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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

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

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message from the editor

New evidence is coming to you inevitably. In this issue, you will the major predictor of post-intubation hypotension. You will also learn whether intravenous pantoprazole is better than omeprazole in term of rebleeding prevention after endoscopy. One of our original articles in this issue will inform you about the relationship between uncontrolled blood pressure and acute intracerebral hemorrhage in those with hypertension. There is also a systematic review of pentoxifylline and prednisolone for improving mortality in those with severe alcoholic hepatitis. Hope you find this evidence is helpful. Enjoy!

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

submission

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All accepted articles are classified into two main categories;
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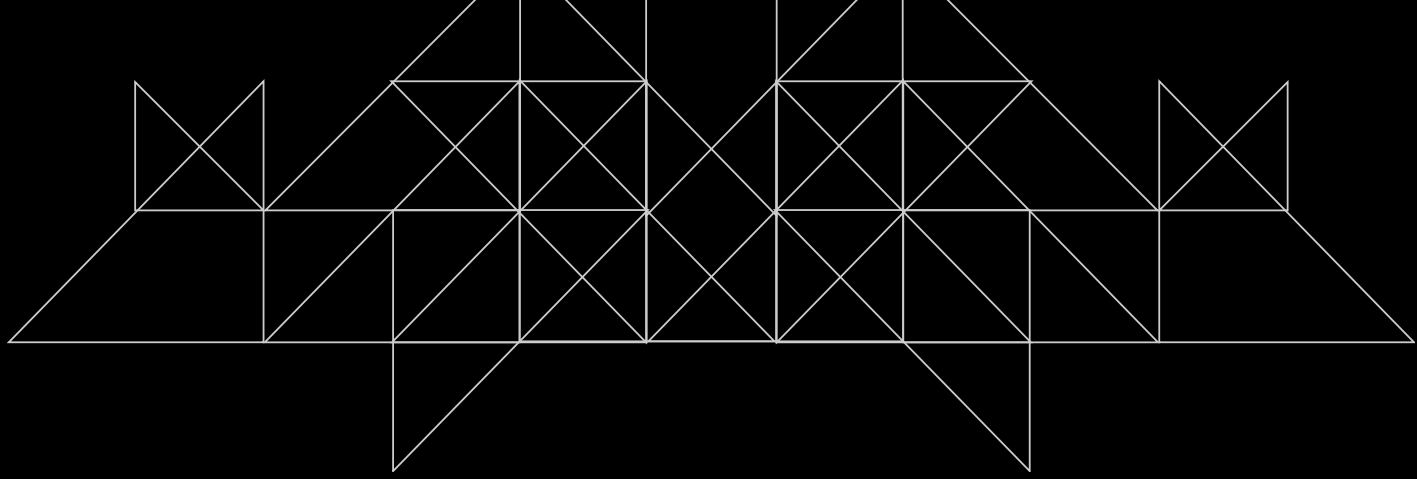
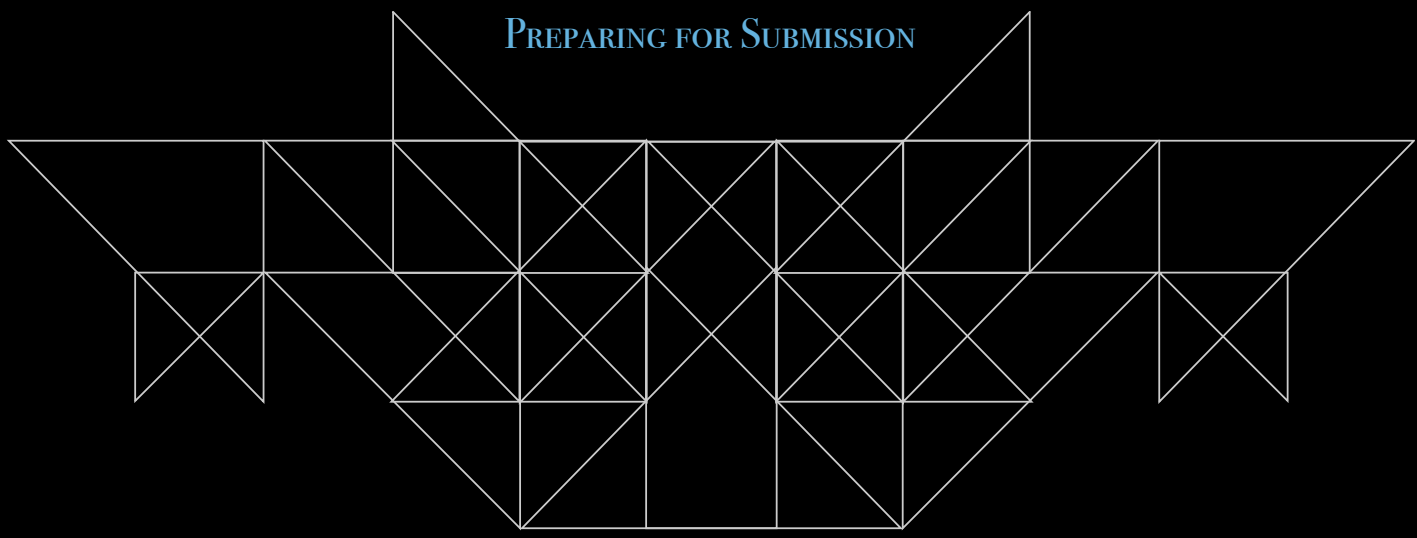


International Committee of Medical Journal Editors (ICMJE) Recommendation for Preparing for Submission



1. General Principles

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

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

2. Reporting Guidelines

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

3. Manuscript Sections

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

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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.

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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.

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iii. Statistics

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

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

ii. Reference Style and Format

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

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

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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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j. Units of Measurement

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Temperatures should be in degrees Celsius. Blood pressures should be in millimeters of mercury, unless other units are specifically required by the journal.

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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.

Predictive factors for post-intubation hypotension after emergency airway management

ORIGINAL ARTICLE

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To identify factors predicting post-intubation hypotension (PIH) after emergency airway management in the emergency department.

METHODS

This was a prospective cohort study enrolling intubated adults with non-traumatic hemodynamic stable patients in the emergency department, Khon Kaen Hospital from September 2016 to September 2017. The factors potentially associated with PIH were collected. The data was analyzed to define predictive factors for PIH and PIH effects, all-cause mortality was analyzed as the secondary outcome.

RESULTS

A total of 483 patients were enrolled. The patients experienced PIH were 33.1% after multiple logistic regression analysis, baseline systolic blood pressure (SBP)>140 mmHg was significant predictive factors for PIH (adjusted odds ratio (AOR) 1.51%; 95% confidence interval (CI), 1.01 to 2.24) and all-cause mortality in PIH group was higher when compared to non-PIH group (AOR, 3.94; 95% CI, 2.61 to 5.95).

CONCLUSION

Baseline SBP>140 mmHg was independently associated with increase PIH after emergency intubation.

INTRODUCTION

Post-intubation hypotension (PIH) is a common and serious complication in emergency endotracheal intubation and its incidence can be varied from 0.5 to 44%.[1-3] It affects about 25% of patients who are hemodynamically stable before intubation.[1] Nearly a half of the patients with this complication need vasoactive agents for support hemodynamic system.[4] Increasing catecholamine production leads to increase blood pressure and heart rate but when the patients are intubated, giving intravenous medications to relax during endotracheal intubation will reduce catecholamine to varying degrees, which may cause abrupt arterial and venous dilatation.[5-8] And initiation of positive pressure ventilation raises mean intra-thoracic pressure is transmitted to the right atrium to increase right atrial pressure. Because mean systemic pressure decreases and right atrial pressure increases, venous return decreases and cause of hypotension. It is explained as a physiologic response to intubation due to multiple mechanisms including induction sympatholytic drug and effects of positive-pressure ventilation, this risk leading physicians to assume that PIH is a benign, transient, or self-limited consequence of airway management.[8] However, PIH is a high-risk sign that is independently associated with increased in-hospital mortality and longer intensive care unit (ICU) and hospital length of stay.[1,9] Many studies that were conducted in various settings; ICU, emergency department and general ward that performed emergency airway management found that there were many factors which associated with a higher rate of this complication such as low body weight patients, high value of shock index, type of sedative drugs and neuromuscular blocking agent use.[2,9-14] But some factors were not included in current studies such as the use of some sedative drugs and methods of intubation. Thus, we designed this study to identify potential predictors for PIH.

METHODS

STUDY DESIGN AND SETTING

We conducted a prospective cohort study of patients who were intubated from September 2016 to September 2017 at Emergency Department, Khon Kaen Hospital, Thailand. The Institutional Review Board of Khon Kaen Hospital approved this study under a waiver of informed consent with the approval number of KE 59039.

STUDY POPULATION AND ELIGIBILITY CRITERIA

Our inclusion criteria were as the followings; (i) patients undergoing intubation with age 18 years or older, (ii) non traumatic patients, (iii) hemodynamic stable i.e., SBP≥90 mmHg or mean arterial pressure (MAP)≥65 mmHg without vasopressor drugs used for 10 consecutive minutes before intubation, (iv) being intubated in the emergency department.

STUDY PROCEDURES

The patients who met the inclusion criteria were enrolled in the study. The methods and medications of intubations were performed according to the physician's decision. Variable of interest data which included: age, body weight, underlying disease, baseline SBP before intubation, shock index, indication for intubation, number attempts of intubation, sedative drug use, neuromuscular blocking agents were records then

Table 1. Baseline characteristics of the patients

Characteristic	Total (n = 483)	PIH group (n = 160)	Non-PIH group (n = 323)
Male sex-no. (%)	289 (59.8)	87 (54.4)	202 (62.5)
Age-year	59.9±17.0	61.0±16.9	59.4±17.1
Body weight-kg	55.9±13.6	54.5±14.0	56.7±13.3
Baseline SBP-mmHg	145.4±36.5	151.0±43.1	142.5±32.4
Shock index (SD)	0.79±0.30	0.80±0.34	0.78±0.26
Underlying disease-no. (%)			
Chronic obstructive pulmonary disease	62 (12.8)	16 (10.0)	46 (14.2)
Hypertension	130 (26.9)	42 (26.2)	88 (27.2)
End stage renal disease	61 (12.6)	19 (11.9)	42 (13.0)
Indications for intubation-no. (%)			
Respiratory failure	349 (72.3)	121 (75.6)	228 (70.6)
Impending airway obstruction	131 (27.1)	37 (23.1)	94 (29.1)

* Plus–minus values are means ±SD

patients were divided into two groups; PIH group and non-PIH group. For the PIH group, the patients must have one of the following criteria; (i) decreased SBP (SBP<90 mmHg), (ii) decrease≥20 percent from baseline SBP or MAP<65 mmHg), and (iii) Initiation use of the vasopressor drug at any time in 30 minutes following intubation. All data were analyzed for the predictive factors of this adverse event.

STATISTICAL ANALYSIS

Continuous data are presented as means±SD. Categorical data are reported as proportions. For the primary outcome, factors that are important in the univariate analysis (P<0.2) were included in the multivariable analysis by using binary logistic regression to determine risk factors independently associated with PIH. The interactions between possible predictive factors also were tested. Results were expressed as adjusted odds ratio (AOR) and 95% confidence intervals (CI). Statistical significance determined as P<0.05. Overall mortality was reviewed for both PIH and non-PIH. The effect of PIH for overall mortality was analyzed and other factors that effect for overall mortality were assessed using multiple logistic regression.

RESULTS

A total of 483 patients were enrolled in this study, the mean age of all patients was 59.9 years and 58.9% were men. There were 160 patients in PIH group and 323 patients in non-PIH (non-PIH) group, respectively. There were no significant differences in baseline characteristics between the two groups (Table 1).

Table 2. Comparison of ventilation variables and drugs use during intubation between PIH and non-PIH group

Ventilation and drug variables	Total (n = 483)	PIH group (n = 160)	Non-PIH group (n = 323)
Method of intubation-no. (%)			
Awake intubation	220 (45.6)	71 (44.4)	149 (46.1)
Sedation without neuromuscular blocking agent	233 (48.2)	76 (47.5)	157 (48.6)
Rapid sequence intubation	30 (6.2)	13 (8.1)	17 (5.3)
Number attempt of intubation -no. (%)			
1	364 (75.4)	122 (76.2)	242 (74.9)
2	89 (18.4)	27 (16.9)	62 (19.2)
≥3	30 (6.2)	11 (6.9)	19 (5.9)
Sedative drug use-no.(%)			
None	224 (46.4)	71 (44.4)	153 (47.4)
Etomidate	36 (7.5)	15 (9.4)	21 (6.5)
Diazepam	223 (46.1)	74 (46.2)	149 (46.1)
Neuromuscular blocking agent-no.(%)			
None	453 (93.8)	147 (92.0)	306 (94.7)
Succinylcholine	25 (5.2)	11 (7.0)	15 (4.6)
Rocuronium	5 (1.0)	2 (1.3)	2 (0.6)

Nearly fifty percent of the patients were intubated using sedative drugs without neuromuscular blocking agent method and most of them were given diazepam. Of total 483 patients, 364 were successful in the first attempt of intubation. From the data of ventilation variables and drugs use, we did not find the statistical difference among PIH and non-PIH groups (Table 2).

From the univariate analysis; sex, body weight, Chronic obstructive pulmonary disease (COPD), baseline SBP, respiratory failure, impending airway obstruction, etomidate use, diazepam use and, etomidate and diazepam use variables may be significant predictors for PIH but after adjusted other variables and analyzed by multiple logistic regression baseline SBP>140 mmHg was only single factor which could predict this adverse outcome (AOR, 1.51; 95% CI, 1.01 to 2.24) (Table 3). After multivariable analysis, we found that PIH was a significant predictor for death in intubated patients adjusted (AOR, 3.94; 95% CI2.61 to 5.95) (Table 4).

DISCUSSION

This study was addressed about predictive factors for developing hypotension after emergency

Table 3. Univariate and multivariable analysis for post-intubation hypotension

Variables	Crude odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Age-year*	1.00 (0.99 - 1.01)	
Male sex	0.71 (0.50 -1.05)	0.77 (0.52 to 1.15)
Body weight-kg*	0.99 (0.97 -1.00)	0.99 (0.97 to 1.00)
Underlying disease		
Chronic obstructive pulmonary disease	0.67 (0.37-1.22)	0.59 (0.32 to 1.11)
Hypertension	0.95 (0.62 -1.46)	
End stage renal disease	0.90 (0.51 -1.61)	
Baseline SBP>140 mmHg	1.36 (0.93-1.99)	1.51 (1.01 to 2.24)
Shock index*	1.30 (0.70 -2.50)	
Indications for intubation		
Respiratory failure	1.30 (0.84-2.00)	0.78 (0.25-2.47)
Impending airway obstruction	0.73 (0.47-1.14)	0.57 (0.18-1.83)
Method of intubation		
Awake intubation	1.00	
Sedation without neuromuscular blocking agent	1.01 (0.69 -1.50)	
Rapid sequence intubation	1.60 (0.74-3.49)	
Number attempt of intubation		
1	1.00	
2	0.86 (0.52 -1.43)	
≥3	1.15 (0.53-2.49)	
Sedative drug use		
None	1.00	1.00
Etomidate	1.65 (0.76-3.58)	1.78 (0.80 -3.95)
Diazepam	1.05 (0.70-1.56)	1.02 (0.67-1.55)
Neuromuscular blocking agent		
None	1.00	
Succinylcholine	1.60 (0.69-3.74)	
Rocuronium	2.08 (0.13-33.51)	

*Increase per 1 unit of variable

Table 4. Univariate analysis and multivariable analysis for overall mortality

Variables	Crude odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Post-intubation hypotension	3.99 (2.67-5.95)	3.94 (2.61-5.95)
Age-year*	1.01 (1.00-1.02)	1.01 (1.00 -1.03)
Male sex	0.86 (0.59-1.25)	
Underlying disease		
Chronic obstructive pulmonary disease	0.41 (0.21-0.77)	0.38 (0.19-0.75)
Hypertension	0.71 (0.47-1.10)	0.65 (0.40-1.06)
End stage renal disease	0.62 (0.34-1.12)	0.67 (0.35-1.29)
Sedative drug use		
None	1.00	
Etomidate	1.32 (0.61-2.86)	
Diazepam	1.01 (0.69 -1.49)	
Neuromuscular blocking agent		
None	1.00	1.00
Succinylcholine	1.89 (0.81-4.37)	1.92 (0.78-4.76)

* Increase per 1 unit of variable

intubation and SBP>140 mmHg was associated with a 1.51- fold risk of this adverse outcome. From previous studies, many factors that can predict hypotension after emergency airway management such as body weight of patients, underlying disease, vital signs before intubation, type of sedative drugs and neuromuscular blocking agent use.[2,9-14] However, we found no relationship between these factors and post intubation hypotension in our study. Result of study differ from result of Lin C-C et al[11] which pre-intubation blood pressure<140 mmHg was associated with post intubation hypotension according to the definition of post intubation hypotension was different and they studied only in RSI method intubated patients. From our result, the patients with high blood pressure (SBP>140 mmHg) had a higher risk to develop hypotension may cause from their high sympathetic stimulation before intubation, when they were created positive pressure ventilation and catecholamine decreased abruptly, post intubation hypotension occurs.

The patients with post intubation hypotension had a 3.94-fold risk of death which confirmed previous reports of the relation between this adverse outcome and mortality.[4,15] Although this outcome was not the primary outcome, we should develop guideline and checklists to avoidance and management of post intubation hypotension to prevent the mortality.

There are several limitations to our study, firstly, our study was performed in one single tertiary care hospital so the results may not be generalized to other patients. Secondly, some factors such as diagnosis or diseases of the patients were not included in the analysis. Thirdly, the method to measure the blood pressure was non-invasive monitoring which may give us the inaccurate values.

In summary, we found that SBP>140 mmHg was an independent factor that associated with higher rate of PIH, a common complication after emergency airway management. For better understanding of this association, a larger cohort study should be conducted as well as trials seeking for an appropriate intervention to prevent PIH especially during emergency airway management should also be conducted.

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Intravenous pantoprazole versus omeprazole for rebleeding prevention in nonvariceal bleeding after endoscopy: a retrospective cohort study

ORIGINAL ARTICLE

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To compare the efficacy of intravenous pantoprazole and omeprazole on the reduction of the rebleeding rate in patients with nonvariceal bleeding after endoscopy.

METHODS

We conducted a retrospective cohort study comparing the rates of recurrent bleeding after successful endoscopic therapy in the patients with intravenous pantoprazole and intravenous omeprazole. Patient medical records were included if they were admitted at Khon Kaen Hospital, Thailand between January 2013 to May 2015 with the first episode of endoscopic diagnostic nonvariceal bleeding with successful hemostasis and received either intravenous pantoprazole or omeprazole immediately for recurrent bleeding prophylaxis. The primary outcome was recurrent bleeding. The secondary outcomes included surgery, blood transfusion after esophagogastroduodenoscopy (EGD) and EGD retreatment.

RESULTS

A total of 1097 medical records of the patients with nonvariceal bleeding after endoscopy were reviewed (806 in the omeprazole group and 291 in the pantoprazole group). Rebleeding occurred in 33 patients. There was no differences between the two groups in term of rebleeding rate, surgery and esophagogastroduodenoscope retreatment (adjusted odds ratio (AOR), 1.56; 95% confidence interval (CI), 0.67 to 3.61; AOR, 1.26; 95% CI, 0.36 to 4.35; AOR, 1.49; 95% CI, 0.58 to 3.81, respectively). However, we founded high-risk gastroscopic findings were the only factor associated with the higher rate of rebleeding after successful endoscopic hemostasis, surgery and EGD retreatment (AOR, 5.55; 95% CI, 2.07 to 14.93; AOR, 9.49; 95% CI, 1.79 to 50.29; AOR, 3.65; 95% CI, 1.32 to 10.08, respectively).

CONCLUSION

In patients with nonvariceal bleeding after endoscopy, using intravenous pantoprazole did not decrease the rate of rebleeding after EGD treatment than using omeprazole.

INTRODUCTION

Thailand confronts with the problem of upper gastrointestinal bleeding (UGIB) with case fatality rate ranging between 0.8 and 14%.[1] Peptic ulcer is the main cause for UGIB,[2,3,4] in which its symptom is presented a decade earlier in Asian patients comparing to the Caucasian.[5] Many studies show that after endoscopic treatment of bleeding peptic ulcer, proton pump inhibitor (PPI) can reduce the risk of rebleeding.[6,7,8] There were two previous studies comparing between intravenous pantoprazole and omeprazole; a randomized controlled trial in 2009 conducted in 90 Indian after successful endoscopic therapy of bleeding peptic ulcer, the rebleeding rate was similar among those with intravenous and oral omeprazole, pantoprazole and rabeprazole, however, it's conclusion was based on small sample size.[9] Another retrospective cohort in 2010 conducted in 807 Spanish with bleeding peptic ulcer, it found that intravenous pantoprazole was not superior to omeprazole for prevention of rebleeding. However, the application might suit the elderly as the participants were generally aged around 60 years old.[10] Hence, we conducted a retrospective cohort study in a group of Thai population with a larger sample size to overcome the limitation of the previous studies.

METHODS

STUDY DESIGN

We conducted a retrospective cohort study comparing the rate of recurrent bleeding after successful endoscopic therapy in the patient with intravenous pantoprazole and intravenous omeprazole.

PATIENT RECORDS

We verified and reviewed medical records retrospectively of all patients who admitted at Khon Kaen Hospital, Thailand between January 2013 and May 2015 with the first episode of endoscopic diagnostic nonvariceal bleeding with successful hemostasis and received intravenous pantoprazole or omeprazole immediately for recurrent bleeding prophylaxis. Successful hemostasis was established if the bleeding had stopped and formerly bleeding vessels were flattened or cavitated.[6,11,12] Patients were excluded if they were referred back to other hospitals after endoscopic, discharged by against advice before 72 hours, on anticoagulants and had multiple sources of bleeding.[13]

EXPOSURE

The use of post-endoscopic intravenous proton pump inhibitors is strongly recommended.[14] In our cohort, there were two study groups; the first group referred to the exposed group that received intravenous pantoprazole 80 mg bolus then infusion drip 8 mg/hr and another group referred to the control group that received intravenous omeprazole 40 mg twice daily.[15,16]

OUTCOME MEASURES

The primary outcome was posted successful endoscopic hemostasis rebleeding.[17] Rebleeding

was established if the ulcer was actively bleeding or if there was either coffee-grounds substance or fresh blood in the stomach.[6,9,17,18] The secondary outcomes included surgery, death, blood transfusion after esophagogastroduodenoscopy (EGD) and EGD retreatment.

DATA COLLECTION

All databases of patients diagnosed with UGIB using the International Classification of Disease (ICD) 10 who admitted in Khon Kaen Hospital. Variables including age, sex, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, hemoglobin on admission, platelet on admission, prothrombin time (PT) on admission, partial thromboplastin time (PTT) on admission, international normalized ratio (INR) on admission, coagulopathy was defined as the PT more than 13.6 sec or PTT more than 41.6 sec or INR more than 1.5,[19] underlying diseases, type of bleeding along Forrest classification, EGD report, blood transfusion after EGD, surgery records. Patients were classified as the high-risk group for recurrent bleeding if the gastroscopic finding was sporting or oozing or non-bleeding visible vessel or adherent clot or Dieulafoy's lesion.[20]

STATISTICAL ANALYSIS

All data were cleaned before the analysis. For descriptive statistics, categorical variables were summarized in term of number and percentage. For continuous variables, they were tested for their normal distributions using Kolmogorov-Smirnov test, mean and standard deviation (SD) were used if they were normally distributed while median and interquartile range (IQR) were used if they were non-normally distributed. For inferential statistics, chi-square and Fisher's exact test were used in appropriate condition for categorical variable comparison. T-test and Mann-Whitney U test were used for normally and non-normally distributed variables respectively. We used relative risk (RR) to analyze the primary outcome, post successful EGD hemostasis rebleeding, surgery, blood transfusion after EGD and EGD retreatment. For the multivariable analysis, the risk factors for the outcomes were interpreted as adjusted odds ratio (AOR) from the binary logistic regression analysis.

RESULTS

PATIENTS

Initially, 2,398 patients diagnosed with UGIB were reviewed, 1,201 were met the inclusion criteria, however, after excluding 104 patients, 1,097 were included in the analysis (Figure 1). Total of 1,097 was included in the analysis 291 were treated with pantoprazole and 806 were treated with omeprazole. Overall, mostly they were male (77.0%) with the median age of 64.1 years old (IQR 52.0 to 73.6). Their median SBP and DBP on admission were 123.0 mmHg (IQR 107.5 to 143.0) and 70.0 mmHg (IQR 60.0 to 80.0) respectively. Nearly half of them were shocked at the admission (41.9%). A quarter of all patients had coagulopathy (28.7%). For laboratory variables, their median PT, PTT, and INR on admission were 13.0 sec (IQR 12.1 to 14.4), 33.7 sec (IQR 30.0 to 39.5) and 1.09 (IQR 1.02 to 1.21), respectively. There were small numbers of patients with cardiac disease (5.0%),

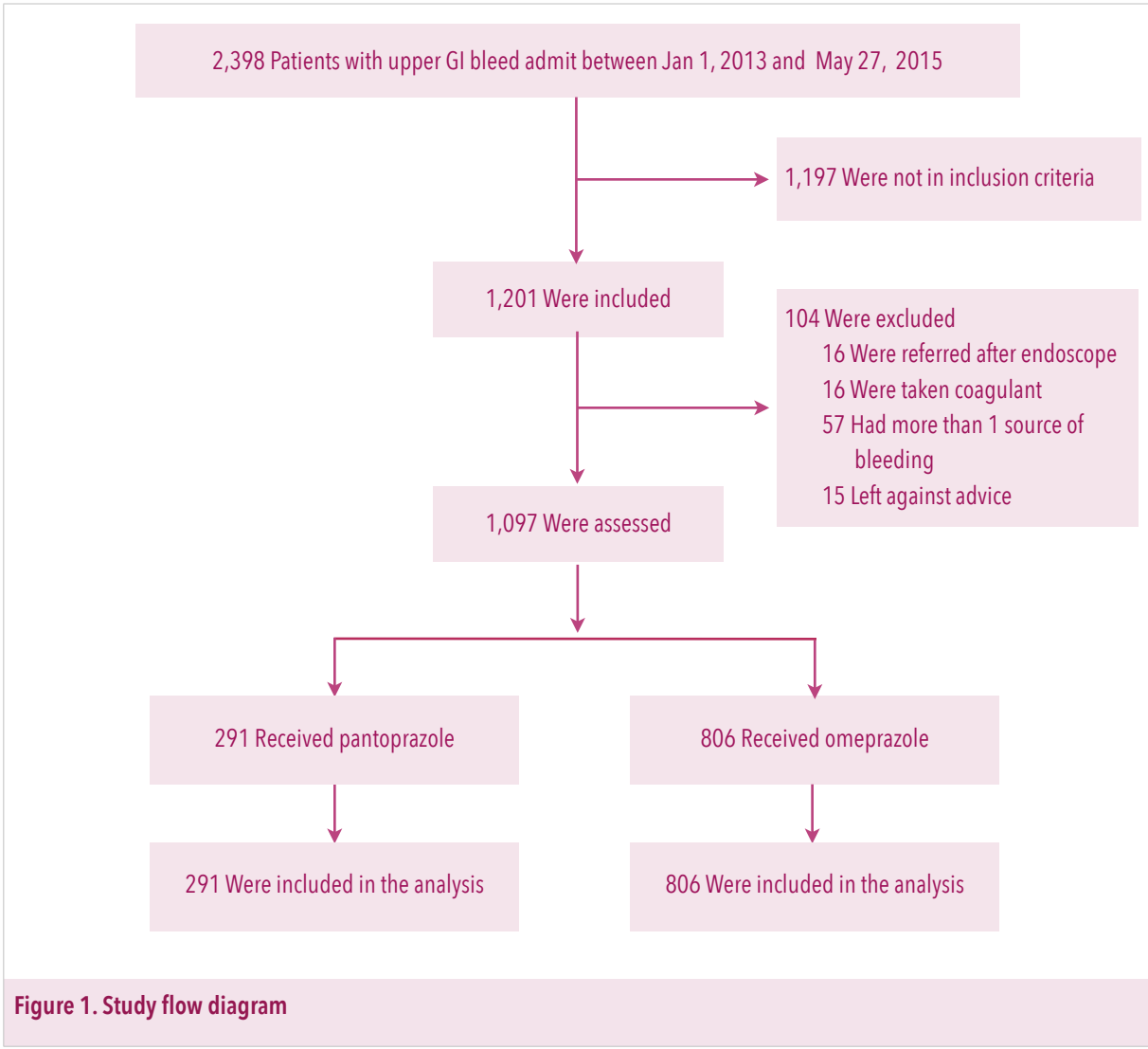

Figure 1. Study flow diagram

renal failure (10.3%) and liver disease (6.7%). For the endoscopic findings, most patients had clean-based ulcer (32.6%), gastritis (25.7%) and non bleeding visible vessel (16.4%) while there were fewer numbers of patients with spurting lesion (3.19%), oozing lesion (7.6%), adherent clot (4.6%) and flat pigmented spot (4.0%).

Comparing between the pantoprazole and the omeprazole group, the former tended to be older (P=0.01), have lower SBP (P<0.001), have lower DBP (P=0.005) and have a higher proportion of patient with shock status on the admission (P=0.03) (Table 1). For the laboratory variables, hemoglobin on admission was lower in the former group (P=0.001). For the diagnosis, patients with clean-based ulcer and gastritis were found less common in the former group (P<0.001 and P<0.001, respectively) while they had a higher

Table 1. Characteristics of the patients

Characteristic	Intravenous pantoprazole (N=291)	Intravenous omeprazole (N=806)	P Value
Age-yr			0.01
Median	65.1	63.4	
Interquartile range	55.6-75.4	50.2-73.0	
Male sex-no. (%)	225 (77.3)	620 (76.9)	0.89
Shock-no. (%)*	138 (47.4)	322 (40.0)	0.03
Systolic blood pressure-mmHg			<0.001
Median	120.0	125.0	
Interquartile range	103.0-138.0	109.0-146.0	
Diastolic blood pressure-mmHg			0.05
Median	67.0	70.0	
Interquartile range	59.0-78.0	61.0-80.0	
Heart rate-bpm			0.31
Median	92.0	90.0	
Interquartile range	80.0-104.0	78.8-102.0	
Hemoglobin-mg/dL			0.001
Median	7.0	7.7	
Interquartile range	5.3-9.1	5.9-9.9	
Platelet-10^3/uL			0.29
Median	221.0	216.0	
Interquartile range	165.0-292.0	153.0-278.3	
Prothrombin time-sec			0.34
Median	13.0	12.9	
Interquartile range	12.1-14.5	12.0-14.3	
Partial thromboplastin time-sec			0.23
Median	34.2	33.5	
Interquartile range	30.1-40.1	30.0-39.3	0.37

Table 1. Characteristics of the patients (continued)

Characteristic	Intravenous pantoprazole (N=291)	Intravenous omeprazole (N=806)	P Value
International normalized ratio			0.37
Median	55.6-75.4	50.2-73.0	
Interquartile range	225 (77.3)	620 (76.9)	
Coagulopathy-no. (%)†	138 (47.4)	322 (40.0)	0.46
Comorbidity-no. (%)			
Cardiac disease	14 (4.8)	41 (5.1)	0.85
Renal failure	32 (11.0)	81 (10.0)	0.65
Liver disease	16 (5.5)	58 (7.2)	0.32
Disseminated malignancy	3 (1.0)	15 (1.9)	0.25
Gastroscopic findings-no. (%)			
Spurting	27 (9.3)	8 (1.0)	<0.001
Oozing	57 (19.6)	26 (3.2)	<0.001
Non bleeding visible vessel	108 (37.1)	72 (8.9)	
Adherent clot	32 (11.0)	18 (2.2)	<0.001
Flat pigmented spot	8 (2.7)	36 (4.5)	0.20
Clean base	30 (10.3)	328 (40.7)	<0.001
Gastritis	14 (4.8)	268 (33.3)	<0.001
Mallory-weiss tear	1 (0.3)	8 (1.0)	0.26
Gastric mass or polyp	4 (1.4)	12 (1.5)	0.58
Dieulafoy lesion	9 (3.1)	14 (1.7)	0.17
High-risk group‡	231 (79.4)	138 (17.1)	<0.001

*Shock was defined as a systolic blood pressure less than 100 mmHg or heart rate more than 100 beats/min

†Coagulopathy was defined as the prothrombin time more than 13.6 sec or partial thromboplastin time more than 41.6 sec or INR more than 1.5

‡Patients were classified as high-risk group for recurrent bleeding if the gastroscopic finding was spurting or oozing or non bleeding visible vessel or adherent clot or Dieulafoy's lesion.

Table 2. The outcomes after endoscopic therapy

Outcome	Intravenous pantoprazole (N=291)	Intravenous omeprazole (N=806)	Relative risk (95% confidence interval)
Rebleeding in patient with first EGD reported-no. (%)	19 (6.5)	14 (1.7)	3.76 (1.91-7.40)
Spurting	6/27 (22.2)	2/8 (25.0)	0.89 (0.22-3.58)
Oozing	4/57 (7.0)	0	
Non bleeding visible vessel	7/108 (6.5)	1/72 (0.14)	4.67 (0.59-37.13)
Adherent clot	2/32 (6.3)	3/18 (16.7)	0.38 (0.07-2.04)
Clean base	0	2/328 (0.6)	
Gastritis	0	5/268 (1.9)	
Dieulafoy's lesion	0	1/14 (7.1)	
High-risk lesion	19/231 (8.2)	7/138 (5.1)	1.62 (0.70-3.76)
EGD retreatment-no. (%)*	14 (4.8)	13 (1.6)	2.98 (1.42-6.27)
Surgery-no. (%)	8 (2.7)	6 (0.7)	3.69 (1.29-10.55)
Blood transfusion after endoscope-unit			<0.001
Mean	0.9	0.3	
Median	0	0	
Interquartile range	0.0-1.0	0.0-0.0	
Death	3(1.0)	5(0.6)	1.66 (0.4-6.91)

EGD=esophagastroduodenoscope.
*High risk was defined as the EGD finding was spurting, oozing, non bleeding visible vessel, adherent clot or Dieulafoy's lesion.Patient with rebleeding was retreated by EGD. If EGD could not stop bleeding, the patient would had controlled bleeding by surgery. Some patients was passed re EGD and shifted to surgery.[21,22]

proportion of patient with spurting, oozing, adherent clot and non bleeding visible vessel (P<0.001, P<0.001, P<0.001 and P<0.001, respectively).

However, proportion of male patients, median of heart rate, level of platelet, PT, PTT, INR, proportion of patient with coagulopathy, comorbidity including cardiac disease, renal failure, liver disease, disseminated malignancy, gastroscopic findings consisting of black spot, Mallory-Weiss tear, gastric cancer, Dieulafoy's lesion were similar between the two groups.

OUTCOMES

From the Table 2, the rebleeding rate was higher in the pantoprazole group (6.5%) than in the omeprazole group (1.7%) (RR, 3.76; 95% CI, 1.91 to 7.40). Similarly, endoscopic retreatment rate was higher in the pantoprazole group (4.8%) than in the omeprazole group (1.6%) (RR, 2.98; 95% CI,

Table 3. Risk factors associated with the outcomes

Factors	Rebleeding	Surgery	EGD retreatment
	Odds ratio (95% confidence interval)		
Age-yr	1.01 (0.99-1.02)	0.97 (0.93-1.01)	1.01 (1.00-1.02)
Male sex	2.94 (0.82-10.49)	1.43 (0.29-7.07)	3.87 (0.79-18.98)
Intervention Pantoprazole	1.56 (0.67-3.61)	1.26 (0.36-4.35)	1.49 (0.58-3.81)
Shock	1.43 (0.69-2.96)	0.82 (0.26-2.60)	2.13 (0.94-4.85)
Hemoglobin-mg/dL	1.02 (0.89-1.17)	0.86 (0.68-1.08)	1.06 (0.91-1.22)
Platelet 10^3/uL	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)
Coagulopathy	1.95 (0.90-4.21)	3.82 (1.11-13.20)	1.81 (0.77-4.26)
High-risk EGD findings	5.55 (2.07-14.93)	9.49 (1.79-50.29)	3.65 (1.32-10.08)
Comorbidity			
Cardiac disease	1.22 (0.25-5.89)	4.41 (0.84-23.31)	1.41 (0.28-7.07)
Renal failure	0.27 (0.04-2.10)		0.36 (0.05-2.78)
Liver disease	0.43 (0.05-3.34)		0.43 (0.05-3.38)
Disseminated malignancy	2.83 (0.30-26.92)		4.08 (0.43-38.59)

EGD=esophagogastroduodenoscopy

1.42 to 6.27). However, receiving a blood transfusion after endoscope was lower in the pantoprazole group than in the omeprazole group (P<0.001 by Mann-Whitney U test). There were no differences between the two study groups in rebleeding rate in those with spurting ulcer, nonbleeding visible vessel ulcer, adherent clot ulcer, high-risk lesion and receiving surgical treatment. For the omeprazole group, there was no rebleeding in those with oozing ulcer, while in the pantoprazole group, there was no rebleeding in the clean-based ulcer, gastritis and dieulafoy's lesion.

FACTORS ASSOCIATED WITH THE OUTCOMES

From the logistic regression analysis, pantoprazole was not associated with lower rate of rebleeding after successful endoscopic hemostasis, surgery and re endoscopy (AOR, 1.56; 95% CI, 0.67 to 3.61; AOR, 1.26; 95% CI, 0.36 to 4.35; AOR, 1.49; 95% CI, 0.58 to 3.81, respectively). However, coagulopathy factor was associated with surgery (AOR, 3.82; 95% CI, 1.11 to 13.20), while high risk gastroscopic findings were the only factors associated with whole of three outcomes such as higher rate of rebleeding after successful endoscopic hemostasis, surgery and re endoscopy

(AOR, 5.55; 95% CI, 2.07 to 14.93; AOR, 9.49; 95% CI, 1.79 to 50.29; AOR, 3.65; 95% CI, 1.32 to 10.08, respectively) (Table 3).

However, median of age, proportion of male patients, proportion of patient with shock status, level of hemoglobin, level of platelet, comorbidity include cardiac disease, renal failure, liver disease, disseminated malignancy were found not associated with rebleed, surgery, and EGD retreatment, while coagulopathy was found not associated with rebleeding and EGD retreatment.

DISCUSSION

MAJOR FINDINGS

In our study, we found that pantoprazole was not associated with a lower rate of rebleeding in the patients with nonvariceal bleeding after successful endoscopic hemostasis. However, coagulopathy factor was associated with surgery, while high-risk gastroscopic findings were the only factors associated with the whole of three outcomes such as higher rate of rebleeding after successful endoscopic hemostasis, surgery and re endoscopy.

STRENGTHS AND LIMITATIONS OF THE STUDY

The sample size which could present the different outcomes between the pantoprazole and the omeprazole group was 1,184 patients but the sample size of this study was 1,097 patient. In this study, the information of patients was presented with many characteristics. The confounders were indicated and used in the analysis.

However, there were limitations to this study. The patients in this study were excluded by the condition with more than one possible source of bleeding. Thus the patients with more than one cause of upper gastrointestinal bleeding were not suitable for using our outcome to treatment in them. In addition, the EGD technique and experience of practitioner were effects to the rate of rebleeding.[12] In Khon Kaen Hospital, there were many patients were treated by residents. Thus the result of treatment in this hospital may be out of standard in some patients with the emergency condition.

COMPARISON WITH OTHER STUDIES

In the previous study, their findings shown that there was no difference between intravenous pantoprazole and omeprazole similarly to ours.[9] In the other hand, the previous study focused in pH to be their primary outcome and found only the hemostatic instability to be risk rebleeding without mentioning the pantoprazole and omeprazole effects to rebleeding directly.[9] While in the present study, we focused on rebleeding and the gastroscopic findings is the only one risk factor of rebleeding.

In addition, the most common cause of our study and other studies were the clean-based ulcer[2,3,23] whereas the older studies suggested that peptic ulcer disease was responsible for approximately half of the upper gastrointestinal bleeding,[4] more recent studies suggest it is now the less common cause.[2,3,24] In 2011, there was a randomized controlled trial comparing the efficacy of oral omeprazole versus intravenous pantoprazole in 106 in Iranian, their findings suggested the similar efficacies of the oral

omeprazole and intravenous pantoprazole on prevention of rebleeding after endoscopic therapy in patients with high risk bleeding peptic ulcers.[25] However, in the present study, we also found the similar efficacies of the intravenous pantoprazole and the intravenous omeprazole on prevention of rebleeding in nonvariceal bleeding with successful hemostasis.

CONCLUSION AND IMPLICATION

Intravenous pantoprazole and intravenous omeprazole had no difference in relation to prevention of rebleeding in the patient with nonvariceal bleeding after endoscopy. Thus, using whether pantoprazole or omeprazole depends on the clinical practice guideline, cost-effectiveness in each settings as well as the patient preference.

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Uncontrolled blood pressure and acute intracerebral hemorrhage in patients with hypertension

ORIGINAL ARTICLE

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To identify the association between the blood pressure (BP) control and the first episode of intracerebral hemorrhage (ICH) in patients with hypertension.

METHODS

We conducted a case-control study among patients with hypertension to identify the risk of acute ICH in patients with uncontrolled hypertension. The cases were included if there were admitted at Khon Kaen Hospital (KKH) with acute ICH with underlying of hypertension from January 2013 to September 2015. The controls were matched by age and gender in the ratio 1:2. BP in each patient was recorded in relation to mean of the last 3 recorded in the patient records during the year before the in the admission date of the cases or visit date of the matched controls. Classification of blood pressure control was based on the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 8 criteria (JNC8).

RESULTS

A total of 225 medical records were included and reviewed (75 patients were the cases and 150 patients were the controls). Patients with uncontrolled hypertension increased the risk of the first episode of ICH were classified regarding JNC8; comparing to those with controlled BP, the patients with hypertension stage 2 were associated with highest rate of intracerebral hemorrhage (adjusted odds ratio (AOR), 4.20; 95% confidence interval (CI), 1.82 to 9.79); the patients with hypertension stage 1 who had underlying diabetes mellitus or chronic kidney disease and the age younger than 60 year-old were also associated with higher rate of intracerebral hemorrhage (AOR, 2.96; 95% CI, 1.33 to 6.57) as well as those who were older than 60 (AOR, 2.16; 95% CI, 0.56 to 8.33).

CONCLUSION

Our findings suggested that in patients with hypertension, inadequate BP control could increase the risk of ICH especially BP in the range of stage 2 hypertension. Randomized controlled trials stating the risks and benefits of tight BP control are suitable to generate high-quality data that can guide recommendation about BP control in patients with hypertension.

INTRODUCTION

Acute intracerebral hemorrhage (ICH), the least treatable form of stroke, affects more than 1 million people worldwide annually.[1,2] Thai Epidemiological Stroke Study in 2014 found that the proportion of hemorrhagic stroke is higher when compared to Caucasian population.[3] Treatment of hypertension has been demonstrated to be the most important factor in reducing the incidence of stroke.[4] The study from the American Stroke Association suggested that treatment of hypertension might prevent 17-28% of all hemorrhagic stroke and this effect did not vary by type of treatment.[5] In the study from the United States, blood pressure (BP) control during follow-up was associated with a higher risk of both lobar and non-lobar ICH recurrence.[6] The BP control is also one of the best ways to prevent recurrent ICH as hypertension is a well-known cause of ICH.[6] Moreover, studies in the United Kingdom and the Netherlands have demonstrated that the quality of control of hypertension is strongly related to the occurrence of stroke in the population.[7,8] However, the role of BP control in the first episode of ICH remains poorly defined. Thus, we conducted a study to assess the relationship between uncontrolled BP and risk of acute ICH among patients with hypertension.

METHODS

STUDY DESIGN

A case-control study was conducted using medical records of the patients with hypertension treated at Khon Kaen Hospital, Thailand to identify risk factors of acute ICH in patients with uncontrolled BP.

PATIENT RECORDS

The cases were verified and reviewed from In-Patient Department (IPD) records of KKH registry, Thailand from January 2013 through September 2015. The controls were verified and reviewed from Out Patient Department (OPD) records of the same hospital and study period. Case-patients were patients with hypertension with a history of first episode acute ICH and the control patients were patients with hypertension without a history of first episode acute ICH matched by age and gender with the ratio of 1:2 with the nearest follow-up date with the index date of the cases. Patients were excluded if they had a traumatic brain injury, bleeding tendencies such as hemophilia or those with a hemorrhagic transformation of ischemic stroke.

DATA COLLECTION

International Classification of Disease (ICD) 10; non-traumatic subarachnoid hemorrhage as I60, non-traumatic intracerebral hemorrhage as I61 and essential (primary) hypertension as I10. BP in each patient was recorded into the mean of the last three BP records in the medical record during the year before the admission date of the cases or visit date of the matched controls. If less than three records were available, we used either the mean of two to assess the level of BP achieved by treatment. Furthermore, following factors such as estimated glomerular filtration rate (eGFR), total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride and coagulogram were also recorded by an average of the laboratory data within 1 years before the index date. The other characteristics regarding matched age-matched gender, body mass index (BMI) and

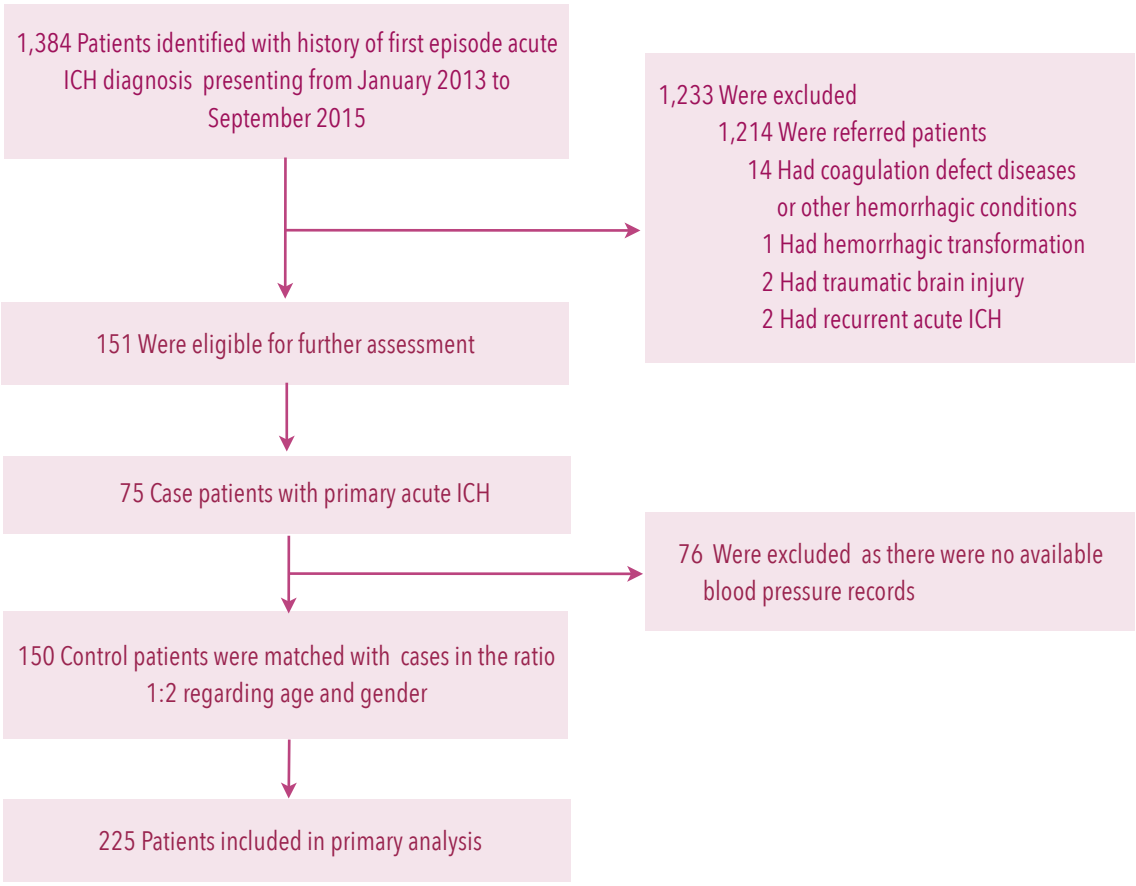

Figure 1. Case with sequential application of eligibility and exclusion criteria

past medical history diabetes mellitus (DM), dyslipidemia (DLD), ischemic stroke, chronic kidney disease (CKD), myocardial infarction (MI) were also recorded.

STATISTICAL ANALYSIS

We designed the study to have an alpha level of 0.05, 90% power to detect a difference, the resulting sample size was 213 participants; 71 cases and 142 controls. Comparing continuous data (e.g., age, mean of eGFR, mean of lipid profile, mean of coagulogram, BMI) between cases and controls were analyzed by using t-test and Mann-Whitney U test and presented as mean with standard deviation (SD) or median with interquartile range (IQR). In contrary, comparing categorical variable data (e.g., gender, lipid profile range, BMI, social history, past medical history and blood pressure) between study groups were analyzed by using chi-square test or Fisher's exact test where appropriate. We used binary logistic regression for univariable and multivariable analysis. Our results from the analysis are reported as crude odds ratio (COR). We also reported an adjusted odds ratio (AOR) to identify the risk association between the variables and ICH.

Table 1. Characteristics of the cases and controls

Characteristic	Patient with hemorrhagic stroke (n=75)	Controls (n=150)	P Value
Age-yr			0.979
Median	63.8	64.6	
Interquartile range	55.5-73.9	54.9-73.70	
Female sex-no. (%)	27 (36.0)	54 (36.0)	1.000
eGFR-ml/min/1.73m2	(n=74)	(n=120)	
Median	73.3	68.2	0.914
Interquartile range	46.4-93.3	51.0-94.9	
Lipid profile-mg/dl			
Total cholesterol12-no. (%)	(n=64)	(n=89)	0.905
<200	16 (41.0)	21 (43.8)	
200-239	16 (4.0)	18 (37.5)	
≥240	7 (17.9)	9 (18.8)	
Mean±SD	184.2±51.5	183.2±50.6	0.908
LDL-cholesterol-no. (%)	(n=55)	(n=89)	0.102
<130	32 (58.2)	65 (73)	
130-159	13 (23.6)	13 (14.6)	
≥160	10 (18.2)	11 (12.4)	
Median	116.5	109.0	0.504
Interquartile range	84.3-146.0	87.3-132.3	
HDL-cholesterol-no. (%)	(n=53)	(n=79)	0.965
<40	19 (35.8)	23 (29.1)	
40-59	24 (45.3)	46 (58.2)	
≥60	10 (18.9)	10 (12.7)	
Median	43.0	45.0	0.733
Interquartile range	37.0-57.5	38.0-54.0	
Triglyceride-no. (%)	(n=51)	(n=23)	0.676
<150	35 (63.6)	54 (66.7)	
150-199	12 (21.8)	8 (9.9)	
≥200	8 (14.5)	19 (23.5)	
Median	113.0	117.5	0.385
Interquartile range	81.5-175.0	89.1-191.5	

Table 1. Characteristics of the cases and controls

Characteristic	Patient with hemorrhagic stroke (n=75)	Controls (n=150)	P Value
Coagulogram			
PT-sec	(n=71)	(n=42)	
Median	11.7	12.0	0.355
Interquartile range	11.1-12.4	11.1-13.1	
PTT-sec	(n=70)	(n=39)	
Median	32.2	33.6	0.099
Interquartile range	28.9-35.7	31.5-36.4	
INR13-sec	(n=71)	(n=43)	
Median	0.99	1.02	0.253
Interquartile range	0.94-1.06	0.95-1.10	
BMI (kg/m^2)-no. (%)	(n=65)	(n=131)	0.535
<18.5	1 (1.5)	6 (4.6)	
18.5-22.9	26 (40)	50 (38.2)	
23.0-24.9	19 (29.2)	28 (21.4)	
25.0–29.9	12 (18.5)	33 (25.2)	
≥30.0	7 (10.8)	14 (10.7)	
Median	23.43	23.88	0.825
Interquartile range	21.5-25.3	21.3-26.5	
Past medical history-no. (%)			
Myocardial infarction5	1 (1.3)	9 (6.0)	0.171
Diabetes mellitus12	22 (29.3)	66 (44.0)	0.034
Hyperlipidemia	10 (13.3)	38 (25.3)	0.038
Ischemic stroke	8 (10.7)	26 (17.3)	0.188
Chronic kidney disease	8 (10.7)	16 (10.7)	1.000

Plus-minus values are means ±SD; The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters

RESULTS

PATIENTS

From January 2013 through September 2015, we identified 1,384 patients with hemorrhagic stroke with underlying hypertension (Figure 1). We excluded 1,214 referred cases from other hospitals, 2 patients with recurrent intracerebral hemorrhage, 1 patient with a hemorrhagic transformation from ischemic stroke, 14 patients with coagulation defect diseases and hemorrhagic condition, 2 patients with traumatic intracerebral hemorrhage and 76 patients without a history of blood pressure in the period of one year before the

Table 2. Risk of acute intracerebral hemorrhage associated with uncontrolled blood pressure in hypertensive patients

Level of blood pressure control	Patients with acute intracerebral hemorrhage	Control patients	Crude odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)‡
	no. (%)			
Controlled Blood pressure			Reference	
DBP<90 and SBP<140 mm Hg*	11 (14.7)	56 (37.3)		
DBP<90 and SBP<150 mmHg†	17 (22.7)	35 (23.3)		
Uncontrolled Blood pressure				
Stage I				
DBP 90-99 or SBP 140-159 mmHg*	20 (26.7)	33 (22.0)	1.97 (0.92-4.18)	2.96 (1.33-6.57)
DBP 90-99 or SBP 150-159 mmHg†	5 (6.7)	7 (4.7)	2.32 (0.53-9.21)	2.16 (0.56-8.33)
Stage II (DBP≥100 or SBP≥160 mmHg)	22 (29.3)	19 (12.7)	3.76 (1.67-8.47)	4.20 (1.82-9.79)

*The range of controlled BP with general <60 year-old, diabetes mellitus, chronic kidney disease was defined as DBP<90 and SBP<140 mmHg
†The range of controlled BP with general ≥60 year-old without diabetes mellitus or chronic kidney disease.
‡The adjusted odds ratio were calculated by including blood pressure level, age, gender, eGFR and underlying diseases (DM, CKD). [16]

index date. After 95 patients were excluded, 75 cases were included in the total. The controls were matched by gender and age with ratio 1:2. Thus, 150 control patients with non-hemorrhagic stroke with underlying hypertension were included. Table 1 gives characteristics of the case and control patients. Two groups of patients were similar regarding age, gender, eGFR, lipid profiles, coagulogram, body mass index (BMI), past medical history of MI, ischemic stroke and CKD. However, a fewer proportion in DM (P=0.034) and dyslipidemia (P=0.038) in the group of case-patients.

From our findings, patients with hypertension stage 2 were associated with the highest rate of acute ICH (AOR, 4.20; 95% CI, 1.82 to 9.79)(Table 2). In addition to this, patients with hypertension stage 1 who had underlying of DM or CKD and age younger than 60 year-old were also associated with higher rate of ICH (AOR, 2.96; 95% CI, 1.33 to 6.57) as well as patients who were older than 60 (AOR, 2.16; 95% CI, 0.56 to 8.33). Other variables included age (AOR, 1.00; 95% CI, 0.98 to 1.03), gender (AOR, 1.24; 95% CI, 0.64 to 2.39), mean eGFR (AOR, 0.997; 95% CI, 0.995 to 0.999) and past medical history of DM (AOR, 0.44; 95% CI, 0.21 to 0.89) and DLD (AOR, 0.49; 95% CI, 0.22 to 1.10) were found not to associated with the occurrence of acute ICH from the binary logistic regression analysis.

DISCUSSION

PRINCIPAL FINDINGS

Our findings suggested that in patients with hypertension, inadequate BP control increased the

risk of ICH especially patients with BP in the range of stage 2 hypertension. In addition to this, patients with hypertension stage 1 who had underlying of DM or CKD and age younger than 60 years old were also associated with higher rate of ICH as well as patients who were older than 60. Other variables included age, gender, mean eGFR and past medical history of DM and DLD were found not to associated with the occurrence of acute ICH from the binary logistic regression analysis.

STRENGTHS AND LIMITATIONS OF THE STUDY

Our findings suggested that in patients with hypertension, inadequate BP control increased the risk of ICH especially patients with BP in the range of stage 2 hypertension. This association appeared to become stronger with worsening severity of hypertension defining through the JNC8 severity stage.[17] To our knowledge, this is the first study to identify the relationship between the proper power between uncontrolled blood pressure and ICH in patients with hypertension. Eligibility criteria were carefully used to define the cases and the controls. However, our study has several limitations. As the selection bias is commonly found in the case-control study; missing of data such as a history of hypertension treatment and duration of underlying of hypertension that may also be the risk factors of ICH.

COMPARISON WITH PREVIOUS STUDIES

In the previous case-control study, they determined the risk of stroke in term of quality of hypertension control which they did not clarify case of a specific type of stroke such as ischemic or hemorrhagic stroke and studied the relationship between the incidence of all types of stroke and blood pressure control but not a hemorrhagic stroke.[7] We specified a case into hemorrhagic stroke patients. Another recently published study investigated the association between blood pressure after index ICH and risk of recurrent ICH. It found that poor BP control during follow-up was associated with higher rate of recurrent ICH.[18] This finding conforms to our study that uncontrolled blood pressure associated with increased the rate of first episode ICH diagnosis.

The JNC8 guideline recommends increasing the threshold of systolic BP to higher than 150 mmHg compared with >140 mmHg in the JNC7 guideline for starting BP-lowering therapy for the elderly.[16,19] However, this recommendation was lack of a clear balance between risks and benefits of less aggressive BP control in this population subgroup.[18] Our findings suggested that stage I hypertension in the patients 60 years or older according to JNC 8 who had the SBP between 150 to 159 mmHg might not be increased the risk of ICH when compared with stage I hypertension in patients younger than 60 years who had the SBP between 140 to 159 mmHg. Thus, it is coherent to the other research. But, Stage II hypertension in general patients exactly increased the incidence of ICH (SBP>160 mmHg). Furthermore, stage I hypertension in patients underlying DM or CKD might be associated increasing the risk of ICH when compared with other patients who no DM or CKD. At the end of our findings suggested that tight BP control could strongly reduce the risk of ICH in patients with hypertension; still, a recent cost-

effectiveness study recommends the benefit of BP control regarding JNC 8 guidelines for those with known cardiovascular and cerebrovascular conditions only.[20]

CONCLUSION AND IMPLICATION

Our findings suggested that in patients with hypertension, inadequate BP control increased the risk of ICH especially patients with BP in the range of stage 2 hypertension.

Multi-center randomized controlled trials with adequate sample size stating the risks and benefits of tight BP control are suggested to generate high-quality data that can guide recommendation about BP control in patients with hypertension.

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Pentoxifylline and prednisolone for improving mortality in severe alcoholic hepatitis: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To identify the efficacy of pentoxifylline and prednisolone on mortality in severe alcoholic hepatitis.

METHODS

We searched studies from Pubmed, the Cochrane Library, and Scopus. For Pubmed, MeSH terms "pentoxifylline", "prednisolone" and "alcoholic hepatitis" but other databases used the following keywords: pentoxifylline and prednisolone and alcoholic hepatitis. All randomized controlled trials (RCTs) that related were included. We included those studies with participants with severe alcoholic hepatitis. The primary outcome was mortality and secondary outcomes were adverse events. We included trials irrespective of language or publication status.

RESULTS

We included seven RCTs with 1,214 patients, carried out between 2009 and 2015. Meta-analysis showed that for 28 days mortality pentoxifylline did not significantly reduce mortality rate in those with severe alcoholic hepatitis compared to prednisolone (relative risk [RR], 1.05; 95% confidence interval [CI], 0.60 to 1.85; I^2=63%), prednisolone did not significantly increase the mortality rate in those with severe alcoholic hepatitis compared to prednisolone plus pentoxifylline (RR, 1.07; 95% CI 0.77 to 1.48; I^2=0%) but pentoxifylline significantly decrease the mortality rate in those with severe alcoholic hepatitis compared to prednisolone plus pentoxifylline (RR, 1.47; 95% CI, 1.00 to 2.18; I^2=0%).

CONCLUSION

For short-term treatment, there were no differences in 28 days mortality rates between pentoxifylline and prednisolone, prednisolone and prednisolone plus pentoxifylline and pentoxifylline and prednisolone plus pentoxifylline and for long-term treatment, there were no differences in the mortality rates between prednisolone and prednisolone plus pentoxifylline, pentoxifylline, and prednisolone plus pentoxifylline.

INTRODUCTION

Alcoholic liver disease includes various forms of liver injuries i.e., fatty liver, alcoholic hepatitis, and cirrhosis.[1] High burden of alcoholic liver disease expected in the next decade.[2,3] Management of alcoholic hepatitis includes alcohol cessation, hemodynamic and nutritional support. In severe alcoholic hepatitis, prednisolone and pentoxifylline might be considered to be used.[4] The use of corticosteroid aims to moderate the immune and proinflammatory cytokine response which is highly increased in alcoholic hepatitis and is one of the causes of liver injury.[5-8] For pentoxifylline, prevention of hepatorenal syndrome without any decrease in proinflammatory cytokines is its main efficacy for alcoholic liver disease.[9-,11] Although many studies have examined the efficacies of prednisolone and pentoxifylline for patients with severe alcoholic hepatitis, their results comparing between prednisolone versus with pentoxifylline, prednisolone alone versus prednisolone plus pentoxifylline and pentoxifylline alone versus pentoxifylline plus prednisolone are still controversy. Hence, we conducted a systematic review to assess the benefits and harms of pentoxifylline and prednisolone in patients with severe alcoholic hepatitis.

METHODS

SEARCH STRATEGY

We systematically searched literature through electronic databases of PubMed, the Cochrane Library, Scopus and to identify further articles we hand searched references lists of included studies. A search in Pubmed was undertaken using MeSH terms "pentoxifylline", "prednisolone" and "alcoholic hepatitis", and for other databases, we used the following keywords: pentoxifylline and prednisolone and alcoholic hepatitis. No language restriction was imposed.

INCLUSION AND EXCLUSION CRITERIA

The selection of articles to be assessed in this review were divided into two steps; firstly, information from the titles and abstracts were screened by three independent review authors to exclude non-relevant articles. Later, all relevant articles were read in full text by three review authors then independently assessed and selected trials to be included in this review when disagreements occur, the fourth review author decided.

The following inclusion criteria had to be met; (i) we included all double-blind randomized controlled trials (RCTs) of pentoxifylline and prednisolone in patients with severe alcoholic hepatitis, (ii) patients were those with severe alcoholic hepatitis (Maddrey's Discriminant Function for Alcoholic Hepatitis ≥32), (iii) studies had to compare between using pentoxifylline versus prednisolone, prednisolone alone versus prednisolone plus pentoxifylline and pentoxifylline alone versus prednisolone plus pentoxifylline for treatment in the patients with severe alcoholic hepatitis, (iv) the primary outcome was mortality and secondary outcomes were adverse events such as upper gastrointestinal hemorrhage, hepatorenal syndrome, hepatic encephalopathy and infection (lung infection, sepsis). There were no exclusion criteria in this systematic review.

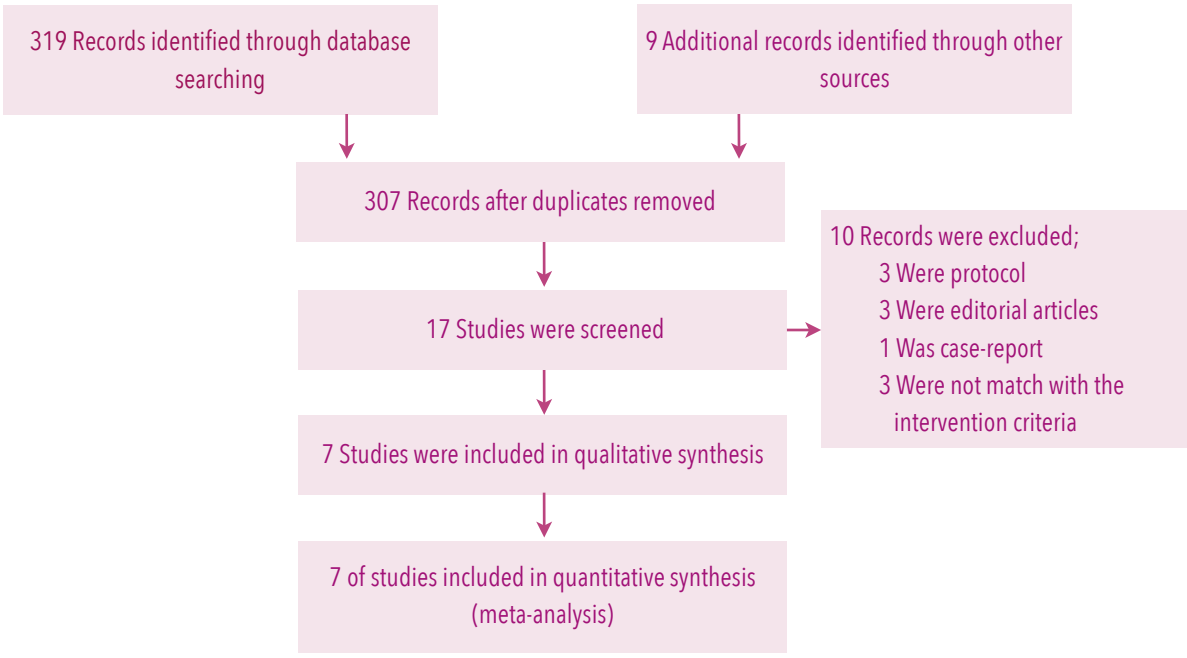

Figure 1. Flowchart presenting the number of articles retrieved, included and excluded in this systematic review

DATA EXTRACTION

Three authors extracted the data from the included studies. Each of them, we abstracted the first author, title, year of publication, number of the patients, interventions, outcome data of various time points.

QUALITY OF REPORTING AND RISK OF BIAS

We assessed the risk of bias of the included studies using the Cochrane risk of bias tool regarding sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other sources of bias. Each domain was classified as "high, unclear or low risk of bias."

STATISTICAL ANALYSIS

For each outcome, we calculated relative risk (RR) and its 95% confidence intervals (CI). $P<0.05$ or CI did not include the value of 1 was considered statistically significant. Heterogeneity between studies was assessed by chi-square and I^2 statistic ($I^2 \geq 50\%$ indicated substantial heterogeneity). We used a random effect model for the meta-analysis when the heterogeneity was statistical significance. Funnel plots were created to evaluate publication bias. Statistical analysis was calculated by Review Manager V5.3 (RevMan, the program provided by the Cochrane Collaboration).

SENSITIVITY ANALYSIS

We conducted a sensitivity analysis comparing results including only low-risk studies.

RESULTS

Our search strategies identified 320 publications. We removed 13 duplicates. Later 290 were

Figure 2. Risk of bias
Panel A, risk of bias summary of the included studies; Panel B, risk of bias graph of the included studies

excluded because of the not relevant of title and abstract or other reasons (Figure 1). A further 10 publications were excluded because they did not match with our inclusion criteria; 3 were protocols, 3 were editorials, 3 did not match our intervention criteria and 1 was a case-report. Any of them were excluded from our exclusion criteria, the remaining 7 records were included in the qualitative analysis and the meta-analysis.

CHARACTERISTICS OF THE INCLUDED STUDIES

We identified and included seven RCTs with 1,274 patients with severe alcoholic hepatitis, four trials compared pentoxifylline to prednisolone, three trials compared prednisolone alone to prednisolone plus pentoxifylline, two trials compared pentoxifylline to prednisolone plus pentoxifylline (Table 1).

BIAS RISK ASSESSMENT

Seven trials were assessed using the Cochrane risk of bias tool. Risk of bias was assessed according to five components: random sequence, generation, allocation concealment, blinding of participant, incomplete outcome data and selective reporting. Of the seven included trials, six was assessed as having a low risk of bias[9-11,13-15] and one was assessed as having a high risk of bias.[12] The risk of bias graph was summarized in Figure 2.

RANDOM SEQUENCE GENERATION

One study did not report the methods of generating a random sequence,[12] while six studies specified the methods and they were classified as "low risk."[9,11,13-16]

ALLOCATION CONCEALMENT

Five studies did not report details on allocation concealment and they were classified as "unclear."[11-13,15,16] One study reported open-labeled method and they were classified as "high risk."[9] While one study specified this method and they were classified as "low risk."[14]

Table 1. Characteristic of the included studies

Study	Participant		Interventions	Results
	N	Sex		
Binay 2009[11]	68	Both male and female	PTX vs. prednisolone	• The mortality rate of prednisolone group was higher than that of PTX at 3 months (35.3% vs. 14.7%; P=0.04). • PTX was associated with a significantly lower MELD score at the end of 28 d of therapy (15.5±3.6 vs.17.8±4.6;P=0.04).
Seung 2014[9]	121	Both male and female	PTX vs. prednisolone	• No difference for the 1-month survival rate of PTX and prednisolone (75.8% and 88.1%, respectively; P=0.08) • No difference for the 6-month survival rate between PTX compared with prednisolone (64.0% vs. 72.9%; P=0.23).
José 2012[12]	60	Both male and female	PTX vs. prednisolone	No difference for the 28-day mortality rate between PTX compared with prednisolone (46.7% vs. 60%; P=0.30).
Philippe 2013[15]	270	Both male and female	Prednisolone vs. prednisolone plus PTX	No difference at the 6-month survival rate between prednisolone compared prednisolone plus PTX (69.9% vs. 69.2%, P=0.91).
Sandeep 2012[14]	140	Only male	Prednisolone vs. prednisolone plus PTX	No difference between survival rate in prednisolone plus PTX vs. prednisolone at the 1 and 6 months (1 month 72.2% vs. 73.5%; P=1.00; 6 month 30.6% vs. 23.5%, P=0.417).
Binay 2014[16]	60	Both male and female	PTX vs. prednisolone plus PTX	No difference between mortality rate in PTX and prednisolone plus PTX in 3 month (16.7% vs. 30%, P =0.37) and 12 months (20% vs. 33.3%, P=0.32)
Mark 2015[13]	1,053	Both male and female	(i) PTX vs. prednisolone, (ii) Prednisolone vs. prednisolone plus PTX, and (iii) PTX vs. prednisolone plus PTX	At the 28-day mortality rate of placebo, PTX, prednisolone and prednisolone plus PTX was 17%, 19%, 14% and 13% • The odds ratio between PTX compared with no PTX was 1.07 (95% CI; 0.77 to 1.49; P=0.69). • The odds ratio between prednisolone compared with no prednisolone was 0.72 (95% CI, 0.52 to 1.01; P=0.06)

PTX= pentoxifylline

BLINDING

Four studies were undertaken on a double-blind study and they were classified as "low risk."[11,13,15,16] Two studies were not double-blind in the patients and physicians and they were classified as "high risk."[9,14] One study did not report details on blinding and they were classified as "unclear."[12]

SELECTIVE REPORTING

All included studies were classified as "low risk."[9,11,12-16]

INCOMPLETE OUTCOME DATA

Five studies were classified as "low risk."[9,11,14-16] One study was classified as "high risk."[13] One study

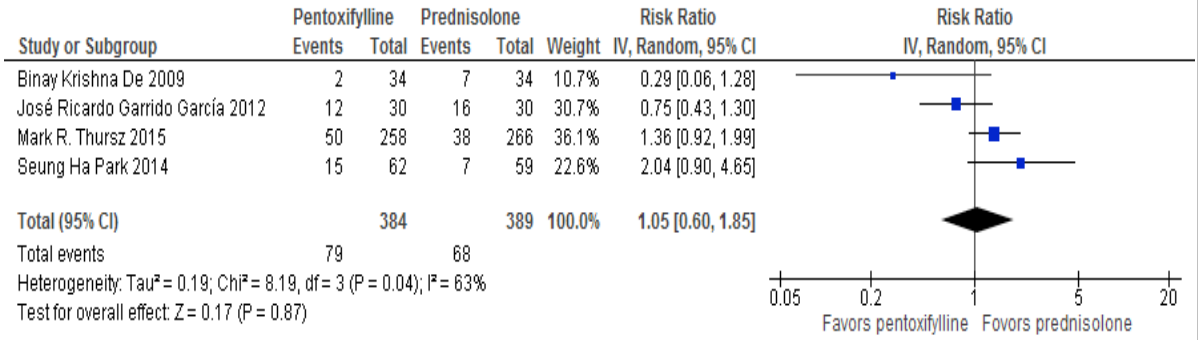

Figure 3. Forest plot of comparison prednisolone versus pentoxifylline, outcome: 28-day mortality

did not report detail on incomplete outcome data and they were classified as "unclear."[12]

OTHER POTENTIAL SOURCES OF BIAS

Three included studies were independent of the industry influence and they were classified as "low risk."[9,13,15] The remaining studies did not report other sources of bias and they were classified as "unclear."[11,12,14,16]

MORTALITY

PREDNISOLONE VS. PENTOXIFYLLINE

28-day mortality

Meta-analysis on data for 28 days mortality showed that pentoxifylline did not significantly increase the mortality rate in participants with severe alcoholic hepatitis compared to prednisolone (RR, 1.05; 95% CI, 0.60 to 1.85, random-effect model) (Figure 3). The heterogeneity was measured as having I^2 equal to 63%.

These findings were also similar to our sensitivity analysis which suggested that pentoxifylline not significantly increase mortality rate in participants with severe alcoholic hepatitis compared to prednisolone (RR, 1.19; 95% CI, 0.56 to 2.51, random-effect model) (Figure S-1). The heterogeneity was measured as having I^2 equal to 61%.

PREDNISOLONE VS. PREDNISOLONE PLUS PENTOXIFYLLINE

28-day mortality

The meta-analysis of 28 days mortality showed that prednisolone alone did not significantly increase the mortality rate in participants with severe alcoholic hepatitis compared to prednisolone plus pentoxifylline (RR, 1.07; 95% CI, 0.77 to 1.48, fixed-effect model) (Figure 4). The heterogeneity was measured as having I^2 equal to 0%.

6-month mortality

The meta-analysis of 6 months mortality showed that prednisolone alone did not significantly increase the mortality rate in participants with severe alcoholic hepatitis compared to prednisolone plus pentoxifylline (RR 1.14; 95% CI, 0.99 to 1.30, fixed-effect model) (Figure 4), The heterogeneity was measured as having I^2=0%.

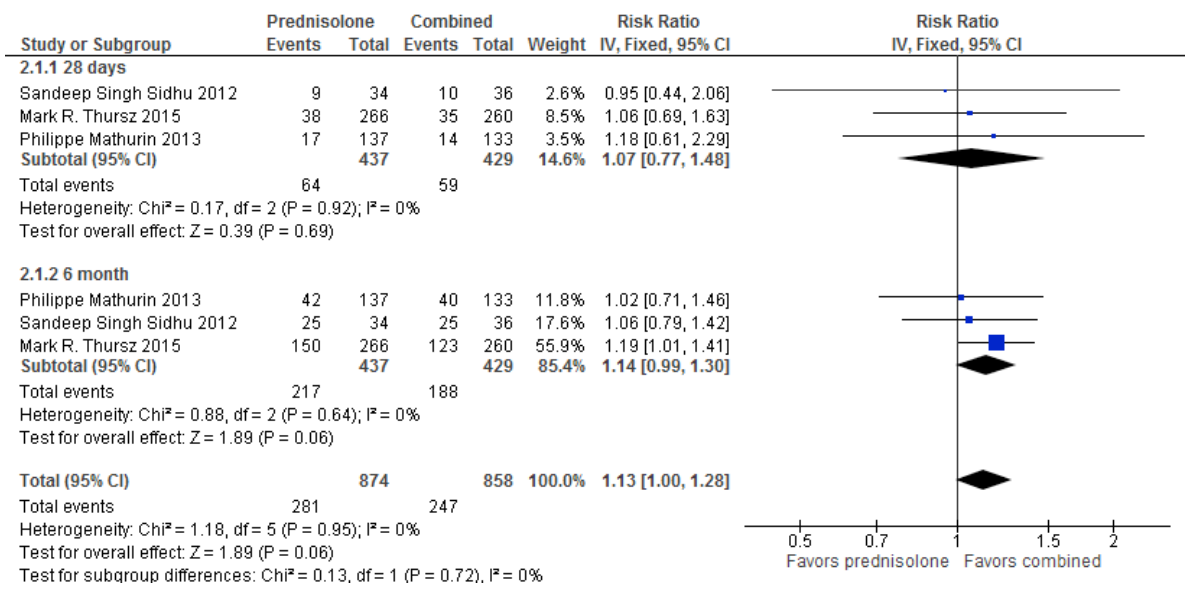

Figure 4. Forest plot of comparison prednisolone versus prednisolone plus pentoxifylline, outcome: 28-day and 6-month mortality

PENTOXIFYLLINE VS. PREDNISOLONE PLUS PENTOXIFYLLINE

28-day mortality

The meta-analysis of 28 days mortality showed that pentoxifylline alone did not significantly increase the mortality rate in participants with severe alcoholic hepatitis compared to prednisolone plus pentoxifylline (RR, 1.47; 95% CI, 1.00 to 2.18, fixed-effect model) (Figure 5). The heterogeneity was measured as having I^2 equal to 0%.

1-year mortality

The meta-analysis of 1-year mortality showed that pentoxifylline alone did not significantly increase the mortality rate in participants with severe alcoholic hepatitis compared to prednisolone plus pentoxifylline (RR, 0.99; 95% CI, 0.88 to 1.12, fixed-effect model) (Figure 5). The heterogeneity was measured as having I^2 equal to 23%.

ADVERSE REACTIONS

PREDNISOLONE VS. PENTOXIFYLLINE

Hepatorenal syndrome

The meta-analysis on data of hepatorenal syndrome showed that pentoxifylline did not significantly increase the rate of hepatorenal syndrome in participants with severe alcoholic hepatitis compared to prednisolone (RR, 0.75; 95% CI, 0.29 to 1.94, random-effect model) (Figure 6). The heterogeneity was measured as having I^2 equal to 52%.

This pattern was also observed in our sensitivity analysis suggested that pentoxifylline

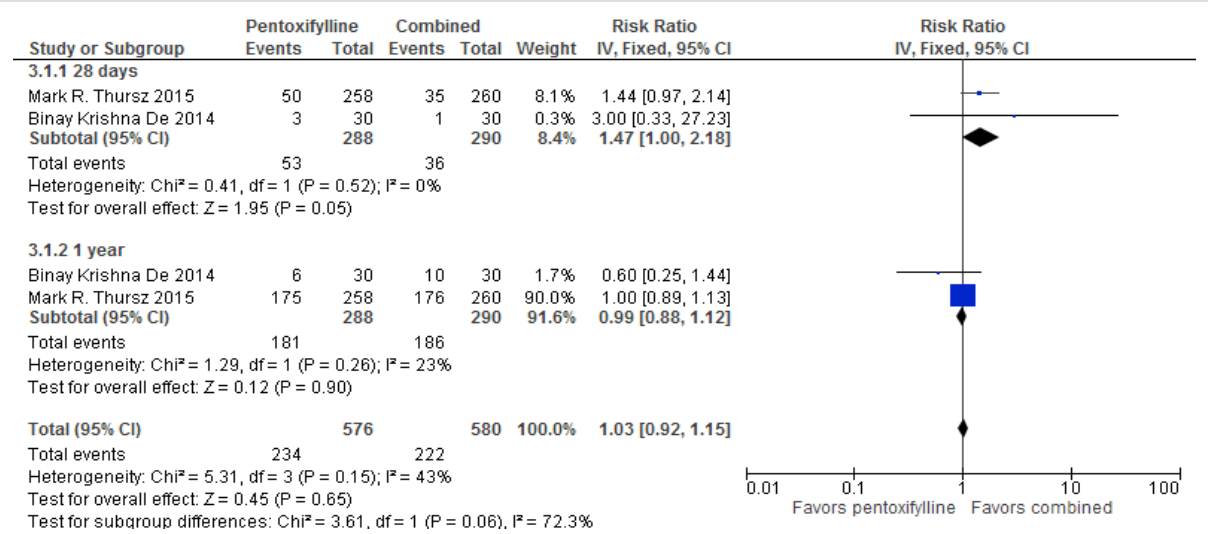

Figure 5. Forest plot of comparison pentoxifylline versus pentoxifylline plus prednisolone, outcome: 28-day and 1-year mortality

did not significantly increase the rate of hepatorenal syndrome in participants with severe alcoholic hepatitis compared to prednisolone (RR, 0.45; 95% CI, 0.03 to 7.44, random-effect model) (Figure S-2). The heterogeneity was measured as having I^2 equal to 73%.

Infection

Our meta-analysis showed that pentoxifylline did not significantly increase the rate of infection in participants with severe alcoholic hepatitis compared to prednisolone (RR, 0.55; 95% CI, 0.29 to 1.06, random-effect model) (Figure 6). The heterogeneity was measured as having I^2 equal to 64% but after we performed the sensitivity analysis, it suggested that pentoxifylline significantly reduced the rate of infection in participants with severe alcoholic hepatitis compared to prednisolone (RR, 0.38; 95% CI, 0.25 to 0.58, random-effect model, I^2 equal to 0% (Figure S-2).

Gastrointestinal bleed

Our meta-analysis showed that pentoxifylline did not significantly decrease the rate of gastrointestinal bleed in participants with severe alcoholic hepatitis compared to prednisolone (RR, 1.14; 95% CI, 0.65 to 2.00, random-effect model) (Figure 6). The heterogeneity was measured as having I^2 equal to 0%. This pattern was also observed in our sensitivity analysis suggested that pentoxifylline did not significantly increase the rate of gastrointestinal bleed in participants with severe alcoholic hepatitis compared to prednisolone (RR, 1.11; 95% CI, 0.60 to 2.05, random-effect model) (Figure S-2). The heterogeneity was measured as having I^2 equal to 0%.

Encephalopathy

Our meta-analysis showed that pentoxifylline did not significantly increase the rate of encephalopathy in participants with severe alcoholic hepatitis compared to prednisolone (RR, 0.72; 95% CI, 0.44 to 1.18, random-effect model)

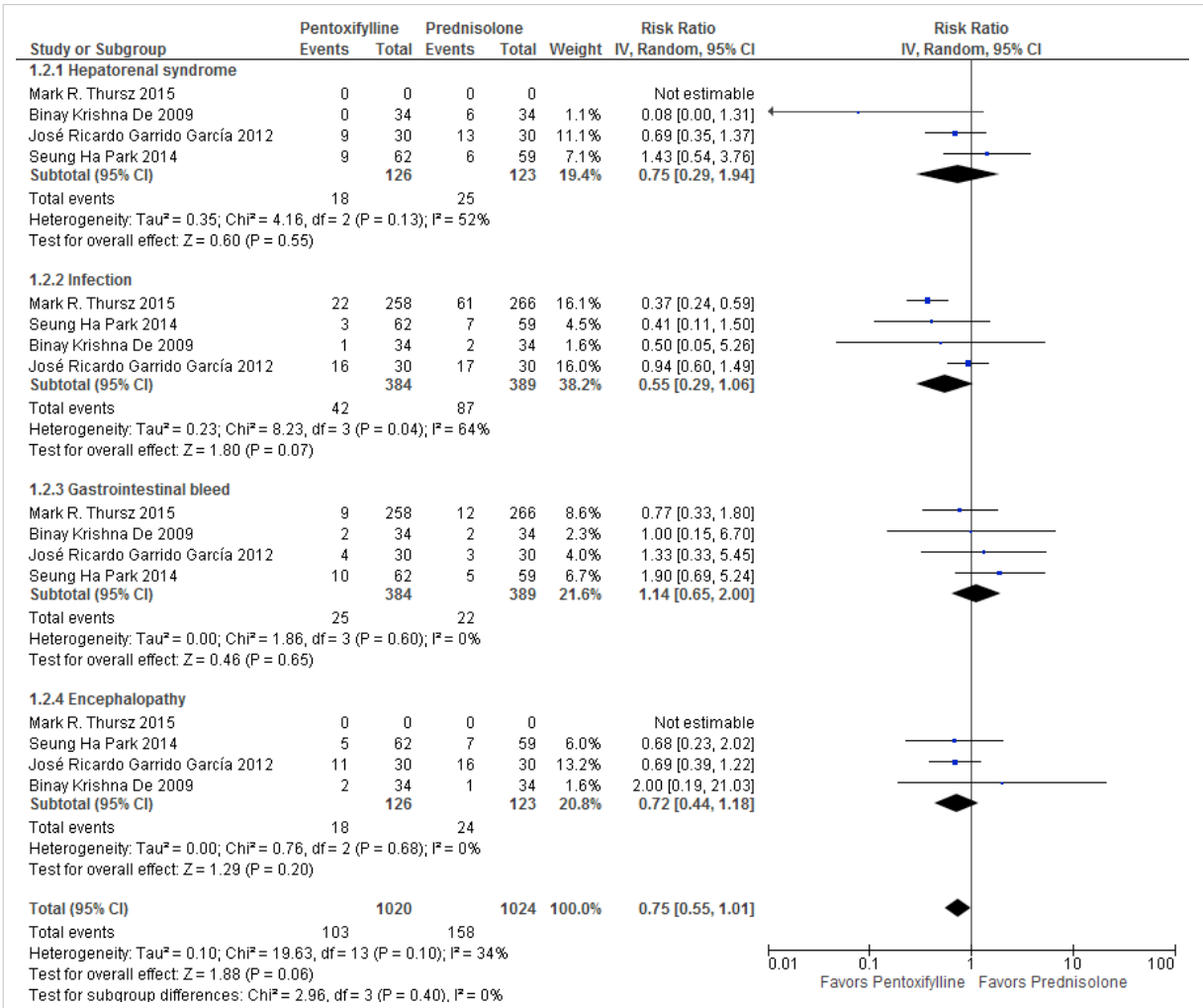

Figure 6. Forest plot of comparison prednisolone versus pentoxifylline, outcome: adverse effect

(Figure 6). The heterogeneity was measured as having I^2 equal to 0%. This pattern was also observed in our sensitivity analysis suggested that pentoxifylline did not significantly increase the rate of encephalopathy in participants with severe alcoholic hepatitis compared to prednisolone (RR, 0.82; 95% CI, 0.31 to 2.21, random-effect model) (Figure S-2). The heterogeneity was measured as having I^2 equal to 0%.

PREDNISOLONE VS. PREDNISOLONE PLUS PENTOXIFYLLINE

Encephalopathy

Our meta-analysis showed that prednisolone did not significantly increase the mortality rate in participants with severe alcoholic hepatitis compared to prednisolone plus pentoxifylline (RR, 1.57; 95% CI, 0.85 to 2.89, fixed-effect model, I^2=0%) (Figure 7).

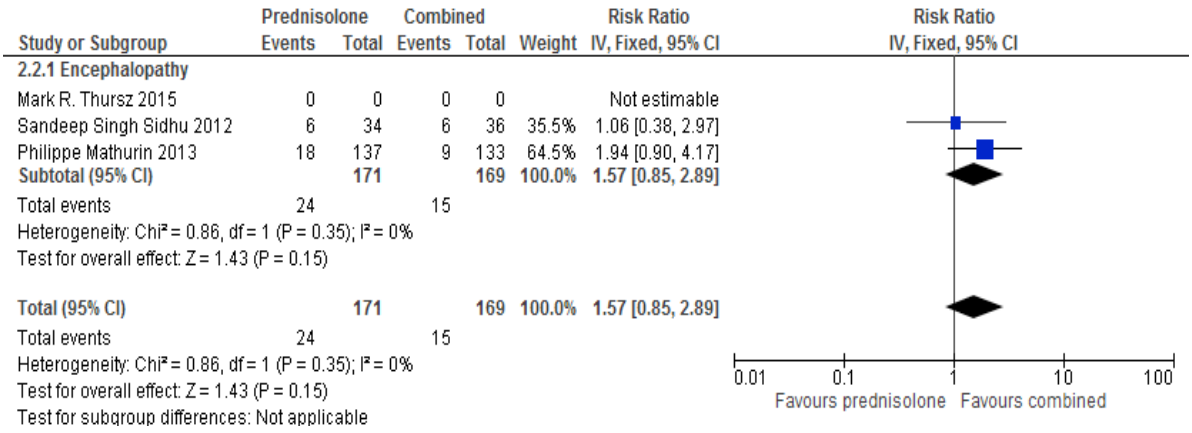

Figure 7. Forest plot of comparison prednisolone versus prednisolone plus pentoxifylline, outcome: adverse effect

PENTOXIFYLLINE VS. PREDNISOLONE PLUS PENTOXIFYLLINE

Gastrointestinal bleed

Our meta-analysis showed that pentoxifylline did not significantly decrease the rate of gastrointestinal bleeding in participants with severe alcoholic hepatitis compared to prednisolone plus pentoxifylline (RR, 0.82; 95% CI, 0.40 to 1.69, fixed-effect model) (Figure 8), The heterogeneity was measured as having I^2 equal to 0%.

Infection

Our meta-analysis showed that pentoxifylline significantly decreased the infection rate in participants with severe alcoholic hepatitis compared to prednisolone plus pentoxifylline (RR 0.45; 95% CI, 0.28 to 0.72, fixed-effect model) (Figure 8). The heterogeneity was measured as having I^2 equal to 0%.

PUBLICATION BIAS

The funnel plots show symmetry in Figure S-3. Hence, we have no evidence to suggest publication bias in these analyses. The results should be considered with carefulness because the number of included studies in each group was relatively small.

DISCUSSION

PRINCIPAL FINDINGS

In our systematic review, a meta-analysis of seven RCTs, the primary outcome suggested that pentoxifylline did not reduce 28-day mortality compared to prednisolone. Prednisolone plus pentoxifylline did not reduce the 28-day and 6-month mortality compared to prednisolone alone and pentoxifylline plus prednisolone also did not reduce 28-day mortality compared to pentoxifylline alone.

For the secondary outcomes, hepatorenal syndrome, infection and encephalopathy were not found less common in pentoxifylline group than that of in prednisolone group. Pentoxifylline did not increase GI bleeding than prednisolone. The incidence of encephalopathy in prednisolone plus pentoxifylline group was not similar to that of

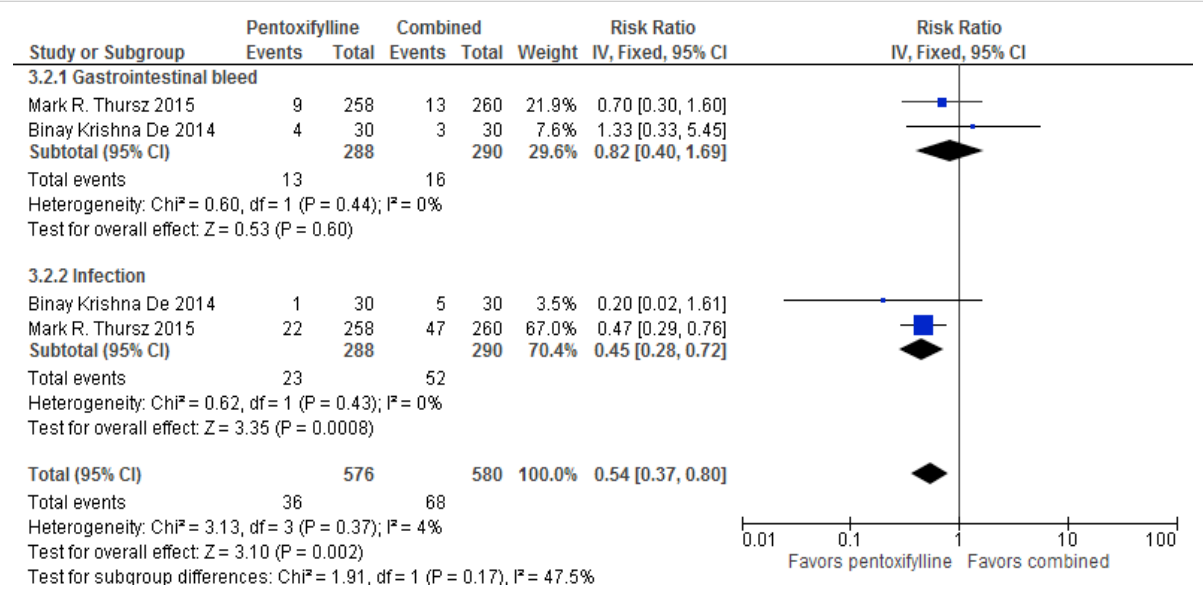

Figure 8. Forest plot of comparison pentoxifylline versus pentoxifylline plus prednisolone, outcome: adverse effect

prednisolone alone group, pentoxifylline alone caused less GI bleeding than pentoxifylline plus prednisolone. Pentoxifylline alone was significantly reduced the infection rate than that of pentoxifylline plus prednisolone.

COMPARISON WITH OTHER STUDIES

There have two meta-analysis[17,18] that compared pentoxifylline and placebo and showed that pentoxifylline had benefit in relation to mortality reduction from hepatorenal syndrome but not survival rate. Our systematic review, however, found no superiority of pentoxifylline over prednisolone because our study is the first systematic review included all RCTs relevant to three trials, pentoxifylline vs. prednisolone, prednisolone alone vs. prednisolone plus pentoxifylline and pentoxifylline alone vs. prednisolone plus pentoxifylline in the patient with severe alcoholic hepatitis.

LIMITATIONS OF THE REVIEW

This meta-analysis is based on the trials with limit sample sizes. Our pool effects of the interventions seemed to be similar, thus, we suggest to have another larger RCT to make the results more clearly. Another limitation of this systematic review is based on many included studies with unclear allocation concealment. We also suggest having a new RCT which free from selection bias.

CONCLUSION

For short-term treatment, there was no difference in 28 days mortality rate between pentoxifylline compared to prednisolone, prednisolone compared to prednisolone plus pentoxifylline and pentoxifylline compared to prednisolone plus pentoxifylline. For long-term treatment, there was also no difference between prednisolone compared to prednisolone plus pentoxifylline and pentoxifylline compared to prednisolone plus

pentoxifylline. For adverse effects between prednisolone compared to pentoxifylline there was no difference in the rates of hepatorenal syndrome, infection rate, gastrointestinal bleed, and encephalopathy but after we performed the sensitivity analysis it suggested that pentoxifylline significantly decreased infection rate in participants with severe alcoholic hepatitis compared to prednisolone. Comparing prednisolone to prednisolone plus pentoxifylline, there was no difference in encephalopathy. Pentoxifylline significantly decreased the infection rate in participants with severe alcoholic hepatitis compared to prednisolone plus pentoxifylline but not for the gastrointestinal bleeding rate. Conducting new RCT to see the precise effects of these various combinations of the interventions is still suggested.

ACKNOWLEDGMENTS & DECLARATION

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COMPETING INTERESTS: This study has no competing on interest.

FUNDING: None

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SUPPLEMENT FIGURES & TABLES

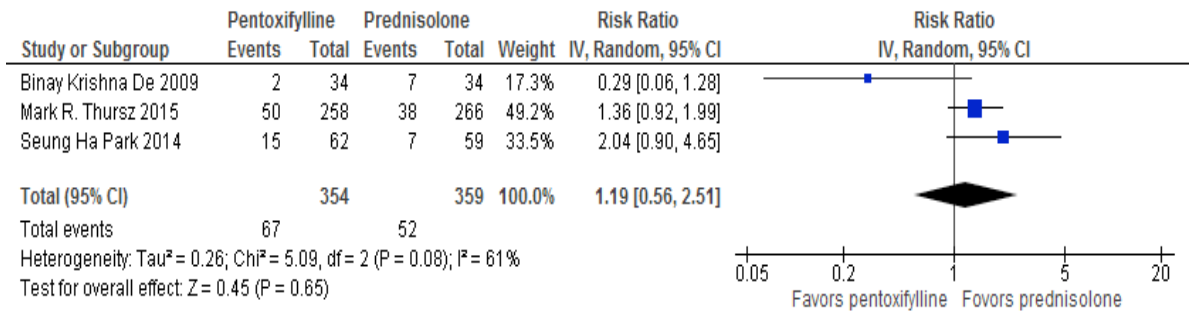


Figure S-1. Forest plot of comparison prednisolone versus pentoxifylline, outcome: 28-day mortality (sensitivity analysis)

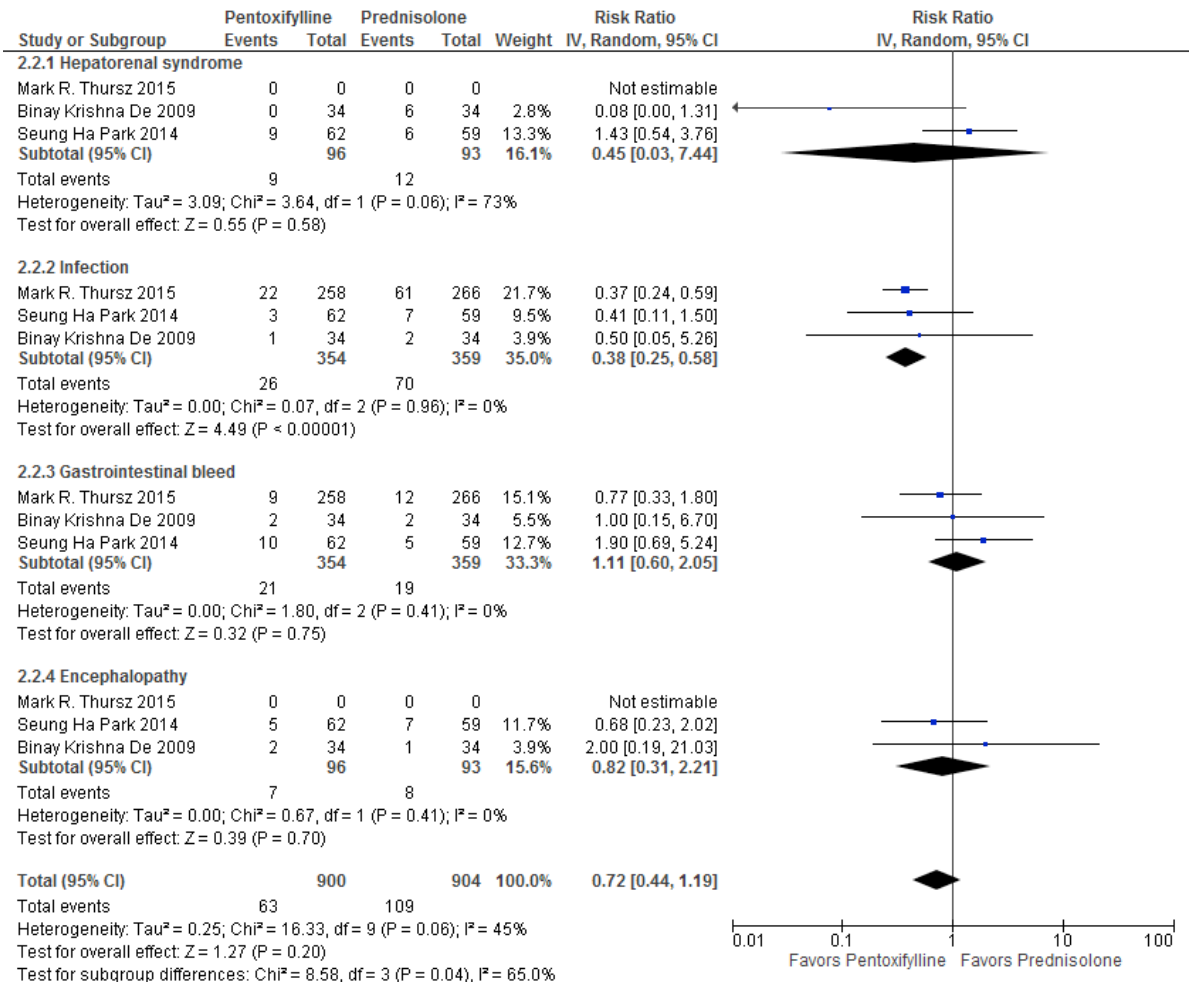


Figure S-2. Forest plot of comparison prednisolone versus pentoxifylline, outcome: adverse effect (sensitivity analysis)

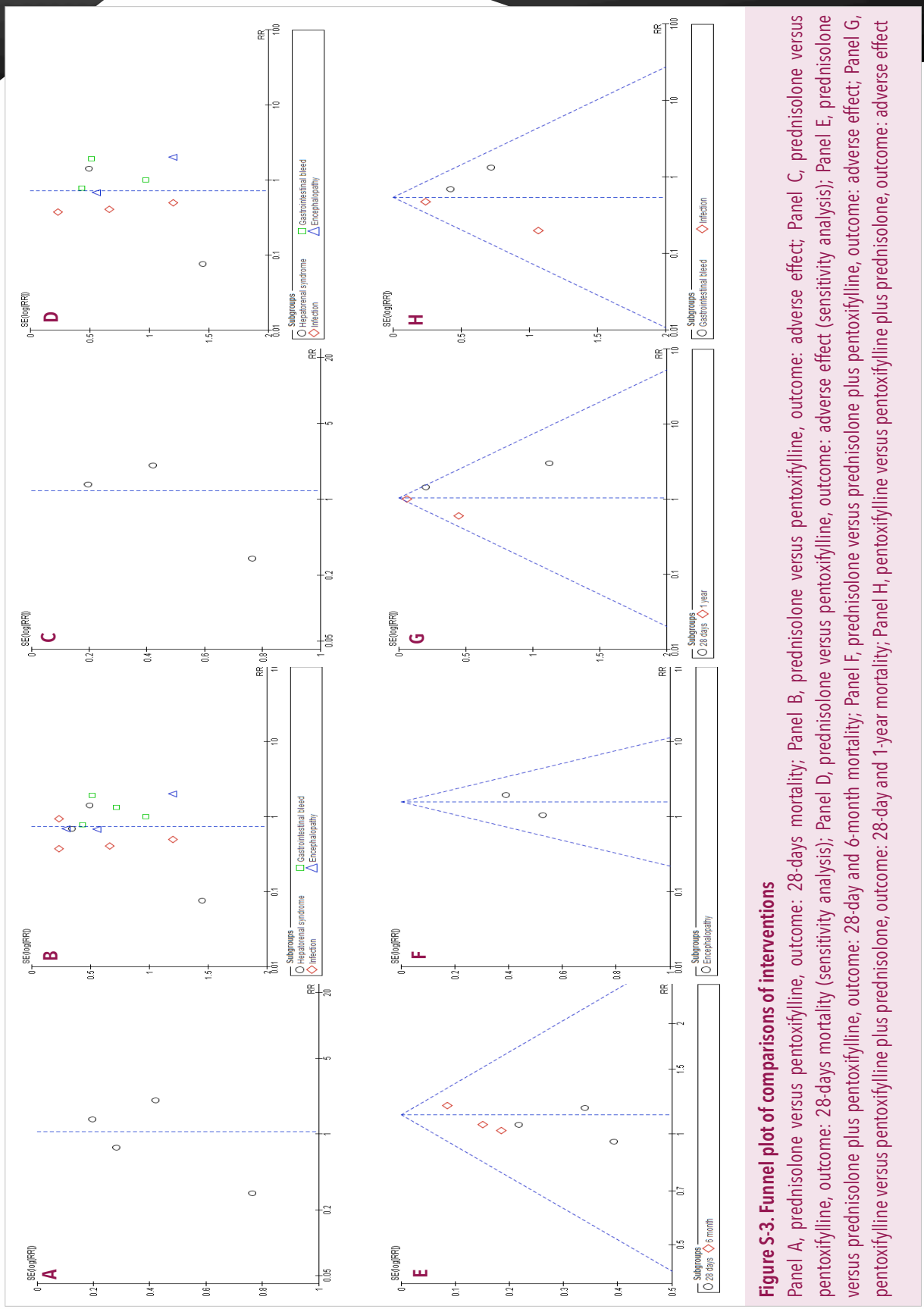
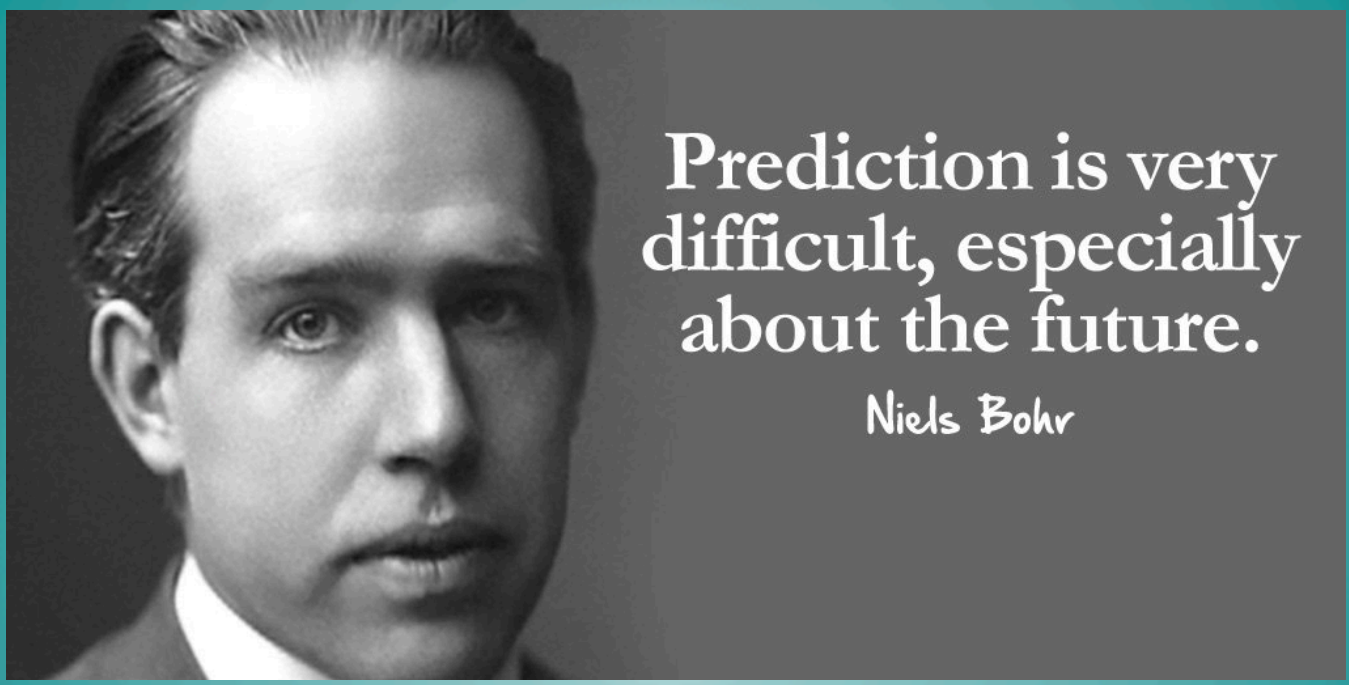


Figure S-3. Funnel plot of comparisons of interventions

Panel A, prednisolone versus pentoxifylline, outcome: 28-days mortality; Panel B, prednisolone versus pentoxifylline, outcome: adverse effect; Panel C, prednisolone versus pentoxifylline, outcome: 28-days mortality (sensitivity analysis); Panel D, prednisolone versus pentoxifylline, outcome: adverse effect (sensitivity analysis); Panel E, prednisolone versus prednisolone plus pentoxifylline, outcome: 28-day and 6-month mortality; Panel F, prednisolone versus prednisolone plus pentoxifylline, outcome: adverse effect; Panel G, pentoxifylline versus pentoxifylline plus prednisolone, outcome: 28-day and 1-year mortality; Panel H, pentoxifylline versus pentoxifylline plus prednisolone, outcome: adverse effect


Prediction is very difficult, especially about the future.
Niels Bohr

"I shall either find a way or make one"

-Hannibal Barca

THE CLINICAL ACADEMIA