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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]

Trials of Corticosteroids to Prevent Postextubation Airway Complications*

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We identified three randomized controlled trials (RCTs) that addressed whether preextubation steroid administration reduces postextubation complications in children. The pooled analysis of primary extubation in children demonstrated significantly less stridor (relative risk [RR], 0.57; 95% confidence interval [CI], 0.40 to 0.81) and a trend toward less reintubation (RR, 0.50; 95% CI, 0.02 to 13.87) with corticosteroids. One non-RCT in children who had failed extubation the first time found a significant reduction in duration of prolonged reintubation (≥ 6 days) and in failed reextubations. The four RCTs in adults reported very low reintubation rates, and no conclusions can be drawn. Only one RCT assessed postextubation stridor and found little difference. Overall, we found that corticosteroids decreased the risk of postextubation stridor in children by about 40%. However, the effect of corticosteroids in children and adults to reduce postextubation complications such as reintubation is uncertain.

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Key words: corticosteroids; extubation; mechanical ventilation; meta-analysis; reintubation; stridor; systematic reviews; weaning

Abbreviations: CI = confidence interval; RCT = randomized controlled trial; RR = relative risk

Laryngeal edema, and the resultant stridor, are common problems in children following tracheal extubation after mechanical ventilation.^{1,2} Not infrequently, airway compromise necessitates endotracheal reintubation. This sequence of events also occurs in adults, although far less often.³

Preextubation corticosteroid administration might, in theory, ameliorate this problem. The anti-inflammatory effect of corticosteroids could prevent or attenuate the degree of laryngeal edema. In cases that might otherwise be mild, corticosteroids might even eliminate significant edema. However, it is plausible that corticosteroid therapy might have insufficient time to act to prevent laryngeal edema or might, for a variety of other reasons, have a minimal therapeutic impact. Randomized controlled trials

(RCTs) represent the only way to definitively resolve this issue, focusing on outcomes of importance to patients. In this section, we review the trials that investigators have conducted in both pediatric and adult populations.

MATERIALS AND METHODS

We have described the methods of our systematic reviews in detail in the introduction to this supplement and in the article concerning alternative discontinuation assessment and weaning mode methods. Herein, we summarize these methods briefly, focusing on aspects specific to this topic.

Eligibility Criteria

We included all studies of adult and pediatric patients who had received mechanical ventilation that compared corticosteroid therapy to placebo therapy or control subjects and that measured at least one outcome related to upper airway complications. We included RCTs and controlled nonrandomized studies.

Search for Relevant Studies

To identify relevant studies, we searched MEDLINE, EMBASE, HEALTHStar, CINAHL, the Cochrane Controlled Trials Registry, and the Cochrane Data Base of Systematic Reviews from 1971 to September 1999, and we examined the reference lists of all included articles for other potentially relevant citations.

Data Abstraction and Assessment of Methodological Quality

Data abstraction and methodological quality rating were done in duplicate by one of five respiratory therapists and five intensivists. One of the investigators rechecked the final data abstraction.

The methodological features of RCTs that we abstracted included the following: the method of randomization and whether randomization was concealed; the criteria for weaning, extubation, and reintubation; the extent to which groups were similar with respect to important prognostic factors; whether investigators conducted an intention-to-treat analysis; whether patients, clinicians, and those assessing outcome were blind to allocation; the extent to which the groups received similar cointerventions; and the reporting of the reasons for study withdrawal.

For non-RCTs, we considered the extent to which groups were similar with respect to important prognostic factors, whether the investigators adjusted for differences in prognostic factors, and the extent to which the groups received similar cointerventions.

Statistical Analysis

We abstracted or, when necessary, calculated effect sizes in terms of relative risks (RRs) and associated 95% confidence intervals (CIs) for binary outcomes. We calculated mean differences and 95% CIs for continuous variables.

We pooled data when, in our judgment, the underlying pathophysiology was such that across the range of populations, management strategies in treatment and control groups, and the key outcomes studied we would expect more or less the same treatment effect. For instances in which we could pool continuous variables, we considered the mean in each group and an estimate of variability from each group that determined the weight given to the study in the pooled analysis. For pooling binary data, we calculated risk ratios using the methods described by Fleiss.⁴

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RESULTS

We identified three RCTs⁵⁻⁷ that had addressed whether preextubation steroid administration can reduce postextubation stridor and the necessity for reintubation in children (Table 1). In all three studies, patients, caregivers, and those assessing outcome were blind to allocation, with patients having received dexamethasone or a matched placebo. Two trials^{5,6} (sample sizes, 66 and 153 children) enrolled patients who had not previously been extubated. A smaller trial⁷ enrolled 23 children who had been reintubated for postextubation stridor, who received two doses of dexamethasone or placebo 6 h before extubation, at extubation, then 6 and 12 h postextubation.

Both of the trials of primary extubation examined both stridor scores and reintubation (Table 2). Early stridor was present more frequently in both trials in the group that did not receive steroids, and the differences persisted until 12 h in the one trial⁶ that measured stridor sequentially (Table 2). Reintubation occurred more frequently in the steroid group in one study,⁵ and more frequently in the placebo group in the other study.⁶ In the trial of secondary extubation,⁷ the stridor score was slightly and not significantly higher (that is, worse stridor) in the placebo group,

which also had a higher incidence of reintubation (5 of 11 vs 3 of 12 reintubations). This difference did not approach statistical significance.

One non-RCT⁸ evaluated the use of corticosteroid therapy to prevent postextubation airway complications in children. In this study, which evaluated steroid therapy in patients who had failed extubation the first time, Freezer et al⁸ reported a statistically significant reduction in prolonged reintubation (≥ 6 days) and in failed reextubations.

The pooled analyses of the two RCTs of primary extubation demonstrated a substantial reduction in the frequency of stridor with a relatively narrow 95% CI (RR, 0.57; 95% CI, 0.40 to 0.81) (Table 3). The pooled analysis also suggested a reduction in reintubation with steroid therapy, but, in part because of the trends in different directions in the two studies, the 95% CI is extremely wide (RR, 0.50; 95% CI, 0.02 to 13.87) (Table 3).

The four trials⁹⁻¹² of steroids in adult patients (Table 1) used different medications (*ie*, methylprednisolone, dexamethasone, and hydrocortisone)^{3,10-12} and were placebo-controlled. Only one of the studies¹¹ assessed postextubation stridor, and it found little difference between the two groups (Table 2). The need for reintubation was very

Table 1—Characteristics of Randomized Trials of Corticosteroids to Prevent Postextubation Airway Complications*

Study/yr	ICU Population	Diagnoses	Method of		Weaning	Extubation	Reintubation
			Randomization	Concealment	Criteria Reported	Criteria Reported	Criteria Reported
Pediatric studies							
Tellez et al ⁵ /1991	153 patients requiring airway stabilization and mechanical ventilation in a pediatric ICU in a children's hospital	Asthma, cardiac surgery, trauma	Not clearly reported	Not reported	No	No	No
Anene et al ⁶ /1996	66 children < 5 yr, intubated and mechanically ventilated for > 48 h, in a tertiary-care pediatric ICU	Pneumonia, postoperative, neurologic, congenital heart disease	Randomization table	Not reported	No	Yes	Yes
Harel et al ⁷ /1997	26 tertiary-care, pediatric ICU patients who had failed extubation with postextubation stridor	Asthma, pneumonia, acute lung injury, postoperative, neurologic, infant RDS, trauma	Not clearly reported	Sealed envelopes	No	No	No
Adult studies							
Gaussorgues et al ⁹ /1987	276 mechanically ventilated patients	Pneumonia, hemodynamic instability, postoperative, neurologic	Not reported	Not reported	No	No	No
Darmon et al ¹⁰ /1992	700 patients > 15 yr who had undergone tracheal intubation	Hemodynamic instability, neurologic, postoperative	Randomization table	Sealed envelopes	No	No	No
Ho et al ¹¹ /1996	77 patients > 14 yr of age who had undergone tracheal intubation for > 24 h in a tertiary-care medical-surgical ICU	Hemodynamic instability, postoperative, neurologic, trauma	Randomization table	Not reported	No	No	No
Chaney et al ¹² /1998	60 patients in a CVICU in a tertiary care hospital	Cardiac bypass surgery	Not clearly reported	Not reported	No	Yes	No

* CVICU = cardiovascular ICU; RDS = respiratory distress syndrome.

Table 2—Results of Individual RCTs of Corticosteroids to Prevent Postextubation Airway Complications*

Study/yr	Outcome	Results	Effect Magnitude	p Value
Pediatric studies				
Tellez et al ⁵ /1991				
Binary variables	Reintubation	Int 1: 9/76 patients Int 2: 4/77 patients	2.14 (0.73–6.28)†	0.17
	Stridor	Int 1: 16/76 patients Int 2: 23/77 patients	0.71 (0.41–1.23)†	0.22
Anene et al ⁶ /1996				
Continuous variables	Croup score at 10 min	Int 1: 1.00 ± NE Int 2: 2.00 ± NE	– 1.00‡	< 0.01
	Croup score at 6 h	Int 1: 0.00 ± NE Int 2: 1.00 ± NE	– 1.00‡	< 0.01
	Croup score at 12 h	Int 1: 0.00 ± NE Int 2: 0.50 ± NE	– 0.50‡	< 0.01
	Croup score at 24 h	Int 1: 1.00 ± NE Int 2: 0.00 ± NE	0.00‡	> 0.05
Binary variables	Reintubation	Int 1: 0/31 patients Int 2: 7/32 patients	0.07 (0.00–1.15)†	0.06
	Stridor at 10 min	Int 1: 14/31 patients Int 2: 28/32 patients	0.52 (0.35–0.79)†	< 0.01
	Stridor at 6 h	Int 1: 8/31 patients Int 2: 22/28 patients	0.34 (0.19–0.63)†	< 0.01
	Stridor at 12 h	Int 1: 2/31 patients Int 2: 13/26 patients	0.16 (0.04–0.54)†	< 0.01
	Stridor at 24 h	Int 1: 1/31 patients Int 2: 4/25 patients	0.27 (0.05–1.60)†	0.15
	Racemic epinephrine therapy	Int 1: 4/31 patients Int 2: 22/32 patients	0.21 (0.08–0.50)†	< 0.01
Harel et al ⁷ /1997				
Continuous variables	Stridor score	Int 1: 5.08 ± 2.84 Int 2: 6.18 ± 3.37	– 1.10 (– 3.64–1.44)‡	0.40
Binary variables	Reintubation	Int 1: 3/12 patients Int 2: 5/11 patients	0.59 (0.20–1.74)‡	0.34
	Tracheostomy	Int 1: 3/12 patients Int 2: 0/11 patients	6.44 (0.37–112.54)‡	0.20
Adult studies				
Gaussorgues et al ⁹ /1987				
Continuous variables	Duration of MV	Int 1: 312.00 ± 264.00 Int 2: 384.00 ± 216.00	– 72.00 (– 128.91– – 15.09)‡	0.01
Binary variables	Reintubation	Int 1: 4/138 patients Int 2: 0/138 patients	9.00 (0.49–165.60)†	0.14
	Laryngeal lesions	Int 1: 4/138 patients Int 2: 2/138 patients	1.80 (0.39–8.30)†	0.45
Darmon et al ¹⁰ /1992				
Binary variables	Reintubation	Int 1: 2/327 patients Int 2: 5/337 patients	0.47 (0.11–2.07)†	0.32
	Laryngeal lesions	Int 1: 11/327 patients Int 2: 17/337 patients	0.68 (0.33–1.40)†	0.29
Ho et al ¹¹ /1996				
Binary variables	Reintubation	Int 1: 0/39 patients Int 2: 1/38 patients	0.33 (0.01–7.74)†	0.49
	Stridor	Int 1: 7/39 patients Int 2: 10/38 patients	0.70 (0.30–1.59)‡	0.39
Chaney et al ¹² /1998				
Continuous variables	Duration of MV, h	Int 1: 12.82 ± 4.90 Int 2: 10.07 ± 5.25	2.75 (0.18–5.32)‡	0.04
Binary variables	Nonextubation	Int 1: 0/30 patients Int 2: 2/30 patients	0.20 (0.01–4.00)†	0.29

*Values given as mean ± SD, unless otherwise indicated. NE = no estimate of variance was available/calculable; MV = mechanical ventilation; Int 1 = intervention 1 (steroid therapy); Int 2 = intervention 2 (no steroid therapy).

†Values given as RR (95% CI).

‡Values given as the differences in the means (95% CI).

Table 3—Pooled Results of Randomized Trials of Corticosteroids to Prevent Postextubation Airway Complications

Outcome	Study/yr	RR (95% CI)	Summary RR (95% CI)	Heterogeneity χ^2 (p Value)	
Pediatric studies	Reintubation	Tellez et al ⁵ /1991	2.14 (0.73–6.28)	0.68 (0.16–2.97)	6.26 (0.04)
		Anene et al ⁶ /1996	0.07 (0.00–1.15)		
		Harel et al ⁷ /1997	0.59 (0.20–1.74)		
	Stridor	Tellez et al ⁵ /1991	0.71 (0.41–1.23)		
		Anene et al ⁶ /1996	0.52 (0.35–0.79)		
Adult studies	Reintubation	Gaussorgues et al ⁹ /1987	9.00 (0.49–165.60)	0.93 (0.15–5.81)	3.45 (0.18)
		Darmon et al ¹⁰ /1992	0.47 (0.11–2.07)		
		Ho et al ¹¹ /1996	0.33 (0.01–7.74)		
	Laryngeal lesions	Gaussorgues et al ⁹ /1987	1.80 (0.39–8.30)		
		Darmon et al ¹⁰ /1992	0.68 (0.33–1.40)		

infrequent in all four studies. As a result, even the pooled analysis demonstrates extremely wide 95% CIs around the pooled estimate of steroid impact on reintubation (Table 3).

DISCUSSION

Two well-designed trials^{5,6} of dexamethasone therapy prior to extubation in children have unequivocally demonstrated that steroids reduce postextubation stridor. The inferences from these trials are strengthened because patients, caregivers, and those assessing outcome were all blind to allocation. In contrast to the effect on stridor, the effect on reintubation is far from clear. In one of the two studies, 7 of 32 patients not receiving steroids required reintubation in contrast to 0 of 31 patients receiving steroids. The trend in the other study was in the opposite direction, with 4 of 77 not receiving steroids and 9 of 76 children receiving steroids requiring reintubation. We found no adequate explanation for this difference.

The three trials of steroid therapy in adults observed so few events that even the results of the pooled analysis have such wide 95% CIs that they are essentially uninformative. The results are consistent with a reduction in the RR of reintubation of 86%, and also with an increase in the RR of reintubation of 58%.

For clinicians who believe that preventing stridor in children after extubation is in itself important, the results of two RCTs provide a definitive answer. Steroids reduce the RR of stridor by > 40%. Even using the more conservative estimate of 21% stridor frequency in patients not receiving steroids, the results suggest that one needs to treat no more than 12 children with dexamethasone therapy to prevent one from developing stridor.

For those who believe that dexamethasone therapy is warranted only if it prevents reintubation, the question remains unanswered. Both trials^{6,7} found reintubation rates of > 10%. Although hundreds of children would ultimately have to be enrolled in RCTs to answer the question, it may well be worth investing the resources to resolve the issue.

In adults, the situation is different. Reintubation for upper airway obstruction is very infrequent.¹³ Tens of

thousands of patients would have to be randomized to detect the absolute differences in effect that could be expected even if steroids substantially reduce the RR of laryngeal edema. Such a trial is almost certainly not worth the resources required. Focusing on a high-risk population, such as patients who have had airway trauma or those undergoing facial reconstruction, may be more fruitful and feasible.

The data included in this systematic review and a more comprehensive discussion of the original articles are included in an Evidence Report of the Agency for Healthcare Research and Quality.¹⁴

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