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Preventing Laryngeal Edema Using Single Dose Methylprednisolone in Critically Ill Patients

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ABSTRACT

Background: Post extubation stridor (PES) is a common concern in mechanically ventilated patients, and various therapies have been explored to prevent its occurrence. This study aimed to compare the effectiveness of a single dose of corticosteroid with a placebo in patients at high risk for PES, as determined by cuff leak volume and laryngeal air column width difference (LACWD). **Methodology:** A randomized clinical trial was conducted in a tertiary care hospital, involving 222 patients aged >18 years of both genders who had been on mechanical ventilation for more than 24 hours and were planned for extubation. Group A (intervention) received methylprednisolone sodium succinate at a dose of 40 mg in 2 ml normal saline, while Group B (placebo) received 2 ml normal saline. Patients were divided into two groups based on cuff leak percentage and LACWD: a low-risk group (Group 1) with cuff leak > 24% and/or LACWD > 0.9 mm, and a high-risk group (Group 2) with cuff leak < 24% and/or LACWD < 0.9 mm. **Results:** Post extubation stridor occurred in 2 (2.7%) patients in Group 1 (low-risk group) and in 34 (23.0%) patients in Group 2 (high-risk group) (p=0.00). In Group 2, PES was observed in 9 (12.2%) patients who received methylprednisolone (Group A) and in 25 (33.8%) patients who received the placebo (Group B) (p=0.00). Reintubation was required in 1 (1.4%) patient in Group 1 and in 18 (12.2%) patients in Group 2 (p=0.00). Among Group 2 patients, reintubation was needed in 5 (5.24%) patients in Group A and 14 (18.9%) patients in Group B (p=0.01). Patients who developed PES had significantly lower mean cuff leak and mean LACWD compared to those who did not develop PES (19.6% vs 22.6%; p=0.00 and 0.79 mm vs 0.85 mm; p=0.004, respectively). Notably, PES was observed more frequently in females. **Conclusions:** Treatment with methylprednisolone significantly reduced the incidence of PES and the need for reintubation in high-risk patients compared to the placebo group. Patients who developed PES had lower cuff leak and LACWD values, and a higher proportion of females experienced PES.

Keywords: Extubation, Laryngeal trauma, Mechanical ventilation, Post extubation stridor

INTRODUCTION

Endotracheal intubation is sometimes necessary in intensive care units to provide mechanical ventilation to hospitalized patients. However, the insertion of the endotracheal tube can cause inflammation and localized swelling of the laryngeal soft tissues, leading to a narrowing of the laryngeal lumen [1]. If the endotracheal tube is removed while this swelling is present, it can result in respiratory difficulties such as post-extubation stridor and other complications that may require emergency treatment, including reintubation [2].

The incidence of respiratory complications after extubation due to laryngeal swelling has been reported to range from 1.5% to 26.3% [3]. The frequency of reintubation in cases of post-extubation airway obstruction varies widely, with reported rates ranging from 10% to 100% [4]. Reintubation, whether due to laryngeal swelling or other factors, has been associated with prolonged mechanical ventilation, increased length of stay in the intensive care unit, higher healthcare costs, and increased mortality rates [5].

To assess airway patency before extubation, the cuff leak test is a quick and non-invasive method. By measuring the air leak around the deflated cuff of the endotracheal tube, it can determine if the leak volume is below a certain threshold, indicating a high risk for post-extubation airway obstruction or stridor [6].

Given these considerations, this study aimed to evaluate the effectiveness of a single dose of methylprednisolone given four hours prior to endotracheal extubation in preventing post-extubation stridor in high-risk critically ill intubated patients. Additionally, the study assessed whether this intervention could prevent reintubation in critically ill patients at high risk of complications after extubation.

METHODS

Study Design and Setting

The study was conducted at the critical care medicine department of a tertiary care hospital, specifically the Shaheed Zulfiqar Ali Bhutto Medical University teaching hospital-PIMS in Pakistan. It had a duration of 12 months and employed a randomized controlled trial (RCT) design, which offers several advantages compared to other study methods [8].

Sampling Technique and Sample Size

A simple random sampling technique was utilized in the study, with a significance level of ±5 and a test power of 90%. Upon admission to the intensive care unit (ICU), all patients were randomized using computer-generated numbers. The allocation of patients to specific groups was based on their cuff leak percentage and LACWD (laryngeal air column width difference). To determine the anticipated population proportion, the incidence of post-extubation stridor (PES) in the intervention group (P1 = 15.8%) [3] and the anticipated population proportion based on the incidence of PES in the low-risk group (P2 = 39.4%) [3] were calculated. Through this calculation, the final estimated sample size was determined to be 74 patients in each group. Consequently, the study included a total of 222 patients.

Procedures for Patients Sample Selection

The eligibility criteria for the present RCT included mechanically ventilated patients who were over 18 years of age and had been intubated with an endotracheal tube for more than 24 hours. The reason for requiring mechanical ventilatory support was improvement in the patient's condition and their ability to initiate respiratory efforts. This was determined by criteria such as a PF ratio (PaO2/FiO2) greater than 200 or SpO2 greater than 90% with FiO2 less than or equal to 0.6 and PEEP less than 5 cm H2O. Additionally, the patients had to have normal peak airway pressures within a specified range. Other criteria for inclusion in the study were hemodynamic stability (no or low-dose vasopressors/inotropes), a pH level above 7.25, hemoglobin levels above 7 g/dl, body temperature below 38-38.5°C, a heart rate between 70 and 130 bpm, and the ability to tolerate pressure support ventilation at 7-10 cm H2O for a duration of 30 minutes to 2 hours. Furthermore, the patients should not have been under sedation or paralysis, and their rapid shallow breathing index needed to be below 105.

Data Collection Procedure

Written informed consent was obtained from a close relative or attendant after receiving clearance from the ethical review board at Pakistan Institute of Medical Sciences. The study enrolled patients who met the inclusion criteria, and their demographic information was recorded. Following the protocol outlined by Wittekamp et al., the cuff leak test was performed [1]. To conduct the test, endotracheal and oral secretions were suctioned, and the ventilator was set to assist control mode with a tidal volume of 8 ml/kg based on the patient's ideal body weight. The cuff was inflated, and the displayed inspiratory and expiratory tidal volumes were recorded to determine the cuff pressure. Subsequently, the cuff was deflated, and the expiratory tidal volume was measured over six breathing cycles, each comprising one cycle of inspiration and one cycle of expiration. After several

iterations, a plateau level was achieved, and the three lowest expiratory tidal volume measurements were averaged. The difference between the inspiratory tidal volume (measured before deflating the cuff) and the averaged expiratory tidal volume represented the cuff leak volume. The cuff leak percentage was calculated using the inspiratory tidal volume prior to cuff deflation and the cuff leak volume.

In addition, the lead investigator performed a laryngeal ultrasound using a Toshiba USG machine, following the procedure outlined by Ding et al. and El-Baradey et al. A linear probe was placed on the cricothyroid membrane in the transverse view to visualize the vocal cords. The ultrasound examination was conducted with the patients lying on their backs and their necks extended. The same settings as the Cuff Leak Test were used for this ultrasound assessment. The laryngeal air column width difference (LACWD) was determined by comparing the breadth of the air column between the vocal cords with and without the inflated endotracheal tube. This measurement was repeated three times consecutively, and the average value was calculated.

Patients with a cuff leak percentage greater than 24% and laryngeal air column width difference (LACWD) greater than 0.9mm were classified as the Low Risk Group and assigned to Group 1. These patients were extubated following the routine ICU protocol. Patients with a cuff leak percentage less than 24% and/or LACWD less than 0.9mm were categorized as the High Risk Group and allocated to Group 2. Within Group 2, patients were further randomly assigned to either Group A or Group B using a computer-generated randomization sequence upon admission.

In Group A, the intervention group, patients received an intravenous injection of methylprednisolone sodium succinate at a dosage of 40 mg in 2 mL of normal saline. In Group B, the placebo group, patients received an intravenous injection of 2 mL of normal saline. The solutions for the placebo and methylprednisolone were prepared by a nurse who was not involved in the trial. The appearance, packaging, and volume of the placebo and methylprednisolone solutions were identical. Both the physician in charge and the staff administering the injections were unaware of the patient's randomization arm. After 4 hours, the cuff leak percentage and LACWD were reassessed and recorded. All patients were extubated 4 hours after receiving the injection and were continuously monitored for 48 hours thereafter to evaluate any respiratory distress. The occurrence of post-extubation stridor, defined as a high-pitched inspiratory wheeze requiring medical intervention, within 48 hours after extubation was recorded. Patients who required reintubation despite medical management of stridor were also documented. The principal investigator collected all the data personally.

Management of respiratory distress with stridor involved nebulization with epinephrine (2 mL of 1:10,000 concentration). If three doses of epinephrine nebulization did not improve the patient's condition, and they displayed clinical signs of respiratory muscle fatigue or increased respiratory effort, a trial of non-invasive ventilation was initiated. Reintubation was performed when necessary, based on criteria such as hypoxemia, acidosis, copious secretions, mental status decline not improved by non-invasive ventilation, respiratory muscle fatigue, and persistent hypotension requiring vasopressor support. A specially designed proforma was used to record all data for each case, which was then verified by a consultant.

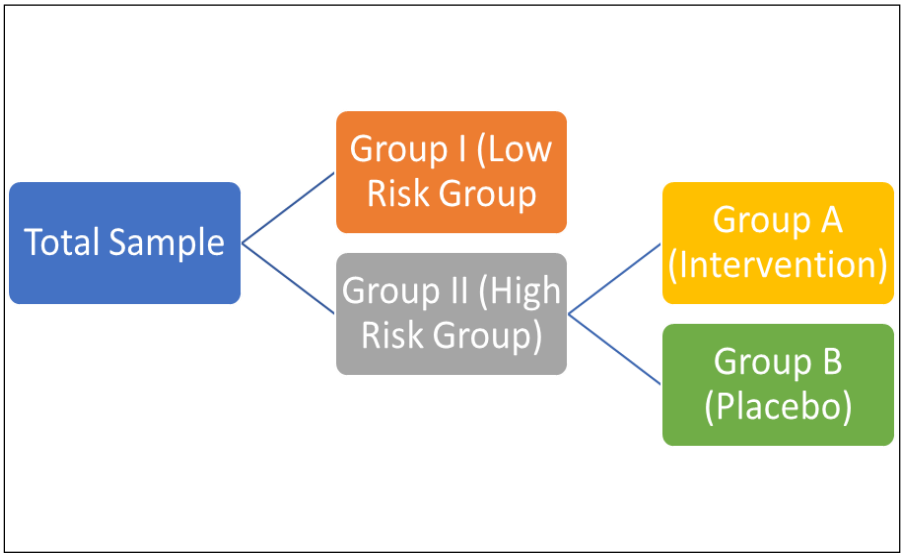

Figure 1. Participants group allocation.

Data Analysis

The data collected for the study was entered into SPSS v23.0 software and analyzed. Descriptive statistics, such as mean and standard deviation, were calculated for variables including age, number of days of ventilation, cuff leak percentage, and air column width difference at baseline and after treatment. The frequencies and percentages of post-extubation stridor and reintubation within 48 hours were recorded for all three groups. To compare the frequency of stridor and reintubation among the groups, the chi-square test was applied. The data was also stratified based on gender, cuff leak percentage, and laryngeal trauma, and evaluated using the chi-square test to assess their association with post-extubation stridor and reintubation. Furthermore, the data was stratified based on age, laryngeal air column width difference (LACWD), and duration of mechanical ventilation, and evaluated using independent sample t-tests to examine their relationship with post-extubation stridor and reintubation. A significance level of $p \leq 0.05$ was considered statistically significant.

RESULTS

Demography and Baseline Patient Characteristics

Table 1 presents the mean age, cuff leak percentage, laryngeal air column width difference (LACWD), and duration of mechanical ventilation for the high risk and low risk groups at baseline. It also provides information on the gender distribution and proportion of patients with laryngeal trauma in both groups.

Table 1. Baseline patients' characteristics (age, gender, laryngeal trauma, cuff leak, LACWD, and MV duration).

Variable		Group		Total	P-Value
		Group 2	Group 1		
Gender	Males	57	30	87	0.771
		38.5%	40.5%	39.2%	
	Females	91	44	135	
		61.5%	59.5%	60.8%	
	Total	148	74	222	
		100.0%	100.0%	100.0%	
Laryngeal Trauma	Present	20	1	21	0.004
		13.5%	1.4%	9.5%	
	Absent	128	73	201	
		86.5%	98.6%	90.5%	
	Total	148	74	222	
		100.0%	100.0%	100.0%	
Group		Mean	SD	N/A	N/A
Age (Years)	Group 2	45.2	19.3		
	Group 1	43.1	19.9		
Cuff Leak (%)	Group 2	19.4	2.4		
	Group 1	27.5	2.4		
LACWD (Mm)	Group 2	0.79	0.06		
	Group 1	0.94	0.02		
MV Duration (Days)	Group 2	4.7	1.7		
	Group 1	3.6	1.2		

Study Outcomes

Table 6 presents the mean cuff leak percentage in Group 1 (cuff leak > 24% and/or LACWD > 0.9 mm), which was 27.5% ± 2.2 SD, and in Group 2 (cuff leak < 24% and/or LACWD < 0.9 mm), which was 19.4% ± 2.4 SD. Additionally, Table 2 displays the mean

laryngeal air column width difference (LACWD) in Group 1, which was 0.94 mm ± 0.02 SD, and in Group 2, which was 0.79 mm ± 0.06 SD.

For further analysis, Group 2 was divided into Group A (methylprednisolone) and Group B (placebo). The mean cuff leak percentage in Group A was 21.1% ± 2.1 SD, and in Group B, it was 19.2% ± 2.2 SD, as indicated in Table 6. Similarly, the mean LACWD in Group A was 0.91 mm ± 0.04 SD, and in Group B, it was 0.80 mm ± 0.05 SD, as presented in Table 2.

Table 2. Mean cuff leak and LACWD after intervention.

Group	Cuff Leak (%) Mean ± SD	LACWD (MM) Mean ± SD
Group 1	27.5±2.4	0.94±0.02
Group 2	19.4±2.4	0.79±0.06
Group A (Steroids)	21.1±2.1	0.91±0.04
Group B (Placebo)	19.2±2.2	0.80±0.05

Post Extubation Stridor (PES)

Table 3 illustrates that post-extubation stridor (PES) was observed in 2 (2.7%) patients in Group 1, while it was present in 34 (23.0%) patients in Group 2. The difference in incidence between the two groups was statistically significant (p=0.001). Further analysis was conducted within Group 2. PES was observed in 9 (12.2%) patients in Group A (methylprednisolone), while it was present in 25 (33.8%) patients in Group B (placebo). The difference in incidence between the two subgroups was also statistically significant (p=0.002).

Table 3. PES in group 1 (low risk patients) and group 2 (high risk patients).

PES	Group (I)		Total	P-value
	Group 2	Group 1		
Present	34	2	36	0.001
	23.0%	2.7%	16.2%	
Absent	114	72	186	
	77.0%	97.3%	83.8%	
Total	148	74	222	
	100.0%	100.0%	100.0%	
GROUP 2				
	Steroids	Placebo		0.002
Present	9	25	34	
	12.2%	33.8%	23.0%	
Absent	65	49	114	
	87.8%	66.2%	77.0%	
Total	74	74	148	
	100.0%	100.0%	100.0%	

Reintubation

Table 4 indicates that reintubation was required in 1 (1.4%) patient in Group 1, while it was needed in 18 (12.2%) patients in Group 2. The difference in reintubation rates between the two groups was statistically significant (p=0.007). Further analysis was performed within Group 2. Reintubation was needed in 5 (5.2%) patients in Group A (methylprednisolone), whereas it was required in 14 (18.9%) patients in Group B (placebo). The difference in reintubation rates between the two subgroups was also statistically significant (p=0.012).

Table 4. Reintubation in high-risk group (Group 2) and low risk group (Group 1).

Reintubation	GROUP (I)		Total	P-value
	Group 2	Group 1		
Present	18	1	19	0.007
	12.2%	1.4%	8.6%	
Absent	130	73	203	
	87.8%	98.6%	91.4%	
Total	148	74	222	
	100.0%	100.0%	100.0%	
GROUP 2				
	Steroids	Placebo		
Present	4	14	18	0.012
	5.4%	18.9%	12.2%	
Absent	70	60	130	
	94.6%	81.1%	87.8%	
Total	74	74	148	
	100.0%	100.0%	100.0%	

Stratification of Data

Across all groups, the mean age and duration of mechanical ventilation were significantly higher in patients who developed post-extubation stridor (PES) compared to those who did not (51.7 years vs 43.1 years, p=0.013, and 5.1 days vs 4.2 days, p=0.004, respectively). Additionally, the mean cuff leak and mean laryngeal air column width difference (LACWD) were significantly lower in patients who developed PES compared to those who did not (19.6% vs 22.6%, p=0.001, and 0.79 mm vs 0.85 mm, p=0.004, respectively, Table 5). Furthermore, a higher proportion of females developed PES compared to males across all groups (22.2% vs 6.9%, p=0.002, Table 5). Similarly, PES occurred in a higher proportion of patients who exhibited signs of laryngeal trauma compared to those without such signs across all groups (47.6% vs 12.9%, p=0.001, Table 5).

Table 5. PES in the study sample (stratification data for age, cuff leak, LACWD and duration of mechanical ventilation).

Variables	PES	Mean	SD	P-value
Age (Years)	Present	51.7	18.2	0.013
	Absent	43.1	19.5	
Cuff Leak (%)	Present	19.6	3.3	0.001
	Absent	22.6	4.6	
LACWD (mm)	Present	0.79	0.06	0.001
	Absent	0.85	0.0.9	
Mv Duration (Days)	Present	5.1	1.75	0.004
	Absent	4.2	1.56	

		PES		
		Present	Absent	
Gender	Males	6	81	0.002
		6.9%	93.1%	
	Females	30	105	
		22.2%	77.8%	
Laryngeal Trauma	Present	10	11	0.001
		47.6%	52.4%	
	Absent	26	175	
		12.9%	87.1%	

Patients who required reintubation had a significantly higher mean age and mean duration of mechanical ventilation compared to those who did not require reintubation (64.9 years vs 42.6 years, p=0.013, and 5.3 days vs 4.2 days, p=0.009, respectively). Additionally, the mean cuff leak and mean laryngeal air column width difference (LACWD) were significantly lower in patients who required reintubation compared to those who did not (19.8% vs 22.3%, p=0.024, and 0.79 mm vs 0.89 mm, p=0.018, respectively, Table 6).

Table 6. Reintubation in the study sample (stratification data for age, cuff leak, LACWD and duration of mechanical ventilation).

Variables	Reintubation	Mean	SD	P-value
Age (Years)	Present	64.9	8.9	0.001
	Absent	42.6	19.1	
Cuff Leak (%)	Present	19.8	3.8	0.024
	Absent	22.3	4.6	
Lacwd (Mm)	Present	0.79	0.06	0.018
	Absent	0.89	0.09	
MV Duration (Days)	Present	5.3	2.2	0.009
	Absent	4.2	1.6	

		Reintubation		
		Present	Absent	
Gender	Males	4	83	0.048
		4.6%	95.4%	
	Females	15	120	
		11.1%	88.9%	
Laryngeal Trauma	Present	4	17	0.041
		19.0%	81.0%	
	Absent	15	186	
		7.5%	92.5%	

Furthermore, a higher proportion of females required reintubation compared to males across all the groups (11.1% vs 4.6%, p=0.048, Table 6). Reintubation was also needed in a higher proportion of patients who exhibited signs of laryngeal trauma compared to those without laryngeal trauma across all the groups (19.0% vs 7.5%, p=0.041, Table 6). The measurements of laryngeal air column width difference (LACWD) with an inflated endotracheal tube (ETT), LACWD with a deflated ETT, and expired tidal volume measurement with an inflated ETT, as well as the results of the cuff leak test demonstrating a decrease in expired tidal volume, are provided in separate supplementary files.

DISCUSSION

The aim of this study was to assess the efficacy of a single dose of methylprednisolone given four hours prior to endotracheal extubation in preventing or reducing post-extubation airway obstruction and reintubation in high-risk critically ill intubated patients. The findings of this study are consistent with previous reported studies.

Multiple trials and meta-analyses conducted on patients at an increased risk for post-extubation stridor have demonstrated that the administration of multiple doses of glucocorticoids prior to extubation can reduce the incidence of post-extubation stridor and reintubation [1, 9, 10]. In our study, we selected patients based on reduced cuff leak volume and laryngeal air column width difference (LACWD) as criteria for glucocorticoid therapy. This approach is supported by the findings of Cheng et al., who conducted a randomized controlled trial involving intubated patients with cuff leak volume <24% of tidal volume and assessed whether corticosteroid treatment reduces the occurrence of post-extubation airway obstruction [11]. Our study also revealed that patients who developed post-extubation airway obstruction had significantly higher mean age and duration of mechanical ventilation compared to those who did not develop airway obstruction. Similar findings have been reported by Venkategowda

et al. Furthermore, Sutherasan et al. demonstrated that measuring the laryngeal air column width during cuff deflation using laryngeal ultrasonography can serve as a reliable predictor of a higher risk of post-extubation stridor [12].

However, some studies have indicated that the absence of a cuff leak alone is not a perfect predictor of post-extubation stridor, with reported sensitivity ranging from 15% to 85% and specificity ranging from 70% to 99% [13]. In our study, we observed similar results, with reintubation being required in 4 (5.4%), 14 (18.9%), and 1 (1.4%) patients in Group A, Group B, and Group 1, respectively. Reintubation was significantly less frequent in the low-risk group compared to the high-risk groups (p=0.001). Existing literature also emphasizes the importance of timely treatment and outcomes to reduce hospital stay [14-17].

It is important to acknowledge the limitations of our study. The sample size was relatively small, although it was sufficient to draw meaningful conclusions. Additionally, we only investigated the effect of a single dose of corticosteroids and did not compare it with multiple doses. Another limitation was that we conducted univariate analysis, and future studies should consider multivariate analysis to examine the interplay of different factors such as age and gender and their independent effects on the outcomes. We recommend future studies with larger sample sizes, multivariate analysis, and a comparison of multiple doses of corticosteroids with a single dose.

CONCLUSIONS

The administration of methylprednisolone resulted in a significantly lower incidence of post-extubation stridor (PES) development and reintubation compared to the placebo group. The patients who experienced PES and required reintubation were predominantly females, had older age, longer duration of mechanical ventilation, laryngeal trauma at admission, lower cuff leak volumes, and reduced laryngeal air column width difference (LACWD) at baseline. Early extubation, following a single dose of steroid administered four hours prior, effectively prevented the occurrence of PES and reintubation in high-risk critically ill intubated patients. The utilization of cuff leak test and LACWD measured through ultrasound proved to be reliable predictors of PES. It is recommended that the impact of early extubation using a single dose of steroid in high-risk patients be further investigated in larger multicenter randomized controlled trials, particularly in terms of its effects on total ICU days, duration of mechanical ventilation, and mortality. Additionally, the assessment of laryngeal edema, including ultrasound-guided measurement of laryngeal air column width, and the implementation of a protocol involving single dose methylprednisolone followed by a 4-hour extubation in high-risk patients should be considered for inclusion in routine ICU practices.

Author Contribution

TUP conceptualized the study, and GLH, FR, SMG helped in data collection, analysis, and drafting the manuscript. SU, SA helped in study design and reviewed the manuscript, and also helped in data analysis and results interpretation. SMA and NK helped in editing the final version of the manuscript and improved the English grammar.

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CONFLICT OF INTEREST

No conflict of interest.

AUTHOR CONTRIBUTION

All the authors equally contributed.

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