Original Article

Comparison of the efficacy of nebulized budesonide and intravenous dexamethasone administration before extubation in prevention of post-extubation complications among patients admitted in intensive care unit

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Abstract

Background: Narrowing of the airway caused by tracheolaryngeal edema is one of the most common complications of endotracheal intubation particularly among patients requiring mechanical ventilation longer than 36 h that can cause other complications and increase mortality rate. The aim of this study was to investigate the efficacy of nebulized budesonide in comparison with intravenous (IV) dexamethasone administration before extubation in prevention of post-extubation complications.

Materials and Methods: This double-blind clinical trial was carried out at the intensive care unit (ICU) of a tertiary care center (Alzahra Hospital in Isfahan). The study's population was comprised of 90 patients who had been admitted in the ICU and required intubation at least for 48 h. All patients were between 18 and 65 years of age. Having randomly divided the patients into two equal groups, the first group received nebulized budesonide while the second group was treated by IV dexamethasone 1 h before extubation. The treatment continued up to 48 h after extubation. The collected data from both groups was then subjected to statistical analyses to come to results.

Results: There was no significant difference between the two groups; hence, both drugs were found to be effective in prophylaxis of the complications due to tracheal extubation. According to the findings of the current study, since nebulized budesonide has no systemic complications of IV corticosteroid, it can be used as the first choice in reducing the complications attributed to extubation.

Conclusion: Considering the very low systemic absorption of nebulized budesonide; however, we recommend it for prevention of post-extubation complications instead of IV dexamethasone.

Key Words: Dexamethasone, extubation, intensive care unit, nebulized budesonide

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INTRODUCTION

Laryngeal edema is a common complication of intubation. Narrowing of the airway caused by tracheolaryngeal edema is one of the most frequent complications after endotracheal extubation

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particularly amongst patients intubated for more than 36 h.[1] Laryngeal edema occurrence might cause post-extubation complications and increase mortality rate and the cost of therapy. Tracheolaryngeal edema causes hoarseness after extubation and in more severe cases can cause laryngospasm and the need for reintubation.[1,2] An estimated 1-17% of intensive care unit (ICU) patients with airway obstruction have been reportedly needed reintubation after extubation.[1] Reintubation makes more complications in turn and increases the mortality rate. These complications usually occur in the first 24 h after extubation and are more common in patients intubated for more than 24-36 h.[2] Mortality rate of reintubation has been estimated to be more than 30-40% in patients.[3] The Incidence of hoarseness might vary between 6% and 37%.[1] Various studies have indicated the administration of corticosteroids like intravenous (IV) dexamethasone can reduce or prevent the occurrence of airway obstruction.[1,4] In contrast, some other investigations have declined the effectiveness of corticosteroids in prevention of reintubation in adults and have not recommended the administration of corticosteroids.[5] Prolonging the hospital stay in ICU patients, reintubation increases the need to tracheostomy and the cost of treatment.[6] Factors that tend to pose a great risk of injury to the airway include reintubation, intubation for more than 24 h, tracheal tube size greater than glottis, old age and low Glasgow Coma Scale. Some investigations have recommended the administration of corticosteroids, nebulizing epinephrine, oxygen and helium to reduce post-extubation edema.[3] Similarly, the effectiveness of corticosteroids in lowering the risk of post-extubation stridor has been reported in other studies.[4] Since more cutting-edge corticosteroids like budesonide with lower systematic absorption and no systematic complication can be used as nebulizing particle,[7] in this study we investigated the efficacy of nebulized budesonide in comparison with IV dexamethasone administration in reducing the post-extubation injuries.

MATERIALS AND METHODS

This study was a randomized double-blind clinical trial that included patients admitted to the ICU of a tertiary care center in 2012. All patients were between 18 and 65 years of age. They had not received corticosteroids and were not on chronic non-steroidal anti-inflammatory drugs medications. They all had been intubated at least for 48 h and none had any prior airway diseases like asthma or chronic obstructive pulmonary disease. They also were ready for ventilator weaning. Sampling method in the study was simple randomization. After obtaining institutional ethics committee approval and taking written informed consent from patients or their relatives prior to the entrance in this trial, patients who had the inclusion criteria were selected and randomly assigned into either budesonide or dexamethasone group upon their admission to the ICU. To have a power of 95% to detect 0.2 difference between the two groups in power of hydrogen PH from baseline, when the standard deviation (SD) of change and Type I error were 0.15 and 0.05, respectively, the sample size was calculated to be 40 patients in each group. Considering a probable lost-to-follow-up rate of less than 10%, we recruited 45 samples in each group. In the first group, patients underwent the therapy with nebulized budesonide at a dosage of 1 mg[8] diluted in 4 cc of sterile water for 20 min, using nebulizer system of ventilator 1 h preceding extubation. During nebulization, the tracheal tube's cuff became deflated. After extubation patients received nebulized budesonide via oxygen nebulizer mask at the same dosage for 48 h with 12 h intervals. Meanwhile, dexamethasone was administered to patients in the second group. Dexamethasone was administered intra venous at a dosage of 0.15 mg/kg[9] 1 h before extubation. After extubation, the administration of IV dexamethasone continued at the same dosage every 12 h for 48 h. The cuff leak ratio (CLR)[4] was calculated for patients as follows: The ventilator's mode: volume-assisted control, tidal volume (TV) = 8 cc/kg, peep = 0. The tracheal tube's cuff was then deflated. Having calculated the TV in 6 cycles of breath, the average of the 3 breaths with the least TV was calculated using the following formula:

$$\text{CLR} = \frac{\text{TV ventilator} - \text{average 3 breath with low TV}}{\text{TV ventilator}}$$

Sequential organ failure assessment score (SOFA score) was also calculated and recorded for all patients.[10] Arterial blood gas test (ABG test) was performed every 12 h for 24 h and vital signs including blood oxygen saturation, respiratory rate, heart rate and post-extubation complication (stridor, respiratory distress) were reported for all patients.

Drug administration for each patient was carried out by a trained nurse and a physician who was not aware of the prescribed medications recorded data.

Patient who developed complication were treated with oxygen and nebulized epinephrine and in case they did not respond to the therapy they were then reintubated. Eventually, a statistical consultant analyzed the collected data, using the statistical package for the social sciences software version 20 (IBM Corporation). Univariate analyses between

the dexamethasone and budesonide groups were conducted using Student *t*-tests for continuous variables and Pearson Chi-square test for categorical variables as indicated. For all tests, a $P < 0.05$ was considered to be statistically significant.

RESULTS

In this study, 90 patients who had been admitted to ICU in a tertiary care center were selected and randomly assigned into two groups to undergo treatment of nebulized budesonide compared with IV dexamethasone administration [Figure 1].

The dexamethasone and budesonide groups were not significantly different with regard to demographic characteristics, SOFA score, intubation time and CLR [Table 1]. The age average in dexamethasone and budesonide groups were respectively 56 ± 3.4 and 51.3 ± 6.2 and the intubation time in the dexamethasone group was 4 ± 0.34 days compared with 4.5 ± 0.53 days in the budesonide group. Based on *t*-test analyses no significant difference existed between the two groups based on *t*-test with regard to mean age and intubation time with *P* values of 0.11 and 0.12, respectively.

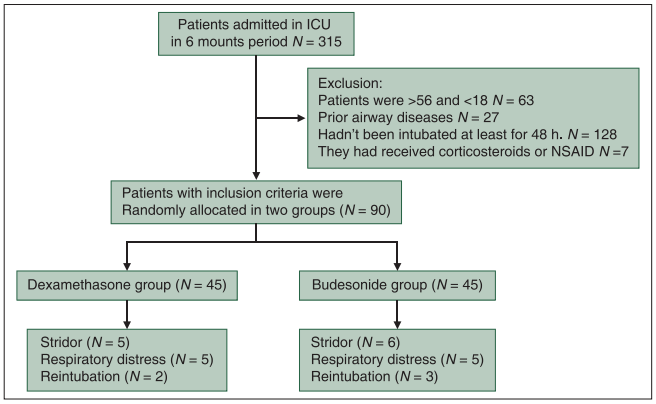

Figure 1: Study flow diagram CONSORT 2010 flow diagram

Table 1: Demographic data of patients*

Variable	Dexamethasone	Budesonides	*P*
Age (years)	56±3.4	51.3±6.2	0.11
Gender			
Men (*n* (%))	31 (68.9)	27 (60)	0.36
Women (*n* (%))	14 (31.1)	15 (40)	
SOFA score	4.03±1.1	3.3±0.9	0.68
CLR	0.14±0.034	0.15±0.09	0.17
Intubation time (day)	0.34±4	0.53±4.5	0.12

*Values are mean ± SD; SOFA: Sequential organ failure assessment; CLR: Cuff leak ratio

No significant difference of the SD and the average was found between ABG parameters of the two groups from extubation up to 48 h [Table 2]. Carbon dioxide partial pressure and Bicarbonate changes also were not significantly different between the two groups. Similarly, variant analysis test with reported observations indicated no meaningful difference of these parameters between the two groups ($P > 0.05$).

During this study, 11 patients suffered from PES (post-extubation stridor) 5 of which belonged to dexamethasone group and the remained patients belonged to budesonide group (11.1% against 13.3%); there was no significant difference between two groups based on Chi-square test ($P = 0.75$). 10 patients developed respiratory distress complication, 5 patients in each group (11.1%) ($P = 1$). From 5 patients that did not respond to treatment with oxygen and nebulized epinephrine and needed reintubation, 2 cases were from dexamethasone group and 3 were from budesonide group (4.4% against 6.7%), thus no statistically meaningful difference exited between the two groups. Finally, 5 patients died (2 patients of dexamethasone and 3 of budesonide group); nevertheless, the post-extubation complication was not the cause of death amongst the patients. In the dexamethasone group, one death was due to the myocardial infarction and another was caused by pulmonary embolism while in the next group one death was due to sepsis and other two were due to pulmonary embolism. Adverse effects of the drugs were reported as; headache in 5 patients and nausea in 2 patients of budesonide group and rising blood sugar in 3 patients of dexamethasone group [Table 3].

Standard deviation and average of vital signs from intubation time up to 48 h after extubation shows in Table 4. As it can be clearly observed, no significant diffrence is detected between the two groups ($P > 0.05$).

Table 2: ABG parameter*

Time	PH		PCO_2 (mm Hg)		HCO_3 (mEq/L)	
	Dexamethasone	Budesonide	Dexamethasone	Budesonide	Dexamethasone	Budesonide
0	7.34±0.05	7.4±0.07	40.1±7	41.5±5.7	23.3±2.8	25.5±4.2
12	7.48±0.17	7.4±0.01	39.5±5.4	41.5±2.5	23.5±1.7	25.3±3.5
24	7.54±0.23	7.41±0.1	38.5±3.3	41.5±2.1	22.5±1.7	24.4±1.4
36	7.65±0.36	7.43±0.04	39.5±4.3	40.5±2.7	23.5±3.2	25.1±1.4
48	7.27±0.18	7.44±0.04	38.5±4.3	37.5±3.4	24.3±3.5	23.3±3.5
P	0.66		0.28		0.21	

*Values are mean ± SD; SD: Standard deviation; PH: Power of ydrogen; PCO_2: Carbon dioxide partial pressure; HCO_3: Bicarbonate; ABG: Arterial blood gas

DISCUSSION

The present study aimed at comparing the efficacy of IV dexamethasone with nebulized budesonide administration in prevention of post-extubation complications amongst patients admitted to ICU.

Budesonide is an anti-inflammatory corticosteroid with weak mineralocorticoid activity. Peak plasma time is 1-2 h and protein bounding is 85-90%. Metabolized by CYP3A4 in the liver to 6-beta-hydroxybudesonide, 16-alpha-hydroxyprednisolone (inactive). Elimination half-life is 2-3.6 h and excretion is 60% in urine; 15.1-29.6% feces. Most common adverse effects are: headache, nausea and respiratory infection.[9] Dexamethasone is the anti-inflammatory corticosteroid. Dexamethasone decreases inflammation by suppressing migration of polymorphonuclear leukocytes and reducing capillary permeability. The half-life is 2-3.5 h and metabolized in the liver and excretion mainly in urine, minimally in bile. Most common adverse effects are: adrenal suppression, myopathy, delayed wound healing and raising blood sugar.[9]

Since the demographic variables, SOFA score and CLR were not significantly different in the two groups, the presumable different results could be attributed to the type of drug administered preceding extubation.

Table 3: Distribution of complication

Complication	Group	Dexamethasone	Budesonides	*P*
Stridor (*n* (%))	Yes	5 (11.1)	6 (13.3)	0.75
	No	40 (88.9)	39 (86.7)	
Respiratory distress (*n* (%))	Yes	5 (11.1)	5 (11.1)	1
	No	40 (88.9)	40 (88.9)	
Reintubation (*n* (%))	Yes	2 (4.4)	3 (6.7)	0.65
	No	43 (95.6)	42 (93.3)	
Death (*n* (%))	Yes	2 (4.4)	3 (6.7)	0.65
	No	43 (95.6)	42 (93.3)	

Based on the findings of this study, it can be observed that there was no meaningful difference between budesonide received and Dexamethasone treated groups with regard to the post-extubation complications as 4.4% in the dexamethasone group and 6.7% in budesonide group needed reintubation. Similarly, the ABG parameters were not significantly different in the two groups up to 48 h after extubation. According to the previous studies the prevalence of reintubation rate is 1-17%.[1,11] The incidence of stridor was 11.1% in the dexamethasone group and 13.3% in budesonide group. Respiratory distress was found in 11.1% in both groups. According to a study by Lee, *et al*., the prevalence of stridor after extubation has been variable between 6% and 37%[1] that is comparable with stridor prevalence in the present study. In Young study also prevalence of post-extubation upper airway obstruction in patients intubated longer than 36 h was estimated about 2.3-22% with the reintubation rate of 1-19%.[5] Mortality rate in the dexamethasone group was 4.4% compared with 6.7% of the budesonide group, none was due to the airway obstruction and no significant difference was found between the two groups. Young's study recommended corticosteroids to prevent the upper airway edema and reduce the reintubation rate.[5] Sinha, *et al*. investigated the effectiveness of a mixture of 1000 μg budesonide and epinephrine 1% on pediatric patients where extubation failure rate declined from 40% to 10%.[8] Wittekamp, *et al*. study on post-extubation edema found that a mixture of IV corticosteroid, nebulizing epinephrine, helium and oxygen was effective; nevertheless, that study was not proved by a randomized control.[3] Using IV dexamethasone, Malhotra, *et al*. reduced the prevalence of extubation failure.[12] In another study by Epstein, *et al*. IV corticosteroid administration in patients intubated longer than 36-48 h reduced post-extubation obstruction and reintubation rate.[13] A study by Wang *et al*. Showed the administration of corticosteroid to be effective in reduction of

Table 4: Vital signs*

Time	SpO2 (%)		RR		HR	
	Dexamethasone	Budesonides	Dexamethasone	Budesonides	Dexamethasone	Budesonides
0	91.96±1.8	91.9±5	32.9±4	32.8±7.5	104.8±1.4	104.7±1.3
30 min	91±2.8	91.1±2.5	31.9±2.1	31.8±5	105±2.8	101.9±2.5
1 h	92.5±2.8	93±1.1	31.5±2.8	29.9±5	103±1.8	102.7±1.3
2 h	94±1.2	94.9±5.2	31.9±4.1	29.8±7.5	99.9±4.1	95.3±2.5
4 h	94.9±4.1	94.8±5.1	29±2.2	31.7±1.1	98±3.8	96.9±
8 h	95±2	95.9±2.5	31.5±2.8	31.5±1.8	94±2.8	94.9±5
12 h	95.8±4.1	96.9±5	32±2.8	32.4±2.3	91±2.8	91.9±5.1
24 h	96.9±2	95.1±2.5	23.9±2.8	24.7±1.3	88.1±4.1	88.7±1
36 h	96.4±3.1	96.6±2.5	19±2.8	19.9±5	88.8±1.4	89.1±3.3
48 h	95.1±4	96.9±2.5	20±1	20.8±7.6	83±2.8	87.5±2
P	0.12		0.13		0.2	

*Values are mean ± SD; HR: Heart rate; RR: Respiratory rate; SD: Standard deviation; SpO_2: Oxygen saturation

post-extubation stridor in 80% of cases.[4] Factors such as sample size, limitations of research (not managing to get the patients' accompanying persons' consent to participate in the study and a wide range of the patients' age) and genetic condition of patients and employed techniques can con for the difference between our study and others.

CONCLUSION

Since no significant difference was observed between the nebulized budesonide and IV dexamethasone, we recommend nebulized budesonide for prevention of post-extubation complications in ICU patients regarding the lower systemic absorption of budesonide.

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