RESEARCH PAPER

Aerosolized L-epinephrine *vs* Budesonide for Post-extubation Stridor: *A Randomized Controlled Trial*

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Objective: To compare the efficacy and adverse effects of aerosolized L-epinephrine *vs* budesonide in the treatment of post-extubation stridor.

Study design: Randomized controlled trial.

Setting: Pediatric intensive care unit (PICU) of a tertiary teaching and referral hospital.

Subjects: Sixty two patients with a stridor score ≥4 following extubation.

Intervention: Patients were randomized to receive either aerosolized L-epinephrine (*n*=32) or budesonide (*n* =30). Respiratory rate, heart rate, stridor score, blood pressure and oxygen saturation were recorded from 0 min to 24 hours.

Outcome measures: Stridor score remaining at ≥4, need for re-nebulization and re-intubation between 20 min –24 hours were primary outcome measures. Tachycardia (HR > normal for age), hypertension (BP >95th centile for age) and hypoxia (SpO2 <92% for 5 min) were secondary outcome measures.

Results: Both drugs showed a significant and comparable decline in the median (95% CI) stridor scores from baseline to 60 min [4 (4.10-4.50) to 2.00 (1.46-2.67) for budesonide *vs* 4 (4.12-5.00) to 2.00 (1.31 -2.75) for epinephrine]. At 2 hours, the stridor scores were significantly lower in the epinephrine as compared to budesonide group [0.00 (0.69-1.81) *vs* 3.00(1.75-3.32); *P* =0.02)]. However, the proportion of patients with stridor score ≥4 at any time between 20min-24 hrs (53.3% *vs* 53.1%; *P*=0.99), need for renebulization (40 % *vs* 43.8 %; *P*=0.76) and re-intubation (20% *vs* 25%, *P*=0.638), and adverse effects were similar in both groups.

Conclusions: Both aerosolized L-epinephrine and budesonide were equally effective in their initial therapeutic response in post-extubation stridor. However, epinephrine showed a more sustained effect.

Key words: *Budesonide, Epinephrine, Extubation, Stridor.*

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The most serious and immediate complication of extubation in young children is laryngeal edema; the incidence of post extubation stridor in the Pediatric intensive care unit (PICU) is described to be between 2-25%(1-5). Aerosolized epinephrine has been found to be an effective therapy in both infective and postextubation stridor(6,7). The action of epinephrine, however, is transient and there is a potential risk of rebound laryngeal edema, which may limit the repeated use of this drug(7). Treatment with steroids provides a sustained effect due to their anti-inflammatory action. Intravenous dexamethasone was found to be effective in pre-extubation and post- extubation states thus decreasing the risk of post-extubation stridor by around 40%(8). Theoretically, inhaled steroids with a similar mechanism of action as systemic steroids should be more advantageous due to direct delivery at the site of action, lesser dose needed and fewer side effects. Thus, aerosolized budesonide when used in the treatment of croup was found to reduce edema without any side effects(9,10). Trials comparing aerosolized epinephrine and budesonide in the treatment of infective croup have shown similar

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efficacy and safety of both the drugs(11). However, there are no studies comparing these two drugs in the treatment of post-extubation stridor.

METHODS

The trial was conducted in the PICU of a multispeciality urban teaching and referral hospital with 1200 beds over a period of 11 months from February 2004 to January 2005, after approval from the Institute's Ethics Committee.

Patients demonstrating hoarseness of voice, barking cough and/or inspiratory stridor with a stridor score ≥4 (***Table* I**) after extubation, were enrolled after obtaining a written informed consent from parents or guardians. The demographic details, admission diagnosis, indication for PICU admission, Pediatric risk of mortality (PRISM) III scores, duration of mechanical ventilation and indication, type and duration of intubation were recorded at the time of inclusion.

Following extubation, all patients were administered humidified oxygen by nasal prongs or facemask with an oxygen flow of 6L/min. Patients who fulfilled the inclusion criteria were randomized to receive either aerosolized L-epinephrine [(Group I (E)] or budesonide [Group II (B)]. Randomization by stratification (varying block randomization) was done so as to distribute patients with primary upper airway disease into both groups evenly. A primary upper airway disease was defined as primary pharyngeal, laryngeal or tracheal infections, trauma to upper airway or anatomical malformations of upper airway. A person who was not directly involved in the study did the random number allocation.

After randomization, Group I(E) received L-epinephrine 1% solution 0.25mL in 2mL normal saline, nebulized over 15-20 min with face mask and 6L/min of oxygen flow. Group II (B) received budesonide 1000µg (2mL) nebulized over 15-20 min with face mask and 6L/min of O_2 flow. Respiratory rate (RR), stridor score, heart rate (HR), blood pressure (BP) and oxygen saturation (SpO_2) were recorded for each patient immediately before aerosol administration (time 0) and at 20, 40 and 60 mins; and at 2, 4, 8, 12 and 24 hours. Stridor score

TABLE I STRIDOR SCORING SYSTEM

Clinical findings	Points
Level of consciousness	
Normal (including sleep)	0
Altered mental status (lethargy)	5
Cyanosis in room air	
None	0
When agitated	4
Cyanosis at rest	5
Inspiratory stridor	
None	0
When agitated	1
At rest	2
Air movement	
Normal	0
Decreased	1
Markedly decreased	2
Retractions	
None	0
Mild (alar flaring)	1
Moderate (suprasternal and intercostal)	2
Severe (all accessory muscles used)	3
Maximum total points	17

Adapted from Nutman, et al.(6).

remaining at ≥4, need for re-nebulisation, and/or re-intubation at any time between 20 min-24 h were identified as primary outcome variables.

Children in whom the stridor score remained ≥4 or worsened after receiving therapy, were re-nebulized with L-epinephrine (conventional protocol). The need for reintubation was decided by the treating physician based on combination of variables *i.e.* HR, RR, stridor score and SpO_2.

*Sample size***:** Assuming a failure rate of 40% in L-epinephrine group and a desired reduction of failure rate to 10% in the budesonide group, with an α error of 5% and power of 80%, we calculated that approximately 30 subjects would be required in each group.

*Statistical analysis***:** Data are presented as mean±SD, median and percentages wherever applicable.

Parametric data were analyzed using the Student's '*t*' test and non-parametric data with Mann- Whitney U test. Categorical data were analyzed with Chi-sqaure or Fisher's exact test. Continuous variables measured at different time intervals between the groups were compared using the repeated measures ANOVA. The linear trend in proportion between the groups was analyzed with Chi-square. The statistical packages used in the study were SPSS (version 10.0) and Epi Info 2000 (version 6.0).

RESULTS

Of the 370 patients admitted to the PICU during the study period, 196 (52.9%) were intubated for various reasons. Sixty-two (31.6%) of the intubated patients fulfilled the inclusion criteria and were randomized (***Fig.*1**). Their baseline characteristics are summarized in ***Table* II.**

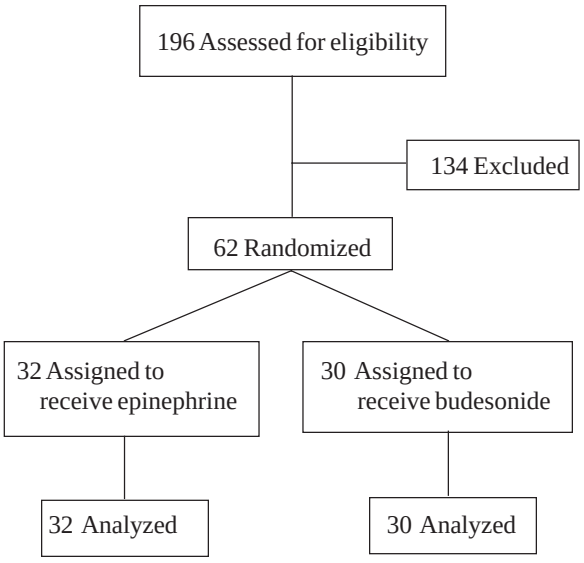

FIG. 1 *Study flow chart.*

TABLE II BASELINE CHARACTERISTICS OF THE STUDY SUBJECTS

	Group I (E) *n*=32	Group II (B) *n*=30	*P* value
Age (mo), mean ± SD	34.7 ± 38.4	38.6±41.9	0.80*
Males	26	24	0.58***
PRISM score, median (Centile range)	17 (5-36)	15 (3-33)	0.72**
Indication for intubation *n* (%)			
Respiratory failure	11(34.4)	11(36.7)	
Shock	6 (18.8)	2 (6.7)	
Respiratory failure + shock	3 (9.4)	3 (10)	0.57***
Low Glasgow Coma score	4 (12.5)	3 (10)	
Raised Intracranial pressure	4 (12.5)	9 (30)	
Upper airway obstruction	4 (12.5)	2 (6.7)	
Duration(d), median (range)			
Intubation	10 (3-33)	8.5 (2-50)	0.55**
Mechanical Ventilation	9 (1-32)	7.5 (2-39)	0.79**
Stridor score, median[#]	4 (4-5.5)	4 (4-5)	0.59**
Respiratory rate, mean ± SD	35.9 ± 6.6	38.3 ± 8	0.19*
Heart rate, mean ± SD	119.8 ± 20.4	132.8 ± 19.3	0.01*
Systolic blood pressure, mean ± SD	98 ± 10.2	100.5 ± 16.2	0.47*
Diastolic blood pressure, mean ± SD	59.6 ± 12.2	64.5 ± 15.7	0.17*
O_2 saturation, mean ± S.D	95.9±15.8	98.7 ± 2	0.25*

**Student's 't' test, **Mann Whitney U test, ***Chi Square test.*

TABLE III STRIDOR SCORE ≥4 AT DIFFERENT TIME INTERVALS

Time Interval	Group II(B)	Group I (E)	*P* value
Baseline			
Stridor score ≥4; *n* (%)	–	–	–
Median score (5-95th centile)	4 (4-5)	4 (4-8)	0.59
20 min			
Stridor score ≥4; *n* (%)	11(36.7%)	9 (28.1%)	0.47
Median (5-95th centile)	2.5 (1-5)	2.5 (0-5)	0.79
40min			
Stridor Score ≥4; *n* (%)	8 (26.7%)	8 (25.0%)	0.88
Median (5-95th centile)	2 (0-4)	2 (0-5)	0.91
60min			
Stridor score ≥4; *n* (%)	6 (20%)	6 (18.8%)	0.90
Median (5-95th centile)	2 (0-5)	2 (0-6)	0.68
2 hours			
Stridor score ≥4; *n* (%)	10 (33.3%)	5 (15.6%)	0.10
Median (5-95th centile)	3 (0-5)	0 (0-4)	0.01*
4 hours			
Stridor score ≥4; *n* (%)	5 (16.7%)	5 (15.6%)	0.91
Median (5-95th centile)	1.00 (0-4)	0.00 (0-4)	0.45
8 hours			
Stridor score ≥4; *n* (%)	4 (13.3%)	4 (12.5%)	0.92
Median (5-95th centile)	1 (0-4)	0 (0-4)	0.09
12 hours			
Stridor score ≥4; *n* (%)	2 (6.7%)	4 (12.5%)	0.44
Median (5-95th centile)	0 (0-4)	0 (0-4)	0.67
24 hours			
Stridor score ≥4; *n* (%)	0	1(3.1%)	0.33
Median (5-95th centile)	0 (0-3)	0 (0-3)	0.35

**P value < 0.05 by Mann Whitney U test.*

The median (95% CI) stridor scores from baseline (0min) to 24 hours and corresponding proportion of subjects with stridor score ≥4 at different time intervals is depicted in ***Table* III**. The proportion of patients with stridor score ≥4 at any time between 20min-24 hrs between budesonide and epinephrine group was 53.3% and 53.1%, respectively (*P*=0.99).

Twelve patients (40%) in the epinephrine group and 14 patients (43.8%) in the budesonide group required re-nebulization (*P*= 0.76). The median time taken from initiation of study treatment to need for subsequent re-nebulization was significantly longer in epinephrine group as compared to budesonide group [(120 (60-720) min *vs* 90 (60-240 min)], (*P*=0.04). Re-nebulized patients who developed hypoxia or showed signs of increased work of breathing were re-intubated. The proportion of patients needing re-intubation was similar in both the groups [epinephrine: 8 (25%) and budesonide: 6 (20%); *P*= 0.64]. The median time to re-intubation was also similar [budesonide: 120 (120-720) min and epinephrine: 150 (60-720) min].

The trends in RR, HR, systolic and diastolic BP and SpO_2 in both groups were not significantly different when assessed over time. Frequency of sinus tachycardia within 2 hours of aerosolized therapy was similar in both the groups [10 (31.3%) in epinephrine *vs* 7 (23.3%) in budesonide group]. Transient hypertension was noted in 4 patients (12.5%) in epinephrine as compared to 2 (6.7%) in budesonide group.

DISCUSSION

The incidence of post-extubation stridor in our patients was 31.6%, similar to that reported previously(12,13). Both aerosolized epinephrine and budesonide were similar with respect to their rapid therapeutic action. Epinephrine, however, showed a statistically significant sustained effect at 2 hours post-nebulization. The proportion of patients with stridor score ≥4, need for re-intubation and re-nebulization were similar in both the groups. The frequency of adverse effects in both the groups were also similar.

The rapid onset of action of aerosolized epinephrine and budesonide postulated due to local vasoconstrictor effect mediated by α–adrenergic receptors has been observed by several authors(6,7, 9,11,15). Our findings in the epinephrine group are in concordance with observations of Westley, *et al.*(7) and Waisman, *et al.*(15) who had shown a similar change in croup score at 30 min post nebulization lasting for 60-90 min. Rapid response with budesonide observed by us was also similar to the findings of Husby, *et al.*(9) and Fitzgerald, *et al.*(11), who reported a significant change in the

WHAT IS ALREADY KNOWN?

- Both epinephrine and budesonide are similar in efficacy and safety in infective croup.

WHAT THIS STUDY ADDS?

- Both aerosolized epinephrine and budesonide are equally effective in their rapid therapeutic response in post-extubation stridor.

mean croup scores from baseline to 30 min post-nebulization(9, 11). The trend of response observed by us at 2 hours post nebulization was different in that epinephrine showed a significant and sustained improvement as compared to budesonide. Majority of the published reviews have, however, reported a trend to the contrary – supporting the contention that the response to nebulized epinephrine is rapid and transitory and that to budesonide more sustained(7, 10,16). Klassen, *et al*.(16) and Godden, *et al*.(10) found a significant reduction in croup scores at 4 hours and 2 hours with aerosolized budesonide in the treatment of children with croup, thus reiterating the sustained nature of the drug effect. The sustained effect of steroids is attributed to their anti-inflammatory effects, which are usually not apparent until 6 hours after treatment(9). The statistically significant difference in the therapeutic response between epinephrine and budesonide observed by us at 2 hours was possibly not clinically meaningful as the proportion of patients with a stridor score of ≥4 in both groups was similar at that point. Additionally, the subsequent rate of re-nebulization and re-intubation was also similar in both the groups. Since there were more patients with raised intracranial pressure in the latter, it is possible that the poor outcomes in the form of worsening stridor scores were related to the effects of raised ICP causing aggravation of airway problems and not to the direct drug effect *per se*.

The incidence of re-nebulization, though similar in both the groups, was higher than that reported previously(11). The lower incidence observed by Fitzgerald, *et al*.(11) was possibly related to the additional effect of systemic steroids that were given in 14 (40%) and 15 (48.4%) patients in the budesonide and epinephrine group, respectively. The reasons for the relatively higher incidence in our patients remains unclear. Nearly one-third of patients in both groups had sinus tachycardia within 2 hours of aerosolized therapy unlike the previously reported trend(6,15,17). Tachycardia in the budesonide group was probably secondary to worsening stridor scores and increased work of breathing rather than to direct drug effect as seen in the epinephrine group. Transient systolic hyper-tension was noted in minority of patients in both the groups. Though the dose used in our study was similar to others, most of the studies have reported lack of significant change in blood pressure with both the drugs(6,7,9,10).

The major limitation of our study is inclusion of patients with upper airway disease. Though evenly distributed, these are different pathologies bearing different post extubation criteria and course. Additionally, the poor therapeutic response noted with either drug needs to be studied in the context of the basic underlying etiology, that can have an important bearing on airway problems.

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