Role of Intravenous Dexamethasone in Prevention of Postextubation Airway Obstruction in Mechanically Ventilated Children in Pediatric Intensive Care Unit: A Double-blind Randomized Controlled Trial

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Received on: 19 May 2024; *Accepted on:* 05 October 2024; *Published on:* 30 October 2024

Abstract

Objective: To study the efficacy of intravenous dexamethasone in preventing postextubation airway obstruction (PEAO).

Design: A double-blinded randomized controlled trial.

Study setting: The study was conducted in level 3 PICU at AIIMS, Raipur, India, from December 2019 to September 2022.

Subjects: Children requiring intubation for at least 24 hours and not beyond 14 days were included. Children with upper airway anomalies or who received corticosteroids within the last 7 days were excluded.

Intervention: The children who satisfied the inclusion criteria were randomized into dexamethasone or placebo group by stratified variable block randomization. Dexamethasone (0.5 mg/kg/dose) or placebo was given four doses (–12 hr., –6 hr., 0 hr., and 6 hr. of extubation).

Outcome: The occurrence of any clinically significant stridor (Westley stridor score ≥3) was the primary outcome.

Measurements and main results: Of the seventy ($n = 70$) children included in the study, 35 received dexamethasone while 35 received placebo. Westley stridor score ≥3 was present in 25.71% ($n = 9$) in dexamethasone group vs 31.42% ($n = 11$) in placebo ($p = 0.792$). Reintubation occurred in 14.28% ($n = 10/70$) patients, 11.42% (4/35) in dexamethasone group, and 17.14% (6/35) in placebo group ($p = 0.734$). Five children in the dexamethasone group and six in placebo group died ($p = 1.00$). There was no difference in the length of PICU stay ($p = 0.84$) and hospital stay ($p = 0.75$) among both the groups.

Conclusion: Administration of multiple doses of dexamethasone may not help in the prevention of reintubation but may help in the reducing the incidence of clinically significant stridor.

Keywords: Dexamethasone, Mechanical ventilation, Pediatric intensive care unit, Postextubation airway obstruction, Stridor score.

Indian Journal of Critical Care Medicine (2024): 10.5005/jp-journals-10071-24830

Highlights

In the context of inconclusive evidence regarding the use of steroids for the prevention of postextubation airway obstruction (PEAO) in children, our study showed that steroids are not effective in preventing the reintubations due to PEAO. Hence, dexamethasone should not be routinely used for the prevention of PEAO.

Introduction

Endotracheal intubation is one of the most frequently performed procedures in critically ill children to maintain patent airways. Despite being a life-saving procedure, endotracheal intubation has its own complications.[1] Newborns and younger children have a relatively narrow subglottic area and show a peculiar airway anatomy at each growth phase, making them more prone to airway injury during endotracheal intubation.[2,3] Even the slightest inflammation at this level can lead to gross distortion of the tissue planes and anatomical positions.[4] Prolonged endotracheal intubation poses the highest risk for the development of postextubation complications.[5–7]

Laryngeal edema is the most severe and immediate complication of extubation in young children commonly presenting as postextubation stridor. The incidence of postextubation stridor in the pediatric intensive care unit (PICU) is described to be between 2 and 25%[8–11] resulting in reintubation up to 6%.[12] Glucocorticoid therapy reduces inflammation by inhibiting inflammatory mediators, such as interleukins, tumor necrosis factor, prostaglandins, leukotriene, and fibroblast proliferation.[10] Studies have shown that intravenous dexamethasone is effective

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How to cite this article: Varghese AR, Kambagiri P, Sahoo MR, Jindal A, Goel AK. Role of Intravenous Dexamethasone in Prevention of Postextubation Airway Obstruction in Mechanically Ventilated Children in Pediatric Intensive Care Unit: A Double-blind Randomized Controlled Trial. Indian J Crit Care Med 2024;28(11):1063–1068.

Source of support: Nil

Conflict of interest: None

in the prevention and treatment of airway edema due to intubation and thereby decreases the risk of postextubation stridor by around 40%.[10]

Studies using dexamethasone for prevention of postextubation stridor in children and reintubation due to postextubation stridor are sparse and conflicting. There are studies that support the use of dexamethasone in the prevention and treatment of PES as well as studies with opposite results too.[13–22] Cochrane review by Khemani et al.[23] in July 2009 concluded that corticosteroids were not effective in preventing postextubation stridor in children. Another systematic review and meta-analysis by Kimura et al.[24] in 2020 concluded that corticosteroids could be considered in children to prevent postextubation stridor. Hence, the intention was to do a double-blinded Randomized control trial to study whether dexamethasone prevents postextubation stridor.

Materials and Methods

This double-blind randomized control trial was conducted in the PICU of a tertiary care hospital from December 2019 to September 2022. The study titled "Role of intravenous dexamethasone in the prevention of PEAO in mechanically ventilated children in PICU: a randomized, double-controlled trial" was reviewed and approved by Institutional Ethics Committee—IEC, AIIMS Raipur on 23-09-2019. The trial was registered in Clinical Trials Registry—India (ctri.nic.in) with the registration number—CTRI/2019/12/022511. The protocol of the trial at CTRI website can be accessed from: https://ctri.nic.in/Clinicaltrials/pmaindet2.php?EncHid=MzgzNDI=&Enc=&userName=. All the procedures were followed in accordance with the standards of IEC, AIIMS Raipur and the Helsinki Declaration of 1975. Written informed consent was obtained before randomization.

Inclusion criteria were—children admitted in the PICU aged more than 1 month and less than 18 years requiring airway stabilization and mechanical ventilation whose duration of intubation was more than 24 hours and not exceeding 14 days were included. Exclusion criteria were—pre-existing vocal cord anomalies and other anatomical abnormalities of the upper airways, prior use of corticosteroids during hospitalization within the past 7 days, contraindication for the use of corticosteroids, surgery or trauma to the upper airway, previous history of upper airway obstruction (subglottic stenosis), patients with pseudobulbar palsy, spontaneous extubation.

The sample size was calculated as 35 in each arm with an incidence of 2–25%[9–11] and allowable error as 10% at a 5% significance level using the standard formula as follows:

$$n = \{[Z^{1-1/2\alpha} + Z^{\beta}]\, 2 \times [P_1(1-P_1) + P_2(1-P_2)]\}/(P_1-P_2)^2$$

n is the sample size, $Z^{1-½\alpha}$ is 1.96 at 5% significance, Z^{β} is 0.84 at 80% power, P_1 is the lower range of incidence and P_2 is the upper range of incidence.

Eligible children were randomized at the time of admission to PICU into two groups (dexamethasone or placebo group) by a computer-generated, stratified, block randomization with variable block sizes. Stratification was done based on the duration of ventilation as less than 3 days, 4–7 days and 8–14 days. Random number allocation was performed by a person not involved in the study. Allocation concealment was done by placing individual assignments in serially numbered, sealed, opaque envelopes. The doctor on duty, the nurses administering the drug as well as the investigator were blinded regarding the patient's identity. Enrollment was done only after approval by the Institute Ethics Committee (IEC).

All the children admitted to PICU and requiring intubation and mechanical ventilation were screened for eligibility and enrolled after obtaining written informed consent from parents or guardians. The demographic details, admission diagnosis, indication for PICU admission, duration of mechanical ventilation, and indication were recorded at the time of inclusion. Following extubation, respiratory support was provided to the patients with high-flow nasal cannula or noninvasive ventilation or continuous positive airway pressure as per the treating physician's discretion. Patients who fulfilled the inclusion criteria were randomized to receive either intravenous dexamethasone or normal saline. After randomization, the intervention group received intravenous dexamethasone 0.5 mg/kg/dose 2 doses prior to extubation at 6 hours interval and two doses postextubation whereas the control group received intravenous normal saline. The timing of extubation was as per the decision of the treating physician. All children received postextubation respiratory support as per the unit's policy. No routine nebulization with adrenaline or budesonide was given. All enrolled children underwent continuous monitoring of vital parameters and were documented. PICU and hospital outcomes were observed and deaths if any recorded. Length of PICU and hospital stay was also documented at the time of discharge.

Westley stridor score was used to assess the severity and a score of ≤2 was defined as mild, 3–7 was defined as moderate and ≥ 8 was considered as severe. The occurrence of any clinically significant stridor (stridor score of ≥3) was studied as the primary outcome. Need for reintubation between 20 min and 24 hours, length of hospital stay and PICU stay, SOFA score and mortality were secondary outcome measures.

Statistical Analysis

Data of all the patients were analyzed according to their assigned group (Intention to treat – ITT). Mean with SD or Median with IQR were used to represent descriptive statistics depending on the nature of the data. Graphs and charts were also applied. Chi-square test, Fisher exact test, Independent *t*-test, Mann–Whitney *U* test were applied. SPSS V25 was used for data analysis. $p < 0.05$ was considered as statistically significant.

Results

One hundred and sixty patients were screened for eligibility of which 70 were randomized into two groups. Ninety patients were excluded according to the pre-set criteria. Figure 1 depicts a CONSORT flowchart showing the selection, randomization, and follow-up of patients. Thirty-five patients were enrolled in the intervention group and thirty-five patients were enrolled in the placebo group. All the baseline characteristics of both groups have been depicted in Table 1. Median duration of ventilation (days) was significantly higher in the intervention group (control – 4 (2, 7) vs 6.5 (4, 10); p – 0.01).

The occurrence of the primary outcome variable, that is, any clinically significant stridor (stridor score ≥3) was found to be comparable in both intervention (25.71%; n = 9/35) and control (31.43%; n = 11/35) groups (p = 0.792). The relative risk of stridor score ≥3 is 1.22 times (CI: 0.580-2.577) higher in the control group and the risk difference is 5.72. Clinically significant stridor at

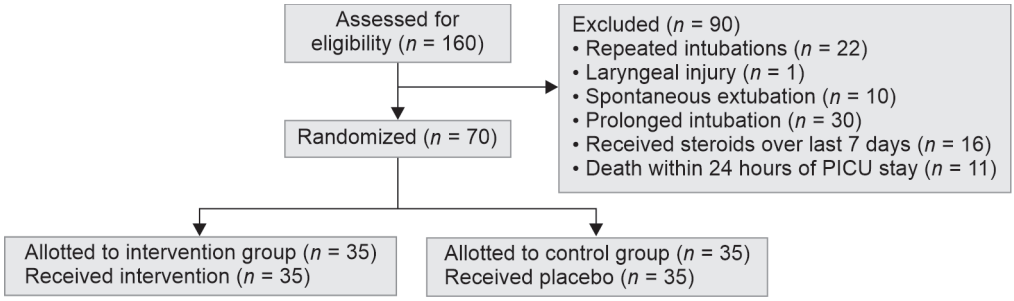

Fig. 1: CONSORT flowchart

Table 1: Baseline characteristics of the group

Baseline characteristics	*Intervention group (n = 35)*	*Control group (n = 35)*	*p-value*
Median age in months	48 (4.5, 120)	24 (7, 96)	0.737
Male	18	12	
Female	17	17	0.332
Underweight	11	13	0.802
SOFA score			
1–6	26	21	0.398
7–12	9	12	
13–18	0	1	
19–24	0	1	
Indication of intubation (*n*)			
Pulmonary	14	9	
Cardiac	7	7	0.287
Postoperative	3	1	
Others	11	18	
Type of endotracheal tube (*n*)			
Cuffed	14	20	0.232
Uncuffed	21	15	
Median duration of ventilation (days)	6.5 (4, 10)	4 (2, 7)	0.01
GCS at extubation (Median, IQR)	14 (13,14)	14 (13,14)	0.892

Table 2: Primary outcome measures

N = number	*Intervention group*	*Control group*	*p-value*
Overall occurrence of stridor (*n* = 70)			
Yes	20	18	0.811
No	15	17	
Clinically significant stridor (Stridor score ≥ 3) (*n* = 70)			
Yes	9	11	0.792
No	26	24	
Stridor at 0 hours (*n* = 70)			
Yes	19	18	1.000
No	16	17	
Severity of stridor (0 hours) (*n* = 37)			
Mild	11	9	0.776
Moderate	7	7	
Severe	0	0	
Impending respiratory failure	1	2	
Stridor score ≥3 at 0 hours			
Yes	8	9	0.746
No	11	9	
Stridor at 6 hours (*n* = 70)			
Yes	16	14	0.809
No	19	21	
Severity of stridor (6 hours) (*n* = 30)			
Mild	14	7	0.05
Moderate	1	6	
Severe	0	1	
Impending respiratory failure	1	0	
Stridor score ≥3 at 6 hours			
Yes	2	7	0.046
No	14	7	
Reintubation (*n* = 70)			
Yes	4	6	0.734
No	31	29	

zero hours was comparable in both the groups ($p = 0.746$) though the occurrence at 6 hours was significantly higher in the control group (50% in control group vs 12.5% in the intervention group, $p = 0.046$). Reintubation occurred in 14.28% ($n = 10/70$) patients overall, 11.42% (4/35) in dexamethasone group, and 17.14% (6/35) in placebo group (risk difference is 5.72) but the difference was not statistically significant ($p = 0.734$) (Table 2). The relative risk of reintubation is 1.5 times (CI: 0.463–4.858) higher in the placebo group.

Out of the other secondary outcomes, there was no significant difference in the length of PICU stay, hospital stay, and mortality in both the groups (Table 3).

It was observed that the majority of patients who received dexamethasone did not have any side effects. Around 20% ($n = 9/35$) of the patients enrolled in the intervention group had episodes of tachycardia while 5.7% ($n = 2/35$) had episodes of hyperglycemia which was not significantly differing from the control group (p -0.165). None of the patients had allergic reactions to dexamethasone in the intervention group.

In the subgroup analysis, there was no significant association between the length of mechanical ventilation and the occurrence of a stridor score of ≥3 in both the groups (0 hours – $p = 0.430$; 6 hours – $p = 0.09$, Table 4). The use of cuffed endotracheal tubes also had no association with the occurrence of stridor (0 hours – $p = 0.515$; 6 hours – $p = 1.0$—Table 5, refer to supplemental digital content).

Table 3: Secondary outcome measures

Parameters	*Intervention group*	*Control group*	*p-value*
Mortality (*n* = 70)			
Alive	30	29	1.00
Dead	5	6	
Median duration of PICU stay (days)	8 (5, 12)	7 (4, 10.5)	0.521
Median duration of hospital stay (days)	10 (8, 18)	14 (9, 19)	0.160
Allergic reaction	0	0	
Adverse side effects (*n* = 70)			
Cardiovascular	7	2	0.165
Endocrine	2	4	
Nil	26	29	

Table 4: Association between duration of ventilation and stridor score ≥3

Characteristics	*Stridor ≥3 at 0 hour (Yes)*	*Stridor ≥3 at 0 hour (No)*	*p-value*
Duration of ventilation			
<72 hours	1	3	0.439
3–7 days	7	6	
7–14 days	12	8	
Characteristics	*Stridor ≥3 at 6 hours (Yes)*	*Stridor ≥3 at 6 hours (No)*	*p- value*
Duration of ventilation			
<72 hours	3	1	0.09
3–7 days	3	7	
7–14 days	3	13	

Table 5: Association between use of cuffed endotracheal tubes and stridor score ≥3

Characteristics	*Stridor ≥3 at 0 hour (Yes)*	*Stridor ≥3 at 0 hour (No)*	*p-value*
Type of ET tube			
Cuffed	10	9	0.515
Uncuffed	7	11	
Characteristics	*Stridor ≥3 at 6 hours (Yes)*	*Stridor ≥3 at 6 hours (No)*	*p-value*
Type of ET tube			
Cuffed	4	10	1.0
Uncuffed	5	11	

Discussion

Airway edema is a commonly observed complication following endotracheal intubation and usually results from injury during intubation, the pressure of the endotracheal tube on surfaces of contact, and the resulting inflammation**.** Although laryngeal edema is documented to occur in nearly 50% of the extubated patients, many are asymptomatic or have only mild symptoms.[11] Laryngeal edema is a common cause for respiratory distress and/or stridor postextubation, and an important cause for extubation failure and reintubation. As every reintubation is associated with increased mortality and morbidity, prevention and prompt management of postextubation laryngeal edema is of utmost importance.[11]

Severity of the stridor was measured objectively by the Westley stridor score and the cutoff for moderate stridor was kept at 3 or more. A study by Anene et al. in 1996 at Detroit[8] showed that the stridor score was significantly less in those who received dexamethasone when compared with the controls and another study by Ritu and Jhamb showed reduced incidence of significant stridor (WCS> 4) in the dexamethasone group.[25] Evidence from a network meta-analysis by Iyer et al.[26] compared different doses and timings of peri-extubation steroids and concluded that early high-dose dexamethasone (0.5 mg/kg/dose 12 hours prior to extubation) was more effective in the prevention of PEAO and reintubation. They also observed that the decision regarding timing (early/late) and dosage (high/low) of dexamethasone should be individualized considering the risk of postextubation airway edema, risk factors for extubation failure (such as respiratory muscle weakness), risk of adverse effects (such as GI bleeding and hypertension) and the time available before planned extubation. A recent multicenter RCT in Spain concluded that pre-extubation dexamethasone was helpful only in children under 2 years of age and did not significantly decrease moderate–severe UAO symptoms in other age-groups.[27] In our study, 20 patients out of 70 had stridor score ≥3, that is, the occurrence of significant postextubation stridor was found to be 28.5%. The occurrence of a significant stridor (stridor score ≥3) at 0 hours was comparable in both the groups ($p = 0.746$); however, significant stridor at 6 hours was significantly higher in the control group ($p = 0.046$). The occurrence of significant stridor was not found to be associated with the length of mechanical ventilation or use of cuffed endotracheal tubes.

Postextubation, patients may be reintubated for various reasons mainly airway edema, pulmonary insufficiency, and neurological impairment. Postextubation stridor being one of the causes, it was studied in our trial. The rate of reintubation was around 14.28% which is similar to the study by Ritu and Jhamb (16%),[25] and slightly higher when compared with Baranwal et al. (11%)[28] and Fontela et al. (10.5%).[29] When compared with the other studies like Harel et al. in 1997 at Texas[30] and Ritu and Jhamb in 2020 at New Delhi,[25] common causes of reintubation were found to be pulmonary and neurological causes while postextubation stridor was not a major cause rather was considered to be a contributory cause. But in this study, postextubation stridor was the most common cause seen leading to reintubation.

Similar findings were observed in the study by Abbasi et al. in 2015 at Iran[17] where the mean SOFA score in the intervention group was 4 while it was 3 in the control group and there was no statistical significance associated with the SOFA score and development of postextubation stridor. Mortality in the control group was 20.6% ($n = 6/29$) and 16.6% ($n = 5/30$) in the intervention group which was not statistically significant ($p = 1.0$). The length of PICU stay and hospital stay in both the groups was similar ($p = 0.836$ and 0.748 respectively).

The most common indications for intubation in the control group include neurological causes, suchg as neuromuscular weakness, encephalitis, and sepsis, whereas the patients enrolled in the intervention group were intubated predominantly due to a pulmonary pathology. As mentioned in the study by Ritu and Jhamb,[25] pulmonary and neurological causes eventually lead to reintubation. This study showed no significant causes which lead to failed extubation. Almost equal number of patients were enrolled in each category of length of ventilation which was observed to be the same in both the intervention and the control group.

The side effects of dexamethasone including tachycardia, hypertension, hyperglycemia, and upper GI bleeding were evaluated—none of the patients had UGI bleed and there was no significant difference in the occurrence of cardiovascular and endocrine complications in both the groups ($p = 0.165$). Tachycardia and hypertension cannot be attributed to dexamethasone alone as they can be associated even with opioid and benzodiazepine withdrawal which is commonly seen in critically ill children.

Strengths and Limitations

The strengths of the study were that it was a double-blinded randomized control trial which was analyzed by intention to treat analysis. This study considered potential confounding factors including age, underlying diagnosis, use of cuffed tubes, and length of mechanical ventilation during analysis.

The limitations of the study were a single-center study, a relatively small sample size which makes it difficult for the results to be generalizable. Observer agreement measurement was not done in this study.

Conclusion

This study helped to conclude that dexamethasone may not be efficacious in the prevention of reintubation due to postextubation airway edema, but may help in reducing the incidence of significant stridor. Hence, it should be considered judiciously like in high-risk conditions including prolonged or multiple intubations, airway injuries, etc. The dose of dexamethasone used in this study was at a higher range than the normal dose. Further studies comparing low-dose and high-dose dexamethasone should be conducted.

Supplementary Material

All the supplementary materials are available online on the website of www.ijccm.org.

Declarations

Ethics Approval

The study was reviewed and approved by the Institutional Ethics Committee—IEC, AIIMS Raipur on 23-09-2019.

Authors' Contributions

AJ was responsible for conception and design. ARV and AJ prepared the research proposal and protocols. ARV and KP performed patient enrollment, data collection and analysis, interpretation, and drafting of the manuscript. MRS, AJ, and AKG critically revised the manuscript. All authors approved the final manuscript.

Availability of Data and Material

Would be made available on request.

Trial Registration

The trial was registered in Clinical Trials Registry, India (ctri.nic.in) on 23/12/2019 with the registration number—CTRI/2019/12/022511.

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