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Nebulized Budesonide vs. Placebo in Adults with Asthma Attack; a Double Blind Randomized Placebo-Controlled Clinical Trial

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Abstract

Introduction: Asthma is one of acute respiratory diseases leading to emergency department (ED) referral. Management of acute attack plays an important role in its outcome.

Objective: This trial was designed to evaluate the effectiveness of nebulized budesonide versus placebo in moderate to severe acute asthma attack in adults in the ED.

Method: In this clinical trial, we enrolled patients with acute exacerbation of asthma and standard treatment of acute asthma attack was administered to all of them. 41 patients in our study were randomly entered into 2 groups. In one group, we prescribed nebulized budesonide and in the other group nebulized placebo (normal saline) was administered. Patients' demographic data, vital signs, symptoms' acuity and the time of symptom relief, patient and physician satisfaction were all recorded and compared between the 2 groups. All cases were followed and disease outcome, readmission, mortality and morbidity rates were documented.

Results: In this study, 20 patients were entered the budesonide group and 19 patients were enrolled in the placebo group. The mean age ranges were 55.70±15.30 and 60.32±18.41 years old respectively. Heart rate, respiratory rate and O2 saturation in the first group were improved significantly after the treatment in comparison to the second group ($p<0.05$). The mean time of recovery and length of hospital stay were better in the first group than the second group but this difference was not significant ($p>0.05$).

Conclusion: The addition of nebulized budesonide to standard asthma treatment might result in more improvement in O2 saturation and less patient's distress.

Key words: Adult; Asthma; Budesonide; Emergency department; Placebos

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INTRODUCTION

Acute asthma attack is one of the reasons, patients refer to the emergency department (ED). Most patients are admitted to the ED in the acute phase and their treatment is focused on relief of bronchospasm by short acting β2 agonist (SABA) and anticholinergic (ipratropium bromide) as inhaled bronchodilators, decrease in airway inflammation and also preventing recurrence of acute symptoms by systemic and inhaled corticosteroid (ICS) (1).

Systemic corticosteroids or ICSs seemed to be ineffective long ago, but many studies have confirmed that they could have an early treatment effect. This role consists of genomic and nongenomic effects which the later includes binding to membrane and cytoplasmic corticosteroid receptors. This binding leads to prohibiting norepinephrine (NEP) reuptake in the neuromuscular junction thus NEP density increases bronchodilation and decreases mucosal blood flow in asthmatic patients. The nongenomic effect is really fast over the very first seconds to minutes (1).

ICS like budesonide is one of asthma symptoms' controller by reducing airway inflammation and mediators involved. This can lead to better lung function, less admission and more desirable life style. Budesonide, a synthetic highly potent ICS, has been studied in children suffering acute asthma attack as different forms of inhaler and nebulized suspension (2-4).

Based on asthma prevalence rate of 1 to 18% in different countries, emergency physicians (EPs) should prescribe drugs with the best effectiveness in the earliest moments of disease exacerbation. Many studies have supported the usage of combination therapy of SABA and ICS in increasing recovery rate and decreasing treatment time (2, 5).

Most studies about the effectiveness of nebulized budesonide are performed on children and in mild or chronic asthma (4, 6-9). In this study, we decided to evaluate its efficacy in adults and in the acute phase in the emergency setting.

METHODS

Study design

This study was a double blind randomized clinical trial (RCT) done in the EDs of 2 tertiary referral centers of university hospitals in 2018. The study was approved by the ethics committee and it was registered in www.irct.ir with the trial number of IRCT20170325033132N3. All patients were interviewed and the method of drug administration and possible complications were explained to them and informed written consent was obtained.

Study population

All adult patients with moderate to severe acute asthma attack were enrolled in our study. The sampling was convenient and we used block randomization. We enrolled 41 patients based on our inclusion criteria; age older than 18 years old, moderate to severe acute asthma attack, known cases of asthma referring to the ED. Asthma attack was diagnosed by deterioration of symptoms from baseline and exacerbation needed early intervention. Our exclusion criteria were new cases of asthma, asthma accompanied by another diagnosis like pneumonia, congestive heart failure (CHF), pneumothorax or any other systemic or structural lung diseases, altered mentation or confusion, sever respiratory failure with cyanosis, intubated patients, illicit drug addiction, pregnancy, unstable vital signs, drug allergy and unwillingness to enter the study. The rate of clinical recovery was considered as the main variable. Based on Blic et al study,[5] in order to show 50% increase in the recovery rate and by considering 10% loss of our samples, we calculated a sample size of 20 cases in each group (α=0.05 and power=90%).

Intervention

All patients received standard asthma attack treatment, O2 therapy, SABA and Atrovent spray (4-10 puffs each 20 min during the first hour) and intravenous systemic corticosteroid (100 mg hydrocortisone) were administered to them. Patients were randomly enrolled in either the

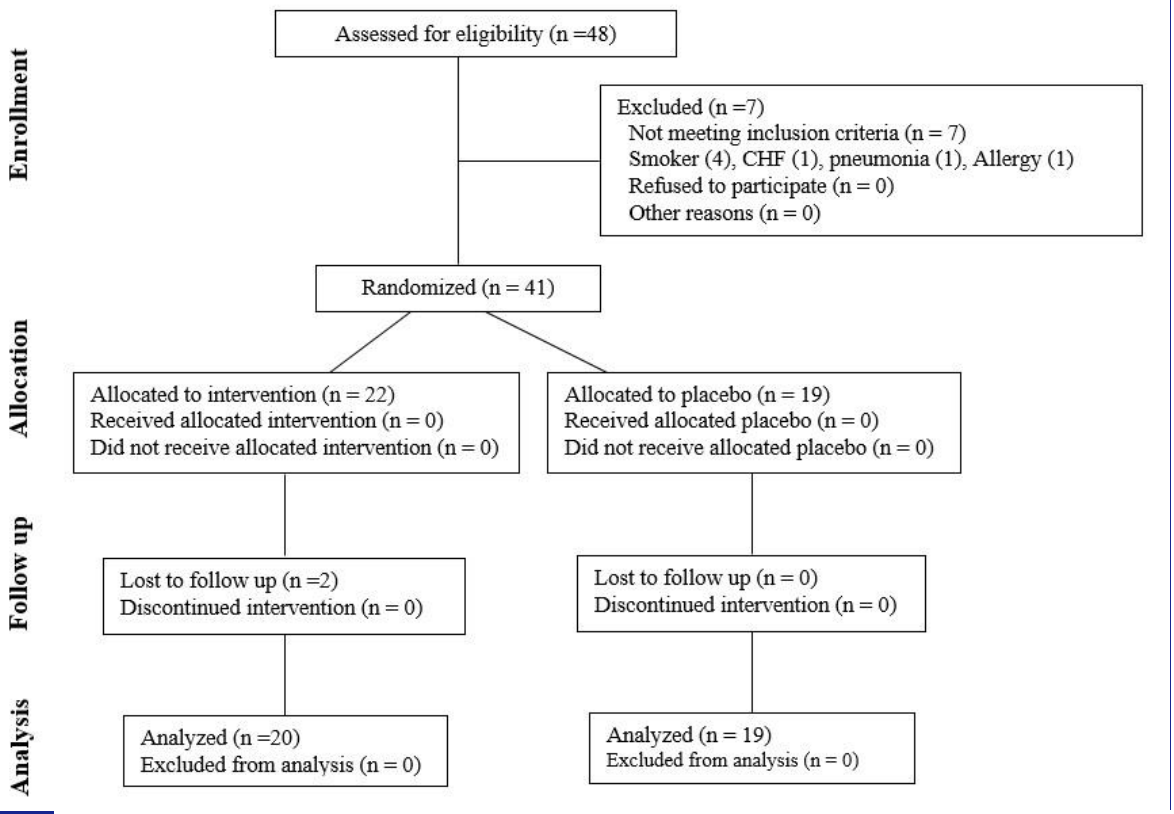

Figure 1: CONSORT flowchart of the participants in the study

control group (nebulized budesonide brand name pulmicort made by AstraZeneca company) or placebo group (nebulized normal saline). In the control group, nebulized budesonide was prescribed 0.5 mg every half an hour till 3 doses (1.5 mg total dose) and in the placebo group the equivalent normal saline was nebulized at the same time. All patients underwent cardiac and respiratory monitoring during the treatment.

At the time of admission and before the treatment was started, the severity of asthma was evaluated by peak flowmeter. All patients with moderate to severe asthma attack [based of peak expiratory flow rate (PEFR)], were enrolled in the study and accurate medical history, physical exam (auscultation of wheeze, its severity, time and location, respiratory accessory muscle use), vital signs including heart rate (HR), respiratory rate (RR) and O2 saturation (SPO2) were evaluated and recorded at baseline and also at 30 min, 1 and 3 hours after the intervention.

Primary and Secondary Endpoints

Our primary endpoint was to compare the effectiveness of nebulized budesonide versus placebo in adults with asthma attack in the ED by evaluating their vital signs, and physical examination. Our secondary endpoints were comparing hospital length of stay, patients and physicians' satisfaction, recurrence, readmission and mortality rates, the mean time of recovery and admission during 1 month follow up.

Statistical Analysis

The data are presented as mean values or proportions, and differences in these values are presented with accompanying 95% confidence intervals (CI). Variables were tested for normality by Kolmogorov–Smirnov test before analysis. Analytical statistical tests included the unpaired, two-tailed t-test for continuous normally distributed data and the Mann–Whitney U test for non-normal and ordinal data. The chi-square and Fisher's exact tests were used to compare proportions of the qualitative variables. We also used repeated measure AVOVA. The level of significance was 0.05. SPSS for Windows software (version 22) was used for all data analysis.

Results

Forty-eight patients were eligible in our study of whom 7 cases were excluded: 4 were smokers, 1 CHF, 1 pneumonia, 1 allergy history. Finally, 41 patients were enrolled in our study; 22 cases in the control group and 19 in the placebo group (figure 1). Two patients in the control group had lost to follow up thus we eventually evaluated 20 patients in the control group and 19 patients in the placebo group. The mean age in the control group was 55.70±15.30 and in the control group was 60.32±18.41 years old. There were 10 males in each group but we evaluated 10 females in the control group and 9 in the placebo group. Baseline PEFR showed no difference in asthma severity between the 2 groups. Data are shown in table 1.

Table 1: Baseline information of studied patients

Variable	Control	Placebo	P
Age (y/old)	55.70±15.30	60.32±18.41	0.06
Gender (N (%))			
Male	10 (50%)	10 (52%)	0.86
Female	10 (50%)	9 (48%)	
PEFR (N (%))			
40-70%	12 (60%)	11 (58%)	0.89
<40%	8 (40%)	8 (42%)	

PEFR: Peak flowmetry

HR had a significant reduction within each group and this reduction was significantly more in the control group (p=0.04). RR also showed the same change (p=0.03). SPO2 increased significantly within each group and this improvement was significantly more in the control group (p=0.01). These results showed that patients in the control group experienced significantly less distress in comparison to the placebo group. In the placebo group, 1 patient still had severe wheeze 3 hours after the intervention. In contrast, all patients' wheeze was completely relieved 1 hour after the treatment in control group. However, this difference was not statistically significant. Data of our primary endpoints are shown in table 2.

Our results failed to show any significant difference in patient or physician satisfaction between the 2 groups. Recurrence or readmission or mortality had similar rate between the 2 groups. Data are shown in table 3.

The mean time of recovery in the control and placebo group were 41.68±3.16 and 60.25±2.04 min, respectively (p= 0.12). The mean length of hospital stay in the control and placebo group were 3.8 and 4.5 days, respectively (p=0.53).

Discussion

Based on the findings of current study, nebulized budesonide in adult acute asthma crisis might be effective in reducing patient respiratory distress by ameliorating HR, RR and SPO2. Nevertheless, it could not decrease recovery time or length of hospital stay and also long term outcomes including recurrence or readmission.

Edmonds et al performed a meta-analysis about the effectiveness of ICS in emergency setting. They

Table 2: Comparison of the study primary endpoints

Variable	Group	Time interval				P
		0 min	30 min	60 min	180 min	
Systolic blood pressure (mmHg)	**Control**	139.42±25.40	130.00±20.54	128.16±20.56	126.58±20.21	0.32
	Placebo	150.47±23.79	148.47±21.15	142.37±18.73	138.95±17.99	
Diastolic blood pressure (mmHg)	**Control**	82.53±12.19	76.84±12.04	76.84±10.43	76.32±8.30	0.31
	Placebo	87.05±12.28	85.68±13.08	81.11±7.88	79.26±6.47	
Heart rate (beats/min)	**Control**	108.60±24.12	102.05±23.43	94.75±22.81	91.25±20.92	0.04
	Placebo	100.37±24.83	97.21±22.85	94.37±22.05	92.16±20.53	
Respiratory rate (n/min)	**Control**	34.60±7.46	27.10±5.66	23.35±4.91	21.00±6.64	0.03
	Placebo	30.11±9.87	29.11±2.35	28.11±2.73	27.11±1.29	
O2 saturation (%)	**Control**	84.05±8.56	90.10±5.54	94.30±3.52	95.85±1.87	0.01
	Placebo	88.79±3.29	91.00±3.36	92.84±2.21	93.79±2.27	
wheeze (n (%))	**Control**	20 (100)	14 (70.0)	9 (45.0)	0 (0.0)	0.48
	Placebo	19 (100)	13 (68.4)	9 (47.4)	1 (5.3)	
Severe wheeze (n (%))	**Control**	13 (65.0)	4 (28.6)	1 (11.1)	0 (0.0)	0.12
	Placebo	7 (36.8)	5 (38.5)	3 (33.3)	0 (0.0)	
Respiratory accessory muscle use (n (%))	**Control**	9 (45.0)	5 (25.0)	2 (10.0)	0 (0.0)	1.00
	Placebo	7 (36.8)	3 (15.8)	1 (5.3)	0 (0.0)	

Table 3: Comparison of the study secondary endpoints

Variable	Control group		Placebo group		P
	Yes	No	Yes	No	
	n (%)				
Patient satisfaction	18 (90%)	2 (10%)	13 (68%)	6 (32%)	0.12
Physician satisfaction	17 (85%)	3 (15%)	12 (63%)	1 (37%)	0.15
Recurrence rate	3 (17%)	15 (83%)	7 (37%)	12 (63%)	0.26
Readmission rate	2 (11%)	16 (89%)	6 (32%)	13 (68%)	0.23
Mortality rate	0 (0%)	20 (100%)	0 (0%)	19 (100%)	-

evaluated clinical trials done on both children and adults. In 2 of these studies, ICS was compared to placebo like our study. They found that patients treated with ICS had significantly less admission rate but we did not find the same result. In conclusion this meta-analysis revealed that although ICS reduced admission rate, but further studies in this field should be designed (9).

Adding ICS, as inhalers by meter dose inhalers (MDIs) or nebulized forms, to systemic corticosteroids failed to show any significant differences in the flow rate or other primary clinical outcomes (10, 11). Our study showed that except HR, RR and SPO2 no significant difference was observed between the 2 groups.

In an RCT published in CHEST journal in 2006, 470 adult patients and 663 children with asthma were evaluated. In this research, ICS was compared with placebo. They found that cases who received 3 or more doses of ICS had a significantly better improvement in clinical signs and also spirometry (1).

In START study the efficacy of ICS as a routine therapy in persistent mild asthma was determined. Both adults and children received daily budesonide for 2 years. Authors concluded that early prescription of ICS could prevent severe asthma attack and reduce the need for more drugs (9). Our study was performed in the acute setting in moderate to severe asthma and we observed higher SPO2 and lesser distress in our patients.

Devidayal et al compared the effectiveness of inhaled budesonide versus oral prednisolone in the ED and in children with acute asthma. They revealed the same results as our adult patients. They showed that HR, RR, SPO2 and respiratory distress were significantly improved in the budesonide group (12).

MacLaughlin et al evaluated the risk of readmission in the ED in children younger than 8-year-old who had received nebulized budesonide. They demonstrated that budesonide decrease recurrence and readmission rates significantly up to 71% (13). We did not document the same results.

Limitations

One limitation of our study was that the sample size might be insufficient to detect the exact drug effects. Further clinical trials with larger sample sizes and longer follow-up should therefore be performed to identify its role. It was difficult to follow patients during 1 month, some of our patients were unwilling to answer our questions or refer for frequent visits. This was the results of 2 tertiary referral centers and might not be extendable to other centers.

Conclusions

It is likely that, nebulized budesonide in adult acute asthma crisis might be effective in reducing patient respiratory distress; But, has not any significant effect on recovery time or length of hospital stay, or long term outcomes including recurrence or readmission or mortality.

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Authors' contribution

All the authors met the standards of authorship based on the recommendations of the International Committee of Medical Journal Editors.

Conflict of interest

None declared.

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