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John McCaffrey
Clare Farrell
Paul Whiting
Arina Dan
Sean M. Bagshaw
Anthony P. Delaney

Corticosteroids to prevent extubation failure: a systematic review and meta-analysis

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J. McCaffrey · A. Dan · A. P. Delaney (✉)
Intensive Care Unit, Royal North Shore Hospital, Pacific Highway, St. Leonards, Sydney, NSW 2065, Australia
e-mail: adelaney@med.usyd.edu.au
Tel.: +61-2-99268656
Fax: +61-2-94398418

C. Farrell
Department of Anaesthesia, Royal North Shore Hospital, St. Leonards, Sydney, NSW, Australia

P. Whiting
Department of Anaesthesia and Critical Care, Sheffield Hospital Trust, Sheffield, UK

S. M. Bagshaw
Division of Critical Care Medicine, University of Alberta Hospital, Edmonton, AB, Canada

S. M. Bagshaw
Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada

A. P. Delaney
Northern Clinical School, University of Sydney, St. Leonards, Sydney, NSW, Australia

Abstract *Purpose:* To determine whether corticosteroids reduce the rate of extubation failure in intensive care patients of all age groups. *Methods:* Medline, EMBASE, the Cochrane Central Register of Controlled Trials, bibliographies of relevant articles, selected conference abstracts and unpublished trial databases were searched. Randomised clinical trials (RCTs) evaluating corticosteroids for the purpose of preventing extubation failure in mechanically ventilated, critically ill patients of all ages were included. Two authors independently assessed the validity of included studies and extracted data regarding characteristics of the studies and the rates of reintubation and manifestations of laryngeal oedema. *Results:* Fourteen RCTs including 2,600 participants were included. The mean duration of ventilation prior to attempted extubation ranged from 3 to 21 days. There was a reduction in reintubation with the use of corticosteroids, with a pooled odds ratio (OR) of 0.56 (95% CI; 0.41–0.77, $P < 0.0005$). The effect of corticosteroids tended to be more pronounced in studies when used at least 12 h prior to attempted extubation (OR 0.41, 95% CI; 0.26–0.64). The results were consistent across neonatal, paediatric and adult populations. There was also a reduction in laryngeal oedema in participants receiving corticosteroids, with a pooled OR of 0.36 (95% CI 0.27–0.49, $P < 0.0005$). *Conclusions:* Corticosteroids reduce laryngeal oedema and importantly reduce the incidence of extubation failure in critically ill patients of all ages.

Keywords Mechanical ventilation · Weaning · Peri-operative care · Artifical airways · Complications

Introduction

Extubation failure, defined as the need for reintubation shortly after removal of an endotracheal tube, is a significant problem in critical care. Extubation failure is associated with an increased duration of mechanical ventilation, higher risk for nosocomial pneumonia, prolonged intensive care and hospital length of stay [1–3] and is independently associated with increased mortality [1–4]. While there are numerous causes for extubation failure [5], laryngeal oedema, a common complication of prolonged intubation [6, 7], either

causes or contributes to extubation failure in many cases [2, 8].

Corticosteroids have been investigated as a measure to alleviate laryngeal oedema and therefore reduce the rate of extubation failure [9]. Theoretically, corticosteroids can reduce the inflammatory response and decrease oedema [10]. Indeed, early randomised studies have shown decreases in subjective manifestations of laryngeal oedema when corticosteroids were used prior to extubation [11–14]. However, no studies have been adequately powered to determine whether the use of corticosteroids influence more clinically important outcome measures, in particular rates of extubation failure.

Therefore, we performed a systematic review and meta-analysis to investigate whether corticosteroids reduce the rate of extubation failure in critically ill patients of all ages.

Methods

Search strategy

Two authors independently conducted an electronic search of the MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials databases. Search terms were individualised for each database. Search terms for corticosteroids (steroids OR glucocorticoids OR corticosteroids) were combined with terms for "extubation" and with sensitive RCT filters [15, 16]. All databases were searched from inception until 22 June 2008. The electronic search strategies are available in Appendix 1. The search was limited to studies conducted in humans and no language restriction was placed on the search. We also searched conference abstracts from American Thoracic Society (2005–2008), the American College of Chest Physicians (2005–2007) and the European Society for Intensive Care Medicine (2005–2007), as well as the meta-register of controlled trials, including the medical editors' trials amnesty register [17], along with the bibliographies of included studies and relevant review articles [18].

Inclusion criteria

Studies were considered eligible for inclusion if they reported a prospective randomised clinical trial that compared any corticosteroid with placebo or standard care, given to intubated patients in intensive care, for the purpose of reducing laryngeal oedema and preventing extubation failure. Two authors independently assessed each potentially eligible study for inclusion. Disagreement regarding the inclusion of studies was resolved by discussion with referral to a third reviewer if required.

Data abstraction

Two authors independently abstracted data from all reports. Data were abstracted regarding the population of participants included in the studies, regimen of corticosteroid used, duration of corticosteroid treatment and the duration of ventilation prior to attempts at extubation. We recorded the rates of reintubation from any cause. We also recorded the rates of manifestation of laryngeal oedema, such as stridor; however, this was recorded in the included studies. When available, we recorded data regarding mortality, ICU and hospital length of stay, total duration of ventilation, as well as rates of hyperglycaemia and infection.

Validity assessment

All included studies were assessed for validity by two authors, with disputes resolved by discussion. A component approach was utilised [19]. Each report was assessed for the adequacy of allocation concealment, blinding and the performance of an intention-to-treat analysis. Studies were considered to have adequate blinding when the control group received a placebo, rendering the participants, the health care workers and the outcome assessors blinded to treatment allocation. We also assessed whether specific criteria were used to define that participants were ready for extubation, and the need for re-intubation and whether a cuff-leak test was used prior to attempts at extubation [20].

Quantitative synthesis

Agreement on the inclusion of studies was assessed using the kappa (κ) statistic. The potential for publication bias was assessed by visual inspection of the funnel plot and the statistical test described by Egger [21]. Statistical heterogeneity was assessed by the χ^2 statistic and the I^2 statistic, with an I^2 value of >50% indicating at least moderate heterogeneity [22]. The rates of reintubation were pooled using the fixed-effect method of Mantel and Haenszel to produce a pooled odds ratio (OR) [23, 24]. Estimates of the number needed to treat (NNT) were obtained by applying the pooled estimate of the OR to the pooled baseline event rate. Sensitivity analysis was performed using a random effects model. Cumulative doses of corticosteroid were calculated as mg equivalents of dexamethasone; 1 mg dexamethasone = 5 mg prednisolone, = 5 mg methylprednisolone, = 25 mg hydrocortisone. To explore possible sources of heterogeneity, studies conducted in neonatal, paediatric and adult populations were pooled separately, and studies that used the corticosteroid for less than 12 h were pooled separately from those that gave at least 12 h of treatment. To test for between-group

heterogeneity, differences between subgroups were assessed using meta-regression to examine for an interaction between subgroups and overall treatment effect. All analyses were conducted using STATA 10.0 (Statacorp, College Station, Tx).

Results

The search retrieved a total of 370 references. After application of the inclusion criteria, 14 studies, including a total of 2,600 participants, were included in this review [11–14, 25–33]. The flow of studies and reasons for exclusion are shown in Fig. 1. Agreement between the two reviewers regarding the inclusion of studies was reached in 45/46 cases ($\kappa = 0.95$).

The characteristics of the included studies are shown in Table 1. There were three studies of neonates, four studies in paediatric populations and, seven in adults. The results of the validity assessment are shown in Table 2. Two studies included participants with known laryngeal oedema [13, 33]; the remaining studies included participants at high risk for laryngeal oedema due to prolonged duration of intubation. A range of different types and doses corticosteroids was used in the studies in adult populations.

A total of 13 of the 14 studies, including 2,541 participants, reported at least one episode of reintubation [11–14, 25–27, 29–33] (Fig. 2). One study in neonates [28] assessed for reintubation; however, there were no episodes of reintubation in either the intervention or control groups. There was no suggestion of bias on inspection of the funnel plot (see Appendix 2), and this was confirmed by the quantitative analysis (Egger's statistic $= -0.74$, $P = 0.31$). There was no evidence of statistical heterogeneity (χ^2 $P = 0.08$), and the $I^2 = 38\%$. The estimate of the pooled OR for reintubation was 0.56 (95%CI 0.41–0.77, $P < 0.0005$), indicating a significant reduction in the rate of reintubation with the use of corticosteroids. The pooled estimate of the baseline rate of reintubation was 8.2%. Utilising this baseline event rate, the estimate of the NNT to prevent one episode of reintubation was 29, this equates to 35 reintubations prevented per 1,000 extubations (95%CI 18–47).

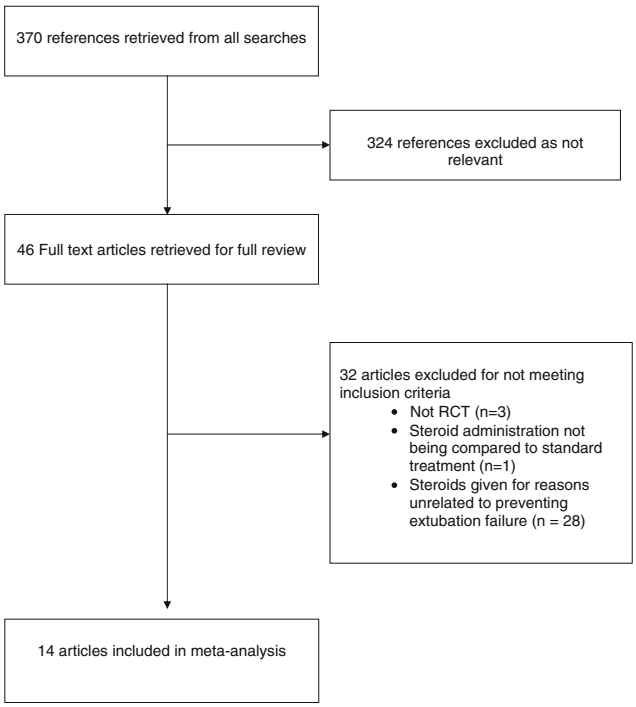

Fig. 1 QUOROM profile showing flow of studies included in meta-analysis

Sensitivity and subgroup analysis

When the results were pooled using a random effects model, the estimate of the pooled OR was 0.54 (95%CI 0.33–0.90, $P = 0.018$). The results of sensitivity analysis based on predefined validity appraisal and trial level covariates are shown in Table 3. There tended to be a greater effect of corticosteroids and less heterogeneity in studies with duration of therapy of greater than 12 h prior to extubation and in studies with adequate allocation concealment, although the tests for between group heterogeneity were not statistically significant.

Effect of corticosteroids on manifestations of laryngeal oedema

There were nine studies that reported subjective manifestations of laryngeal oedema. There was a significant degree of heterogeneity, with the χ^2 <0.005 and the $I^2 = 71\%$. There was a reduction in the subjective manifestations of laryngeal oedema with the estimate of the pooled OR of 0.36 (95% CI 0.27–0.49, $P < 0.0005$).

Effect of corticosteroids on other outcomes

The effect of corticosteroids on the other outcomes was infrequently reported, as were potential adverse effects of corticosteroids. A summary of these outcomes is shown in Table 4.

Overall strength and quality of the evidence

The overall strength and quality of the evidence is summarised according to the GRADE recommendations [34] in Table 5.

Table 1 Characteristics of the included studies

Author	Year	Population	Mean age	Mean duration of ventilation	Corticosteroid	Dose	Corticosteroid regimen	Cumulative corticosteroid dose (equivalent mg of dexamethasone)
Neonatal								
Ferrara [28]	1989	Neonates intubated >48 h	33.5 weeks[a]	6 days	Dexamethasone	0.25 mg/kg	30 min prior	0.25 mg/kg
Couser [26]	1992	Neonates at high risk for airway edema	21.2 days	20 days	Dexamethasone	0.25 mg/kg	4 h prior then Q8 h × 2	0.75 mg/kg
Courtney [36]	1992	Neonates intubated for >3 days	33.3 weeks[a]	10 days	Dexamethasone	0.5 mg/kg	25 h prior then Q8 h × 2	1.5 mg/kg
Paediatric								
Tellez [14]	1991	General PICU	2.5 years	3.3 days	Dexamethasone	0.5 mg/kg (max 10 mg)	6–12 h prior then Q6H × 5	3 mg/kg
Tibballs [33]	1992	Children intubated for croup	19 months	3.5 days	Prednisolone	1 mg/kg	12 h post intubation then Q12 h until 24 h post extubation	Variable
Annene [25]	1996	General PICU	3.5 months	Median 3.4 days	Dexamethasone	0.5 mg/kg (max 10 mg)	6–12 h prior then Q6H × 5	3 mg/kg
Harel [13]	1997	Children with one previous failed extubation	34.6 months	21 days	Dexamethasone	0.5 mg/kg (max 15 mg)	6 h prior then Q6H × 2	1.5 mg/kg
Adult								
Gassorgues [29]	1987	Adults	54 years	14 days	Methylprednisolone	80 mg	30 min prior	16 mg
Darmon [27]	1992	Medical/surgical	52.9 years	1) <36 h 2) 10 days[b]	Dexamethasone	8 mg	1 h prior	8 mg
Ho [30]	1996	Medical/surgical	62.5 years	5.3 days	Hydrocortisone	100 mg	1 h prior	4 mg
Cheng [11]	2006	Medical/surgical	66.1 years	6.9 days	Methylprednisolone	40 mg	1. 40 mg 24 h prior 2. 40 mg Q6H prior ×4	1. 8 mg 2. 32 mg
Francois [12]	2007	Medical/surgical/ trauma	66 years	Median 6 days	Methylprednisolone	20 mg	12 h prior then Q4H × 3	12 mg
Lee [31]	2007	Medical/surgical	72.6 years	6.8 days	Dexamethasone	5 mg	24 h prior Q6H × 4 then extubated after another 24 h	40 mg
Shih [32]	2007	Medical/surgical	NR	NR	Hydrocortisone	NR	24 h prior then Q6 h × 3	NA

PICU Paediatric Intensive care Unit, *NR* not reported

[a] Mean gestational age

[b] The study by Darmon et al. [27] stratified patients into two groups, those intubated for <36 h and those intubated for >36 h; those in the latter strata had a mean duration of ventilation of 10 days

Table 2 Validity appraisal of the included studies

Author	Allocation concealment	ITT	Blinding	Cuff-leak test	Criteria for extubation	Criteria for reintubation
Gassorgues [29]	Unclear	No	No	No	No	No
Ferrara [28]	Unclear	No	Yes	No	Yes	No
Tellez [14]	Unclear	Yes	Yes	No	No	No
Couser [26]	Unclear	Yes	Yes	No	Yes	Yes
Courtney [36]	Yes	No	Yes	No	No	No
Darmon [27]	Yes	No	Yes	No	No	No
Tibballs [33]	Yes	No	Yes	Yes	Yes	Yes
Annene [25]	Yes	No	Yes	Yes	Yes	Yes
Ho [30]	Yes	Yes	Yes	No	No	No
Harel [13]	Yes	Yes	Yes	Yes	Yes	No
Cheng [11]	Yes	Yes	Yes	Yes	Yes	Yes
Francois [12]	Yes	Yes	Yes	No	No	No
Lee [31]	Yes	No	Yes	Yes	Yes	Yes
Shih [32]	Unclear	Yes	No	Yes	Yes	No

ITT Intention to treat analysis

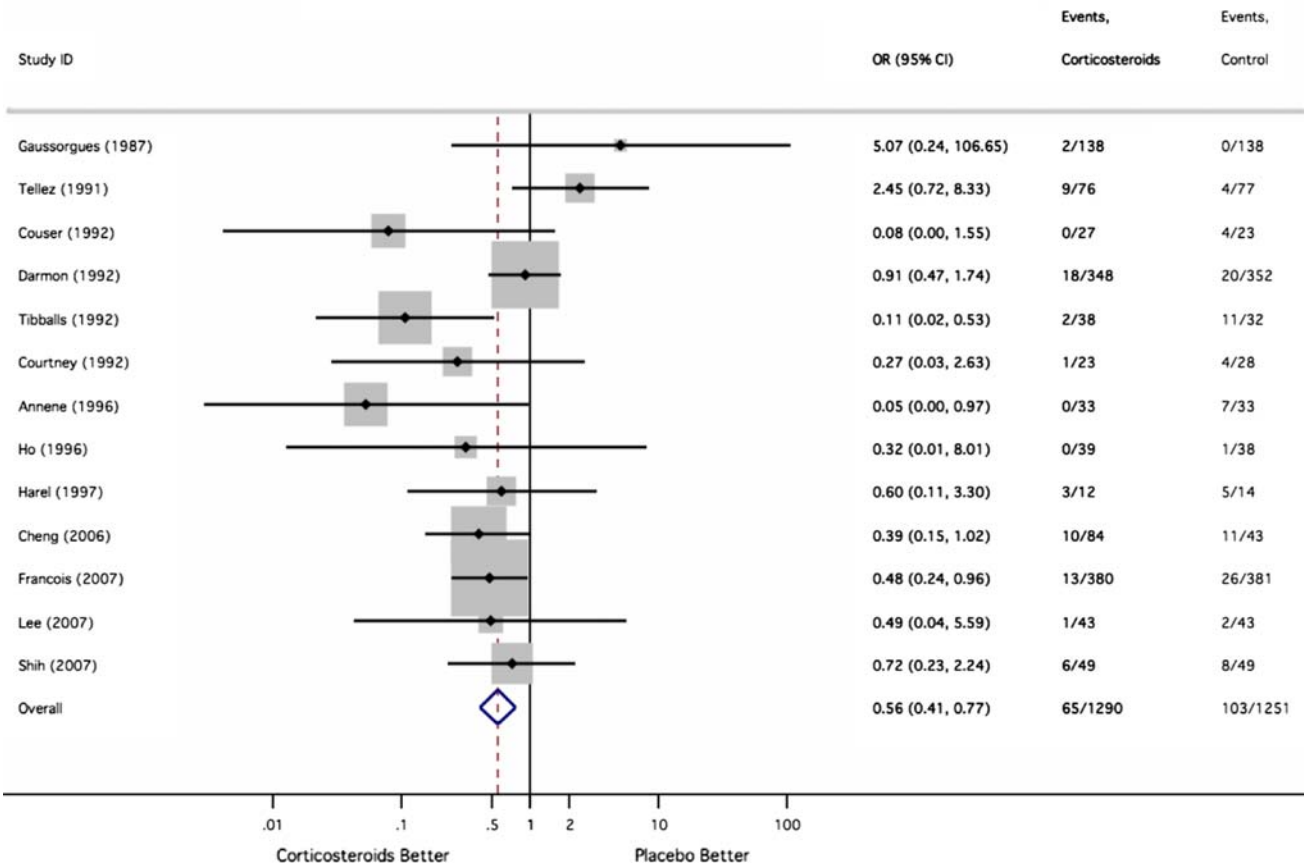

Fig. 2 The effect of corticosteroids on reintubation

Discussion

We conducted a systematic review and meta-analysis to investigate the effect of corticosteroids on the rates of reintubation in critically ill patients of all ages. We found that corticosteroids significantly reduce the rate of reintubation for patients in intensive care undergoing mechanical ventilation. These results are consistent across neonatal, paediatric and adult populations, and robust to the model used to pool the data. The effect of steroids

Table 3 Summary of the estimated odds ratios for the trial quality and trial level covariates

Subgroup		Number of studies	Estimate of OR	95% CI	I^2(%)	Test for between group heterogeneity
Allocation concealment	Unclear	4	1.04	0.52–2.10	52	$P = 0.12$
	Yes	9	0.47	0.32–0.68	19	
Intention to treat analysis	No	7	0.56	0.35–0.88	47	$P = 0.77$
	Yes	6	0.56	0.36–0.88	38	
Population	Neonatal	2	0.16	0.03–0.94	0	$P = 0.59$
	Paediatric	4	0.48	0.25–0.93	76	
	Adult	7	0.64	0.44–0.93	0	
Duration of treatment[a]	<12 h	7	0.79	0.49–1.26	43	$P = 0.09$
	>12 h	6	0.41	0.26–0.64	0	

[a] Duration of treatment refers to the duration of steroid therapy prior to attempts at extubation

Table 4 Mortality and adverse outcomes potentially attributable to corticosteroid use

Outcome		Study	Control	Steroids
Mortality		Francois [12]	1/380	1/381
		Darmon [27]	0/352	0/348
Adverse effects of steroids	Sepsis	Courtney [36]	1/28	1/23
		Francois [12]	0/380	1/381
	Hyperglycaemia	Courtney [36]	Mean serum glucose 87 mg/dl	Mean serum glucose 101 mg/dl
	Glycosuria	Couser [26]	0/23	7/27

may be more pronounced when the treatment is commenced at least 12 h prior to extubation. We also found that the use of corticosteroids was associated with a significant reduction in clinically evident manifestations of laryngeal oedema such as stridor.

There are a number of strengths to our systematic review and meta-analysis. By following current standards for the conduct and reporting of meta-analyses [35], systematic bias should be minimised. The thoroughness of the search has identified unpublished [32] and previously unrecognised studies [33, 36]. This review is also strengthened by the choice of a robust, objective, clinically important primary outcome. There are also some limitations of this study. In common with all meta-analyses, the strength of the conclusions that can be drawn relies on the validity of the studies included in the review. While the majority of the studies described methods to maintain allocation concealment and blinding, only one study fulfilled all of the validity criteria in this review, thus limiting the strength of the conclusions. The populations included in the studies covered by this review were mechanically ventilated for prolonged periods; therefore, the results of this review should not be extrapolated to patients who require only a short duration of intubation.

The results of this meta-analysis are consistent with those of the largest randomised trial in this area [12], a finding that adds credence to the results. The finding that corticosteroids reduce the rates of reintubation and stridor in a number of populations in different intensive care settings, even allowing for different corticosteroid regimens, adds to the generalisability of the findings. A recent review published in the Cochrane Database of Systematic Reviews [18], that utilised reintubation due to severe stridor and airway obstruction as the primary outcome, did not find a significant reduction in rates of reintubation, although there were non-significant trends supporting the use of corticosteroids to prevent reintubation and the incidence of stridor. Compared to this current review, the Cochrane review contains fewer studies and fewer events, therefore reducing its power to detect a clinically important treatment effect. The primary outcome used in the Cochrane review, reintubation attributable to severe stridor and airway obstruction, is also prone to ascertainment bias. It may be difficult to determine whether the laryngeal oedema is the primary cause for reintubation, or a contributing factor to the requirement for reintubation. We contend that all-cause reintubation is more clinically important and more robust, and offers greater value to clinicians and patients alike. Previous reviews have examined the effect of corticosteroids on the prevention of reintubation in adult populations [37]. This study extends these results to paediatric and neonatal populations.

The reduction in the rate of reintubation found in this analysis was accompanied by a significant reduction in the subjective manifestations of laryngeal oedema, such as stridor. This suggests that a reduction in laryngeal oedema associated with the use of corticosteroids is responsible for at least part of the reduction in the rate of

Table 5 GRADE table summarising the overall quality of evidence for the use of corticosteroids to prevent extubation failure

Quality assessment					Summary of findings					
					No. of patients		Effect			
No. of Studies	Design	Quality	Consistency	Directness	Steroids	Placebo	Relative (95% CI)	Absolute (NNT)	Quality	Importance
Reintubation										
13	RCTs	No serious limitations	Some inconsistency with regards to dose and duration of therapy	Direct evidence of effectiveness	1290	1251	OR = 0.56 (0.41–0.77)	35/1,000	High	Critical
Subjective manifestation of laryngeal oedema										
9	RCTs	No serious limitations	Significant heterogeneity	Surrogate outcome measure	1174	1134	OR = 0.36 (0.26–0.49)	84/1,000	High	Important

No. Number, *CI* confidence interval, *RCT* randomised controlled trial, *NNT* number needed to treat (this refers to the number of events prevented per 1,000 extubations), *OR* odds ratio

reintubation. There are also a number of other possible mechanisms by which corticosteroids may reduce the rate of extubation failure. Corticosteroids have been shown to have a beneficial effect on patients with pneumonia [38] and have also been shown to improve the rate of ventilator weaning in patients with relative adrenal insufficiency [39]. It is also possible that corticosteroids may produce their action by influencing other factors that are known to be associated with extubation failure [40]. Future studies need to consider incorporating these factors into their study designs, to further elucidate other possible mechanisms of action of corticosteroids with respect to the prevention of reintubation.

For clinicians caring for intubated critically ill patients, the results of this systematic review and meta-analysis offer some guidance. For patients similar to those included in the studies in this review, i.e. those who have been intubated for more than 3 days, who are at significant risk for reintubation, or who are not already receiving corticosteroids, corticosteroid therapy should be considered at least 12 h prior to extubation. In neonatal and paediatric populations, dexamethasone at doses of 0.25–0.5 mg/kg (or equivalent) would be appropriate. In adult populations, the type and dose of corticosteroid used in the studies included in this review were more varied. Given this variation, it would be prudent to follow the dosing given in the largest high-quality RCT [12].

Further research in this area is still required. In particular, as the overall rate of reintubation is low, further studies aimed at defining a population most likely to benefit from corticosteroids in preventing reintubation are warranted [41]. Patients with difficult or traumatic intubations or who have required multiple intubations may constitute high-risk groups who are more likely to benefit from this therapy. Future studies should consider utilising the cuff-leak test to define a group of patients at greater risk of extubation failure secondary to laryngeal oedema. It should be noted that, while a longer course of therapy appeared to confer additional benefit, patients who received a longer course of treatment also received a higher cumulative dose of corticosteroid. Defining an optimal regimen of therapy with regards to the type of corticosteroid used, dose and timing warrants further study. Future studies should report other important outcomes such as total duration of ventilation, intensive care and hospital length of stay and all-cause mortality.

This systematic review and meta-analysis demonstrated that corticosteroids, when used in patients in intensive care undergoing prolonged endotracheal intubation, significantly reduce the rate of extubation failure and also reduce the manifestation of laryngeal oedema. As extubation failure is associated with significant morbidity and mortality, clinicians should consider the use corticosteroids in patients at high risk of extubation failure.

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Conflict of interest statement All authors declare that they have no conflict of interest including specific financial interests and relationships and affiliations relevant to the subject of this manuscript.

Appendix 1: search strategies

PUBMED

((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) AND (extubation) AND ((steroids) OR (glucocorticoids)).

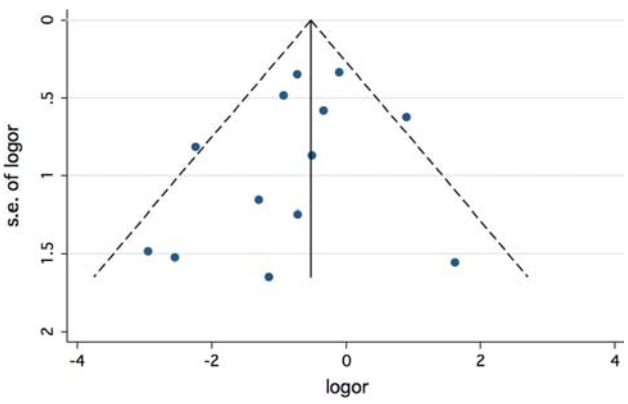
CENTRAL

1 glucocorticoids.mp. [mp = title, original title, abstract, mesh headings, heading words, keyword] (2582)
2 steroids.mp. [mp = title, original title, abstract, mesh headings, heading words, keyword] (3372)
3 corticosteroids.mp. [mp = title, original title, abstract, mesh headings, heading words, keyword] (3555)
4 1 or 2 or 3 (8285)
5 extubation.mp. [mp = title, original title, abstract, mesh headings, heading words, keyword] (1385)
6 4 and 5 (26)

EMBASE

1 RANDOMIZED CONTROLLED TRIAL.pt. (0)
2 CONTROLLED CLINICAL TRIAL.pt. (0)
3 RANDOMIZED CONTROLLED TRIALS.sh. (0)
4 RANDOM ALLOCATION.sh. (0)
5 DOUBLE BLIND METHOD.sh. (0)
6 SINGLE BLIND METHOD.sh. (0)
7 1 or 2 or 3 or 4 or 5 or 6 (0)
8 (ANIMALS not HUMAN).sh. (0)
9 7 not 8 (0)
10 CLINICAL TRIAL.pt. (0)
11 exp CLINICAL TRIALS/ (493,448)
12 (clin$ adj25 trial$).ti,ab. (131,765)
13 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (90,501)\
14 PLACEBOS.sh. (0)
15 placebo$.ti,ab. (102,691)
16 random$.ti,ab. (356,558)
17 RESEARCH DESIGN.sh. (0)
18 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (782,546)
19 18 not 8 (782,546)
20 19 not 9 (782,546)
21 COMPARATIVE STUDY.sh. (101,880)
22 exp EVALUATION STUDIES/ (50,880)
23 FOLLOW UP STUDIES.sh. (0)
24 PROSPECTIVE STUDIES.sh. (0)
25 (control$ or prospectiv$ or volunteer$).ti,ab. (1,611,246)
26 21 or 22 or 23 or 24 or 25 (1,722,125)
27 26 not 8 (1,722,125)
28 27 not (9 or 20) (1,414,085)
29 9 or 20 or 28 (2,196,631)
30 exp CORTICOSTEROD/ or corticosteroids.mp. or exp CORTICOSTEROID THERAPY/ (361,933)
31 exp CORTICOSTEROID/ or corticosteroids.mp. or exp CORTICOSTEROID THERAPY/ (361,933)
32 glucocorticoid.mp. or exp GLUCOCORTICOID/ (286,723)
33 steroids.mp. or exp Steroid/ (567,141)
34 30 or 31 or 32 or 33 (576,495)
35 extubation.mp. or EXTUBATION/ (5,588)
36 29 and 34 and 35 (228)
37 from 36 keep 1–199 (199)
38 from 36 keep 200–228 (29)

Appendix 2: corticosteroids to prevent reintubation. Funnel plot with pseudo 95% confidence limits



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