Original Article

Comparison of Nebulized Budesonide and Intravenous Dexamethasone Efficacy on Tracheal Tube Cuff Leak in Intubated Patients admitted to Intensive Care Unit

Saeed Abbasi, Abbas Emami Nejad, Parviz Kashefi, Babak Ali Kiaei

From the Anesthesiology and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: Tracheal intubation is a common action in intensive care unit (ICU); however, it may cause laryngeal edema or laryngotracheal injury which leads to edema. The cuff-leak test is usually done to define the upper airway patency. Considering the point that laryngeal edema would be treated by anti-inflammatory agents, our aim was to evaluate the impact of nebulized budesonide on ICU patients' relief and comparison between nebulized budesonide efficacy and intravenous (IV) dexamethasone. **Materials and Methods:** In our clinical trial, 270 intubated patients from ICU were randomly selected and divided into three groups (each group was included 90 patients) as follows: IV dexamethasone, nebulized budesonide, and placebo group. All the patients were monitored at 0, 12, 24, 36, and 48 h of starting follow-up. Hemodynamic parameters and cuff-leak ratio were measured and data were analyzed using SPSS (ver. 20). **Results:** Our findings revealed that dexamethasone and budesonide treatment approaches were beneficial for an increase of cuff-leak volume ($P < 0.001$). Furthermore, the superiority of mentioned methods in patients' relief was significant compared with placebo group ($P < 0.001$). Moreover, hemodynamic parameters were not altered and were within the normal range in both dexamethasone and budesonide groups ($P > 0.05$). **Conclusion:** Our findings demonstrated that the use of budesonide and dexamethasone is beneficial in intubated ICU patients, and the above-mentioned approaches can reduce the complications of tracheal intubation. Furthermore, budesonide could be a trustworthy substitute treatment strategy instead of IV dexamethasone.

Keywords: *Cuff-leak ratio, intravenous dexamethasone, laryngeal edema, nebulized budesonide, tracheal intubation*

Introduction

Tracheal intubation is a common action in intensive care unit (ICU) for those people with breathing difficulty, due to laryngeal inflammation; however, it may cause laryngeal edema or laryngotracheal injury and stridor.[1] These complications occur during intubation and also after extubation which leads to morbidity and death.[2] On the other hand, about 1%–17% of ICU patients need reintubation after extubation due to their clinical conditions.[3] Usually, ICU patients need reintubation in the first 24 h of extubation which is more common in patients during 24–36 h of intubation,[4] resulting in higher mortality rate.[5] In addition, the mentioned issue causes to incur additional hospital and health cost on ICU patients.[6] Although clinicians and nurses know that most of the intubated patients might have laryngeal edema, recognition of this complication is often hard because endotracheal tube makes it impossible to see directly. Thereby, the cuff-leak test is performed to define the upper airway patency indirectly.[3] Reduced cuff-leak volume (CLV) in ICU patients can previse laryngeal edema caused by inflammation.[7] Actually, cuff leak is a quantitative test predicting the laryngeal edema as well as postextubation stridor. The cuff-leak test is the difference between expired tidal volume (TV) with cuff inflated and with cuff deflated. It means that higher leak leads to increased risk for postextubation stridor.[8-10]

Some studies revealed that laryngeal edema results from infiltrated immune cells to injured area.[11] Furthermore, joining between larynx with a wall of

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Address for correspondence:
Dr. Abbas Emami Nejad, Anesthesiology and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: abbas_emaminejad@yahoo.com

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endotracheal tube leads to upper airway inflammation which might consider for reintubation.[1,8] Thus, the use of antiedema drugs is mandatory. In experimental animal studies, it has been demonstrated that corticosteroids have a prominent role in the decline of infiltrated inflammatory cells. It also causes decrease in permeability and dilation of capillaries.[12] It has been stated that prophylactic corticosteroid therapy is beneficial in children that can rise down up to 40% of postextubation laryngeal edema, while in adults, the controversial results have been reported.[6,13,14]

On the other hand, the alternate approach to decrease laryngeal edema, aerosolized budesonide, was found an advantageous approach for treatment without any side effects.[3,15] Budesonide is glucocorticoid used for the treatment of lung diseases which is metabolized and inactivated highly fast in the liver.[16] Having the brilliant advantages, today, clinicians use this approach in various disorders such as chronic obstructive pulmonary disease[17] and asthma.[18]

Due to considerable inhibitory property of budesonide on inflammation, and according this point that laryngeal edema would be treated by anti-inflammatory agents, our aim was to evaluate the impact of nebulized budesonide on ICU patients' relief and compare nebulized budesonide efficacy with IV dexamethasone as a common treatment strategy for postextubation laryngeal edema that consequently leads to postextubation stridor.

Materials and Methods

The current study was a randomized controlled clinical trial. The population of the study included all patients hospitalized in ICU of Al-Zahra Hospital from 2012 to 2013. Inclusion criteria were the age range of 18–45 years, been intubated at least for 48 h, lack of receiving corticosteroids by any means, lack of respiratory disease such as asthma or chronic lung disease, lack of chronic consumption of nonsteroidal anti-inflammatory drugs, hospitalization in ICU, and consent to participate in the study written by patient or his family's. In addition, death before the intervention and extubation before ending the intervention were considered as exclusion criteria. The sample size required for this study was estimated 90 participants in each group using the formula to compare the two rations considering 95% of confidence level, 80% test power, at least square significant difference among groups of 0.032, and tracheal tube cuff leak of 0.25. The method of sampling in this study was convenient method in which patients who meet the inclusion criteria were selected based on their sequential admissions to ICU, and they were assigned to each of the three studied groups using blocked randomized diagnosis method. The procedure was that patients entering to ICU were distributed into three Groups A, B, and C after obtaining the approval by the Ethical Committee of Isfahan University of Medical Sciences (Ethical code: IR.MUI.REC.1395.291) and written consent of the patients. Furthermore, it was registered in the Iranian Registration System with IRCT2017061734598N1 before starting participant recruitment [Figure 1].

In Group A, the patients underwent nebulized budesonide approach with a dose of 2 mg reached to 4 ml and with oxygen flow rate of 6 l/min through nebulizer over 20 min every 12 h. In addition, they received intravenous (IV) normal saline 2 ml every 8 h. Group B underwent the IV injection of dexamethasone for the amount of 8 mg every 8 h during 48 h. In addition, they received 4-ml normal saline every 12 h through nebulizer received, and Group C, as controls, received 2-ml normal saline every 8 h intravenously and 4-ml normal saline every 12 h through nebulizer.

(Notable point: Due to conducting this study in a hospital, we had the same condition of intubation for all patients).

To calculate the cuff-leak ratio (CLR) of patients, the mode of the device was placed at volume-assisted control mode and TV = 8 cc/kg and peep = 0. Then, tracheal tube cuff was emptied, and the amount of the expiratory TV was checked at six respiratory cycles, and the mean of three samples that had the minimum amount of the TV was calculated.

Then, the CLR ratio was calculated for each patient as follows:

$$\text{CLR} = \frac{\text{TV ventilator} - \text{The mean of expiratory TV at three respirations with low TV}}{\text{TV ventilator}}$$

During the study, all patients were under cardiac and respiratory monitoring without knowing the type of treatment, and clinical and hemodynamic parameters of patient such as peripheral capillary oxygen saturation (SPO_2), mean arterial pressure (MAP) and heart rate (HR), and CLR were recorded at the beginning of the study (0 h) and 12, 24, 36, and 48 h after intubation.

Finally, all collected data were analyzed using SPSS software (20.0) (SPSS - Chicago, IL, United States). Qualitative data in the forms of frequency and frequency percentage and quantitative data in the forms of mean and standard deviation have been demonstrated. As the inferential statistics, respectively, the Chi-square test has been applied to compare frequency distribution of sex and cause of intubation between three groups while one-way ANOVA used to compare the age between these three groups. Furthermore, according to the results of the Kolmogorov–Smirnov normality test indicating normal distribution of variables; we used one-way ANOVA test to compare the means of continuous variables between three groups, and Tukey's *post hoc* test was used to two by two comparing of the groups and repeated measure test compares the means of variables by passing the time from baseline to 48 h after intervention in each group.

In all analyzes, we considered the statistical significance level <0.05.

Results

In this study, 270 patients underwent intubation in three groups (each containing 90 participants) receiving nebulized budesonide, IV dexamethasone, and normal saline. Three studied groups were matched regarding factors such as age, gender, weight, reason of intubation, and time of intubation ($P > 0.05$) [Table 1].

Results of the mean status of the minimum TV respiration (MTV) and CLR of patients up to 48 h after the intubation at three groups suggest that, in general, 48 h after intubation in each of the three groups, MTV and CLR improved significantly ($P < 0.001$). In addition, comparative study (paired comparison) of the studied groups in each of the follow-up times showed that both treatment groups had significant difference with control group from 12 to 48 h after the intubation ($P < 0.05$). However, two treatment groups had no significant difference up to 24 h after the intubation ($P > 0.05$), and they were different only in 36 and 48 h after the intubation so that the mean leak ratio in budesonide treatment group was better than dexamethasone group ($P < 0.05$) [Table 2 and Figure 2].

On the other hand, the comparative study of critical factors such as mean HR, SpO_2, and MAP showed no significant

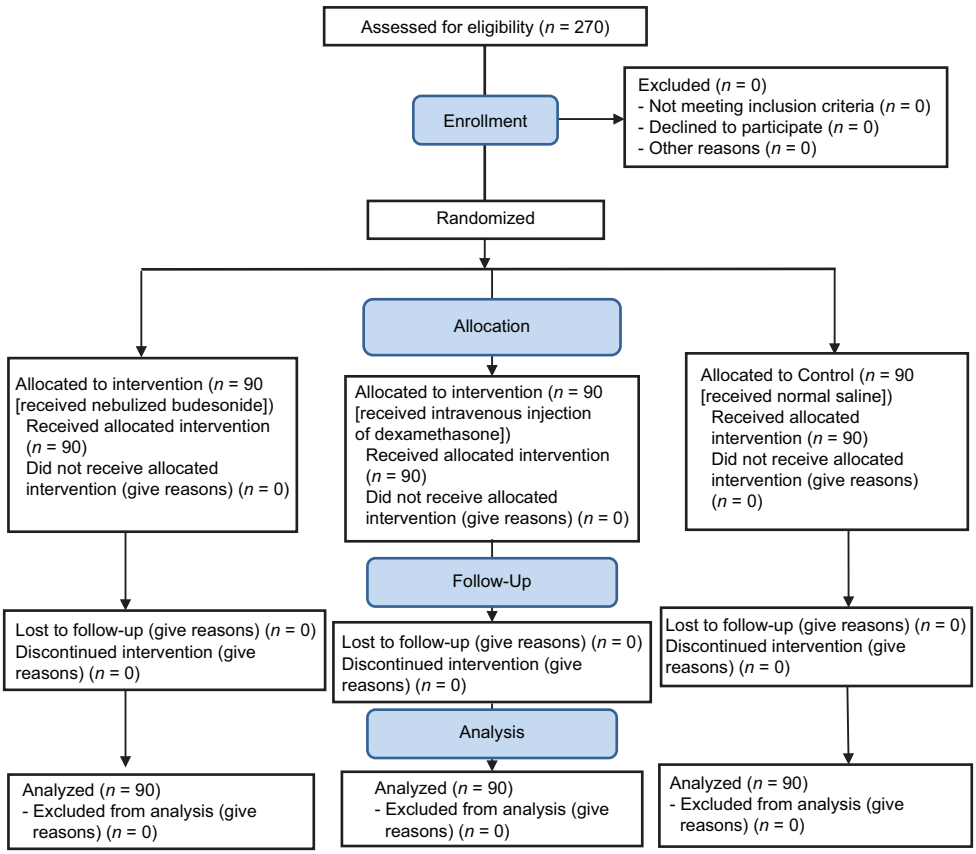

Figure 1: Flowchart consort

Table 1: Demographic and clinical characteristics

Characteristics	Budesonide (*n*=90), *n* (%)	Dexamethasone (*n*=90), *n* (%)	Control (*n*=90), *n* (%)	*P*
Gender; male	55 (62.5)	48 (53.3)	43 (47.8)	0.138
Age (year)	45.19±14.54	40.76±13.77	44.80±15.65	0.083
Weight (kg)	72.22±9.75	70.12±10.53	73.19±9.63	0.110
Cause of intubation				
Trauma	30 (33.3)	42 (46.7)	52 (57.8)	0.056
Loss of consciousness	28 (31.1)	22 (24.4)	25 (27.8)	
Surgery	22 (24.4)	20 (22.2)	9 (10)	
Poisoning	10 (11.1)	6 (6.7)	4 (4.4)	
Intubation time (day)	7.29±5.98	9.46±6.83	8.93±7.19	0.083

Data shown *n* (%) or mean±SD. SD: Standard deviation

Table 2: Comparison the mean minimum tidal volume respiration and cuff-leak ratio in three groups up to 48 h after intubation

Variables	Groups	0 h	12 h	24 h	36 h	48 h	$P^{\#}$
MTV	Budesonide (*n*=90)	501.44±82.67	474.66±82.97	435.04±82.80	414.79±80.71	390.81±80.87	<0.001
	Dexamethasone (*n*=90)	499.84±84.39	454.29±84.97	415.11±84.56	391.69±83.09	367.32±80.60	<0.001
	Control (*n*=90)	522.08±67.93	503.21±65.80	488.17±68.11	473.85±67.8	461.84±67.97	<0.001
	*P**	0.068	0.011	<0.001	<0.001	<0.001	
	*P***	0.530	<0.001	<0.001	<0.001	<0.001	
	*P****	0.383	0.105	0.112	0.060	0.052	
CLR	Budesonide (*n*=90)	0.16±0.07	0.22±0.10	0.27±0.05	0.34±0.05	0.40±0.06	<0.001
	Dexamethasone (*n*=90)	0.16±0.12	0.23±0.05	0.28±0.07	0.33±0.06	0.37±0.08	<0.001
	Control (*n*=90)	0.14±0.07	0.15±0.02	0.16±0.02	0.18±0.02	0.24±0.02	<0.001
	*P**	0.056	<0.001	<0.001	<0.001	<0.001	
	*P***	0.173	<0.001	<0.001	<0.001	<0.001	
	*P****	0.482	0.397	0.271	<0.001	0.004	

#Level significant to comparison each group in follow-up, *Level significant to comparison control group versus budesonide group, **Level significant to comparison control group versus dexamethasone group, ***Level significant to comparison budesonide group versus dexamethasone group. MTV: Minimum TV respiration, CLR: Cuff-leak ratio, TV: Tidal volume

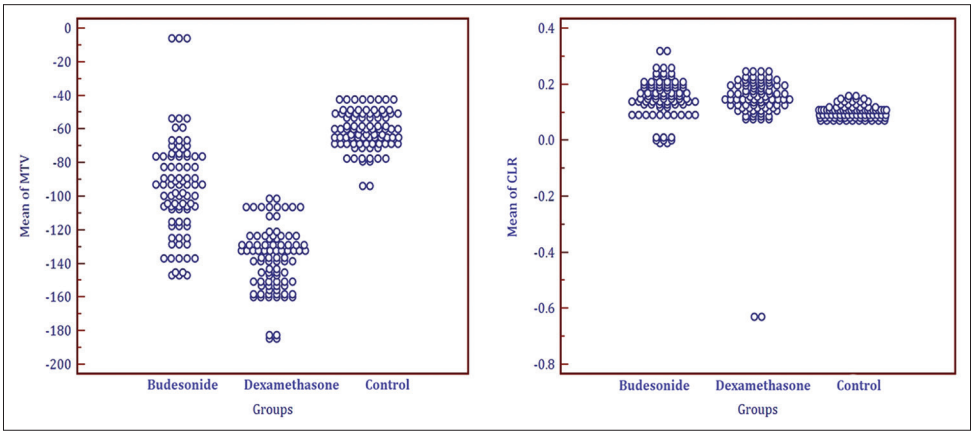

Figure 2: Change of cuff-leak ratio and MTV up to 48 h after intubation in three groups

difference between any of the three groups at the time of intubation ($P > 0.05$). Three groups have equal position; however, a significant difference was found between two treatment groups and control group over time in 24–48 h after intubation ($P < 0.05$). On the other hand, while vital signs in budesonide treatment group were better, this difference was not statistically significant compared to dexamethasone treatment group ($P > 0.05$) [Table 3].

Finally, investigating the effective role of demographic factors on cuff-leak alteration showed that in the two treatment groups of budesonide and dexamethasone, none of the demographic factors have a significant role in cuff-leak changes ($P > 0.05$); however, in the control group, gender, age, and body weight had a significant role in cuff-leak changes ($P < 0.05$) [Table 4].

Discussion

Tracheal intubation is a demanded approach for operation theater or ICU to assist mechanical ventilation.[19] It is a common administration in acute-care hospitals, however, might result in morbidity.[20,21] The patients with general anesthesia or being in ICU after performing the tracheal intubation have laryngeal inflammation (sore throat) with the incidence of 21%–65%;[22] notwithstanding, there are other factors included in the development of inflammation such as gender, lung or inflammatory diseases, tracheal tube size, cuff design, and duration of surgery.[23,24] These complications are not contentment for the discharged patients.[25] Different studies have mentioned that the use of corticosteroids is beneficial for airway obstruction.[3,4,26,27] Nevertheless, there are some investigations declining the mentioned useful effects on reintubation laryngeal edema.[28-30] However, for a long time, clinicians use corticosteroids for inhibition or treatment of postextubation laryngeal edema due to its anti-inflammatory effects.[1,31]

Our assessment revealed that MTV was significantly decreased in three groups; although in budesonide and dexamethasone groups, the decrease trends were considerably higher than the control group. Thus, both methods are beneficial for the patients with difficulty in breathing due to laryngeal edema.

Table 3: Comparison of the mean of vital signs in three groups up to 48 h after intubation

Vital signs	Groups	0 h	12 h	24 h	36 h	48 h	$P^{\#}$
HR	Budesonide (*n*=90)	88.61±16.33	85.58±15.54	81.08±13.65	76.93±12.38	75.05±8.83	<0.001
	Dexamethasone (*n*=90)	91.36±13.10	86.30±13.06	81.60±11.27	78.28±9.02	75.76±5.86	<0.001
	Control (*n*=90)	93.24±15.19	88.96±8.60	84.98±10.39	81.96±12.72	77.81±8.01	<0.001
	*P**	0.051	0.077	0.032	0.008	0.029	
	*P***	0.374	0.163	0.037	0.026	0.049	
	*P****	0.197	0.704	0.781	0.404	0.522	
SpO_2	Budesonide (*n*=90)	95.38±2.22	95.84±1.61	95.88±1.81	95.95±1.18	96.83±1.00	0.037
	Dexamethasone (*n*=90)	95.20±1.89	94.61±1.62	95.68±2.59	95.91±1.06	96.19±2.97	<0.001
	Control (*n*=90)	95.22±1.59	95.06±2.40	94.81±2.01	95.42±1.81	95.50±1.04	<0.001
	*P**	0.579	0.299	0.001	0.021	<0.001	
	*P***	0.938	0.299	0.013	0.028	0.024	
	*P****	0.558	0.299	0.549	0.811	0.142	
MAP	Budesonide (*n*=90)	86.92±12.06	85.08±11.63	82.10±10.04	82.77±10.18	80.14±9.16	<0.001
	Dexamethasone (*n*=90)	89.21±10.95	85.96±12.42	80.88±8.39	81.20±9.02	79.82±9.64	<0.001
	Control (*n*=90)	90.03±12.38	88.58±8.49	86.81±10.69	86.91±9.67	83±8.77	<0.001
	*P**	0.089	0.022	0.001	0.005	0.040	
	*P***	0.638	0.100	<0.001	<0.001	0.021	
	*P****	0.184	0.592	0.400	0.287	0.819	

$^{\#}$Level significant to comparison each group in follow-up, *Level significant to comparison control group versus budesonide group, **Level significant to comparison control group versus dexamethasone group, ***Level significant to comparison budesonide group versus dexamethasone group. HR: Heart rate, SpO_2: Oxygen saturation, MAP: Mean arterial pressure

We used as the same dose (8 mg/kg) of IV dexamethasone as Cheng and Zhang[4] and Lee *et al*. did.[3] However, other investigations used 10 ml/kg, as a standard volume.[7-9] Furthermore, we used 1 mg budesonide diluted in 4 ml of sterile water for 48 h, as same as previous clinical investigations.[15,32] The assessment of CLR in our investigated groups has demonstrated a beneficial effect of budesonide and dexamethasone in 48 h of our follow-up during intubation. Our follow-up revealed that the budesonide group had the best decent effect on CLR. The outcomes presented that after 24 h use of dexamethasone, the CLV was increased more than 24% and this increasing trend continued to 38% at 48 h. The main change started from 24 h from treatment initiation, was upper than 24% of reported CLR cutoff,[4] increased by 40%. While we found the significant superiority of budesonide treatment compared to dexamethasone usage after 36 h of follow-up, previous studies did not show any significant difference between both mentioned groups.[32] However, same as our report, Wang *et al*. confirmed that the use of corticosteroids caused improvement in CLV after 72 h using 5 mg every 8 h.[27] Similarly, Baloch *et al*. stated that the use of steroids after 18 h (four times injection at 1, 6, 12, and 18 h) led to increase in CLV more than 54%.[33]

In addition, in the current study, we evaluated the efficacy of nebulized budesonide in comparison with IV dexamethasone in intubated ICU patients. Hemodynamic monitoring was done to not having any adverse effects. HR in three groups was decreased ($P < 0.001$). The meticulous assessment about the efficacy of treatment methods revealed that at the begin time and 12 h, there was not any significant association among three groups, but after 24, 36, and 48 h, dexamethasone and budesonide had significant beneficial effects on HR reduction. Moreover, budesonide had the best impact on HR decline compared to dexamethasone and placebo groups. In previous research done by Kashefi *et al*., HR was not significantly different between dexamethasone and budesonide groups in different times.[32]

On the other hand, the amount of SpO_2 factor was higher in three groups after 48 h of follow-up. Similar to the HR trend, at the 0 h and 12 h, there was not any significant different among three groups for SpO_2, but at 24, 36, and 48 h both, budesonide and dexamethasone treatment methods have shown to be more efficient than the placebo group. Again, budesonide had the greatest effect on level of SpO_2 (96.38 budesonide vs. 96.19 dexamethasone vs. 95.50 control); however, there was not any superiority between budesonide and dexamethasone approaches. In agreement with our results, other studies found no significant difference in efficacy between dexamethasone and budesonide groups after 48 h.[32] Similarly, it has been stated that SpO_2 in the budesonide group was significantly higher than the control placebo group ($P = 0.017$).[34]

Moreover, MAP was decrease dramatically in three groups. The decreasing trend of dexamethasone and budesonide groups was considerably higher than that of in placebo group after 24 h. Dexamethasone has shown to have the highest influence on the MAP after 48 h. To the best of our knowledge, no study has pointed out straight about the relationship between the way of treatment and MAP levels in intubated ICU patients; however, both treatments methods had not an adverse effect on patients'

Table 4: Investigating the role of demographic factors on cuff-leak changes in patients up to 48 h after intubation

Groups	Factors	Mean±SD	*P*
Budesonide	Gender		
	Male	0.16±0.06	0.600
	Female	0.15±0.08	
	Age (years)		
	≤30	0.14±0.09	0.535
	>30	0.16±0.06	
	Weight (kg)		
	≤73	0.16±0.08	0.114
	>73	0.14±0.05	
	Cause of intubation		
	Trauma	0.16±0.03	0.500
	Loss of consciousness	0.16±0.08	
	Surgery	0.15±0.06	
	Poisoning	0.12±0.09	
Dexamethasone	Gender		
	Male	0.22±0.19	0.394
	Female	0.24±0.04	
	Age (years)		
	≤30	0.25±0.04	0.349
	>30	0.22±0.16	
	Weight (kg)		
	≤73	0.24±0.17	0.440
	>73	0.21±0.04	
	Cause of intubation		
	Trauma	0.21±0.19	0.613
	Loss of consciousness	0.26±0.04	
	Surgery	0.25±0.05	
	Poisoning	0.22±0.050	
Control	Gender		
	Male	0.09±0.02	0.012
	Female	0.11±0.02	
	Age (years)		
	≤30	0.09±0.02	0.001
	>30	0.11±0.03	
	Weight (kg)		
	≤73	0.11±0.03	0.004
	>73	0.09±0.02	
	Cause of intubation		
	Trauma	0.11±0.02	0.157
	Loss of consciousness	0.09±0.02	
	Surgery	0.11±0.03	
	Poisoning	0.09±0.01	

SD: Standard deviation

hemodynamic parameter, and regarding the normal range of MAP,[35] there was not any disadvantage for treatment approaches.

In our last evaluation, the results showed that most of the general factors such as gender, age, and weight had a significant role on cuff-leak alteration; however, in dexamethasone and budesonide groups, none of the mentioned factors could make an effect on patients' cuff-leak volume after 48 h of follow-up. The evaluation of hemodynamic parameters did not show any harmful effect such as tachycardia, bradycardia, or hypertension. Our hypothesis is toward the powerful impact of steroids on treatment trend, which causes limiting the confounders and might be promising therapeutic strategy which can be used as a supportive care accompanied with intubation.

Since endotracheal tube and cuff-leak test are known to be a predictor for postextubation stridor,[36] and as corticosteroids are used to prevent laryngeal edema[37] and also because previous investigations have stated that in patients with high risk for laryngeal edema, after extubation they demand reintubation again in first 48–72 h,[38,39] and patients always complaint about the relative complications,[23] we are standing with this fact that the use of corticosteroids is beneficial for intubated ICU patients. Furthermore, concerning the positive effects of budesonide on CLV and MTV, it could be a worthy approach that can substitute with dexamethasone treatment.

Conclusion

According to our findings, the use of budesonide and dexamethasone was beneficial in intubated ICU patients which can reduce the complications of tracheal intubation. Moreover, budesonide could be a trustworthy substitute treatment strategy instead of IV dexamethasone.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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