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

the clinical academia

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message from the editor

We are in now living in the society where truth is expensive. Making money with lies. Governments are corrupted. Systems are weak. We have laws to protect corporates, not the people. I am so impressed with the quote by Henry David Thoreau he once said: "rather than love, than money, than fame, give me truth". We all can be the producer of our knowledge. In this issue, we provide the evidence for that as all articles in this issue are by the medical students at Khon Kaen Medical Education Center, Thailand. Now they are all graduates.

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

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

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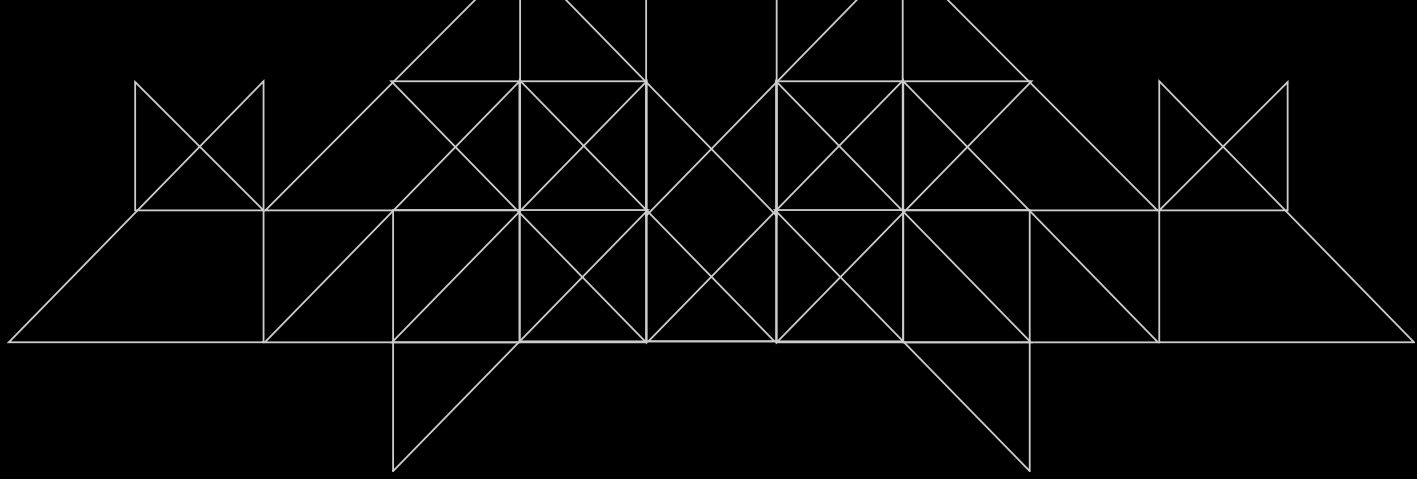
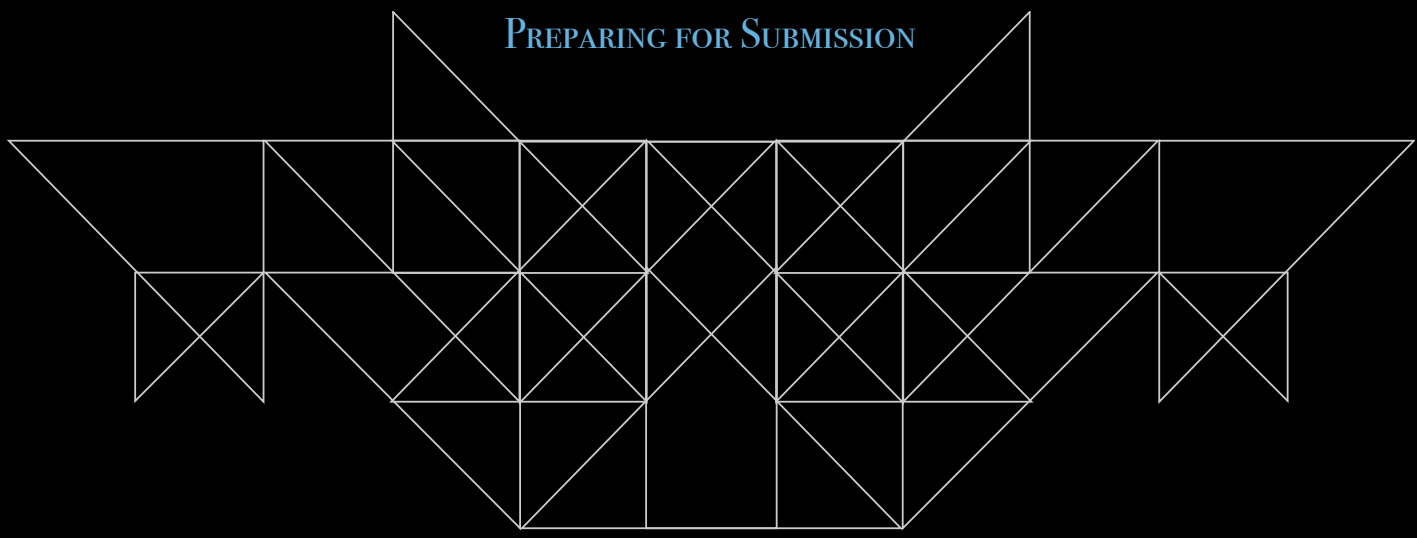
Contents



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



1. General Principles

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

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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.

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a. Title Page

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

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

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

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References 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

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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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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.

Low-dose methotrexate and the risk of pneumonia in patients with rheumatoid arthritis

ORIGINAL ARTICLE

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To identify the risk of pneumonia in patients with rheumatoid arthritis from using low-dose methotrexate.

METHODS

We conducted a case-control study of 42 cases of patients with rheumatoid arthritis with pneumonia and 191 matched controls, those with rheumatoid arthritis without pneumonia to evaluation associations between low-dose methotrexate and pneumonia in the patient with rheumatoid arthritis. Individual patient information was obtained from the medical record in Khon Kaen Hospital between August 2010 and June 2014.

RESULTS

There was no significant association between low-dose methotrexate and incidence of pneumonia (adjusted odds ratio, 0.83; 95% confidence interval, 0.17 to 3.92). Moreover, factors including age, gender, serum erythrocyte sedimentation rate, functional class, the use of chloroquine, sulfasalazine, nonsteroidal anti-inflammatory drug, and diabetes were found not to be associated with having pneumonia in patients with rheumatoid arthritis.

CONCLUSION

Low-dose methotrexate was found not to be associated with the risk of pneumonia in patients with rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease with chronic inflammation and destruction of joint.[1] Low-dose methotrexate (MTX) is the first line drug for the treatment in those with no response to nonsteroidal anti-inflammatory drugs alone (NSAIDs).[1] Although it is accepted in clinical and functional improvement but immunosuppressive effect of this agent may cause patients to have an increased susceptibility to develop infection.[1] However, this is still inconclusive; three previous studies suggested that low-dose MTX increased rate of infections.[2,3,4] While, one has high incidence of worse functional status, and other can not confirm diagnosis of RA. Another study found that low-dose MTX was a protective factor,[5] it is unable to confirm diagnosis of RA. Five studies found no association between low-dose MTX and rate of infection.[6,7,8,9,10], one has small patient numbers, three studies are unable to confirm diagnosis RA, and the other has no direct measurement of disease severity. Moreover, only two of these nine studies use The American College of Rheumatology (ACR) 1987 criteria to diagnose RA.[4,10] Thus, we conducted the present study to investigate risk of pneumonia among patients with RA, diagnose by ACR 2010 criteria who received low-dose MTX for therapy.[11]

METHODS

STUDY DESIGN

A population-based case-control study of incidence of pneumonia was conducted in RA in-patients who received low-dose MTX compared with does not from August 2010 to June 2014 to identify the association between MTX and incidence of pneumonia in RA patients.

SELECTION OF CASE PATIENTS AND CONTROLS

Cases were patients with RA using the ACR 2010 criteria with the first episodes of admission for pneumonia.[11] Mostly pneumonia patients was diagnosed by physician at Khon Kaen Hospital using The Management of Community Acquired Pneumonia in Adults Guidelines; update 2009.[12] Referred patients were confirmed diagnosed at Khon Kaen Hospital. Pneumonia was defined as symptoms (cough and at least one other lower respiratory tract symptom) and signs (new focal chest signs on examination) consistent with an acute lower respiratory tract infection associated with new radiographic shadowing for which there is no other explanation (e.g., not pulmonary oedema or infarction).[12] thus, 42 case patients were included. Patients who received other treatment that increase risk of infection e.g., chemotherapy, and radiation, unknown history of medical record, using moderate or high dose of MTX and not received treatment for RA at least 1 year were excluded. We individually matched each case patients with up to five control with the same sex and $\pm$4 years age with a total of 191 controls. There were five male case patients that were unable to match for five controls; two cases were matched for only two controls each, two cases were matched only one control each and the last case were not matched for any control due to too different regarding age.

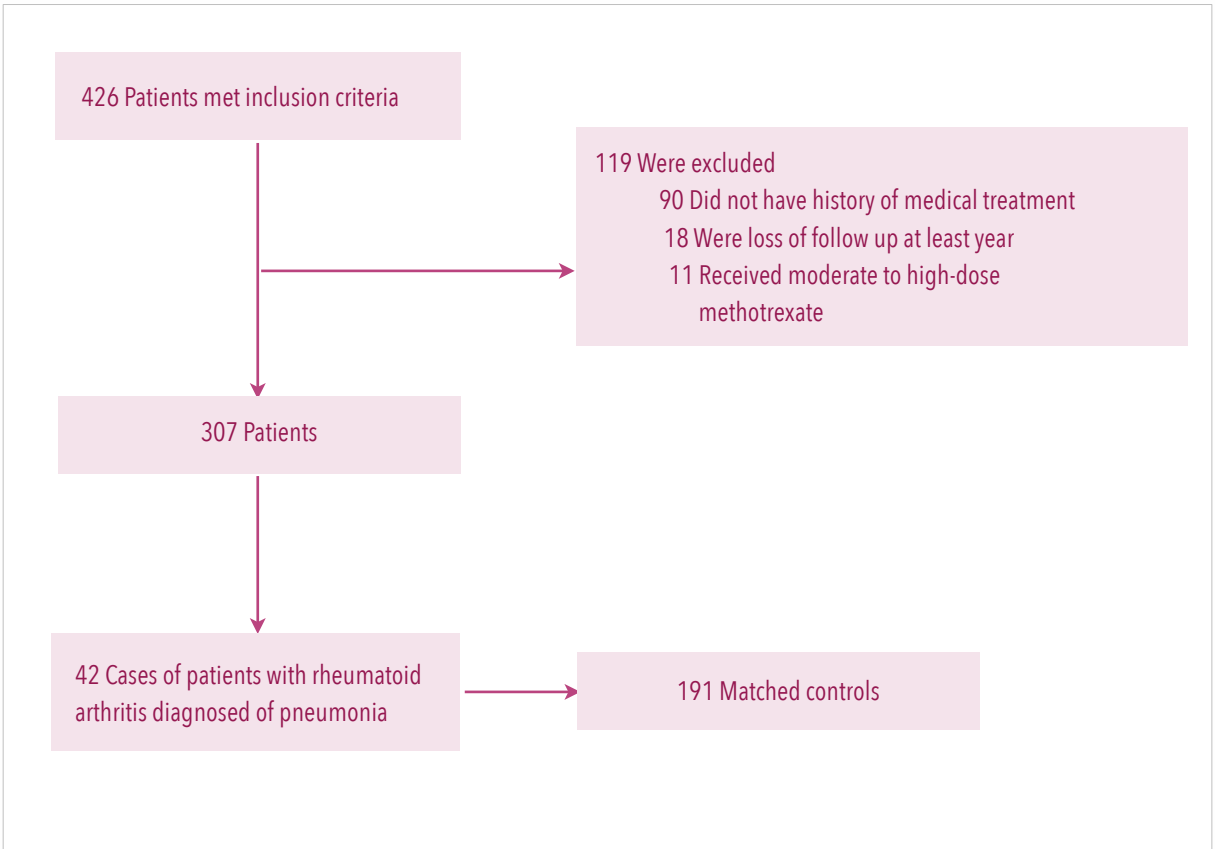

Figure 1. Flow of the study

DATA COLLECTION

Patients who were included in this study were reviewed and recorded baseline characteristics. These included age, sex, titer of rheumatoid factor, titer of serum C-reactive protein (CRP), level of serum erythrocyte sedimentation rate (ESR), functional class, current medication e.g., low-dose MTX, chloroquine, sulfasalazine, NSAIDs and prednisolone, comorbidities of patients e.g., diabetes, chronic obstructive pulmonary disease (COPD), systemic lupus erythematosus (SLE) and chronic kidney disease (CKD).

STATISTICAL ANALYSIS

We imputed data by double entry and cleaned all data before analysis. Frequency tables for all variable were generated to identify wild value. All statistical were performed using the Statistical Package for the Social Science (SPSS) software version 18 and Epi Info software version 7. We described variables by using number and % for categorical variables. For Non-normal distributed scale data e.g., level of serum ESR, we described using median and interquartile range (IQR). For inferential statistics, we used Chi-square test or

Table 1. Characteristics of the patients.

Characteristic	Case Patients (N=42)	Controls (N=191)	P Value
Age-yr, mean-SD	64.1±10.2	61.6±8.7	0.10
Female-no. (%)	26 (62)	130 (68)	0.44
Positive rheumatoid factor-no./total no. (%)	6/6 (100)	63/71 (89)	1.00
Positive serum C-reactive protein-no./total no. (%)	1/1 (100)	17/18 (94)	1.00
Level of serum erythrocyte sedimentation rate-mm./hr.			0.77
Median	92	81	
Interquartile range	34.5-100.5	56.0-99.0	
Functional class-no. (%)			0.14
I	15 (36)	91 (48)	
II	17 (41)	76 (40)	
III	7 (17)	20 (11)	
IV	3 (7)	4 (2)	
Current medication-no. (%)			
Disease-modifying antirheumatic drugs			
Low-dose methotrexate	11 (26)	76 (40)	0.11
Chloroquine	15 (36)	98 (51)	0.09
Sulfasalazine	5 (12)	21 (11)	0.79
Nonsteroidal anti-inflammatory drug	19 (45)	107 (56)	0.23
Prednisolone	26 (62)	109 (57)	0.61
Comorbidity-no. (%)			
Diabetes	8 (19)	30 (16)	0.65
Chronic obstructive pulmonary disease	5 (12)	4 (2)	0.01
Systemic lupus erythematosus	1 (2)	2 (1)	0.45
Chronic kidney disease	1 (2)	10 (5)	0.69

Fisher's exact test to analyze association between two categorical variables where appropriate.

The association between using low-dose MTX and the outcomes was presented in term of crude odds ratio (COR) and its 95% confidence interval (95% CI). The others factor that related to the outcomes we used binary logistic regression analysis to identify adjusted odds ratio (AOR).

Table 2. Risk of pneumonia according to type of drugs.

Drugs	No. of Case Patients (%) (N=42)	No. of Controls (%) (N=191)	Odds Ratio	95% CI
Low-dose methotrexate	11 (26)	76 (40)	0.54	0.25-1.13
Chloroquine	15 (36)	98 (51)	0.53	0.26-1.05
Sulfasalazine	5 (12)	21 (11)	1.09	0.39-3.09
Nonsteroidal anti-inflammatory drugs	19 (45)	107(56)	0.65	0.33-1.27
Prednisolone	26 (62)	109 (57)	1.22	0.62-2.43

RESULTS

CHARACTERISTICS OF THE PATIENTS

In the present study, there were 42 cases of patients with RA diagnosed of pneumonia between August 2010 and June 2014 and 191 matched controls (Figure 1). The mean age of the participants was 62 years; 67% of the them were female with the mean age of 61 years old. Mostly they had functional class 1 (54%).

From Table 1, the only difference between cases and controls were that the case group tended to have higher proportion of patients with COPD comparing to the control group (P=0.01). However, their age, gender, proportion of patients with positive RF, proportion of patients with serum CRP, level of serum ESR, proportion of patients with functional class 1, 2, 3, and 4, proportion of patients with low-dose MTX, chloroquine, sulfasalazine, NSAIDs, and prednisolone,
and proportion of patients with diabetes, SLE, and CKD were similar between the two groups.

RISK OF PNEUMONIA

The risks of pneumonia regarding drugs used in the patients are presented in Table 2. We found that low-dose MTX was not associated with the incidence of pneumonia (COR, 0.54; 95% confidence interval (CI), 0.25 to 1.13). Moreover, other drugs including chloroquine, sulfasalazine, NSAIDs, and prednisolone were also not associated with the incidence of pneumonia.

FACTOR DETERMINING PNEUMONIA

From the binary logistic regression analysis, it also confirmed that low-dose MTX was not associated with the incidence of pneumonia (AOR, 0.83; 95% CI, 0.17 to 3.92). Moreover, factors including age, gender, serum ESR, functional class, chloroquine, sulfasalazine, NSAIDs, and diabetes were found not associated with having pneumonia in patients with RA as well (Table 3).

DISCUSSION

PRINCIPAL FINDINGS

In our case-control study with 42 RA patients who diagnosed pneumonia and admission in the hospital, we found that low-dose MTX was not increase the incidence of pneumonia in RA patient. This includes other drugs e.g., chloroquine, sulfasalazine, NSAIDs, and

Table 3. Adjusted odds ratios of factors independently associated with pneumonia

Factor	Adjusted Odds Ratio	P Value	95% CI
Age	1.02	0.66	0.94-1.11
Female	2.32	0.36	0.38-14.31
Level of serum erythrocyte sedimentation rate	0.98	0.25	0.95-1.01
Functional class			
I	Reference		
II	2.11	0.36	0.43-10.31
Current medication			
Disease-modifying antirheumatic drugs			
Low-dose methotrexate	0.83	0.81	0.17-3.92
Chloroquine	0.31	0.18	0.06-1.74
Sulfasalazine	0.66	0.73	0.06-6.95
Nonsteroidal anti-inflammatory drugs	0.51	0.41	0.10-2.52
Diabetes	0.75	0.80	0.08-7.35

prednisolone were also not associated with the incidence of pneumonia. Although there are many factor that associated with the incidence of pneumonia. From the binary logistic regression analysis we found factors including age, gender, serum ESR, functional class, and diabetes were not associated with having pneumonia in patients with RA.

COMPARISON WITH OTHER STUDIES

In our study we found low-dose MTX was not associated with incidence of pneumonia in RA patient. Although no other studies we found use ACR 2010 criteria for diagnosed RA but there were two studies used ACR 1987 criteria. A retrospective longitudinal cohort study from Minnesota with 609 RA patients and a prospective study from Netherlands with 77 RA patients on MTX and 151 RA patients not on MTX were according to ours (hazard ratio, 0.96; 95% CI, 0.64 to 1.45 and RR, 1.43; 95% CI, 0.96 to 2.14 respectively).[4,10]

The largest previous study of pneumonia in RA patients who use low-dose MTX was a prospective cohort study published in United States with 16,788 patients. However, these patients were not confirmly diagnosed thus non RA patients may included into this study. The result is low-dose MTX was not associated with incidence of pneumonia (hazard ratio, 1.00; 95% CI, 0.8 to 1.2).[8]

Additionally, our study found that there are no association between incidence of pneumonia and the other drug e.g., sulfasalazine (AOR, 0.66; 95% CI, 0.06 to 6.95, chloroquine (AOR, 0.31; 95% CI, 0.06 to 1.74), and prednisolone (OR, 1.22; 95%

CI, 0.62 to 2.43) including diabetes (AOR, 0.75; 95% CI, 0.08 to 7.35). While the study from United States found that incidence of pneumonia is increased in patient with RA who used prednisolone (adjusted hazard ratio (AHR), 1.70; 95% CI, 1.5 to 2.1) and have diabetes (AHR, 2.00; 95% CI, 1.6 to 2.5).[8] However, the other factors are according to ours (sulfasalazine (AHR,0.7; 95% CI, 0.4 to 1.0), chloroquine (AHR, 0.9; 95% CI, 0.7 to 1.1).[8]

STRENGTHS AND LIMITATIONS

In this study, all in-patients who included were diagnosed RA by using newly recent criteria, resulting in increased validity in the diagnosis of RA. There were 42 cases and 191 matched controls. There are two studies use ACR 1987 criteria for diagnosed RA; one has 609 patients and the other has 228.[4,10] Therefore, our study is likely to a large study when compare with one study.[4] Nonetheless, Our study is a new database that collected data from 2010 to 2014. Thus, mostly data of patients can collect completely and correctly. Moreover, Patients with repeated episode of admission during the study period were included in the study only for the first episode. Thus, It can reduce selection bias of study. However this study had limitations, including small number of patients. We could identify only 42 cases over the period of 4 years due to the new database was recently collected in 2010. Some patients was referred from others hospitals. As a result incomplete data. The study design was case-control study using secondary data that might risk for missing data. However, we tried to verify all the data before we collected on the data collection sheets as well as we excluded those with incomplete data.

Although the results of this study we found that low-dose MTX was not increase the incidence of pneumonia in RA patient but we also can not surely assume it. It might be a much more involved such as the status of the patient at that time, patients compliance to the medication as we did not have data regarding this and other drug use that have not received from the hospital, thus, we might not conclude the relationship between using low-dose MTX and incidence of pneumonia properly.

CONCLUSIONS AND IMPLICATIONS

In this study, low-dose MTX was not increased the risk of pneumonia infection rate in RA patients. Moreover, other drugs including chloroquine, sulfasalazine, NSAIDs, and prednisolone were not associated with the incidence of pneumonia. Ideally, for research, the study should be repeated with a larger sample size with prospective cohort study using primary data collection. For practise, We can be comfortable to use MTX and other DMARDs for treatment in RA patients without worrying about complication in increasing the rate of infection.

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Postoperative fever in teenagers undergoing appendectomy using purse string suture versus double ligation technique

ORIGINAL ARTICLE

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ABSTRACT

OBJECTIVE

To compare the rate of postoperative fever in teenagers undergoing appendectomy using purse string suture versus double ligation technique

METHODS

We conducted a retrospective cohort study by reviewing all medical records of patients age between 10 and 19 years old who were diagnosed uncomplicated acute appendicitis intraoperatively in Khon Kaen Hospital. from January 1, 2010, through July 1, 2014. The primary outcome was the postoperative fever. Secondary outcomes included wound dehiscence or evisceration, intraperitoneal or pelvic abscess, positive bacterial culture, postoperative peritonitis, intraoperative bleeding, operation time and length of hospital stay.

RESULTS

The study comprised a total of 579 patients (123 in purse string suture group and 456 in double ligation technique group).There were no significant difference between the purse string suture group and double ligation group regarding the postoperative fever (hazard ratio [HR], 0.92; 95% confidence interval [CI], 0.44 to 1.93; P=0.832), there was one patient who had wound dehiscence in the latter group. There was no intraperitoneal or pelvic abscess, positive bacterial culture and postoperative peritonitis occurred in the admission during the study period. The former group tended to have the higher amount of blood loss (P=0.021) longer operative time (P=0.030) and longer length of hospital stay (P=0.001).

CONCLUSION

The rate of postoperative fever using purse string suture and double ligation technique in appendectomy were no significant difference.

INTRODUCTION

Acute appendicitis is the most common surgical emergency in the abdomen.[1] The worldwide incidence of acute appendicitis is 7.5 to 22.7 per 10,000 population per year.[2–6] The incidence is highest in 10 to 19 year of age.[4,7] Appendectomy for appendicitis is the most common procedure that performed in the emergency operation in the world.8 The appendectomy can be classified as the open and laparoscopic appendectomy.[8] For open appendectomy, the appendiceal stump can be managed by simple ligation,[8] double ligation,[9,10] sutured ligation,[10] purse string and Z stitch.[8–10] There was a randomized controlled trial comparing between purse string suture and simple ligation for postoperative complication found that there was no statistically significant difference between the two groups concerning postoperative complications.[11] Moreover, there was a systematic review comparing between these two techniques for surgical wound infection showed that no significant differences were noted.[12] However, there is no study regarding the management using purse string suture compared with double ligation technique in open appendectomy which is commonly performed in teenagers. We, thus, aim to conduct a study to evaluate the rate of postoperative fever in teenager after using purse string suture technique compared with double ligation technique in the appendectomy.

METHODS

PATIENTS

We reviewed medical records of patients who were diagnosed uncomplicated acute appendicitis intraoperatively in teenage group, between 10 and 19 years of age admitted to Khon Kaen Hospital from January 1, 2010, through July 1, 2014. Key exclusion criteria are complicated appendicitis, pregnancy, HIV infection, autoimmune disease, no evidence of stump management in operative note and patients with other infection.

STUDY DESIGN

This retrospective cohort study was comprised of patients who had appendectomy with stump management by purse string suture and double ligation technique from the operative note in the patient medical records.

DATA COLLECTION

Each teenage patient data that included into the study were reviewed and recorded regarding patients' characteristics including age, sex, anemia, diabetes, history of previous surgery, body weight, height, body temperature as well as preoperative laboratory findings e.g., white cell count, platelet count, and hematocrit. Detail of prescribed treatment and operation were also recorded. These included preoperative antibiotics, type of skin incision and type of surgeon.

STUDY OUTCOMES

The primary study outcome was the postoperative fever in a medical record defined by the body temperature>38.5oc in first 24-48 hours, persistent fever (temperature>38oc) more than 48 hours and new onset body temperature>38oc in postoperative body temperature<38oc. Secondary outcomes included wound dehiscence or evisceration, intraperitoneal or pelvic abscess,

Table 1. Characteristics of the patients

Characteristic	Purse string suture (N=123)	Double ligation (N=456)	P Value
Age–yr			<0.001
Median	12.51	16.11	
Interquartile range	11.36-14.11	14.53-17.45	
Male sex–no. (%)	72 (58.5)	212 (46.5)	0.018
Anemia–no. (%)	30 (24.6)	132 (29.1)	0.328
Previous abdominal surgery–no. (%)	2 (1.6)	4 (0.9)	0.612
Weight–kg.			<0.001
Median	43	50	
Interquartile range	33-50	44-56	
Height–cm.			<0.001
Median	150	160	
Interquartile range	144.5-160	155-166	
Body temperature–°C			0.157
Median	37.6	37.5	
Interquartile range	37.1-38.0	36.9-38.0	
Preoperative white-cell count–cell/μL			0.456
Median	15000	15200	
Interquartile range	11540-17892	12300-17880	
Preoperative platelet count–x10^3/μL			0.079
Median	291.0	282.0	
Interquartile range	251.8-333.8	238.5-322.0	
Preoperative hematocrit–%			0.269
Median	38.0	38.3	
Interquartile range	36.0-40.1	35.8-41.6	
Preoperative antibiotics–no. (%)			
Ampicillin	72 (58.5)	93 (20.4)	<0.001
Gentamicin	88 (71.5)	106 (23.2)	<0.001
Ceftriaxone	4 (3.3)	143 (31.4)	<0.001
Metronidazole	89 (72.4)	240 (52.6)	<0.001
Incision–no. (%)			<0.001
Gridiron incision	11 (8.9)	155 (34.0)	
Lanz incision	33 (26.8)	260 (57.0)	
Other incision	79 (64.2)	41 (9.0)	
Resident surgeon–no. (%)	44 (35.8)	437 (95.8)	<0.001

Table 2. Postoperative complications in open appendectomy patients.

Complication	Purse string suture	Double ligation technique	Relative risk (95% CI)	P Value
Postoperative fever–no. (%)	21 (17.1)	66 (14.5)	1.18 (0.75-1.85)	0.474
Intraoperative blood loss–ml.				0.021
Median (Mean±SD)	5 (5.4±2.7)	5 (5.1±0.8)		
Interquartile range	5-5	5-5		
Operative time–min.				0.030
Median (Mean±SD)	30 (34.6±14.2)	30 (31.8±13.0)		
Interquartile range	25-40	24-37		
Length of hospital stay–day.				0.001
Median (Mean±SD)	3 (2.8±1.0)	3 (2.5±0.8)		
Interquartile range	2-3	2-3		

positive bacterial culture, postoperative peritonitis, intraoperative blood loss, operative time and length of hospital stay.

STATISTICAL ANALYSIS

We reported variables as number and percentage (%) for categorical variables. For scale data, we summarized as median and interquartile range (IQR). We used chi-square tests or Fisher's exact test for categorical variables and Mann-Whitney U tests for continuous variables to assess differences in characteristics among study groups. Relative risk (RR), adjusted odds ratios (AOR) estimated from binary logistic regression models, hazard ratios (HR) estimated from Cox proportional-hazard models with number of hours from immediate postoperative period to the time that fever happens as the time scale together with their 95% confidence intervals (CI) were used to interpret the risk of developing postoperative fever. For the Cox model, there were adjusted for age, sex, anemia, body weight, preoperative antibiotics, type of skin incision, type of surgeon, and operative time. All data were analyzed using statistical software package.

RESULTS

Initially, we reviewed 1,612 medical records of those diagnosed with acute appendicitis (Figure 1). However, we excluded 1,033 patients due to the conditions of ruptured appendicitis, appendiceal abscess, appendiceal phlegmon, gangrenous appendicitis, pregnancy, HIV infection, autoimmune disease, no evidence of technique recorded in the operative note and other infection. There were, in total, 579 patients included in the present study. Half of them were male with the median age of 16 years. One hundred and twenty-three patients and 456 patients underwent purse string suture and double ligation technique, respectively.

In the group undergone purse string suture, they tended to be younger (P<0.001)

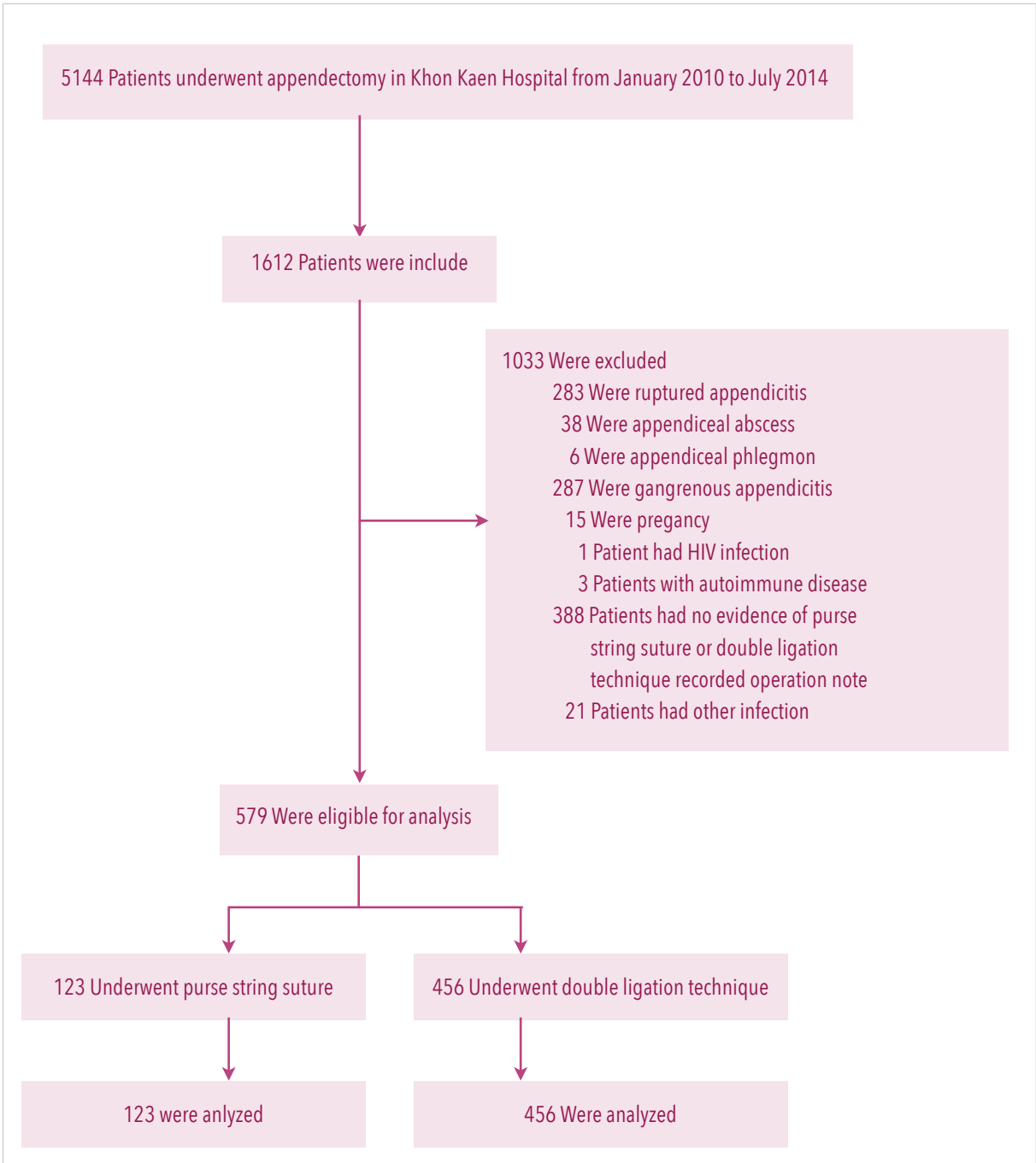

Figure 1. Flow of the study

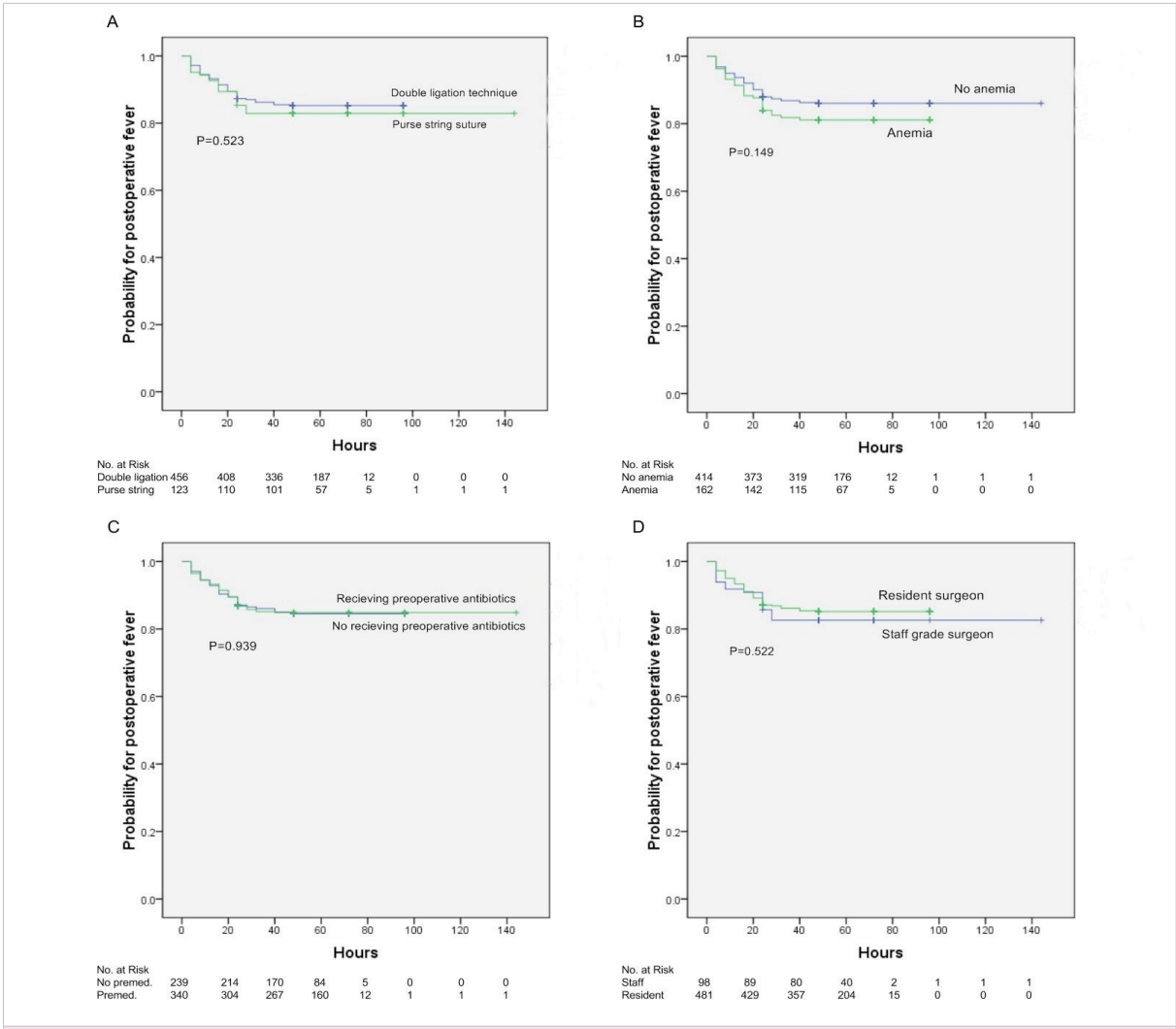

Figure 2. Kaplan-Meier estimates of the probability for postoperative fever.

(Table 1), higher body weight (P<0.001), shorter (P<0.001), more proportion of patients receiving ampicillin (P<0.001), gentamicin (P<0.001) and metronidazole (P<0.001), less proportion of patients receiving ceftriaxone (P<0.001), less proportion of patients undergone Gridiron incision and Lanz incision (P<0.001), less proportion of patients performed appendectomy by surgical resident (P<0.001). However, proportions of patients having anemia, history of previous abdominal surgery and median preoperative body temperature, white-cell count, platelet count, and hematocrit were relatively similar across the two groups.

Table 3. Adjusted odds ratio and hazard ratio for postoperative fever

Variable	Adjusted OR (95% CI)	P Value	HR (95% CI)	P Value
Age–yr	0.94 (0.82-1.06)	0.308	0.94 (0.84-1.06)	0.342
Male sex	1.07 (0.65-1.76)	0.805	1.06 (0.68-1.66)	0.806
Body weight–kg	1.02 (1.00-1.04)	0.052	1.02 (1.00-1.04)	0.059
Anemia	1.59 (0.95-2.67)	0.079	1.52 (0.96-2.41)	0.076
Operative time–min	1.03 (1.01-1.04)	0.001	1.02 (1.01-1.04)	0.001
Gridiron incision	1.03 (0.57-1.85)	0.927	1.07 (0.63-1.82)	0.794
Purse string suture	0.97 (0.44-2.15)	0.941	0.92 (0.44-1.93)	0.832
Surgical resident	0.68 (0.26-1.83)	0.449	0.68 (0.27-1.71)	0.412
Preoperative antibiotics	0.91 (0.55-1.51)	0.715	0.92 (0.58-1.45)	0.715

OUTCOMES

In relation to the primary outcome, the rate of postoperative fever using purse string suture and double ligation technique were no significant difference (RR, 1.18; 95% CI, 0.75 to 1.85; P=0.474) (Table 2). There was one patient who had wound dehiscence in the group undergone double ligation technique but none in purse string suture group. There was no intraperitoneal or pelvic abscess, positive bacterial culture and postoperative peritonitis occurred in the admission during the study period. The former group tended to have the higher amount of blood loss (P=0.021) longer operative time (P=0.030) and longer length of hospital stay (P=0.001).

RISK FACTORS ASSOCIATED WITH POSTOPERATIVE FEVER

After adjustment for age, sex, body weight, anemia, operative time, type of skin incision, type of surgeon and receiving preoperative antibiotics on the basis of multivariate Cox regression models, the two stump management techniques have the similar incidences of postoperative fever (HR, 0.92; 95% CI, 0.44 to 1.93; P=0.832) (Table 3). The only factor found to be associated with postoperative fever was the operative time, the longer the operative time, the higher the risk of developing the postoperative fever (HR, 1.02; 95% CI, 1.01 to 1.04; P=0.001). However, age, sex, body weight, anemia, type of skin incision, type of surgeon and receiving preoperative antibiotics were not found to be associated with developing the postoperative fever.

DISCUSSION

PRINCIPAL FINDINGS

In this cohort study of 579 patients age between 10 and 19 years old who were diagnosed uncomplicated acute appendicitis intraoperatively, we compared the rate of postoperative fever after using purse string suture technique with double ligation technique. We found that the rate of postoperative fever using purse string suture and double ligation technique were not significantly

different from each other and there was no intraperitoneal or pelvic abscess, positive bacterial culture and postoperative peritonitis occurred in the admission during the study period.

The group undergone purse string suture tended to have the higher amount of blood loss, longer operative time and longer length of hospital stay. In addition, we found that the longer operative time, the higher risk of the developing postoperative fever.

COMPARISON WITH PREVIOUS STUDIES

Our study shows that the rate of postoperative fever in patients undergone purse string suture is 17.1%. There are three previous studies showed that the rates of postoperative fever in patients undergone this technique are 39%[11], 30%[23], and 24%[24]. The rate of postoperative fever in our study is lower than these studies because the previous studies included complicated appendicitis for outcome analysis[11], did not mention about preoperative antibiotics[11,23,24] and the patients in these studies were followed up for 6-8 weeks.[23,24]

For secondary outcome, we did not find the patient who had wound dehiscence in the purse string suture group and there was no other postoperative wound infection occurred. There were three randomized controlled trials showed that the rates of wound infection in patients undergone this technique were 6%[23], 12%.[24] and 4.6%[25]. And there was a systematic review that included 7 studies for analysis of postoperative infection after appendectomy showed that the rate of wound infection was 4.0%-22.5% in patients undergone this technique.[12] The rate of wound infection in our study is lower than this all studies due to the short duration of admission that we cannot collect the data of postoperative infection after discharging.

STRENGTHS AND LIMITATIONS OF STUDY

Our retrospective cohort study is the first study regarding outcome in relation to the postoperative fever of teenagers undergone appendectomy using purse string suture and double ligation technique. However, this study also has a number of limitations. First, the postoperative fever can be underestimated because it should be generally observed about 3-5 days but most patients have a short duration of admission in this study. If they had not a fever in 2-3 days, we recorded as no fever so it might be not exactly accurate. Second, our findings may not be generalizable to other age groups as we included patients age between 10 and 19 years. Third, we did not collect the data about the type of appendix in each patient that may be the cause of long operative time. Some types of appendix, such as retrocecal type can be difficult to find in operation. The last one, there are 388 medical records that we included to review have missing data about the type of stump management in operative note, so we could not use them to analyze in our study.

CONCLUSION AND IMPLICATIONS OF FINDINGS

In conclusion, this retrospective cohort study suggested that using purse string suture comparing with double ligation technique was not different in the rate of postoperative fever. Both techniques are equally safe in relation to postoperative infection for management of

appendiceal stump. However, the group undergone purse string suture tended to have the higher amount of blood loss, longer operative time and longer length of hospital stay. This retrospective cohort study includes only teenage group. We suggested that a further larger prospective cohort studies with all age groups may be needed.

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COMPETING INTERESTS: This study has no competing on interest.
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ORIGINAL ARTICLE

Glyburide and risk of melioidosis in type 2 diabetes: a case-control study

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ABSTRACT

OBJECTIVE

To identify the association between glyburide and risk of melioidosis in patients with type 2 diabetes.

METHODS

We performed a case-control study of 68 case patients with preexisting type 2 diabetes and melioidosis infection and 359 control patients with preexisting type 2 diabetes without melioidosis to evaluate and compare the risk of melioidosis in type 2 diabetes of those with and without glyburide use. Logistic regression analysis was used for the case control comparison.

RESULTS

Patients who current user of glyburide had a non-significantly increased risk of melioidosis (crude odds ratio, 1.53; 95% confidence interval (CI), 0.89 to 2.63; further adjusted by sex, age, history of diabetic treatment and hypertension did not alter this result: adjusted odds ratio (AOR), 0.98; 95% CI, 0.48 to 2.02) but only hypertension was associated with lower risk of melioidosis (AOR, 0.30; 95% CI, 0.17 to 0.53). In the subgroup analysis, we found no significant association between glyburide, other sulfonylureas, metformin, insulin and first diagnosis of melioidosis. Moreover, we also found that chronic kidney disease was significantly associated with lower risk melioidosis.

CONCLUSION

We concluded that glyburide use was not associated with the risk of developing melioidosis among type 2 diabetic patients and we did not found an association between other antidiabetic drugs and risk of melioidosis as well.

INTRODUCTION

Melioidosis is a serious infection and epidemic in the Northeastern Thailand and the Northern Australia with the crude case fatality rate between 19% and 43%.[1,2] In Thailand, the annual incidence rate rose from 8.0 case per 100,000 people in 2000 to 23.1 in 2006.[1] The evidence from a case-control and a population-based studies in Thailand and Australia showed that 37-60% of the patients with melioidosis were also had type 2 diabetes.[3]

The majority of diabetic patients with melioidosis are already receiving antidiabetic therapy and glyburide is one of the oral hypoglycemic agents that commonly has been used in many countries.[4,5] One recent study showed that glyburide may control modulating capabilities on host immune response by inhibiting the production of active interleukin (IL)-1b and IL-18.[4] Moreover, a cohort study in 2011 found the benefit of glyburide in reducing the mortality rate of melioidosis.[6] But another cohort study in 2014 found that using sulphonylurea in diabetic patients with melioidosis may make patients to the higher risk for adverse outcomes.[7] However, the risk of developing melioidosis in type 2 diabetic patients who prescribed with glyburide has not been evaluated.Thus, we conducted a case-control study to calculate and compare the risks of melioidosis in type 2 diabetes with and without glyburide treatment.

METHODS

STUDY DESIGN

This case-control study was conducted using data from the medical records of the case and control patients who admitted at Khon Kaen Hospital, Thailand from January 2011 to August 2014.

STUDY POPULATION

We included case patients with the following criteria; (i) patients with melioidosis infection confirmed by positive culture for *B. pseudomallei*[3], (ii) patients who had a documentary of preexisting type 2 diabetes (fasting plasma glucose≥126 mg/dL or random venous plasma glucose≥200 mg/dL in a patient with classic symptoms of hyperglycemia or plasma glucose≥200 mg/dL measured two hours after a glucose load of 1.75 g/kg (maximum dose of 75 g) in an oral glucose tolerance test (OGTT) or hemoglobin A1C≥6.5 percent (47 mmol/mol))[7], and (iii) age 15 years or older. We excluded those without data using glyburide. For the control patients, we randomly selected four controls to one case matched by age and sex from those admitted at same study period with a laboratory confirmation of no *B. pseudomallei* infection. In addition to this, they must have to be confirmed diagnosed of preexisting type 2 diabetes using the criterion given above as well.

EXPOSURE AND CONFOUNDERS

Glyburide use was reviewed from the medical records of the case and control patients.

The most recent dosage of glyburide was also collected. Other exposures included other sulfonylureas, metformin, insulin were also reviewed and collected. The potential confound included sex, age, chronic kidney disease, nephrolithiasis, chronic liver disease, hypertension, body mass index, glycated hemoglobin, triglyceride, HDL cholesterol, and hemoglobin.

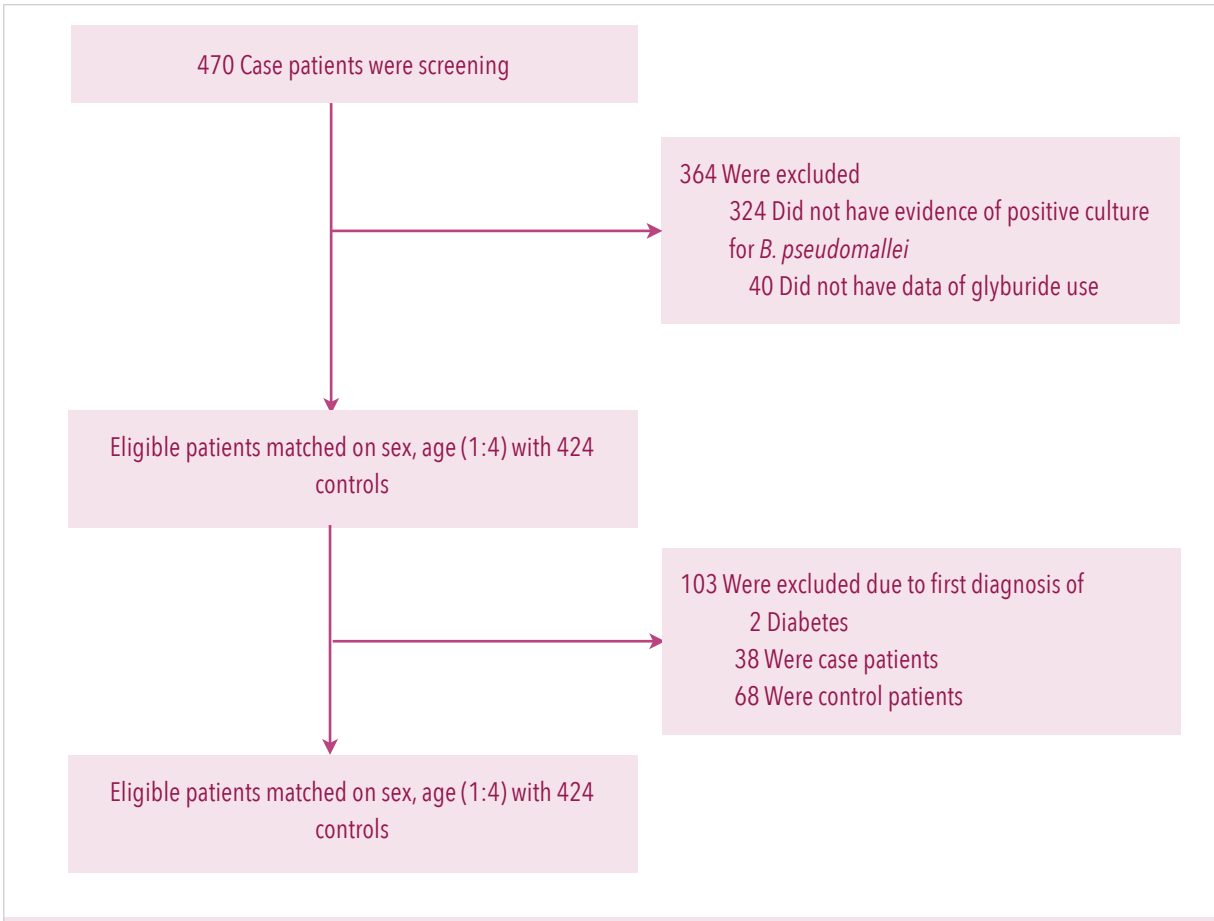

Figure 1. Selection of People to Include as Cases and Controls in Study of Glyburide and Risk of Melioidosis in Type 2 Diabetes.

HbA1c using the latest result for calculation. CKD is defined as abnormalities of kidney structure or function, present for 3 month; Markers of kidney damage (one or more) (i) Albuminuria (AER 30 mg/24 hours; ACR 30 mg/g [3 mg/mmol]), (ii) urine sediment abnormalities (iii) electrolyte and other abnormalities due to tubular disorders, (iv) abnormalities detected by histology, (v) structural abnormalities detected by imaging, (vi) history of kidney transplantation, and (vii) decreased GFR GFR <60 ml/min/1.73 m^2. Chronic liver disease was diagnosed from liver biopsy and clinical, laboratory test and radiologic data. Anemia was diagnosed by initial laboratory studies. Malignancy had to be from official pathologic reported by pathologist. Nephrolithiasis was diagnosed by radiologic evidence. Metabolic syndrome was defined as the presence of any three of the following five traits (i) abdominal obesity, defined as a waist circumference in men ≥102 cm (40 in) and in women ≥88 cm (35 in), (ii) serum triglycerides ≥150 mg/dL (1.7 mmol/L) or drug

Table 1. Characteristics, Crude Odds Ratio and Adjusted Odds Ratio of Patients with Melioidosis and Control Patients

Characteristic	Case Patients	Control Patients	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio(95% CI)
Male – no. (%)	50 (73.5)	260 (72.4)	1.06 (0.59-1.90)	1.08 (0.58-1.99)
Age – yr				
Median	53.5	54.7	0.99 (0.96-1.01)	1.00 (0.97-1.03)
Interquartile range	45.5-59.3	47.4-60.8		
History of diabetic treatment– no. (%)				
Glyburide	25 (36.8)	99 (27.6)	1.53 (0.89-2.63)	0.98 (0.48-2.02)
Other sulfonylurea	15 (22.1)	76 (21.2)	1.05 (0.56-1.97)	0.87 (0.39-1.94)
Metformin	41 (60.3)	150 (41.8)	2.11(1.25-3.59)	1.90 (1.03-3.50)
Insulin	15 (36.8)	132 (22.1)	0.49 (0.26-0.90)	0.65 (0.30-1.41)
Chronic kidney disease	5/64 (7.8)	94/314 (29.9)	0.20 (0.08-0.51)	–
Nephrolithiasis– no./total no. (%)	4/37 (10.8)	23/128 (18.0)	0.55 (0.18-1.72)	–
Chronic liver disease– no./total no. (%)	7/61 (11.5)	35/218 (16.1)	0.68 (0.29-1.61)	–
Hypertension – no. (%)	19 (27.9)	204 (56.8)	0.29 (0.17-0.52)	0.30 (0.17-0.53)
Body mass index – kg/m^2				
No. of patients with data of weight and height	23	111		
Body mass index	21.53.2	24.84.7	0.84 (0.74-0.94)	–
Glycated hemoglobin% – no./total no. (%)	12/13 (92.3)	42/67 (62.7)	7.14 (0.88-58.29)	–
Triglyceride– mg/dL				
No. of patients with data of triglyceride	7	50		
Median	181	128	1.00 (1.00-1.01)	–
Interquartile range	95.0-348.0	97.0-160.3		
HDL cholesterol-mg/dL				
No. of patients with data of HDL cholesterol	5	40		
HDL cholesterol	22.419.1	36.213.5	0.92 (0.85-1.00)	–
Hemoglobin – g/dL				
No. of patients with data of hemoglobin level	49	234		
Hemoglobin	10.42.4	10.73.0	0.97 (0.88-1.06)	–

treatment for elevated triglycerides, (iii) serum HDL cholesterol <40 mg/dL in men and <50 mg/dL in women or drug treatment for low HDL-C, and (iv) blood pressure ≥130/85 mmHg or drug treatment for elevated blood pressure

STATISTICAL ANALYSIS

Most characteristics of cases and controls were described with numbers and percentages. Other characteristics of cases and controls (e.g., age, triglyceride level, HDL cholesterol level, body mass

Table 2. Association of diabetes treatment and first diagnosis melioidosis

History of Diabetes Treatment	Case Patients	Control Patients	Adjusted Odds Ratio (95% CI)
Glyburide	23 (37.1)	99 (27.6)	1.00 (0.48-2.11)
Other sulfonylureas	14 (22.6)	76 (21.2)	1.12 (0.49-2.55)
Metformin	37 (59.7)	150 (41.8)	0.57 (0.30-1.07)
Insulin	13 (21.0)	132 (22.1)	1.67 (0.74-3.76)

index, hemoglobin level) were described with median and interquartile range or mean and standard deviation. We used binary logistic regression analysis to estimate crude odds ratio (COR) and adjusted odds ratio (AOR) and corresponding 95% confidence intervals (CI) for the association between glyburide use and the risk of melioidosis, the diagnosis of melioidosis and glyburide use being the dependent variable and the main independent variable, respectively. Logistic regression models were adjusted for the confounders listed above. Subgroup analysis was also performed regarding first diagnosis melioidosis, sex, age, glyburide density exposure, presence or absence of chronic kidney disease, presence or absence of anemia. P values of less than 0.05 for associations were considered to indicate statistical significance.

RESULTS

PATIENTS' CHARACTERISTICS

In the present study, initially, 470 diagnosed with melioidosis and type 2 diabetes were screened for the inclusion as case patients (Figure 1). However, only 146 were confirmed with positive for B. pseudomallei culture. Forty case patients were excluded due to unknown data of glyburide use. For control, 424 patients that matched for sex and age were included. One hundred and three of cases and controls were later excluded due to their diagnosis as the first episode of diabetes which indicated the co-existing findings rather than the potential risk factor. In total, there were 427 patients included in the analysis; 68 case patients and 359 control patients. Mostly there were male 50 (73.5%) for case and 260 (72.4%) for control. The medians of age were similar in both groups. But case patients were more likely to have lower body mass index (Table 1).

MAIN ANALYSIS

Twenty-five (36.8%) patients with melioidosis were current users of glyburide; among controls, the proportion of current user was 99 of 359 (27.6%) resulting in COR of 1.53 (95% CI, 0.89 to 2.63) (Table 1). For the other, insulin use, chronic kidney disease, hypertension and body mass index were also associated with lower risk of melioidosis (COR, 0.49; 95% CI, 0.26 to 0.90, COR, 0.20; 95% CI, 0.08-0.51, COR, 0.29; 95% CI, 0.17 to 0.52, COR, 0.84 ; 95% CI, 0.74 to 0.94, respectively). But in logistic regression analysis adjusted for sex, age, antidiabetic drugs, and hypertension, only hypertension was associated with lower risk of melioidosis (AOR, 0.30; 95% CI, 0.17-0.53) (Table

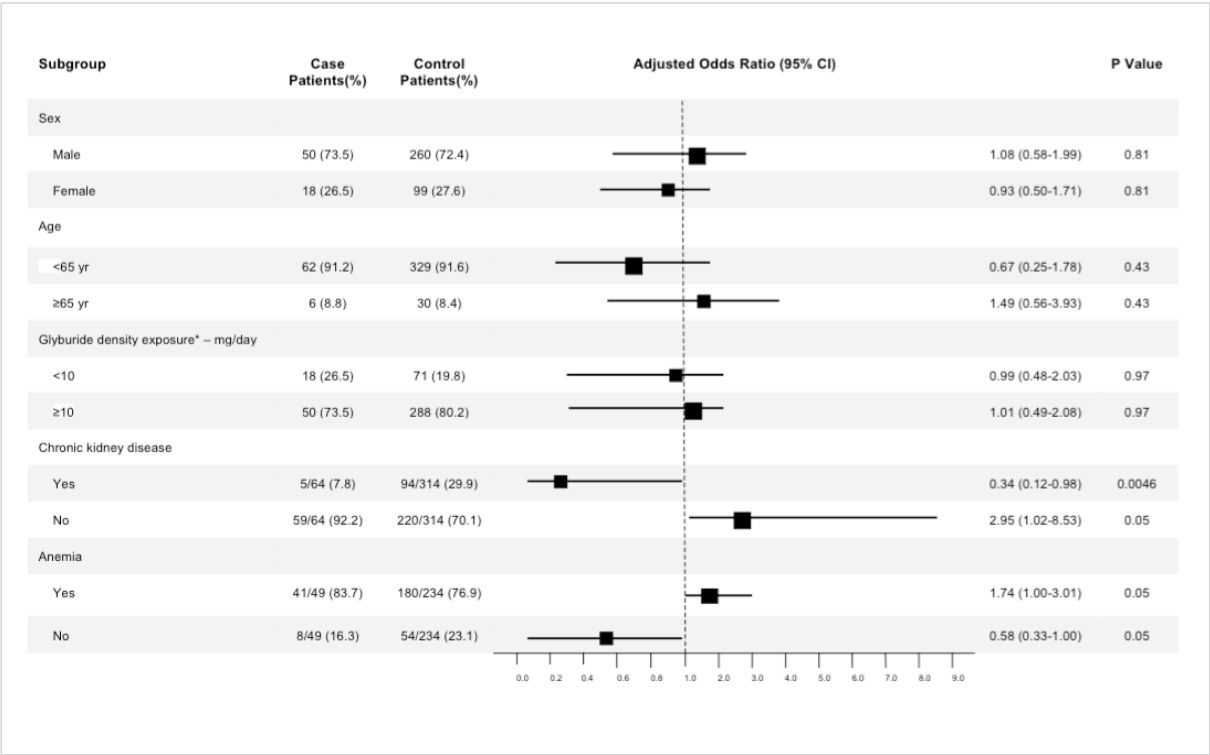

Figure 2. Adjusted odds ratio, according to the subgroup and prescribed daily dose

1). In subgroup analysis, we found no significant association between first diagnosis melioidosis and glyburide, other sulfonylureas, metformin, and insulin (Table 2). We also found that chronic kidney disease was significantly associated with lower risk melioidosis. (Figure 2.)

DISCUSSION

PRINCIPAL FINDINGS

In the present study, the association between glyburide and risk for developing melioidosis was not found. Further adjustment of confounders including age, sex, other antidiabetic drugs, and hypertension did not meaningfully alter the result. For other sulfonylureas, metformin and insulin, we did not find the association with risk for developing melioidosis as well.

COMPARISON WITH OTHER STUDIES

We did not find the association between other underlying diseases (such as nephrolithiasis, and chronic liver disease) that are known as risk factors for melioidosis according to our prior studies6,[11,23]. Moreover, we found that chronic kidney disease was significantly associated with lower risk of melioidosis that was different from the other studies.[11,18,21] One of the possible explanation for the discrepancy is the difference in methods and criteria used for the diagnosis of

chronic kidney disease. These incongruent results may be caused by the smaller sample size and a lot of missing data for diagnosis these comorbidities that made the accuracy of our results slightly low. Other findings we found that male sex and age more than 45 years were predominant in case patients that congruent to the study (Cheng AC et al, 2005) but we did not find the association of these factors due to the control patients were matched by these factors.

STRENGTH AND LIMITATION

The strength of this study is the method of selecting case by using the culture confirmation that makes sure all of case patients were truly infected by B. pseudomallei. However, the present study also has several limitations. Firstly, most of melioidosis patients had been diagnosed by other evidences of melioidosis infection such as serological diagnosis thus we had to exclude them that made our sample size slightly small. Secondly, people who had missed the information of diabetic treatment prior to admission were not included as they could not be ascertained for exposure status. Thirdly, we did not have the data for the dose-time exposure due to many of patients received diabetes prescription from primary and secondary hospitals. From this reason, we can review only the last diabetes prescription prior to admission.

CONCLUSION AND IMPLICATION

Overall, the risk of melioidosis among type 2 diabetic patients was not found to be associated with glyburide. Therefore, the further studies with larger sample size for more accurate estimation of the association between glyburide use and risk of melioidosis in type 2 diabetes is suggested.

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COMPETING INTERESTS: This study has no competing on interest.
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SYSTEMATIC REVIEW

Dexamethasone versus placebo to prevent re-intubation and post-extubation stridor in children: a systematic review

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ABSTRACT

OBJECTIVE

To identify the efficacy of dexamethasone for prevention of re-intubation and post-extubation stridor in children.

METHODS

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Clinicaltrials.gov, ScienceDirect, Scopus, Google scholar by using search strategies. The titles and abstracts of relevant articles including children between 4 weeks and 18 years of age requiring airway intubation at least 24 hours and reintubation as primary outcome were individually screened from four reviewers. We extensively searched reference lists of those eligible articles for additional relevant studies. The full texts of four included studies were appraised risk of bias and extracted data.

RESULTS

Three randomized controlled trials and one cohort study were included in this systematic reviews with a total of 336 patients; 160 in dexamethasone group and 176 in the placebo group. There was no difference of reintubation rate between dexamethasone and placebo groups (relative risk (RR), 0.49; 95% confidence interval (CI), 0.13 to 1.83; chi-square 9.47; I^2=68%; P=0.02). The incidence of postextubation stridor was decreased in dexamethasone group (RR, 0.57; 95% CI, 0.41 to 0.78; chi-square 3.02; I^2=1%; P=0.39).

CONCLUSION

Dexamethasone did not prevent reintubation in children. However, our conclusion was based on 336 patients, high heterogeneity of the included studies and possibility of publication bias. A larger randomized controlled trial is suggested.

INTRODUCTION

Airway intubation can cause inflammation of larynx, vocal cord and tracheal mucosa leading to postextubation upper airway obstruction from laryngeal and vocal cord edema.[1-9] Some of the intubated children develop postextubation laryngeal edema diagnosed by respiratory sound; stridor and cuff leak test.[5, 10-7] After extubation, patients may suffer from severe postextubation upper airway obstruction, they later need reintubation to maintain their airways but reintubation lets them have a longer length of hospital stay with higher mortality rate than those with successful extubation.[18-22] Some studies suggested that dexamethasone may have the benefit on preventing postextubation upper airway obstruction and decrease reintubation rate from an anti-inflammatory property of dexamethasone.[23]

Due to scarce evidence, the efficacy of dexamethasone in the dimension of preventing or treat postextubation upper airway obstruction in children could not be definitely estimated.[24] A previous systematic review stated that, in neonates and adults, it is clear that dexamethasone has advantages in reducing reintubation rate and preventing postextubation stridor in high-risk neonates as well as in adults who were administered multiple doses of dexamethasone.[24] In children, two included trials; Tellez, 1991 and Anene, 1996 in this Cochrane's systematic review showed controversial results. The authors summarized that the study needed more data to evaluate.[24]

More literature were sought, more studies have been identified, however, there has been no study having strong evidence to support that dexamethasone is effective to decrease reintubation rate and prevent postextubation stridor in children due to negligible patients of each study. Thus, we conducted a systematic review to evaluate whether dexamethasone is effective to decrease reintubation rate and prevent postextubation stridor in intubated children.

METHODS

SEARCH STRATEGIES

We searched without language restriction for studies through the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Clinicaltrials.gov, ScienceDirect, Scopus, Google scholar. We used a combination of Medical Subject Headings (MeSH) for MEDLINE and Cochrane Library searching; ("airway extubation"[Mesh] OR "laryngeal edema"[Mesh] OR "airway obstruction"[Mesh] OR stridor* OR "laryn* edema*" OR "airway obstruct*" OR intubation) AND ("dexamethasone"[Mesh] OR "dexamethasone isonicotinate"[Mesh]) and used keyword; "dexamethasone AND extubation", "corticosteroid AND extubation", "decameth AND extubation", "decaspray AND extubation", "dexasone AND extubation", "dexpak AND extubation", "maxidek AND extubation", "oradexon AND extubation", "decaject AND extubation", "hexadrol AND extubation" in Clinicaltrials.gov, Scopus, ScienceDirect and Google scholar. We used Google translate for translating keywords into French, German, Korean, Japanese, and Chinese, then used these words for searching through Google scholar without limits of language. We checked every

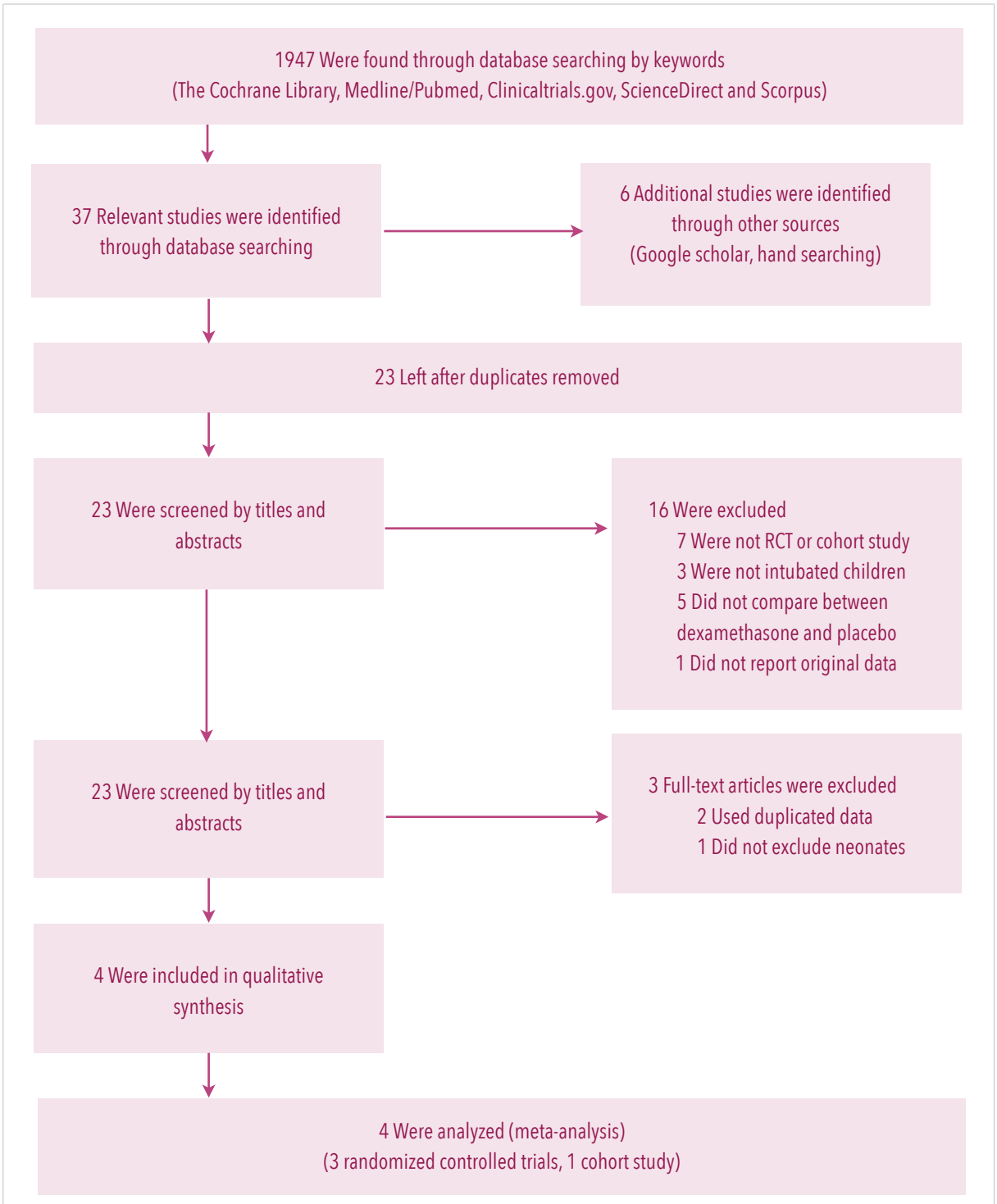

Figure 1. Flow of the review.

Table.1 Characteristics of Included Studies.

Author	Location	Design	population	Duration of study	Sample size (I/C)	Mean age	Mean duration of intubation	Dose of dexamethasone	Regimen of dexamethasone	Studies quality score*
Tellez, 1989	USA	Double blind RCT	General PICU <8 years	Jan 1986 to Jul 1987	153 (76/77)	2.5 years	>72 hr =53% <72 hr =47%	0.5 mg/kg (max 10 mg)	6-12 hr prior then q 6 hr X5	Jadad scale 5
Anene, 1996	USA	Double blind RCT	General PICU, <5 years	Jul 1994 to Jun 1995	63 (31/32)	3.5 months	Median 3.4 days	0.5 mg/kg (max 10 mg)	6-12 hr prior then q 6 hr X5	Jadad scale 3
Ingrid, 2006	The Netherlands	Retrospective cohort study	High risk PICU, aged between 4 weeks and 6 years	Aug 1999 to May 2002	60 (23/37)	16.6 months	11.6 days	0.6-2 mg/kg/d	least 4 hr prior to extubation and continued for 24 hr	NOS score 9
Malhotra , 2009	India	Double blind RCT	General PICU	Jan 2003 to Feb 2006	60 (30/30)	7.78 years	>72 hr =55% <72 hr =45%	0.5 mg/kg (max 8 mg)	4 hr prior,at extubation then q 6 hr x2	Jadad scale 5

Abbreviations: I/C, Intervention/control group; PICU, pediatric intensive care unit; NOS, Newcastle-Ottawa Scale; hr, hour; q,every.
*Studies quality was assessed by Jadad scale for RCTs and NOS for cohort study.

reference of the included studies and manually searched for additional studies which were relevant. Overall 23 titles and abstracts were reviewed.

INCLUSION CRITERIA

PATIENTS

We included studies with patients age between 4 weeks and 18 years with requiring airway stabilization and mechanical ventilation at least 24 hours.

INTERVENTIONS

Patients received dexamethasone versus placebo before extubation. We included regardless of the route (oral or parenteral), dosage, and duration of administration of the therapies.

OUTCOMES

We included the study with the primary outcome of our interest as re-intubation. The secondary outcome was postextubation stridor.

EXCLUSION CRITERIA

We excluded study with patients who had received corticosteroid therapy within 7 days before extubation or had upper airway infection.

DATA EXTRACTION

We independently assessed for all titles and abstracts to include and exclude the studies.Then we read full texts of all final included studies. Every problem was solved by the discussion of us. Data were extracted from included studies and recorded by four authors individually. We used the Cochrane

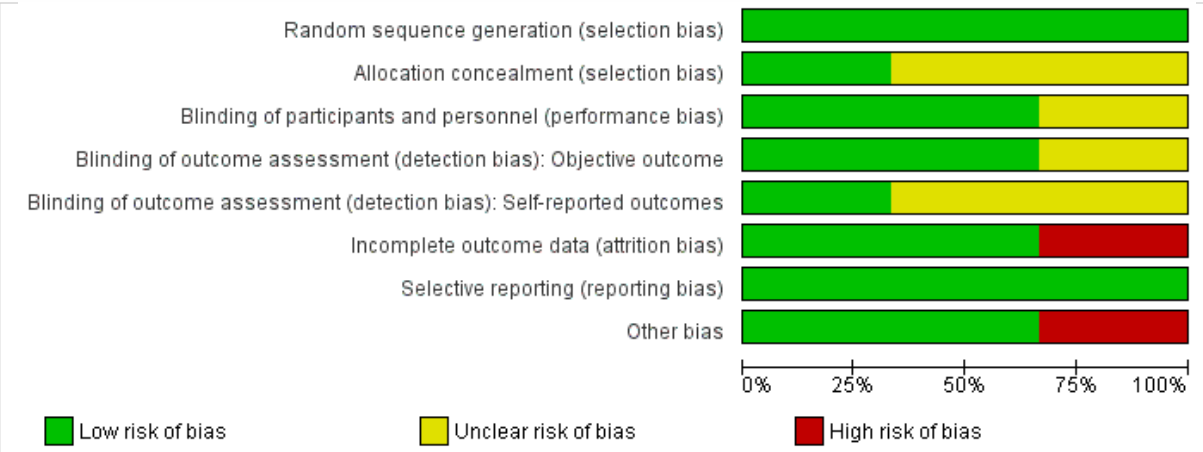

Figure 2. Risk of bias graph.

Handbook for Systematic Reviews of Interventions version 5.1.0 to organize the standard forms to extract data.[25]

QUALITY OF REPORTING AND RISK BIAS

The four authors appraised the quality and risk of bias of the included studies with Jadad scale to assess the quality of the included RCTs; Jadad scale was regarded in randomization, blinding and an account of all patients to evaluate whether RCT's quality is high if the score is three or higher.

Newcastle-Ottawa Scale (NOS) was also used to assess the quality of the included cohort study in three parts; selection, comparability, and outcome of the study. NOS gave the quality of cohort study as high if the score is nine or higher. Moreover, we used the criteria according to The Cochrane Handbook for Systematic Reviews of Interventions version 5.3.0 for judging the risk of bias of the included RCTs.25 Risk of bias was weighed in random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment

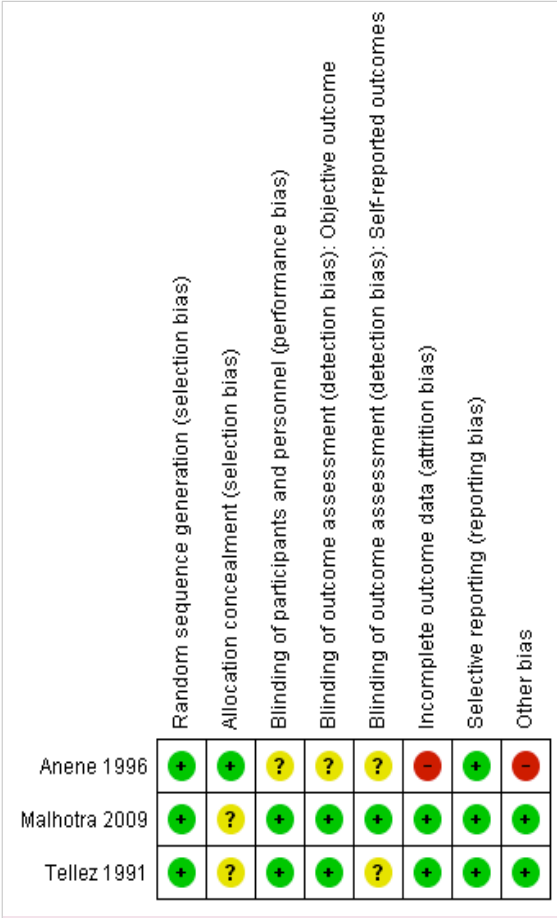

Figure 3. Risk of bias summary.

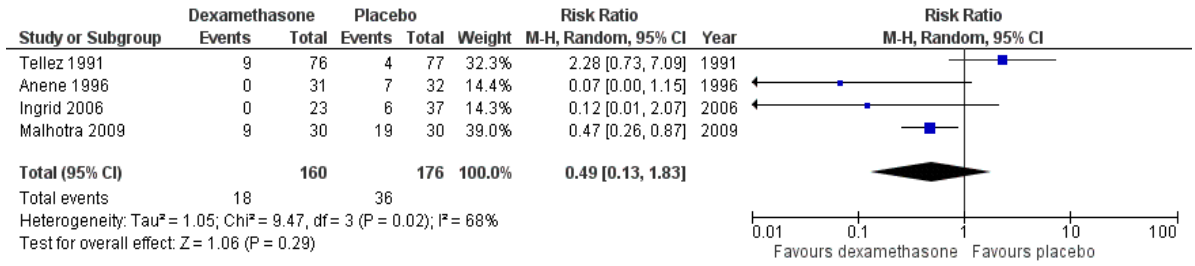

Figure 4. Forest plot of comparison of dexamethasone versus placebo, outcome: reintubation.

(detection bias), incomplete outcome data (attribution bias), selective reporting and other biases. Then the RCTs were classified into three groups; low risk, high risk and unclear risk by the risk of bias score. Potential publication bias was assessed by using a funnel plot.

DATA ANALYSES

We conducted four data configurations; (i) three RCTs together with a cohort study, (ii) only RCTs, (iii) only high-risk pediatric patients, (iv) only low-risk pediatric patients. We calculated relative risk (RR) with 95% confidence interval (CI) from dichotomous data in each group for every trial. All analyses were performed with Revman 5.3.0 statistical software using random effect model meta-analyses to assess the effectiveness of dexamethasone compared with placebo in reducing reintubation rate and postextubation stridor.

The statistical test of heterogeneity was high if P<0.1 and I2 statistic was more than 50%. We used a random effect model for the meta-analysis when heterogeneity was high and used a fixed effect model for the meta-analysis when heterogeneity was low.

RESULTS

The search strategies yielded 1947 articles from electrical searches then 37 articles were identified as relevant studies through the five databases searching (Figure 1). Six articles were identified as relevant studies from manual searching reference lists of the 37 previously identified articles. The removal of duplicates left 23 articles. Based on title and abstract screening, 16 articles were excluded; seven articles were neither RCTs nor cohort study, three articles could not be defined children from whole patients, two articles regarding intervention groups were given with other steroids; prednisolone and methylprednisolone, three articles regarding control groups were given with placebo, one article did not report original data. Seven full-text articles were assessed for eligibility. Three studies were excluded; two studies used duplicated data and one study included neonate. Finally, four articles, consist of three RCTs and one cohort study, were included as eligible data.

INCLUDED STUDIES

The characteristics of four included studies were summarized in Table 1. All four studies; three RCTs

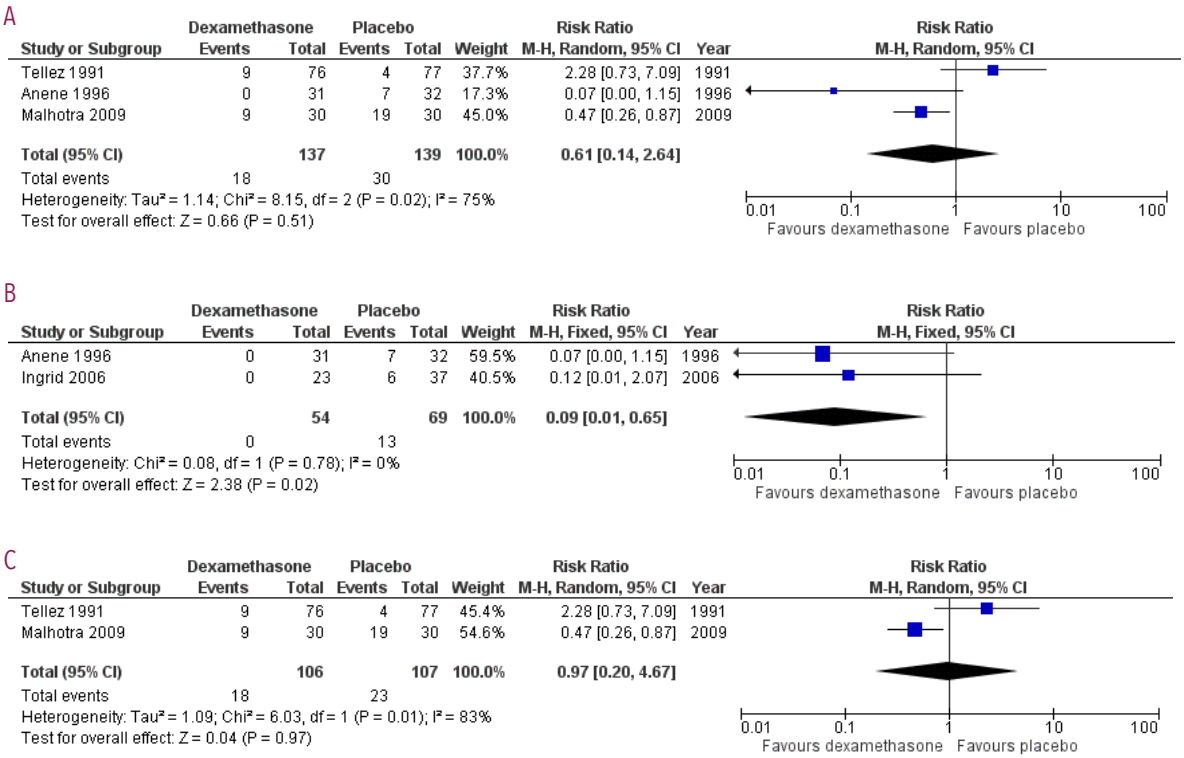

Figure 5. Forest plot of comparison of dexamethasone versus placebo, outcome: reintubation.
Subgroup analysis; Panel A, incidence-rate ratio for reintubation in only RCTs; Panel B, incidence-rate ratios for reintubation in only high risk pediatric patients; and Panel C, incidence-rate ratios for reintubation in only low risk pediatric patients

and one cohort study determined the effect of dexamethasone to prevent reintubation and stridor in intubated pediatric patients, they were designed and performed between 1991 and 2009 and assigned 336 patients; 160 patients received dexamethasone and 176 patients received placebo. The exclusion criteria of each study were further described.

Tellez 1991,[26] RCT including 153 patients. They excluded patients that used corticosteroids therapy within the previous seven days, primary upper airway infection, surgical trauma to the upper airway, a previous upper airway obstruction history or a medical condition that did not indicate the use of corticosteroid. Anene 1996,[27] RCT of 63 patients included patients with comorbid airway abnormalities (tracheomalacia, subglottic stenosis, unilateral vocal cord paralysis and vascular ring). They excluded patients with laryngotracheal infections, steroid use within the previous seven days, hypertension, gastrointestinal hemorrhage or hyperglycemia with glucosuria. Ingrid 2006,[28] the only retrospective cohort study in our systematic review, studied 60 patients intubated for more than

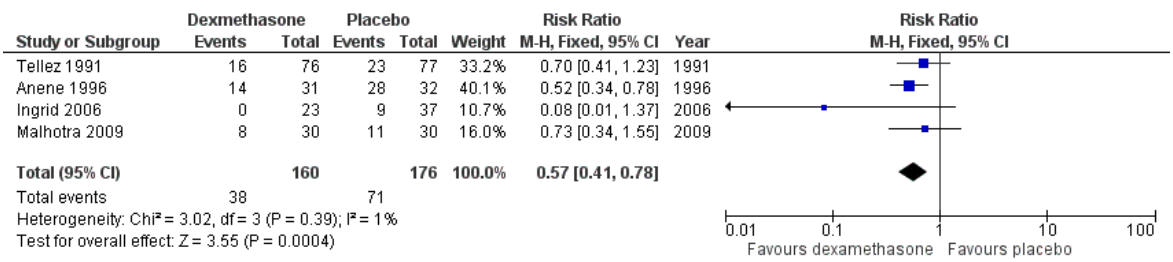

Figure 6. Forest plot of comparison of dexamethasone versus placebo, outcome: postextubation stridor.

24 hours. They excluded patients who were treated with glucocorticosteroids recently, dexamethasone prescription, intubated for laryngotracheal disease or patients who had a history of failed extubation owing to upper airway obstruction. Malhotra 2009,[29] RCT of 60 patients. They excluded patients that had upper airway disease, underwent neck surgery, any anatomical deformity of upper airways, patients already on steroids or a history of extubation during the same admission in the hospital.

EXCLUDED STUDIES

One trial (AK kalloghlian 2000)[30] was presented in abstract form with no full texts published and we were unable to contact the authors for confirmation of the study methods.

BIAS RISK ASSESSMENT

There was no disagreement among four independent reviewers regarding Jadad scale, NOS and Cochrane risk of bias tool to assess the quality of studies. Three RCTs[26, 27, 29] were assessed using Jadad scale; both Tellez, 1991's and Malhotra, 2009's were scored 5 but Anene, 1996's scale was scored 3 because of no detailing methods of blinding and dropped-out patients. One included cohort study; Ingrid, 2006[28] was assessed using NOS with score of 9. All four studies were high quality. Furthermore, three RCTs were assessed the risk of bias using Cochrane risk of bias tool.[25] A risk of bias graph expressed methodological quality showed in Figure 2 and the risk of bias summary in each included study showed in Figure 3.

SEQUENCE GENERATION, ALLOCATION CONCEALMENT, AND BLINDING

Three studies (Tellez, 1991; Anene, 1996; Malhotra, 2009)[26-27, 29] were randomized, double-blind and placebo-controlled trial. All studies were adequately described random sequence generation methods, but only one study (Anene 1996)[27] was adequately described allocation concealment methods. And two studies (Tellez 1991, Malhotra 2006)[26,29] were adequately described the method of blinding outcome assessment.

INCOMPLETE OUTCOME DATA

Only one study (Anene 1996)[27] had high-risk of bias because they had three dropped-out patients from the study due to having complication; two

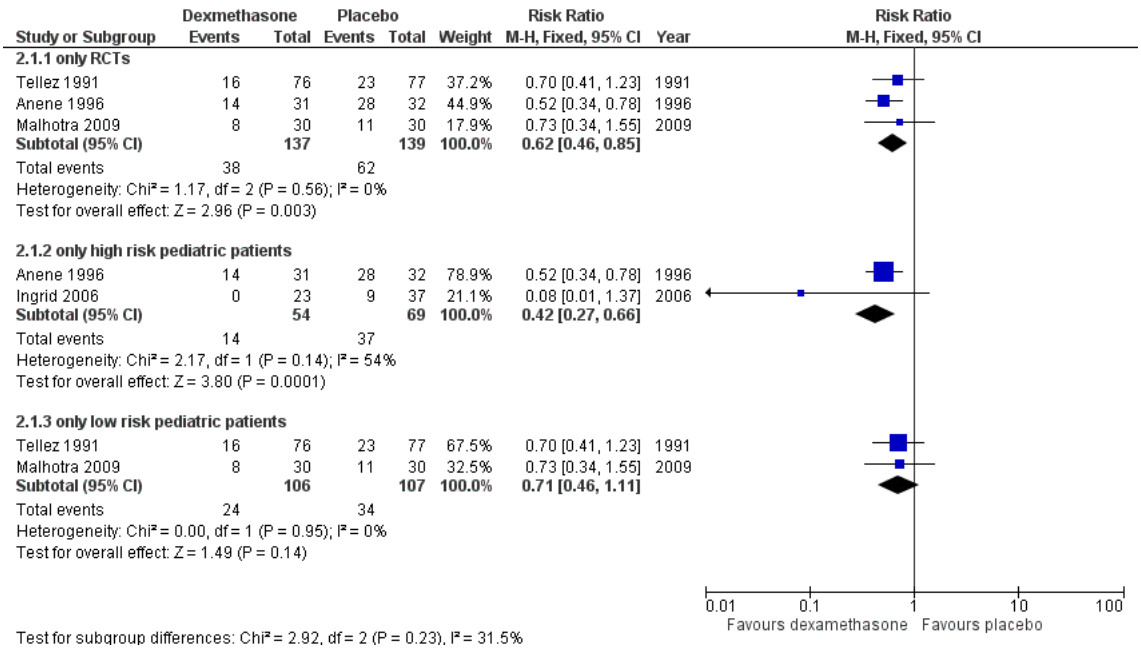

Figure 7. Forest plot of comparison of dexamethasone versus placebo, outcome: postextubation stridor. Subgroup analysis; only RCTs, only high risk pediatric patients and only low risk pediatric patients

patients had hypertension and one had gastrointestinal bleeding.

SELECTIVE OUTCOME REPORTING

All RCTs (Tellez 1991, Anene 1996, Malhotra 2009)[26, 27, 29] had low-risk of bias in the domain of selective reporting.

OTHER POTENTIAL SOURCES OF BIAS

Only one study (Anene 1996)[27] had high-risk of bias because they included patients with underlying airway anomalies in the study. A funnel plot was drawn and shown asymmetrical on the natural logarithm scale of the RR that indicated a potential publication bias.

PRIMARY OUTCOME

The primary outcome of this study was reintubation. The meta-analysis of three RCTs and one cohort study of preventing reintubation showed reintubation rate was not different between dexamethasone and placebo groups: RR, 0.49; 95% CI, 0.13 to 1.83; chi-square 9.47; I^2=68%; P=0.02 (Figure 4).

We analyzed three subgroups consisting of that including (i) only RCTs: RR, 0.61; 95% CI, 0.14 to 2.64; chi-square 8.15; I^2=75%; P=0.02 (Figure 5A), (ii) only high risk pediatric patients: RR, 0.09; 95% CI, 0.01 to 0.65; chi-square 0.08; I^2=0%; P=0.78 (Figure 5B) and (iii) only low risk pediatric patients: RR, 0.97; 95% CI, 0.20 to 4.67; chi-square

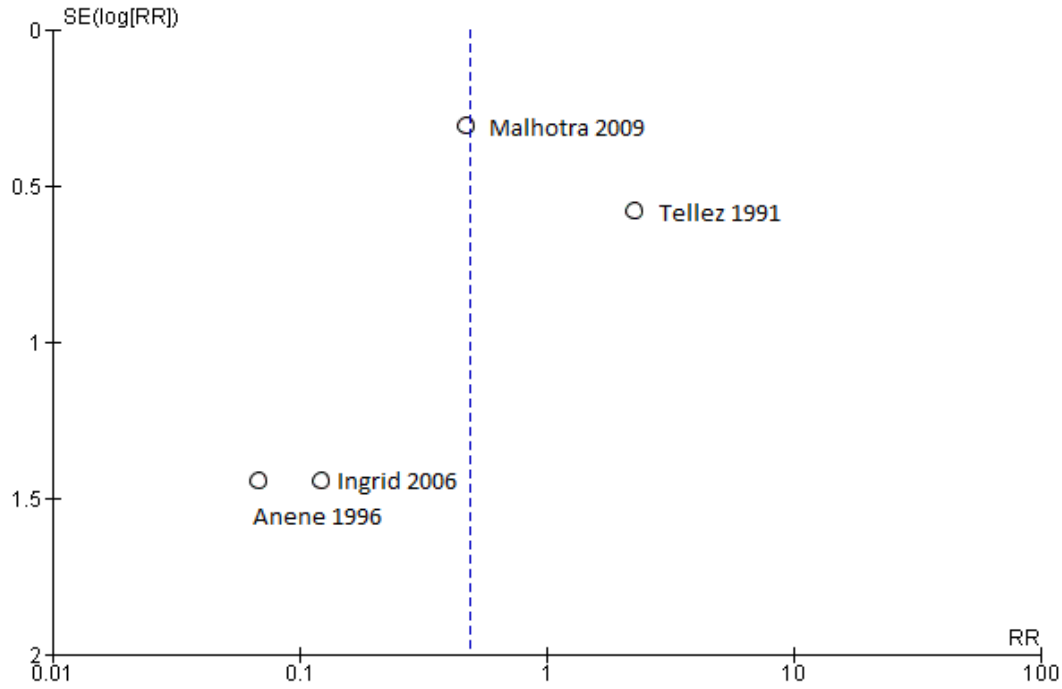

Figure 8. Funnel plot of comparison; dexamethasone versus placebo; outcome: reintubation.

6.03; I^2=83%; P=0.01 (Figure.5C), subgroup (i) and (iii) showed were no differences between dexamethasone and placebo groups in the reintubation rate, but subgroup (ii) showed significantly lower reintubation rate in dexamethasone group.

SECONDARY OUTCOME

The secondary outcome was postextubation stridor. The meta-analysis of three RCTs and one cohort study showed statistically significant lower incidence rate of postextubation stridor in dexamethasone group when compared with placebo group: RR, 0.57; 95% CI, 0.41 to 0.78; chi-square 3.02; I^2=1%; P=0.39 (Figure 6). We also analyzed three subgroups consisting of that including (i) only RCTs: RR, 0.62; 95% CI, 0.46 to 0.85; chi-square 1.17; I^2=0%; P=0.56, (ii) only high risk pediatric patients : RR, 0.42; 95% CI, 0.27 to 0.66; chi-square 2.17; I^2=54%; P=0.14 and (iii) only low risk pediatric patients : RR, 0.71; 95% CI, 0.46 to 1.11; chi-square 0.00; I^2=0%; P=0.95 (Figure 7), subgroup (i) and (ii) showed significantly lower incidence rate of postextubation stridor in dexamethasone group, but subgroup (iii) showed incidence rate of postextubation stridor was not different between dexamethasone and placebo groups. A funnel plot was drawn and shown asymmetrical on the natural logarithm scale of the RR that indicated a potential publication bias. However, the number of studies were to few to assessed the bias (Figure 8).

DISCUSSION

This systematic review demonstrated that dexamethasone was not effective on prevention of reintubation but effective on prevention of postextubation stridor in intubated children. The meta-analysis of all subgroups demonstrated in a similar way, except the subgroup analysis of high-risk pediatric patients who had airway anomalies or previous reintubation showed dexamethasone was effective on prevention of both reintubation and postextubation stridor.

STRENGTH AND LIMITATION OF THE REVIEW

We used intensive search strategies and independently evaluated several hundred relevant studies and all of the included studies were precisely assessed quality and bias using the standard assessment tools for each study, and the results showed all of them were high quality with low risk of bias. In limitations, the conclusion of this study was based on 336 patients, high heterogeneity of included studies and possible publication bias. A randomized controlled trial with a larger number of participants is suggested for stronger evidence to support the effect of dexamethasone to prevent reintubation and postextubation stridor.

COMPARISON WITH OTHER STUDIES

In our systematic review, one RCT and one cohort study were added from the Cochrane systematic review in 2009 and we included only children aged 4 weeks to 18 years which is different from the systematic review in 2001.[24,28-29,31] Our primary and secondary outcomes were reintubation and postextubation stridor, which were similar to previous reviews. The primary outcome was that dexamethasone did not prevent reintubation in intubated children, which were similar to the results of all previous reviews.[24,31] Although such results had no benefit, but our subgroup analysis showed dexamethasone was effective on prevention of reintubation in high-risk pediatric patients who had airway anomalies or history of the previous reintubation, and this conclusion was similar to the Cochrane systematic review in 2009,[24] however, this subgroup analysis was based on only one RCT and one cohort study that was different from subgroup of high-risk pediatric patients in the Cochrane review, which was based on only one RCT.[24,27]

For the secondary outcome, our results were similar to previous reviews that showed dexamethasone was effective for postextubation stridor prevention in children.[24,31] In addition to previous reviews, we also studied the effect of dexamethasone on the prevention of postextubation stridor in low-risk pediatric patients who did not have airway anomalies or history of the previous reintubation, and the meta-analysis of this subgroup showed dexamethasone had no benefit in preventing postextubation stridor in low risk pediatric patients.

CONCLUSION AND IMPLICATION

Dexamethasone did not prevent reintubation in children. However, this conclusion was based on 336 patients, high heterogeneity of included studies and possible publication bias. A larger randomized controlled trial is suggested for better estimation of the association.

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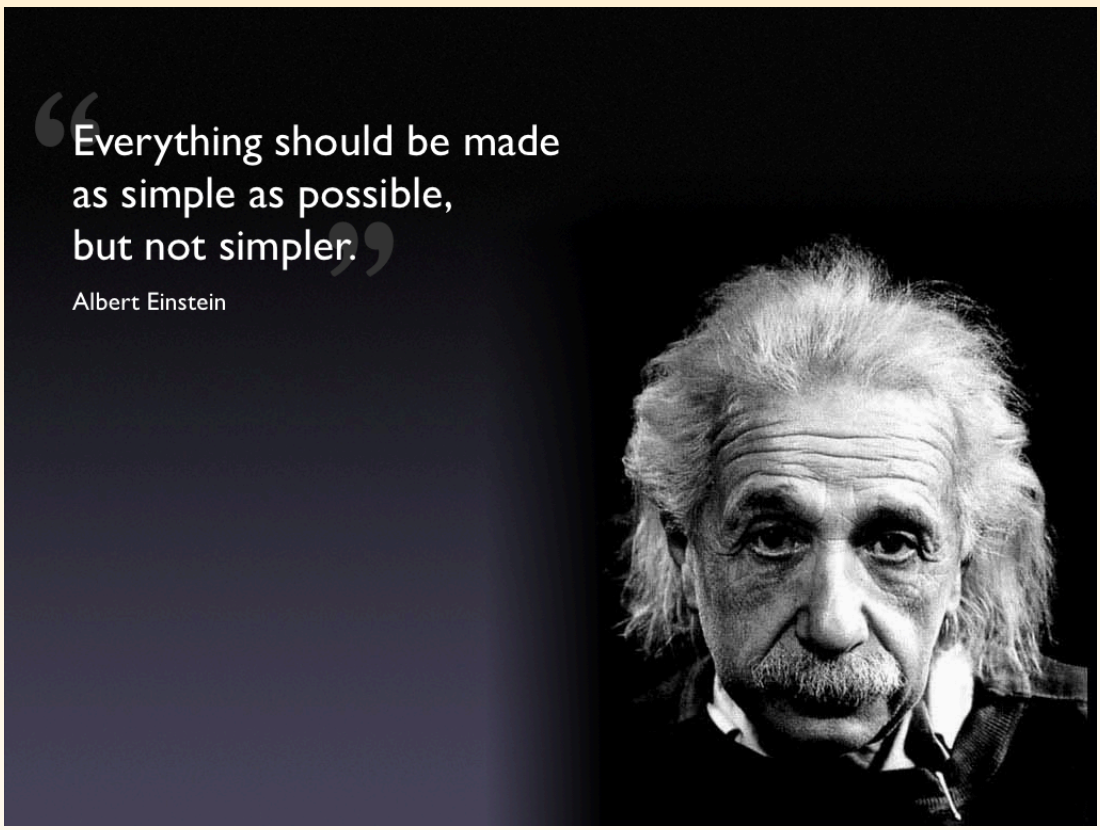
“Everything should be made as simple as possible, but not simpler.”
Albert Einstein

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