Evaluation of Risk Factors for Laryngeal Edema after Tracheal Extubation in Adults and Its Prevention by Dexamethasone

A Placebo-controlled, Double-blind, Multicenter Study

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Because laryngeal edema (LE) after tracheal extubation is likely to result from an exudative response, corticosteroids often are given routinely as a preventive treatment. No adequate controlled study supports this strategy, however. A prospective, randomized, placebo-controlled, double-blind, multicenter trial that included 700 consecutive patients requiring tracheal intubation and mechanical ventilation was conducted to determine risk factors for LE occurrence after tracheal extubation in adults and to evaluate the efficacy of corticosteroids in its prevention. One hour before extubation, patients were given either an intravenous bolus of 8 mg dexamethasone or a placebo. Patients were divided into two groups: 1) those in whom short-duration intubation (SDI, less than 36 h) was administered; and 2) those in whom long-duration intubation (LDI, more than 36 h) was administered. Minor LE was diagnosed when either stridor or laryngeal dyspnea, or both, occurred; major LE was diagnosed when reintubation due to LE was required, with LE evidenced during direct laryngoscopy. The overall incidence of LE was 4.2% and varied among the six participating centers from 2.3 to 6.9% (not significant). In only seven patients (1%), all with LDI, was tracheal reintubation required for LE. Laryngeal edema occurred more frequently after LDI than after SDI (7.2 vs. 0.9%; $P < 0.001$). It also was more frequent in female than in male patients (20/284 vs. 8/379; $P < 0.05$), irrespective of intubation duration and treatment. There was no association between LE and either difficulty/route of intubation or admission diagnosis. Its overall incidence was not different between patients given dexamethasone and those given placebo, whether they were in the SDI or LDI group (0.7 vs. 1.2% and 5.7 vs. 8.7%, respectively). Dexamethasone did not affect the number of patients reintubated. Assuming an incidence of LE in each group similar to that found in our study, more than 7,000 patients would need to be studied to evaluate adequately the presence of a type 2 error. Therefore, we conclude that the overall incidence of postextubation LE in adults is small and that risk factors for LE include an intubation duration of more than 36 h and female gender. In addition, 8 mg dexamethasone given as an intravenous bolus 1 h before extubation does not appear to prevent either minor or major forms of LE. (Key words: Anesthetic techniques: tracheal intubation. Complications: laryngeal edema. Corticosteroids.)

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ALTHOUGH TRACHEAL INTUBATION is a routine maneuver in intensive care units and during anesthesia, it can cause complications, both during intubation and after extubation.[1–3]

Laryngeal edema (LE) has been reported to occur from 2%[4] to 15.4%[5] in patients after tracheal extubation, and it is one of the most severe complications of tracheal intubation because it causes significant morbidity and can lead to death.[6–8]

Postextubation LE has been thought to result from fibrinous exudation associated with a marked polymorphonuclear infiltration of the traumatized area.[9,10] In experimental animals, corticosteroids given at the time of extubation decreased capillary dilatation and permeability as well as edema formation and inflammatory cells infiltration.[11] Therefore, the preventive use of steroids in patients has been proposed and now is widely accepted in many countries.[2,5,12] Adequate controlled studies supporting this strategy are, however, lacking.

This study was designed to determine the possible risk factors for LE occurrence after extubation and to evaluate the potential efficacy of corticosteroids to reduce its incidence.

Materials and Methods

PATIENTS

In a randomized, double-blind, placebo-controlled, multicenter study, 700 consecutive patients hospitalized in six intensive care units were studied prospectively from November 1986 to November 1987. The study included all patients of both sexes who had undergone tracheal intubation. Patients were not included if they were less than 15 yr of age; presented with ear, nose, or throat disease or surgery; had experienced LE after tracheal extubation during the current hospital stay; or were being treated with corticosteroids or nonsteroidal antiinflammatory drugs. Patients were included only once.

METHODS

For each patient, the following characteristics were recorded prospectively: age, gender, admission diagnosis, simplified acute physiology score (SAPS)[13] at the time of tracheal intubation, difficulty and route of intubation, ID of endotracheal tubes, number of tubes inserted for each patient, and number of days of intubation. Each patient was intubated *via* the orotracheal or nasotracheal route with a low-pressure, large-volume (high-compliance) cuffed tube. As part of routine airway management, the endotracheal tube cuffs were checked at least every 6 h in accordance with the least-leak technique.[14]

Because in previous studies intubation duration has been considered a risk factor for LE occurrence,[5,6,9] patients were stratified in each center into two groups: 1) those in whom short-duration intubation (SDI, less than 36 h) was administered; and 2) those in whom long-duration intubation (LDI, more than 36 h) was administered. Although a 24-h dividing point might have been more appropriate,[5,15] we chose 36 h as the dividing point because, in our institutions, tracheal extubations usually are performed during the morning. Many patients hospitalized during the night (particularly drug-overdose patients), whose tracheas often are extubated during the morning of the following day (24–36 h after admission), otherwise would have been classified in the LDI group. Thus, a possible relationship between LE incidence and admission diagnoses would have been altered. Furthermore, in a previous prospective study,[15] the incidence of postextubation stridor was not different between a tracheal intubation lasting less than 24 h and one lasting less than 48 h.

Patients in both the SDI and LDI groups were allocated randomly to receive, 1 h before extubation, either an 8-mg intravenous (iv) bolus of dexamethasone sodium phosphate or a placebo. Randomization was carried out within each participating center and was balanced in both groups in blocks of eight patients according to a random table. This scheme was designed so that, in each center, the number of patients in the SDI and LDI groups receiving dexamethasone or placebo would be approximately the same. Placebo and dexamethasone were packaged by Merck Sharp Dohme-Chibret Laboratories, so that the vials were identical in volume and appearance and were labeled with a coded number. When assigning a patient to a treatment group, the investigator had to open an envelope to learn which coded number would be given to that patient. Data were collected prospectively in each center, and the double-blind conditions (for patients, attending physicians, and investigators) were maintained until the study was completed. This protocol was approved by the Institutional Review Board on Human Research of the French Critical Care Society. This institution waived the need for written informed consent prior to inclusion into the study.

Patients were observed for LE occurrence 24-h postextubation. Minor LE was diagnosed when either laryngeal dyspnea or stridor, or both, occurred[6,15,16]; major LE was diagnosed when reintubation due to LE was required, with LE evidenced during direct laryngoscopy. According to Deming and Oech,[16] laryngeal dyspnea was defined as the occurrence of signs of upper obstruction, *i.e.*, a prolonged inspiratory phase associated with recruitment of accessory respiratory muscles (subcostal, suprasternal, or intercostal retraction, or all three); stridor was defined as a crowing sound present with inspiration. In minor cases, there was no systematic attempt to confirm the diagnosis of LE by laryngoscopy because we thought this procedure would be unsafe in some patients; moreover, indirect laryngoscopy could not be performed routinely on a 24-h basis.

To overcome the inherent variability resulting from use of clinical criteria as end points, in addition to the randomization process and double-blind conditions, the following precautions were taken. The investigators reached a preliminary consensus regarding the threshold for diagnosis; in the great majority of cases, the judgment had been made in each center by the same physician because tracheal extubations usually were performed during the morning and because, when present, signs of LE occur shortly after tracheal extubation.[4,6–8,16] In the rare cases when LE occurred during the night, the judgment was made by the attending physician according to the recommendations issued from the consensus reached by all investigators before the study concerning the threshold for diagnosis.

STATISTICAL ANALYSIS

Patients were excluded from the analysis if 1) the scheduled extubation was not performed after they were

given dexamethasone or placebo; or 2) if they needed reintubation within 24 h of extubation for reasons other than LE.

Data were analyzed by the chi-square test, Fisher's exact test, and the Mantel–Haenszel test for qualitative results. Analysis of variance and Tukey's *post hoc* test were used for quantitative data.[17] Risk factors other than intubation duration were analyzed by the receiver operating characteristic curve method.[18]

Values are given as mean ± standard deviation or median (range); $P < 0.05$ was considered statistically significant.

Results

The characteristics of the 700 patients included in the study are shown in table 1. The number of patients included in each of the six participating centers was 141, 151, 113, 80, 82, and 133, respectively. In each center, the number of patients receiving dexamethasone or placebo in both SDI and LDI groups was similar (data not shown).

Of the 700 patients, data from 37 (5.3%) were not analyzed; in 6 of those patients (3 after SDI, 3 after LDI), the scheduled extubation was postponed because of clinical deterioration within 1 h of dexamethasone administration (5 patients) or placebo (1 patient). In each of the remaining 31 patients (8 after SDI, 23 after LDI) the trachea was reintubated during the follow-up period because of clinical deterioration, in the absence of symptoms suggesting LE or signs of LE at direct laryngoscopy during reintubation (16 were in the dexamethasone group and 15 in the placebo group). These 31 patients did not differ from the others with respect to age, gender, admission diagnosis, SAPS, and characteristics of intubation. Thus, data from 663 patients were analyzed. The median (range) ID of the endotracheal tubes inserted was 8 mm (6 mm–9 mm) for men and 7.5 mm (6 mm–8.5 mm) for women ($P < 0.001$). No patient died during the follow-up period.

INCIDENCE OF LARYNGEAL EDEMA

The overall incidence of LE was 28/663 (4.2%) and varied among the six centers between 2.3% and 6.9%

TABLE 1. Characteristics of 700 Patients with Tracheal Intubation in a Study of Risk Factors
for Laryngeal Edema and its Prevention by Dexamethasone

	Patients with SDI (< 36 h)		Patients with LDI (> 36 h)	
	DXM* (n = 162)	Placebo* (n = 166)	DXM* (n = 186)	Placebo* (n = 186)
Mean age (yr) ± SD	49 ± 18.8	47.7 ± 19.4	55.4 ± 17.9	59.4 ± 19.8
Gender				
Male	98	94	112	101
Female	64	72	74	85
Median (range) SAPS at the time of intubation	8 (1, 24)	9 (2, 23)	12 (2, 27)	12 (2, 27)
Admission diagnosis				
Drug overdose	57	75	29	31
Postoperative	78	68	31	27
Respiratory failure	3	1	42	54
Shock	5	11	31	33
Neurologic disease	12	4	31	31
Miscellaneous	7	7	22	10
Median (range) internal diameter of endotracheal tube (mm)	7.5 (6, 9)	7.5 (6, 9)	7.5 (6.5, 9)	7.5 (7, 9)
Route of intubation				
Oral	102	98	29	27
Nasal	60	68	157	159
Difficulties at intubation				
None	146	154	166	168
Difficult	7	8	14	12
Not known	9	4	6	6
Number of tubes inserted in each patient before study period				
1	156	162	150	156
2	4	4	27	22
>2	2	0	9	8
Mean duration (days) of intubation ± SD			9.6 ± 9.7	10.3 ± 10.9

SAPS = simplified acute physiology score.

* There was no significant difference in the characteristics of patients given dexamethasone (DXM) or placebo, either in patients with short-duration intubation (SDI, < 36 h) or in those with long-duration intubation (LDI, > 36 h).

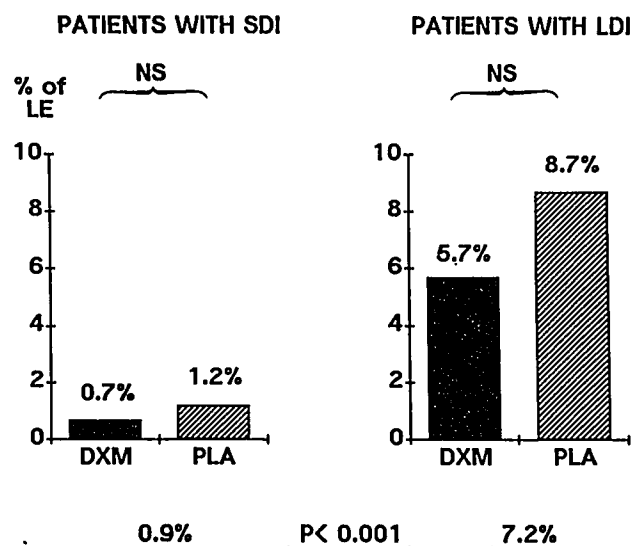## PATIENTS WITH SDI   ## PATIENTS WITH LDI

RISK FACTORS

FIG. 1. Incidence of laryngeal edema (LE) in endotracheally intubated patients given dexamethasone (DXM) *versus* those given placebo (PLA). No difference in the incidence of LE was found between patients given DXM or PLA, whatever the duration of intubation. Note that LE was more frequent after prolonged intubation. SDI = short-duration intubation (<36 h); LDI = long-duration intubation (>36 h).

Of the 663 patients analyzed, the trachea had been intubated in 317 for less than 36 h (SDI) and in 346 for more than 36 h (LDI). The overall incidence of LE was significantly greater in patients with LDI than in those with SDI: 25/346 (7.2%) and 3/317 (0.9%), respectively ($P < 0.001$; fig. 1). Furthermore, no patient with SDI needed reintubation of the trachea for LE. The mean duration of tracheal intubation in patients who had undergone reintubation for LE was 10.1 ± 5.5 days (not different from that of other patients presenting with LE; table 2). Patients with LDI were older ($P < 0.001$) and had a higher SAPS at the time of intubation ($P < 0.001$; table 1). Age and SAPS, however, were not predictive of LE when studied by the ROC curve method.

Apart from an intubation duration greater than 36 h, gender was the second factor identified as a risk factor for LE: 70% of the patients who experienced LE were women (table 2). The relative risk for LE occurrence in female patients was 3.3 ($P < 0.001$). Reintubation for LE was needed in five women and two men.

Nasotracheal intubation appeared to be a risk factor for LE ($P < 0.01$; table 2). This route was used more frequently, however, for patients with LDI (270/324 [83%]) than for those with SDI (123/311 [40%]) ($P < 0.001$). Analysis of the data with the Mantel–Haenszel test, which avoids the confounding effect of intubation duration, showed that the nasal route was not associated with LE occurrence (table 3).

(not significant). Reintubation for LE was required in 7 patients (1%). In 21 of the 28 patients experiencing LE (75%), symptoms of LE developed within 8 h of extubation.

TABLE 2. Risk Factors for Occurrence of Laryngeal Edema after Tracheal Intubation

	All Patients (n = 635)	Laryngeal Edema (n = 28)	P
Mean age (yr) ± SD	52 ± 19	59 ± 22	NS
Median SAPS (range) at the time of intubation	10 [1, 27]	10 [4, 27]	NS
Median (range) internal diameter of tubes (mm)	7.5 [6, 9]	7.5 [7, 8.5]	NS
Mean duration (days) ± SD in patients in whom trachea was intubated for more than 36 h	9.9 ± 9.1 (n = 321)	10.8 ± 9.4 (n = 25)	NS
Difficulties of intubation			
None	576	23	NS
Difficult	34	5	
Not known	25	0	
Number of tubes inserted in each patient during study period			
1	577	20	NS
2	46	6	
>2	12	2	
Route of intubation			
Oral	242	3	< 0.01*
Nasal	393	25	
Gender			
Female	264 (42%)	20 (70%)	< 0.05
Male	371 (58%)	8 (30%)	

Only the 663 patients analyzed were considered (see text).
NS = difference not significant; SAPS = simplified acute physiology score.
* Chi-square test: this difference was no longer significant for the duration of intubation (< or > 36 h) when the data were analyzed by the Mantel and Haenszel's test, which takes account of the duration of intubation (see table 3).

TABLE 3. Incidence of Laryngeal Edema According to the Route of Tracheal Intubation

	Patients with SDI		Patients with LDI	
	All Patients	LE Patients	All Patients	LE Patients
Oral route	191	0	51	3
Nasal route	123	3	270	22

The incidence of laryngeal edema (LE) was higher in patients intubated by the nasal route. However, this route and LE were more frequent in patients with long-duration intubation (LDI) than in those with short-duration intubation (SDI). When this incidence was calculated according to the route of intubation using a Mantel and Haenszel's test, which takes account of the duration of intubation, the nasal route was no longer a risk factor ($X^2 = 1.45$; difference not significant).

EFFECT OF DEXAMETHASONE

There was no significant difference in the characteristics of patients receiving dexamethasone or placebo in either the SDI or LDI group (table 1).

Dexamethasone did not prevent LE onset, regardless of intubation duration: in patients who had undergone intubation for less than 36 h, LE occurred in 1/153 given dexamethasone (0.7%: 95% confidence interval [CI] = 0.02–3.66%) and in 2/164 given placebo (1.2%; CI = 0.15–4.44%) (not significant); in patients who had undergone intubation for more than 36 h, LE occurred in 10/174 given dexamethasone (5.7%; CI = 2.85–10.59%) and 15/173 give placebo (8.7%; CI = 5.02–14.17%) (not significant; fig. 1). In the LDI group, the difference in incidence of LE between the two treatment groups was 3% (CI = 0.95–6.8%).

The distribution of clinical symptoms was not different between the two treatment groups. Further, the number of patients who had undergone reintubation for LE was similar in the dexamethasone and placebo groups (2/11 and 5/17, respectively; fig. 2).

Discussion

To our knowledge, this is the first prospective, randomized, controlled study evaluating risk factors of LE after tracheal extubation in adults and prevention of LE by corticosteroids. The major finding was that, regardless of intubation duration, administration of an iv bolus of 8 mg dexamethasone 1 h before extubation did not reduce either the overall incidence of LE after extubation or the incidence of tracheal reintubation for LE. Among the prospectively defined risk factors, only female gender and an intubation duration of more than 36 h were significant for LE occurrence. In addition, none of the patients who had undergone intubation for less than 36 h required reintubation for LE.

Acute LE after extubation is a rare event in adults,[4,12,15] and its precise incidence is difficult to determine. The differences in rates observed in several prospective studies

can be ascribed to differences in the populations studied and in tube materials or criteria used for diagnosis of LE: LE has been reported to occur in 2–15.4% of patients after extubation.[3–5,15] Edema seems to be an extremely common finding at laryngoscopy, however, even in patients with uncomplicated postextubation courses.[12,19] According to our criteria, the overall incidence of LE stands within the range of incidences found in other studies because LE occurred in 28/663 patients (4.2%), of which 75% were classified as minor cases. The incidence of reintubation for LE in our series was 1%, which is close to the proportion reported by Gaussorgues et al.[4] (0.7%) and Dixon et al[15] (1.8%). As observed in several other studies,[4,6–8,16] symptoms of LE occurred shortly after extubation (75% within 8 h in our study).

An increased risk of tracheolaryngeal injury after tracheal intubation in humans has been associated with trauma during intubation,[6,19] intubation duration,[5,6,9] use of large tubes,[6,10,16] overinflation of cuffs,[20–23] intubation by the oral route,[12,24] and alteration of tracheal tube position.[6,25] The specific risk factors for LE occurrence, however, have not been well documented thus far. In our study, we found no relationship between LE incidence, age, SAPS, ID of tube, difficulty of intubation, route of intubation, or number of tubes inserted. We did find, however, that LE was significantly more frequent in patients with LDI than in those with SDI. In the SDI group, LE occurred in only 3 (0.9%) of 317 patients; no patient with SDI needed reintubation for LE. In the LDI group,
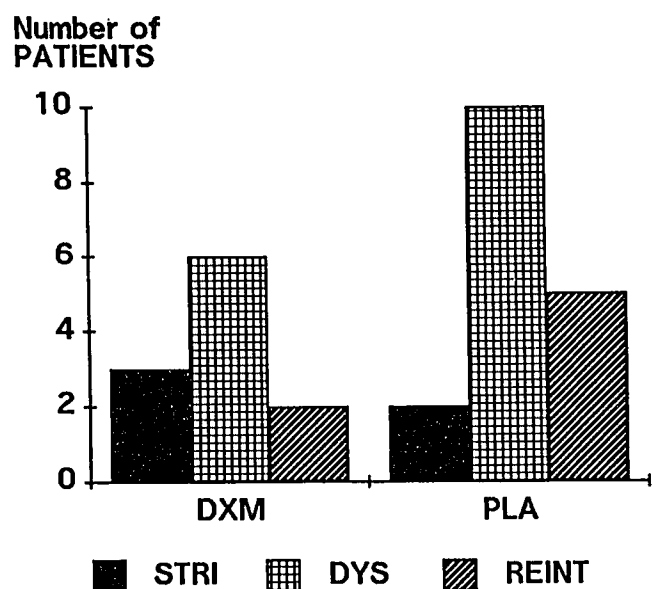
Number of PATIENTS

FIG. 2. Distribution of symptoms of laryngeal edema after endotracheal intubation. No difference in the incidence of stridor (STRI), dyspnea (DYS), or reintubation for laryngeal edema (REINT) was found between patients receiving placebo (PLA) or dexamethasone (DXM).

the mean intubation duration in patients with LE was not different from that of patients without LE (table 2), and the incidence of LE did not correlated with intubation duration. Although LDI was associated with a more severe clinical status at the time of intubation, analysis of our results by the ROC curve method[18] showed that age and SAPS (which takes into account the severity of admission diagnosis) were not predictive of LE. Moreover, LE was not related to admission diagnosis (data not shown). The relatively low number of patients in each of the six admission diagnosis groups, however, precludes any definitive conclusion.

Female gender was the second risk factor for LE identified in our study. Several authors have stressed gender as a risk factor for tracheolaryngeal injury after tracheal intubation[1,4,12,15,19]; to explain this, it has been suggested that the mucous membrane in male patients is more resistant to trauma[19] and that the smaller diameter of the female larynx relative to endotracheal tube diameter makes women more prone to LE.[1,19] Although in our study the ID of the tubes used for women was significantly smaller than that of the tubes used for men, the smaller dimensions of the female larynx indeed might have facilitated occurrence of LE symptoms. Thus, the use of smaller tubes for long-term tracheal intubation in women may reduce LE occurrence in this population. Such a reduction in tube size, however, could prevent or reduce the use of routine fiberoptic bronchoscopy.

Although corticosteroids inhibit early stages of the inflammatory process,[26] their role in preventing and treating LE has been controversial in both experimental and clinical studies. In monkeys undergoing trachea intubation with an excessively large tube, intramuscular administration of 4 mg dexamethasone at the time of extubation reduced polymorphonuclear infiltration but had no effect on edema formation, as assessed histologically.[10] However, LE was significantly reduced in monkeys given 4 mg dexamethasone iv 1 h after extubation and prevented when dexamethasone was given at the time of extubation.[11] In clinical studies, several authors have reported that steroids appeared to hasten the resolution of posttraumatic LE.[4,6,7,10,19] Therefore, steroids often are given routinely before extubation,[2,12] but no controlled study supports this strategy. In a recent prospective but uncontrolled study of 276 patients, Gaussorgues et al.[4] found that administration of 40 mg methylprednisolone intramuscularly plus 40 mg iv 30 min before extubation did not prevent LE after extubation.

Since the completion of our analysis, two prospective, randomized, double-blind studies have been carried out in children. Ferrara et al.[27] found that dexamethasone (0.25 mg/kg) given iv 30 min before extubation was not effective in preventing postextubation stridor. Likewise,

Tellez et al.[28] found that dexamethasone (0.5 mg/kg) given iv 6 h before extubation and continued every 6 h for a total of six doses was ineffective in preventing stridor.

It can be argued that a regimen other than ours could have been effective in preventing postextubation LE; however, we chose to give 8 mg dexamethasone 1 h before extubation because it was our routine practice and, more importantly, it was shown in a previous experimental study that the interval between dexamethasone injection and a measurable decrease in LE varied from 15 to 60 min.[11] Furthermore, in addition to having a long biological half-life of 36–72 h,[26] dexamethasone is a potent antiinflammatory agent.

Our results in 700 patients, indicate that, whatever the intubation duration, dexamethasone was no more effective than placebo in preventing either postextubation LE or its major complication, i.e., reintubation due to LE. It can be argued that the absence of a detectable effect of dexamethasone may be related to too small a study population relative to the low incidence of LE. However, assuming an incidence of LE in each group similar to that found in our study, as well as type 1 and 2 errors of 5%, a very large number of patients (7,000) would need to be studied to find a significant difference between dexamethasone and placebo. In addition, although the chance of missing a real effect of dexamethasone in our study population appears to be very high (greater than 49%), the large overlap of the 95% CIs for the incidence of LE in dexamethasone and placebo groups and the large 95% CI of the difference between these incidences make these estimations hazardous.

It also can be argued that, if the cost of dexamethasone is compared to the cost of additional days spent in an intensive care unit because of LE, systematic administration of dexamethasone may be cost-effective, especially in patients in whom the trachea is intubated for more than 36 h. Again, the large overlap of the 95% CIs for the incidence of LE in the two treatment groups does not allow us to suggest that dexamethasone may be cost-effective in preventing LE.

In conclusion, our study confirms that the overall incidence of LE after tracheal extubation in adults is low, but occurs significantly more often in patients with LDI and in female patients undergoing intubation. Dexamethasone does not appear to be useful for LE prevention after tracheal extubation, regardless of intubation duration.

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