

# Acute effect of nebulized budesonide in asthmatic children

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**Summary.** The acute anti-inflammatory effects of inhaled steroids at high doses and their use at home and as emergency treatment of acute asthma attacks in children have been evaluated in many clinical studies. However very little is known about their additional bronchodilator response to systemic steroids plus nebulized salbutamol in the early management in children.

Asthmatic patients aged between 5-15 years were investigated in a double-blind, placebo-controlled fashion. Both the study group (Group I) and the control group (Group II) received three consecutive doses of nebulized salbutamol (0.15 mg/kg/dose) and one dose of parenteral methylprednisolone (1 mg/kg/dose, intramuscularly). After this treatment, nebulized budesonide (1 mg/dose) was administered to patients in the study group and placebo (nebulized saline) was administered to patients in the control group. Pulmonary index scoring and peak flow meter was performed to both groups before and after the treatment.

There were twelve patients in Group I (mean age:  $7.90 \pm 2.34$  years) and fourteen patients in Group II (mean age:  $9.36 \pm 2.55$  years). There was no difference between the two groups with respect to age ( $p=0.1421$ ), gender ( $p=1.000$ ) and inhaled steroid prophylaxis rate ( $p=0.2177$ ).

No statistically significant difference was detected between the two groups with respect to the pulmonary index score ( $p=0.3528$ ). Yet, there was a statistically significant difference between the two groups with respect to the increase in PEF (p=0.0155).

The positive acute effect of nebulized budesonide in addition to systemic steroids and nebulized salbutamol in improving the spirometric indices in asthmatic children is an encouraging finding for further investigations of its routine use in the pediatric emergency department.

**Key words:** Budesonide, nebulized, asthma, acute, children.

## Introduction

Asthma is one of the most common conditions seen in the pediatric emergency department. Expert Panel Report II recommends systemic corticosteroids to be used in the early emergency treatment of moderate and severe acute asthma attacks, together with three consecutive doses of salbutamol and humidified oxygen. After this initial treatment it is recommended that the patients are assessed for their clinical and spirometric response. If there is a complete response, the patient is sent home with an anti-inflammatory treatment; but if the response is incomplete the bronchodilator treatment

with salbutamol is recommended to be continued for the next 4 hours [1].

The acute anti-inflammatory effects of inhaled steroids at high doses and their use at home and as emergency treatment of acute asthma attacks in children have been evaluated in many clinical studies. However very little is known about their additional bronchodilator response to systemic steroids plus nebulized salbutamol in the early management in children.

In this double blind, placebo controlled study, we aimed to find out whether addition of one high dose of nebulized budesonide to three doses of nebulized salbutamol and one dose of systemic steroids would

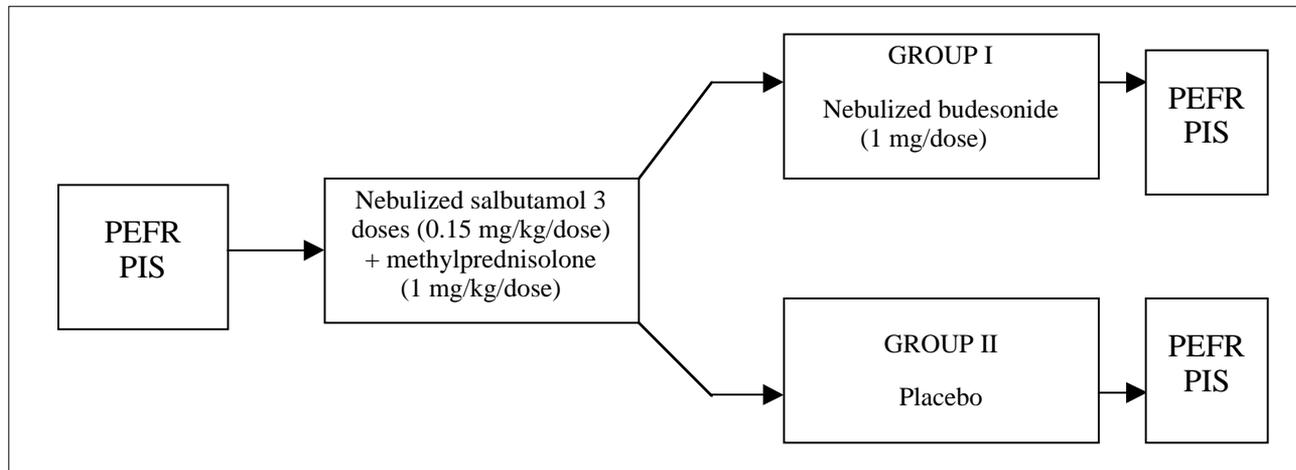


Figure 1. The study design. PEFR: Peak expiratory flow rate, PIS: pulmonary index score.

further improve the peak expiratory flow rate and the clinical response in the pediatric population.

## Materials and Methods

Patients who attended the pediatric emergency unit due to an acute attack of asthma over a six month period were evaluated for the study. At the admittance ages, usage of an inhaled prophylactic steroid was documented for each patient.

All patients met the American Thoracic criteria for asthma [2] in which asthma was defined as a clinical syndrome characterized by paroxysmal coughing, wheezing and dyspnea and caused by the hyperresponsiveness of the tracheo-bronchial system to different stimuli, resulting in airway obstruction. Physical examination and pulmonary index scoring (PIS) [3] were performed to the patients by a blinded pediatrician. Children with a moderate acute asthma attack (pulmonary index scoring  $\geq$  or = to three and  $\leq$  or = to six) [4] were included in the study.

Inclusion criteria were as follows:

1. Having a diagnosis of asthma
2. Age between 5-15 years old
3. Being able to perform peak flow meter
4. Having a pulmonary index score (PIS) more than or equal to three and less than or equal to six.

The Hospital's Ethics Committee approved the study and the parents of the participating children signed informed consent forms.

## Study Design

The study was designed as double-blind and placebo controlled. After the patients' demographic data (age, gender, present asthma treatment) was recorded, subjects fulfilling the above mentioned criteria were entered in a double-blind, randomized manner into one of two groups. The randomization was performed according to the patients' social security number. Odd numbers got into Group I, even numbers got into Group II.

Table 1. Pulmonary index score.

Score	Breathing Rate/ /min	Presence of Wheezing	Insp.: Exp.*	Retraction
0	< 30	(-)	1:1.5	(-)
1	30-40	End Expiratory	1:2	Intercostal or Subcostal
2	41-50	Throughout Expiration	1:3	Intercostal + Subcostal
3	> 50	Throughout Inspiration and Expiration	> 1:3	Intercostal + Subcostal + Cervical

\*Inspiration / Expiration ratio.

After the pulmonary index score and the peak expiratory flow rates were measured in all patients at the beginning of the study by a blinded pediatrician, both groups received three consecutive doses of nebulized salbutamol (0.15 mg/kg/dose) and one dose of parenteral methylprednisolone (1 mg/kg/dose, intramuscularly). After this treatment, nebulized budesonide (1 mg/dose) was administered to patients in Group I and placebo (nebulized saline) was administered to patients in Group II. One hour later, the pulmonary index score and the peak expiratory flow rates were measured once more by a blinded pediatrician (Figure 1).

## Clinical Evaluation

Physical examination findings were evaluated by pulmonary index scoring system modified from Becker by DiGiulio et al. [3]. In this system breathing rate, presence and severity of wheezing, inspiratory / expiratory ratio and use of accessory muscles were evaluated (Table 1).

## Peak Expiratory Flow Rate

Peak expiratory flow rate was measured by using a peak flow meter (Clement Clarke, Essex, England). The best of three successfully performed maneuvers was accepted.

## Statistical analysis

Groups I and II were compared with respect to age and the increase in PEFR with Mann-Whitney U test (unpaired, nonparametric test). Gender and the ratio of patients having been using a prophylactic inhaled steroid were compared using the Fisher's Exact test. A p value < 0.05 was considered statistically significant. The statistical analysis was made with GraphPad InStat version 3.05 (GraphPad Software Inc. San Diego, CA, USA).

## Results

A total of 25 consecutive children who presented to the pediatric emergency unit with an acute exacerbation of asthma were considered for the study. There were no drop outs from the study.

Twelve patients were in Group I (nebulized budesonide group). The mean age was  $7.90 \pm 2.34$  years (Range: 5-13). There were 5 girls and 7 boys in this group. Six patients were having inhaled budesonide prophylaxis (50 %). There were 14 patients in Group II (placebo). The mean age was  $9.36 \pm 2.55$  years. There were 6 girls and 8 boys. Three patients were having

inhaled budesonide prophylaxis (21%). There was no difference between the two groups with respect to age ( $p=0.1421$ ), gender ( $p=1.000$ ) and inhaled steroid prophylaxis rate ( $p=0.2177$ ).

The mean value of baseline PIS was  $6.08 \pm 1.00$  in Group I and  $6.07 \pm 1.44$  in Group II. After the treatment the mean PIS was  $2.25 \pm 0.87$  in Group I and  $2.71 \pm 1.38$  in Group II. The mean increase in PIS was  $3.83 \pm 0.94$  in Group I and  $3.36 \pm 1.50$  in Group II. There was no statistically significant difference between the two groups with respect to PIS ( $p=0.3528$ ).

The mean value of baseline PEFR in Group I was  $150.00 \pm 32.19$ . Mean PEFR after the treatment was  $222.50 \pm 40.48$ . None of the patients knew their best PEFR, therefore % of the best value was not used in the study. The mean increase in PEFR was  $72.50 \pm 23.79$  in the nebulized budesonide group.

The mean value of baseline PEFR in Group II was  $192.86 \pm 58.63$ . Mean PEFR after the treatment was  $240.71 \pm 64.03$ . The mean increase in PEFR was  $47.86 \pm 18.88$  for the placebo group.

There was a statistically significant difference between the two groups with respect to the increase in PEFR ( $p=0.0155$ ).

## Discussion

Early use of anti-inflammatory therapy with systemic steroids is effective in the emergency room treatment of acute moderate and severe exacerbations of asthma [5-7]. Previous studies have shown that oral corticosteroids can decrease the need for hospital admission [8,9]. However, despite these medications, many children still require admission to hospital.

Nonrandomized trials have shown an acute benefit of inhaled budesonide in asthma [10-12]. Budesonide has a very rapid onset of action, due to its acute anti-inflammatory effect [4,13], and may therefore have an additive effect in decreasing admission rates when used as an adjunct to systemic steroids.

This double-blind, placebo controlled study showed that use of nebulized budesonide in addition to systemic steroids and nebulized salbutamol as first-line therapy in the emergency room further improved the peak expiratory flow rates in children with moderate asthma exacerbations but had no additional effect in improving the clinical status.

There are very few studies investigating the effect of this adjunctive therapy. One study dealt with adults, whereas another one dealt with children. Guttman and his colleagues conducted a double-blind, randomized, placebo-controlled study on 60 adult emergency room patients with acute asthma [14]. All patients received nebulized salbutamol and IV methylprednisolone. In addition to this therapy, the experimental group received beclomethasone dipropionate via a metered-dose inhaler 7 mg over 8 hours attached to a holding chamber, while

the control group received placebo in the same fashion. The primary outcome was the change in the percentage of predicted FEV1. They observed no differences between the two groups with respect to changes in spirometry measures, dyspnea, and vital signs. In our study, in addition to dealing with children, budesonide was the inhaled steroid used which was twice as potent as beclomethasone dipropionate after topical application [15] and it was in the nebulized form. The results were similar with respect to clinical outcome; yet they were different, since we observed a further improvement in peak expiratory flow rates. This difference might be due to the type and form of inhaled steroid that has been used.

One study investigated children in this respect. It was conducted by Sung et al. [16]. The investigators had conducted a randomized, double-blind, placebo-controlled study in 44 children aged 6 months to 18 years with acute asthma attacks. The method was very similar to our study. All patients received prednisone 1 mg/kg orally and nebulized salbutamol (0.15 mg/kg) every 30 minutes for three doses and then every hour for 4 hours. The study duration was longer than ours. The intervention was 2 mg (4 ml) of nebulized budesonide or 4 ml of nebulized saline. The dose of budesonide was higher than ours. The primary outcome measure was the pulmonary index score. No spirometric analysis was performed. The study revealed no differences between the two groups with respect to PIS. Yet a more rapid discharge rate was observed in the ones who had received budesonide. Our results were similar with respect to the PIS scores but we observed an additional improvement in PEFr which was not investigated in this study.

One study that had been conducted by Singhi et al. on sixty children aged between 3 and 12 years with an acute moderate exacerbation of asthma, had searched for the acute effect of inhaled budesonide in addition to nebulized salbutamol only [17]. In this study, all patients received nebulized salbutamol (0.15 mg/kg in 3 ml saline) and were randomized to receive either budesonide (400 mcg) or placebo inhalation (MDI and Spacer) at half hourly intervals for three doses. The investigators reported that children in the intervention group showed greater improvements in PEFr. This result was similar to ours with respect to showing the additional effect of inhaled budesonide to salbutamol in increasing the PEFr in children.

In conclusion: the positive acute effect of nebulized budesonide in addition to systemic steroids and nebulized salbutamol in improving the spirometric indices in asthmatic children is an encouraging finding for further investigations of its routine use in the pediatric emergency department.

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