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Two different dosages of nebulized steroid versus parenteral steroid in the management of COPD exacerbations: A randomized control trial

Authors' Contribution:
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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The study aimed to compare the efficacy and safety of nebulized steroid (NS) with systemic corticosteroids (SC) and to determine optimal NS dose in the treatment of patients with COPD exacerbations requiring hospitalization.

Material/Methods: The study was a randomized, parallel design trial. Eligible patients (n=86) were randomly allocated to 1 of the 3 treatment groups: parenteral corticosteroid (PS) (n=33), 4 mg (NB) (n=27), or 8 mg NB (n=26). Partial pressure of arterial oxygen (PaO_2), carbon dioxide ($PaCO_2$), pH, and oxygen saturation (SaO_2) were evaluated at baseline, 24 h, 48 h, and discharge. Airway obstruction (forced vital capacity [FVC] and forced expiratory volume 1 s [FEV_1]) was evaluated at admission and discharge.

Results: There were no significant differences between the groups for all parameters at all time periods, except for higher FEV_1 value in the 8-mg NB group at baseline. In groups, significant differences were determined for FVC, FEV_1, PaO_2, and SaO_2 ($p<0.001$), but not for $PaCO_2$ and pH, in comparison to their baseline values. As adverse events, hyperglycemia and oral moniliasis were observed in the PS group (n=4) and in the NB groups (n=5), respectively, and treatment change was required in 9 patients (2 patients in the PS group and 7 patients in the NB groups) (p=0.57).

Conclusions: Nebulized budesonide may be used as an alternative to SC because of its equal effectiveness and lesser systemic adverse effects. The choice of optimal dosage needs to be evaluated carefully because adverse effect and dropout rates varied according to dosage. However, there is a need for further studies including more severe cases and evaluating long-term outcomes or relapses comparing the 3 arms.

MeSH Keywords: Budesonide – therapeutic use • Methylprednisolone – therapeutic use • Pulmonary Disease, Chronic Obstructive – drug therapy

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Background

Chronic obstructive pulmonary disease (COPD) is a common disease that has a chronic and progressive course. In patients with COPD, exacerbation history is an important component in therapeutic decision-making. The number of exacerbations is important because of increased morbidity, mortality, and healthcare costs [1].

Systemic corticosteroids (SC) are recommended by all international guidelines in the management of exacerbations of COPD as well as bronchodilator, oxygen, and antibacterial treatment [2,3]. However, there are still some concerns about systemic corticosteroid use because COPD patients tend to be older, relatively immobilized, and prone to development of steroid-related complications. Exacerbation rate is significantly higher in COPD patients, and these patients need higher amounts of SC to control their exacerbation [4,5]. Because of its potential and frequent use, SC results in adverse effects such as osteoporosis and bone fractures, thinning of the skin, posterior subcapsular cataract formation, glucose intolerance, and myopathy [6–11]. Thus, this condition leads clinicians to seek alternative options such as nebulized steroid use. However, there are few studies showing that nebulized steroids (NS) are as effective as SC in controlling exacerbations of COPD [13–18] and the optimal NS dose is still uncertain.

We aimed to compare the efficacy and safety of NS with SC and determine optimal NS dose in the treatment of patients with COPD exacerbations requiring hospitalization.

Material and Methods

Study population

One hundred patients with moderate or severe COPD exacerbation who were older than 40-years-old, had a smoking history of at least 10-pack-years, and who required hospitalization were included in the study. COPD diagnosis was based on clinical evaluation as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [2]. The patients were excluded if they had asthma, allergic rhinitis, atopy, or any systemic disease (such as diabetes mellitus or hypertension); were exposed to systemic corticosteroids in the preceding month; used more than 1500 microg/d of inhaled beclomethasone equivalent; were admitted to the intensive care unit (pH <7.30 and/or $PaCO_2$ >70 mm Hg, and/or PaO_2 <50 mm Hg despite supplemental oxygen); or if a specific cause for the exacerbation, such as pneumonia, pneumothorax, or heart failure, was diagnosed.

Study design

The study was as a randomized, parallel design trial. The randomization order was determined using a computer-generated list of random numbers. Eligible patients were randomly allocated to 1 of the 3 treatment groups: parenteral corticosteroid (PS), 4 mg nebulized budesonide (NB), or 8 mg NB. The efficacy of the study medications was assessed at hospitalization, 24 h, 48 h, and discharge. Patients were monitored during the hospitalization. Patients were withdrawn from the study if they required intubation and were managed in the intensive care unit. The Karadeniz Technical University Faculty of Medicine Ethics Board approved the protocol of the study (IRB. 74. KTU. 0.02.012/148). Informed consent was obtained from all the patients at the beginning of the study.

Treatments

Treatment in the PS group consisted of methylprednisolone 40 mg (intravenous ampoule); treatment in the NB groups consisted of nebulized budesonide suspension (Pulmicort Nebuampul® 0.5 mg/ml; Astra-Zeneca Pharmaceutical Production) during hospitalization. Budesonide were given as 2 mg twice daily or 4 mg twice daily; methylprednisolone were given intravenously once daily.

Nebulization procedures were performed by using a jet nebulizer (Porta Neb® Ventstream® 1803; Medic-Aid) with 80% of output of less than 5 microns. Patients received standard treatment with a nebulized β-agonist (salbutamol 3.01 mg) and anticholinergic (ipratropium bromide 0.5 mg) combination every 6 h and intravenous aminophylline (0.5 mg/kg/h). Supplementary oxygen therapy was used to maintain oxygen saturation (SaO_2) >90%.

Measurements

Patients were assessed every 12 h during the acute phase (from H_0 to H_{48}), and at hospital discharge. Arterial blood samples were taken at baseline, 24 h, 48 h, and discharge for the determination of PaO_2, $PaCO_2$, and pH, when the patient was on room air. Post-bronchodilator spirometry (Sensor Medics, Vmax22) was performed according to ATS standards [19]. Dyspnea was assessed according to the modified Borg scale [20]. Complete blood cell counts were obtained at entry, and blood glucose, sodium, potassium were measured at H_0 and H_{48}.

Endpoints

The primary endpoint was to assess treatment efficacy by the change of arterial blood gases (ABG) from H_0 to H_{24}, H_{48}, and before discharge. Secondary endpoints included the changes in FEV_1 (forced expiratory volume in 1 s), dyspnea score, duration of hospitalization, and occurrence of adverse events. An adverse event was defined as any medical event reported by the attending physician or events resulting in discontinuation

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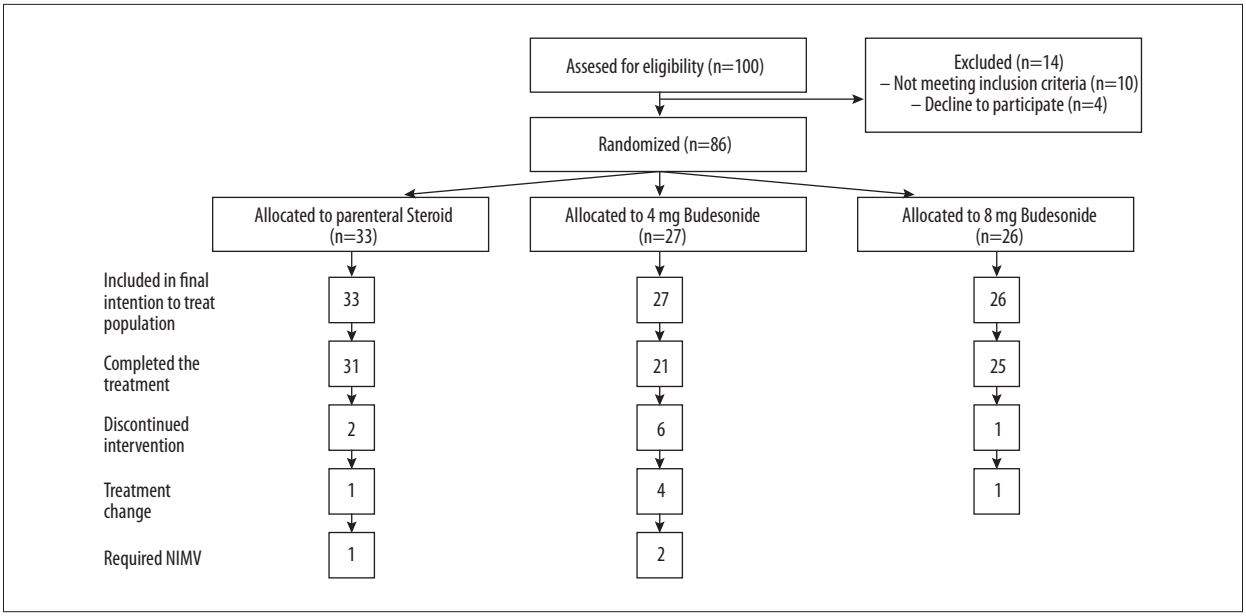

Figure 1. Disposition of patients by treatment groups.

Table 1. Patient characteristics at baseline#.

Group	PS group (n=33)	4 mg NB (n=27)	8 mg NB (n=26)
Age, yr.	66.6 (9.6)	66.7 (9.7)	69.6 (8.5)
Sex (F/M)	9/24	2/25	4/22
Current smoker, n(%)	25 (78%)	21 (78%)	22 (85%)
Mean of pack year	51.3 (26.1)	47.0 (23.6)	56.1 (34.2)
Post-bronchodilator FEV_1	39.4 (11.3)	41.0 (13.4)	49.0 (14.7)
pH	7.38 (0.06)	7.38 (0.05)	7.39 (0.04)
$PaCO_2$*	44.6 (10.1)	42.8 (8.4)	40.9 (7.1)
PaO_2*	43.8 (11.1)	44.5 (10.1)	46.0 (9.4)
SaO_2 (%)	76.9 (11.8)	77.9 (8.4)	79.8 (9.6)

Values are mean (SD) or number (%); PS – parenteral steroid; NB – nebulized budesonide; $PaCO_2$ – arterial partial pressure of carbon dioxide; PaO_2 – arterial partial pressure of oxygen; * mmHg; SaO_2 – arterial oxygen saturation.

of study medication and/or treatment change or that prolonged hospitalization.

Definitions (modified from Burge S and Wedzicha JA) [21]

COPD exacerbation: An acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication [2].

Moderate exacerbation: A respiratory failure with mild hypoxemia (PO_2: 60–80 mmHg) but no carbon dioxide retention or acidosis; PCO_2 <45 mmHg.

Severe exacerbation: A respiratory failure with moderate hypoxemia (PO_2: 40–60 mmHg) but no carbon dioxide retention or acidosis; PCO_2 <45 mmHg.

Very severe exacerbation: A respiratory failure with carbon dioxide retention or acidosis; PCO_2 >45 mmHg and pH >7.35.

Statistical analysis

Statistical analysis was performed with SPSS for Windows version 17.0 (SPSS Inc., Chicago, USA). The sample size of 22 subjects per treatment arm was selected to provide 80% power to

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Table 2. Mean values in the groups at different follow-up times.

Parameter	Baseline	24th h	48th h	Discharge day
PaO_2				
PS	43.8	47.7	49.8	54.3
4 mg NB	44.5	49.1	52.7	56.0
8 mg NB	46.0	50.0	52.6	53.6
SaO_2				
PS	76.9	82.0	83.5	87.0
4 mg NB	77.9	82.3	84.5	86.8
8 mg NB	79.8	83.5	86.4	86.6
pH				
PS	7.38	7.39	7.39	7.40
4 mg NB	7.38	7.39	7.38	7.39
8 mg NB	7.39	7.40	7.40	7.41
$PaCO_2$				
PS	44.6	44.2	45.1	43.0
4 mg NB	42.8	43.2	46.2	42.0
8 mg NB	40.9	40.3	40.0	40.4
FVC				
PS	64.9			69.1
4 mg NB	66.6			76.5
8 mg NB	74.8			79.4
FEV_1				
PS	39.4			44.5
4 mg NB	41.0			50.7
8 mg NB	49.8			54.8

PS – parenteral corticosteroid group; NB – nebulized budesonide group; PaO_2 – arterial partial pressure of oxygen, SaO_2 – arterial oxygen saturation, $PaCO_2$ – arterial partial pressure of carbon dioxide; FVC – forced vital capacity; FEV_1 – forced expiratory volume in 1 second.

detect an increase of PaO_2 of 5 mmHg in each group assuming a 2-sided test and type I error rate of 5%. All analyses were done on an intent-to-treat basis, including all data available on patients who received at least 1 dose of study drugs, irrespective of discontinuation of study drug or treatment change from the trial. For comparison of changes in continuous variables between and within the groups, ANOVA, paired t-test, and univariate analysis were used, respectively. Pearson's chi-square test was used to compare categorical variables between the groups. If p-value is <0.05, was considered to be statistically significant.

Results

A total of 86 patients (71 male and 15 female) with an average age 67.5±9.3 were randomized into 3 groups. Thirty-three patients were randomly allocated to PS, 27 to 4-mg NB, and 26 to 8-mg NB (Figure 1). The characteristics of patients are summarized in Table 1. The groups were similar except for FEV_1, which was higher in the 8-mg NB group (49.0±14.7 *vs.* 41.0±13.4 and 39.4±11.3 in the 4-mg NB group and the PS group, respectively).

Mean values of PaO_2, SaO_2, pH, $PaCO_2$ (H_0 to H_{24}, H_{48}, and discharge day), FEV_1, and FVC (H_0 and discharge day) are shown in Table 2. We found that increases in PaO_2, SaO_2, FEV_1, and FVC (forced vital capacity) values within the groups were statistically significant compared to baseline values ($p<0.001$ for all parameters). However, the changes in pH and $PaCO_2$ values in each group were not statistically significant ($p>0.05$). In the comparison of the groups, the changes of PaO_2 (Figure 2), SaO_2 (Figure 3), and FVC, but not FEV_1, between the groups were

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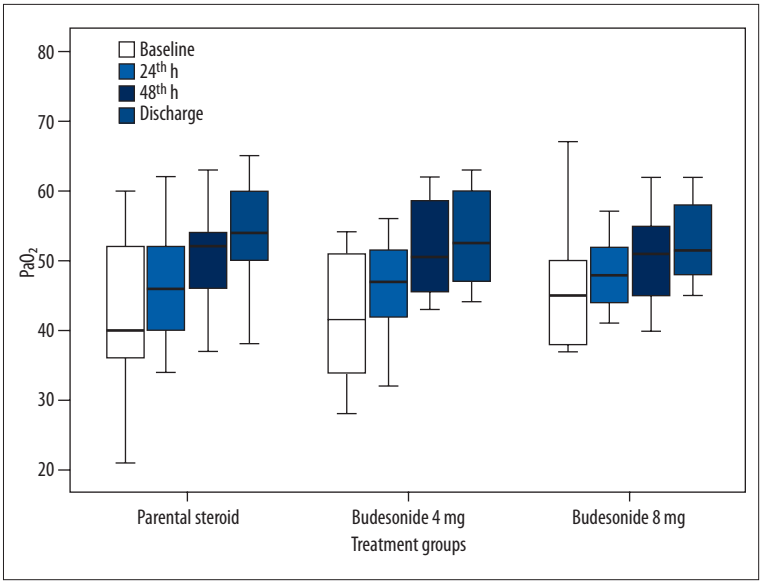

Figure 2. Partial pressure of arterial oxygen (PaO_2): mean values, 95% CIs, minimum and maximum values (whiskers) for the 3 groups (parenteral steroid, budesonide 4 mg and budesonide 8 mg).

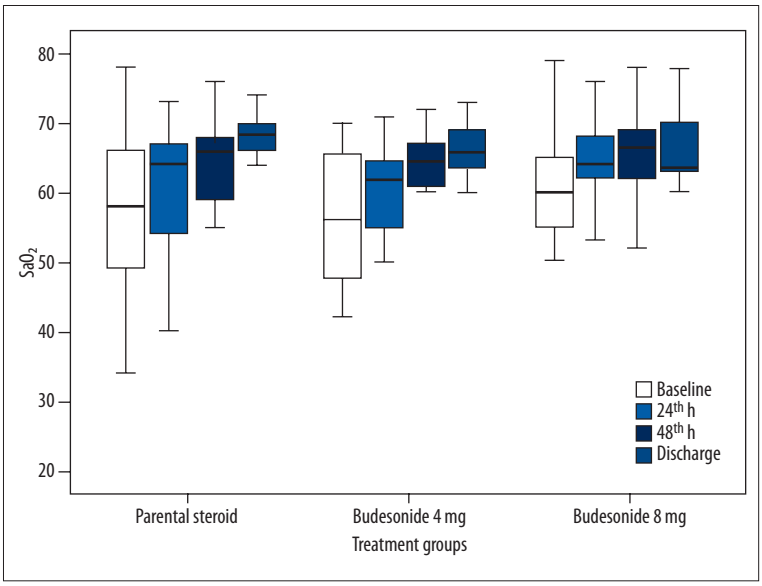

Figure 3. Arterial oxygen saturation (SaO_2): mean values, 95% CIs, minimum and maximum values (whiskers) for the three groups (parenteral steroid, budesonide 4 mg and budesonide 8 mg).

not statistically significant in all assessment periods (p=0.68, p=0.90, p=0.14 and p=0.04 for PaO_2, SaO_2, FVC, and FEV_1, respectively). Because baseline FEV_1 values were different between the groups, we performed univariate analysis and the difference was not statistically significant (p=0.13).

The reduction in Borg scale ratings was statistically significant in each group (p<0.001). However, in the comparison of the groups, there was no statistically significant difference (p=0.34). Mean duration of hospitalization was 9.3±4.5 and the difference between the groups was not statistically significant (p=0.74).

During the study period, non-invasive mechanical ventilation (NIMV) or discontinuation of study medication and/or treatment change was required in 9 patients. Three patients required NIMV and 6 patients required discontinuation of study medication and/or treatment change, as adverse events (hyperglycemia and oral moniliasis) developed in 4 and 5 cases, respectively. However, the overall occurrence of adverse events over the study period was not statistically significant (p=0.57).

Discussion

Our study findings show that both dosages of nebulized steroid can be as effective as PS in the management of COPD exacerbation. Adverse events, including hyperglycemia and oral moniliasis, were determined in the PS group and both NB groups, respectively. In the comparison of NB groups, discontinuation

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Table 3. Studies showing results of utilization of nebulized corticosteroids in COPD exacerbation.

Authors	Number of patients	Treatment given	Primary outcome	Results	Side effects
Morice et al. [6]	19	Nebulized budesonide – 4 mg daily Oral prednisolone – 30 mg	To compare the FEV_1 increase and biochemical parameters between the groups	Similar clinical efficacy in both groups	Urinary steroid metabolites were higher in budesonide group
Maltais et al. [7]	199	Nebulized budesonide – 8 mg daily Oral prednisolone – 60 mg Placebo	To compare the changes in FEV_1 between the groups	FEV_1 improvement was similar to oral prednisolone Nebulized budesonide was associated less side effects	Higher incidence of hyperglycemia with oral prednisolone
Mirici et al. [8]	40	Nebulized budesonide – 8 mg Daily IV prednisolone – 40 mg	To compare the FEV_1, PEF and ABG changes between the groups	Similar clinical efficacy as parenteral steroids in PEF, ABG parameters	No adverse effects
Gunen et al. [9]	159	Nebulized budesonide – 6 mg Oral prednisolone – 40 mg Standard bronchodilator therapy	To compare the FEV_1 and ABG changes between the groups	Significant improvement in FEV_1 and PaO_2 in budesonide group	Hyperglycemia in oral prednisolone group
Wei et al. [10]	60	Nebulized budesonide Oral prednisolone Control group	To compare dyspnea score, FEV_1 and ABG changes between the groups	Dyspnea score, FEV_1 and improvement in ABG were significantly better in budesonide group	Minimal side effects
Gaude and Nemagouda. [11]	125	Nebulized budesonide – 4 mg Daily IV Hydrocortisone – 400 mg	To compare the Spirometry variables and saturation between the groups	Spirometry variables and saturation similar in both groups	Minimal side effects
Our study	86	Nebulized budesonide – 4 mg Nebulized budesonide – 8 mg IV prednisolone – 40 mg	To compare the PaO_2 and FEV_1 changes between the groups	PaO_2 and FEV_1 improvement similar between the groups. 8 mg seems to be first choice	Treatment failure Oral moniliazis Hyperglycemia

FEV_1 – forced expiratory volume in 1 second; ABG – arterial blood gases; PEF – peak expiratory flow; PaO_2 – arterial partial pressure of oxygen.

study medication and/or treatment change was higher in the 4-mg NB group, but frequency of oral moniliasis was higher in the 8-mg NB group without reaching statistical significance. Discontinuation of study medication and/or treatment change was higher in the 4-mg NB group compared to the other groups. However, there was no statistically significant difference between the groups.

Systemic steroids (SS) have long been used in the treatment of COPD exacerbation [22]. Recent guidelines suggest using 30–40 mg prednisone or an equivalent SS in addition to the treatment for COPD exacerbation including bronchodilator, antibiotics, and oxygen [2,3]. Exacerbations in COPD patients result in rapid decline of respiratory function, frequent hospitalization, poor quality of life, several comorbidities, and mortality [4,23–25]. In patients with an exacerbation, frequent SS use may cause complications such as hyperglycemia, weight gain, osteoporosis, insomnia, anxiety, and depression, which increase treatment costs and jeopardize life. The development of hyperglycemia requiring treatment in the PS groups of our study also supports this conclusion. Thus, choosing NB may be appropriate in patients with COPD who are either at risk for the development of hyperglycemia or who have diabetes mellitus.

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Nebulized steroids (NS) have been available for the past 2 decades. They have a high level of topical anti-inflammatory activity and a low level of systemic activity. They are safely used when necessary as a substitute for inhaled steroids in patients with bronchial asthma and stable COPD. Previous studies [26–28] have shown that nebulized steroids may be beneficial during both stable asthma and asthma exacerbation, which suggests that they may also be used for COPD exacerbation. Considering the findings of our study and previous ones [13–18], NB can be used as an alternative for patients with COPD exacerbations.

Previous studies have shown that use of nebulized steroid has similar or better effect on the parameters of spirometry or arterial blood gases with acceptable aadverse effects (Table 3). Morice et al. [13] studied the role of 4-mg NB in exacerbation of COPD by comparing it with 30-mg oral prednisolone. They found a similar increase of FEV_1 in SS and NB groups during a 5-day course of treatment; the biochemical markers associated with corticosteroid adverse effects were higher in the PS group, but urinary steroid metabolites were higher in the NB group. Maltais et al. [14] showed that 8-mg NB has beneficial effects comparable to 60-mg oral prednisolone in the first 72 h of COPD exacerbation and NB was associated with fewer adverse effects, in contrast to SS, which was associated with higher incidence of hyperglycemia. The evaluated parameters in their study were ABG, FEV_1, change in dyspnea score, duration of hospitalization, and adverse effects; they found no statistically significant differences between the treatment groups in any of the study parameters. Mirici et al. [15] compared the efficacy of 8-mg NB with parenteral 40-mg prednisolone in the treatment of COPD exacerbation. They evaluated peak expiratory flow rate and ABG changes between the groups. They found similar clinical efficacy and no adverse effects. Gunen et al. [16] studied the role of 6-mg NB in the treatment of COPD exacerbation by comparing it with 40-mg oral prednisolone. They showed that NB achieved significant improvement in spirometry parameters and PaO_2. The relapse and re-hospitalization rates were reduced by half in the NB group and oral prednisolone was associated with hyperglycemia. Gaude et al. [18] compared the role of 4-mg NB with 100-mg parenteral hydrocortisone every 6 h in the treatment of COPD exacerbation. They found spirometry variables and saturation improvements were similar in both groups and there were no adverse effects.

Our study evaluated ABG, FEV_1, change in dyspnea score, duration of hospitalization, and adverse effects and we found no statistically significant differences between the study groups. Although it was not statistically significant, in the comparison of NB groups, discontinuation of study medication, and/or treatment change was higher in the 4-mg NB group and oral moniliasis was higher in the 8-mg NB group; however, only 1 case required treatment change due to oral moniliasis. In previous studies there is no consistency in NB dosage or data, suggesting an optimal NB dose. In the current study, treatment with 4-mg and 8-mg NB were compared and found to be about equally effective.

Our study not only confirmed the findings of previous studies showing the equivalency of NB use to SC use in the treatment of COPD exacerbations, but also contributes to determining the optimal dose of NB by comparing 2 doses of NB. Because we did not include any patients with very severe COPD exacerbation, we cannot claim that nebulized steroids can be used as an alternative to PS in the treatment of all COPD patients with exacerbation. The fact that this was not a double-blind a study with a placebo group makes it difficult to generalize the results of the study.

Conclusions

Nebulized budesonide may be used as an alternative to SC because of its equal effectiveness and lesser systemic adverse effects. The choice of optimal dosage need to be evaluated carefully because adverse effect and dropout rates were varied according to dosage (i.e., high dropout rate and lesser adverse effects with 4 mg or low dropout rate and higher adverse effects with 8 mg). However, further studies are required that include more severe cases and that evaluate long-term outcomes or relapses comparing the 3 arms.

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