Dexamethasone in Prevention of Postextubation Stridor in Ventilated Children: A Randomized, Double-blinded, Placebo-controlled Trial

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Abstract

Background and aims: Postextubation stridor (PES) is a serious complication in ventilated patients which increases the length of stay in intensive care units (ICUs). We studied the efficacy of dexamethasone in prevention of PES in ventilated children.

Materials and methods: A randomized, double–blinded, placebo-controlled trial was carried out in pediatric ICU. Children (2 months to 12 years) who underwent mechanical ventilation for 48 hours were randomized into two groups to receive either dexamethasone at 0.15 mg/kg/dose or normal saline for 6 doses with first dose given 6–12 hours prior to planned extubation. Patients were hourly monitored for vital signs and appearance of stridor using Westley croup score (WCS) within 72 hours after extubation. Whenever the score exceeded 4, nebulized adrenaline (1:1,000 at 0.5 mL/kg/dose) was given. The primary outcome was occurrence of PES.

Results: Dexamethasone group comprised of 42 children while placebo group had 38 children. Baseline characteristics of two groups were similar. Overall PES occurred in 48.7% patients, 42.8% (18/42) in dexamethasone group, and 55.2% (21/38) in placebo group [$p = 0.26$, odds ratio (OR) 95% confidence interval (CI) = 0.60 (0.25–1.47)]. WCS >4 was present in 28.5% (12/42) of dexamethasone group vs 47.3% (18/38) of placebo group [$p = 0.08$, OR (95% CI) = 0.37 (0.12–1.06)]. There was no difference in reintubation rates in two groups [$p = 0.9$, OR (95% CI) = 1.06 (0.32–3.51)].

Conclusion: We found no beneficial role of the studied dose of dexamethasone (0.15 mg/kg) over placebo on the incidence of PES.

Keywords: Adrenaline nebulization, Dexamethasone, Extubation failure, Postextubation stridor, Reintubation.

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Introduction

Endotracheal intubation is one of the lifesaving procedures frequently performed in intensive care units (ICUs) to ventilate patients. The presence of endotracheal tube (ETT) in the trachea during the period of mechanical ventilation has the potential for development of glottic and subglottic edema causing airway obstruction, resulting in stridor on extubation. The incidence of postextubation stridor (PES) may occur in 2–73% of critically ill pediatric patients.[1,2] PES is a serious complication of endotracheal intubation and may prolong the length of stay in ICU and increases morbidity. PES is cited as the causative factor in as many as 17–22% of extubation failures.[3,4]

Various therapies are being used for prevention and treatment of PES but have shown inconsistent results in pediatric population.[3–8] Dexamethasone is a potent glucocorticoid which is often used prophylactically to prevent PES.[9] The potential benefit of dexamethasone is based on its anti-inflammatory actions, which inhibits the release of inflammatory mediators and decreases capillary permeability. Although being commonly used in ICUs as prophylaxis for PES,[9] there is scarcity of data from developing countries regarding its efficacy in children.[10,11] A systematic assessment of efficacy of corticosteroids in PES is required before widespread recommendation of this treatment. We conducted a randomized controlled trial (RCT) in a tertiary care hospital to study the effects of dexamethasone therapy in preventing PES in children.

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Materials and Methods

A randomized, double-blinded, placebo-controlled study was conducted in children admitted to the pediatric ICU (PICU) of a tertiary hospital from March 2014 to February 2015. This is a seven-bedded dedicated and fully equipped (except ECMO) PICU facility staffed by trained intensive care consultants, round the clock registrars helped by pediatric postgraduate students along with skilled nursing personnel. The study was approved by the institutional ethical committee (F.11/IEC/MAMC/10/No.199, dated November 20, 2013) in accordance with Helsinki declaration. A written informed consent was taken from the parents and guardians

of the patients before enrolling them in the study. The endotracheal intubation was performed by trained registrars in all patients.

Participants and Sample Size

Children in the age group of 2 months to 12 years who were ventilated for at least 48 hours and in whom extubation was planned in next 6–12 hours were included in the study. Extubation criteria included hemodynamic stability, arterial blood gas within normal range, FiO_2 requirement ≤45%, positive end expiratory pressure (PEEP) ≤5 cm H_2O and either weaned to low set frequency of respiration (around 5–7/minute for children more than 1 year of age and 10–12/minutes for infants) or were directly taken for spontaneous breathing trial by pressure support. Finally, all were given a short T piece trial (around 2 hours) before extubation. Children who had received steroids within 7 days prior to extubation, previous failed extubations, self-extubations, and tracheostomized patients were excluded from the study.

Sample size calculation was based on a mean value of outcomes of the few available pediatric studies (RCTs).[1,10,12] Using an alpha of 0.05 and beta of 0.2, the calculated sample size was 36 in each group. We included 40 patients in each group.

Randomization and Blinding

All eligible children were stratified into less than 1 year and more than 1 year. Block randomization was done within each group into group I (dexamethasone group) and group II (placebo group). Randomization was done by a person who was not directly involved with the study. It was placed in serially numbered opaque sealed envelopes and handed to another doctor posted outside PICU and not involved in monitoring or case management. The injection of saline/dexamethasone was prepared by him after opening the envelope which was then handed over to the staff nurse for administering to cases. All the six doses for all patients were prepared by the same doctor at one time and kept in the refrigerator by the name of the patient. Both dexamethasone and saline are colorless solutions and therefore the patient and the investigator as well as the entire PICU team were unaware of the treatment.

Intervention

Group A received dexamethasone at 0.15 mg/kg/dose[13] every 6 hourly for 6 doses with the first dose administered at least 6–12 hours prior to planned extubation. Group B received normal saline in equivalent volume and at same timings. Immediately after extubation humidified oxygen by venturimask (older children) or hood (infants) was given to all patients and then weaned off as possible. Patient vitals, oxygen saturation, and stridor scoring using Westley croup score (WCS) were recorded half hourly for 2 hours and then hourly till 24 hours postextubation.[14] Whenever WCS exceeded 4, intervention in the form of nebulized adrenaline 1:1,000 at 0.5 mL/kg/dose mixed with saline to make a volume of 4 mL (total adrenaline in a dose did not exceed 4 mL) was given and repeated continuously till the stridor subsided and again repeated whenever there was reappearance of stridor.

Failure of therapy was considered when WCS remained >4 for 1 hour after adrenaline nebulization or >4 at any time later in spite of trying continuous adrenaline nebulization. Rescue dexamethasone was given at 0.15 mg/kg/dose for 6 doses to such patients. Reintubation was done at any time when patient had significant respiratory distress/respiratory fatigue or desaturation to <90% on oxygen, presence of cyanosis, bradycardia, or had CO_2 retention (PCO_2 = 60 mm Hg with pH<7.25). The decision to reintubate was taken by the intensive care consultant/registrars. To look for adverse effects of dexamethasone, blood sugar by glucostix was done 6 hourly, till 12 hours after the last dose of dexamethasone, blood pressure was monitored 4 hourly and any gastrointestinal bleed was checked 3 hourly by nasogastric tube aspiration.

Data Collection

Baseline demographic data of the patients were recorded. Clinical data included indication of ventilation, date of intubation and extubation, duration of intubation, type of ETT used (cuffed or uncuffed), leak around ETT, place of intubation (e.g., in PICU or operation theater by trained intensivists or anesthetists, respectively, or in wards by registrars), the number of reintubations and GCS at the time of extubation. After extubation vital parameters, oxygen saturation, time of onset of PES, and stridor score (WCS) were recorded.

Outcomes and Measurements

The primary outcome was the occurrence of PES (inspiratory sound within 72 hours after extubation). The secondary outcomes were rate of reintubation and the severity of stridor (WCS > 4).

Statistical Analysis

Analysis was done using SPSS (version 16). Results were expressed as proportions for categorical data, mean ± standard deviation for normal distributed variables and as median for non-normal distributed variables. Univariate comparisons for categorical data were performed by using Chi-square test or Fisher's exact test. The difference among the two groups was tested by using parametric (Student's *t* test) and nonparametric (Mann–Whitney *U*) tests. Multivariate logistic regression was done for baseline variables with $p < 0.05$. Repeated measures analysis of variance (ANOVA) was used for comparing WCS over different time intervals and between the groups. A *p* value of less than 0.05 was considered significant.

Results

A total 109 patients were intubated and mechanically ventilated for >48 hours during the study period. Twenty-nine of these were excluded and 80 were randomized into 2 groups. Flowchart 1 shows the enrolment of patients in the two groups. Stratification of the patients based on age group (<1 and >1 year) ensured that we had equal representation of children in the two intervention groups. However, due to small number of cases in individual strata, we did not separately analyze the results in infants and older children. Table 1 shows that both groups matched for age, sex, diagnosis at admission, indication of ventilation, leak around ETT, and GCS at the time of extubation. However, the patients in dexamethasone group had longer duration of PICU stay (p = 0.03) were ventilated for a longer duration (p = 0.02) and had received skeletal muscle relaxant for a longer duration (p = 0.03) than the placebo group.

In the present study, 48.7% (39/80) patients developed PES. Table 2 shows comparison of various characteristics of patients who developed PES and those who did not. Median age of cases who developed PES was 6 months as against 18 months in those who did not develop PES (p = 0.05).

The incidence of PES was 42.8% in dexamethasone group (n = 18) compared with 55.2% in placebo group (n = 21) which was not statistically different [p = 0.26, odds ratio (OR) 95% confidence interval (CI) = 0.60 (0.25–1.47)]. On multivariate logistic regression

Flowchart 1: Flow diagram showing enrolment of patients in two groups

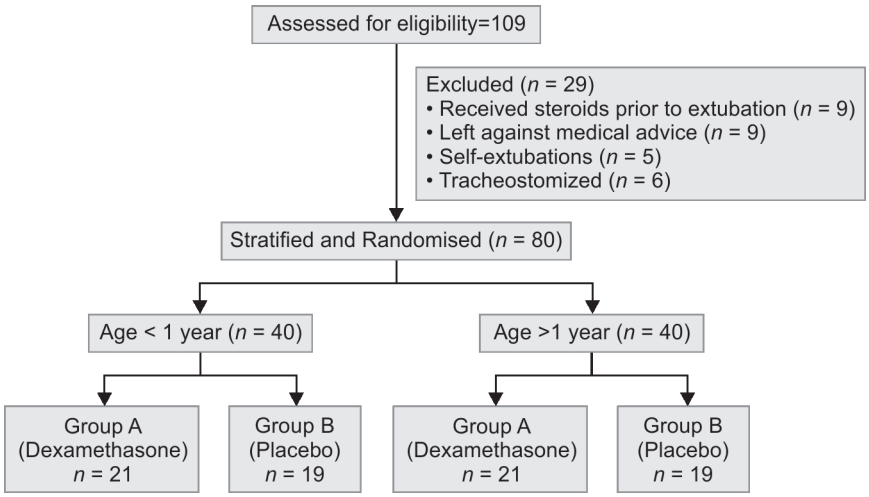

Table 1: Demographic and clinical characteristics of the study population

Variable		*Group A (n = 42)*	*Group B (n = 38)*	*p value*
Males (*n*,%)		32 (76.2%)	23 (60.5%)	0.13*
Median age in months (range)		14.5 (2–144)	11.5 (2–132)	0.88**
Mortality, *n* (%)		5 (11.9%)	4 (10.5%)	0.84#
Median ventilation in days (range)		6 (2–35)	4 (2–23)	0.02**
Median PICU stay in days (range)		14 (3–62)	12 (3–38)	0.03**
System involved, *n* (%)				
Respiratory	17 (21.2%)	11 (26.1%)	6 (15.7%)	0.25*
CNS	27 (33.7%)	16 (38%)	11 (28.9%)	0.38*
CVS	6 (7.5%)	1 (2.3%)	5 (13.1%)	0.06#
GI	4 (5%)	1 (2.3%)	3 (7.8%)	0.25#
Postoperative	26 (32.5%)	13 (30.9%)	13 (34.2%)	0.75*
Endotracheal tube (ETT) cuffed		14 (33.3%)	7 (18.4%)	0.13*
Median leak volume % (range)		1.6 (0–31)	2 (0–31)	0.91**
Reintubations during the period of ventilation, *n* (%)		4 (9.5%)	4 (10.5%)	
Place of intubation, *n* (%)				
PICU/operation theater		24 (57.2%)	22 (57.8%)	
Ward/other hospitals		18 (42.8%)	16 (42.2%)	
Mean GCS at extubation (±SD)		13.4 ± 2.1	13.8 ± 1.5	0.94***
Median paralysis duration (range)		48 (0–192) hours	48 (0–72) hours	0.03**

*Chi-square test. #Fisher exact test. **Mann–Whitney *U* test. ***Student's *t* test
CNS, central nervous system; CVS, cardiovascular system; GI, gastrointestinal; GCS, Glasgow coma scale

Table 2: Comparison between cases with PES vs no PES

Patient characteristics	*PES present (n = 39)*	*PES absent (n = 41)*	*p value*
Median age in months (range)	6 (2–84)	18 (2–144)	0.05*
Males (%)	28 (71.7%)	27 (65.8%)	0.41**
Median duration of ventilation in days (range)	6 (2–20)	5 (2–35)	0.75*
Median duration of PICU stay in days (range)	13 (3–60)	12 (3–62)	0.76*
Diagnosis			0.74**
Respiratory	9 (23%)	8 (19.5%)	
CNS	11 (28.2%)	16 (39%)	
CVS	3 (7.6%)	3 (7.3%)	
GIT	3 (7.6%)	1 (2.4%)	
Postoperative	13 (33.3%)	13 (31.7%)	
Median leak around ET tube	2%	1.2%	0.80*

*Mann–Whitney *U* test. **Chi-square test
CNS, central nervous system; CVS, cardiovascular system; ET, endotracheal; GIT: gastrointestinal tract

Table 3: Comparison of outcomes in dexamethasone and placebo groups

Outcome	*Dexamethasone group (n = 42)*	*Placebo group (n = 38)*	*p value OR (95% CI)*
Postextubation stridor	18 (42.8%)	21 (55.2%)	0.26*
			0.60 (0.25–1.47)
Median WCS (range)	2 (0–5)	2 (0–4)	0.12**
WCS >4, *n* (%)	12 (28.5%)	18 (47.3%)	0.08*
			0.37 (0.12–1.06).
Median time of stridor onset (range)	30 minutes (5–240)	5 minutes (5–360)	0.46**
Adrenaline nebulization requirement	16 (38.1%)	18 (47.3%)	0.40
Median time to start adrenaline nebulization (range)	30 minutes (5–420)	15 minutes (5–960)	0.42**
Median time of adrenaline nebulization in minutes (range)	52.5 (30–240)	60 (30–180)	0.14
Median time to start dexamethasone in hours (range)	2 (0.5–6)	2 (1–14)	0.44**
Reintubation, *n* (%)	7 (16.6%)	6 (15.7%)	0.9*
			1.06 (0.32–3.51)

*Chi-square test. **Mann–Whitney *U* test
WCS, Westley croup score

Table 4: Causes and outcome of reintubation in the two groups

Outcome	*Group A (n = 7)*	*Group B (n = 6)*	*p value*
Reason for reintubation, *n* (%)			0.5*
PES	1 (14.2%)	0	
Pulmonary cause	3 (42.8%)	5 (83.3%)	
CNS (apnea/seizure)	2 (28.5%)	1 (16.7%)	
Hemodynamic instability (shock)	1 (14.2%)	0	
Median time of reintubation in hours (range)	25 (6–51)	13.75 (0.5–56)	0.39**
Median duration of reintubation in days (range)	11 (0.5–26)	3.5 (1.5–12)	0.17**
Tracheostomy, *n* (%)	2 (28.5%)	1 (16.6%)	0.62***
Mortality, *n* (%)	2 (28.5%)	4 (66.6%)	0.28***

*Chi-square test. ***Fisher exact test.** Mann–Whitney *U* test

after adjusting for the baseline confounders, we found no difference in the outcome between two groups ($p = 0.17$). Table 3 shows that onset of stridor, stridor score (WCS), presence of severe stridor (WCS > 4), requirement and duration of adrenaline nebulization, and reintubation rates were not significantly different in two groups.

The appearance of stridor (median time was 5 minutes in placebo group vs 30 minutes in dexamethasone group, $p = 0.46$) and the time of starting adrenaline nebulization (15 vs 30 minutes, $p = 0.42$) were not significantly different (Table 3). There was no difference in the duration of adrenaline nebulization (52.5 minutes in dexamethasone group and 60 minutes in placebo group, $p = 0.14$).

A rescue dexamethasone therapy was given in 6 patients (14.2%) in dexamethasone group and 13 patients (34.2%) in placebo group ($p = 0.06$). Median time to start rescue dexamethasone in any of the group was 2 hours. The mean WCS at all the time intervals was higher in placebo group when compared with dexamethasone group (Fig. 1). However, on comparing the WCS using repeated measures ANOVA, there was no statistical effect between dexamethasone and placebo groups ($p = 0.21$) and also no effect of time seen within the groups ($p = 0.39$).

Seven patients in dexamethasone group and six patients in placebo group were reintubated. Only one reintubation was due to PES (Table 4). Most common cause of reintubation was pulmonary dysfunction followed by CNS causes. In the dexamethasone group, 42.8% were reintubated due to pulmonary dysfunction and 28.5% due to CNS causes. In placebo group, 83.3% were reintubated due to pulmonary dysfunction and 16.7% were due to CNS causes. The time of reintubation, duration of reintubation and need for tracheostomy was not significantly different in two groups. Mortality was also not significantly different in two groups ($p = 0.28$).

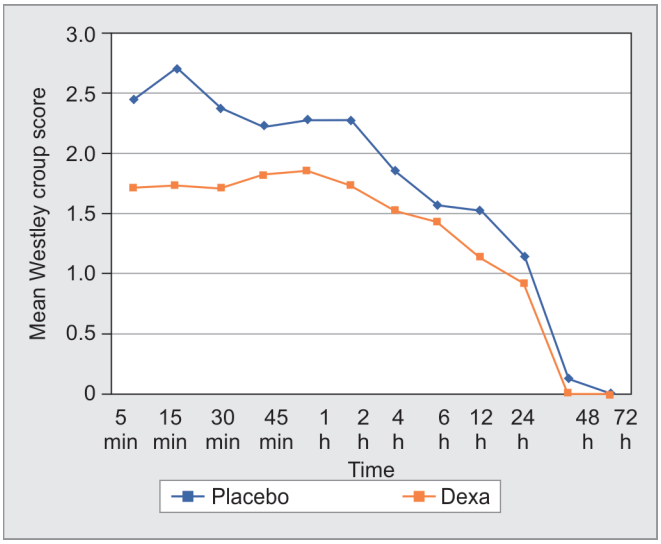

Fig. 1: Mean Westley croup score in the two groups at different time intervals

There were no adverse effects such as upper gastrointestinal bleeding and hypertension in patients receiving dexamethasone. Mean random glucose levels were normal in both the groups.

Discussion

This clinical trial was conducted to evaluate the effects of dexamethasone therapy given 6 hourly for 6 doses starting 6 to 12 hours before extubation, in preventing PES caused by laryngeal edema in children in ICU setting. We used dexamethasone in the study as this was the most frequently used steroid in other studies as well as in our ICU protocol for preventing laryngeal edema.[1,2,8,10,12] Dexamethasone has high anti-inflammatory potency, negligible mineralocorticoid effects at therapeutic doses, and long duration of action.[15] The recommended dose of dexamethasone for airway edema is 0.15–0.5 mg/kg/dose.[13] Most effective dose of steroids for prevention and treatment of postextubation laryngeal edema is not known. Various studies have used different doses of dexamethasone ranging from 0.15 to 0.5 mg/kg.[1,2,9,12,16,17] Studies have shown that a low dose of dexamethasone (0.15 mg/kg) is equally effective in treatment of croup.[18] As we had been using a dose of 0.15 mg/kg in our current practice for managing PES, we wanted to evaluate its efficacy in prevention of PES through this study.

The overall incidence of PES in our study was 48.7%. PES was reported in 25–73% cases in various pediatric studies.[1,2,5,8,10] We did not find any difference in occurrence of PES between the dexamethasone and placebo groups. The median age in PES group was younger (6 months) compared to 18 months in patients without PES; however, it was not significant. Study by Tellez et al. did not find statistical association between age and development of stridor.[1]

In our study, the median WCS was similar in the two groups as also found by Harel et al.[3] In contrast, Anene et al. showed that the median stridor score after extubation was significantly lower in dexamethasone group than placebo.[12] We observed that occurrence of PES was earlier in placebo compared to dexamethasone group though not statistically significant. Cesar et al. observed that PES occurred as early as 5 minutes similar to our study.[8] Baranwal et al. also found that the majority patients developed postextubation airway obstruction within 30 minutes.[2]

There was no difference in the requirement and the duration of adrenaline nebulization in the two groups which was also reported in other studies.[1,2] However, a significant difference in requirement of adrenaline nebulization in placebo group compared to dexamethasone group was found in the study by Anene et al.[12]

The overall reintubation rate (though only one case was due to PES) in our study was higher (16%) than that found in other studies by Baranwal et al. (11%), Baisch et al. (4.1%), Kurachek et al. (6.2%), and Fontela et al. (10.5%).[2,19–21] There was however no difference in reintubation in the two groups in our study similar to other studies.[1,11] We found that pulmonary and neurological causes were more important causes of extubation failure compared to PES. PES was a contributory factor for reintubation in one case only (in dexamethasone group). Kurachek et al. found that the common causes of extubation failure was upper airway obstruction followed by pulmonary dysfunction, respiratory muscle weakness, hemodynamic instability, and neurological causes.[20] In their study by Edmunds et al. and Harel et al.,[3,4] the most frequent cause of extubation failure was pulmonary dysfunction and neurological impairment, respectively, compared to upper airway obstruction. It may be likely that PES is not the most common cause of extubation failure as pulmonary dysfunction and neurological causes are more frequently implicated.

The use of dexamethasone can result in adverse effects such as hypertension, gastrointestinal bleeding, and hyperglycemia.[15] Although these effects were not seen in our study, some have reported the occurrence of these adverse effects which may be attributed to the use of a higher dose of dexamethasone.[12,17]

The strengths of this double-blinded randomized study were that we had equal representation of patients less than 1 year of age and 1–12 years of age to account for any anatomical differences in the size of airway that could have resulted in PES. There was a single observer recording the stridor score. The limitation of our study was that it was a single center study with a small number of patients. Due to ethical considerations, rescue dexamethasone was essential to be administered to patients with severe stridor persisting even after adrenaline nebulization. This might have confounded the difference in severity of stridor in the two groups.

We could not demonstrate the beneficial effects of dexamethasone in PES prevention in the dose and schedule used by us. Further studies with large sample size with higher dose of dexamethasone and longer pretreatment are needed.

Conclusion

We found no beneficial role of the studied dose of dexamethasone (0.15 mg/kg starting 6–12 hours before extubation given 6 hourly for total of 6 doses) over placebo on the incidence of PES. There was no difference in severity of PES, in placebo and dexamethasone groups, which however might have been confounded by the use of rescue dexamethasone in severe cases of stridor even in the placebo group.

Highlights

- Postextubation stridor (PES) is a serious complication in ventilated children that increases morbidity and mortality.
- Dexamethasone is a potent anti-inflammatory agent used for airway edema.
- The benefits of dexamethasone in preventing PES have shown inconclusive results in pediatric population and can have adverse effects.

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