The Addition of Inhaled Budesonide to Standard Therapy Shortens the Length of Stay in Hospital for Asthmatic Preschool Children: A Randomized, Double-Blind, Placebo-Controlled Trial

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Key Words

Asthma · Exacerbation · Inhaled budesonide · Hospital length of stay

Abstract

Background: Asthma exacerbations lead to frequent emergency visits and hospitalizations, and are associated with high morbidity and occasionally mortality. New therapeutic strategies are needed. We sought to investigate whether the addition of high-dose inhaled budesonide to standard therapy would shorten the length of stay (LOS) in hospital of children admitted for asthma exacerbations. **Methods:** The study was designed as a single-center, double-blind, placebo-controlled and parallel-group trial. Children aged 7–72 months and admitted with an asthma exacerbation clinical asthma score (CAS) of between 3 and 9 were allocated to either the budesonide (n = 50) or the placebo (n = 50) group. Hospital LOS was compared between children who received 2 mg/day of budesonide versus placebo in addition to standard management of asthma exacerbation involving oxygen inhalation and β_2 -agonist, anticholinergic and oral corticosteroid therapy. All patients were assessed every 4 h. Children with a CAS <3, a peripheral oxygen saturation >95%

and normal pulmonary function, and those with a symptom-free period of at least 4 h after salbutamol treatment were discharged. **Results:** Total hospital LOS was significantly shorter in the budesonide group than in the placebo group (median: 44 vs. 80 h, respectively; p = 0.01). When compared with placebo, the number of inpatients was significantly less in the budesonide group at all the assessed end points (Kaplan-Meier; p = 0.022). Additionally, nebulized budesonide was found to reduce the overall cost of treatment. **Conclusion:** We demonstrated that, for children hospitalized for asthma exacerbations, an additional 2 mg/day of nebulized budesonide significantly reduced hospital LOS as well as the overall cost of treatment.

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Introduction

Asthma is the most common chronic pulmonary disease among children, with an overall incidence of about 30% in developed countries. Despite the advent of new diagnostic tests and treatments, asthma exacerbations still cause significant morbidity and mortality. While the frequency of these exacerbations depends on the type and severity of the

disease itself and the level of disease control, the majority of patients experience a repeat attack on average every 3 years. Asthma exacerbations lead to frequent emergency visits and hospitalizations, and are associated with high morbidity and occasionally mortality. Additionally, they are a major burden on health care resources. Prompt management of these exacerbations in the emergency department (ED) or on admission is thus imperative [1–4].

Standard management involves oxygen inhalation and β_2 -agonist, anticholinergic and oral corticosteroid (OCS) therapy. Inhaled corticosteroids (ICS) are considered the first line of therapy for chronic asthma [2, 5, 6]. Based on limited studies, several clinicians have recommended the use of high doses of ICS in the treatment of asthma exacerbations in the ED [5], but there is no study which has assessed their efficacy in hospitalized children so far.

Current treatment protocols for asthma exacerbations in hospitalized children involve the use of oxygen, β_2 -agonists, anticholinergics and OCS. We hypothesized that the addition of high-dose inhaled budesonide to standard therapy would shorten the length of stay (LOS) in hospital of children admitted for asthma exacerbation, and that the shortening of the hospital LOS would also reduce the overall cost of treatment.

Methods

Study Patients

Children aged 7–72 months and with a clinical asthma score (CAS) of between 3 and 9 who were hospitalized for asthma exacerbations were enrolled in the study. Written informed consent was obtained from all parents. The study was initiated once approved by the local ethics committee in accordance with the Declaration of Helsinki. Inclusion criteria included a medical history of at least 4 wheezing attacks and a history of prophylactic ICS use for asthma. Children with chronic diseases (e.g. malnutrition, anatomic malformation of the respiratory tract, chronic lung or heart disease, gastroesophageal reflux disease and cystic fibrosis) and those with a history of chronic drug use (e.g. antiepileptics and immune suppressives) were excluded from the study.

Atopy in the asthma group was investigated using a skin-prick test and specific IgE measurements. If the skin test demonstrated a wheal with a mean diameter of at least 3 mm greater than that of a saline control, it was considered positive. Each child was tested with a core battery of allergens (e.g. dust mite, cockroach, cat, dog, mould, milk, egg, peanut and pollen from grass, trees and weeds) and a clinic-specific battery of locally relevant allergens (ALK Abelló, Hørsholm, Denmark).

Study Design

The study was designed as a single-center, double-blind, placebo-controlled, parallel-group trial. Children hospitalized for asthma exacerbations between September 2007 and January

2010 were enrolled in the study. Demographic data (age, gender and current asthma treatment) were documented upon admission. Children were initially classified into 2 groups based on a positive or negative asthma predictive index (API). Children who had had recurrent episodes of wheezing during the first 3 years of life and 1 of 2 major criteria (physician-diagnosed eczema or parental physician-diagnosed asthma) or 2 of 3 minor criteria (physician-diagnosed allergic rhinitis, wheezing without having a cold or peripheral eosinophilia $\geq 4\%$) were defined as API positive [7].

All patients enrolled in the study were assigned consecutive numbers (double-blind code) in balanced blocks of 10 by using a random-allocation software computer program. An independent pediatrician prepared the randomization list. The double-blind codes of the treatment numbers were enclosed in opaque, sealed envelopes available to the researchers in the case of a serious adverse event. Sealed envelopes were recovered by the primary investigator (C.H.R.) upon completion of the trial. All investigators were blinded to group allocation until data analysis was completed. This study is registered at ClinicalTrials.gov (NCT00733473).

Study Protocol

Children presenting to the pediatric service with an asthma exacerbation CAS of between 3 and 9 and complying with the inclusion criteria were invited to participate in the study. Patients received 1 mg/kg/day intravenous (i.v.) methylprednisolone for up to 5 days, and 0.15 mg/kg of salbutamol (Ventolin®) nebula every 4 h and ipratropium bromide (Atrovent®) 250 μ g every 6 h for 2 days as standard of care. Children with a peripheral oxygen saturation (SpO_2) $\leq 92\%$ received oxygen treatment. Following enrollment, children assigned to the study group received budesonide (1 mg/2 ml) and those in the control group received 2 doses of preservative-free normal sterile saline (NSS; 2 ml) placebo. The two types of syringes, covered with aluminum foil, were similar in appearance. The investigators and patients were blinded to group allocation and syringe content. Medications were administered by a nurse from the pediatric service; children in the treatment group received 2 doses of budesonide (1 mg/2 ml) and the control group received NSS (2 ml) for up to 5 days. The CAS, SpO_2 levels and peak heart rates were documented every 4 h. Discharge criteria were as follows: (1) CAS < 3 points, (2) $\text{SpO}_2 > 95\%$, (3) good aeration, no/mild wheezing and minimal respiratory distress upon physical examination and (4) a symptom-free period of at least 4 h following salbutamol treatment.

Study Outcome

The primary outcome was the difference between groups in mean hospital LOS. Differences in CAS, factors associated with treatment response and cost analysis were denoted as secondary outcomes.

Assessment of CAS

We used a CAS validated for children aged 1–5 years and strongly correlated to drug-dose interval, hospital LOS and discharge [8, 9]. The score includes 5 items: respiratory rate, wheezing, inspiratory-expiratory ratio, chest retraction and observed dyspnea. Each variable is scored as 0, 1 or 2, and then summed to give a total score (a maximum of 10). The clinical scoring of asthma is presented in table 1.

Fig. 1. Profile of patient recruitment and enrollment into the study.

Table 1. Clinical asthma score [8]

Score	Respiratory rate	Wheezing	I/E ratio	Chest retraction	Dyspnea
0	<40	none	I > E	none	none
1	40–60	E	I = E	subcostal	mild
2	>60	I and E	I < E	sub- and intercostal	severe

I/E = Inspiratory/expiratory. Respiratory note was measured in breaths/min.

Statistical Analysis

Statistical analysis was performed with Statistical Package for Social Sciences 20.0 software (SPSS Inc., Chicago, Ill., USA). The Shapiro-Wilk test determined whether the distributions of continuous variables were normal or not. Continuous variables were expressed as a median (range). The median differences were compared by the Mann-Whitney U test. Nominal data were evaluated by the Pearson χ^2 or the Fisher exact test, where appropriate. The comparison of inpatient numbers in the 2 groups was performed using the Kaplan-Meier analysis. A p value <0.05 was considered statistically significant.

Estimation of Sample Size

The primary aim of this study was to compare the 2 groups according to hospital LOS. A sample size of 47 per group was required to detect at least 18 h difference (SD = 36.1) with a power of 80% at the 5% significance level. The difference of 18 h was taken from both the pilot study and from clinical experience. Sample size estimation was performed with NCSS and PASS 2000 software.

Results

During the study period, 135 children hospitalized with a diagnosis of moderate-to-severe asthma were eligible for inclusion. Of these, 31 were excluded because they did not meet the inclusion criteria and 4 because their parents did not consent, leaving a total of 100 patients enrolled. Patients' demographics and baseline characteristics are presented in figure 1. Patients were randomized to receive either budesonide or placebo in a double-blind manner. The mean age, sex distribution, total duration of illness and number of emergency visits and hospitalizations in the previous year were similar in the 2 groups

Table 2. Comparison of demographic features

	Budesonide group (n = 50)	Placebo group (n = 50)	p value
Age, months	19 (7–72)	18 (8–59)	0.8
Gender			
Male	34 (68.0)	36 (72.0)	0.6
Female	16 (32.0)	14 (28.0)	
Duration of asthma, months	12 (1–45)	10 (1–48)	0.4
Exacerbations in the last year	4 (1–10)	4 (1–11)	0.3
ED visits in the previous year	4 (2–10)	4 (2–10)	0.1
Hospitalizations in the previous year	2 (1–5)	2 (1–5)	0.6
Exposure to smoking	23 (46)	30 (60)	0.1
Atopy	10 (20)	14 (28)	0.3
Atopic dermatitis	11 (22)	9 (18)	0.6
Family history of asthma	15 (30)	11 (22)	0.3
Positive API	19 (38)	17 (34)	0.6

Values are presented as n (%) or median (range).

Table 3. Comparison of clinical features between groups

	Budesonide (n = 50)	Placebo (n = 50)	p value
Duration of symptoms in the previous episode, days	3 (1–19)	3 (1–15)	0.8
URTI before wheezing, n	39 (78%)	41 (82%)	0.6
SpO ₂ at admission, %	90 (83–97)	88 (82–92)	0.3
CAS at admission	7 (5–9)	7 (6–9)	0.8
Total length of stay, h	44 (14–140)	80 (12–192)	0.01

Values are median (range), unless otherwise indicated. The value in bold type denotes a statistically significant difference ($p < 0.05$). URTI = Upper respiratory tract infections.

Table 4. Comparison of discharge rates between the groups at different end points

Time point	Budesonide (n = 50)	Placebo (n = 50)	p value
24 h	3 (6.0)	2 (4.0)	0.6
36 h	12 (24.0)	10 (20.0)	0.6
48 h	30 (60.0)	12 (24.0)	<0.001
60 h	34 (68.0)	16 (32.0)	<0.001
72 h	38 (76.0)	24 (48.0)	0.004
96 h	40 (80.0)	34 (68.0)	0.1
120 h	44 (88.0)	41 (82.0)	0.4
144 h	50 (100.0)	46 (92.0)	0.04
168 h	50 (100.0)	48 (96.0)	0.1

Values denote n (%). Values in bold type denote statistically significant differences ($p < 0.05$).

Fig. 2. Comparison of inpatient percentages between the budesonide and placebo groups during the study period. The comparison was performed using Kaplan-Meier analysis ($p = 0.028$). Note that percentages were lower in the budesonide group between 48 and 72 h and at 144 h.

($p > 0.05$). The rate of atopy, the history of atopic dermatitis, family history of asthma and positive API did not differ significantly between groups ($p > 0.05$; table 2). The groups were also well-matched with regard to the duration of symptoms and the rate of upper respiratory tract infection before admission, CAS upon admission and SpO₂ levels ($p > 0.05$). Total hospital LOS was significantly shorter for children in the budesonide group than the placebo group (median: 44 vs. 80 h, respectively; $p = 0.01$; table 3).

Discharge rates were compared at several end points. While discharge rates were similar between the groups at 36 h (12 vs. 10 patients; $p > 0.05$), they were significantly higher in the budesonide group at 48, 60 and 72 h (i.e. 30 vs. 12, 34 vs. 16 and 38 vs. 24 patients, respectively; $p < 0.01$). As the number of inpatients decreased, i.e. after 96 h, the difference was no longer significant ($p > 0.05$). Of note, at 144 h, the total number of discharged children was significantly higher in the budesonide group than in the placebo group ($p = 0.04$; table 4). Hospital LOS was significantly shorter in the budesonide than in the placebo group ($p = 0.028$; fig. 2). CAS, SpO₂ and heart and respiratory rates in the first 96 h are presented in figure 3.

The cost of standard care of patients admitted for asthma exacerbations in Turkey is around USD 100 for 24 h. The approximate daily cost of treatment with budesonide (4 nebulae of 1 mg/2 ml) is USD 5 (median hospital LOS:

Fig. 3. Presentation of median CAS (a), SpO₂ (b), heart rates (c) and respiratory rates (d) of patients in the budesonide and placebo groups during the 96-hour follow-up. Because healed patients were consistently discharged, the data at each end point reflect the results of analysis performed on the patients not yet discharged.

Therefore, a between-group statistical comparison was not performed. Nevertheless, the CAS, heart and respiratory rates seemed to be lower and the SpO₂ higher in the budesonide group than in the placebo group.

44 h). Given the fact that the median hospital LOS for patients in the budesonide group was 36 h shorter than the placebo group, the cost of treatment for a patient treated with budesonide was USD 130 less than for a patient in the placebo group. No drug-related adverse effects were identified during hospitalization.

Discussion

We identified that 2 mg/day of budesonide added to standard care shortened the hospital LOS by 36 h for children hospitalized due to asthma exacerbation. We also

found that ICS significantly reduced the overall cost of treatment for children with asthma exacerbations, owing, particularly, to a reduction in hospital LOS. The cost for each child treated with budesonide was USD 130 less than for children who did not receive budesonide.

Exacerbations, emergency visits and hospitalization are common among children with asthma. In the study by Rabe et al. [4], 57% of children with asthma experienced symptoms consistent with asthma exacerbation in the previous month, 28% suffered an unforeseen attack, 18% presented to the ED and 75% had a history of hospitalization. On the economic side, asthma treatment constitutes a major burden on health care resources [10] and

causes absence from work by the parents of the asthmatic children. So shortening the hospital LOS by 36 h provides significant social and economic benefits.

Treating asthma exacerbations with ICS is faster than with OCS [11]. Moreover, single-dose fluticasone has been shown to reduce airway responsiveness within 2 h [12]; this partially explains the positive effects of ICS on hospital LOS. Given the fact that OCS are already efficient in the treatment of asthma exacerbations, their combination with ICS in the treatment of moderate-to-severe exacerbations may be considered the treatment of choice [11]. While daily ICS use for asthma prophylaxis is common, several authors recommend ICS for the management of acute exacerbations [13–15], having assessed their efficacy in the ED setting. Recently, Chen et al. [16] demonstrated that the use of nebulized corticosteroids (1,500 µg) in the first hour of ED presentation facilitated better clinical healing than when placebo was administered to patients experiencing a moderate-to-severe asthma exacerbation. This study demonstrated that early use of ICS may prove efficient in the ED treatment of asthma exacerbation. Several studies have compared ICS to OCS in asthma exacerbation treatment. Volovitz et al. [17] compared a single dose of oral prednisone (2 mg/kg) to a dose every 4 h for 1 week with a 1,600-µg budesonide turbuhaler in children with asthma exacerbations presenting to the ED, and found that the CAS and pulmonary functions were similar. They also found that ICS decreased serum cortisol concentration. Schuh et al. [18], on the other hand, found that OCS administration (2 mg/kg oral prednisone) reduced hospitalization rates and improved FEV₁ significantly more than ICS (2,000 µg of fluticasone propionate) in children >5 years old with moderate-to-severe asthma.

Studies assessing the efficacy of a combination of OCS and ICS for the treatment of asthma in children are lim-

ited and usually conducted in the ED setting. Alangari et al. [19] conducted a study on children aged 2–12 years who were diagnosed with asthma exacerbation in the ED. They compared the admission rates between children who received 1,500 µg budesonide versus children who received placebo; both groups received salbutamol, ipratropium bromide and a single dose of 2 mg/kg of prednisolone). Overall, the admission rates did not differ. When stratified according to disease severity, however, there was a lower rate of admission for children with severe asthma (CAS ≥13) who received budesonide. Upham et al. [20] demonstrated that when a single dose of 2 mg of budesonide was added to standard therapy, the CAS did not improve and admission rates were not reduced in comparison to placebo treatment.

Guideline recommendations on the use of ICS in children with asthma exacerbations are limited to the ED. While The Global Initiative for Asthma (GINA) report recommends the use of ICS in the first hour of treatment for children aged >5 years with asthma exacerbation in the ED, it also states that the evidence that the combination of ICS and OCS therapy improves pulmonary function or CAS in acute exacerbations is insufficient (this is because the administration of ICS reduces admission rates) [5]. Results concerning the benefits of ICS therapy for asthma exacerbation in small children are conflicting.

To conclude, we demonstrated that an additional 2 mg/day of nebulized budesonide administered to children hospitalized for asthma exacerbations significantly reduced hospital LOS and the overall cost of treatment. Given the social and economic implications of this finding, adding this budesonide dose to standard care may indeed be an option in the future for the treatment of children hospitalized for asthma exacerbations.

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