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Corticosteroids for the prevention and treatment of post-extubation stridor in neonates, children and adults (Review)

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[Intervention Review]

Corticosteroids for the prevention and treatment of post-extubation stridor in neonates, children and adults

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ABSTRACT

Background

Post-extubation stridor may prolong length of stay in the intensive care unit, particularly if airway obstruction is severe and re-intubation proves necessary. Some clinicians use corticosteroids to prevent or treat post-extubation stridor, but corticosteroids may be associated with adverse effects ranging from hypertension to hyperglycaemia, so a systematic assessment of the efficacy of this therapy is indicated.

Objectives

To determine whether corticosteroids are effective in preventing or treating post-extubation stridor in critically ill infants, children, or adults.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and reference lists of articles. The most recent searches were conducted in January 2011.

Selection criteria

Randomized controlled trials comparing administration of corticosteroids by any route with placebo in infants, children, or adults receiving mechanical ventilation via an endotracheal tube in an intensive care unit.

Data collection and analysis

Three review authors independently assessed trial quality and extracted data.

Main results

Eleven trials involving 2301 people were included: six in adults, two in neonates, three in children. All but one examined use of steroids for the prevention of post-extubation stridor; the remaining one concerned treatment of existing post-extubation stridor in children. Patients were drawn from heterogeneous medical/surgical populations. Dexamethasone given intravenously at least once prior to extubation was the most common steroid regimen utilized (uniformly in neonates and children). In neonates the two studies found heterogeneous results, with no overall statistically significant reduction in post extubation stridor (RR 0.42; 95% CI 0.07 to 2.32). One of these studies was on high-risk patients treated with multiple doses of steroids around the time of extubation, and this study showed a significant reduction in stridor. In children, the two studies were clinically heterogeneous. One study included children with underlying airway abnormalities and the other excluded this group. Prophylactic corticosteroids tended to reduce reintubation and significantly reduced post-extubation stridor in the

study that included children with underlying airway abnormalities ($N = 62$) but not in the study that excluded these children ($N = 153$). In six adult studies (total $N = 1953$), the use of prophylactic corticosteroid administration did not significantly reduce the risk of re-intubation (RR 0.48; 95% CI 0.19 to 1.22). While there was a significant reduction in the incidence of post extubation stridor (RR 0.47; 95% CI 0.22 to 0.99), there was significant heterogeneity ($I^2=81\%$, $X^2=26.36$, $df=5$, $p<0.0001$). Subgroup analysis revealed that post extubation stridor could be reduced in adults with a high likelihood of post extubation stridor when corticosteroids were administered as multiple doses begun 12-24 hours prior to extubation compared to single doses closer to extubation; the test for interaction for multiple versus single doses indicated RRR 0.22 (95% CI 0.10 to 0.47) for stridor with multiple doses. Side effects were uncommon and could not be aggregated.

Authors' conclusions

Using corticosteroids to prevent (or treat) stridor after extubation has not proven effective for neonates or children. However, given the consistent trends towards benefit, this intervention does merit further study, particularly for high risk children or neonates. In adults, multiple doses of corticosteroids begun 12-24 hours prior to extubation do appear beneficial for patients with a high likelihood of post extubation stridor.

PLAIN LANGUAGE SUMMARY

Does taking inhaled steroids either before or after being intubated (having a tube down the throat to help you breathe) prevent the painful swelling that can result?

When people in intensive care need assistance breathing, they may need to have a breathing tube inserted down through their windpipe (trachea or airway - the passage to the lungs). After it is taken out (extubation), the airways can be swollen (inflamed). This swelling can make it hard to breathe, cause stridor (noisy breathing), and the tube may need to be replaced. Corticosteroids are anti-inflammatory drugs that might reduce this swelling. The review of 11 trials involving 2301 people found that using corticosteroids to prevent (or treat) stridor after extubation has not been proven overall effective for babies or children, but this intervention does merit further study particularly for those at high risk to fail extubation. For high risk adults, multiple doses of corticosteroids begun 12-24 hours before extubation appear to be helpful.

BACKGROUND

Endotracheal intubation, although vital to facilitate mechanical ventilation in the intensive care unit and operating room, is associated with the potential development of glottic or sub glottic edema, resulting in stridor upon extubation (Koka 1977; Thompson 1992). Such extra-thoracic airway obstruction following endotracheal intubation may occur in up to 37% of critically ill paediatric patients (Kemper 1991). Either extrapolating from studies assessing their role in the treatment of laryngotracheobronchitis (Kairys 1989; Super 1989), or based upon early anecdotal reports of postoperative patients (Deming 1961), some clinicians administer corticosteroids in varying ways to intubated patients prior to extubation, in an effort to avoid the development of post-extubation stridor. Others use steroids to treat patients who develop stridor following extubation. On the assumption that reactive edema develops in the glottic or subglottic mucosa due to pressure or irritation from the endotracheal tube, steroids may offer protection or treatment by virtue of their anti-inflammatory actions.

Post-extubation stridor may prolong length of stay in the intensive care unit, particularly if airway obstruction is severe and re-intubation proves necessary. Corticosteroids, however, may be associated with adverse effects ranging from hypertension to hyperglycemia, and a more systematic assessment of the efficacy of this therapy is indicated prior to widespread adoption of this practice (Haynes 1980).

Differences between neonates, children, and adults with regard to airway anatomy and management are sufficient to warrant separate evaluation of these groups. In children, the narrowest portion of the airway is at the level of the cricoid cartilage, compared to the vocal cords in adults. For this reason, cuffed endotracheal tubes are used less commonly in infants and children, as a natural seal is formed between the tube and the trachea at the level of the cricoid. Edema related to the presence of a tight-fitting endotracheal tube in infants and children is therefore more likely to develop in the subglottic region, while in adults, laryngeal edema is more likely. Finally, due to the absolute size differences between ages, a small amount of edema in an infant represents much more significant infringement of the cross-sectional area of the airway (area is a function of the square of the radius), causing more severe airflow limitation and possible symptoms. For these reasons, we chose, a priori, to examine these three populations separately.

OBJECTIVES

To determine whether corticosteroids are effective in preventing or treating post-extubation stridor and reducing the need for subsequent re-intubation of the trachea in critically ill infants, children, or adults. To determine the extent of adverse effects of steroid therapy in this context.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled clinical trials in humans.

Types of participants

Infants, children, or adults (we examined these three populations separately), receiving mechanical ventilation via an endotracheal tube in an intensive care unit. Patients with known tracheitis, laryngitis, laryngotracheobronchitis, or external or surgical trauma to the larynx or subglottis were excluded.

Types of interventions

Any comparison of the administration of parenteral corticosteroids (intravenous (IV), intramuscular (IM), inhalation; any number of doses) versus placebo in the 24 hour period prior to and following the elective extubation of patients. Trials assessing prevention of, and treatment for, existing post-extubation stridor were analyzed separately.

Types of outcome measures

The primary outcome measure assessed was the need for re-intubation of the trachea due to severe stridor and airway obstruction. Trials that failed to distinguish re-intubation due to airway obstruction as evidenced by stridor or laryngeal edema from that due to other causes were not included. A secondary endpoint was the presence of stridor within six hours following extubation. Croup scores (Backofen 1987) and treatment with nebulized vasoconstrictor therapy were also examined if data were available. The incidence of the following complications was examined: hypertension, hyperglycemia, gastrointestinal bleeding.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) Issue1, 2011; MEDLINE 1960 to Jan wk 1 2011; and EMBASE 1980 to wk 2, 2011. For the full database search strategies please see Appendix 1. For the strategies used in earlier versions of this review please see Appendix 2 and Appendix 3.

The most recent searches were conducted in January 2011.

Searching other resources

We reviewed reference lists of all primary studies and review articles for additional references.

Data collection and analysis

Two review authors (BPM and RGK) selected citations (titles and abstracts) that appeared to fit the criteria for inclusion for full text review. Only citations that were clearly not relevant or not randomised controlled trials were not reviewed in full. The numbers of citations rejected (and the reason for rejection) were tracked. The three review authors (BPM, AGR, RGK) independently selected trials for inclusion in the review and assessed the methodological quality of the included trials using two approaches. First, the allocation concealment was ranked using the Cochrane approach:

Grade A: Adequate concealment

Grade B: Uncertain

Grade C: Clearly inadequate concealment

and the likelihood of bias was assessed on a 5-point score, based on the approach of Jadad et al. (Jadad 1996):

1. Was the study described as randomized?
2. Was the study described as double blind?
3. Was there a description of withdrawals and dropouts?

If there was uncertainty, we contacted authors to clarify the methodology used. Disagreement between review authors was resolved by consensus.

We extracted data and entered this into the Cochrane Collaboration software program (Review Manager version 5) for analysis. Relative risk was assessed for dichotomous variables, and mean difference (MD) or standardized mean difference (SMD) was applied to continuous data as appropriate. Ordinal data with more than four categories, e.g. the croup score, was treated as continuous. The random-effects model was used throughout. Heterogeneity of results was assessed with the DerSimonian and Laird test with a $P < 0.1$ as significant, as well as the I^2 statistic.

Sub-group analysis was performed to assess the role of age (infants versus children versus adults), and the purpose of corticosteroid use (i.e. for the prevention versus treatment of post-extubation stridor) as stated above. Additional post-hoc subgroup analysis was performed to assess the role of multiple doses of corticosteroids begun 12-24 hours prior to extubation for adults. To compare treatment regimens in adults, differences between two subgroups is reported with relative risk ratios (RRR), using the method of Altman and Bland for interaction (Altman 2003).

RESULTS

Description of studies

Results of the search

From literature searches conducted over the period 1999-2011, a total of 3828 citations were identified and screened for inclusion; no additional trials were identified by bibliographic review or contact with investigators. The 2011 update search returned 367 references, none of which we judged eligible for inclusion.

Included studies

Eleven randomized trials were identified from the searches which addressed the effects of treatment with corticosteroids on post-extubation airway obstruction in intensive care unit patients. A full description of each is included in the table [Characteristics of included studies](#).

Ten studies involved corticosteroid (six dexamethasone, one hydrocortisone, three methylprednisolone) treatment given prophylactically before a patient's first elective extubation, and one assessed the effect of dexamethasone on secondary extubation in pediatric patients already re-intubated for stridor following a previous extubation attempt (Harel 1997). An overview of the different corticosteroid regimens is given in [Table 1](#).

Two studies involved neonates, three studied non-neonatal pediatric patients, and six examined adults.

Neonatal studies (N = 2):

Ferrara 1989 included 59 neonates intubated at least 48 hours, but excluded infants intubated more than once, while Couser 1992 selected 50 "high risk" babies who underwent traumatic or multiple endotracheal intubations, or who were intubated for at least 14

days. Ferrara 1989 used a single dose of 0.25 mg/kg of intravenous dexamethasone 30 minutes prior to extubation, while Couser 1992 gave a total of three doses (one four hours prior to extubation, then every eight hours x 2 doses following extubation).

Pediatric studies (N = 3):

Anene 1996 studied 63 patients (age range 1 to 59 months) in the pediatric intensive care unit (PICU) who were intubated for more than 48 hours, included patients with underlying airway abnormalities (e.g., subglottic stenosis, vocal cord paralysis). They only excluded patients with laryngotracheal infections or steroid use within seven days. Tellez 1991 included 153 intubated patients (mean age 2.5 years, range 1 month to 18 years) in two PICU's. They excluded patients with primary upper airway infection, surgical trauma to the upper airway, or a history of previous upper airway obstruction. Both studies used dexamethasone 0.5 mg/kg (up to a maximum of 10 mg), with the first dose 6 to 12 hrs before extubation, then every six hours for six doses in total.

The sole study designed to assess the effect of dexamethasone on the re-intubation rate following an initial "failed" extubation (due to post-extubation stridor) studied 26 pediatric patients (Harel 1997). Dexamethasone (0.5 mg/kg) was given six hours prior to the second extubation attempt, and then at 6 and 12 hours following extubation. This was the only study to utilize a scoring system for stridor, adapted from Leipzig 1979. This assessed audible stridor, cyanosis, sternal retractions, respiratory and heart rates. Scores could range from zero to 11 (maximum).

Adult studies (N = 6):

Gaussorgues 1987 examined 276 adults intubated for at least four days, administering methylprednisolone 40 mg IV and 40 mg IM 30 minutes prior to elective extubation. Darmon 1992 studied 700 intubated patients. They excluded those less than 15 years old, patients with ear, nose, or throat disease or surgery, patients who had stridor after extubation during their current hospital stay, or those who were already on steroids or non-steroidal anti-inflammatory agents. In this study, dexamethasone 8 mg IV was given one hour prior to extubation. In Ho 1996, 77 intubated adults with a planned extubation were eligible; excluded were those less than 15 years old, patients already extubated during their current stay, and those with throat disease or surgery. The treatment was 100 mg of hydrocortisone IV administered one hour prior to extubation. Cheng 2006 studied 128 adults intubated for > 24 hours with a cuff leak volume < 24%. They excluded patients with previous steroid use in the week prior, nasal or throat surgery, GI bleed, post cardiac surgery or myocardial infarction, or history of previous extubation during the same hospitalization. They had two treatment arms: four doses of methylprednisolone 40 mg IV q six hours for 24 hours prior to extubation, or one dose of methylprednisolone 40 mg IV 24 hours prior to extubation. Francois 2007 examined 698 adults > 18 years of age intubated for > 36 hours. They excluded those with a previous history of upper airway obstruction post extubation, throat disease or surgery, tracheostomy, those chronically treated with NSAIDs or steroids, or those enrolled in another study. They administered methylprednisolone 20 mg IV q 4 hours for four doses starting 12 hour prior to extubation. Lee 2007 examined 80 adults intubated for >48 hours with a cuff leak volume <110 ml. They excluded patients previously extubated during the same hospitalization or who had received corticosteroids within the previous week. They

administered dexamethasone 5mg IV q 6 hours for four doses starting 24 hours prior to extubation.

Excluded studies

One trial was excluded ([Courtney 1992](#)) because stridor or laryngeal edema was not assessed; re-intubation due to airway obstruction could therefore not be confirmed. One trial was presented in abstract form, but we were unable to contact the authors for confirmation of the methodology ([Shih](#)).

Risk of bias in included studies

There was no disagreement between review authors with respect to quality assessment done independently. After discussion, there was also no disagreement regarding data extraction. Some of the information detailing methods of concealment and randomization were only obtained after direct contact with authors. [Gaussorgues 1987](#) (adults) and [Tellez 1991](#) (children) were unavailable for additional information. It is possible their methodologic quality was higher than reported.

In [Gaussorgues 1987](#) (adults) and [Tellez 1991](#) (children) allocation concealment was uncertain (Grade B). All others had adequate concealment (Grade A).

All studies were described as randomized. Appropriate methods of randomization were specified in all except [Gaussorgues 1987](#) where no description of the randomization technique was noted, and [Cheng 2006](#) where the only description of randomization was "random numbers."

Nine of the ten investigations were described as double-blind, with adequate descriptions of control treatment (saline) in all but [Darmon 1992](#) ("placebo"). [Gaussorgues 1987](#) did not state that the study was double-blind and did not describe the use of a control injection.

[Couser 1992](#), [Gaussorgues 1987](#), [Ho 1996](#) and [Tellez 1991](#) made no mention of withdrawals or dropouts. In the remainder of the studies, all post-randomization patients were accounted for.

The adult studies had Jadad's scores of 1 ([Gaussorgues 1987](#)), 4 ([Ho 1996](#) and [Cheng 2006](#)), and 5 ([Darmon 1992](#), [Francois 2007](#), and [Lee 2007](#)); the pediatric studies were rated as 3 ([Tellez 1991](#)), 5 ([Anene 1996](#)), and 5 ([Harel 1997](#)); the neonatal studies as 4 ([Couser 1992](#)) and 5 ([Ferrara 1989](#)).

Effects of interventions

Prophylactic intervention

In the two neonatal studies, the trial of [Couser 1992](#) showed a trend towards reduced rate of re-intubation with prophylactic intervention, but no infants in either group of the patients studied by [Ferrara 1989](#) were re-intubated. The trials together demonstrated no significant difference in stridor incidence with intervention in 109 patients (RR 0.42; 95% CI 0.07 to 2.32), although the "high-risk" patients, with traumatic or multiple intubations in the study by [Couser 1992](#) had a lower incidence of stridor when treated with corticosteroids ([Figure 1](#)).

Figure 1. Forest plot of comparison: Treated vs. Controls; all, outcome:Re-intubation Rate.

There was heterogeneity in both outcomes between studies, suggesting that the multiple dose strategy in the higher risk patients of the [Couser 1992](#) study may be more effective than the single dose regimen in lower risk patients of the [Ferrara 1989](#) trial. Other outcome measures sought, such as number of vasoconstrictor treatments or croup scores were not reported in these studies.

The two pediatric trials were quite heterogeneous, with conflicting results. The study that included patients with underlying airway anomalies ([Anene 1996](#)) showed a reduction in reintubation,

although not statistically significant (RR 0.07; 95% CI 0.001 to 1.15), while the study that excluded such patients ([Tellez 1991](#)), in fact showed a higher incidence of reintubation in the treatment group (RR 2.28; 95% CI 0.73 to 7.09), although again not statistically significant ([Figure 1](#)). There was a reduction in post-extubation stridor with intervention in 216 patients (RR 0.53; 95% CI 0.36 to 0.97), although the studies were too heterogeneous to reliably interpret the significance of the estimate of relative risk ($I^2 = 53\%$, $X^2 = 2.13$, $df=1$, $P=0.14$). A trend towards a reduction in vasoconstrictor use for post-extubation stridor was observed in these studies (RR 0.38; 95% CI 0.1 to 1.43, [Figure 2](#)).

Figure 2. Forest plot of comparison: Treated vs. Controls; all, outcome: Stridor Incidence.

Analysis of the six adult studies demonstrates a non-significant trend for reduction in re-intubation rates with prophylactic steroid administration (RR 0.48; 95% CI 0.19 to 1.22) and a reduction in post-extubation stridor (RR 0.47; 95% CI 0.22 to 0.99). However, the studies were too heterogeneous to reliably interpret the significance of the estimate of relative risk ($I^2=81$, $\chi^2=26.36$, $df=5$, $p<0.0001$, Figure 1).

Compared to placebo, the treatment groups in Cheng 2006 and Francois 2007 experienced significant reductions in both re-intubation rates and post-extubation stridor, and treated patients in the Lee 2007 trial had a significant reduction in post extubation stridor. The earlier three studies showed no difference in either of these outcomes. The Cheng 2006 and Lee 2007 studies only enrolled patients with a cuff leak volume $< 24\%$ or <110 ml respectively, so perhaps represented a higher-risk patient group. In addition the Cheng 2006, Francois 2007 and Lee 2007 trials used repeated doses of corticosteroids begun 12 to 24 hours prior to extubation, unlike the previous studies which utilized single corticosteroid doses given within one hour of extubation.

Post hoc subgroup analysis

Given the level of statistical heterogeneity observed between the six adult studies, a subgroup analysis was preformed to explore

possible reasons for variation in effect size between the studies. We tested whether there was a difference between the risk of reintubation and stridor between regimens employing multiple doses of corticosteroids begun 12-24 hours prior to extubation with regimens using a single dose administered closer to extubation. Three studies employed a multiple dosing strategy. Since this post-hoc analysis is intended to specifically compare the risk for those given multiple doses of corticosteroids to those with single doses of corticosteroids we employed a test of interaction using the method described by Altman 2003, in order to generate a Ratio of Relative Risks (RRR). There was no statistically significant difference between the relative risks between the two subgroups of studies for re-intubation (RRR 0.26; 95% CI 0.07 to 1.04). However, there was a statistically significant reduction in post extubation stridor favouring the multiple dosing strategies (RRR 0.23 95% CI 0.11 to 0.48). Within subgroup I^2 measurements were low for both outcomes (re-intubation: 22% and 0%; stridor: 25% and 0% for multiple and single dosing strategies respectively). Figure 3 and Figure 4 display the relative risks (RR) for each of the two subgroups of treatment regimens compared to placebo. The ratio of relative risk (RRR) described above directly compares the relative risk of reintubation or post extubation stridor for those given multiple doses of corticosteroids 12-24 hours prior to extubation, to those given single doses closer to extubation.

Figure 3. Forest plot of comparison: Post hoc subgroup analysis: Adults, Multiple Doses, 12-24 hours prior to extubation, outcome: Re-intubation Rate.

Figure 4. Forest plot of comparison: Post hoc subgroup analysis: Adults, Multiple Doses, 12-24 hours prior to extubation, outcome: Stridor Incidence.

Treatment of existing post-extubation stridor

Harel 1997 was the sole study that examined the effect of dexamethasone on post-extubation stridor and re-intubation in children already re-intubated for post-extubation airway obstruction. In these 33 patients, dexamethasone had no effect on post-extubation stridor score (MD -1.1; 95% CI -3.7 to 1.5). Although the relative risk reduction on re-intubation rate was 45%, this did not achieve statistical significance (RR 0.55; 95% CI 0.17 to 1.78).

Complications of treatment

Few studies noted significant complications attributable to steroid therapy, and those that were reported could not be pooled. In Couser 1992, 7 of 27 treated infants developed glucosuria, compared to 0 of 23 controls. Anene 1996 noted one treated patient with gastrointestinal bleeding, and two patients (one treated and one control) developed hypertension. Francois 2007 reported one patient in the treatment group that died of septic shock 26 hours after extubation, although this death cannot be linked directly to steroid use.

DISCUSSION

Systemic corticosteroids have been advocated to either prevent or treat post extubation stridor in intensive care unit patients. This systematic review does not support routine steroid use for prevention of re-intubation due to upper airway obstruction or post extubation stridor in children or neonates. However corticosteroids

may be beneficial in reducing post extubation stridor if employed in a multiple dose strategy 12-24 hours prior to extubation for certain high risk adults.

From two trials of preventative dexamethasone therapy in neonates, post extubation stridor was reduced. However, there was heterogeneity between these two studies, and benefit appeared to be confined to higher risk patients receiving multiple doses of dexamethasone around the time of extubation.

A previous Cochrane Review examined the role of steroids given to neonates prior to elective extubation (Davis 2001). The primary outcome was the rate of re-intubation from all causes. The study of Courtney 1992 was included in that review. We excluded this trial because it failed to distinguish re-intubation due to airway obstruction from that of other causes. With this study included in their review, Davis did find that dexamethasone prior to extubation reduced the risk of endotracheal re-intubation (RR 0.18, 95% CI 0.04 to 0.97). Like us, however, they concluded that dexamethasone is indicated for elective extubation of "high risk" neonates on the same grounds as us - namely that a clear benefit of dexamethasone was seen only in the "high risk" patients studied by Couser 1992.

The two pediatric studies that examined elective dexamethasone treatment prior to extubation showed similar efficacy in preventing stridor but differed in terms of the effect on re-intubation rates. This may be in part due to the high rate of stridor and re-intubation in the control group of Anene 1996; seven of 32 control patients required re-intubation and 22 of 28 still had stridor six

hours following extubation. This suggests that Anene's population was at higher risk, although this is only subtly suggested in the description of included and excluded patients. [Anene 1996](#) included patients with multiple airway manipulations (for example, re-intubation), while [Tellez 1991](#) excluded such patients. Analogous to the neonatal studies, it appears that dexamethasone only confers benefit on "high risk" children, e.g. those with additional airway instrumentation.

The neonatal and pediatric studies contained relatively few patients, and despite the use of meta-analysis, the apparent lack of a statistically significant effect of steroids on re-intubation rates may be due to insufficient sample sizes. Assuming a reduction in re-intubation rates from 10% to 5%, a two-tailed alpha of 0.05 and beta of 0.2, 475 patients per arm would be required in a prospective trial sufficiently powered to detect such a difference.

The three most recent trials of corticosteroids in adults ([Cheng 2006](#); [Francois 2007](#), and [Lee 2007](#)) show that corticosteroids are beneficial in preventing post extubation stridor, and contradict results from the three previous adult studies ([Gaussorgues 1987](#); [Ho 1996](#); [Darmon 1992](#)). The reported incidence of stridor in the control group was remarkably different in each of the six adults studies (1.45%, 9.1%, 22%, 26.3%, 27.5% 30.2%). The 30.2% reported by [Cheng 2006](#) and the 27.5% of [Lee 2007](#) certainly overestimate the overall risk of post extubation stridor, as these were high-risk populations with a low cuff leak volume percentage. While the predictive ability of cuff leak volume is quite variable throughout the literature ([DeBast 2002](#); [Jaber 2003](#); [Sandu 2000](#); [Miller 1996](#)), the incidence of post extubation stridor was quite low for patients who did not meet cuff leak criteria in both the [Cheng 2006](#) (2.6%) and [Lee 2007](#) (4.9%) studies. [Francois 2007](#) and [Ho 1996](#) also report a relatively high incidence of post extubation stridor (22% and 26.3% respectively), although inclusion and exclusion criteria are similar to the studies by [Gaussorgues 1987](#) and [Darmon 1992](#), which had relatively low incidence of post extubation stridor. Nonetheless, the three trials demonstrating benefit have been performed in populations with relatively high incidence of stridor. In addition, these trials employed regimens using multiple doses of corticosteroids begun 12-24 hours prior to extubation. As such, one can speculate that the more recent trials have shown benefit for corticosteroids because the dosing regimen may be more effective and is targeted towards a population with a higher incidence of post extubation stridor. A recently published meta analysis incorporating these same six adult studies echo these conclusions ([Roberts 2008](#)).

Interestingly the sole study to utilize two treatment arms- single versus multiple dose methylprednisolone begun 24 hours prior to extubation ([Cheng 2006](#)) demonstrated no significant difference for rates of reintubation (RR 1.47; 95% CI 0.26 to 8.33) or post extubation stridor (RR 0.61; 95% CI 0.16 to 2.41) between treatment arms, but both interventions in this single study were

significantly better than placebo. While this may argue that timing of corticosteroid administration may play the largest role, it is still possible that the benefits of corticosteroids for the prevention of post extubation stridor stem from either repeated doses of corticosteroids, or administration 12-24 hours prior to planned extubation.

The implications that steroids may confer the most benefit for patients who have undergone additional airway manipulations - does not appear to hold true for patients who have already failed extubation due to post-extubation stridor, although conclusions are difficult to draw from the one small trial ([Harel 1997](#)).

AUTHORS' CONCLUSIONS

Implications for practice

In children, there is insufficient evidence to conclude that prophylactic intervention with corticosteroids prior to elective extubation reduces the incidence of re-intubation due to airway obstruction or post-extubation stridor. In neonates, trends towards reduced rates of re-intubation or stridor could be demonstrated only in high-risk patients. In adults, single doses of corticosteroids do not appear to prevent re-intubation due to airway obstruction or post extubation stridor. However, compared to single doses, there is a trend towards reduced rates of reintubation and a reduction in post extubation stridor when multiple doses of corticosteroids are started 12-24 hours prior to extubation, particularly for cohorts with a high incidence of post extubation stridor. The evidence to suggest that steroid therapy can reduce re-intubation rates in children already re-intubated once for post-extubation stridor is lacking.

Implications for research

Additional study is warranted to prospectively identify high-risk patients who might benefit from prophylactic steroid administration prior to extubation, and future trials in children or neonates should explore a multiple dose strategy, begun at least 12 hours prior to extubation. However, evidence does not support routine use of corticosteroids in infants or children who are not otherwise high risk. For adults, cuff leak volume has been used to identify "higher risk" patients, with mixed results. However, additional study is warranted to determine whether this adequately identifies higher risk patients and if regimens that utilize repeated doses of corticosteroids initiated at least 12 hours prior to extubation improve outcome in populations where the incidence of post extubation stridor is high.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Anene 1996

Methods	Pediatric: Stratified randomization on presence or absence of airway abnormalities by random number table by blinded pharmacist.	
Participants	63 children < 5 yrs, intubated > 48 hrs, undergoing a first elective extubation. Excluded patients with laryngotracheal infections or steroids within 7 days.	
Interventions	Dexamethasone 0.5 mg/kg IV (max 10 mg) vs equal volume of saline. 1st dose 6 - 12 hrs before extubation, then q 6h for total 6 doses.	
Outcomes	Stridor, croup score, need for racemic epinephrine, pulsus paradoxus, reintubation	
Notes	The treatment group had more audible air leaks 23/33 vs 16/33 (P = 0.07). Included "airway abnormalities" - tracheomalacia, SGS, unilateral VC paralysis, vascular ring. 3 patients removed from study and not analysed; 1 treated patient with GI bleeding and 1 in each group with hypertension. Jadad score: 5	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Anene 1996 (Continued)

Allocation concealment (selection bias)	Low risk	Stratified randomisation on presence or absence of airway abnormalities by random number table by blinded pharmacist (Cochrane Grade A)
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Cheng 2006

Methods	Adults: Randomized by "random number." Blinded by respiratory therapist not involved in trial.	
Participants	128 adults > 18 years, intubated > 24 hours, Cuff Leak Volume < 24%. Excluded if steroids up to 1 week before, nasal or throat surgery, GI bleed, hyperglycemia, post cardiac surgery or MI, previous extubation during same hospitalization.	
Interventions	2 treatment arms: 4 doses of methylprednisolone 40 mg IV q 6 hours for 24 hours prior to extubation. Other treatment group 1 dose of methylprednisolone 40 mg IV 24 hours prior to extubation vs saline placebo.	
Outcomes	Stridor requiring medical intervention (epinephrine inhalation or BiPAP). Reintubation, with edema confirmed with laryngoscopy or bronchoscopy.	
Notes	No data on confirmatory test results (edema on laryngoscopy). Non intervention arm with CLV > 24%, 2.4% incidence of post extubation stridor. No mention of randomisation strategy. Jadad Score:4	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Blinded by respiratory therapist not involved in trial (Cochrane Grade A)

Couser 1992

Methods	Neonatal: Randomized by blinded pharmacist using random number table.	
Participants	50 infants receiving mechanical ventilation who had either traumatic or multiple intubations or if duration of intubation > 14 days. Excluded those with congenital anomalies of airways or lungs and those who had received dexamethasone for chronic lung disease or had received pancuronium or other sedation within 12 hrs before extubation.	
Interventions	Dexamethasone 0.25 mg/kg IV ~ 4 hrs before extubation and q 8h for total of 3 doses vs. saline placebo.	
Outcomes	Stridor, infant pulmonary function tests, reintubation rates, blood gases	
Notes	More glucosuria noted in treated patients (7/27 vs 0/23). Subglottic stenosis diagnosed in 3 controls at 1.5, 5, and 7.5 mos after extubation vs. 1 treated patient 3.5 mos after extubation. Some babies placed on NPCPAP after extubation. No mention of post-randomization exclusions. Jadad score: 4	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Randomized by blinded pharmacist using random number table (Cochrane Grade A)

Darmon 1992

Methods	Adults: Randomized in blocks of 8 by random number table; stratified into short (< 36 hr) or long (> 36 hr) duration of intubation. Blinded by pharmaceutical company with numbers on vials.
Participants	694 endotracheally intubated adults. Excluded if less than 15 years of age or presented with ear, nose, or throat disease or surgery, had laryngeal edema after extubation during current hospital stay, or were receiving steroids or non-steroidal anti-inflammatory agents.
Interventions	8 mg dexamethasone IV 1 hr before extubation vs. saline placebo.
Outcomes	Minor laryngeal edema: stridor or "laryngeal dyspnoea" and major laryngeal edema: required reintubation with laryngeal edema confirmed by direct laryngoscopy.
Notes	Of 700 pts enrolled, 37 dropped; for 6 patients, scheduled extubation postponed after treatment (1 placebo, 5 dexamethasone); in 31, trachea reintubated for reasons other than laryngeal edema (with no signs/symptoms or direct laryngoscopy evidence of laryngeal edema). Jadad score: 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Blinded by pharmaceutical company with numbers on vials (Cochrane Grade A).

Ferrara 1989

Methods	Neonatal: Randomized with sealed envelopes by pharmacist.
Participants	59 infants intubated > 48 hours after single intubation. Excluded those with more than one intubation, receiving steroids, or with congenital airway anomalies
Interventions	Dexamethasone 0.25 mg/kg IV or saline 30 minutes before elective extubation.
Outcomes	Downes score, stridor, pH/pCO ₂ , atelectasis, reintubation
Notes	One infant diagnosed with central hypoventilation after extubation and excluded. Infants < 1500 grams were extubated to NCPAP. Jadad score: 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Randomized with sealed envelopes by pharmacist. (Cochrane Grade A)

Francois 2007

Methods	Adults: Patients randomized in balanced blocks of unequal size for each participating center. Blinded by nurse not involved in patient care.
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Francois 2007 (Continued)

Participants	698 adults > 18 years intubated > 36 hours. Excluded those with previous history of UAO post extubation, throat disease or surgery, tracheostomy, chronically treated with NSAIDS or steroids, in another study.
Interventions	Methylprednisolone 20 mg IV q4 hours starting 12 hours prior to extubation for 4 doses vs. saline placebo.
Outcomes	Minor laryngeal edema: stridor, respiratory distress. Major laryngeal edema: required re-intubation with upper airway obstruction confirmed on laryngoscopy.
Notes	More nasal intubations in intervention group. 1 patient in intervention group died of septic shock 26 hours post extubation. 24 patients re-intubated without evidence of laryngeal edema. Jadad Score: 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Blinded by nurse not involved in patient care (Cochrane Grade A)

Gaussorgues 1987

Methods	Adults: Patients "randomised" but no description of methods or blinding.
Participants	276 adults 18-82 years old intubated at least 4 days.
Interventions	Methylprednisolone 30 min before extubation - 40 mg IV and 40 mg IM. No mention of placebo.
Outcomes	Stridor, laryngeal edema confirmed by laryngoscopy, need for reintubation.
Notes	No contact with author. No mention of post-randomization exclusions. Jadad score: 1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information available to ascertain degree of bias in concealment of allocation (Cochrane Grade B)

Harel 1997

Methods	Pediatric: Patients randomised by "numbers from a hat." Blinded by pharmacist.
Participants	23 children in two PICUs who failed initial extubation due to post-extubation stridor. Excluded those treated with steroids in previous 7 days.
Interventions	Dexamethasone 0.5 mg/kg/dose (max 15 mg) IV 6 hr prior to extubation, at extubation, then 6, and 12 hr after extubation vs. saline placebo.
Outcomes	Stridor score and extubation success/failure.

Harel 1997 (Continued)

Notes 3 controls got steroids post-randomization, 2 because clinicians thought they were "failing" - intention-to-treat analysis included. Jadad score: 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Blinded by pharmacist (Cochrane Grade A)

Ho 1996

Methods	Adults: Blinded randomisation by random number table in blocks of 4.
Participants	77 intubated adults. Excluded if < 15 years of age, had been extubated during current stay, throat disease or surgery, prolonged or traumatic intubation.
Interventions	Hydrocortisone 100 mg IV or saline 1 hr before extubation.
Outcomes	Stridor and reintubation rates
Notes	No mention of post-randomization exclusions. Jadad score: 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Blinded randomization by random number table in blocks of 4 (Cochrane Grade A)

Lee 2007

Methods	Adults: Blinded randomization by respiratory therapist not involved in care, computer generated list in blocks of 4.
Participants	80 adults >18 years, intubated >48 hours, Cuff Leak Volume <110 ml. Excluded if previous extubation during same hospitalization or corticosteroids within previous week.
Interventions	Dexamethasone 5 mg IV 24 hours prior to extubation then q 6 for a total of 4 doses vs. saline placebo
Outcomes	Post extubation stridor, reintubation rates
Notes	No data on confirmatory test results (edema on laryngoscopy). Non intervention arm with CLV >110 ml, 4.9% incidence of stridor. Protocol in place for non invasive ventilation after extubation if treatment with racemic epinephrine failed. Jadad score: 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Blinded randomisation, computer generated list in blocks of 4 (Cochrane Grade A)

Tellez 1991

Methods	Pediatric: Stratified randomised design on age, intubation duration, upper airway trauma, circulatory compromise, tracheal infection.
Participants	153 intubated children. Excluded those who had received steroids within 1 week, had a primary airway infection, surgical trauma to the airway, or a history of previous airway obstruction.
Interventions	Dexamethasone 0.5 mg/kg (max 10 mg) IV between 6 - 12 hrs prior to extubation, then q 6 hr for total of 6 doses vs. saline placebo.
Outcomes	Stridor (defined as need for racemic epinephrine), reintubation
Notes	No mention of post-randomization exclusions. Jadad score: 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information available to ascertain degree of bias in concealment of allocation (Cochrane Grade B)

BiPAP: Bi-level positive airway pressure

CLV: Cuff leak volume

IM: intra-muscular

IV: intravenous

MI: Myocardial infarction

mos: months

NPCPAP: Nasal continuous positive airway pressure

NSAIDs: non steroidal anti-inflammatory drugs

PICUs: Paediatric intensive care unit

pts: patients

UAO: Upper airway obstruction

vs: versus

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Courtney 1992	Did not evaluate stridor or laryngeal edema and thus could not distinguish reintubation due to airway obstruction from that of other causes.

Characteristics of studies awaiting assessment [ordered by study ID]

Shih

Methods	Adults: Randomized (methods unclear)
Participants	98 patients intubated >24 hours, and met weaning criteria
Interventions	Hydrocortisone begun 24 hours prior to extubation then q 6 hours x 4 doses versus saline placebo
Outcomes	Post extubation stridor, reintubation, cuff leak volume

Shih (Continued)

Notes

Presented in abstract form. Unable to contact author. Unable to verify methodology, blinding, randomisation. Reintubation (4/49 (8.2%) control vs 5/49 (10.25) intervention, $p=0.776$); Post Extubation Stridor (9/49 (18.4%) control vs. 11/49 (22.4%) intervention, $p=0.616$)

DATA AND ANALYSES

Comparison 1. Treated vs. Controls; all

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Re-intubation Rate	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Neonates	2	109	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.01, 1.68]
1.2 Children	2	216	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.01, 19.65]
1.3 Adults	6	1953	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.19, 1.22]
2 Stridor Incidence	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Neonate	2	109	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.07, 2.32]
2.2 Children	2	216	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.28, 0.97]
2.3 Adults	6	1953	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.22, 0.99]

Analysis 1.1. Comparison 1 Treated vs. Controls; all, Outcome 1 Re-intubation Rate.

Analysis 1.2. Comparison 1 Treated vs. Controls; all, Outcome 2 Stridor Incidence.

Comparison 2. Treated vs. Controls, prophylactic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stridor score	1	23	Mean Difference (IV, Random, 95% CI)	-1.10 [-3.66, 1.46]
2 Reintubation rate	1	23	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.17, 1.78]

Analysis 2.1. Comparison 2 Treated vs. Controls, prophylactic, Outcome 1 Stridor score.

Analysis 2.2. Comparison 2 Treated vs. Controls, prophylactic, Outcome 2 Reintubation rate.

Comparison 3. Post hoc subgroup analysis: Adults, Multiple Doses, 12-24 hours prior to extubation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Re-intubation Rate	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Multiple Doses, 12-24 h prior to extubation	3	841	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.07, 0.83]
1.2 Single Dose, within 12 hours of extubation	3	1047	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.52, 1.72]
1.3 Single Dose, 24 hours prior to extubation	1	65	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.05, 1.29]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Stridor Incidence	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Multiple Doses, 12-24 h prior to extubation	3	841	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.11, 0.37]
2.2 Single dose, within 12 h of extubation	3	1047	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.57, 1.30]
2.3 Single dose, 24 h prior to extubation	1	65	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.13, 1.02]

Analysis 3.1. Comparison 3 Post hoc subgroup analysis: Adults, Multiple Doses, 12-24 hours prior to extubation, Outcome 1 Re-intubation Rate.

Analysis 3.2. Comparison 3 Post hoc subgroup analysis: Adults, Multiple Doses, 12-24 hours prior to extubation, Outcome 2 Stridor Incidence.

ADDITIONAL TABLES

Table 1. Corticosteroid regimens

Study	Corticosteroid	Route	Dose	Frequency	Total dose
Anene 1996	Dexamethasone	IV	0.5 mg/kg	6-12h before extubation, then Q6h x 5	3 mg/kg (Max=60mg)
Cheng 2006	Methylprednisolone	IV	40 mg	Q6h x 4 doses for the 24h prior to extubation	160 mg
	Methylprednisolone	IV	40 mg	Once, 24h prior to extubation	40 mg
Couser 1992	Dexamethasone	IV	0.25 mg/kg	4h before extubation, then Q8h x 2	0.75 mg/kg
Darmon 1992	Dexamethasone	IV	8 mg	Once, 1h before extubation	8 mg
Ferrara 1989	Dexamethasone	IV	0.25 mg/kg	Once, 30 min. before extubation	0.25 mg/kg

Table 1. Corticosteroid regimens (Continued)

(Max=10mg)					
Francois 2007	Methylprednisolone	IV	20 mg	Q4h x 4 doses for the 12h prior to extubation	80 mg
Gaussorgues 1987	Methylprednisolone	IV/IM	40 mg	Once, 30min before extubation	80 mg
Harel 1997	Dexamethasone	IV	0.5 mg/kg	6h before extubation, then at 6h,12h after extubation	1.5 mg/kg
Ho 1996	Hydrocortisone	IV	100 mg	Once, 1h before extubation	100 mg
Lee 2007	Dexamethasone	IV	5 mg	Q6h x 4 doses for the 24h prior to extubation	20 mg
Tellez 1991	Dexamethasone	IV	0.5 mg/kg	6-12h before extubation, then Q6h x 5	3 mg/kg (Max=60mg)
(Max=10mg)					

APPENDICES

Appendix 1. Search strategies 2009-2011

CENTRAL search strategy

- #1 MeSH descriptor Intubation, Intratracheal explode all trees
- #2 MeSH descriptor Laryngeal Edema explode all trees
- #3 MeSH descriptor Airway Obstruction explode all trees
- #4 stridor*
- #5 laryn* near/3 edema*
- #6 "airway obstruction"
- #7 intubation
- #8 extubation
- #9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
- #10 MeSH descriptor Adrenal Cortex Hormones explode all trees
- #11 steroid* or corticosteroid* or glucocorticoid*
- #12 prednisone or prednisolone or methylprednisolone or dexamethasone or cortisone or hydrocortisone
- #13 budesonide or fluticasone or ciclesonide or triamcinolone or beclomethasone or flunisolide or mometasone
- #14 (#10 OR #11 OR #12 OR #13)
- #15 (#9 AND #14)

MEDLINE search strategy

1. exp Intubation, Intratracheal/
2. exp Laryngeal Edema/
3. exp Airway Obstruction/
4. Stridor\$.mp.
5. (laryn\$ adj3 edema\$).mp.
6. "airway obstruct\$.mp.
7. intubation.mp.
8. extubation.mp.
9. or/1-8
10. Adrenal Cortex Hormones/
11. (steroid\$ or corticosteroid\$ or glucocorticoid\$).mp.
12. (prednisone or prednisolone or methylprednisolone or dexamethasone or cortisone or hydrocortisone).mp.

13. (budesonide or fluticasone or ciclesonide or triamcinolone or beclomethasone or flunisolide or mometasone).mp.
14. or/10-13
15. 9 and 14

NOTE: This search was combined with an RCT filter as outlined in the [Airways Group methods](#) on the Cochrane Library

EMBASE search strategy

1. exp respiratory tract intubation/
2. exp Larynx Edema/
3. exp Airway Obstruction/
4. (laryng\$ adj3 edema\$).mp.
5. exp Stridor/
6. stridor\$.mp.
7. "airway obstruct\$".mp.
8. intubation.mp.
9. extubation.mp.
10. or/1-9
11. exp Corticosteroid/
12. (steroid\$ or corticosteroid\$ or glucocorticoid\$).mp.
13. (prednisone or prednisolone or methylprednisolone or dexamethasone or cortisone or hydrocortisone).mp.
14. (budesonide or fluticasone or ciclesonide or triamcinolone or beclomethasone or flunisolide or mometasone).mp.
15. or/11-14
16. 10 and 15

NOTE: This search was combined with an RCT filter as outlined in the [Airways Group methods](#) on the Cochrane Library

Appendix 2. Search strategies 2003-2008

CENTRAL search strategy

- #1. INTUBATION INTRATRACHEAL
- #2. LARYNGEAL EDEMA
- #3. AIRWAY OBSTRUCTION
- #4. (intubat* or extubat*)
- #5. stridor*
- #6. (laryng* near edema*)
- #7. (airway* near obstruct*)
- #8. (#1 or #2 or #3 or #4 or #5 or #6 or #7)
- #9. STEROIDS
- #10. ANTI-INFLAMMATORY AGENTS
- #11. ADRENAL CORTEX HORMONES
- #12. (steroid* or corticosteroid* or glucocorticoid*)
- #13. (hydrocort* or beclomet* or dexamet*)
- #14. (anti-inflammat* or (anti next inflammat*))
- #15. (adrenal near cortex near hormone*)
- #16. (#9 or #10 or #11 or #12 or #13 or #14 or #15)
- #17. (#8 and #16)

MEDLINE search strategy

1. exp INTUBATION, INTRATRACHEAL/
2. exp LARYNGEAL EDEMA/
3. exp AIRWAY OBSTRUCTION/
4. (intubat\$ or extubat\$ or stridor\$).mp.
5. (laryngeal adj3 edema\$).mp.
6. (airway\$ adj3 obstruct\$).mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp STEROIDS/
9. exp ANTI-INFLAMMATORY AGENTS/
10. exp ADRENAL CORTEX HORMONES/
11. (hydrocort\$ or beclomet\$ or dexamet\$).mp.
12. (steroid\$ or anti-inflammator\$ or anti inflammator\$).mp.
13. (adrenal adj3 cortex adj3 hormone\$).mp.

14. 8 or 9 or 10 or 11 or 12 or 13
15. 7 and 14

EMBASE search strategy

1. exp RESPIRATORY TRACT INTUBATION/
2. exp LARYNX EDEMA/
3. exp AIRWAY OBSTRUCTION/
4. (laryng\$ adj3 edema\$).mp.
5. (airway\$ adj3 obstruct\$).mp
6. exp STRIDOR/
7. stridor\$.mp.
8. (intubat\$ or extubat\$).mp.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp STEROID/
11. exp ANTIINFLAMMATORY AGENT/
12. exp beclometasone/ or exp beclometasone dipropionate/
13. (Steroid\$ or corticosteroid\$ or glucocorticoid\$).mp.
14. (hydrocort\$ or beclomet\$ or dexamet\$).mp.
15. (anti-inflammator\$ or anti inflammator\$).mp.
16. (adrenal adj3 cortex adj3 hormone\$).mp.
17. 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 9 and 17

Appendix 3. Search methods 1999 to 2003

"Controlled trials were identified by MEDLINE, EMBASE and Cinahl searching using the following strategy:

An initial search was carried out (in the Cochrane Clinical Trials Register, CINAHL, Embase and Medline) using the search terms:

[glucocorticoids OR anti-inflammatory agents OR steroid* OR dexamethasone OR hydrocortisone OR adrenal cortex hormones OR beclomethasone] AND [intubation, intratracheal OR airway obstruction OR laryngeal edema OR stridor OR extubation].

Searches were then made in those records after they had been imported to a database on the following terms: 'placebo* OR trial* OR random* OR double-blind OR double blind OR single-blind OR single blind OR controlled study OR comparative study'."

FEEDBACK

Multiple versus single dose administration, 11 September 2008

Summary

The conclusion of this review does not clarify that administering multiple doses of corticosteroid has a beneficial effect on development of stridor, as compared to a single dose (post-hoc analysis). Analyzing only those trials that used multiple doses of corticosteroid starting at least 12 hours prior to extubation shows that there is a clear beneficial effect on risk of reintubation ((RR 0.20, 95% CI 0.08-0.47, 3 trials with 906 participants, I² = 15.9%), and development of stridor (RR 0.19, 95% CI 0.12-0.30, 3 trials with 906 participants, I² = 47.9%). The respective numbers needed to treat (NNT) are 20 (95% CI 14-50) and 5 (95% CI 4-7). These three trials were in adult patients; two were included in the review while the third was published after the search date in the review (Lee CH, Peng MJ, Wu CL. Dexamethasone to prevent postextubation airway obstruction in adults: a prospective, randomised, double-blind, placebo-controlled study. *Crit Care* 2007;11:R72.). There were no similar trials in neonates and children. Therefore, current evidence shows that multiple doses of parenteral corticosteroids are beneficial when started at least 12 hours prior to extubation. Future paediatric and neonatal trials ought to be conducted with this administration protocol because it may not be appropriate to extrapolate data from adults to children, considering that airway geometry and site of post-extubation upper airway obstruction are different in them.

Reply

Based on this comment, we have performed a substantive update of the review to incorporate all new studies. While two new studies were identified, only one was included in the review (Lee 2007) because the Shih study was published in only abstract form, and the authors could not be contacted. Three trials in adults (Francois 2007, Cheng 2006, Lee 2007) have included intervention arms with multiple doses of corticosteroids, begun a minimum of 12 hours prior to extubation. Both the Cheng 2006 study and the Lee 2007 study have included only a subset of patients (who meet cuff leak volume criteria). In addition, the Cheng 2006 study had three arms, with only 63 patients (of the 128 randomised) receiving multiple doses of corticosteroids or placebo, begun 24 hours prior to extubation.

Moreover, because this subgroup analysis is post-hoc, we felt it important to directly compare the estimates of relative risk derived from multiple dose regimens to those of single dose regimens, rather than simply limiting our analysis to trials which utilized multiple doses.

Using the methods of Altman and Bland, we have performed a test of interaction, and reported ratios of relative risks. It appears that for adults, multiple doses of corticosteroids administered 12-24 hours prior to extubation are more beneficial to prevent post extubation stridor than regimens employing single doses closer to extubation (RRR 0.23; 95% CI 0.11 to 0.48). Multiple dose regimens did not demonstrate a significant advantage over single dose regimens for reintubation, although trends for benefit are seen (RRR 0.26; 95% CI 0.07 to 1.04).

However, in addition to differences in dosing regimens, the three trials demonstrating benefit for corticosteroids had high incidence of post extubation stridor. Two of these studies ([Cheng 2006](#), [Lee 2007](#)) only included patients who met cuff leak volume criteria, and as such may be "higher risk." In fact, these two studies had the highest incidence of post-extubation stridor in the control group (27.5% in [Lee 2007](#), and 30.2% in [Cheng 2006](#)) compared to the other adult studies. For the non-intervention arm of both of these studies (patients who did not meet the cuff leak volume criteria), the incidence of postextubation stridor was quite low (4.9% in [Lee 2007](#), 2.6% in [Cheng 2006](#)). Such information on cuff-leak volume was not available from the [Francois 2007](#) study, although the incidence of post-extubation stridor was 22%, higher than many previously reported adult studies. Therefore, this therapy may show the most benefit for patients who meet certain high risk criteria.

There have been no significant additions to the paediatric or neonatal literature on this topic, and as such generalizing this information to these groups is not warranted. However, we would agree that future trials in children or neonates should explore a multiple-dose strategy, begun at least 12 hours prior to extubation.

Contributors

Joseph Mathew

WHAT'S NEW

Date	Event	Description
4 June 2014	Amended	PLS title amended

HISTORY

Protocol first published: Issue 4, 1998

Review first published: Issue 2, 2000

Date	Event	Description
19 January 2011	New search has been performed	New literature search run. No new studies identified.
23 March 2009	New citation required and conclusions have changed	Findings of review changed with addition of new study and assessment of different dosing strategies in adult studies. Lee 2007 employed multiple doses of dexamethasone begun 24 hours prior to extubation in adults who had a cuff leak volume <110 ml. The authors demonstrated no difference in re-intubation rates between treatment and placebo groups, but a significant reduction in post extubation stridor for the treatment group. When combined with the other studies, the overall results of the meta analysis show non-significant trends towards reduction in reintubation and a significant reduction in stridor for adults, although the studies were very heterogeneous. Post-hoc subgroup analyses suggest that multiple doses started 12-24 hours before extubation in "high risk" adults are beneficial in reducing post extubation stridor, and there is a trend towards reduction in reintubation. There have been no additional studies for neonates or children.
12 March 2009	New search has been performed	Literature searches re-run; new study added to the review. Reply to J Mathew incorporated into the review.

Date	Event	Description
1 December 2008	Feedback has been incorporated	Comment from J Mathew added to the review
22 April 2008	Amended	Converted to new review format.
18 February 2008	New citation required and conclusions have changed	Substantive amendment:

CONTRIBUTIONS OF AUTHORS

BM: Assessed search results, data extraction, entry and analysis, interpretation and write-up.

AR: Assessed search results, data extraction, entry and analysis, interpretation and write-up.

RK: Assessed search results, data extraction, entry and analysis, interpretation and write-up.

DECLARATIONS OF INTEREST

None applicable.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NHS Research and Development, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

*Ventilator Weaning; Adrenal Cortex Hormones [*therapeutic use]; Anti-Inflammatory Agents [therapeutic use]; Dexamethasone [therapeutic use]; Respiration Disorders [*drug therapy] [etiology]; Respiration, Artificial [*adverse effects]; Respiratory Sounds [*drug effects]

MeSH check words

Adult; Child; Female; Humans; Infant, Newborn; Male