CHEST

Prophylactic Corticosteroids for Prevention of Postextubation Stridor and Reintubation in Adults

A Systematic Review and Meta-analysis

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BACKGROUND: Corticosteroid administration before elective extubation has been used to prevent postextubation stridor and reintubation. We updated a systematic review to identify which patients would benefit from prophylactic corticosteroid administration before elective extubation.

METHODS: We searched PubMed, EMBASE, the Wanfang Database, the China Academic Journal Network Publishing Database, and the Cochrane Central Register of Controlled Trials for eligible trials from inception through February 29, 2016. All randomized controlled trials were eligible if they examined the efficacy and safety of systemic corticosteroids given prior to elective extubation in mechanically ventilated adults. We pooled data using the DerSimonian and Laird random-effects model.

RESULTS: We identified 11 trials involving 2,472 participants for analysis. Use of prophylactic corticosteroids was associated with a reduced incidence of postextubation airway events (risk ratio [RR], 0.43; 95% CI, 0.29-0.66) and reintubation (RR, 0.42; 95% CI, 0.25-0.71) compared with placebo or no treatment. This association was prominent in participants at high risk for the development of postextubation airway complications, defined using the cuff-leak test, with a reduced incidence of postextubation airway events (RR, 0.34; 95% CI, 0.24-0.48) and reintubation (RR, 0.35; 95% CI, 0.20-0.64). This association was not found in trials with unselected participants. Adverse events were rare.

CONCLUSIONS: Administration of prophylactic corticosteroids before elective extubation was associated with significant reductions in the incidence of postextubation airway events and reintubation, with few adverse events. It is reasonable to select patients at high risk for airway obstruction who may benefit from prophylactic corticosteroids.

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KEY WORDS: airway obstruction; corticosteroids; cuff-leak test; elective extubation; extubation; extubation failure; meta-analysis; reintubation; stridor; systematic review

ABBREVIATIONS: RR = risk ratio

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Extubation failure is defined as the inability to tolerate removal of an endotracheal tube.[1] Laryngeal edema following extubation is one cause of extubation failure and potentially leads to reintubation. Postextubation stridor is an important clinical sign of laryngeal edema. Reintubation takes place in 10% to 100% of patients with postextubation stridor.[2] Given that extubation failure and reintubation are associated with a prolonged duration of mechanical ventilation and ICU stay, as well as increased morbidity, mortality, and costs,[2-8] it is essential to prevent airway obstruction following extubation.[5] Corticosteroids reduce inflammatory laryngeal edema caused by direct mucosal injury. In guidelines for the management of tracheal extubation, their prophylactic use is indicated in patients with airway compromise.[9]

Four systematic reviews on the use of prophylactic corticosteroids before elective extubation were published in 2008 and 2009; they suggested the potential of corticosteroids to prevent postextubation stridor and reintubation.[10-13] One review, however, also raised the question as to which patients would benefit from prophylactic corticosteroids and whether identifying patients at high risk for the development of airway obstruction is necessary.[12] Although some new trials have been published in the past 8 years, no new systematic reviews have provided an answer to this question.

We conducted an updated systematic review and meta-analysis to assess the efficacy of prophylactic corticosteroids to prevent postextubation stridor and subsequent reintubation in intubated and mechanically ventilated adults. We examined the necessity of selecting patients who would benefit from prophylactic corticosteroids.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for reporting systematic reviews.[14] Our protocol was registered at PROSPERO (CRD42016025997). We searched PubMed, EMBASE, the Wanfang Database, the China Academic Journal Network Publishing Database, and the Cochrane Central Register of Controlled Trials. We also reviewed the references of retrieved articles for potentially eligible trials and searched Google Scholar and Web of Science for studies that cited these trials. Our search followed the strategy outlined in the previous Cochrane systematic review on this topic (e-Table 1).[12] We imposed no language restrictions, and our search was updated on February 29, 2016.

We included parallel randomized controlled trials that examined the efficacy and safety of systemic corticosteroid administration given prior to elective extubation in mechanically ventilated adults. We excluded trials that administered corticosteroids after extubation and those that focused on nebulized corticosteroids. The comparators were placebo or usual care.

At least two of the three authors (A. K., N. U., R. S.) independently reviewed the list of articles obtained by the search criteria and selected potentially relevant articles. The same two authors extracted the data independently. In each study, the following information was extracted: (1) patient demographics (age and sex), (2) study characteristics (study sites), (3) information on interventions (dose and timing of corticosteroids given to the intervention group vs the comparator group), and (4) outcomes of interest. Any discrepancy was resolved through consensus. We also assessed the risk of bias using the Cochrane risk of bias assessment tool,[15] and any disagreements were resolved through consensus.

Our primary outcomes were (1) postextubation airway events (defined as airway obstruction, laryngeal edema, or stridor that occurred following extubation), (2) reintubation, and (3) adverse effects among groups. We preferentially pooled the frequency of reintubation due to postextubation airway events. When trials had more than one intervention arm, we pooled the data into a single group, as recommended by the Cochrane Collaboration.[15] Dichotomous outcomes were combined using risk ratios (RRs). When trials had zero events in either arm, continuity corrections were applied with the addition of 0.5 to each cell of 2 × 2 tables from the trial.[16] We attempted to ask the original authors for necessary information if an e-mail address was provided in the abstracts or full texts. The authors were considered unresponsive when three e-mails were sent and no reply was obtained. We pooled data using the DerSimonian and Laird random-effects model.[17] Statistical heterogeneity was assessed visually with Galbraith plots[18] and statistically with I^2 and Q statistics.[19] We tested small study effect or publication bias using Egger's method.[20]

We conducted subgroup analysis by considering the risk of postextubation airway obstruction (unselected participants or those considered at high risk estimated with the cuff-leak test). We also performed meta-regression by sex, cumulative dose of corticosteroids equivalent to hydrocortisone, number of doses, timing of first corticosteroid administration before extubation, and duration of mechanical ventilation as potential covariates. Corticosteroid doses were standardized to hydrocortisone equivalents, according to the relative anti-inflammatory potency of each drug—25 mg hydrocortisone being equivalent to 5 mg methylprednisolone, 4 mg prednisolone, or 1 mg dexamethasone. We also conducted sensitivity analysis by excluding (1) trials of high or unclear risk of bias in sequence generation, allocation concealment, and blinding of outcome assessors and (2) trials in which it was unclear whether the incidence of reintubation was due to postextubation airway events. The threshold of statistical significance was set at $P < .05$. All analyses were conducted using Stata SE, version 11.2 (Stata Corp.). Institutional review board approval was unnecessary.

Results

Overview of Included Trials

The search produced 3,741 articles (Fig 1). After application of our inclusion and exclusion criteria, we considered 11 parallel randomized controlled trials that examined the efficacy of systemic corticosteroids given prior to elective extubation in mechanically ventilated adults.[21-31] A total of 2,472 mechanically ventilated adult patients were included in the analysis (Table 1). The mean age of participants was 61.9 years (range, 39.6-74 years), and 47% of these subjects were women. The median sample size was 128 (range, 71-700). Two trials were conducted in medical ICUs,[29,31] one in a surgical ICU,[22] and eight in mixed (medical and surgical) ICUs.[21,23-28,30] Five trials used dexamethasone,[21,22,25,29,31] four trials used methylprednisolone,[24,27,28,30] and two trials used hydrocortisone.[23,26] Four trials used a single steroid dose,[24-26,30] and four trials used four doses.[22,23,28,29] One trial compared the use of one or two administrations of the same dose,[21] one trial compared one vs four administrations of the same dose,[27] and one trial compared four administrations of different doses.[31] Seven trials explicitly showed the frequency of reintubation due to postextubation airway events.[23-28,30] All trials except one[23] were published in full texts. Ten trials were reported in English[22-31] and one in Chinese.[21] Six trials were performed in Taiwan,[23,26,27,29-31] three in France,[24,25,28] and one each in China[21] and Pakistan.[22] We attempted to contact four authors from five trials, but only one author from two trials responded.[27,30]

Risk of Bias Assessment

Overall, seven trials (63.6%) had adequate sequence generation and eight (72.7%) had adequate concealed allocation (Table 2). Outcome assessors were judged to be adequately blinded in five trials. Eight studies (72.7%) were deemed to be at low risk of incomplete outcome data, and only two (18.2%) were registered trials and thus free of selective reporting. Two trials were assessed as having a low overall risk of bias.

Postextubation Airway Events

Prophylactic corticosteroids were associated with a reduced incidence of postextubation airway events when compared with placebo or no treatment (RR, 0.43; 95% CI, 0.29-0.66; $Q = 27.17$; $df = 10$; $I^2 = 63.2\%$; $P = .002$) (Fig 2). Subgroup analysis revealed that although the use of prophylactic corticosteroids was associated with a reduced incidence of postextubation airway events (RR, 0.34; 95% CI, 0.24-0.48; $Q = 0.56$; $df = 5$; $I^2 = 0.0\%$; $P = 0.99$) in trials that selected patients at high risk for airway obstruction, this association was not found in trials with unselected participants. Publication bias was not evident ($P = .08$).

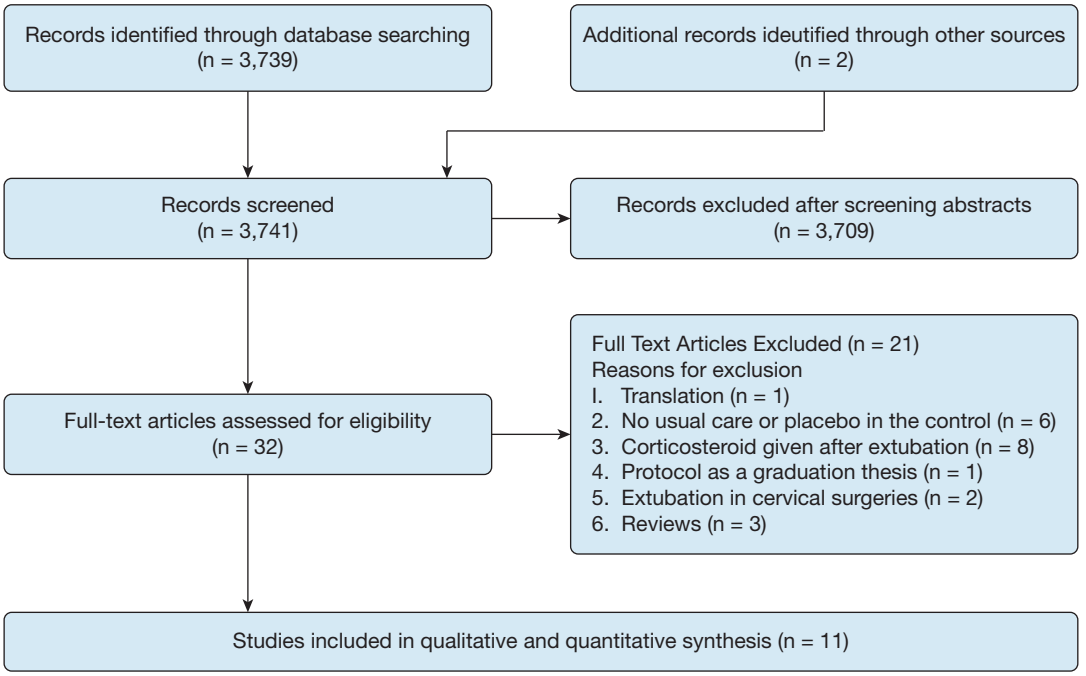

Figure 1 – *Study selection.*

TABLE 1] Characteristics of Included Studies

Study/Year	Location	Type of ICU	Sample Size (% Female)	Age, y	Duration of MV (d)	Corticosteroid Regimen	Cumulative Equivalent Dose of Hydrocortisone (mg)	Cuff-Leak Test Done?	Comparator	Observation Period After Extubation (h)
Gaussorgues et al[24]/ 1987	France	Mixed	276 (34.8)	54	14.5	Methylprednisolone: 40 mg IV and 40 mg IM 30 min before extubation	400	No	NR	48
Darmon et al[25]/ 1992[a]	France	Mixed	700 (42.1)	53.2	10.0	Dexamethasone: 8 mg IV 60 min before extubation	200	No	Placebo	24
Ho et al[26]/ 1996	Taiwan	Mixed	77 (23.4)	62.5	5.4	Hydrocortisone: 100 mg IV 1 h before extubation	100	No	Saline placebo	24
Cheng et al[27]/ 2006	Taiwan	Mixed	128 (61.7)	66.1	6.9	Methylprednisolone: 40 mg IV every 6 h (4 doses); 40 mg IV followed by 3 saline injections every 6 h over 24 h (1 dose), until 1 h before extubation	800 or 200	Yes	Placebo	48
François et al[28]/2007	France	Mixed	761 (36.4)	66	NR	Methylprednisolone: 20 mg IV every 4 h (4 doses), initiated 12 h before extubation and last injection just before extubation	400	No	Saline placebo	24
Lee et al[29]/ 2007	Taiwan	Medical	86 (33.8)	72.6	6.8	Dexamethasone: 5 mg IV every 6 h (4 doses), initiated 24 h before extubation, with the last injection 24 h before extubation	500	Yes	Saline placebo	48
Shih et al[23]/ 2007	Taiwan	Mixed	98 (44.9)	NR	11.3	Hydrocortisone: 4 doses every 6 h, initiated 24 h before extubation	NR	No	Saline placebo	NR
Baloch et al[22]/ 2010	Pakistan	Surgical	100 (44.6)	39.6	3.0	Dexamethasone: 5 mg IV every 6 h (4 doses) over 24 h before extubation	500	Yes	Saline placebo	48
Cheng et al[30]/ 2011	Taiwan	Mixed	71 (77.5)	60.5	5.0	Methylprednisolone: 40 mg IV 4 h before extubation	200	Yes	Saline placebo	48
Yu et al[21]/ 2014	China	Mixed	162 (58.6)	67.0	7.6	Dexamethasone: 5 mg IV at 24 h (1 dose); 5 mg at 24 and 12 h (2 doses) before extubation	125 or 250	Yes	None	NR
Lin et al[31]/ 2016	Taiwan	Medical	138 (78.6)	74.1	7.2	Dexamethasone: 5 mg IV every 6 h (4 doses); 10 mg IV every 6 h (4 doses), with the last injection 24 h before extubation	500 or 1,000	Yes	Saline placebo	48

MV = mechanical ventilation; NR = not reported.
[a]For Darmon 1992 study, the duration of MV was calculated for those intubated for more than 36 h.

TABLE 2] Risk of Bias in Included Studies

Study/Year	Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Source of Bias
Gaussorgues et al[24]/1987	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Darmon et al[25]/1992	Low	Low	Low	Low	Low	Unclear	Low
Ho et al[26]/1996	Low	Low	Low	Unclear	Unclear	Unclear	Low
Cheng et al[27]/2006	Low	Low	Low	Low	Low	Unclear	Low
François et al[28]/2007	Low	Low	Low	Low	Low	Low	Low
Lee et al[29]/2007	Low	Low	Low	Low	Low	Low	Low
Shih et al[23]/2007	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Baloch et al[22]/2010	Unclear	Low	Unclear	Unclear	Low	Unclear	Low
Cheng et al[30]/2011	Low	Low	Low	Low	Low	Unclear	Low
Yu et al[21]/2014	Low	Unclear	Unclear	Unclear	Low	Unclear	Low
Lin et al[31]/2016	Unclear	Low	Low	Unclear	Low	Unclear	Low

Reintubation

Prophylactic corticosteroids were associated with a reduced incidence of reintubation compared with placebo or no treatment (RR, 0.42; 95% CI, 0.25-0.71; $Q = 11.21$; $df = 10$; $I^2 = 10.8\%$; $P = .34$) (Fig 3). Subgroup analysis showed that although prophylactic corticosteroids were associated with a reduced incidence of reintubation (RR, 0.35; 95% CI, 0.20-0.64; $Q = 2.32$; $df = 5$; $I^2 = 0.0\%$; $P = .80$) in trials with participants at high risk for postextubation airway obstruction, this association was not found in trials with unselected participants. Publication bias was not evident ($P = .63$).

Adverse Effects

Six trials involving 1,231 participants screened adverse effects; the most commonly screened was GI bleeding (five trials[21,22,27,29,30]), hyperglycemia (four trials[21,22,27,30]), and infection (five trials[21,22,27,28,30]).

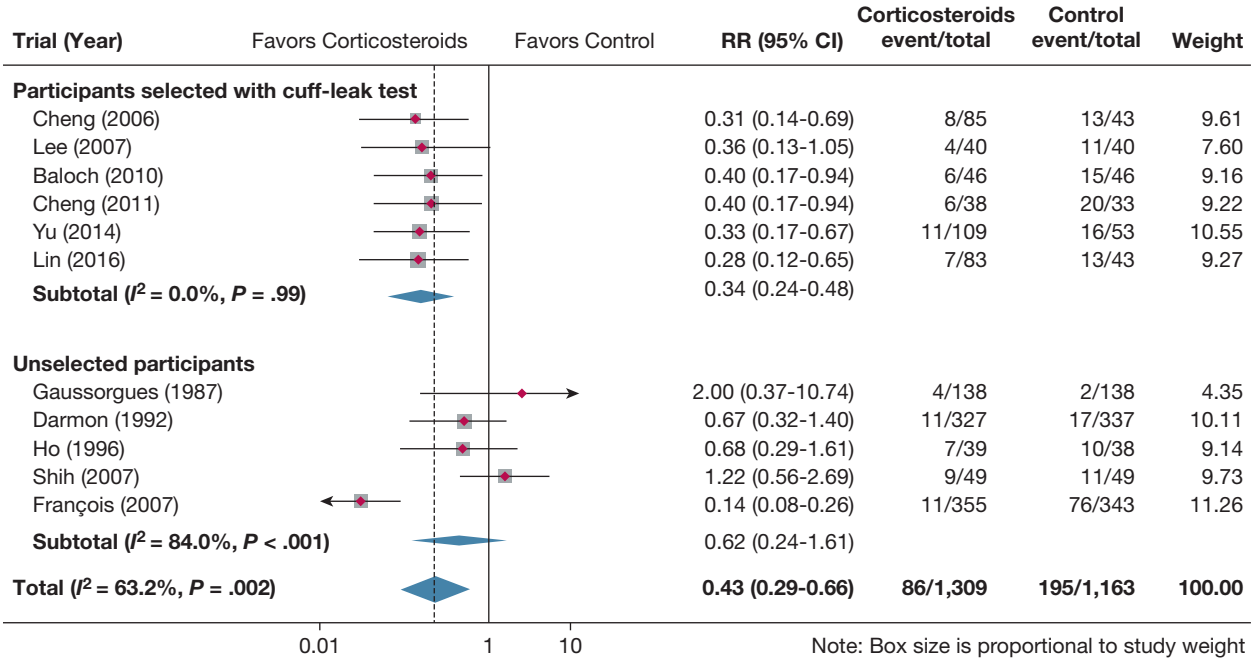

Figure 2 – *Relative risk of postextubation airway events in randomized controlled trials of prophylactic corticosteroids before extubation. RR = risk ratio.*

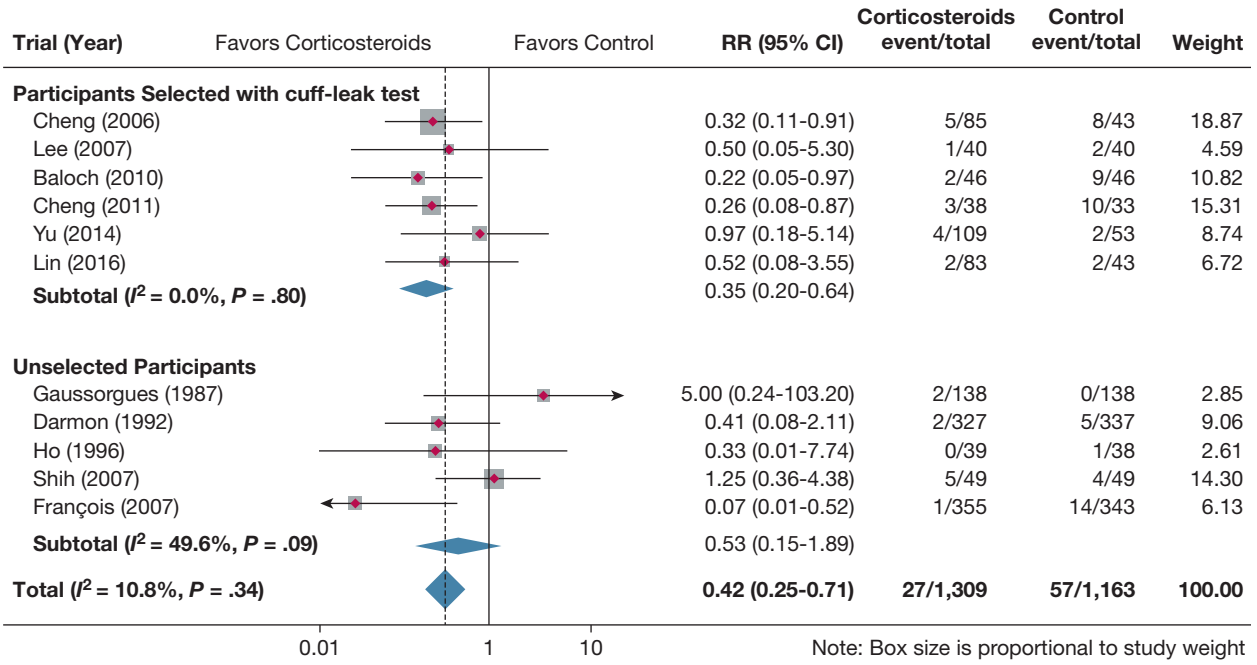

Figure 3 – *Relative risk of reintubation in randomized controlled trials of prophylactic corticosteroids before extubation. See Figure 2 legend for expansion of abbreviations.*

There was no occurrence of GI bleeding or hyperglycemia. Only one of 380 patients who received methylprednisolone experienced infection.[28]

Meta-regression Analysis

We conducted meta-regression analyses on each outcome to examine the association between the effect size and some covariates. As the duration of mechanical ventilation increased, the effect size for postextubation airway events (regression coefficient, 0.13; 95% CI, –0.02 to 0.28; $P = .07$) and reintubation (regression coefficient, 0.25; 95% CI, 0.02-0.48; $P = .04$) tended to decrease. Patients thus tended to benefit from prophylactic corticosteroids to prevent postextubation airway events and subsequent reintubation when the duration of mechanical ventilation was short. Other variables were not considered as effect modifiers (Table 3).

Sensitivity Analysis

All sensitivity analyses showed effect sizes and precisions similar to the primary analysis (Table 4).

Discussion

Our analysis suggested that the use of prophylactic corticosteroids before elective extubation in mechanically ventilated adults was associated with a 57% reduction in the incidence of postextubation airway events and reintubation. Our subgroup analysis showed that the beneficial effects of prophylactic corticosteroids were found in the subgroup of participants considered at high risk for airway obstruction, estimated through a cuff-leak test. All sensitivity analyses in trials with a low risk of bias were consistent with the primary outcome analysis. Thus, the evidence for the efficacy of prophylactic corticosteroids given before elective extubation was robust and reconfirmed.

The latest systematic reviews on this topic show that prophylactic corticosteroids effectively reduce the incidence of postextubation stridor and reintubation.[10-13,20] However, only one review mentioned the efficacy of prophylactic corticosteroids in high-risk populations, as defined with the cuff-leak test, and this subgroup analysis pooled only three trials.[11] We included four newly published trials,[21,22,30,31] and our findings were mostly consistent with previous reviews.[10-13] However, six trials selected patients at high risk for airway obstruction,[21,22,27,29-31] and our analysis showed that prophylactic corticosteroids were beneficial only in this population. The number needed to prevent one episode of postextubation airway events and reintubation in individuals at high risk for postextubation airway obstruction was five (95% CI, 4-7) and 16 (95% CI, 8-166), respectively. This also supported the selection of patients to whom

TABLE 3] Meta-regression Analysis of Outcomes

Variable	Postextubation Airway Events		Reintubation	
	Regression Coefficient (95% CI)	*P* Value	Regression Coefficient (95% CI)	*P* Value
Proportion of women	−0.65 (−3.04 to 1.73)	.55	0.51 (−3.30 to 4.32)	.77
Cumulative dose of corticosteroids equivalent to hydrocortisone	−0.001 (−0.002 to 0.001)	.20	0.00 (−0.002 to 0.002)	.95
No. of doses	−0.15 (−0.42 to 0.12)	.25	−0.003 (−0.39 to 0.38)	.98
Time from the first dosing to extubation	−0.01 (−0.04 to 0.02)	.38	0.01 (−0.04 to 0.06)	.64
Duration of mechanical ventilation	0.13 (−0.02 to 0.28)	.07	0.25 (0.02–0.47)	.04

corticosteroids should be administered. Routine administration of corticosteroids before elective extubation is not recommended.

Cuff-leak testing was the screening modality used in six trials to determine which individuals were at high risk for airway obstruction.[21,22,27,29-31] The definitions and cutoff values of cuff-leak testing varied across studies; two trials used a cuff-leak volume < 24% of tidal volume during inflation, three used a cuff-leak volume < 110 mL, and one used a cuff-leak volume < 25% of tidal volume. Meta-analyses pooled studies on several methods of cuff-leak testing and suggested that a positive cuff-leak test accurately predicted patients at high risk for the development of airway obstruction.[32,33]

Our subgroup analysis showed little statistical heterogeneity in the subgroup of participants at high risk for airway obstruction in contrast to moderate heterogeneity in the subgroup of unselected participants. This potentially indicates that cuff-leak testing, although applied with varying cutoff values, might be able to select those at similar risk for airway obstruction and underlines the importance of screening for high-risk patients. Although the use of prophylactic corticosteroids was associated with few adverse events, it is reasonable to use the cuff-leak test as a screening method and administer prophylactic steroids only to those who are at risk of the development of postextubation obstruction given our study findings.

Our meta-regression analysis showed that the efficacy of prophylactic corticosteroids tended to be greater with shorter periods of mechanical ventilation, suggesting that a shorter duration of mechanical ventilation is associated with a higher risk for postextubation airway obstruction. However, this hypothesis remains controversial.[2] Although one trial with unselected participants included a period exceeding 10 days of mechanical ventilation, six trials (with participants at

TABLE 4] Sensitivity Analysis

Outcome	No. of Trials	Total Sample Size	Summary Estimate (95% CI)	Heterogeneity		
				Q	*df*	I^2, %
Analyses excluding trials with unclear or high risk of bias in the domain of sequence generation						
Postextubation stridor	7	1,880	RR, 0.36 (0.23–0.56)	13.93	6	56.9
Reintubation	7	1,880	RR, 0.33 (0.18–0.59)	4.26	6	0.0
Analyses excluding trials with unclear or high risk of bias in the domain of allocation concealment						
Postextubation stridor	8	1,936	RR, 0.36 (0.24–0.54)	14.28	7	51.0
Reintubation	8	1,936	RR, 0.28 (0.16–0.50)	2.85	7	0.0
Analyses excluding trials with unclear or high risk of bias in the domain of blinding of outcome assessors						
Postextubation stridor	5	1,641	RR, 0.33 (0.18–0.59)	10.95	4	63.5
Reintubation	5	1,641	RR, 0.28 (0.15–0.53)	2.35	4	0.0
Analysis limited to trials that explicitly showed the frequency of reintubation due to postextubation airway events						
Reintubation	7	2,012	RR, 0.41 (0.19–0.89)	9.44	6	36.4

RR = risk ratio.

high risk for, and an actual high incidence of, postextubation airway events) included periods of < 8 days of mechanical ventilation. This association might explain the significant findings of the meta-regression analysis and does not justify the routine administration of prophylactic steroids according to the duration of mechanical ventilation.

Our study has some strengths. First, a comprehensive search for relevant studies was conducted. Two new trials and two additional ones were identified in the database as well as in Google Scholar and Web of Science searches, respectively. The number of included trials was the largest to date. Second, subgroup and meta-regression analyses were adequately performed with the large number of trials identified. Significantly, subgroup analysis, by considering the risk of postextubation airway obstruction, provided information relevant to clinical practice. Third, the risk of bias in many of the included trials was deemed low. Seven of 11 included trials were published after 1996, when the Consolidated Standards of Reporting Trials statement was developed to enhance researchers' complete, clear, and transparent reporting of randomized trials.[34] Most of these trials had well-reported methodology. We also retrieved information on the methodology of two trials from the original investigators. This strengthened the validity of the original trials and our study findings.

Our study also has some limitations. First, the included trials differed regarding populations, corticosteroid protocols, and observation periods. Primary outcome analysis revealed high levels of statistical heterogeneity, but subgroup analyses indicated that this heterogeneity was due to the risk of postextubation airway obstruction. Only one corticosteroid protocol was examined in multiple trials,[27,30] and the effect sizes of prophylactic corticosteroids in the subgroup of participants at high risk for the development of postextubation airway complications were similar between protocols. This precluded an analysis to determine which corticosteroid protocol was the most optimal. Thus, tailoring the corticosteroid protocol to each clinical scenario, including the time to the planned extubation, is needed. Second, we did not discuss the adverse effects of prophylactic corticosteroids in detail, a factor that could be of crucial relevance to critically ill patients. The Consolidated Standards of Reporting Trials statement requires that trial investigators report "harms" associated with interventions,[34] and six of seven trials published after this statement reported few adverse events.[21,22,27-30] Our review suggests that the occurrence of hyperglycemia, GI bleeding, and infections associated with corticosteroid use was extremely rare.

Conclusions

The use of prophylactic corticosteroids before elective extubation is associated with significant reductions in the incidence of postextubation airway events and reintubation, with few adverse events. Current available evidence suggests that it is reasonable to screen for patients at high risk for airway obstruction, as they may benefit most from prophylactic corticosteroids.

Acknowledgments

Author contributions: A. K. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. A. K., N. U., and R. S. contributed substantially to the study design, data analysis and interpretation, and writing of the manuscript.

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Additional information: The e-Table can be found in the Supplemental Materials section of the online article.

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