THE CLINICAL ACADEMIA

VOLUME 41 ISSUE 1
JANUARY-FEBRUARY 2017

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WWW.THECLINICALACADEMIA.ORG

PRINTED IN THE USA
ISSN: 2465-4027


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

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message from the editor

Happy New Year to all readers, I hope you notice that we have changed our cover which we tend to do yearly for every new year. Not just only our look, but we aim to improve our quality as well. Our editorial board comprises the scholars from the USA, Japan, Malaysia and of course Thailand. This strategy is to level up our journal to meet the international audiences in the near future. Moreover, every manuscript must be checked for plagiarism since the submission, every document related to ethical consideration and original database must be submitted together with the submitted manuscript for its integrity and transparency.

The world of medicine is ever changing. Here now and then are its places. Keep going is the best suggestion for all of us. Hope you enjoy reading The Clinical Academia.

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

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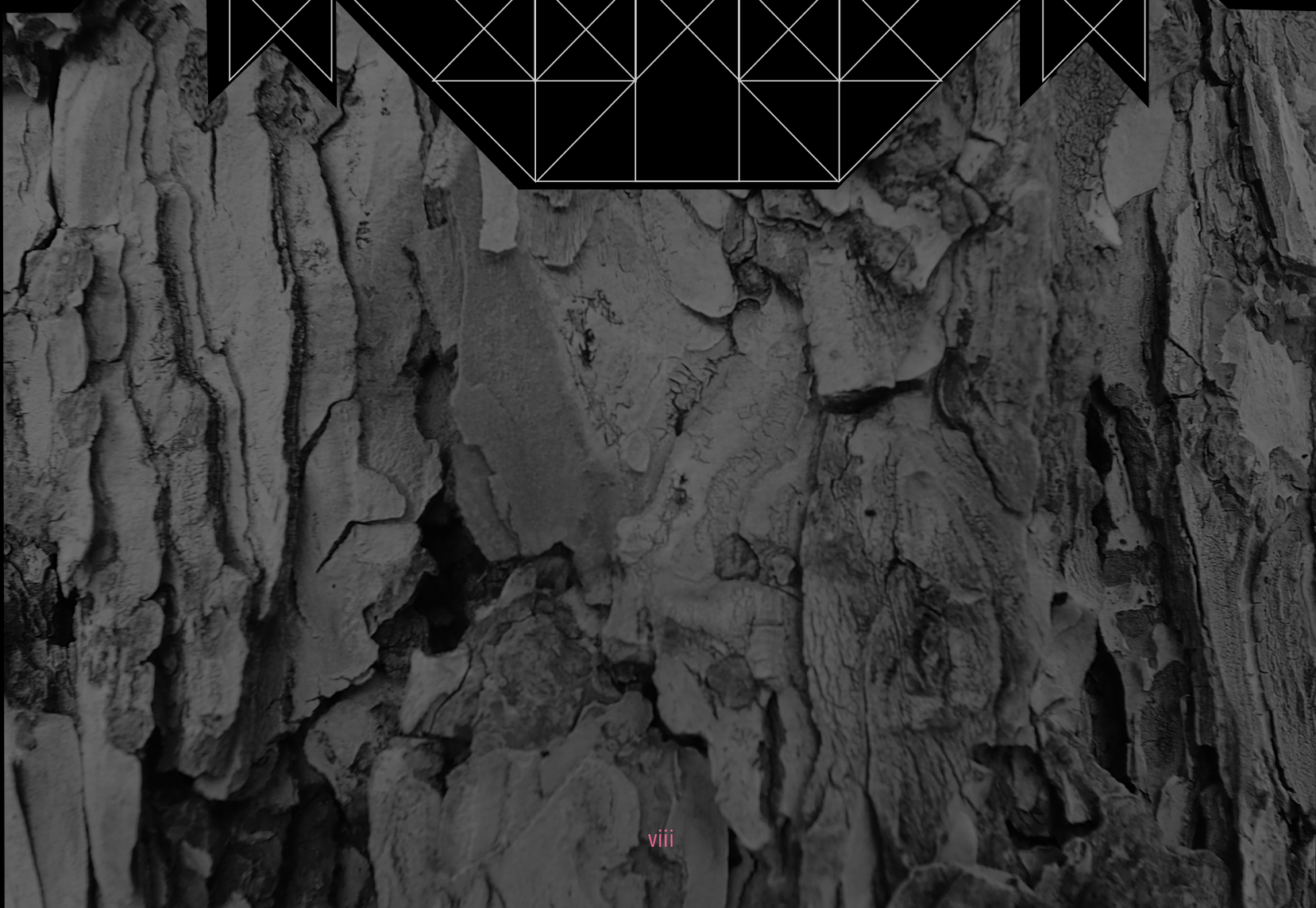
International Committee of Medical Journal Editors (ICMJE)

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.

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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.

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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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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."

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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.

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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

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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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Staging of chronic kidney disease and severe periodontitis

ORIGINAL ARTICLE

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To evaluate the association between staging of chronic kidney disease (CKD) and severe periodontitis.

METHODS

This was a cross-sectional analytical study gathering clinical data by reviewing patient medical records, patient interviewing and oral examining during the period of December 2016 at CKD clinic, Kalasin Hospital, Thailand. Interesting exposure was staging of CKD and our primary outcome was severe periodontitis.

RESULTS

There were 428 patients participated in this study including 125 patients with no kidney damage and 303 patients with CKD. Of 428, 163 had no periodontitis while 58, 116 and 91 had mild, moderate and severe periodontitis, respectively. Secondary education or higher were associated with non-severe periodontitis (AOR, 0.49; 95% CI, 0.26 to 0.93). Factors associated with severe periodontitis included older age (AOR, 1.04; 95% CI, 1.01 to 1.07), gingival bleeding (AOR, 4.38; 2.50 to 7.67) and CKD stage IV (AOR, 3.28; 95% CI, 1.23 to 8.79).

CONCLUSION

CKD stage IV was associated with more frequent severe periodontitis. Older age and gingival bleeding were also have positive association with severe periodontitis. older age and gingival bleeding were also have positive association with severe periodontitis. However, secondary education or higher were associated with non-severe periodontitis.

Accepted: December 2016
Latest revision: January 2017
Printed: February 2017

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INTRODUCTION

Chronic kidney disease (CKD), a gradual reduction of the glomerular filtration rate (GFR) of the kidney.[1,2] It is estimated that X% of the world population suffer from the disease.[3] Common causes of CKD are hypertension, diabetes mellitus, chronic glomerulonephritis, obstructive uropathy, autoimmune disease and obesity.[4-10] Uremia develops and adversely affects every system of the body.[11] The goal of treatment for patients with CKD is to maintain kidney function and homeostasis for as long as possible.[9]

Oral manifestations of CKD are common during the progression of uremia.[10] Uremic patients have more dental problems than healthy controls in oral mucosa, teeth, salivary glands [12] and jaw bones, problems that seem to develop before dialysis.[13-14] Various manifestation e.g., radiological alteration of mandibular and maxillary findings, periodontal disease, xerostomia and uremic stomatitis can be found in those with CKD.[15] Among them, periodontal diseases are highly prevalent specifically gingivitis, excessive plaque formation and poor oral hygiene in uremic patients.[10,13,16-18]

Periodontitis increase with decreasing levels of kidney function.[18] Meanwhile, individuals with periodontitis were also more likely than those without periodontitis to have CKD.[19-21] he disease is a major cause of tooth loss.[22] It contributes to the systemic inflammatory burden in end-stage renal disease.[23,24] Bacterial pathogen causing periodontitis leading systematic inflammation as induced by lipopolysaccharide coats and thus trigger atherogenesis thrombus formation and platelet aggregation,[25] causing cardiovascular disease which is the main cause of death in CKD.[26, 27] However periodontal disease is treatable and modifiable risk factor of CKD.[28, 29]

Periodontal treatment aims at controlling the biofilm, biofilm debridement in periodontal pockets, dental plaque and calculus removal from tooth-crown and root surfaces and regularly maintain and support follow-up therapy after active treatment which can slow or stop periodontitis, reduce tissue inflammation and pocket depths, improve clinical periodontal attachment and tooth loss.[30-34] A systematic review in 2015 also reported a positive relationship between periodontitis and CKD from four observational studies.[35] However, no staging of CKD was taken into consideration of the analysis, and the analysis did not categorize regarding the severity of periodontitis. Thus, the objective of this study was to identify the association between staging of CKD and periodontitis.

METHODS

STUDY DESIGN

This was a cross-sectional analytical study gathering clinical data by reviewing patient medical records, patient interviewing and oral examining during the period of December 2016 at CKD clinic, Kalasin Hospital, Thailand. Informed consent to participate in the study was obtained from all participants. The study was approved by Kalasin Hospital Ethic Committee (HEA-01Den-5901-036).

PARTICIPANTS

Patients who had been diagnosed with CKD for at least 90 days and aged 20 years or older were asked to participate in the current study. CKD patients were

Box 1. The Stages of Chronic Kidney Disease*

Stage 1: Kidney damage with normal or increased GFR (>90 mL/min/1.73 m 2)
Stage 2: Mild reduction in GFR (60-89 mL/min/1.73 m 2)
Stage 3a: Moderate reduction in GFR (45-59 mL/min/1.73 m 2)
Stage 3b: Moderate reduction in GFR (30-44 mL/min/1.73 m 2)
Stage 4: Severe reduction in GFR (15-29 mL/min/1.73 m 2)
Stage 5: Kidney failure (GFR <15 mL/min/1.73 m 2 or dialysis)

**Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 1-150.*

divided by eGFR into five stages (Box 1).[36] This included patients on peritoneal and hemodialysis. Patients with normal eGFR and no evidence of kidney damage[36] were included as a control in this study.

The patients were excluded if they had any systemic disease that could acutely affect the GFR (rapidly progressive glomerulonephritis, active glomerular diseases, pregnancy) and/or oral health status (immunodeficiency syndrome, recurrent or active cancer) or any medication that could affect oral health status, such as immunosuppressive drugs (corticosteroid drugs or chemotherapy).

OUTCOMES

The studied clinical and baseline characteristics were age, gender, education, smoking, diabetes mellitus, hypertension. Oral health status including good oral care (tooth brushing twice or more per day, using dental floss and seeing dentist at least once a year), dental caries, subgingival calculus, gingival bleeding were also recorded. Degrees of periodontitis were classified according to the standard case definition developed by the Centers for Disease Control and Prevention (CDC) in partnership with the American Academy of Periodontology (AAP) into no, mild, moderate and severe periodontitis.[37, 38]

DATA COLLECTION

After informed consent was done, the included patients were interviewed and received an oral examination by the researcher. Other clinical data such as the stages of CDK were reviewed and verified from the medical record.

STATISTICAL ANALYSIS

This study used frequency and percentage to describe categorical variables. Mean and standard deviation (SD) were used to describe normal distributed continuous data. We assessed the association between the stages of CKD and severe periodontitis using crude and adjusted odds ratios (COR and AOR, respectively) together with 95% confidence interval (CI) from binary logistic regression. $P<0.05$ was considered statistical significance.[39]

RESULTS

BASELINE CHARACTERISTICS

There were 428 patients participated in this study including 125 patients with no kidney damage and 303 patients with CKD (Table 1). Of 428, 163 had no periodontitis while 58, 116 and 91 had mild, moderate and severe periodontitis, respectively.

Table 1. Characteristics of the participants and odds ratios of factors determining severe periodontitis

Characteristic	Periodontitis				Odds ratio (95% confidence interval) for severe periodontitis	
	No (N=163)	Mild (N=58)	Moderate (N=116)	Severe (N=91)	Crude	Adjusted
Age	53.4±12.0	57.6±10.0	61.1±10.3	63.2±9.5	1.06 (1.03-1.08)	1.04 (1.01-1.07)
Male-no. (%)	58 (35.6)	27 (46.6)	52 (44.8)	42 (46.2)	1.25 (0.79-1.99)	1.40 (0.69-2.80)
Education-no. (%)						
No formal or primary education	61 (37.4)	44 (75.9)	77 (66.4)	71 (78.0)	Reference	
Secondary education or higher	102 (62.6)	14 (24.1)	39 (33.6)	20 (22.0)	0.33 (0.19-0.57)	0.49 (0.26-0.93)
Smoking-no. (%)						
Non smoker	133 (81.6)	42 (72.4)	83 (71.6)	64 (70.3)	Reference	
Former smoker	25 (15.3)	12 (20.7)	26 (22.4)	21 (23.1)	1.34 (0.76-2.36)	0.95 (0.43-2.09)
Current smoker	5 (3.1)	4 (6.9)	7 (6.0)	6 (6.6)	1.51 (0.57-4.02)	1.61 (0.48-5.44)
Diabetes-no. (%)	46 (28.2)	26 (44.8)	66 (56.9)	54 (59.3)	2.11 (1.31-3.37)	1.27 (0.73-2.20)
Hypertension-no. (%)	96 (58.9)	46 (79.3)	95 (81.9)	76 (83.5)	2.14 (1.17-3.90)	1.32 (0.64-2.72)
Good oral care-no. (%)	23 (14.1)	1 (1.7)	4 (3.4)	2 (2.2)	0.25 (0.06-1.06)	0.84 (0.16-4.37)
Dental caries -no. (%)	114 (69.9)	51 (87.9)	101 (87.1)	75 (82.4)	1.25 (0.69-2.28)	0.85 (0.42-1.71)
Subgingival calculus -no. (%)	141 (86.5)	55 (94.8)	114 (98.3)	91 (100.0)	0.99	-
Gingival bleeding -no. (%)	39 (23.9)	22 (37.9)	56 (48.3)	65 (71.4)	4.70 (2.83-7.81)	4.38 (2.50-7.67)
Chronic kidney disease-no. (%)						
No kidney damage	75 (46.0)	10 (17.2)	25 (21.6)	15 (16.5)	Reference	
Stage I	23 (14.1)	11 (19.0)	12 (10.3)	5 (5.5)	0.80 (0.27-2.32)	0.63 (0.20-2.03)
Stage II	9 (5.5)	1 (1.7)	10 (8.6)	13 (14.3)	4.77 (1.97-11.52)	2.46 (0.90-6.75)
Stage III	20 (12.3)	11 (19.0)	25 (21.6)	21 (23.1)	2.75 (1.32-5.74)	1.45 (0.61-3.45)
Stage IV	7 (4.3)	7 (12.1)	11 (9.5)	16 (17.6)	4.69 (2.05-10.74)	3.28 (1.23-8.79)
Stage V	29 (17.8)	18 (31.0)	33 (28.4)	21 (23.1)	1.93 (0.94-3.97)	1.63 (0.69-3.85)

Plus minus values are mean±SD

The participants' age tended to around 50 to 60 years old, nearly half were male with no formal or primary education (Table 1). The majority of them were non smokers. Diabetes and hypertension were the common underlying diseases in this group of patients. For those with CKD, most of them were in stage V.

ORAL HEALTH STATUS

Good oral care was found relatively rare. Meanwhile, dental caries, subgingival calculus, gingival bleeding were found relatively common and high in this group of patients (Table 1). In those with severe periodontitis, the participants in this group all had subgingival calculus (100%).

FACTORS ASSOCIATED WITH PERIODONTITIS

Table 1 also presents the factors associated with severe periodontitis interpreting as COR and AOR. Secondary education or higher were associated with non-severe periodontitis (AOR, 0.49; 95% CI, 0.26 to 0.93). Factors associated with severe periodontitis included older age (AOR, 1.04; 95% CI, 1.01 to 1.07), gingival bleeding (AOR, 4.38; 2.50 to 7.67) and CKD stage IV (AOR, 3.28; 95% CI, 1.23 to 8.79).

DISCUSSION

MAJOR FINDINGS

From our findings, we found that CKD stage IV were associated with more frequent severe periodontitis. Moreover, older age and gingival bleeding were also have positive association with severe periodontitis. However, secondary education or higher were associated with non-severe periodontitis.

COMPARISON WITH OTHER STUDIES

Periodontitis was found common in those with CKD in the present study and relatively high compared with the previous studies which found only 5.5 to 14.7% in CKD patients.[40-42]

We also found positive association between CKD in various stages and severe periodontitis, However only CKD stage IV was found to have significant association with severe periodontitis. This was consistent with a previous study which found Mexican Americans with reduced kidney function were twofold more likely to have periodontitis compared with Mexican American with normal kidney function.[18]

STRENGTH AND LIMITATIONS

To our knowledge, this is the first study mentioning the association between CKD in various stages and severe periodontitis. However, there were also several limitations of the current study. Firstly, this is a cross-sectional design. Casual relationship was then unable to be derived. Secondly, number of the participants were also very few in some stages of CKD for instance, stage II. Thus clear association might not be achieved. Finally, oral health examining was also done solely by the researcher., generaliziablity of the findings then might be limited.

CONCLUSION AND IMPLICATION

CKD stage IV was associated with more frequent severe periodontitis. Older age, gingival bleeding and low education were also have positive association with severe periodontitis. For a better understanding of the casual relationship between

CKD and severe periodontitis or vice versa, a larger prospective cohort study should be conducted. Moreover, a randomized controlled trial should be done to investigate whether periodontal treatment in CKD patients would slow CKD progression or delayed eGFR declination.

ACKNOWLEDGMENTS & DECLARATION

I would like to express sincere thanks to health personnel in CKD clinic Kalasin Hospital for data collection. Mr. Siwanon Rattanakanokchai for data analysis and Professor Dr. Malinee Laopaiboon for great advice, study design and analysis.

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

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Intravenous versus intramuscular magnesium sulfate for severe preeclampsia and fetal hypoxia

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To compare the rate of fetal hypoxia in those with intravenous and intramuscular magnesium sulfate in pregnant women with severe preeclampsia.

METHODS

We conducted a retrospective cohort study to assess maternal and neonatal outcomes in pregnant women with severe preeclampsia between given intravenous magnesium sulfate and intramuscular magnesium sulfate. The study was conducted using the medical records of the patients with severe preeclampsia admitted at Khon Kaen Hospital and Srinagarind Hospital, Thailand between January 2007 and December 2012.

RESULTS

There were 372 patients included in the study; 218 to intravascular magnesium sulfate and 154 to intramuscular magnesium sulfate. It found that intravenous magnesium sulfate were associated with lower risk for fetal hypoxia (AOR, 0.33; 95% CI, 0.21 to 0.54). Gestational diabetes and chronic hypertension were also associated with higher risk for fetal hypoxia (AOR, 2.53; 95% CI, 1.10 to 5.78 and AOR, 2.62; 95% CI 1.01 to 6.79, respectively). Moreover, advanced maternal age. and previous preeclampsia were not associated with fetal hypoxia.

CONCLUSION

Intravascular magnesium sulfate was associated with lower risk for fetal hypoxia. Gestational diabetes and chronic hypertension increased the risk for fetal hypoxia

Accepted: June 2016
Latest revision: December 2016
Printed: February 2017

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INTRODUCTION

Preeclampsia affects 3% to 5% of all pregnancies and is estimated to result in 60,000 maternal deaths annually worldwide.[1] Preeclampsia is a multiorgan syndrome of pregnancy, defined by the new onset of hypertension and proteinuria after 20 weeks' gestation.[2] Major maternal complications include disseminated coagulopathy, hemolysis elevated liver enzymes and low platelets (HELLP) syndrome, pulmonary edema, placental abruption, acute renal failure, eclampsia, long-term cardiovascular or maternal death.Neonatal complications also include preterm delivery, fetal growth restriction, perinatal death, hypoxia-neurologic injury or long-term cardiovascular morbidity associated with low birth weight (fetal origin of adult disease).[3,4]

Severe preeclampsia can develop into eclampsia. Magnesium sulfate ($MgSO_4$) is one of the modalities to reduce the risk of seizures and mortality for women with preeclampsia and eclampsia.[5] It may also protect the blood-brain barrier and limit cerebral edema formation.[6] It is usually given by either the intramuscular or intravenous routes.[7] Although there are many studies identified the effects of magnesium sulfate on maternal and infantile outcomes but none of them comparing those outcomes regarding routes of magnesium sulfate administration; intravenous versus intramuscular in patients with severe preeclampsia. Thus we conducted a study to compare maternal and neonatal outcomes especially fetal hypoxia in the pregnant women with severe preeclampsia between those administered magnesium sulfate intravenously and intramuscularly.

METHODS

STUDY DESIGN

We conducted a retrospective cohort study to assess maternal and neonatal outcomes in pregnant women with severe preeclampsia between given intravenous magnesium sulfate and intramuscular magnesium sulfate. The study was conducted using the medical records of the patients with severe preeclampsia admitted at Khon Kaen Hospital and Srinagarind Hospital, Thailand between January 2007 and December 2012.

PATIENTS

We reviewed women with severe preeclampsia which was a group of related hypertensive disorders of pregnancy and were diagnosed by one or more of the following criteria; sustained systolic blood pressure (BP)>160 mmHg or diastolic BP>110 mmHg while on bed rest, nephrotic-range proteinuria, sudden oliguria, central nervous system disturbances, pulmonary edema or cyanosis, epigastric or right upper quadrant pain, liver dysfunction.[8]

We divided the patients into two groups regarding their received regimens; (i) the group with intravenous magnesium sulfate was from Srinagarind Hospital; its regimen was given as 4 g intravenous loading dose, followed by a maintenance infusion of 1 to 2 g per hour by controlled infusion pump[9], and (ii) those with intramuscular magnesium sulfate, they were from Khon Kaen Hospital. its regimen was 4 g intravenous loading dose, immediately followed by 10 g intramuscularly and then by 5 g intramuscularly every 4 hours in alternating buttocks.

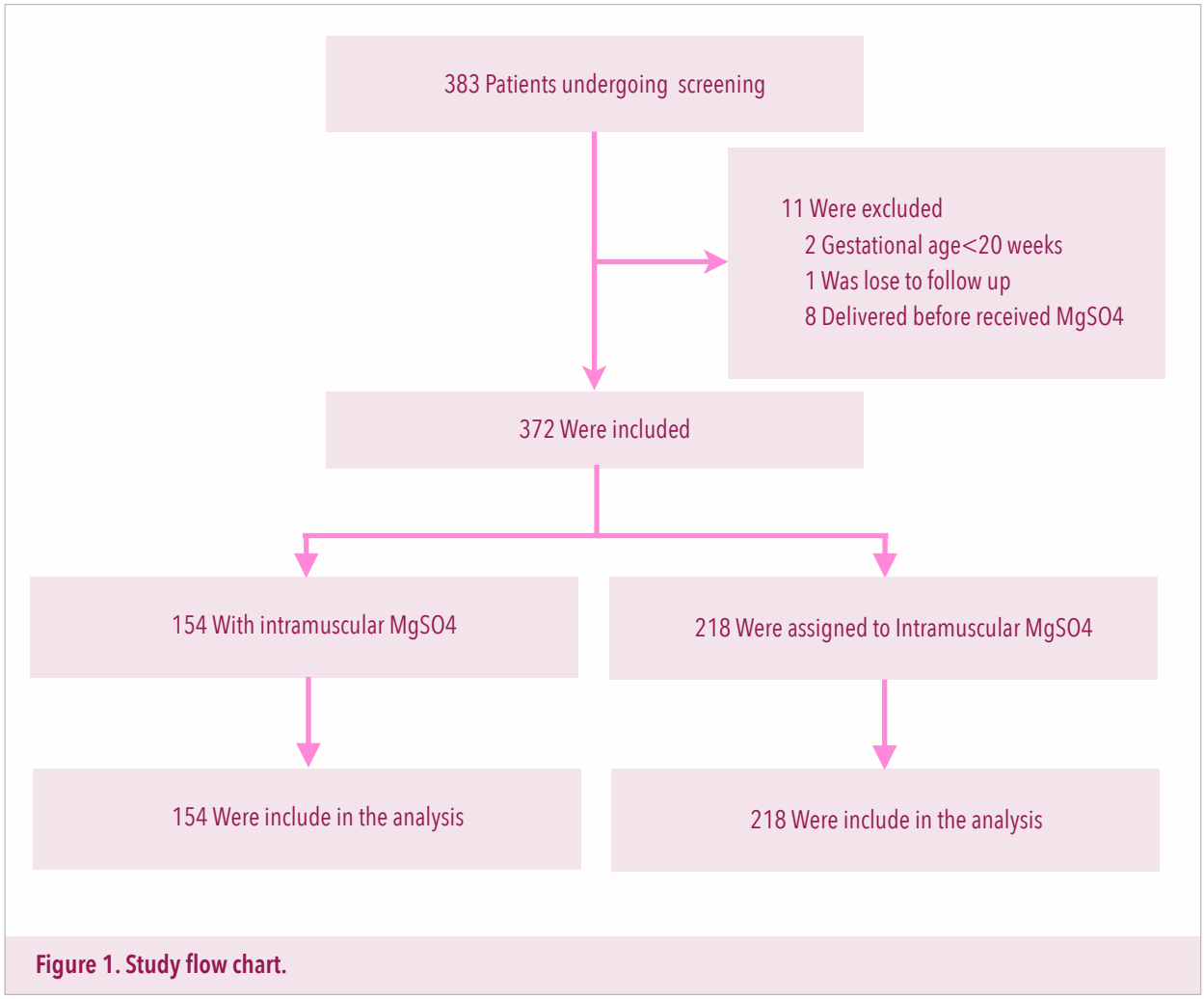

Figure 1. Study flow chart.

OUTCOMES

The outcomes of this study were major maternal complications including pulmonary edema from clinical and radiographic diagnosis, HELLP syndrome using the criteria of platelet count<100×10^9/L, aspartate aminotransferase>40 μ/L, alanine aminotransferase>53 μ/L, haemolysis as demonstrated by lactate dehydrogenase > 350 μ/L, peripheral blood smear or haptoglobin level, loss of blood pressure control, placental abruption-retroplacental clot covering more than 15% of placental surface, maternal death, eclampsia and severe renal impairment which was defined as serum urea value>10 mmol/L before delivery and rising further after delivery or with a lower value before delivery, rising to>10 mmol/L after delivery.[3]

Neonatal complications included preterm delivery diagnosed by delivery with gestational age (GA) 28 to less than 37 weeks, fetal growth restriction (IUGR), fetal hypoxia perinatal death and long-term cardiovascular morbidity associated with low birthweight.

Table 1. Characteristics of the patients

Characteristic	Intravenous MgSO4 (N = 218)	Intramuscular MgSO4 (N = 154)	P Value
Maternal age-yr			<0.001
Median	26	29	
Interquartile range	20-33	26-33	
Nulliparous-no. (%)	117 (53.7)	77 (50.0)	0.485
Gestational age-wk			<0.001
Median	38	36	
Interquartile range	35-39	32-38	
Antenatal visits-no. (%)			0.667
Median	8	8	
Interquartile range	6-10	6-10	
Blood pressure-mm Hg			
Systolic blood pressure-mm Hg			0.750
Median	169	167	
Interquartile range	160-180	160-180	
Diastolic blood pressure-mm Hg			0.771
Median	104	102	
Interquartile range	98-110	97-111	
Proteinuria-no. (%)			0.020
Trace	14 (6.6)	2 (1.3)	
1+	55 (25.8)	41 (26.6)	
2+	81 (38.0)	51 (33.1)	
3+	43 (20.2)	32 (20.8)	
4+	20 (9.4)	28 (18.2)	
Platelet count-x1000cells/mm^3			<0.001
Median	237	195	
Interquartile range	187-291	160.25-233.50	
Gestational diabetes mellitus-no. (%)	17 (7.8)	11 (7.1)	0.813
Preeclampsia in a prior pregnancy-no. (%)	4 (1.8)	0	0.145

Table 1. (Continued)

Characteristic	Intravenous MgSO4 (N = 218)	Intramuscular MgSO4 (N = 154)	P Value
Preeclampsia in a prior pregnancy-no. (%)	4 (1.8)	0	0.145
Chronic hypertension-no. (%)	19 (8.7)	3 (1.9)	0.006
Urine output-ml			0.116
Median	1390	1560	
Interquartile range	1005-2000	1060-2224	
Features of HELLP syndrome-no. (%)	1 (0.5)	10 (6.5)	0.001
Type of delivery-no. (%)			<0.001
Cesarean section	113 (51.8)	118 (76.6)	
Normal labor	74 (33.9)	24 (15.6)	
Vacuum extraction	29 (13.3)	10 (6.5)	
Forceps extraction	2 (0.9)	2 (1.3)	
Cesarean section after failed normal labor	0	0	
Duration of delivery-min			<0.001
Median	9	13	
Interquartile range	4-15	8-19	
Type of anesthesia-no. (%)			<0.001
None	27 (12.4)	33 (21.4)	
Localized anesthetic	67 (30.7)	3 (1.9)	
Spinal block	65 (29.8)	92 (59.7)	
General anesthesia	49 (22.5)	22 (14.3)	
Pudendal nerve block	4 (1.8)	0	
Epidural block	0	3 (1.9)	
Localized anesthetic and pudendal nerve block	6 (2.8)	0	
Spinal block + General anesthesia	0	1 (0.6)	
Abruptio placentae-no. (%)	3 (1.4)	0	0.270
Pre-term delivery	70 (32.1)	90 (58.4)	<0.001
Fetal growth restriction	10 (4.6)	23 (14.9)	0.001

Table 2. Outcomes of delivery

Characteristic	Intravenous MgSO4 (N = 218)	Intramuscular MgSO4 (N = 154)	P Value
Fetal hypoxia-no. (%)	50 (22.9)	67 (43.5)	<0.001
Neonatal outcomes-no. (%)			
APGAR score at 5th minute			<0.001
Median	10	9	
Interquartile range	9-10	8-10	
Birth weight-g			<0.001
Median	2700	2316	
Interquartile range	2230-3057	1587.50-2816.50	
Perinatal death-no. (%)	8 (3.7)	9 (5.8)	0.323
Maternal outcomes			
Maternal death-no. (%)	1 (0.5)	0	1.000
Eclampsia-no. (%)	2 (0.9)	1 (0.6)	1.000
Loss of blood pressure control -no. (%)	45 (20.6)	42 (27.3)	0.137
Severe renal impairment -no. (%)	3 (1.4)	1 (0.6)	0.645
Pulmonary edema -no. (%)	4 (1.8)	2 (1.3)	1.000
Disseminated coagulopathy/HELLP syndrome -no. (%)	3 (1.4)	6 (3.9)	0.171

STATISTICAL ANALYSIS

Before analyses, data were cleaned. Median and interquartile range (IQR) were used to summarized non normally distributed data. Number together with percentage were used to summarized categorical data. Comparing the outcomes between the two groups of those administered magnesium sulfate intravenously and intramuscularly, Mann Whitney U test and relative risk were used for continuous and categorical outcomes, respectively. To identify risk factors for fetal hypoxia, binary logistic regression analysis was used and presented in term of adjusted odds ratio (AOR) together with 95% confidence interval (CI), respectively.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Between January 2007 and December 2012, 383 patients from the two hospitals in Khon Kaen underwent screening for inclusion in the development the present cohort. We dropped 11 out after screening. The analysis includes the remaining 372 patients; 218 to intravascular magnesium

Table 3. Factor associated with fetal hypoxia

Factor	Adjusted odds ratio (95% confidence interval)	P Value
Intravenous MgSO4	0.33 (0.21-0.54)	<0.001
Advanced maternal age than 35 years	0.91 (0.50-1.65)	0.758
Gestational diabetes mellitus	2.53 (1.10-5.78)	0.029
Chronic hypertension	2.62 (1.01-6.79)	0.047
Previous preeclampsia	3.34 (0.44-25.63)	0.245

sulfate and 154 to intramuscular magnesium sulfate (Figure 1). Most of them were aged between 26 and 29 years old (Table 1). A bit more than half of them were nulliparous with the median gestation age of 37 weeks.

Between the two groups, the former group tended to be younger (P<0.001), older gestational age (P<0.001), have higher platelet count (P<0.001), more proportion of those with chronic hypertension (P=0.006), features of HELLP syndrome (P=0.001) and shorter duration of delivery (P<0.001).

OUTCOMES

From the univariable analysis in Table 2, fetal hypoxia were found less common in those with intravenous magnesium sulfate compared to those with intramuscular magnesium sulfate (22.9% vs. 43.5%; P<0.001) with better APGAR score at 5th minutes and greater birth weight (P<0.001 and P<0.001 respectively). However, the other outcomes including rates of perinatal death, maternal death, eclampsia, loss of blood pressure control, severe renal impairment, pulmonary edema and disseminated coagulopathy/HELLP syndrome were not different between the two groups.

FACTOR DETERMINE HYPOXIA

In Table 3, AOR for each factor predicting fetal hypoxia are presented. It found that intravenous magnesium sulfate were associated with lower risk for fetal hypoxia (AOR, 0.33; 95% CI, 0.21 to 0.54). Gestational diabetes and chronic hypertension were also associated with higher risk for fetal hypoxia (AOR, 2.53; 95% CI, 1.10 to 5.78 and AOR, 2.62; 95% CI 1.01 to 6.79, respectively). Moreover, advanced maternal age. and previous preeclampsia were not associated with fetal hypoxia.

DISCUSSION

MAJOR FINDINGS

In this retrospective cohort study, intravascular magnesium sulfate was associated with lower risk for fetal hypoxia. Gestational diabetes and chronic hypertension increased the risk for fetal hypoxia.

STRENGTH AND LIMITATION

This was the first study to examine the association between route of administration of magnesium sulfate and fetal hypoxia. The study had adequate sample size to ascertain the association. All data were reviewed and verified before proceeding the

analyses. Missing data were few. However, there were also several limitation. In the current study, we did not observe level of MgSO4 in each patient that made us unaware of serum level of MgSO4. Dosage of magnesium sulfate is one of the major confounders which is not available in the current study. As the current study was a retrospective cohort, to ascertain risks and benefit of different routes of magnesium sulfate administration and dosages, a randomized, double-blind, controlled trial should be conducted.

COMPARISON WITH OTHER STUDIES

Our study analysis found that intravascular magnesium sulfate was associated with lower risk for fetal hypoxia. We also found that the rate of maternal death were similar between using intravenous an d intramuscular magnesium sulfate. The findings were contrary with the previous study which showed that low dose intravenous magnesium sulfate regimen was equally effective in prevention of convulsion and maternal deaths when compared with an intramuscular magnesium sulfate regimen.[11,10] The difference might be due to that our study investigated the outcome in term of fetal hypoxia not maternal death. Size of the sample might not be enough to see the effect of the drug on maternal outcomes.

In a previous study, magnesium sulfate was given intravenously beginning with a 6 g, followed by 2- to 3-g/h infusion, it showed several neonatal complications are significantly related to increasing concentrations of magnesium in the maternal circulation, most research studied of Hispanic ancestry, maternal age 16-34 years and nulliparous.[24] [(11)] However, the current study, dosage of magnesium sulfate and serum magnesium level were not included n the analysis. side from route of administration, various dosage of magnesium with

CONCLUSION AND IMPLICATION

In summary, Intravascular magnesium sulfate was associated with lower risk for fetal hypoxia. Gestational diabetes and chronic hypertension increased the risk for fetal hypoxia. For better understanding of the effect of magnesium on routes of administration and dosages, a randomized, double-blind, controlled trial should be conducted.

ACKNOWLEDGMENTS & DECLARATION

The authors would like to thank :Thammasorn Jeeraaumponwat, M.D, Ph.D. for their supervision. We also would like to thank Khon Kaen Medical Education Center, Khon Kaen Hospital for their supports.

COMPETING INTERESTS: This study has no competing of interests.
FUNDING: None

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Factors predicting postoperative symptom clusters after lumbar spine surgery

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To identify factors influencing symptom clusters in patients undergoing lumbar spine surgery.

METHODS

This was a prospective observational study design. The sample patients who had undergone lumbar spine surgery with internal fixation using plates and screws and with general anesthesia at the Department of Orthopedics, Nakhon Phanom Hospital, Thailand. Data were collected between May 2015 and July 2016 using self-reported questionnaire, interview form and physical examination on day one and day three after surgery. The research instruments consisted of postoperative complications questionnaire and symptoms assessment scale.

RESULTS

There were 80 patient included in the present study. Our finding showed that multiple symptoms and tended to improved over time after the operations. However, from binary logistic regression analysis, male sex, age, history of surgery, duration of surgery, incisional length and type of surgery were found not to be associated with symptom clusters two or more on Day 1.

CONCLUSION

Non of the factors including male sex, age, history of surgery, duration of surgery, incisional length and type of surgery were found to be associated with symptom clusters two or more on Day 1.

Accepted: November 2016
Latest revision: January 2017
Printed: February 2017

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INTRODUCTION

Lumbar spine surgery is a surgery conducted to treat spine patients suffering from incurable severe back and leg pain due to lumbar spondylolysis, leading to persistent pain and loss of physical functioning.[1,2] After undergoing lumbar spine surgery, patients have to endure pain caused by stimulation of the sensory neurons in the areas with a lower pain threshold including the skin, joints, tendons, and periosteum.[3] In the US, the rates of patients who received spinal fusion range from 169 to 252 per thousand from 2006 to 2011.[4] In 2011, 10.4% of patients with low back diagnosis were operated on with a fusion.[4] A review of the literature has revealed that previous studies tend to focus on only a particular postoperative symptom after lumbar spine surgery, especially pain.[2,5,6] However, it has been found that there are more symptoms which result after lumbar spine surgery.[7] According to the theory of unpleasant symptoms, symptoms refer to patients' perception of changes in physical functioning that affect their health status. A single symptom or a cluster of symptoms may occur, and once a symptom has occurred, it will become a factor that stimulates other symptoms to follow.[8] At present, multiple symptoms that simultaneously occur are called symptom groups or symptom clusters.[8,9]

Symptom clusters refer to two or more symptoms that occur simultaneously and are interrelated. They do not necessarily share the same cause, but their causes may be related.[10] An extensive review of the literature has shown that factors that are generally investigated in patients undergoing lumbar spine surgery are physiologic factors including age, gender, and postoperative complications; psychological factor of anxiety, and situational factors including type of surgery, duration of surgery, length of hospital stay, and social support. Such factors lead to symptoms, which, in turn, affect the patients' physical performance, psychological performance, ability to carry out activities of daily living, and quality of life,[2,7] particularly postoperative complications and duration of surgery. In fact, duration of surgery is considered a situational factor which has an impact on postoperative symptom clusters, the longer the duration of surgery, the more postoperative symptom clusters.[11] In addition, postoperative complications are considered an important physiologic factor affecting postoperative symptoms and symptom clusters associating with postoperative functioning and performance.

The primary objective of this study was to identify factors influencing symptom clusters in patients undergoing lumbar spine surgery including experience with surgery, duration of surgery and postoperative complications.

METHODS

STUDY DESIGN AND OVERSIGHT

This was a prospective observational study aimed to explore factors influencing symptom clusters in patients undergoing lumbar spine surgery including experience with surgery, duration of surgery, and postoperative complications. This study was conducted at the inpatient unit, Department of

Orthopedics, Nakhon Phanom Hospital, Thailand from May 2015 to July 2016.

PARTICIPANTS

The study sample consisted of patients with lumbar spondylolysis, spondylolisthesis and spinal stenosis undergoing lumbar spine surgery with or without decompression, spinal fusion and internal fixation using plates and screws. All of them underwent general anesthesia. Convenience sampling was employed to recruit the sample based on the following inclusion criteria; (i) they were at least 20 years of age, (ii) they underwent lumbar spine surgery for the first time, (iii) they did not suffer from spinal injury, (iv) they had never been diagnosed with cancer (v) they did not have chronic conditions such as thalassemia, asthma, hypertension, diabetes mellitus, or heart disease, (vi) they were fully conscious, (vii) they were able to communicate in Thai and (viii) they were willing to participate in the study. The exclusion criterion was severe complications on the first or third days after lumbar spine surgery including shock, mechanical ventilation or re-surgery.

As regards sample size, since the number of population was unspecified, the G*Power computer program which was widely used and accepted was utilized. The power of test was set at 0.80, the level of significance was set at 0.05 (α=0.05), and the medium effect size was chosen at 0.15. The calculated number of participants was 77. However, to prevent the problem with participants loss, ten percent was added to the calculated sample size, and the final number of participants was 85. In this study, five out of the total number of participants were excluded as on the first or third days after the surgery; three of them required the use of mechanical ventilation and two had to undergo the second surgery. The final number of participants was 80.

OUTCOME MEASURES

The postoperative complications assessment scale was developed by the researcher based on an extensive review of the literature and related research. The scale assessed postoperative complications as follows; blood clots in the surgical wound, the paralytic ileus, and infection of the surgical wound. The instrument assessed whether the patients had or did not have postoperative complications on Day 1 and Day 3 days after lumbar spine surgery.

As for scoring criteria of postoperative complications, if the patients had all signs and symptoms of all aforementioned postoperative complications, a score of one point was given to indicate a diagnosis of postoperative complications. If they did not have all of the symptoms, they would get a score of 0 point. The CVI was equal to 0.71. The instrument was used after it had been revised based on the experts' comments and suggestions. Inter-rater reliability was determined when it was implemented with ten patients undergoing lumbar spinal surgery who were not the subjects of the main study. Inter-rater reliability was equal to 100%.

Postoperative symptoms are measured using the Memorial Symptom Assessment Scale (MSAS) in a previous study.[12] It was used to assess postoperative symptoms considering frequency, severity, and distress with high internal consistency

Table 1. Characteristics of the participants

Characteristic	N=80
Female gender-no. (%)	44 (55)
Age-years	
Median	54.5
Interquartile range	44.0-60.0
Between 50 and 59	44 (55)
Education-no. (%)	
No education	1 (1)
Primary	68 (85)
Secondary	11 (14)
Marital status-no. (%)	
Single	9 (11)
Married	67 (84)
Widowed	3 (4)
Divorced	1 (1)
Diagnosis-no. (%)	
Spinal stenosis L3-4-5	37 (46.2)
Spinal stenosis L3-4-5-T1	1 (1)
Spinal stenosis L4-5	32 (40)
Spinal stenosis L5-S1	8 (10)
Herniated nucleus pulposus	2 (3)

coefficients suggesting highly inter-correlated of severity, frequency, and distress dimensions.[12] The scale ranges from 0 to 12. In the present study, MSAS was adapted to be used to evaluate post operative symptom symptoms e.g., pain, insomnia, abdominal distension, fatigue, anxiety, leg pain, leg numbness, and motor weakness at the feet rather than the original version[13], which called system assessment scale (SAS). The test-retested reliability of SAS in the current study was found to have a significant correlation amongst symptoms ($r=0.99$, $P<0.001$).

Post operative symptom cluster can be categorized into three cluster; symptom cluster 1 included leg pain, leg numbness, and motor weakness in the feet. Symptom cluster 2 included three symptoms of surgical wound pain, fatigue, and

Table 2. Information regarding operations and complications

Information	N=80
Type of surgery-no. (%)	
Decompressive laminectomy	6 (8)
Decompressive laminectomy with posterolateral lumbar fusion	3 (4)
Decompressive laminectomy with posterolateral lumbar with pedicular screw	60 (75)
Decompressive laminectomy with posterolateral lumbar fusion with pedicular screw with discectomy	11 (14)
Duration of surgery-minutes	
Median	135
Interquartile range	115 .0-168.7
<60	1 (1)
60-120	33 (41)
>120	46 (58)
Experience with surgery-no. (%)	26 (33)
Postoperative complications	
Paralytic ileus	1 (1)
Blood clot in the surgical wound	2 (3)
Incisional length-centimeters	
Median	14
Interquartile range	
5-10	5 (6)
11-15	60 (75)
16-20	15 (19)

insomnia. Symptom cluster 3 consisted of two symptoms, which were anxiety and abdominal distention.

DATA COLLECTION

The data were then collected in the following order: The researcher surveyed the name of the patients who underwent lumbar spine surgery on the first and third days at the orthopedics ward and selected those who met the inclusion criteria. After that, the researcher met the prospective participants to introduce herself and explain the research objectives and protected the rights of human by giving them explanation on the information sheet and informed consent form and asking for their cooperation in data collection. If the prospective participants agreed to

Table 3. Outcomes from system assessment scale

System assessment scale	Day 1	Day 3	P value
	Median (IQR)		
Pain	9 (6-11.8)	6 (3-6)	<0.001
Insomnia	6 (3-6.8)	3 (0-3)	<0.001
Abdominal distension	0 (0-0)	3 (0-3)	<0.001
Fatigue	6 (3-6.8)	3 (0-3)	<0.001
Anxiety	0 (0-3)	0 (0-3)	0.064
Leg pain	9 (6-9)	3 (3-6)	<0.001
Leg numbness	6 (6-9)	3 (0-6)	<0.001
Motor weakness at the feet	6 (0-9)	3 (0-6)	<0.001

participate in the study, they would be asked to sign the informed consent form. The researcher collected data using the demographic characteristics questionnaire and interviewed the participants using the symptoms assessment scale (SAS).

Data regarding postoperative complications were gathered from the medical records, interviews, and physical examinations of the participants. If the participants were unable to read, the researcher would give them the description of the assessment scale and read each item to the participants who would then be asked to respond verbally. Data were collected from each participants twice on Day 1 and Day 3 after lumbar spine surgery. Interview session lasted approximately 20-30 minutes.

STATISTICAL ANALYSIS

Data regarding demographic characteristics of the participants, their illness, postoperative complications and postoperative symptoms were analyzed in terms of descriptive statistics, number and percentage while median and interquartile range were used to summarized non-normally distributed data. The outcomes between symptom Day 1 and symptom Day 3 were compared using Wilcoxon Signed Rank test.

Numbers of symptoms cluster for Day 1 and Day 3 were summarized. To identify factors predicting symptoms cluster two or more on day 1, binary logistic regression analysis and were interpreted in term of adjusted odds ratio (AOR) together with 95% confidence interval (CI).

RESULTS

In the current study, there were 80 patients included in the study. In general, most of them were middle aged female with primary education. Majority of them were married (Table 1). More than half of the operations were decompressive laminectomy with

Table 4. Number of symptom clusters on Day 1 and Day 3

Number of symptom cluster	Day 1	Day 3
	No. (%)	
No	10 (13)	45 (56)
One	24 (30)	25 (31)
Two	45 (56)	10 (13)
Three	1 (1)	0

PL fusion with pedicular screw as their diagnoses were spinal stenosis L3-4-5. The median operation time was 135 minutes. Most of them were non-experience with surgery (Table 2). One patient suffered from a postoperative complication of paralytic ileus on the first day after the surgery and two patient developed blood clot in the surgical wound on the third day after the surgery. The median incisional length of 14 centimeters.

From Table 3, SAS was used to assess eight symptoms; pain, insomnia, abdominal distention, fatigue, anxiety, leg pain, leg numbness and motor weakness in the feet of the patients. Comparing between the symptoms on Day 1 and the symptoms on Day 3, patients tended to have more pain ($P<0.001$), more insomnia ($P<0.001$), more abdominal distention ($P<0.001$), more fatigue ($P<0.001$), more leg pain ($P<0.001$), more leg numbness ($P<0.001$), more motor weakness at the feet ($P<0.001$) on Day 1 comparing to Day 3.

Table 4 presents number of factors for Day 1 and Day 3. On Day 3, number of patients with one, two or three symptom clusters tended to decrease while number of patients with no symptom clusters tended to increase comparing to Day 1.

Table 5 shows factors predicting cluster symptoms. From the binary logistic regression, it found that no factors; male sex, age, history of surgery, duration of surgery, incisional length and type of surgery were found to be associated with symptom clusters two or more on Day 1.

DISCUSSION

MAJOR FINDINGS

Our finding showed that multiple symptoms and tended to improved over time after the operations. However, from binary logistic regression analysis, male sex, age, history of surgery, duration of surgery, incisional length and type of surgery were found not to be associated with symptom clusters two or more on Day 1.

COMPARISON WITH OTHER STUDIES

In one previous study from the prospective study in 208 patients spinal surgery, they found that the effects of postoperative complications after surgery were not related to mental condition and pain, with regard to experience with surgery and duration of surgery, they were not able to predict postoperative

Table 5. Factors predicting cluster symptom

System assessment scale	Adjusted odds ratio (95% confidence interval)
Male	2.49 (0.85-7.31)
Age-years	0.99 (0.93-1.04)
History of surgery	3.34 (0.96-11.57)
Duration of surgery-minutes	0.99 (0.99-1.01)
Incisional length-cm	1.01 (0.80-1.28)
Type of surgery	
Decompressive laminectomy with posterolateral lumbar fusion	0.27 (0.01-7.70)
Decompressive laminectomy with posterolateral lumbar with pedicular screw	0.22 (0.02-2.28)
Decompressive laminectomy with posterolateral lumbar fusion with pedicular screw with discectomy	0.46 (0.03-6.50)

symptom clusters.[14] In our study, 46 had duration of surgery (>2 hours) 57.5 %. This was similar to the previous meta-analysis of 12 studies with a total of 13,476 patients spinal surgery, the most important predictors of postoperative complication (surgical-site infection) were prolonged operative times (>3 hours) (RR = 2.16, 95% CI 1.12–4.19; P = 0.009).[15] However, our study showed no factors had influence in on having two symptom clusters or more.

LIMITATIONS OF THE STUDY

There were several limitation of the current study. Firstly, the sample size of the present study was small with prospective study. Generalization of findings is then still limited. Moreover, the factors predicting selection was not extensive, and factors that affect the symptoms of the present study in the short term.

CONCLUSION AND RESEARCH IMPLICATION

Non of the factors including male sex, age, history of surgery, duration of surgery, incisional length and types of surgery were found to be associated with symptom clusters two or more on Day 1. The result of present study suggested that the present-day clinical nursing care practices should acknowledge the significance of postoperative symptoms, particularly pain. This is because the symptom experienced by postoperative patients is not a single symptom, but it is a cluster or group of symptoms. A larger cohort should done in the future for better estimation of the risks.

ACKNOWLEDGMENTS & DECLARATION

COMPETING INTERESTS: This study has no competing of interests.

FUNDING: This project was financially supported by the Boromarajonani College of Nursing Nakhon Phanom, Nakhon Phanom University, Fiscal year 2015.

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Metronidazole plus transdermal aspiration versus metronidazole alone in amebic liver abscess: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To analyze the available evidence comparing the efficacy of metronidazole plus transdermal aspiration versus metronidazole alone in patients with amebic liver abscess.

METHODS

This was a systematic review comparing the efficacy of aspiration versus drainage versus medication alone. Data sources included four online databases. Additional source were bibliographic databases, conference proceeding, were searched thoroughly (last update November 2016) as well as hand searching was done to identify relevant randomized controlled trial (RCT) without language restriction. All included studies were reviewed for risk of bias and risk assessment by two investigators independently assessed eligibility.

RESULTS

Six RCTs including 436 patients were included in the analysis. Most of the included study had unclear risks of biases. Comparing between using metronidazole plus TA and metronidazole alone in patients with an amebic liver abscesss, there were no significant difference in relation to the resolution of pain at Day 10 (relative risk, 1.15; 95% confidence interval (CI), 0.50 to 2.63; I^2=0), days to resolution of abdominal tenderness was shorter in the former group than that of the latter group (mean difference (MD), -1.96; 95% CI, -2.60 to -1.32; I2=0), and the length of hospital stays was also shorter in the former group than that of the latter group (MD, -0.86; 95% CI, -2.39 to -0.72; I^2=78%).

CONCLUSION

Metronidazole plus TA did not significantly increase the proportion of patients with pain resolution at Day 10. comparing to metronidazole alone. Benefits could be observed in term of shorter days to resolution of abdominal tenderness, length of hospital stays in those using metronidazole plus TA than that of using metronidazole alone.

Accepted: November 2016
Latest revision: January 2017
Printed: February 2017

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INTRODUCTION

Amebic liver abscess is still prevalent in Asia.[1] India, Africa, Mexico and some parts of Central and South America are areas with high incidence rates of amebic infection.[1] Its treatments comprise antiparasitic drugs e.g., metronidazole or tinidazole with more than 90% cure rate.[2,3,4]

Transdermal aspiration (TA) under ultrasound or computed tomography guidance (CT) or insertion of percutaneous catheter drainage may be required for with risk of abscess rupture, clinical deterioration, lack of response to empiric treatment, or if the differential diagnosis is required.[5] In some cases, TA can be used both for diagnosis and treatment.[6,7]

In 2009, there was a systematic review comparing the efficacy of metronidazole plus TA versus metronidazole alone.[5] It concluded that TA metronidazole plus TA was not superior over metronidazole alone.[5] Its conclusion, however, was from three homogeneous randomized controlled trials (RCT) out of seven low-quality RCTs.[5] Moreover, the review included three RCTs that used other drugs e.g., chloroquine, iodoquinol and dehydroemetine adjunct to metronidazole rather than metronidazole alone.[8-10] Since then, there were at least two additional RCTs with a large number of patients.[11,12] We thus aimed to update focusing on the evidence of efficacy comparing metronidazole plus TA versus metronidazole alone. Thus, we conducted a systematic review integrating all available evidence comparing metronidazole plus TA versus metronidazole alone.

METHODS

This study is a systematic review comparing the efficacy of metronidazole plus TA versus metronidazole alone in an amebic liver abscess. It was conducted according to Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0.[13] and followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[14]

SEARCH STRATEGIES

Two independent reviewers systematically searched for articles through PubMed, the Cochrane Library, Trip Database and Scopus. Searching in Pubmed and Cochrane library were undertaken using MeSH terms; "Liver Abscess, Amebic" AND "Paracentesis". We used PICO search in Trip Database and various combinations of following keywords in Scopus; "amebic liver abscess", "amoebic liver abscess" "paracentesis", "aspiration", "transdermal aspiration", "percutaneous needle aspiration" and "needle aspiration". All search had to performed since the beginning of all databases till November 2016.

INCLUSION AND EXCLUSION CRITERIA

We, the reviewers, included only RCT in patients with the serological diagnosis of amebic liver abscess or other proper diagnosis methods treating with metronidazole or plus TA comparing to metronidazole alone. The outcomes of this review including any outcomes of both benefit and adverse outcomes. We did not have any specific exclusion criteria for the current systematic review.

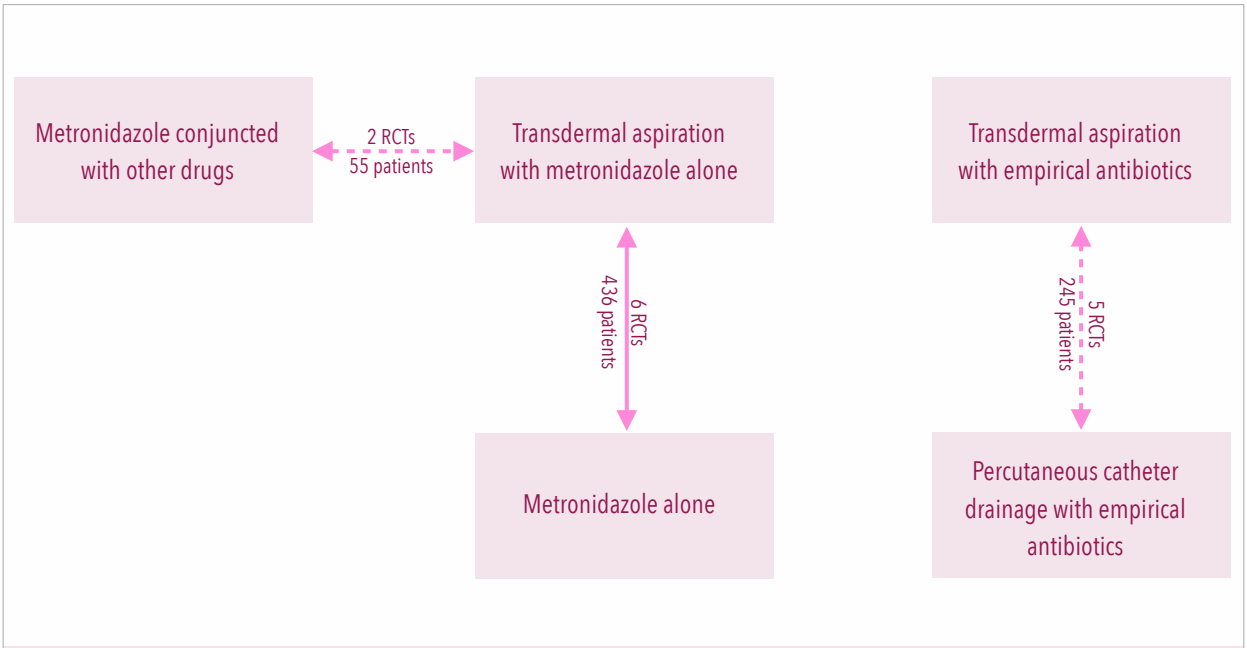


Figure 1. Network of comparisons included in analyses.
From the results of comprehensive searching, lines represent direct comparisons within randomized controlled trials (RCTs). Solid line indicates our interested comparison. Numbers denote trials comparing corresponding interventions, with overall number of patient.

QUALITY OF REPORTING AND RISKS OF BIAS

We, the reviewers, independently evaluated quality and risk of bias of the included trials using the Cochrane Collaboration's tool, recommended by Cochrane Handbook for Systematic Reviews of interventions.[15] The Cochrane Collaboration's tool classifies the study's biases into three groups (low risk, high risk and unclear risk) and regards the following evaluation: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other biases.

DATA EXTRACTION

We extracted data regarding the first author's name, year of publication, the country where the study was conducted, a number of participants, interventions and outcomes in term of benefit and adverse effects. Disagreeable data were determined by discussion between the two reviewers.

DATA ANALYSIS

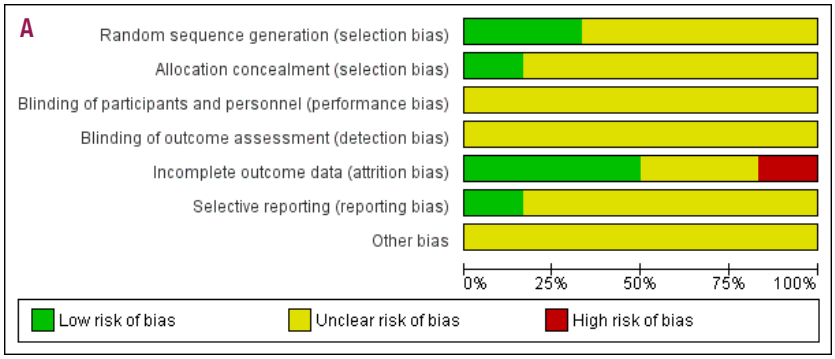
We identified different type of outcome data; for continuous data, we calculated the mean difference (MD) and its 95% confidence interval (CI) while we calculated relative risk (RR) and its 95% CI for dichotomous data comparing both efficacy and adverse event in between metronidazole plus TA

Table 1. Characteristics of the included studies

Author and year	Participants (N)	Intervention	Outcome (fomer values are from TA group)
Metronidazole plus transdermal aspiration (TA group) vs. metronidazole alone (control group)			
Sharma 1989[16]	37 patients with amebic liver abscess	17 patients in TA group vs. 20 patients in control group; all received metronidazole 2-4 g/day for 10 days.	(i) Pain resolution at Day 10 (10/17 vs. 12/20) (ii) Fever resolution at Day 10 (16/17 vs. 16/20) (iii) Anorexia resolution at Day 10 (10/17 vs. 9/20) (iv) Hepatomegaly reduction at Day 10 (0/17 vs. 0/20) (v) Complete resolution at 1 year (5/17 vs. 6/20) (vi) Resolution at 1 year>50% (10/17 vs. 10/20) (vii) Resolution at 1 year<50% (2/17 vs. 4/20) (viii) Diameter of cavity at 1 year (25±23 mm vs. 21±17 mm)
de la Rey Nel 1989[17]	80 patients with amebic liver abscess	37 patients in TA group vs. 43 patients in control group; all received metronidazole 800 mg three times a day for 5 days.	(i) Time to resolution of abdominal tenderness; 4.5±2.2 vs. 6.9±2.3 (ii) Proportion of non-responders; 13/37 vs.15/43
Tandon 1997[18]	29 patients with large amebic liver abscess larger than 5 cm diameter	15 Patients in TA group vs. 14 patients in control group; all received metronidazole 800 mg every 8 hours for 10 days.	(i) Pain reducation from Grade 2 to 1; 0.7±0.7 vs. 2.9±0.9 days (ii) Moderate fever to mild fever; 1.4±0.8 vs. 2.3±0.9 days (iii) Mild fever to afebrile; 2.3±0.9 vs. 2.2±1.3 days (iv) Abdomial tenderness from Grade 2 to I; 1.1±0.8 vs. 2.9±1.2 days (v) Length of hospital stay; 5.8±0.8 vs 7.4±1.5 days
Blessmann 2003[19]	39 patients with amebic liver abscess size 6-10 cm in diameter	20 patients in TA group vs. 19 in control group; all received metronidazole 30 mg/kg thrice a day for 10 days alone	(i) Resolution of right upper quadrant pain at day 3, 5 and 10; 8/20 vs. 5/19; 11/20 vs. 8/19; 20/20 vs. 18/19. (ii) Resolution of liver tender at day 3, 5 and 10; 9/20 vs. 1/19; 10/20 vs. 7/19; 13/20 vs. 12/19) (iii) Resolution of abscess volume (mm) at day 3 and 10; -74 vs. -10; -97 vs. -60)
Bammigatti 2013[11]	57 patients with amebic liver abscess 5-10 cm in diameter	28 patients in TA group vs 29 patients in control group; all received metronidazole 40 mg/kg/day three times per day intravenously or orally for 10 days.	(i) Resolution of fever (hours); median [IQR] (17 [0-49] vs. 30 [0-72]) (ii) Resolution of abdominal pain (hours); median [IQR], (27 [14-56] vs. 48 [24-72]) (iii) Treatment failure (2/28 vs. 4/29) (iv) Duration of hospitalization (4.46±2.39 vs 4.5±1.88) (v) Days to normalize total leukocyte count (3.7±2.83 vs. 2.45±1.96) (vi) Death (0/28 vs. 0/29) (vi) Rupture of abscess (0/28 vs. 2/29)
Ghosh et al, 2015[12]	194 patients with amebic liver abscess not mor than 10 cm in diameter	96 patients in TA group vs 98 patients in control group. All received oral metronidazole 800 mg thrice a day for 14 days.	Reduction of abscess cavity diameter at Day 8, 15, 1 month and 3 months; 1.71±0.35 vs.-0.59±0.39; -2.60±0.35 vs. -1.06 ±0.41; -3.00±0.28 vs-1.68±0.35; -3.86±0.28 vs.-2.17±0.29

Plus–minus values are means ±SD.

versus metronidazole alone. All data were analyzed by Review Manager 5.3 statistical software (RevMan 5.3) and shown the result in form of forest plots. Statistical significance was described as $P<0.05$. If I^2 more than 40%, heterogeneity will be observed and we will use random-effects model for the meta-analysis. If I^2 less than 40%, we will use fixed-effects model.



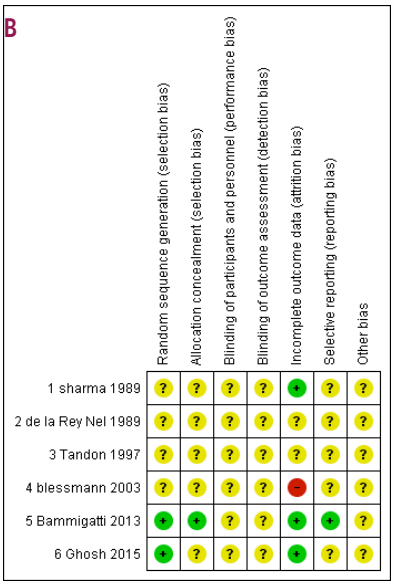


Figure 2. Risk of bias by review authors' judgements about each risk of bias item for each included study
Panel A, Risk of bias graph; Panel B, Risk of bias summary

RESULTS

After the elimination of duplicates and nonRCTs, six RCTs including 436 patients met our inclusion criteria (Figure 1).[11,12,16-19] Details of the six included trials are outlined in Table 1. All of them were published in English. The number of participants per trial ranged from 29 to 194 participants. However, description of their participants was not provided in all of the included studies. Sizes of the abscess were varied and were not stated in some studies (Table 1). Most of the studies conducted in developing countries. TA was done under either ultrasonography or CT. Doses of metronidazole were relatively similar while the treatment durations were varied greatly from 5 days to 14 days.

RISKS OF BIAS OF THE INCLUDED STUDIES

The two reviewers assessed the quality of the six included studies using The Cochrane Collaboration's Tool for Assessing Risk of Bias.[15] The risk of bias graph and summary are presented in Figure 2 (Panel A and B). Most of the included studies had unclear risks of biases.

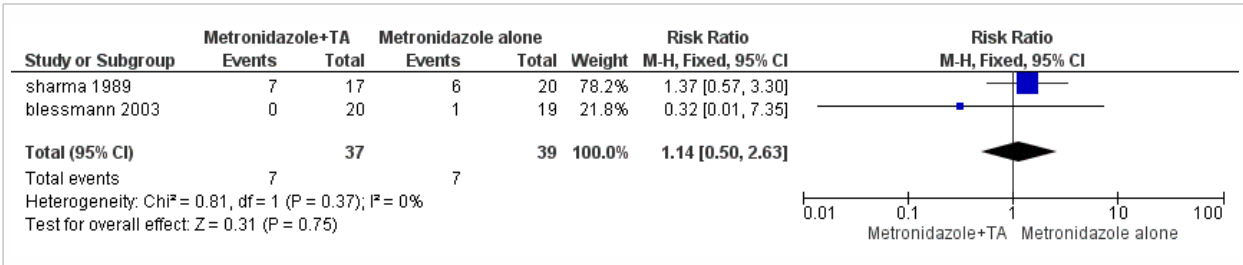


Figure 3. Estimates of the treatment effect in relation to resolution of pain at Day 10 of metronidazole plus transdermal aspiration (TA) compared with metronidazole alone

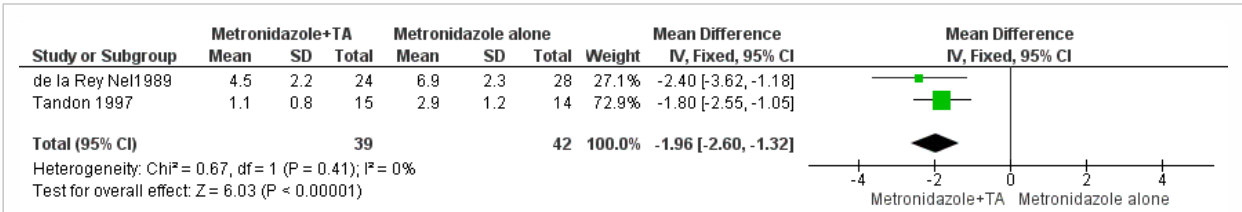


Figure 4. Estimates of the treatment effect in relation to days to resolution of abdominal tenderness metronidazole plus transdermal aspiration (TA) compared with metronidazole alone

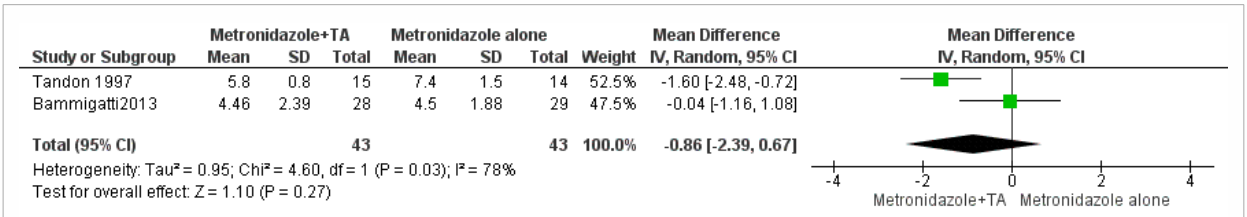


Figure 5. Estimates of the treatment effect in relation to length of hospital stay of metronidazole plus transdermal aspiration (TA) compared with metronidazole alone

OUTCOMES OF THE INTERVENTIONS

In all of the included study, a wide variety of outcomes were collected (Table 1). However, very few of them were able to combine in the meta-analysis. There were three combinable outcomes; resolution of pain at Day 10, days to resolution of abdominal pain and length of hospital stay.

Resolution of pain at Day 10

From Figure 3, there were no significant in relation to the resolution of pain at Day 10 comparing between using metronidazole plus TA and metronidazole alone in patients with an amebic liver abscess (RR, 1.15; 95% CI, 0.50 to 2.63; I^2=0).

Days to resolution of abdominal tenderness

From Figure 4, days to resolution of abdominal tenderness was shorter in those using metronidazole plus TA than that of metronidazole alone in patients with an amebic liver abscess (MD, -1.96; 95% CI, -2.60 to -1.32; I^2=0).

Length of hospital stay

From Figure 5, the length of hospital stays tended to be shorter in patients with amebic liver abscess using metronidazole plus TA than that of metronidazole alone (MD, -0.86; 95% CI, -2.39 to -0.72; I^2=78%).

DISCUSSION

MAJOR FINDINGS

Six low-quality RCT were included in the present review. Due to selective outcome reporting bias, fewer patients were able to include in our meta-analyses. Only three treatment outcomes were able to be combined. Pooled analysis of two homogenous RCTs showed that metronidazole plus TA did not

significantly increase the proportion of patients with pain resolution at Day 10. Benefits could be observed in term of shorter days to resolution of abdominal tenderness, the length of hospital stays in those using metronidazole plus TA than that of using metronidazole alone. However, high heterogeneity was also found the later outcome. These pooled conclusions were based on RCTs with methodological flaws and with insufficient sample sizes and require further confirmation in larger well-designed RCT.

COMPARISON WITH OTHER STUDIES

Metronidazole is the anti-parasitic drug of choice for treating amoebic liver abscesses followed the eradication of the parasite using luminal agent.[20] Cure rates was found in 95% with resolution of fever, pain and anorexia within three to four days [21,22] Complete radiologic resolution can take up to three to nine months with greater than a half reduction in liver size within a week. [20]

We found no evidence that adjunct TA to metronidazole yield additional benefits in relation to the resolution of pain and the length of hospital stays. Out of the included RCTs, three of them conducted after 2000 and most of them conducted in resource-limited settings. Nearly all of them were limited-quality RCTs which later made the inconclusive evidence.

Comparing to the previous systematic review in 2009 [5], our findings were relatively similar. From each included RCT, various outcomes are collected. However, very few can be combined and the results from our meta-analysis are somehow different from the previous systematic review; for instance, we used 1.1±0.8 for mean days to resolution of abdominal tenderness while it was 0.7±0.7 in a previous systematic review.[5] Thus, our forest plots were based on reasonably combined outcomes and verified extracted data from each RCT. We also focused on the RCTs using metronidazole rather than the combination of metronidazole and other drugs.

There was also another systematic review comparing the efficacy of TA versus catheter drainage in 2014.[23] It concluded that drainage was more effective than TA. However, the reviewed comprised patients with pyogenic liver abscess and unidentified liver abscess rather than amebic liver abscess alone. Moreover, the review also included RCTs which using empirical antibiotics e.g., anti-parasitics with antibiotics rather than metronidazole alone. The implication of the results, thus, might not be directly compared with the findings of the current review.

STRENGTH AND LIMITATIONS

Our review is the first systematic review comparing the efficacy of using metronidazole plus TA versus metronidazole alone. We systematically searched from databases and other sources for published and unpublished trials. We applied comprehensive search with no language restrictions. We tended to identify all relevant trials. We conducted this review follow the Cochrane handbook and meta-analyses checklist.

Our systematic review, however, has several limitations. The first limitation was the small numbers of participants for each outcome comparison as we found as only six RCTs, most of them had relatively small sample. Combinable outcomes were very few. The second limitation is that there are various doses and durations of

metronidazole use. This is one of the reasons for high heterogeneity in our findings. The third limitation is the included trials did not report adverse effects, implementation of the findings should be careful.

CONCLUSION AND IMPLICATION

Metronidazole plus TA did not significantly increase the proportion of patients with pain resolution at Day 10. comparing to metronidazole alone. Benefits could be observed in term of shorter days to resolution of abdominal tenderness, length of hospital stays in those using metronidazole plus TA than that of using metronidazole alone. These pooled conclusions were based on RCTs with methodological flaws and with insufficient sample sizes. A larger well-designed RCT, thus, is required for further confirmation.

ACKNOWLEDGMENTS & DECLARATION

The authors would like to express sincere thanks fifth year medical students, Khon Kaen Hospital i.e., Kiattida Boonasa, Pijak Sirirattanakul, Kittiya Jitpreeda, Sirinat Suriyachai, Nut Laorueangwatthana, Anchaleephon Srinathom, Santhita pimonbut, Rattanawan Mitrapanont, Sopanut Akkakraise, Rattanapa Kesonsombat, Watchara Lunchak, Napachanun Wisitjaroen and Piyangkoon Jumboonfor their helps regarding electronic and hand searching full text articles, drafting of the figures shown in the present study.

COMPETING INTERESTS: This study has no competing on interest.

FUNDING: None

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-Hannibal Barca

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