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

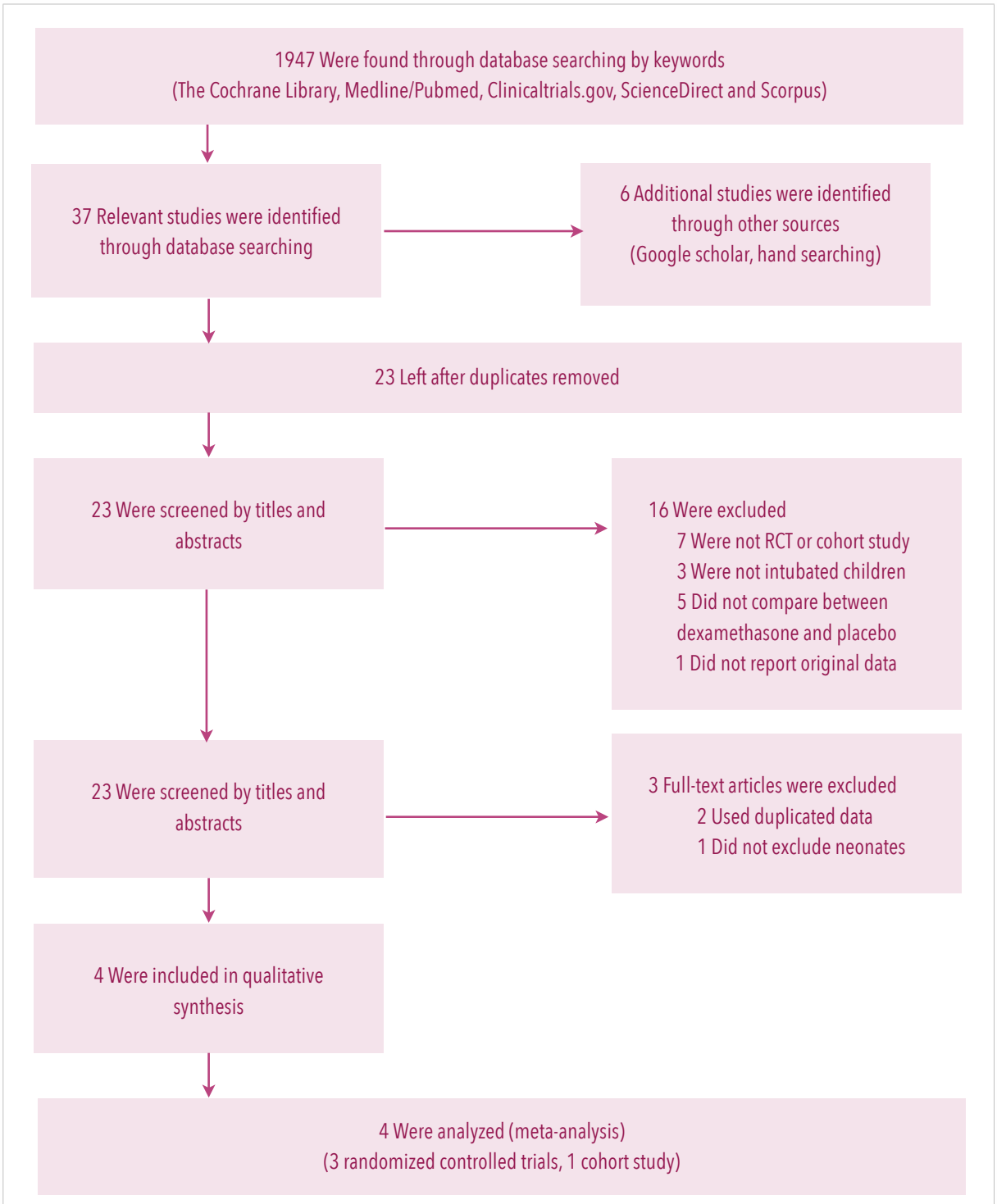

Figure 1. Flow of the review.

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

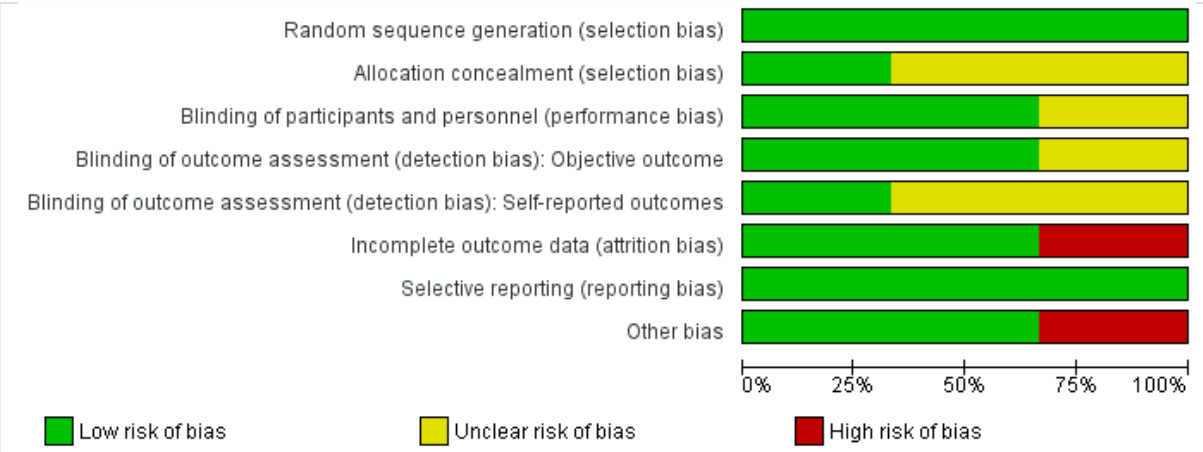

Figure 2. Risk of bias graph.

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

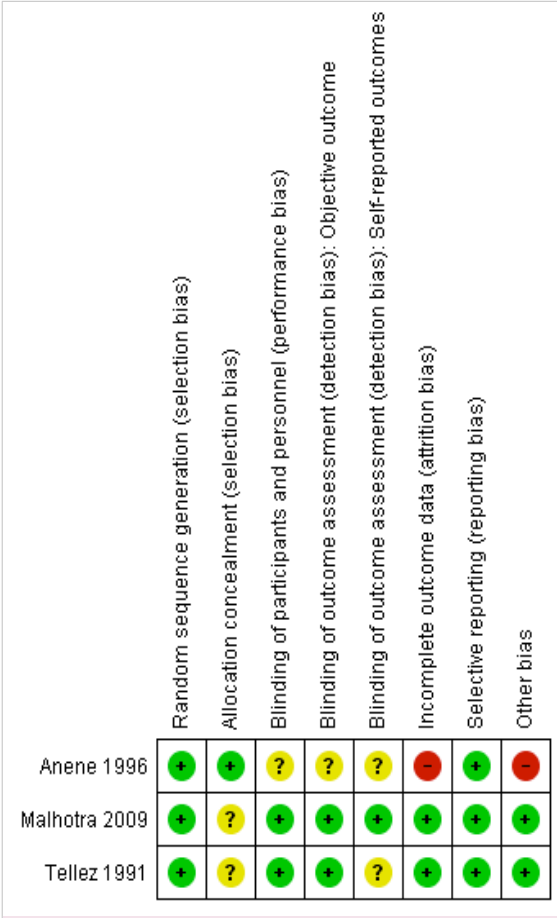

Figure 3. Risk of bias summary.

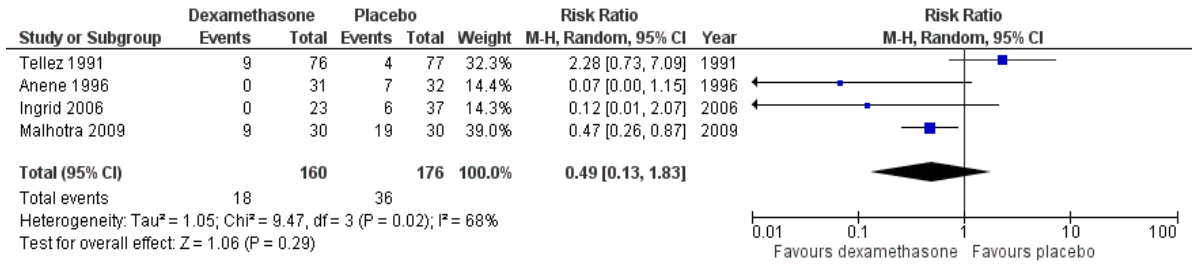

Figure 4. Forest plot of comparison of dexamethasone versus placebo, outcome: reintubation.

(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

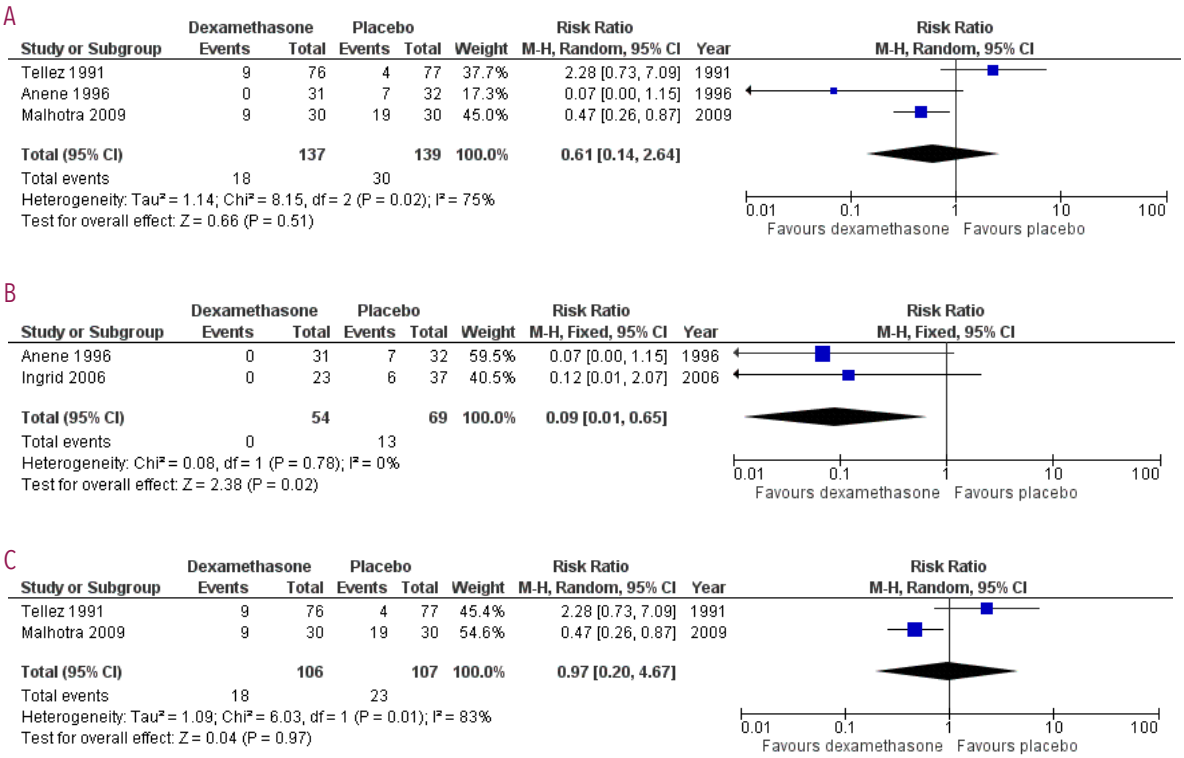

Figure 5. Forest plot of comparison of dexamethasone versus placebo, outcome: reintubation.
Subgroup analysis; Panel A, incidence-rate ratio for reintubation in only RCTs; Panel B, incidence-rate ratios for reintubation in only high risk pediatric patients; and Panel C, incidence-rate ratios for reintubation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

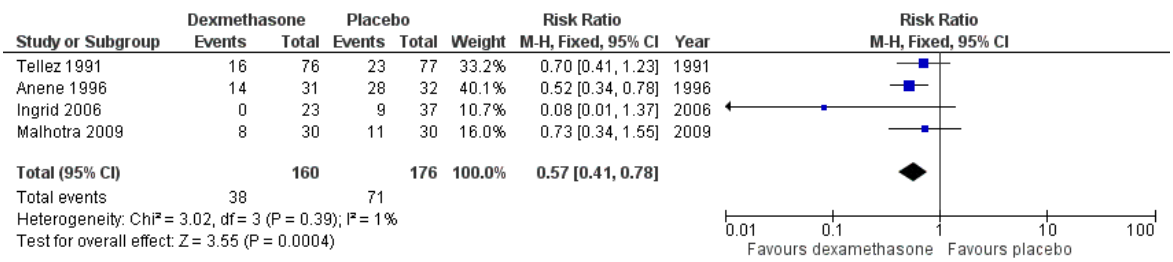

Figure 6. Forest plot of comparison of dexamethasone versus placebo, outcome: postextubation stridor.

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

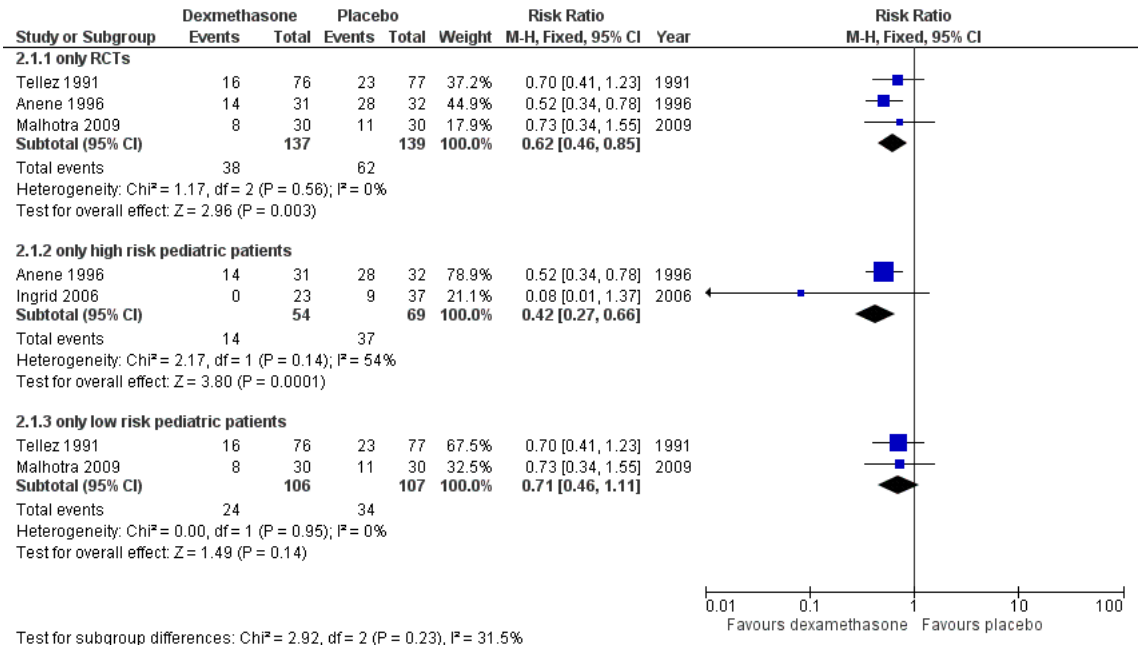

Figure 7. Forest plot of comparison of dexamethasone versus placebo, outcome: postextubation stridor. Subgroup analysis; only RCTs, only high risk pediatric patients and only low risk pediatric patients

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

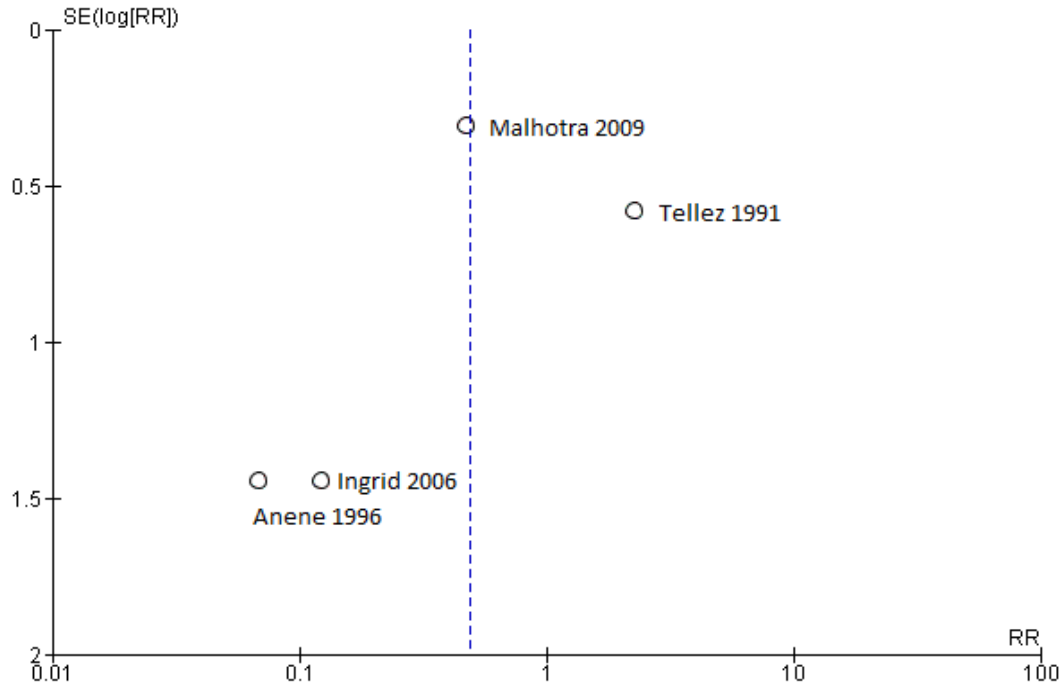

Figure 8. Funnel plot of comparison; dexamethasone versus placebo; outcome: reintubation.

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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COMPETING INTERESTS: This study has no competing on interest.
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