12-h pretreatment with methylprednisolone versus placebo for prevention of postextubation laryngeal oedema: a randomised double-blind trial

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Summary

Background **The efficacy of corticosteroids in reducing the incidence of postextubation laryngeal oedema is controversial. We aimed to test our hypothesis that methylprednisolone started 12 h before a planned extubation could prevent postextubation laryngeal oedema.**

Methods **We did a placebo-controlled, double-blind multicentre trial in 761 adults in intensive-care units. Patients who were ventilated for more than 36 h and underwent a planned extubation received intravenous 20 mg methylprednisolone (n=380) or placebo (381) 12 h before extubation and every 4 h until tube removal. The primary endpoint was occurrence of laryngeal oedema within 24 h of extubation. Laryngeal oedema was clinically diagnosed and deemed serious if tracheal reintubation was needed. Analyses were done on a per protocol and intention-to-treat basis. This trial is registered at ClinicalTrials.gov, number NCT00199576.**

Findings **63 patients could not be assessed, mainly because of self-extubation (n=16) or cancelled extubation (44) between randomisation and planned extubation. 698 patients were analysed (343 in placebo group, 355 in methylprednisolone group). Methylprednisolone significantly reduced the incidence of postextubation laryngeal oedema (11 of 355, 3% *vs* 76 of 343, 22%, p<0·0001), the global incidence of reintubations (13 of 355, 4% *vs* 26 of 343, 8%, p=0·02), and the proportion of reintubations secondary to laryngeal oedema (one of 13, 8 % *vs* 14 of 26, 54%, p=0·005). One patient in each group died after extubation, and atelectasia occurred in one patient given methylprednisolone.**

Interpretation **Methylprednisolone started 12 h before a planned extubation substantially reduced the incidence of postextubation laryngeal oedema and reintubation. Such pretreatment should be considered in adult patients before a planned extubation that follows a tracheal intubation of more than 36 h.**

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Introduction

Tracheal intubation for respiratory support is part of the routine acute care provided to critically ill patients, but can lead to substantial morbidity.[1,2] Despite use of high-volume and low-pressure cuff, postextubation laryngeal oedema is one of the most frequent and severe complications of tracheal intubation, since its incidence can reach 22%[3] and can result in death.[4] Laryngeal oedema typically occurs shortly after extubation,[5–7] but is more common after a tracheal intubation for longer than 36 h.[5] Importantly, severe laryngeal oedema is one of the main causes of respiratory distress after extubation[8] that might require tracheal reintubation.[3,5,6,9,10] The occurrence of post-extubation laryngeal oedema can therefore result in prolonged mechanical ventilation with potential morbidity, additional cost, and longer intensive-care unit stay.

Experimental, autopsy, and clinical studies have shown that prolonged tracheal intubation can lead to oedema, inflammation, and ulceration of both the laryngeal and tracheal mucosa, especially at the level of the vocal cords and at the site of the cuff.[1,11–15] Animal studies have suggested that corticosteroids could reduce laryngeal infiltration by inflammatory cells secondary to prolonged intubation.[15] However, only a few randomised studies have been done to investigate the ability of corticosteroids to prevent postextubation laryngeal oedema,[3,5,7,16–19] and particularly few have been done in patients in intensive-care units.[3,5,19] These studies have used different regimens, resulting in discrepant findings. We tested the hypothesis that pretreatment with corticosteroids initiated 12 h before a planned extubation might efficiently prevent the occurrence of postextubation laryngeal oedema in critically ill adults who had been mechanically ventilated for more than 36 h in an intensive-care unit.

Methods

Patients

The study protocol was approved by the Institutional Review Board on human research of Limoges teaching hospital on May 25, 2000 (00015). All patients or their next-of-kin gave written informed consent before enrolment into the study.

The eligibility criteria for the study were: referral to one of the 15 participating intensive-care units of the Association des Réanimateurs du Centre-Ouest (ARCO) between March, 2001, and January, 2002; age older than 18 years, duration of mechanical ventilation more than 36 h, and planned extubation during the stay in the intensive-care unit. Patients were excluded if they were

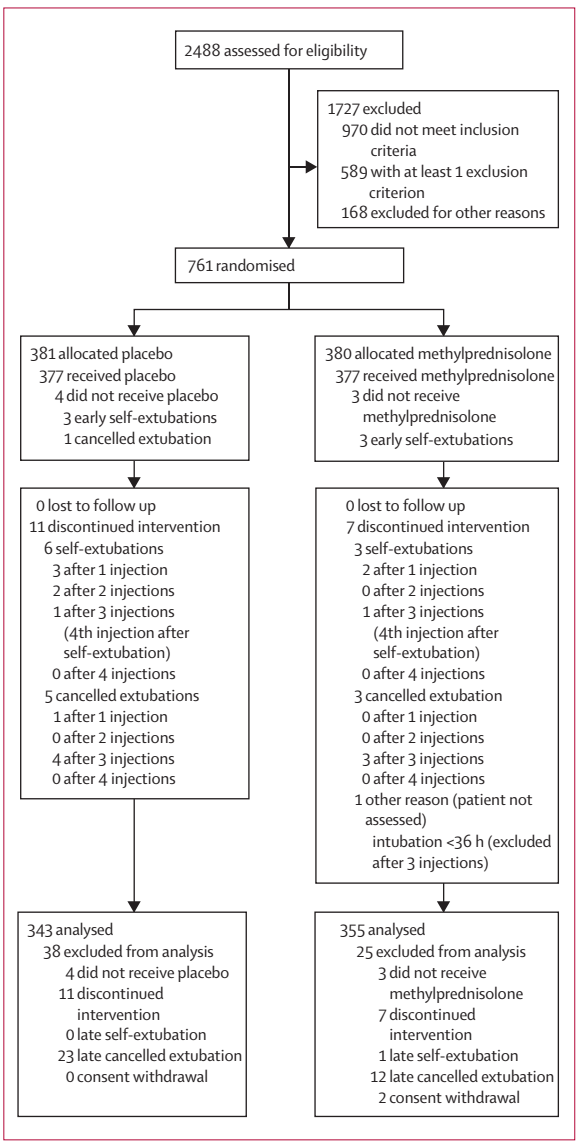

Figure: **Trial profile**

pregnant, had a history of postextubation upper-airway obstruction, presented with throat disease or surgery, had a tracheostomy, were chronically treated with non-steroidal anti-inflammatory drugs or corticosteroids, had already participated in this study, or were already included in another trial.

Procedures

We randomly assigned patients either intravenous methylprednisolone hemisuccinate (methylprednisolone, Merck, Lyon, France), initiated 12 h before planned extubation at a dose of 20 mg and continued every 4 h with the last injection immediately before tube removal (total dose: 80 mg), or a placebo (intravenous isotonic saline) that was identical in appearance to the active drug. A computer generated randomisation list in balanced blocks of unequal size was attributed to each participating intensive-care unit. Treatment assignments were contained in sealed opaque individual envelopes which were numbered sequentially.

After randomisation, a nurse who was not involved in patient care opened the next envelope and independently prepared the solution to be injected (in four syringes). Syringes were labelled with the date and time of injection, fully covered, and all contained the same volume of solution (10 mL) to ensure they were given in double-blind conditions for patients, nurses, attending physicians, and all co-investigators. In no instance was the treatment code broken until the follow-up of the last enrolled patient was completed. Treatment of postextubation laryngeal oedema was left to the discretion of attending physicians, including the use of corticosteroids and the indication of tracheal reintubation, according to standard care in each participating unit.

We recorded the following characteristics at the time of enrolment into the study: age, sex, height, weight, body-mass index, reason for admission to the intensive-care unit, Simplified Acute Physiology Score (SAPS) II on admission, difficulties at intubation defined as more than two attempts before successful intubation of the trachea, number of intubations, route of intubation, internal diameter of the cuffed tube, duration of intubation for mechanical ventilation, and administration of vasopressors.

The primary endpoint of the study was the occurrence of laryngeal oedema within the 24 h after the planned extubation. Laryngeal oedema was clinically defined as the development of upper-airway obstruction after extubation,[4] and classified as minor or major according to the severity of respiratory distress. Minor laryngeal oedema corresponded to a stridor defined as an audible high-pitched inspiratory wheeze associated with a respiratory distress needing medical intervention.[19,20] Respiratory distress was typically characterised by a prolonged inspiratory phase and the recruitment of accessory respiratory muscles (ie, subcostal or suprasternal or intercostal retraction, or two of three, or all three).[4] Major laryngeal oedema was defined as severe respiratory distress needing tracheal reintubation secondary to upper-airway obstruction visualised during laryngoscopy. Minor laryngeal oedema was purposely not confirmed by direct laryngoscopy or fibrescopic examination, because these procedures are unsafe in unstable critically ill patients.[3,5] To minimise the variability with respect to clinical diagnosis of postextubation laryngeal oedema, the study endpoint was assessed by the same investigator in every unit. This approach was made possible because planned extubation is generally done during the morning and laryngeal oedema usually occurs shortly after extubation.[5–7,9]

At each clinical assessment, the patient was examined for at least 2 min and the previously described clinical signs of laryngeal oedema were systematically sought. Clinical assessment for the presence of laryngeal oedema

was done at 10 min, 30 min, 1 h, 1·5 h, 3 h, 6 h, 12 h, and 24 h after extubation. Delay of occurrence of laryngeal oedema corresponded to the time lag separating the extubation and the clinically documented upper-airway obstruction. The need for reintubation was recorded during the study period—ie, up to 24 h after the planned extubation. Treatment safety was assessed from randomisation to 24 h after the planned extubation and mainly focused on the occurrence of serious adverse events. Adverse events were declared to our institution within 24 h and were validated during visits of monitoring in each participating centre.

Statistical analysis

The sample-size was calculated on the basis of preliminary data obtained in participating centres. During 1 month, 99 patients underwent planned extubation and 14 of them received corticosteroids initiated 12 h before extubation, as decided by the attending physicians. Postextubation laryngeal oedema occurred in one of the 14 patients given corticosteroids (7%) and in 13 of the 85 patients not given the drug (15%). A sample size of 736 patients was therefore calculated to be able to detect a reduction of 50% of the 15% incidence of laryngeal oedema within the 24 h after extubation with a two-sided test with a type 1 error of 5% and a power of 90%.

Statistical analyses were done with SAS statistical software (version 9.1). Continuous variables (expressed as medians and IQR [1st–3rd]) were compared between groups at randomisation and at time of assessment with Wilcoxon tests. Categorical variables (expressed as numbers and percentages) were compared between groups at randomisation and at time of assessment with χ^2 tests. Fisher's exact test was used when necessary. In the efficacy analysis, patients were a priori deemed unassessable (and excluded from the analysis) if self-extubation occurred or if the extubation was cancelled (ie, deterioration of patient status precluding the scheduled extubation) between randomisation and planned extubation, as specifically mentioned in the protocol. We did not specify risk factors for postextubation laryngeal oedema in the protocol, but determined them using univariate analysis (with the same tests as for between group comparisons) followed by multivariate (using Cox regression) analysis. We incorporated the variables associated with postextubation laryngeal oedema with a p value of less than 0·15 in univariate analyses into the multivariate analysis using forward and stepwise selection procedures. Hazard ratios and their 95% CI were estimated. In the Cox model, patients who did not develop postextubation laryngeal oedema, but needed reintubation for clinical deterioration or died during the 24-h follow-up, were censored at the time of their reintubation or at the time of their death, respectively. Similar analyses were done to assess risk factors for postextubation major laryngeal oedema. In the Cox model, the patients who needed reintubation for clinical deterioration (whether or not they had developed postextubation laryngeal oedema before—if they had, we checked that reintubation was not on account of postextubation laryngeal oedema), or the patients who died without being reintubated during the 24-h follow-up were censored at the time of their reintubation or at the time of their death, respectively. For all tests, a p value less than 0·05 was deemed significant. Analyses were done on a per protocol and intention-to-treat basis. This study was registered at ClinicalTrials.gov, number NCT00199576.

	Placebo (n=381)	Methylprednisolone (n=380)	Total (n=761)
Age (years)	66 (48–74)	65 (45·5–75)	66 (47–74)
Sex			
Male	246 (65%)	238 (63%)	484 (64%)
Female	135 (35%)	142 (37%)	277 (36%)
Height (cm)	170 (161–175)*	170 (162–175)†	170 (162–175)
Weight (kg)	72 (63–85)‡	73·5 (62–83)§	72 (63–83)
Body-mass index (kg/m²)	¶	†	
Underweight (<18·5)	14 (4%)	23 (6%)	37 (5%)
Healthy (18·5–25)	182 (48%)	171 (46%)	353 (47%)
Overweight (>25–30)	102 (27%)	107 (29%)	209 (28%)
Obese (>30)	79 (21%)	74 (20%)	153 (20%)
Reason for admission			
Medical	229 (60%)	240 (63%)	469 (62%)
Surgical	74 (19%)	74 (19%)	148 (19%)
Trauma	78 (20%)	66 (17%)	144 (19%)
SAPS II	38 (29–48)‡	40 (30–51)‡	39 (29–50)
Difficulties at intubation			
Yes	11 (3%)	5 (1%)	16 (2%)
No	370 (97%)	375 (99%)	745 (98%)
Number of intubations			
1	317 (83%)	318 (84%)	635 (83%)
2	48 (13%)	55 (14%)	103 (14%)
>2	16 (4%)	7 (2%)	23 (3%)
Route of intubation	‡		
Orotracheal	359 (94%)	343 (90%)	702 (92%)
Nasotracheal	21 (6%)	37 (10%)	58 (8%)
Tube diameter (mm)	‡	‡	
<7	1 (0%)	2 (1%)	3 (0%)
7	23 (6%)	19 (5%)	42 (6%)
7·5	176 (46%)	181 (48%)	357 (47%)
8	132 (35%)	137 (36%)	269 (35%)
8·5	48 (13%)	40 (11%)	88 (12%)
Duration of intubation (days)			
<7	187 (49%)	194 (51%)	381 (50%)
≥7	194 (51%)	186 (49%)	380 (50%)
Vasopressors			
Yes	146 (38%)	152 (40%)	298 (39%)
No	235 (62%)	228 (60%)	463 (61%)

Data are median (IQR [1st–3rd]) for continuous variables and number (%) for categorical variables. Data missing for *three patients; †five patients; ‡one patient; §two patients; ¶four patients.

Table 1: **Baseline characteristics**

	Placebo (n=343)	Methylprednisolone (n=355)	Total (n=698)	p
Laryngeal oedema				<0·0001
No	267 (78%)	344 (97%)	611 (88%)	
Yes	76 (22%)	11 (3%)	87 (12%)	
Severity of oedema				0·68
Minor	62 (82%)	10 (91%)	72 (83%)	
Major	14 (18%)	1 (9%)	15 (17%)	
Delay of occurrence*				0·83
≤5 min	36 (47%)	5 (45%)	41 (47%)	
6–30 min	26 (34%)	3 (27%)	29 (33%)	
>30 min	14 (18%)	3 (27%)	17 (20%)	
Reintubation				0·02
No	317 (92%)	342 (96%)	659 (94%)	
Yes	26 (8%)	13 (4%)	39 (6%)	
Context of reintubation				0·007
No laryngeal oedema	9 (35%)	11 (85%)	20 (51%)	
Laryngeal oedema				
Reintubation linked to oedema	14 (54%)	1 (8%)	15 (38%)	
Reintubation not linked to oedema	3 (12%)	1 (8%)	4 (10%)	

Data are number (%). Comparisons between groups were done with χ^2 test (or Fisher's exact test, when necessary). Minor laryngeal oedema=stridor defined as audible high-pitched inspiratory wheeze associated with respiratory distress needing medical intervention. Major laryngeal oedema=severe respiratory distress needing tracheal reintubation secondary to upper-airway obstruction visualised during laryngoscopy. *Delay of occurrence relative to extubation.

Table 2: **Main and secondary endpoints**

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, or interpretation of data, or writing of this report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

The figure shows the trial profile. The main reasons for non-inclusion were age younger than 18 years (n=60), duration of mechanical ventilation less than 36 h (759), unplanned extubation (122), consent refusal (29), pregnancy (4), history of laryngeal oedema (29), tracheostomy (205), chronic treatment with non-steroidal anti-inflammatory drugs or corticosteroids (297), and participation in another trial (54).

Table 1 shows the baseline characteristics of the study population. The two groups were similar apart from a higher rate of nasotracheal intubation in patients given methylprednisolone (37 of 380 [10%] *vs* 21 of 381 [6%]). The median duration of intubation before randomisation was 6 days (IQR 4–11). Of randomised patients, 63 could not be assessed, mainly because of self-extubation (n=16) or cancelled extubation (44) between randomisation and planned extubation, or because of consent withdrawal in two patients, or because of an inclusion criterion violation (duration of mechanical ventilation <36 h), which led to exclusion in one patient. Finally, 698 patients were included in the analysis (figure). The main characteristics at randomisation of these assessable patients were similar to those of the study population (data not shown).

Table 2 shows the findings for the main and secondary endpoints. Methylprednisolone significantly reduced the incidence of postextubation laryngeal oedema, with a more than seven-fold reduction in incidence. When the analysis was adjusted by the route of intubation with a Mantel-Haenszel test, the p value for difference between the two groups did not change (p<0·0001). Methylprednisolone did not affect the severity of laryngeal oedema or the delay of occurrence relative to extubation, which did not differ between the two groups (table 2). Similar results were obtained in an intention-to-treat analysis of all assessed patients (11 of 358 [3%] *vs* 76 of 345 [22%], p<0·0001). This analysis included five additional patients (two in the placebo group, three in the methylprednisolone group) who were deemed non-assessable according to the protocol, but who were followed-up. When the intention-to-treat analysis was done in all randomised patients with the maximal bias hypothesis (non-assessed patients were recorded as not having laryngeal oedema if they belonged to the placebo group and as having the disorder if they belonged to the methylprednisolone group), the difference between groups for the primary endpoint was unaltered (33 of 380 [9%] *vs* 76 of 381 [20%], p<0·0001). The median delay of occurrence of postextubation laryngeal oedema was 10 min (IQR 5–30) in the placebo group and 30 min (IQR 0–120) in the methylprednisolone group (p=0·73), with a large variability (<5 min in 47% of patients, 6–30 min in 33%, >30 min in 20%). Methylprednisolone also reduced the global incidence of reintubations (13 of 355 [4%] *vs* 26 of 343 [8%], p=0·02), reintubations owing to postextubation laryngeal oedema—ie, those for major laryngeal oedema—being almost totally abolished (one of 13 [8%] *vs* 14 of 26 [54%], p=0·005).

Table 3 shows the results of the univariate analysis undertaken to identify risk factors for postextubation laryngeal oedema. Patients who developed this disorder were mainly of female sex, of shorter height, more often admitted to the intensive-care unit for trauma, and more often intubated via the orotracheal route with larger tubes and for a shorter period of time (table 3). To better assess the relation between patient size, tube size, and risk of laryngeal oedema, we also investigated the prognostic value of the ratio of height divided by tube diameter in a post-hoc analysis. This ratio was significantly linked to occurrence of postextubation laryngeal oedema, with smaller ratios in patients who had the disorder than in those who did not. Moreover, although median internal diameter of tracheal tubes was significantly smaller in women than in men (200 of 255 [78%] in women *vs* 170 of 441 [39%] in men, p<0·0001, for <7·5 mm tubes), the incidence of laryngeal oedema was significantly higher in women than in men (45 of 255 [18%] *vs* 42 of 443 [9%], respectively, p=0·002).

Table 4 shows the results of the multivariate analysis undertaken to identify the independent risk factors for postextubation laryngeal oedema (Cox regression). In each case, forward and stepwise selection procedures yielded the same results. The absence of pretreatment with methylprednisolone was the most important risk factor, with a hazard ratio of more than 8. Other independent risk factors were the female sex, admission to the intensive-care unit for trauma, short duration of intubation, and smaller height to tube diameter ratio. For major postextubation laryngeal oedema, the absence of pretreatment with methylprednisolone (hazard ratio 15·7, 95% CI 2·06–119·16, p=0·008) and female sex (3·82, 95% CI 1·31–11·17, p=0·01) were the only two variables which remained in the two models.

Table 5 shows the number and type of adverse events reported between randomisation and end of follow-up. Of randomised patients, none died during the 12 h of treatment. One patient in each group died after extubation. The patient from the placebo group, for whom a decision of limitation of care had been taken, died nearly a day after extubation from respiratory failure. This patient had not developed postextubation laryngeal oedema and had not been reintubated. The patient from the methylprednisolone group died just over a day after extubation from a septic shock, which had necessitated reintubation 12 h after extubation. Atelectasia was reported for one patient a day after extubation. This event regressed 12 h after with symptomatic treatment.

	No laryngeal oedema (n=611)	Laryngeal oedema (n=87)	Total (n=698)	p
Age (years)	66 (48–74)	66 (44–75)	66 (47–74)	0·86
Sex				0·002
Male	401 (66%)	42 (48%)	443 (63%)	
Female	210 (34%)	45 (52%)	255 (37%)	
Height (cm)	170 (163–175)*	165 (159–175)	170 (162–175)	0·006
Weight (kg)	72 (63–83)†	70 (61–85)	72 (63–83)	0·55
Body-mass index (kg/m²)	‡			0·24
Underweight (<18·5)	30 (5%)	4 (5%)	34 (5%)	
Healthy (18·5–25)	285 (47%)	46 (53%)	331 (48%)	
Overweight (>25–30)	172 (28%)	16 (18%)	188 (27%)	
Obese (>30)	117 (19%)	21 (24%)	138 (20%)	
Reason for admission				0·14
Medical	377 (62%)	51 (59%)	428 (61%)	
Surgical	130 (21%)	14 (16%)	144 (21%)	
Trauma	104 (17%)	22 (25%)	126 (18%)	
SAPS II	39 (29–50)	38 (28–48)	39 (29–50)	0·41
Difficulties at intubation				0·71
Yes	14 (2%)	1 (1%)	15 (2%)	
No	597 (98%)	86 (99%)	683 (98%)	
Number of intubations				0·68
1	508 (83%)	75 (86%)	583 (84%)	
2	84 (14%)	9 (10%)	93 (13%)	
>2	19 (3%)	3 (3%)	22 (3%)	
Route of intubation				0·01
Orotracheal	555 (91%)	86 (99%)	641 (92%)	
Nasotracheal	56 (9%)	1 (1%)	57 (8%)	
Tube diameter (mm)	§			0·13
<7	1 (0%)	0 (0%)	1 (0%)	
7	32 (5%)	6 (7%)	38 (5%)	
7·5	289 (47%)	42 (48%)	331 (48%)	
8	222 (36%)	23 (26%)	245 (35%)	
8·5	65 (11%)	16 (18%)	81 (12%)	
Duration of intubation (days)				0·09
<7	291 (48%)	50 (57%)	341 (49%)	
≥7	320 (52%)	37 (43%)	357 (51%)	
Vasopressors				0·84
Yes	239 (39%)	35 (40%)	274 (39%)	
No	372 (61%)	52 (60%)	424 (61%)	
Height/tube diameter	219 (210–227)¶	213 (206–224)	217 (208–226)	0·002
Treatment				<0·0001
Placebo	267 (44%)	76 (87%)	343 (49%)	
Methylprednisolone	344 (56%)	11 (13%)	355 (51%)	

Data are median (IQR [1st–3rd]) for continuous variables and number (%) for categorical variables. Comparisons between groups done with Wilcoxon test for continuous variables and χ^2 test (or Fisher's exact test, when necessary) for categorical variables. Data missing for *six patients; †one patient; ‡seven patients; §two patients; ¶eight patients. No data missing in laryngeal oedema group.

Table 3: **Univariate analysis of risk factors for postextubation laryngeal oedema**

Discussion

We have shown the efficacy of corticosteroids in preventing the occurrence of postextubation laryngeal oedema after a planned extubation in adult patients in intensive-care units. Importantly, the 12-h pretreatment with methylprednisolone not only reduced the global incidence of postextubation laryngeal oedema, but also the incidence of tracheal reintubation owing to major laryngeal oedema.

The various incidences of postextubation laryngeal oedema reported in clinical studies range from 2% to 22%.[1,3,5,9,20–22] This variation is presumably explained by the use of subjective clinical diagnostic criteria in various study populations. With previously proposed diagnostic criteria,[4,19,20] the overall incidence of laryngeal oedema in the patients in our study was 13%, whereas it ranged from 7% in 346 patients intubated for a mean duration of about 10 days[5] to 22% in 77 patients ventilated for a mean duration of about 6 days.[3] Although the clinical diagnosis of minor laryngeal oedema remains subjective, major laryngeal oedema needing tracheal reintubation is a more objective endpoint since upper-airway obstruction can be documented during the direct laryngoscopy required for the procedure. In our trial, the incidence of tracheal reintubation secondary to the development of major laryngeal oedema reached 2%. This result is in accord with the rates of reintubation for severe upper-airway obstruction previously reported in adult patients, ranging between 0·7% and 4·7%.[3,5,9,10,19,20] Finally, as already reported,[5–7] symptoms of laryngeal oedema occurred shortly after extubation regardless of their severity.

	Regression coefficient β (SE)	Hazard ratio (95% CI)	p
Methylprednisolone (n)	2·13 (0·32)	8·44 (4·48–15·92)	<0·0001
Female sex	0·70 (0·22)	2·02 (1·31–3·11)	0·0015
Reason for admission (trauma *vs* others)	0·75 (0·25)	2·12 (1·29–3·49)	0·0030
Duration of intubation (<7 days *vs* ≥7 days)	0·57 (0·22)	1·77 (1·15–2·73)	0·0092
Height/tube diameter	–0·02 (0·01)	0·978 (0·962–0·995)	0·0102

Variables introduced in both models (forward and stepwise): treatment, sex, height, reason for admission, route of intubation, tube diameter (<8, ≥8 mm), duration of intubation (<7, ≥7 days), height/tube diameter.

Table 4: **Multivariate analysis of risk factors for postextubation laryngeal oedema (Cox regression)**

	Placebo (n=381)	Methylprednisolone (n=380)	Total (n=761)
Patients with at least one serious adverse event	1 (0·3%)	1 (0·3%)	2 (0·3%)
Respiratory failure and death 23 h 15 min after extubation	1	0	1
Septic shock and death 26 h after extubation	0	1	1
Patients with at least one other adverse event	0 (0·0%)	1 (0·3%)	1 (0·1%)
Atelectasia 24 h after extubation	0	1	1

Data are number (%).

Table 5: **Adverse events**

The rationale for treatment with corticosteroids before a planned extubation relies on the drug's ability to reduce the inflammatory process associated with the tracheal injuries that develop after extubation[14] and can lead to upper-airway obstruction.[12] However, with the exception of one trial in children[7] and one in adults,[19] all randomised double-blind studies in ventilated patients in intensive-care units showed that corticosteroids did not efficiently prevent the occurrence of postextubation laryngeal oedema.[3,5,16,17] Interestingly, the positive trials started corticosteroids 6–24 h before planned extubation,[7,19] whereas the negative trials started their regimens 30 min to 6 h before extubation.[3,5,16,17] As previously postulated by several investigators,[3,5,16] those negative trials might have used inappropriate regimens. In the present trial, methylprednisolone was highly effective when started 12 h before planned extubation and given every 4 h for a total dose of 80 mg. This regimen, which combines early initiation of treatment and repeated administration every plasma half-life,[23] presumably allowed the anti-inflammatory effects of methylprednisolone to begin with the endotracheal cuffed tube in place, thus limiting the mucosal swelling after extubation.[14,15] A study in high-risk adults ventilated in the intensive-care unit with a low cuff-leak volume,[19] showed that methylprednisolone efficiently prevented postextubation laryngeal oedema when started 24 h before a planned extubation. A single injection of 40 mg of methylprednisolone given 24 h before the planned extubation had a similar protective effect to when given every 6 h for 24 h (for a total dose of 160 mg). Our results are in keeping with these results and support the initiation of methylprednisolone at least 12 h before planned extubation for optimum prevention of postextubation laryngeal oedema in adults.

In addition to study group allocation, female sex, admission to the intensive-care unit for trauma, and duration of tracheal intubation were independent risk factors for postextubation laryngeal oedema in our patients. The incidence of postextubation laryngeal oedema was higher in women than in men despite the use of smaller tracheal tube diameters in women. This result might be explained by an increased tracheal tube size to laryngeal and tracheal size ratio in women[14] that promotes mechanical injuries to the tracheal mucosa and subsequent swelling.[1,3,5,9,10] Admission to the intensive-care unit for trauma when compared with medical or surgical causes was another independent risk factor for the occurrence of postextubation laryngeal oedema. Most patients sustaining multisystem trauma were ventilated by a prehospital medical team under suboptimum conditions and might have undergone more traumatic tracheal intubations than did patients referred for surgery and intubated in more controlled settings. The duration of tracheal intubation was another independent factor of postextubation laryngeal oedema in our patients. Surprisingly, prolonged tracheal intubation seemed to be protective for the occurrence of postextubation laryngeal oedema. Clinical studies have reported discrepant results[1,3,5,14,17,20,21,24] and animal studies suggest that laryngeal infiltration by inflammatory cells declines after 48 h of tracheal intubation.[15] All other variables, including the use and duration of vasopressor therapy that might limit mucosal swelling after extubation, were not predictive of postextubation laryngeal oedema.

Our study population was not restricted to patients deemed at high risk of developing postextubation laryngeal oedema. Specifically, a cuff-leak test was not done to screen patients before study enrolment.[25] In studies of patients in intensive-care units selected on the basis of a low cuff-leak volume, methylprednisolone efficiently reduces the incidence of postextubation stridor and reintubation.[19] Although use of pretreatment with methylprednisolone could be restricted to the subset of patients at high risk of postextubation laryngeal oedema, one should bear in mind that this complication is unpredictable and that the positive predictive value of a failed cuff-leak test is fairly low in adults.[26] The 12-h pretreatment with a total dose of 80 mg of methylprednisolone seemed to be safe, since no serious adverse event occurred that could be related to steroid therapy. Similar results have been reported in other trials of the effects of short-term (<24 h) steroid therapy.[19,27]

In conclusion, we have shown that 12-h pretreatment with methylprednisolone before a planned extubation in patients in intensive-care units ventilated for more than 36 h is highly effective in reducing the incidence of postextubation laryngeal oedema and tracheal re-intubation for upper-airway obstruction. Since post-

extubation laryngeal oedema is one of the most common causes of extubation failure in intensive-care units and its development is unpredictable, this pretreatment could be considered in adult patients before a planned extubation that follows a tracheal intubation of more than 36 h.

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Contributors

B François, E Bellissant, PM Preux, and P Vignon contributed to the design of clinical study, data analysis, and preparation of the manuscript. B François, V Gissot, A Desachy, S Normand, T Boulain, O Brenet contributed to the recruitment and clinical assessment of patients throughout the study.

Conflict of interest statement

We declare that we have no conflict of interest.

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