Clinical effectiveness of nebulised budesonide in the treatment of acute asthma attacks

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ÖZET

Akut astım atağı tedavisinde nebülize budesonidin klinik etkinliği

Akut astım tedavisinde kullanılan nebülize budesonid (NB) topikal antiinflamatuvar etki sağlayabilir ve sistemik kortikosteroidlere (SC) alternatif olabilir. Bu çalışmada, akut astımı olan erişkin hastalarda NB ile SC'nin akciğer fonksiyonları ve klinik bulgular üzerine olan etkisinin karşılaştırılması amaçlanmıştır. Kliniğimize akut astım tanısı ile yatırılan 30 hasta (K/E: 26/4; ortalama yaş= 47.1 ± 2.1 yıl) çalışmaya alındı. Hastalar üç gruba ayrıldı; Grup I yalnızca NB ile tedavi edildi (4 mg/gün), Grup II yalnızca SC ile (1 mg/kg/gün metilprednizolon), Grup III NB ile birlikte SC aldı. Solunum fonksiyonları ve solunum semptom skorları çalışmanın başında ve yedi gün boyunca her sabah ölçüldü ve kaydedildi. Solunum fonksiyon parametreleri tüm gruplarda çalışmanın yedinci gününde başlangıca göre anlamlı şekilde artış gösterdi ($p< 0.05$), gruplar arasında anlamlı fark saptanmadı ($p> 0.05$). FEV_1 % beklenen düzeyleri Grup I ve III'te ilk günden itibaren istatistiksel olarak anlamlı artış gösterirken ($p< 0.05$), Grup II'de beşinci güne kadar anlamlı değişiklik bulunmadı. Ortalama semptom skorları Grup I'de ikinci günde, diğer iki grupta ise dördüncü günde istatistiksel yönden anlamlı şekilde azaldı ($p< 0.05$). Akut astım atağı ile hastaneye yatan hastalarda SC olsun ya da olmasın verilen NB tedavisi, hava yolu obstrüksiyonunu ve semptomları tedavinin ilk gününde düzeltmekte ve bu etkisi yedi gün devam etmektedir. NB'nin güvenilirliğine ve SC ile karşılaştırılabilir etkilerine bakıldığında orta-ağır şiddetteki astım ataklarında alternatif bir tedavi olarak düşünülebilir.

Anahtar Kelimeler: *Budesonid, nebülize, sistemik kortikosteroid, astım atağı, etkinlik.*

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SUMMARY

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Nebulized budesonide (NB) might offer topical anti-inflammatory activity and be an alternative to systemic corticosteroid (SC) in the treatment of acute asthma. The aim of this study was to compare the effect of NB with SC on lung function and clinical findings of adult patients with acute asthma. Thirty patients admitted to clinic with asthma attack (F/M: 26/4; mean age: 47.1 ± 2.1 years) were enrolled to the study. The patients were randomized into three groups; Group I were treated with NB alone (4 mg/day), Group II SC alone (1 mg/kg/day methylprednisolone), Group III NB plus SC. Pulmonary functions and respiratory symptom scores were measured and recorded before and during 7 days of study. Spirometric parameters significantly improved in all groups at 7th day significantly ($p< 0.05$) without a difference among groups ($p> 0.05$). FEV_1 % levels increased significantly at the first day of study in Group I and III ($p< 0.05$), but didn't change in Group II until 5th day of study. The mean symptom scores decreased significantly at the second day in Group I ($p< 0.05$), and at the 4th day in other groups. NB with or without SC improved successfully airway obstruction and symptoms in patients hospitalized with acute asthma attack as the 1st treatment day in comparison with SC alone and this effect lasted for 7 days. Regarding the superior safety profile and comparable efficacy with SC, NB might be an alternative to the patients with moderate-severe asthma attacks.

Key Words: *Budesonide, nebulized, systemic corticosteroid, asthma attack, efficacy.*

Systemic corticosteroids (SC) are effective medications in the treatment of acute asthma attacks. International asthma guidelines recommend SC for rescue therapy of asthma attacks (1,2). Despite good effects for controlling asthma attacks, prolonged or regular short courses therapies with SC have been reported to associate with some adverse effects such as hyperglycemia, miyopathy, osteoporosis, suppression of the adrenal response which limits the long term use of the drug (3-5). The discovery of inhaled form of the corticosteroids led to an important revolution in the management of airway obstruction. The inhalation route is known to allow the delivery of anti-inflammatory agent directly to the airway and is relatively free from systemic effects as rapid first-pass hepatic metabolism ensures little systemic bioavailability and causes fewer systemic effects, although the majority of any inhaled dose is swallowed (3).

Inhaled corticosteroids (IC) which are known as a safe and effective treatment of chronic asthma improve lung functions and reduce episodes of acute bronchospasm in asthmatics. Moreover, ICs have high level of topical anti-inflammatory activity while minimizing systemic side effects (4).

Budesonide, one of the inhaled steroids, can be delivered via dry powder, metered dose inhaler or nebulizer as an inhalation suspension that is the formulation designed to deliver inhaled steroids way of nebulization. Budesonide is the first IC to be approved for administration with a nebulizer; this formulation was particularly developed in response to the specific delivery needs of infants and young children (6,7). In acute bronchospasm, nebulized corticosteroids might offer topical anti-inflammatory activity whilst allowing the reduction of SC dose in chronic severe asthma (6). Considering this studies, nebulized budesonide (NB) seems to be as an alternative to SC in the treatment of acute asthma.

The efficacy trials with NB which have been studied in infants and young children having severe asthma and acute exacerbation demonstrated that both in acute wheezing and chronic stage, treatment of NB improved pulmonary functions and asthma symptoms (8-14). However, there are only a few studies about use of NB in asthma attacks in adults. So, the aim of this study was to compare the effect of NB suspension (Pulmicort Nebules) with SC and combinations both on lung function and clinical findings of patients with acute asthma attacks. The primary endpoint was the change in FEV_1 values from the basal to 7^{th} day and the initial time for increase in FEV_1, the secondary endpoint includes changes in symptom scores during the study week.

MATERIALS and METHODS

Patient Selection

This study was approved by the Uludag University School of Medicine Ethical Committee and informed consent was obtained from all patients. Among adult patients who had been admitted to emergency department after deterioration in their asthma with increasing breathlessness, the ones with generalized rhonchus and predicted FEV_1 values lower than 60%. They had been previously diagnosed of asthma with recurrent symptoms of wheezing, shortness of breath, cough and demonstration of objective sign of reversible airway obstruction as stated by the American Thoracic Society (ATS) and International Asthma Guidelines (1,2). Asthmatic patients with other specific cause for the exacerbation such as pneumonia, pneumothorax, interstitial pulmonary fibrosis, heart failure; taking SC therapy in the preceding month; the risk of acute respiratory failure taking mechanic ventilation or admission to the intensive care unit because of arterial blood gases: pH < 7.3, and/or $PaCO_2$ > 70 mmHg, and/or PaO_2 < 50 mmHg despite supplemental oxygen were not included. Subjects were randomized into three groups according to the treatment protocol;

Group I: The patients were treated with budesonide nebules 4 mg/day,

Group II: The patients were treated with only SC (1 mg/kg/day methylprednisolone),

Group III: The patients were treated budesonide nebules (4 mg/day) plus SC (1 mg/kg/day methylprednisolone).

NB was delivered via a nebulizer with a compressor (medic aid porto nebulizator) and through a mouthpiece. All asthma patients received salbutamol solution 5 mg four times per day and ipratropium bromide solution 0.5 mg four times per day via nebulizer. Oxygen therapy was also supplemented to maintain SaO_2 > 90%.

Study Design

Pulmonary function parameters of FEV_1 pred%, FEF_{25-75} pred%, and PEF pred% were measured before the start of treatment and also during every morning of the following week. Spirometry was performed using a portable spirometer (MIR Spirobank) according to ATS criteria at the same time of each morning, before the administration of relevant drug (1).

Evaluation of Symptoms Scores

Respiratory symptoms at day-time and night-time in study week were evaluated as follows:

No symptom= 0,

Symptoms of cough, wheeze, dyspnea= 1.

"Total symptom score" was calculated as sum of the day-time and night-time scores for each patient (maximum score= 14 for 7 days).

Safety of the study medication was assessed by observing the occurrence of any adverse effect during study. Complete blood cell counts and blood glucose, sodium, potassium and chloride levels were measured at the beginning and at the end of study.

Statistical Analysis

Numeric results were expressed as mean ± standard error of mean (SEM). Nominal variables were expressed as percentage of the patients. Intergroup comparisons were made by ANOVA variance analysis tests. Repeated measurement of variance analysis was performed in the evaluation of intra-group comparisons. p value less than 0.05 was considered significant. The Statistical Package for Social Sciences (SPSS) for Windows version 10.0 was used to analyze the data.

RESULTS

A total of thirty patients were included into the study (F/M: 26/4; mean age: 47.1 ± 2.1 years). Demographic features and diseases characteristics of groups are given in Table 1. There were no differences by means of age, sex distribution, disease duration and initial FEV_1 pred%, FEF_{25-75} pred% and PEF pred% among groups ($p > 0.05$).

Primary end Point

The mean daily measurement of FEV_1 pred%, FEF_{25-75} pred% and PEF pred% of three groups are shown in Figure 1, 2, and 3.

a. Percent increase in PFT values at 7th day in comparison with baseline: Mean FEV_1 % increased from 49.1% ± 3.4 to 77.6% ± 4.7 in Group I; from 45.5% ± 6.8 to 76.4% ± 4.4 in Group II;

Age (mean ± SEM) (years)	45.1 ± 2.7	49.7 ± 2.9	49.2 ± 6.0	NS
Age range (years)	21-65	35-58	33-75	NS
Female/male	13/3	7/0	6/1	NS
Female (%)	76	100	83.3	
Disease duration (mean ± SEM)	10.7 ± 1.7	10.7 ± 2.0	11.5 ± 2.5	NS
Initial FEV_1 pred% (mean ± SEM)	49.1 ± 3.4	45.5 ± 6.8	46.4 ± 6.8	NS
Initial FEF_{25-75} pred% (mean ± SEM)	28.1 ± 3.0	38.7 ± 17.1	22.6 ± 4.2	NS
Initial PEF pred% (mean ± SEM)	42.8 ± 3.7	40.5 ± 8.3	34.1 ± 6.8	NS

NB: Nebulized budesonide, SC: Systemic corticosteroid, NS: Not significant, SEM: Standard error of mean, pred: Predicted.

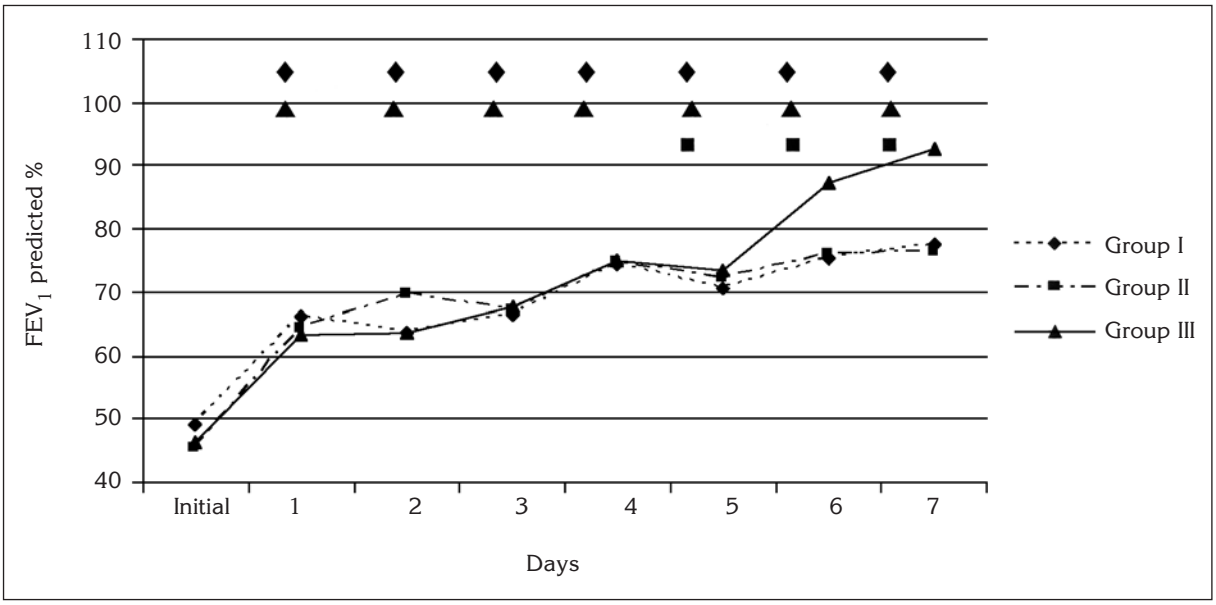

Figure 1. The mean FEV_1 predicted % values of the groups during study week (NS, $p > 0.05$).

◆: Group I (NB), ■: Group II (SC), ▲: Group III (NB + SC): Significant difference, $p < 0.05$.

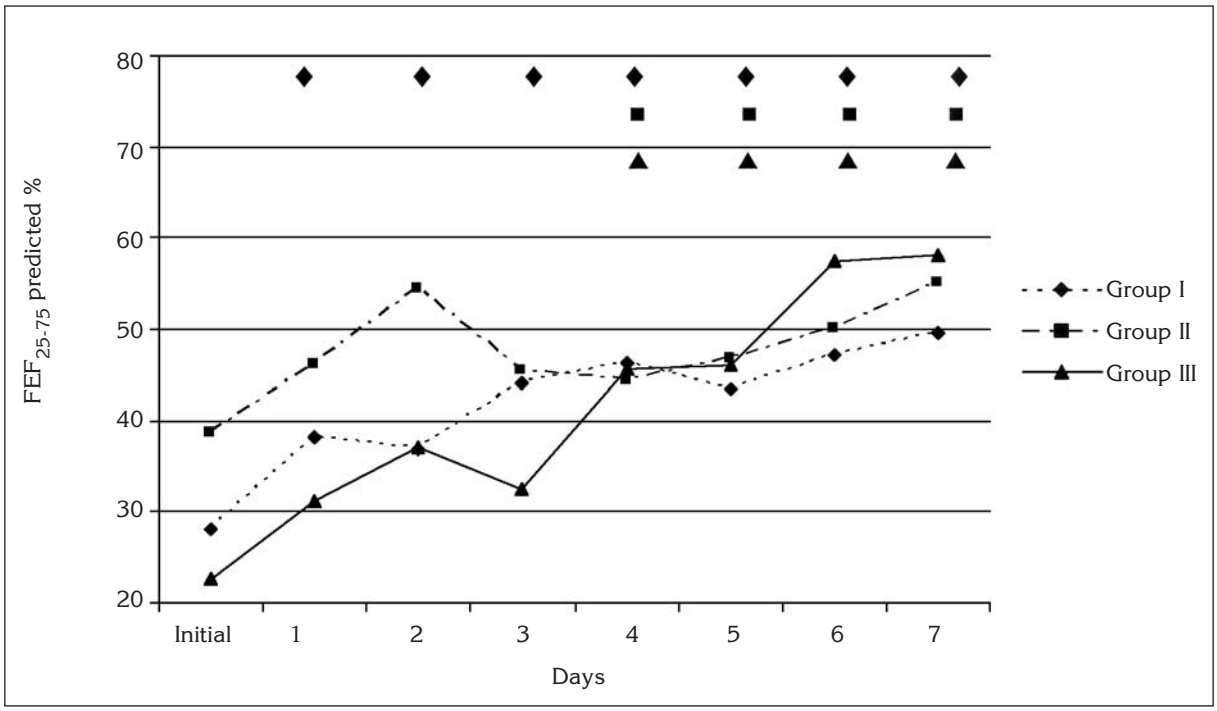

Figure 2. The mean FEF_{25-75} predicted % values of the groups during study week (NS, p> 0.05).

◆: Group I (NB), ■: Group II (SC), ▲: Group III (NB + SC): Significant difference, p< 0.05.

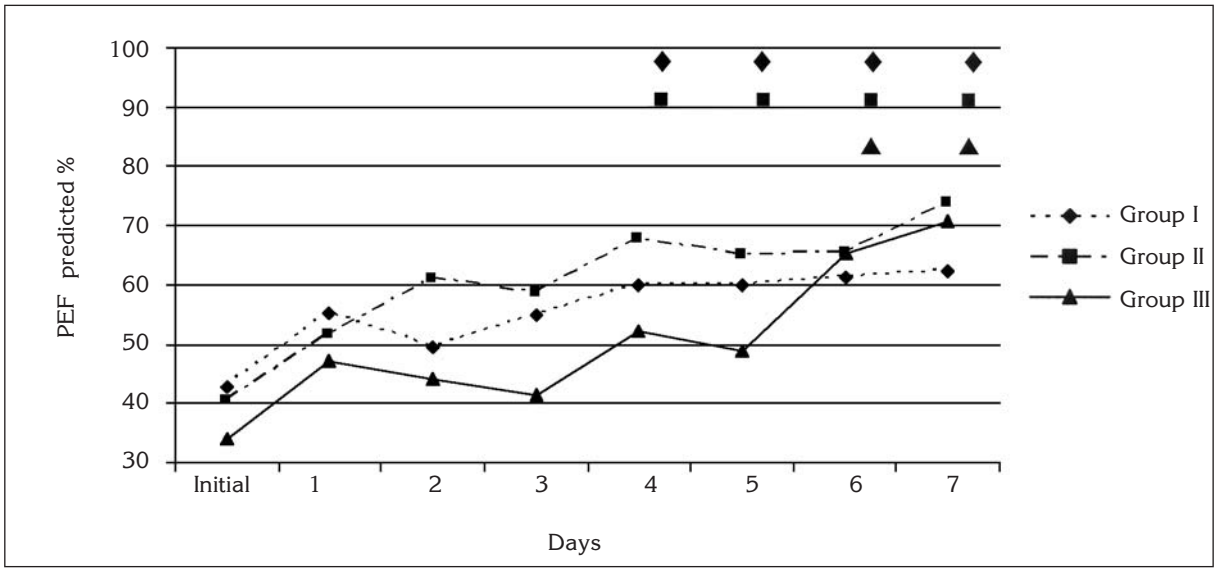

Figure 3. The mean PEF predicted % values of the groups during study week (NS, p> 0.05).

◆: Group I (NB), ■: Group II (SC), ▲: Group III (NB + SC): Significant difference, p< 0.05.

and from 46.4% ± 6.8 to 92.7% ± 8.1 in Group III at 7th day (Figure 1). The mean FEF_{25-75} % increased from 28.1 ± 3.0 to 49.5% ± 5.4 in Group I; from 38.7% ± 17.1 to 55.0% ± 10.2 in Group II; and from 22.6% ± 4.2 to 58.0% ± 8.2 in Group III and at 7th day (Figure 2). PEF % increased from 42.8% ± 3.7 to 62.3% ± 6.5 in Group I, from 40.5% ± 8.3 to 73.8% ± 9.7 in Group II; and from

34.1% ± 6.8 to 70.7% ± 3.5 in Group III, and (Figure 3). After the treatment, spirometric parameters significantly improved in all groups ($p< 0.05$), however there was no significant difference among the groups ($p> 0.05$).

During the treatment, the mean percent change in FEV_1 pred% levels were 89.8% ± 38.8 in Group I, 89.8% ± 27.7 in Group II, and 134.9% ± 50.1 in Group III. The mean percent change in FEF_{25-75} pred% levels were 106.0% ± 36.8 in Group I, 164.7% ± 66.2 in Group II, and 287.5% ± 155.8 in Group III at the end of the week. The mean percent change in PEF pred% levels were 80.2% ± 35.6 in Group I, 126.7% ± 53.2 in Group II, and 287.9% ± 180.3 in Group III (Figure 4). There was no significant difference among groups according to the percent change of spirometric values ($p> 0.05$). Although there was no significant difference in response to treatments; change of spirometric values was higher in group which was treated with combination of NB and SC than administration of each drug alone.

b. Initial time for increase in PFT values: FEV_1 pred% levels increased significantly at the first day of study from 49.1% ± 3.4 to 66.3% ± 3.9 in Group I ($p< 0.05$) and from 46.4% ± 6.8 to 63.2% ± 7.1 in Group III ($p< 0.05$), but didn't change in Group II until 5th day of study (Figure 1). FEF_{25-75} % levels increased significantly at the first day in Group I, at the 4th day in Group II and III ($p< 0.05$) (Figure 2). PEF % values increased at the 4th day in Group I and II at the 6th day in Group III ($p< 0.05$) (Figure 3).

Secondary end Point

The mean symptom scores of day-time and night-time were 2.8 ± 0.4 and 3.5 ± 0.3 in Group I, 3.2 ± 1.0 and 4.2 ± 0.8 in Group II, 3.0 ± 0.7 and 3.4 ± 0.4 in Group III. Symptom scores was not significantly different among the groups ($p> 0.05$) (Figure 5).

During the treatment, the mean daily total symptom decreased from 1.84 ± 0.3 to 0.06 ± 0.2 in Group I; from 1.85 ± 0.3 to 0.5 ± 0.7 in Group II; and from 1.85 ± 0.3 to 0.0 ± 0.0 in Group III at 7th day ($p< 0.05$) (Figure 6).

The mean total daily symptom scores decreased significantly at the second day of study in Group I ($p< 0.05$), and 4th day of study in other groups.

All patients tolerated the treatment schedules well with no apparent adverse event. There were no further acute exacerbations that needed emergency treatment or patient withdrawal from the trial during the study.

DISCUSSION

Nebulized form of budesonide has been demonstrated to have an oral corticosteroid-sparing effect in adults with chronic asthma in previous trials (15-18). It has a rapid onset of action, i.e. within 2 to 24 hours of NB administrati-

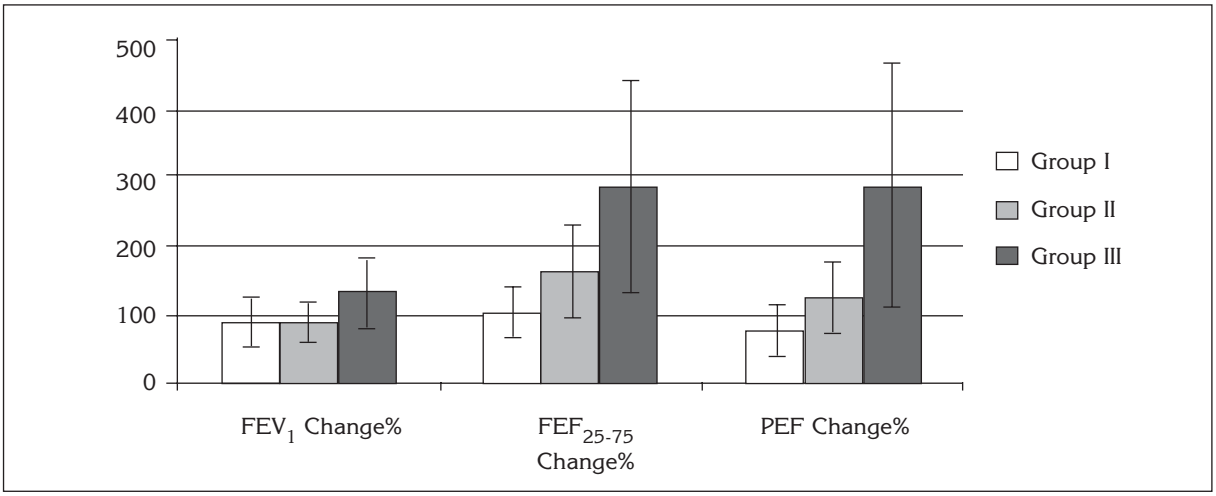

Figure 4. The percent change of FEV_1, FEF_{25-75} and PEFR values of groups (mean ± SEM) (NS, $p> 0.05$).

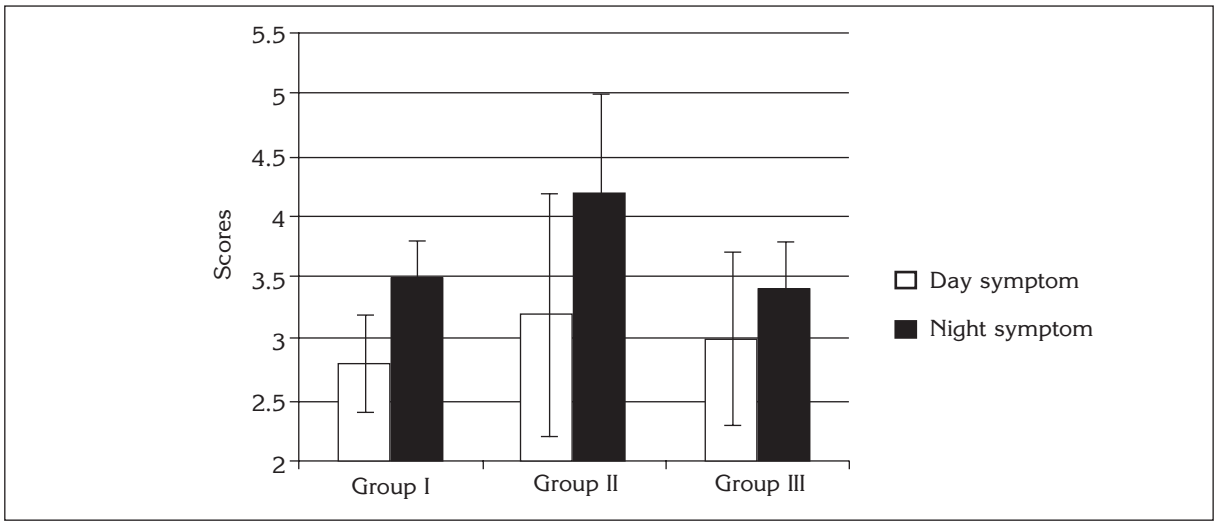

Figure 5. The mean day and night symptom scores of the groups in study week (mean ± SEM) (NS, p> 0.05).

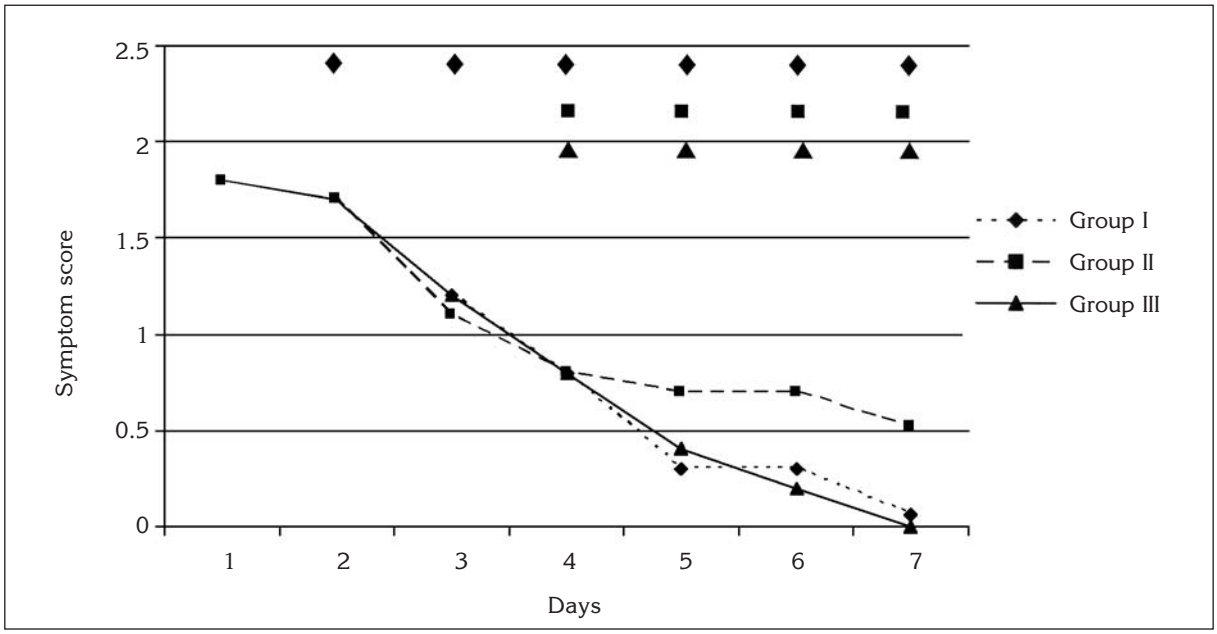

Figure 6. The mean total symptom scores of groups (NS, p> 0.05).
◆: Group I (NB), ■: Group II (SC), ▲: Group III (NB + SC): Significant difference, p< 0.05.

on in conjunction with a β_2-agonist bronchodilator, improvements from baseline in mean asthma symptom scores and/or FEV_1 and PEF levels were apparent in budesonide recipients. In patients with asthma, budesonide suppresses the number of inflammatory cells in the lungs, inhibits synthesis and release of cytokines, reduces bronchial hyper responsiveness to a variety of substances and attenuates both the early and late asthmatic response. It has been reported to be as effective as oral corticosteroids during acute exacerbations of asthma or chronic obstructive pulmonary disease (COPD) (19).

In the current study, we demonstrated that efficacy of NB, SC, and combinations of each drug for the acute attack of asthma in hospitalized patients were comparable to each other at the end of the 7th day. Combination of NB and SC

did not produce additional improvement on the FEV_1 values and asthma symptom scores of patients compared each drug alone. Supporting this data, Higgenbottam et al. demonstrated that NB and SC have comparable effects at 72^{nd} hours in patients with asthma attacks (6). Other trials also showed similar effect with both drugs. Morice et al. compared the effect of NB (2 mg/day) with that of oral prednisolone (30 mg/day) in a randomized parallel-group study of 19 patients with severe acute airway obstruction. Over five days of the study, baseline FEV_1 increased from 1.8 L to 2.1 L in the group that received SC compared with 1.9 L to 2.0 L in the group that received NB. There was no significant difference between the groups according to the treatments (3). Our trial differs from the others by means of longer treatment duration.

Regarding early effects of the medications on pulmonary functions and symptoms, we found a significant improvement in FEV_1 beginning from the first day of treatment in NB and combination therapy groups, unlike SC group which had significant improvement of FEV_1 at the 5^{th} day of study. In patients treated with NB only (Group I), significant increases in FEF_{25-75} was observed from the first treatment day, whereas decrease in symptom scores were apparent from the second day in the same group. Higgenbottam et al. demonstrated significantly better improvement in symptom severity at 24^{th} and 48^{th} hours with NB compared to SC (6). In contrast to the data above, Mitchell et al. investigated the effects of NB and two different doses of SC in 135 patients with acute severe asthma and showed no difference between the clinical efficacy of 20 mg NB and either 30 or 160 mg oral prednisolone over 24 hours (20). Rowe et al. have demonstrated that the addition of inhaled corticosteroids (budesonide 1600 µg/day) to therapy with oral corticosteroids reduced the number of relapses of patients with acute asthma who had been discharged from the emergency department (21). Rodrigo et al. have also demonstrated that extremely high doses of inhaled corticosteroids together with salbutamol in patients with acute asthma who were treated in the emergency department significantly improved pulmonary function when compared to the use of salbutamol alone, with the difference being evident by 90 min (22).

The reason that the effect of budesonide via inhalation could be explained by the fact that this early response would be produced by a topical effect on airway and/or vascular smooth muscle tone, and caused local vasoconstriction and thereby decrease edema formation and plasma exudation that was no achievable by parenteral steroid administration (23,24).

Regarding the safety profile of the treatment schedules, we did not find any differences for seven days of treatment. However, the safety profile with longer administration of both drugs would provide better data for this comparison.

One limitation in this study is the lack of placebo-treated patients, since it would not to be ethical to refrain from corticosteroid treatment in patients with moderate-severe asthma attack.

In conclusion NB with or without SC improved successfully airway obstruction and symptoms in patients hospitalized with acute asthma attack as the 1^{st} treatment day in comparison with SC alone and this effect lasted for seven days. Regarding the superior safety profile and comparable efficacy with SC, NB might be an alternative to the patients with moderate-severe asthma attacks. However; future trials with larger group of patients and evaluation of cost-effectiveness are required for before regular prescription of this drug.

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