and during CCTA (MD -2.64, 95% CI -6.54 to -0.74, fixed-effect model; I^2=0%).

CONCLUSION

Ivabradine had a statistically significant reduction of HR more than that of metoprolol inpatient ongoing CCTA comparing pre-medication and during CCTA.

INTRODUCTION

Coronary computed tomography angiography (CCTA) is a non-invasive equipment studying the images of the coronary vessels.[1–6] If the patient's heart rate (HR) over 70 beats per minute (bpm), it would reduce the visibility of the study.[7–10] The Society of Cardiovascular Computed Tomography Guideline recommended to administer 50 mg of metoprolol in patients with baseline HR over 55 bpm, but less than 65 bpm and blood pressure (BP) over 90 mmHg for reducing HR during the scan.[11] Ivabradine is a heart rate lowering drug that selectively inhibits sinus node pacemaker activity.[12–16] It is used as an alternative drug because of rapidly reduce HR to reach the target and make patients exposure minimal radiation during CCTA.[17] However, there are some randomized controlled trials (RCTs) comparing the HR reduction between ivabradine and metoprolol in patients who ongoing CCTA, but not all studies provided the similar results.[18,19] For instance, a previous two Turkish studies in 2012 stated that Ivabradine has the deduction of HR than that of metoprolol when pre-medication compare with during CCTA ivabradine could reduce HR 14 bpm and metoprolol could reduce HR 9 bpm thus they concluded that ivabradine could be used as alternatives drug in patients ongoing CCTA.[20,21] Moreover, an Austrian study in 2012 stated that there was no difference in relation to HR reduction between ivabradine and metoprolol in patient ongoing CCTA.[19] On the contrary, an Indian study in 2012 stated that ivabradine was able to lower the HR than that of metoprolol.[18] We, thus, conducted a systematic review to compare the HR reduction between ivabradine and metoprolol in patient ongoing CCTA.

METHODS

We conducted a systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist[22] for reporting this systematic review.

ELIGIBILITY CRITERIA

TYPES OF STUDY

We included all RCTs that compared the HR reduction between ivabradine and metoprolol in patients who ongoing CCTA.

TYPES OF PARTICIPANTS

Any age of patients with normal sinus rhythm who suspected coronary artery disease (CAD) and ongoing CCTA was included in this review.

TYPES OF INTERVENTIONS

Ivabradine and metoprolol were used for reducing HR in patients who ongoing CCTA.

TYPES OF OUTCOMES

The outcomes were (i) HR reduction between pre-medication and during CCTA and (ii) HR reduction between pre-medication and prior CCTA in patients who received either ivabradine or metoprolol. The mean heart rate during CCTA was recorded. The adverse events were recorded.

INFORMATION SOURCES

We systematically searched the electronic database including PubMed, the Cochrane Library,

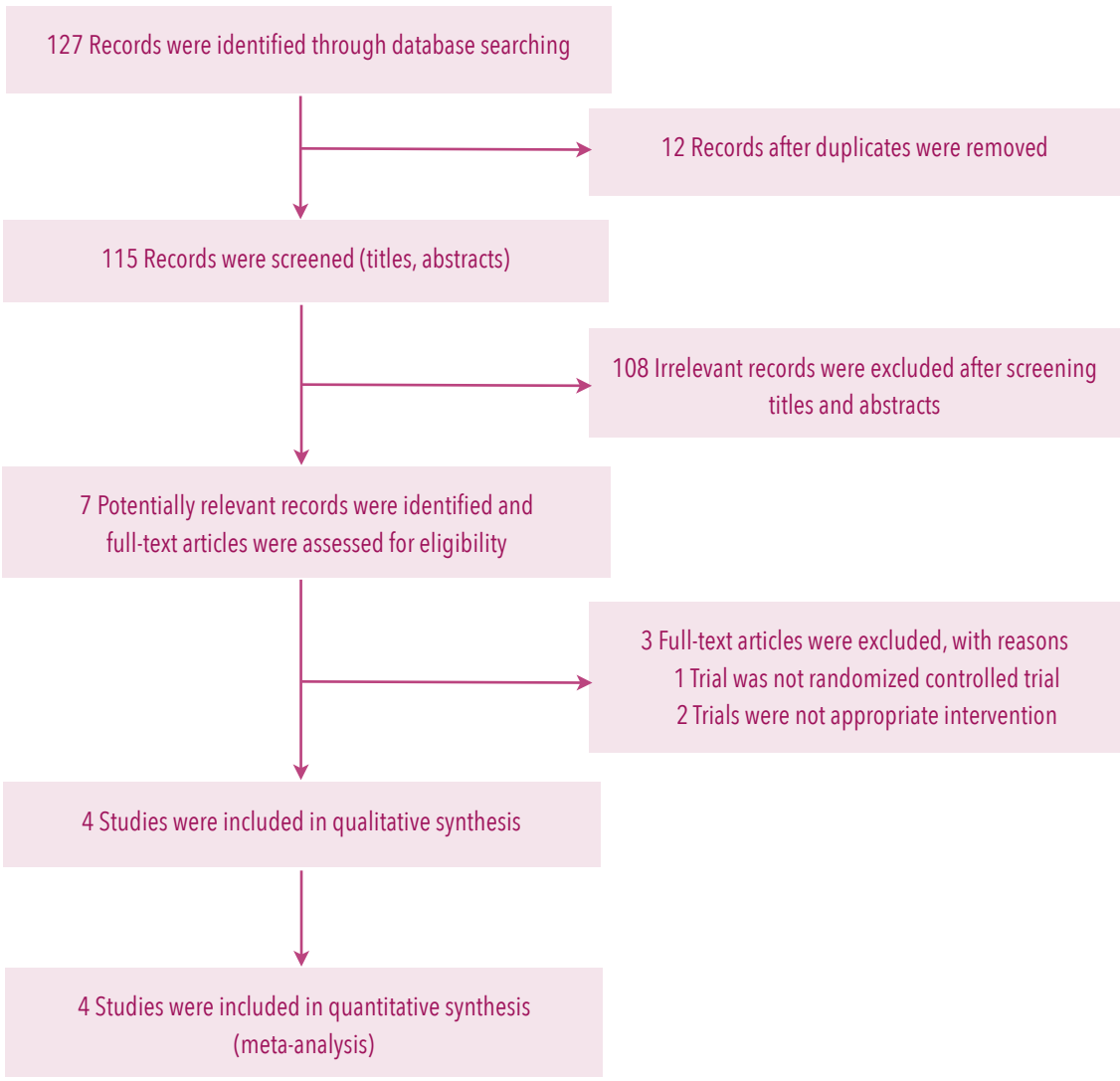

Figure 1. Process of study selection

Scopus, UpToDate and Trip Database with no language restriction. The last search was performed on December 2015. In addition, we hand searched the reference lists and relevant articles of all included studies to identify the further studies.

SEARCH STRATEGIES

We used an integration of keywords to search in Pubmed using MeSH terms "ivabradine" and "metoprolol" and "coronary angiography", "ivabradine" and "metoprolol", "ivabradine" and "coronary angiography", "metoprolol" and

Table 1. Characteristics of studies included in the analysis

Study	N	Study duration (month)	Details of participants	Interventions	Outcomes
Adile 2012	100	N/R	Suspected CAD	Group 1: oral ivabradine 5 mg BID at least 48 hrs Group 2: oral metoprolol 50 mg BID at least 48 hrs If the HR on arrival was >65 bpm, the patients would receive additional doses of the drugs (one dose of either 5 mg ivabradine or 50 mg of metoprolol). If the HR was still >65 bpm 3 hour after the additional first dose, another dose of 5 mg ivabradine or 50 mg metoprolol was administered.	Ivabradine has statistically significant deduction of HR between pre-medication and during CCTA (MD -2.5, 95% CI -4.3 to -0.7) than that of metoprolol as well as when compared pre-medication with prior CCTA (MD -7.7, 95% CI -10.3 to -5.1).
Bayraktutan 2012	110	3	Suspected CAD	Group 1: oral ivabradine 5 mg BID for 3 days Group 2: intravenous metoprolol 5 mg/ml bolus	Ivabradine has statistically significant deduction of HR between pre-medication and during CCTA (MD -3.0, 95% CI -5.0 to -1.0) than that of metoprolol as well as when compared pre-medication with prior CCTA (MD -4.0, 95% CI -6.6 to -1.4).
Celik 2014	125	12	Suspected CAD or mild or moderate-risk of coronary disease or progression of CAD	Group 1: oral ivabradine 15 mg single dose Group 2: initial intravenous metoprolol 5 mg was administered. If the HR was >65 bpm during a test breath hold command immediately prior the scan, an additional 5 mg intravenous metoprolol was administered in addition to the initial 5 mg. No additional dose was administered after the total dose of 10 mg intravenous metoprolol.	Ivabradine has statistically significant deduction of HR between pre-medication and during CCTA (MD -3.0, 95% CI -5.1 to -0.9) than that of metoprolol as well as when compared pre-medication with prior CCTA (MD -3.0, 95% CI -5.4 to -0.6).
Pichler 2012	120	N/R	Suspected CAD or progression of CAD	Group 1: oral ivabradine 15 mg Group 2: oral metoprolol 50 mg If the HR was >60 bpm during a test breath hold command immediately prior the scan, additional medication (5 to 20 mg metoprolol) was administered intravenously until a HR of ≤60 bpm was reached. Moreover, all patients received 0.8 mg nitroglycerin sublingually before the examination.	The difference of HR reduction was not statistically significant between ivabradine and metoprolol between pre-medication and during CCTA (MD -2.0, 95% CI -5.2 to 1.2). But ivabradine has statistically significant deduction of HR between pre-medication and prior CCTA (MD 5.0, 95% CI 2.1 to 8.0) than that of metoprolol.

N/R, not reported; CAD, coronary artery disease; BID, bis in die; HR, heart rate; bpm, beat per minute; CCTA, Coronary computed tomography angiography; MD, Mean difference; CI, confidence interval

Table 2. Jadad Scale

Study	Adile 2012	Bayraktutan 2012	Celik O 2014	Pichler 2012
How the study explained as randomized ?	1	1	1	1
What was the study explain how to create a sequence of randomize? Was it appropriate?	0	0	1	1
Was the study explained as double-blind?	0	0	0	0
Was the double-blind explained the method? Was it appropriate?	0	0	0	0
Had there a detail of withdrawals and dropouts?	1	1	1	1
Scale	2	2	3	3

"coronary angiography" and used keyword "ivabradine CT angiography", "metoprolol CT angiography" as well as in the Cochrane Library. We also used the search term "ivabradine" and "metoprolol" and "coronary angiography" for Scopus. For other databases, we used the following keywords: ivabradine and coronary computed tomography angiography as well as their synonyms for searching.

SELECTION OF STUDIES

Four authors screened titles and abstracts of relevant studies and independently selected of included trials depend on full texts assessment. If disagreement opinion occurred, consensus between four authors was used to resolve.

DATA EXTRACTION AND QUALITY ASSESSMENT

Four authors independently extracted the data from the included studies. We extracted author, year of publication, number of participants, study duration, details of participants, interventions and outcomes. We used the Jadad scale for assessing the quality of selected articles in term of randomization, blinding and an account of all patients. If the scale was 3 or more, the study was considered as a good quality study. We used the Cochrane Collaboration's tool[23] for independently evaluating the risk of bias of the included RCTs. Criteria for judging the risk of bias explained in Part 2; Chapter 8 of The Cochrane Handbook for Systematic Reviews of Interventions was used. The criteria consist of sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other of bias. The result was classified as "high, unclear or low risk of bias".

DATA ANALYSIS

To standardize our outcome, we computed the mean difference (MD) with 95% confidence interval (CI) for continuous data in each group for every trial. The chi-square and I^2 statistics were

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

used to evaluate statistical heterogeneity across trials. The statistical test of heterogeneity was significant if $P<0.05$ and heterogeneity was considered high if the I^2 were more than 50%. We also used sensitivity analysis for disregarding studies that were poor quality. In our meta-analysis, we used both the fixed-effect model and random-effect model according to heterogeneity for the analysis. All analyses were performed with Revman 5.3 (RevMan, the programme provided by the Cochrane Collaboration) statistical software.

RISK OF BIAS ACROSS STUDIES

The funnel plot was used to identify publication bias.

RESULTS

Our search strategies recognized 127 publications, 12 were removed due to duplication, 108 were excluded in the first round of assessment because titles and abstracts were not relevant (Figure 1).

Further three publications were excluded by discussion in the second round of assessment because they did not match with our inclusion criteria; the one trial was not RCTs and the two trials did not match our intervention. The remaining four records were included in the qualitative analysis and included in the meta-analysis.

STUDY CHARACTERISTICS

We identified and included 4 RCTs with 455 patients who suspected CAD and ongoing CCTA. Details of all included trials are shown in Table 1. All trials compared the HR reduction between ivabradine and metoprolol in patients who ongoing CCTA. Three were published in 2012 and one in 2014.

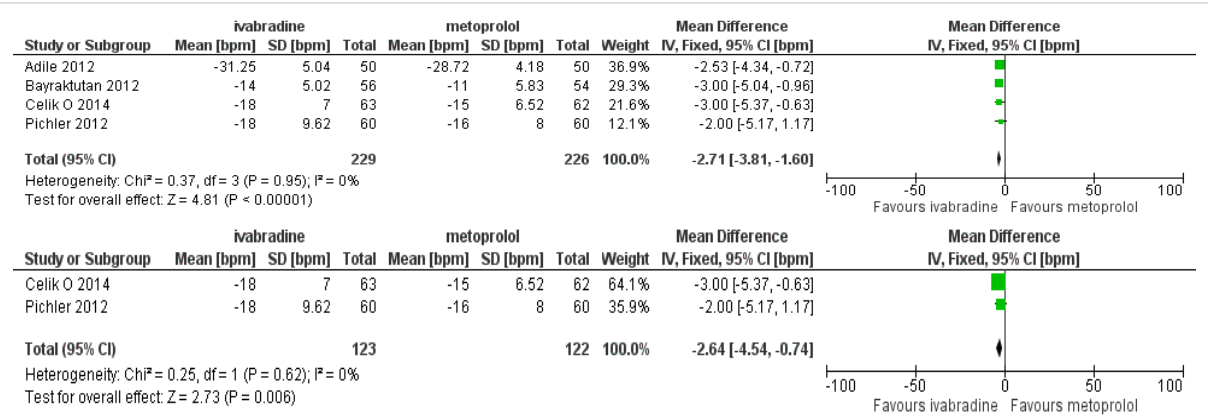

Figure 3. The forest plot of comparison: HR reduction between pre-medication and during CCTA inpatient who used ivabradine and metoprolol

QUALITY AND RISK OF BIAS

The quality of all studies was assessed using the Jadad scale (Table 2). The two trials were poor quality. Moreover, Figure 2 summarize the assessment of the risk of bias for individual trials (domain based-evaluation) using Cochrane Collaboration's tool.[23] Sequence generation process was appropriate in the two trials thus we classified as low-risk selection bias but the one trial was high risk and the one trial was an unclear risk. All trials did not explain concealment or how to conceal thus they were classified as an unclear risk. All trials did not explain the blinding of participants thus we classified as an unclear risk. The three trials did not describe tools for measuring the outcome but we considered that the outcome was not disturbed despite lack of blinding hence they were classified as low risk. All the trials did not have missing outcome data thus they were classified as low risk of attrition bias. All

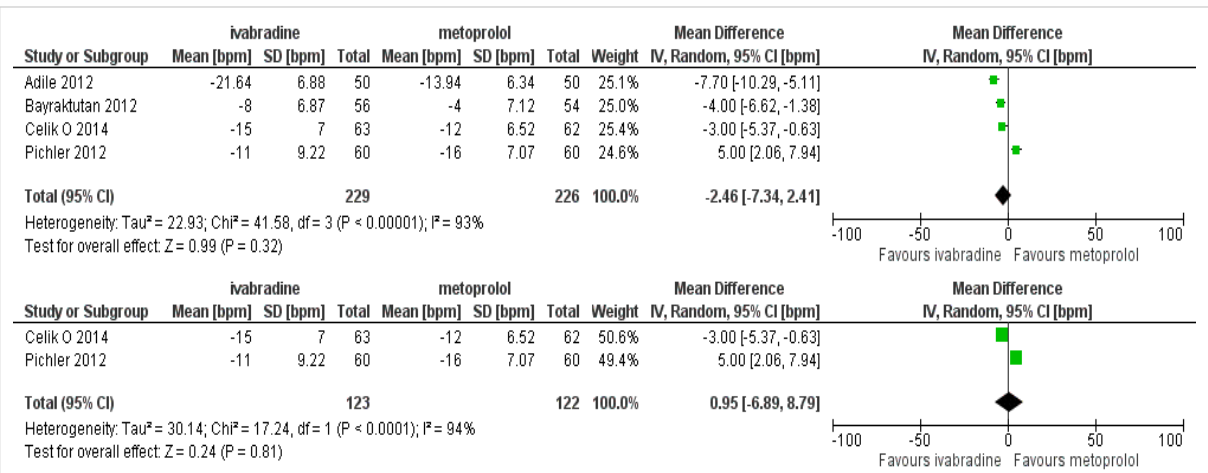

Figure 4. The forest plot of comparison: HR reduction pre-medication and prior CCTA inpatient who used ivabradine and metoprolol

Table 3. The mean HR during CCTA

Study	Ivabradine	Metoprolol
Adile 2012	58.8±1.3	63.2±1.4
Bayraktutan 2012	59.0±4.1	64.0±6.7
Celik 2014	62.0±7.0	66.0±6.0
Pichler 2012	58.0±8.0	60.0±8.0
Average	59.5±5.7	63.3±6.1

Plus–minus values are means ±SD.

trials reported pre-specified outcomes, we, then, classified them as low risk of reporting bias. The one trial did not classify other biases thus we classified as unclear risk and the one trial was classified as high risk.

PRIMARY OUTCOME

The four trials with a total of 455 patients were contributed to the meta-analysis of (i) HR reduction between pre-medication and during CCTA and (ii) HR reduction between pre-medication and prior CCTA in patients who received either ivabradine or metoprolol. Ivabradine had a statistically significant reduction of HR more than that of metoprolol inpatient ongoing CCTA comparing pre-medication and during CCTA (MD -2.71, 95% CI -3.81 to -1.60, fixed-effect model; I^2=0%) (Figure 3). Though comparing pre-medication and prior CCTA, the difference of HR reduction was not statistically significant between ivabradine and metoprolol (MD -2.46, 95% CI -7.34 to 2.41, random-effect model; I^2=93%) (Figure 4).

SENSITIVITY ANALYSIS

The meta-analysis of the two studies that were high quality, we found that ivabradine had a statistically significant reduction of HR more than that of metoprolol inpatient ongoing CCTA comparing pre-medication and during CCTA (MD -2.64, 95% CI -6.54 to -0.74, fixed-effect model; I^2=0%) (Figure 3). Though comparing pre-medication and prior CCTA, the difference of HR reduction was not statistically significant between ivabradine and metoprolol (MD 0.95, 95% CI -6.89 to 8.79, random-effect model; I^2=94%) (Figure 4). The results were similar to the meta-analysis of the four study, so we concluded that the poor quality studies did not affect the results.

HEART RATE DURING CCTA

Table 3. shows HR during CCTA; The mean heart rate was 59.5±5.8 bpm for patients who used ivabradine and 63.3±6.1 bpm for patients who used metoprolol. Both ivabradine and metoprolol could reduce HR to target which less than 70 bpm.

ADVERSE EVENTS

Table 4. shows the adverse events in the four studies; one case experienced hypotension and six cases experienced a visual disturbance in patients who received ivabradine whereas one case experienced hypotension in patients who received metoprolol.

Table 4. Adverse events in randomized controlled trials of this review

Study	Trial arm	No. of adverse events		
		Bradycardia	Hypotension	Visual disturbance
Adile 2012	Ivabradine (n=50)	0	0	N/R
	Metoprolol (n=50)	0	0	N/R
Bayraktutan 2012	Ivabradine (n=56)	0	1	1
	Metoprolol (n=54)	0	1	0
Celik 2014	Ivabradine (n=63)	0	0	1
	Metoprolol (n=62)	0	0	0
Pichler 2012	Ivabradine (n=60)	0	0	4
	Metoprolol (n=60)	0	0	0

N/R=not report

RISK OF BIAS ACROSS

Figure 4 shows the potential of publication bias that was identified by using a funnel plot. The funnel plot of the four trials included in the meta-analysis appeared to be asymmetrical as there were not many studies to be included.

DISCUSSION

STUDY SUMMARY EVIDENCE

The four trials with a total of 455 patients were contributed to the meta-analysis of HR reduction in patient who received either ivabradine or metoprolol, we found that ivabradine had a statistically significant reduction of HR more than that of metoprolol inpatient ongoing CCTA comparing pre-medication and during CCTA but though comparing pre-medication and prior CCTA, the difference of HR reduction was not statistically significant between ivabradine and metoprolol. For adverse events; one case experienced hypotension and six cases experienced a visual disturbance in patients who receive ivabradine whereas one case experienced hypotension in patients who received metoprolol.

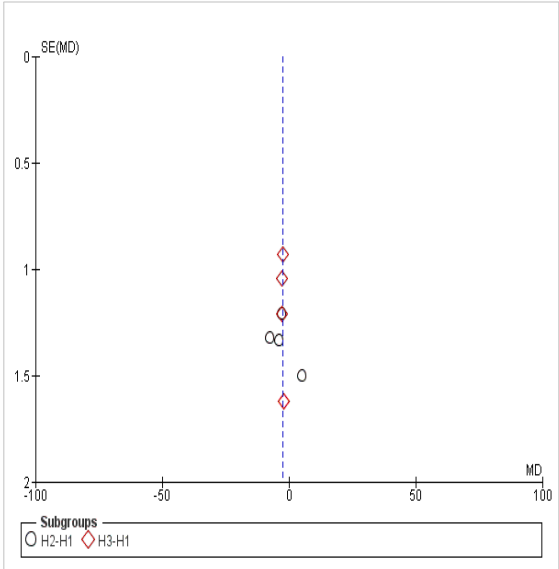

Figure 4. Funnel plot based on mean difference for HR reduction

COMPARISON WITH OTHER STUDIES

Our study found that ivabradine was superior over metoprolol, a beta-blocker in term of heart rate reduction. The findings were similar to an Italian study in 2012 stated that the rate of patients achieved the target heart rate in ivabradine 7.5 mg was higher than that of atenolol another beta-blocker.[24] Several minor adverse events were reported in our review. Many studies have reported the incidence of serious adverse events found higher in a group with ivabradine than that of placebo in stable CAD. These consisted of bradycardia, visual disturbance, and atrial fibrillation.[25-27] The study in 2009 show vasovagal reaction was found in patients who received oral or intravenous metoprolol,[28] but did not found the vasovagal reaction in our study.

STRENGTHS AND LIMITATIONS OF REVIEW

Our study is the first systematic review that described (i) HR reduction between pre-medication and during CCTA and (ii) HR reduction between pre-medication and prior CCTA in patients who received either ivabradine or metoprolol. However, our meta-analysis has limitations. The daily dose and duration of administration were various among the four studies.

Our systematic search had no dose limitation and thus allowed us to search for all dose ranges. There was a small number of included studies with the different outcome thus when we systematically included studies they were high heterogeneity and cause adverse events reported as minimal. The other limitation is a risk of bias in some of the included studies. The one study had many unclear risks of bias, the one study had a high risk of bias of random sequence generation and the one study had a high risk of bias of reporting. Others limitation was quality of studies, there are the two studies had poor quality when evaluated by Jadad scale. Another limitation is methodological heterogeneity among included studies. None of the included studies identified point of time for calculating the HR reduction thus we calculated the HR reduction from means and standard deviations that reported in included studies.

CONCLUSION

Ivabradine had a statistically significant reduction of HR more than that of metoprolol inpatient ongoing CCTA comparing pre-medication and during CCTA. But in clinical practice, both ivabradine and metoprolol can reduce HR to reach the target. When comparing pre-medication and prior CCTA, the difference in HR reduction was not statistically significant between ivabradine and metoprolol. We recommend that ivabradine can be used as an alternative heart rate-lowering agent in patients who have the contraindication to beta-blocker. For further study, we suggest having the new study that clear study design in relation to allocation concealment and blinding with long-term assessment of the adverse events.

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Bladder infusion versus standard catheter removal in urinary retention: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

BACKGROUND

To compare the outcomes of bladder infusion and standard catheter removal in patients with urinary retention.

METHODS

We searched for the studies through Trip Database, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and Scopus without any language restriction. We checked the references of included studies and manually searched for additional studies which were relevant. Criteria for inclusion in our meta-analysis included participants with urinary retention who were assigned randomly to remove the indwelling catheter by bladder infusion or standard catheter removal and the outcome was the time to discharge.

RESULTS

We identified four trials that met our inclusion criteria involving a total of 294 participants, who removed indwelling catheter by infusion bladder (132 patients) and standard catheter removal (162 patients). There was a statistically significant shorter time to discharge in the bladder infusion group than in the standard group (mean difference (MD) -5.6 hours; 95% confidence interval (CI), -9.06 to -2.21). In the inpatient's subgroup, there was no statistically significant difference in time to discharge between the bladder infusion group and the standard group (MD -9.06 hours; 95% CI, -19.36 to 1.23). In the dawn TOV subgroup, there was no statistically significant difference time to discharge between the bladder infusion group and the standard group (MD -6.41 hours; 95% CI -20.69 to 7.86). According to the time to decide to TOV, there was a statistically significant shorter time to decision to TOV in the bladder infusion group than the standard group (standard MD -0.69 hours; 95% CI, -1.02 to 0.37).

CONCLUSION

The bladder infusion method can reduce the time to discharge in the patients with urinary retention compared to the standard method.

INTRODUCTION

Urinary retention is an inability to empty the bladder completely, which can be acute urinary retention (AUR) or chronic urinary retention (CUR).[1,2] AUR is common in men.[3,4] The incidence of AUR dramatically increases with age, approximately 10 percent of men older than 70 and one-third of men in their 80s will develop AUR.[2] The initial management of AUR is immediate and complete bladder decompression by catheterization.[2,5-7] There are no uniform guidelines for bladder decompression.[8] Most patients will have an initial attempt at urethral catheterization.[8] The indwelling catheter should be inserted as first-line therapy and it was important because that effected to time to discharge, returning to normal voiding and rate of re-catheterization.[9-15] In addition, many techniques had been modified by various authors for shorter hospital stay such as early catheter removal, clamping before removal catheter and bladder infusion.[10,11,16-22] The previous studies have shown that the bladder infusion method before removing the catheter was found to be effective and patients could be discharged earlier once satisfactory voiding was attained.[10] Bladder infusion procedure was attaching an intravenous administration set to irrigating channels of the catheter then infused normal saline 300 to 500 cc until the patient had sensation of fullness and the catheter was then removed.[10]

There have been four randomized controlled trials (RCTs) comparing the bladder infusion method and the standard method regarding the outcomes in the patients with urinary intention published since 1996. Two RCTs in 1996 and 2010 showed that the bladder infusion method gives a significant result about the time to discharge when comparing to the standard method.[10,23] And the study in 1996 recommended applying this method for all patients.[23] One study in 2000 showed the significant difference in the timing of readiness to discharge including the ability to control and pass void in adequate volume but the day of discharge in this study was not statistically significant.[24] One study in 2012 showed no statistically significant relationship between bladder infusion and time to discharge even if it could decrease the time to discharge in practical.[25] It still has a controversy about the advantages of bladder infusion that it can apply in the patients or not that why the systematic review of this knowledge should be concerned.

METHODS

SEARCH STRATEGY

We searched for studies through Trip Database, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and Scopus without any language restriction. We used keyword standard catheter removal OR trial of void catheter removal OR "urinary retention AND foley catheter" and the asterisk for the synonyms searching in Trip Database, MEDLINE, Scopus, and CENTRAL. We checked the references of included studies and manually searched for additional studies which were relevant. Three authors have been performed by the individual and independently.

INCLUSION CRITERIA

PARTICIPANTS

Studies in the participants with urinary retention who were assigned randomly to remove the indwelling catheter.

INTERVENTIONS

Indwelling catheter removal by bladder infusion compared to standard catheter removal.

OUTCOMES

The primary outcome was the time to discharge from the hospital. Secondary outcomes included time to reach a decision to a trial of void (TOV) and adverse events measures according to failure to void within 24 hours and urinary tract infection.

EXCLUSION CRITERIA

None

DATA EXTRACTION

Data were extracted and recorded from three authors by individual and independently as the number of participants, interventions, and outcomes. Disagreements resolved by discussion and consensus.

QUALITY OF REPORTING AND RISK OF BIAS

Three authors evaluated the quality and risk of bias of the included studies with Jadad scale and Cochrane risk of bias tool to assess the quality of selected studies (table 2, figure 2, 3). Moreover, we used the domain based-evaluation following The Cochrane Handbook for Systematic Reviews of Interventions version 5.3.0 (the programme provided by the Cochrane Collaboration). The domain based-evaluation evaluated in random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias) and others bias. They classified the study into low risk, high risk and unclear risk for each bias tool. Potential publication bias was assessed by using a funnel plot (Figure 4).

DATA ANALYSIS

To standardize the reporting of our results. The primary outcome and some secondary outcomes, we calculated the mean difference (MD) and standard MD where appropriate with 95% confidence interval (CI) from continuous data in each group for three trials. All analyses were performed with Revman 5.3.0 statistical software using random effect model meta-analyses to assess time to discharge, time to decide to TOV of bladder infusion compared with standard catheter removal in patients with urinary retention and applied indwelling urinary catheter. The secondary outcome, the rate of failure to void within 24 hours, we calculated relative risk (RR) with 95% CI from dichotomous data. The chi-square and I^2 statistics were used to evaluate statistical heterogeneity across trials. The statistical test of heterogeneity was significant if $P<0.05$ and heterogeneity was considered high if the I^2 statistic was more than 50%. We used a random effect model for the meta-analysis when heterogeneity was of statistical significance.

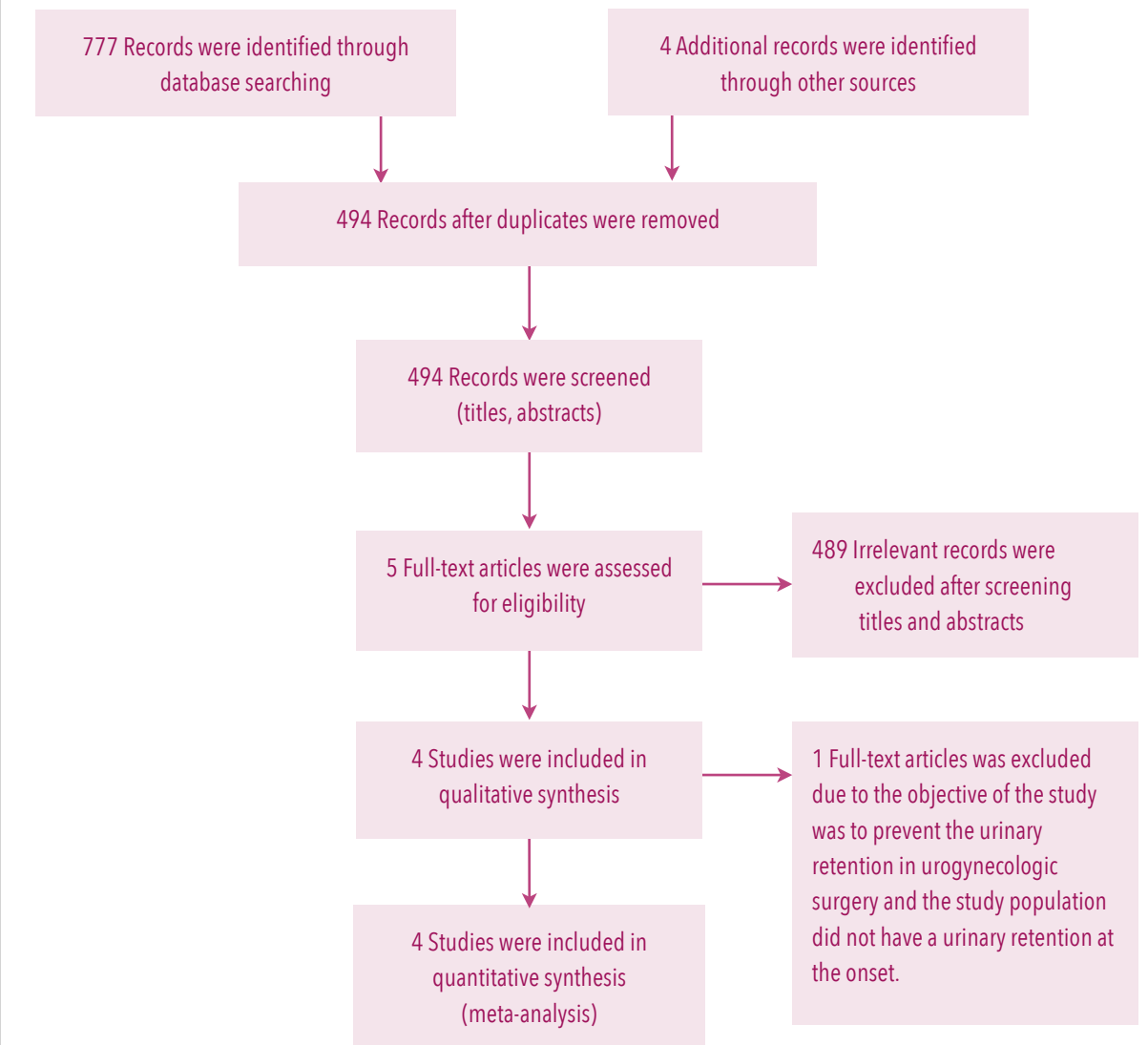

Figure 1. Process of study selection

RESULTS

The literature search retrieved 781 citations (Figure 1). Of these, after duplicates removed 494 citations were identified. All studies were RCTs. After screened the title and abstracts, 489 citations were excluded and then five full-text articles assessed for eligibility according to inclusion and exclusion criteria. Finally, four studies were included. The included studies assigned 294 participants, who were treated by bladder infusion method (n=131) and standard method (n=163).

STUDY CHARACTERISTICS

Table 1 summarizes the characteristics of the selected RCTs. All trials compared the outcomes between the bladder infusion and the standard method in patients with urinary retention.

Table 1. Characteristics of studies included

Study	Year	Population	Intervention	Control	Outcome
Lyth	1996	107 consecutive patients with postoperative TURP or BNI. Divided into 3 groups A midnight TOM group (n=39) A dawn TOM group (n=33) Bladder infusion group (n=35)	Fast drip rate of NSS with IV administration set infused to IDC by nursing staff	Standard catheter removal at midnight and dawn	Bladder infusion could reduce in time to decision to TOV and time to discharge but four patients in infusion group failed to void
I.D.Wilson	2000	75 consecutive patients undergoing TURP Divided into 2 groups Bladder infusion group (n=37) Standard catheter removal group (n=38)	Nursing staff used IV giving set to infuse NSS into the irrigating channel of IDC	Standard catheter removal at 06.00 hours by nursing staff	No significant in the day of discharge but significant increasing readiness for discharge
Mark A.Boccola	2010	60 participants who discharged after failing their operative and came to ED with AUR were recruited Divided into 2 groups Bladder infusion group (n=32) Control group (n=28)	Infusion of warm NSS 300-500 mL into urinary bladder	Standard catheter removal	Significant shortening time to discharge and time to decision to TOV and no significant in failure to void within 24 hours
Jason Du	2012	52 participants who underwent TURP, BNI or went the hospital with UR were recruited. Divided into 2 groups Bladder infusion group (n=27) Control group (n=25)	Infusion of NSS to IDC at 06.00 hours	Removing of IDC without infusion at 06.00 hours	No significant in time to discharge but increasing risk of failure to void within 24 hours

TURP, transurethral resection of prostate; BNI, bladder neck incision; NSS,normal saline solution; IV, intravenous; IDC, indwelling catheter; ED,emergency department

BIAS RISK ASSESSMENT

Four trials were assessed using the Jadad scale and Cochrane risk of bias tool (Table 2).

COCHRANE RISK OF BIAS TOOL

Figure 2A and 2B summarised the assessment of the risk of bias for individual trials (domain based-evaluation) using Cochrane Collaboration's tool.

SEQUENCE GENERATION, ALLOCATION CONCEALMENT AND BLINDING

All were randomized, open-labeled and compared between the bladder infusion method and the standard method with no blinding.[10,23-25] One study did not described randomization.[10] Two studies described inadequately about the allocation concealment.[23,25]

Table 2. Jadad Scale

Questions	Lyth 1996	I.D.Wilson 2000	I.D.Wilson 2000	Jason Du 2012
1. Was the study described as randomized?	1	1	1	1
2. Was the method used to generate the sequence of randomization described and appropriate?	0		1	1
3. Was the study described as double blind?	0	0	0	0
4. Was the method of double blinding described and appropriate?	0	0	0	0
5. Was there a description of withdrawals and dropouts?	1	1	1	1
Summary	2	2	2	3

TURP, transurethral resection of prostate; BNI, bladder neck incision; NSS,normal saline solution; IV, intravenous; IDC, indwelling catheter; ED,emergency department

INCOMPLETE OUTCOME DATA

All studies had no reports according to the incomplete outcome data or drop out of patients .[10,23-25]

SELECTIVE OUTCOME REPORTING

One of the studies had the selective outcome reporting because it showed the secondary outcome, the catheter-free rate at 4 weeks in the method but it was not reported in the result.[24]

OTHER POTENTIAL SOURCES OF BIAS

There were not the other potential sources of bias due to the study design that the intervention had to be done by the personnel. According to our funnel plot which constructed from the four trials included in the analysis appeared to be asymmetrical and suggested potential publication bias in this review.

CLINICAL OUTCOME

For the primary outcome, Figure 3 shows the results of the time to discharge, the primary outcome was MD of timing to discharge from the hospital. The meta-analysis of the three studies, there was a statistically significant shorter time to discharge in the bladder infusion group than in the standard group (MD -3.86 hours; 95% CI, -7.04 to -0.68; heterogeneity: $\chi^2=25.76$, $I^2=92\%$).[10,24,25] Two trials compared the time to discharge in the inpatients subgroup and outpatient subgroup, there was no statistically significant difference in time to discharge between the bladder infusion group and the standard group in the inpatients subgroup (MD -6.89 hours; 95% CI, -19.43 to 5.62; heterogeneity: $\chi^2=25.73$, $I^2=96\%$).[10,25] There was a statistically significant difference in time to discharge between the bladder infusion group and the standard group in the outpatients'

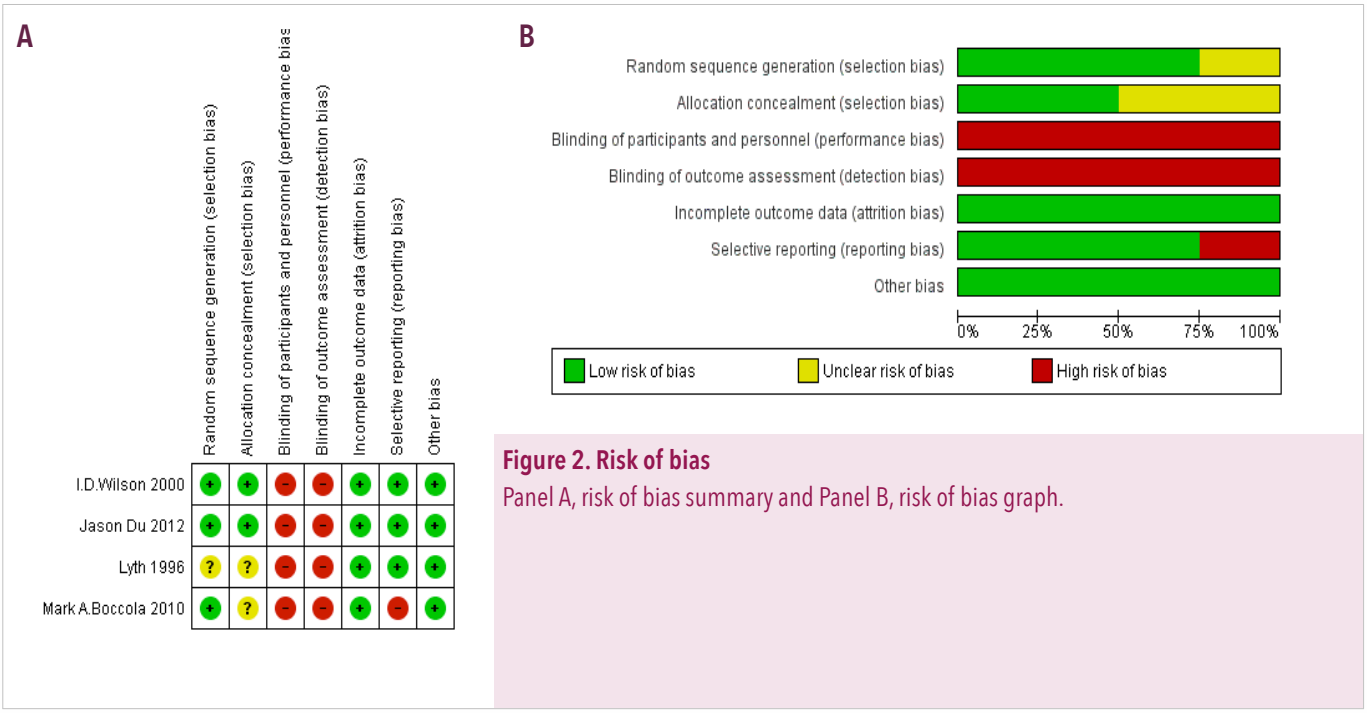

Figure 2. Risk of bias
Panel A, risk of bias summary and Panel B, risk of bias graph.

subgroup (MD -1.70 hours; 95% CI, -2.08 to -.132).[24] In the high-quality studies subgroup, there was a significant shorter time to discharge in the bladder infusion group than in the standard group (MD -1.46 hours; 95% CI, -2.30 to -0.62; heterogeneity: χ^2=1.69, I^2=41%).[24,25] In the low-quality studies subgroup, there was a statistically significant shorter time to discharge in the bladder infusion group than in the standard group (MD -13.50 hours; 95% CI, -18.23 to -8.77).[10]

For the secondary outcome, Figure 4 shows the results of the time to decide to TOV, there was no statistically significant shorter time to decision to TOV in the bladder infusion group than the standard group (standard MD -1.19 hours; 95% CI, -2.46 to 0.08; heterogeneity: χ^2=11.86, I^2=92%).[10,24] Figure 5 shows the results of the rate of failure to void within 24 hours and the urinary tract infection, There was no statistically significant difference in the rate of failure to void within 24 hours between the bladder infusion group and the standard group (RR 0.99; 95% CI, 0.32 to 3.12; heterogeneity: χ^2=6.22, I^2=52%).[10,23-25] In the inpatient subgroup, there was no statistically significant difference in the rate of failure to void within 24 hours between the bladder infusion group and the standard group (RR 1.90, 95% CI, 0.61 to 5.87; heterogeneity: χ^2=1.6, I^2=0%).[10,23,25] In the outpatient subgroup, there was a statistically significant difference in the rate of failure to void within 24 hours between the bladder infusion group and the standard group (RR 0.44, 95% CI, 0.21 to 0.93).[24] In the low-quality studies subgroup, there was no statistically significant difference in the rate of failure to void within 24 hours between the bladder infusion

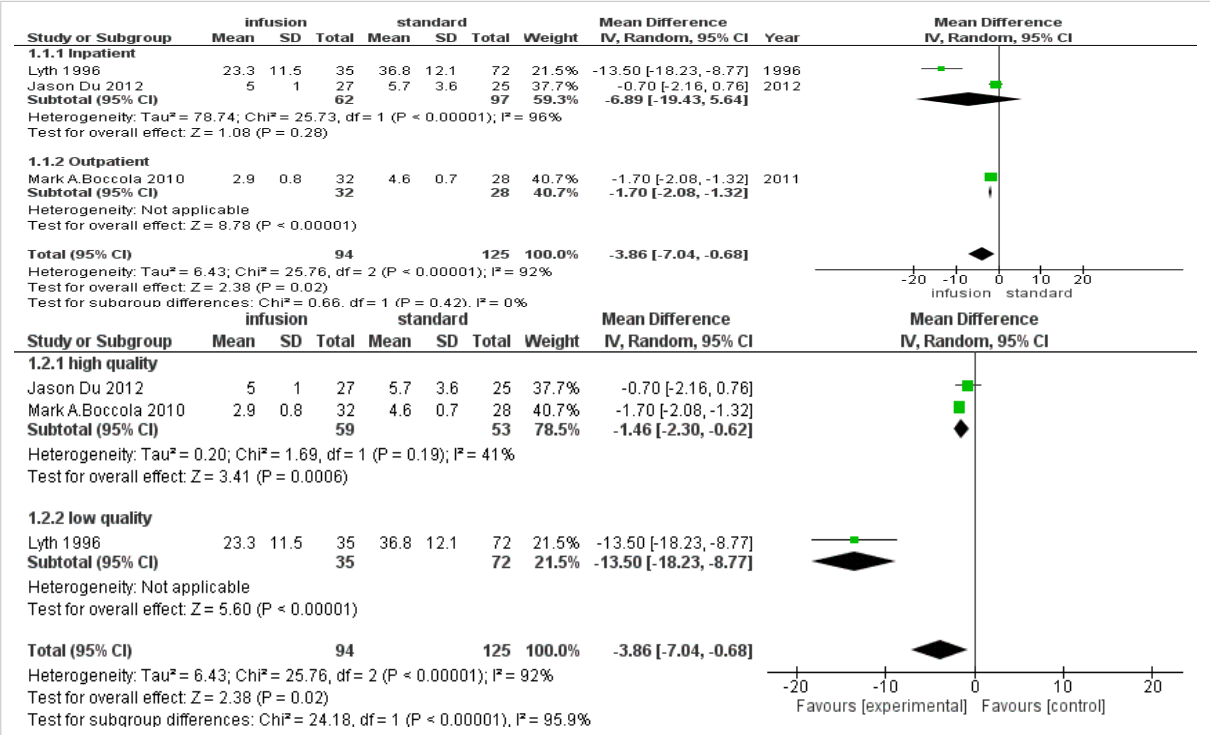

Figure 3. The forest plot of comparison: The time to discharge between the bladder infusion group and the standard group

group and the standard group (RR 2.84; 95% CI, 0.69 to 11.66; heterogeneity: χ^2=0.73, I^2=0%).[10,23] In the high-quality studies subgroup, there was a statistically significant difference in the rate of failure to void within 24 hours between the bladder infusion group and the standard group (RR 0.49; 95% CI, 0.24 to 0.98; heterogeneity: χ^2=0.53, I^2=0%).[24,25] There were no reports of urinary tract infection in all studies.*+

DISCUSSION

In this systematic review, a meta-analysis indicates that the infusion bladder method might reduce the time to discharge in the patients with urinary retention compared to the standard method. The heterogeneity is 92% that means it had a lot of variations either clinical heterogeneity or statistical heterogeneity such as the patient's conditions, the method to apply interventions, the measurement of outcomes and the assessor. In high-quality subgroup analysis, it indicates that the infusion bladder method might reduce the time to discharge in the patients with urinary retention compared to the standard method and the heterogeneity is 92%. Even if the result from a meta-analysis indicates the advantages of the infusion bladder method but the reliability could

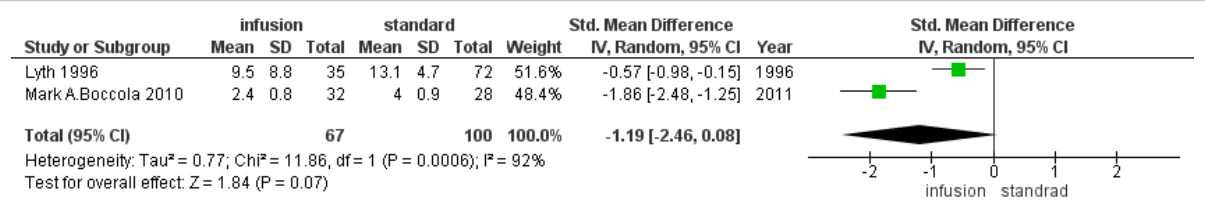

Figure 4. The forest plot of comparison: The time to decision to TOV between the bladder infusion group and the standard group

be reduced by the significant statistical heterogeneity between the trials. However, the primary outcome in this systematic review, the time to discharge could give the wrong information and make the statistics changed because almost patients would be discharged in the late afternoon of the first day after removing catheter but they could not come back due to the distance between their house and the hospital.[23] So if it has a further study, the measurement of this outcome should be the time of the first void after removing the catheter.

According to the secondary outcomes in this systematic review, a meta-analysis indicates that the infusion bladder method could not reduce the time to TOV in the patient with urinary retention compared to the standard method. To analyze the time to decide to TOV, the reviewers use the standard MD because of the various ways that two studies assessed the same outcome. One study made the decision according to when the TOV should commence and confirmed by the medical staff.[10] Meanwhile, another study decided and measured by monitoring with two-hourly bladder ultrasonography.[24]

In this systematic review, a meta-analysis indicates that the bladder infusion method might not increase the rate of failure to void in 24 hours compared to the standard method. However, in the high-quality subgroup and the outpatients' subgroup, a meta-analysis indicates that the bladder infusion method increased the rate of failure to void in 24 hours compared to the standard method. The reason for this result could occur from the outpatient with AUR who needed the intermittent indwelling catheter for initial management.[24] The patients in that group relieved symptoms but the underlying disease was still remaining. When the assessors applied the interventions and recorded the adverse events. It would not classify that the adverse events were from the interventions or their own underlying.

STRENGTH AND LIMITATION OF THE REVIEW

The strength in this systematic review is three authors searched for eligible RCTs by screening all titles and abstracts and reading the full-text articles to assess relevant studies, so we got eligible studies and assured not to miss the important data. The data extraction had been performed by individual reviewers and independently.

The limitation in this systematic review is the risk of bias thoroughly using Jadad scale and Cochrane risk bias tool. Only two studies were high

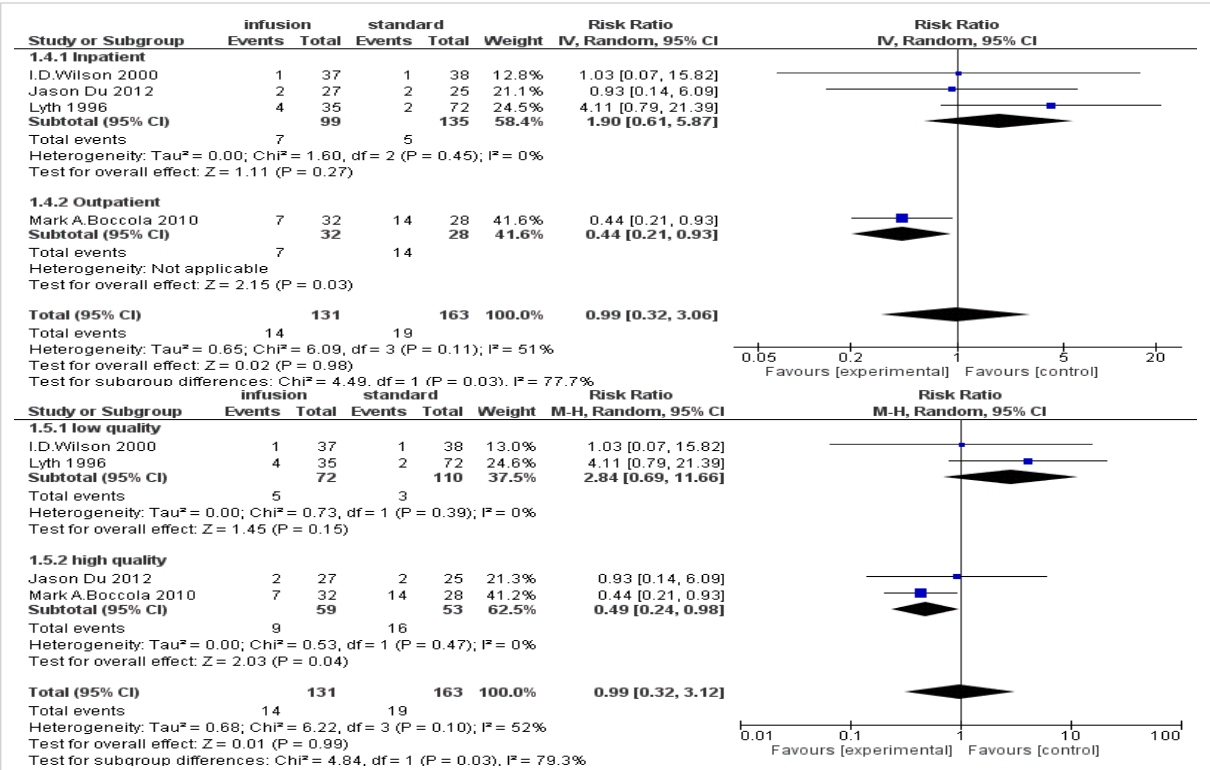

Figure 5. The forest plot of comparison: the rate of failure to void within 24 hours between the bladder infusion group and the standard group

methodological quality with a low risk of bias and the blinding method did not apply in all RCTs.[24,25] According to the primary outcome; Time to discharge, It had a lot of factors that affected the result such as the variation of an individual decision of the doctors and the readiness of patients including the distance between a house and a hospital, caregiver and poor financial support.

Each study had different methods to assess the same outcomes such as the assessment of the time to decide to TOV, One study made the decision according to when the TOV should commence and confirmed by the medical staff.[10] Meanwhile, another study decided and measured by monitoring with two-hourly bladder ultrasonography.[24]

COMPARISON WITH OTHER STUDIES

The primary outcome of this systematic review was the time to discharge that compared between bladder infusion method and standard catheter removal. There was one systematic review in 2007 that studied in the advantage of the bladder infusion method compared to the standard catheter removal in the patients with urinary retention and the primary outcome was the length of hospitalization.[11] The results indicate that the

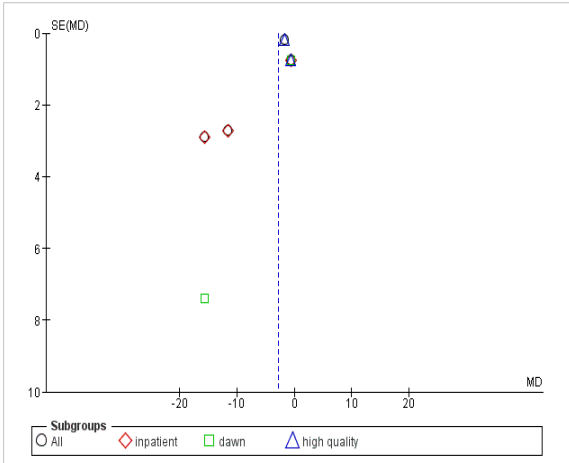

Figure 6. Funnel plot of overall catheter removal outcomes

midnight catheter removal method decreased the length of hospitalization of the patients with urinary retention compared to the morning catheter removal method with significant statistical heterogeneity similar to our systematic review.[11] Another outcome was the duration of catheterization, the results indicate that the early catheter removal did not decrease the length of hospitalization of the patients with urinary retention compared to the late catheter removal.[11]

There were two systematic reviews in 2009 and 2015 that reported the successful rate of spontaneous voiding in the patients with urinary retention by taking the alpha-blocker prior to catheter removal compared between the alpha-blocker group and the placebo group.[26,27] Both of the results indicate that taking the alpha-blocker prior to catheter removal increased the success rate of spontaneous voiding compared to the placebo in the patients with urinary retention.[26,27]

CONCLUSION

A meta-analysis of four RCTs indicates that the bladder infusion method might decrease the time to discharge in the patients with urinary retention compared to the standard method. However, this result should apply to the individual patient due to the various factors including the patient's conditions, the method to apply interventions, the measurement of outcomes and the assessor. Even though this systematic review concluded that there were no the adverse events in the bladder infusion method. For further studies, the RCTs should be performed with the larger number of sample studies and blinding method.

ACKNOWLEDGMENTS & DECLARATION

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COMPETING INTERESTS: This study has no competing on interest.
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Flunarizine versus betahistine in vertigo: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE
To compare the efficacies of flunarizine and betahistine in patients with vertigo.

METHODS
We systematically searched electronic databases from the Cochrane Library, PubMed, Trip Database and Scopus. The other resource that we searched included web directory (google scholar). We also made hand searching. We included the previous randomized controlled trials (RCTs) regarding the efficacy of flunarizine comparing with betahistine. Our primary outcome was vegetative symptoms improvement after 2 months and the secondary outcome was vegetative symptoms improvement after 1 month, free attack of vertigo, gastrointestinal (GI) disorders, and drowsiness.

RESULTS
It showed that the percentage of patients with improvement of vegetative symptoms after 2 months was significantly higher in flunarizine 10 mg once a day than in betahistine 8 mg three times a day (65% vs. 43.9%; relative risk (RR), 0.62; 95% confidence interval (CI), [0.41 to 0.94]. There were similar percentages of patients with improvement of vegetative symptoms after 2 months in those using flunarizine 10 mg once a day and betahistine 16 mg three times a day (52.0% vs. 61.4%; RR, 1.24; 95% CI, [0.74 to 2.08]; I^2=25%). There were also a similar proportion of patients with improvement of vegetative symptoms after 1 month in those using 10 mg of flunarizine and in any doses of betahistine (40.2% vs. 40%; RR, 1.08; 95% CI, [0.62 to 1.88]; I^2=70%). The rate of free attack of vertigo was significantly higher in 10 mg of flunarizine than in any doses of betahistine (73.6% vs. 41.2%; RR, 0.49; 95% CI, [0.25 to 0.94]; I^2=64%). There was no significant difference between flunarizine and betahistine in rate of GI disorders (5.7% vs. 15.3%; RR, 1.06; 95% CI, [0.80 to 1.42]; I2=87%) but rate of drowsiness was significantly higher in flunarizine group than in betahistine group (23.0% vs. 7.1%; RR, 0.70; 95% CI, [0.25 to 1.99]; I2=94%).

CONCLUSION
Among patients experiencing vertigo, flunarizine and betahistine did not significantly reduce vegetative symptoms after 2 months.

INTRODUCTION

Vertigo is a type of dizziness with an illusion or hallucination of movement, usual rotation of environment either or around oneself.[1,2] It can be caused by vestibular disorders e.g., Ménière's disease and migraine that symptom disturbs patient's quality of life.[1,3-4] It is usually treated by flunarizine, one of calcium channel blocker.[5-9] Moreover, it is also can be treated with betahistine which is a strong histamine-3 antagonist and a weak histamine-1 agonist.[10-17] However, the efficacy of flunarizine and betahistine are still controversy. For instance, there was a randomized controlled trial in 1988 comparing 10 milligrams (mg) of flunarizine once a day with 8 mg of betahistine three times a day revealed that flunarizine was more effective than betahistine in the improvement of vegetative symptoms.[18] However, the second and the third trials in 1991 and 2003 which comparing 10 mg of flunarizine once a day with 16 mg of betahistine three times a day found that betahistine was more superior than flunarizine in an improvement of vegetative symptoms.[19-20] Thus, it is still a debate in efficacy between flunarizine and betahistine in vegetative symptoms improvement. Hence, we conducted a systematic review of RCTs to compare benefits of flunarizine and betahistine.

METHODS

SEARCH STRATEGIES

We systematically searched to identify all RCTs, electronic databases from their inception to January 2016: totally four resources are the Cochrane Library, PubMed, Trip Database, and Scopus. We used Medical Subject Headings (MeSH) for Pubmed and the Cochrane Library searching; (("Vertigo"[Mesh]) AND "Flunarizine"[Mesh]) and other databases, we used the following keywords: vertigo, flunarizine, and betahistine. We also perform hand searching as well as searching through web directory i.e., google scholar.

STUDY SELECTION

We independently searched and screened the titles and abstracts to exclude irrelevant articles then relevant articles were read the full text to select studies into the systematic review. Any disagreement among the authors resolved by consensus and discussion. After that, we exclusively reviewed the remain full-text papers and chose some qualified studies.

INCLUSION CRITERIA

STUDY DESIGN

We included all randomized controlled trials that compared the efficacies of flunarizine and betahistine in patients with vertigo.

PARTICIPANTS

Participants are any ages of patients with clinical diagnosis of vertigo.

INTERVENTIONS

Medical treatments of our interest were flunarizine and betahistine regardless their dosing.

OUTCOMES

The primary outcome was the improvement of vegetative symptoms in 2 months. The secondary

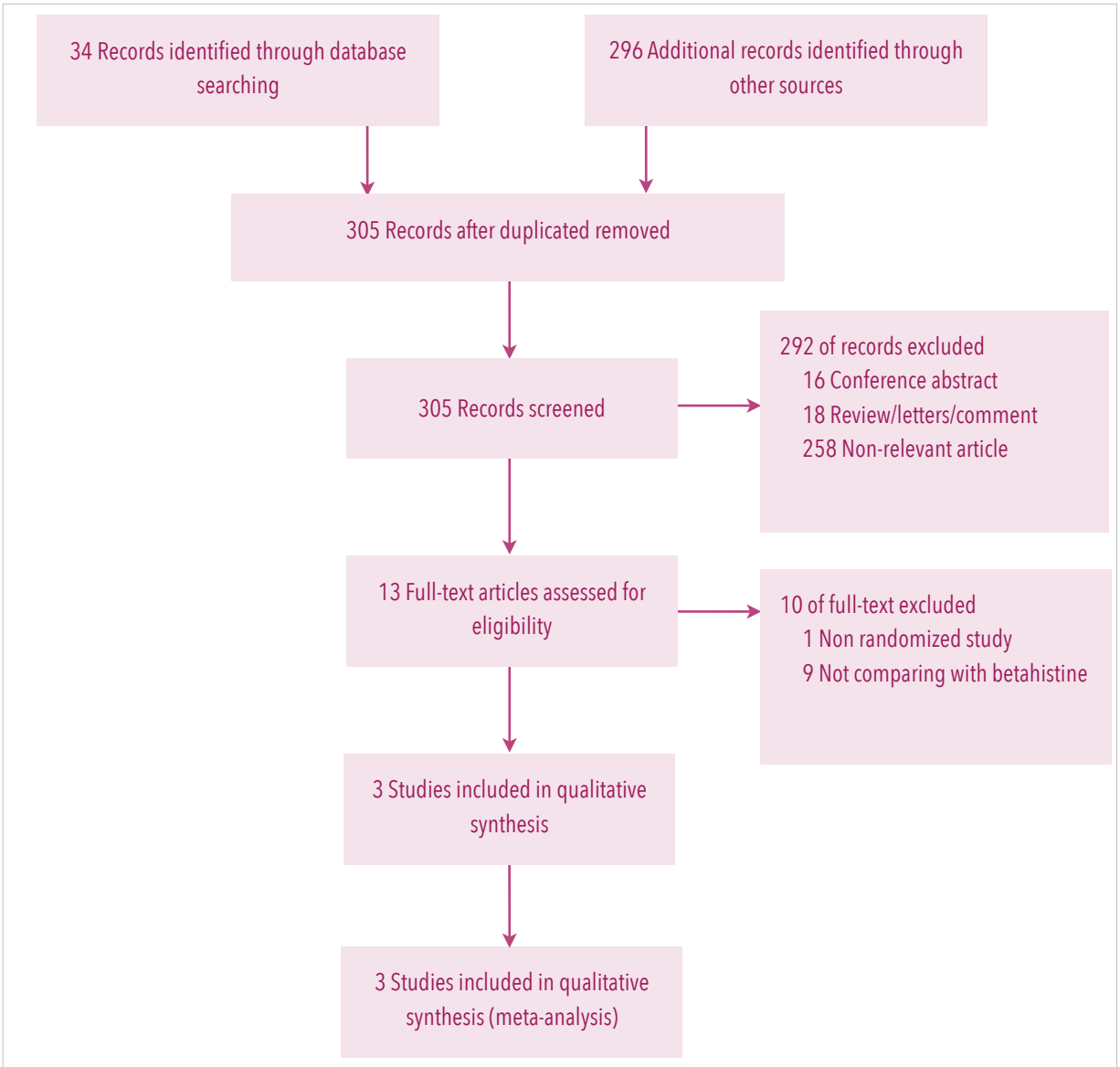

Figure 1. Study flow diagram

outcome was the improvement of vegetative symptoms in 1 month, free of vertigo attack in 2 months, adverse events in GI disorders and drowsiness.

EXCLUSION CRITERIA

We have no specific exclusion criteria.

ASSESSMENT OF STUDY QUALITY

Four review authors used the funnel plot and the Cochrane risk of bias tool to assess the methodological quality. We assessed every study that was included by concerning random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and

Table 1. Characteristics of studies included in systematic reviews

Study	Country	Study design	N	Participants	Intervention	Outcome
P.Elbaz et al. 1988	France	Randomised, double blinded controlled trial	117	patients with vertigo	60 patients with 10 mg of flunarizine tablet in the evening once a day compared with 57 patients with 8 mg of betahistine tablet three times per day	Flunarizine is more effective than betahistine in improving clinical symptoms (vertigo, feeling of instability, neurovegetative disorders, anxiety, auditory problems, tinnitus and headache, signs of disturbances of equilibrium and frequency of the attack.
B.Fraysee et al. 1991	France	Randomised, double blinded controlled trial	55	patients suffering from recurrent paroxysmal vertigo, with or without cochlear syndrome	27 patients with 10 mg of flunarizine tablet in the evening once a day and two doses of placebo taken at morning and noon compared with 28 patients with 16 mg of betahistine tablet three times per day	Betahistine is more effective than flunarizine in decreased frequency of attack, duration of attack, severity of attack, unsteadiness of attack, concomitant vegetative symptoms and cochlear symptoms and spontaneous vestibular dysfunction.
R.Albera et al. 2003	Italy	Randomised, double blinded controlled trial	52	patients aged 18-65 years with recurrent vertigo of peripheral vestibular origin	23 patients with 10 mg of flunarizine tablet in the evening once a day and two doses of placebo taken at morning and noon compared with 29 patients with 16 mg of betahistine tablet three times per day	Betahistine is significantly more effective than flunarizine in improving mean difference total DHI score, three subscores of DHI and vegetative or cochlear symptoms.

personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other biases. We classified the study into low risk, high risk, and unclear risk. We discussed with our advisor when we had a disagreement if the discussion could not solve a disagreement, authors of original articles were contacted.

DATA EXTRACTION

Four reviewers extracted data from included trials, any disagreement was solved by discussion, and when necessary we contacted the authors of the studies. The reasons for excluding studies from the review were recorded. The following data was extracted, (i) characteristics of each study were country of study, study design, the number of participants in each group, intervention, and outcome (ii) baseline characteristics of participants were vegetative symptoms.

DATA SYNTHESIS

We measured the efficacy of the medication expressed as dichotomous data; ratio with 95% from RevMan, the programme provided by the Cochrane Collaboration. Then the systematic review was made by comparing parameters.

MEASURES OF TREATMENT

Data was double checked by four reviewers. We evaluated improvement of vegetative symptoms, free attack of vertigo, adverse events in GI disorders and drowsiness for synthesized data.

ASSESSMENT OF HETEROGENEITY AND SENSITIVITY ANALYSIS

Heterogeneity in the results was evaluated by means of the chi-square test and I^2 test. High heterogeneity was considered when $P<0.05$ in statistically the chi-square test and I^2 statistic more than 50%. A random effect model was used for the meta-analysis when heterogeneity was statistical significance and funnel plots were created to showing the standard error and the effect size to identify potential of publication bias. The chi-square test and I^2 test were calculated from Review Manager version 5.3 (Revman); The Cochrane Collaboration's software.

RESULTS

We systematically searched 330 studies from electronic databases, web directory and made hand searching. After excluding the duplicated the studies, there were 13 studies met the inclusion criteria. We excluded 10 studies; 1 observational study, 9 RCTs not compared with betahistine (Figure 1). Totally the final selection contained 3 studies for analysis.

STUDY CHARACTERISTICS

We included 3 RCTs with 224 participants experiencing vertigo. One study that compared 10 mg of flunarizine once a day with 8 mg of betahistine three times a day and two studies compared 10 mg of flunarizine once a day with 16 mg of betahistine three times a day (Table 1).

BIAS RISK ASSESSMENT

All studies were assessed quality by the Cochrane Collaboration's tool. For the Cochrane Collaboration's tool, one was assessed as having a low risk of bias.[20] Two were assessed as having an unclear risk of bias (Figure 2A).[19-20] The risk of bias graph was summarized in (Figure 2B).

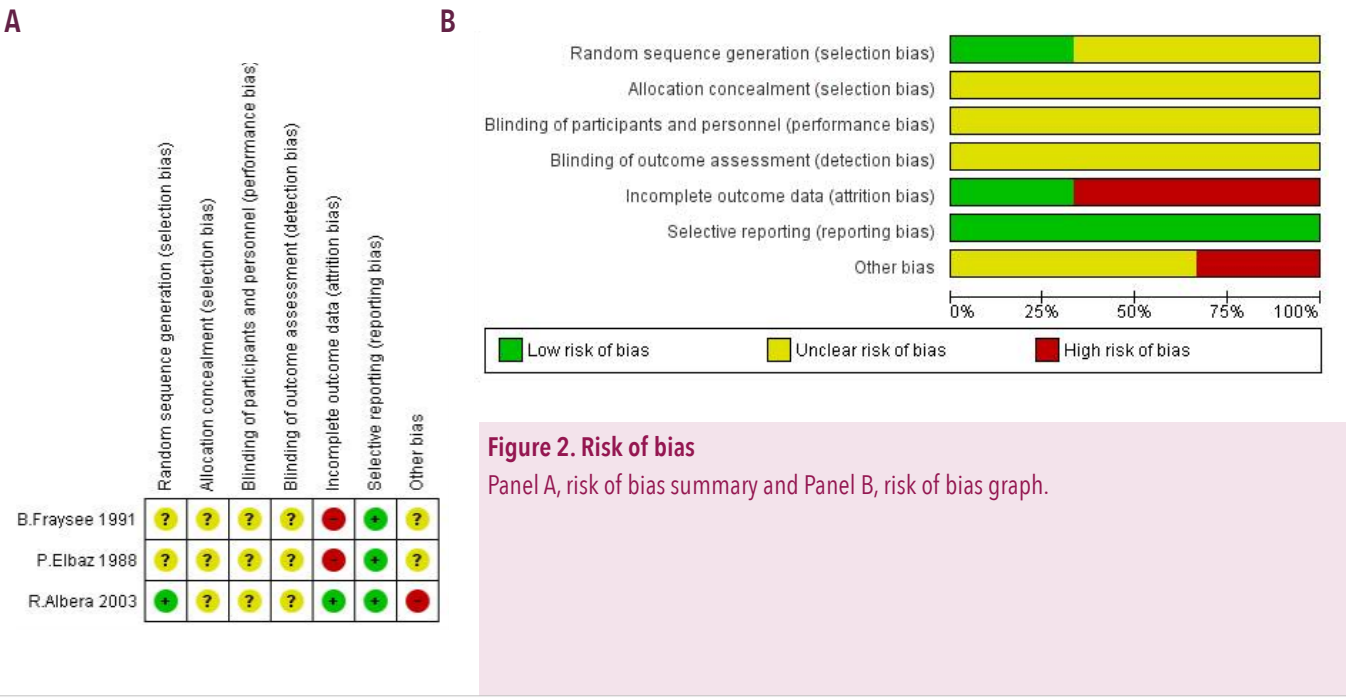

Figure 2. Risk of bias
Panel A, risk of bias summary and Panel B, risk of bias graph.

RANDOM SEQUENCE GENERATION

Two studies did not report the methods of generating a random sequence, while one study did and it was classified as "low risk".[18-20]

ALLOCATION CONCEALMENT

All included studies did not report details on allocation concealment and they were classified as "unclear risk".[18-20]

BLINDING OF PARTICIPANT AND PERSONNEL

All studies did not report details on blinding of participant and personnel and they were classified as "unclear".[18-20]

BLINDING OF OUTCOME ASSESSMENT

All studies did not report details on blinding of outcome assessment and they were classified as "unclear risk".[18-20]

INCOMPLETE OUTCOME DATA

One study were classified as "low risk".[20] Two studies were classified as "high risk".[18-19]

SELECTIVE REPORTING

All included studies properly described the adverse events and they were classified as "low risk".[18-20]

OTHER POTENTIAL SOURCES OF BIAS

One studies were supported by Solvay Pharma S.p.A and reported results as per-protocol thus it was classified as "high risk".[20] Two studies had no conflict of interest were classified as "low risk".[18-19]

OUTCOMES

IMPROVEMENT OF VEGETATIVE SYMPTOMS IN 2 MONTH

The systematic review of the three studies showed flunarizine 10 mg once a day had a higher

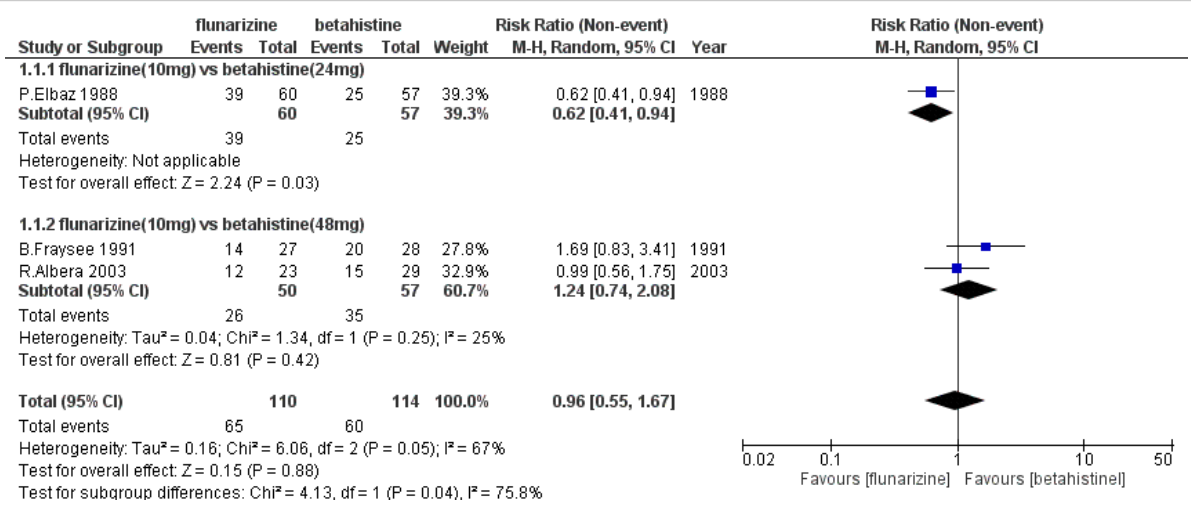

Figure 3. The forest plot of comparison: flunarizine 10 mg once daily versus betahistine 8 mg, 16 mg three times a day, outcome: the improvement of vegetative symptoms in 2 months

percentage of patients with improvement of vegetative symptoms after 2 months more than betahistine 8 mg three times a day (65% vs. 43.9%; RR, 0.62; 95% CI, [0.41 to 0.94]). The heterogeneity was not applicable due to 1 trial in this subgroup. There were similar percentages of patients with improvement of vegetative symptoms after 2 months in those using flunarizine 10 mg once a day and betahistine 16 mg three times a day (52.0% vs. 61.4%; RR, 1.24; 95% CI, [0.74 to 2.08]; I^2=25%) (Figure 3).

IMPROVEMENT OF VEGETATIVE SYMPTOMS IN 1 MONTH

The systematic review of the two studies showed a similar proportion of patients with improvement of vegetative symptoms after 1 month in those using flunarizine 10 mg and any doses of betahistine (40.2% vs. 40%; RR, 1.08; 95% CI, [0.62 to 1.88]). The heterogeneity was measured as having I^2 equal to 70% (Figure 4).

FREE VERTIGO ATTACK

The systematic review of the two studies showed the statistically significant difference improved rate of free vertigo attack compared 10 mg of flunarizine once a day with any doses of betahistine three times a day after 2 months (73.6% vs. 41.2%; RR, 0.49; 95% CI, [0.25 to 0.94]). The heterogeneity was measured as having I^2 equal to 64% (Figure 5).

ADVERSE EVENTS

The systematic review of two studies showed no statistically significant difference rate of adverse events compared flunarizine with betahistine after 2 months (14.4% vs. 11.2%; RR, 0.94; 95% CI, [0.78 to 1.15]). The heterogeneity was measured as having I^2 equal to 84%. There was no significant difference between flunarizine and betahistine in the rate of GI disorders (5.7% vs. 15.3%; RR, 1.06; 95% CI, [0.80 to 1.42]). The heterogeneity was measured as having I^2 equal to 87% but rate of drowsiness was significantly higher in flunarizine

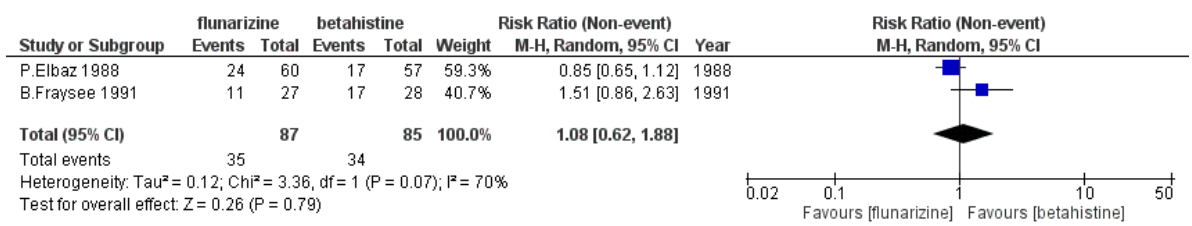

Figure 4. The forest plot of comparison: flunarizine 10 mg once daily versus betahistine 8 mg, 16 mg three times a day, outcome: the improvement of vegetative symptoms in 1 month

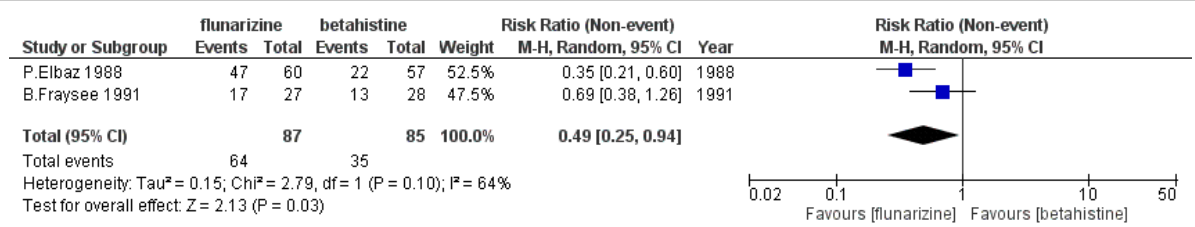

Figure 5. The forest plot of comparison: flunarizine 10 mg once daily versus betahistine 8 mg, 16 mg three times a day, outcome: free of vertigo attack in 2 month

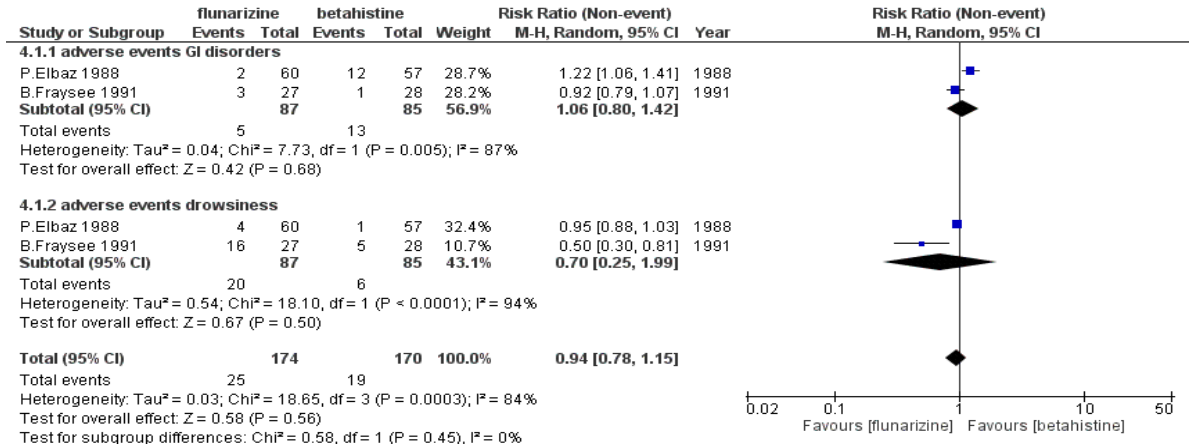

Figure 6. The forest plot of comparison: Flunarizine 10 mg once daily versus betahistine 8 mg, 16 mg three times a day, outcome: adverse events in GI disorders and drowsiness

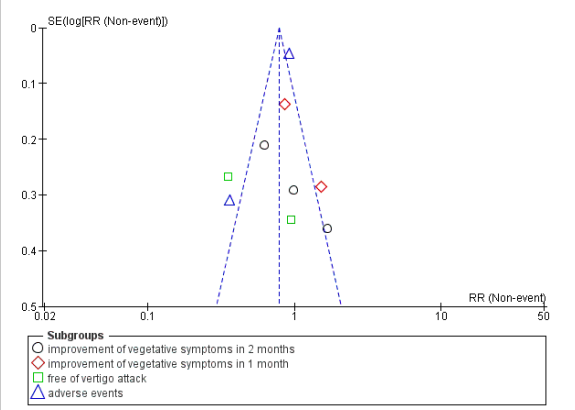

Figure 7. Funnel plot of comparison: Flunarizine 10 mg once daily versus betahistine 8 mg, 16 mg three times a day, outcome: the improvement of vegetative symptoms in 2 months, improvement of vegetative symptoms in 1 month, without attack of vertigo, adverse events

group than in the betahistine group (23.0% vs. 7.1%; RR, 0.70; 95% CI, [0.25 to 1.99]) The heterogeneity was measured as having I^2 equal to 94% (Figure 6).

DISCUSSION

MAJOR FINDINGS

In our study, we found that acetazolamide was not associated with the opening CSF pressure change, hypokalemia, and metabolic acidosis. However, opening CSF pressure at admission was associated with the opening CSF pressure change.

STRENGTHS AND LIMITATIONS OF THE STUDY

Our study is the first retrospective cohort design, that did in children and any causes of infectious meningitis.

Several limitations of this study should be mentioned firstly the sample size that the study required was 100 patients, but, in fact, ours was 85 patients, it was slightly different. Secondly, the medical records were not complete as some cases had no records of CSF pressure especially the record before discharge because in the case of improved clinical symptoms, the physician would not repeat LP for measuring CSF pressure and the patient would reject the procedure for those reasons the CSF pressure change could not access and it also was the one reason why we excluded some cases. Thirdly, the interval in each LP was varied. In addition, the LP technique, the measurement technique and the experiences of the practitioner were affected by the measure of the CSF pressure.

COMPARISON WITH PREVIOUS STUDIES

In our study, we found that adjunct acetazolamide to standard treatment in children with any causes of infectious meningitis and increased intracranial pressure had no difference in reduction of CSF pressure and adverse effects to standard treatment alone similar to the previous randomized single-blinded pilot study, from Uganda in 2005, the result showed no adverse effects and reduction in intracranial opening pressure.[16] However, the study performed in 18 AIDS adult patients with cryptococcal meningitis and increased intracranial pressure, which the intervention also combined with serial LP and the primary outcome was focused on clinical improvement. But one study that was affected by the adverse effects of acetazolamide, an RCT in 2002, comparing CSF pressure between

those using adjunct acetazolamide to standard treatment and those with standard treatment alone in 22 Thai patients, also studied in adults with cryptococcal meningitis and elevated intracranial pressure, was terminated as patients who were prescribed acetazolamide developed severe metabolic acidosis and hyperchloremia.[15] Anyway, there was a case series of 24 children, in 1979, suggested that repeated LP combined with acetazolamide adjunct to standard treatment could reduce the CSF pressure.[14] But there was no comparison group and performed in only children patients with tuberculous meningitis and communicating hydrocephalus.

On the other hand, in practice, acetazolamide is used as the main medical treatment for idiopathic
intracranial hypertension (IIH) for reduction of CSF production.[11,13] The evidence supports in this condition are the same as our condition that there are no studies to confirm the effectiveness of acetazolamide. Prior case series in children with IIH mentioned the success for improving symptoms of increased intracranial pressure and vision more than half patients.[26,27] Subsequently, the pilot RCT of 50 patients in United Kingdom, 2010, is difficult to practice due to poor recruitment and compliance.[28] And theirs limitation is the same as ours in the term of sample size. Later, in 2014, a multi-center, double-blinded, RCT of 86 patients in United States showed the improvement of visual field function but did not mention of other symptoms.[29]

CONCLUSION AND IMPLICATION

Adjunct acetazolamide to standard treatment had no difference in reduction of CSF pressure in children with meningitis and increased intracranial pressure. However, for better estimation effects of acetazolamide, larger sample size is needed. Multi-center retrospective cohort design should be conducted in settings where acetazolamide is of use for preliminary approximation effects of acetazolamide before conducting an RCT.

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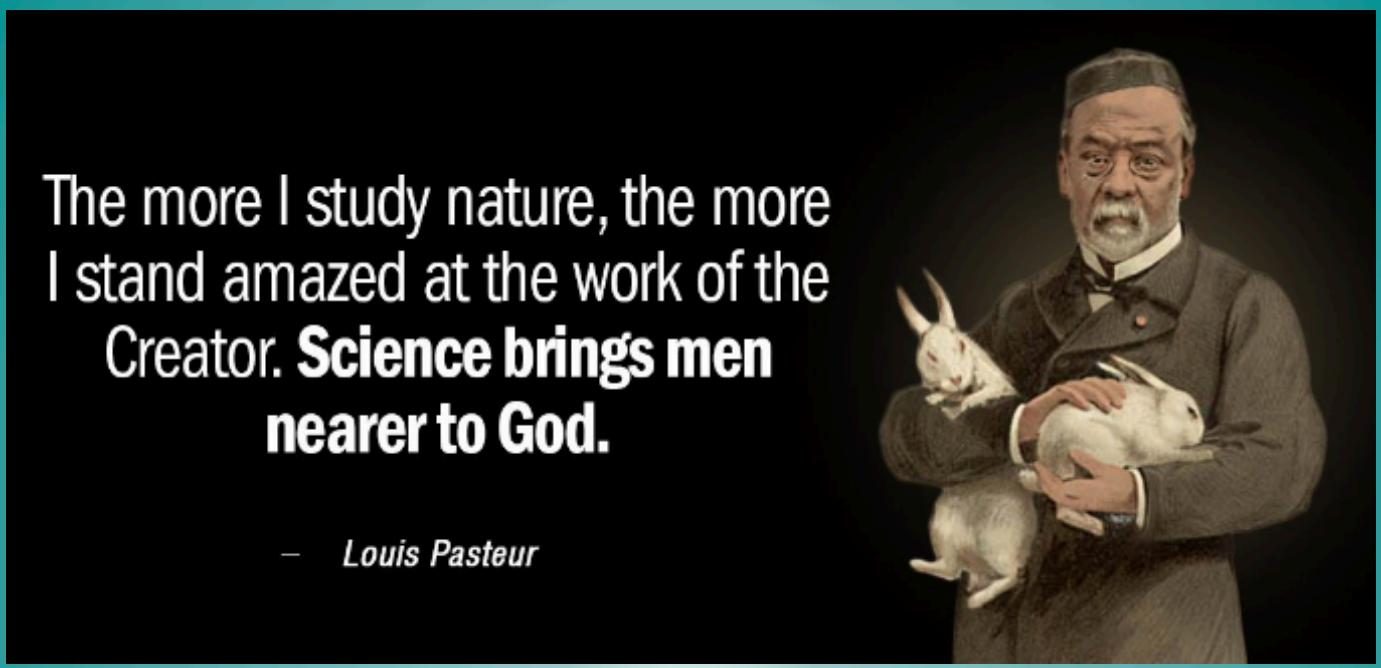
The more I study nature, the more I stand amazed at the work of the Creator. **Science brings men nearer to God.**
– *Louis Pasteur*

"I shall either find a way or make one"

-Hannibal Barca

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