

ORIGINAL ARTICLE

Effects of nebulized high-dose budesonide on moderate-to-severe acute exacerbation of asthma in children: A randomized, double-blind, placebo-controlled study

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ABSTRACT

Background and objective: The efficacy of inhaled corticosteroids (ICS) in asthma exacerbation are yet to be clarified. The aim of this study was to investigate the efficacy of nebulized ICS in children with moderate-to-severe acute exacerbation of asthma in an emergency room setting in order to elucidate the potential use of ICS as the first-line therapy in the management of acute exacerbation of asthma.

Methods: This was a prospective, randomized, double-blind, placebo-controlled study. Paediatric patients with moderate-to-severe acute exacerbation of asthma in emergency room were randomized to receive nebulized salbutamol and ipratropium bromide, with the addition of nebulized high-dose budesonide (BUD group, $n = 60$) or normal saline (control group, $n = 58$), three doses in the first hour.

Results: The improvement in forced expiratory volume in 1 s was similar in both groups at 0 h after three doses of nebulization, but there was significantly further improvement at 1 and 2 h in the BUD group (0.095 ± 0.062 L and 0.100 ± 0.120 L, respectively) compared with the control group (0.059 ± 0.082 L and 0.021 ± 0.128 L, respectively), $P = 0.013$ and 0.001 , respectively. Complete remission rate was significantly higher (84.7% vs 46.3%, $P = 0.004$) and need for oral corticosteroids was significantly lower (16.9% vs 46.3%, $P = 0.011$) in BUD group than in control group.

Conclusion: On the basis of nebulized short-acting bronchodilators, addition of nebulized high-dose budesonide resulted in clinical improvement in children with moderate-to-severe acute exacerbation of asthma, suggesting that nebulized high-dose ICS can be used as first-line therapy for non-life-threatening acute exacerbation of asthma in children.

Key words: acute exacerbation, bronchial asthma, child, nebulized corticosteroid.

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SUMMARY AT A GLANCE

This prospective, randomized, double-blind, placebo-controlled study showed that on the basis of nebulized salbutamol and ipratropium bromide, nebulized high-dose budesonide as the first-line therapy for paediatric patients with moderate-to-severe acute exacerbation of asthma is effective in improving symptoms and reducing the need of systemic corticosteroid and hospitalization.

Abbreviations: BUD, budesonide; FEV₁, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; SABA, short-acting β_2 -receptor agonist; SaO₂, percutaneous oxygen saturation; SCS, systemic corticosteroid.

INTRODUCTION

Inhaled short-acting bronchodilators (short-acting β_2 -receptor agonists (SABA) alone or in combination with anti-cholinergics) and systemic corticosteroids (SCS) remain the mainstay treatment for moderate-to-severe asthma exacerbation.¹ In the management of acute exacerbation of asthma in emergency room, three doses of nebulized short-acting bronchodilators in the first hour is recommended by Global Initiative for Asthma as the first-line therapy. Then, the response to the first hour nebulization therapy is to be assessed to determine the need for further treatment, including oral corticosteroid and hospitalization. Despite the well-recognized role of SCS in the treatment of acute exacerbation of asthma, the slow onset of its actions (not until 3–4 h after administration) and its prominent systemic side-effects remain notable concerns. It is therefore of clinical importance to explore other anti-inflammatory therapies that are effective and have better safety profiles as an alternative to SCS for the treatment of acute exacerbation of asthma. Inhaled corticosteroid (ICS) has

been documented as an effective and safe therapy for chronic asthma. Moreover, direct delivery to airways renders the rapid onset of ICS action possible. While ICS has been used as the first-line therapy in the long-term control of persistent asthma in children, the efficacy and clinical significance of ICS in acute exacerbation of asthma are yet to be clarified. From the limited number of international studies using ICS in acute exacerbation of asthma, conclusions are mixed.²⁻⁴ There is also a lack of randomized, double-blind and placebo-controlled trials related to this topic in China. We aimed to investigate the therapeutic effects of nebulized corticosteroids as the first-line therapy in moderate-to-severe acute exacerbation of asthma, with attempt to explore a safer and more effective treatment for acute exacerbation of asthma in Chinese paediatric patients.

METHODS

Patient recruitment

From August 2007 to February 2010, consecutive paediatric patients diagnosed with moderate-to-severe acute exacerbation of asthma in the Department of Emergency Medicine, First Affiliated Hospital of Guangzhou Medical College, were consecutively enrolled in this study. Asthma was diagnosed according to the Guidelines for Prevention and Treatment of Childhood Asthma developed by the Paediatric Society of Chinese Medical Association in 2003.⁵ Moderate-to-severe asthma exacerbation was defined as acute onset or progressive worsening of symptoms, such as coughing, chest tightness and wheezing, coupled with a forced expiratory volume in 1 s (FEV₁) between 30% and 60% (pre-bronchodilator) or between 40% and 70% (within 2 h post-bronchodilator) of normal predicted values (FEV₁/(predicted)). Exclusion criteria were (i) life-threatening exacerbation attack (FEV₁/(predicted) <30% or a condition necessitating intubation owing to organ failure or disordered consciousness); (ii) history of admission to intensive care unit due to severe acute exacerbations; (iii) major comorbidities of the heart or lungs, such as congenital heart disease, viral myocarditis, bronchiectasis and severe pulmonary infection; and (iv) allergy to any component of drugs in the present study. Finally, a total of 118 children (86 boys and 32 girls, aged 5–15 years) were included in the study.

This study was approved by the Ethics Committee of First Affiliated Hospital of Guangzhou Medical College and has been registered in the Chinese Clinical Trial Registry (ChiCTR-TRC-13003343). Written informed consent was obtained from the legal guardian of each participant after a clear description of the study protocol.

Study design and treatment protocol

This was a prospective randomized, double-blind, placebo-controlled trial conducted in a single emergency department setting. By using a random digit table, the children eligible for inclusion in the study

were randomized into one of two groups (budesonide (BUD) and control groups) to receive oxygen-driven (6 L/min) nebulized inhalation of a mixed solution that contained 0.5% salbutamol (150 µg/kg, up to a maximum of 5 mg) and 0.025% ipratropium bromide (1 mL), plus 0.05% BUD (2 mL) (BUD group, *n* = 60) or normal saline (2 mL) (control group, *n* = 58). The final volume of the mixture for each dose was standardized to 4 mL by the addition of normal saline, so that the volume of all solutions was identical across the two groups. The nebulization was given every 20 min, three times in the first hour. The patient randomization was known only to a designated, well-trained nurse who was exclusively responsible for assignment of the study medication and delivery of nebulized inhalation alone. The physicians and parents involved in the present trial were both blinded to the treatments until completion of the statistical analysis. Immediately after the three sessions of inhalation, the patients were re-evaluated to determine whether or not oral corticosteroid should be given. For subjects with FEV₁% (predicted) persistently <70%, a single dose of oral prednisone (1.5 mg/kg, up to a maximum of 40 mg) was given. Thereafter, all children were monitored for 2 h in the observation room and were re-evaluated every hour. Children with FEV₁ < 60% predicted any time during the monitoring period were treated with a repeated nebulized inhalation of 0.5% salbutamol (150 µg/kg, up to a maximum of 5 mg) in 3 mL of normal saline. Subjects with unimproved condition were hospitalized and those with significant improvement were transfer to outpatient clinic for maintenance therapy.

Clinical measures

Spirometry, heart rate, respiratory rate and percutaneous oxygen saturation (SaO₂) were assessed at baseline immediately 1 and 2 h after completion of all three inhalation sessions. Spirometry was measured by using a portable spirometer (MicroLab Co. Ltd, Rochester, UK). The severity of symptoms related to asthma exacerbation was evaluated by the clinical scoring system (Table 1). Complete remission was defined as resolution of wheezing and dyspnoea, no signs of laboured breathing, a clinical score of 0, and improvement in FEV₁/(predicted) ≥75%.

The primary end-points are hospital admission rate and need for SCS. Secondary end-points include improvement of clinical score, spirometry, SaO₂ and adverse events.

Statistical analysis

All statistical analyses were performed using Statistical Package for Social Sciences version 13.0 (SPSS, Inc., Chicago, IL, USA). Within-group differences between pretreatment and post-treatment in heart rate, respiratory rate, SaO₂, FEV₁ and FEV₁% were compared using paired *t*-test. Between-group differences in heart rate, respiratory rate, SaO₂, FEV₁, FEV₁%, age, bodyweight and height were compared by using unpaired *t*-test. Mann-Whitney test was employed to compare differences in clinical scores

Table 1 Clinical scores for severity of acute asthma exacerbation

Score	Use of accessory respiratory muscles	Wheezing	Dyspnoea
0	Negative	Negative	Negative
1	Intercostal recession	End-expiratory	Mild (not interfering with usual conversations)
2	Intercostal and suprasternal recession	Expiratory	Moderate (speaking in short sentences)
3	Nasal flaring	Inspiratory and expiratory	Severe (speaking in phrases or single words)

Table 2 Baseline characteristics of the subjects

Parameters	BUD group (n = 59)	Control group (n = 54)	Statistics	P-value
Age (years)	7.9 ± 1.8	8.2 ± 1.6	1.018	0.311
Gender (male/female)	41/18	42/12	0.887 [†]	0.346
Height (cm)	127.6 ± 10.2	130.3 ± 9.5	1.448	0.151
Body weight (kg)	26.7 ± 6.2	26.3 ± 5.2	0.746	0.690

[†] χ^2 value. All other statistics are *t*-value unless otherwise stated.
BUD, budesonide.

between the two groups. Chi-square test was adopted to compare the differences in need of SCS administration, hospitalization rate and complete remission between the two groups. $P < 0.05$ was considered statistically significant.

RESULTS

One patient from the BUD group and four patients from the control group declined the third session of nebulized inhalation with complete remission condition and thereby dropped out of the study. There were no statistically significant differences in age, male-to-female ratio, bodyweight or height between the two groups of children (all $P > 0.05$) (Table 2).

Immediately and at 1 and 2 h after the three inhalation sessions (0, 1 and 2 h post-treatment) in each of the groups, there were significant improvements from baseline in clinical scores, respiratory rate, SaO_2 , FEV_1 and $\text{FEV}_1\%$ (predicted), but not in heart rate (Tables 3,4). While the clinical scores were comparable between the two groups at baseline, 0 and 1 h post-treatment (all $P > 0.05$), however, the mean clinical score at 2 h post-treatment was significantly lower in BUD group than in control group (0.00 ± 0.00 vs 0.56 ± 1.00 , $Z = 2.522$, $P = 0.012$). There were no significant differences in respiratory rate, heart rate and SaO_2 at all time points between the two groups (all $P > 0.05$).

At baseline, FEV_1 and $\text{FEV}_1\%$ (predicted) were comparable between the two groups ($t = 1.218$, $P = 0.223$; $t = 1.242$, $P = 0.215$, respectively). After treatment, there were greater improvements in FEV_1 and $\text{FEV}_1\%$ (predicted) at 1 and 2 h post-treatment in the BUD group as compared with the control group (all $P < 0.05$) (Table 5).

The rates of complete remission at 0, 1 and 2 h post-treatment were 35.6% (21/59), 71.2% (42/59) and

84.7% (50/59) in the BUD group and were 31.5% (17/54), 42.6% (23/54) and 46.3% (25/54) in the control group, respectively, showing that complete remission rate of asthma exacerbation at 2 h post-treatment in the BUD group was significantly higher than those in the control group ($\chi^2 = 8.333$, $P = 0.004$). The need for SCS therapy was 16.9% (10/59) in the BUD group, significantly less than that in the controls group (46.3% (25/54)) ($\chi^2 = 6.429$, $P = 0.011$). The hospitalization rate was 5.1% (3/59) in the BUD group and 18.5% (10/54) in the control group.

DISCUSSION

In the management protocol of acute exacerbation of asthma, inhaled SABA is recommended as the first line and first step of treatment according to the guidelines. SCS is recommended as the second-line therapy for patients with incomplete response to inhaled SABA. This approach has the advantage of avoiding overuse of SCS but with the disadvantage of delayed use of corticosteroid, which is the key medicine for management of severe exacerbation of asthma. Delayed use of SCS may lead to poor control of airway inflammation, which is the major cause leading to hospital admission and unnecessary deaths in patients with asthma. For this reason, Global Initiative for Asthma guideline also recommends the combined use of SCS and bronchodilators in moderate-to-severe asthma exacerbation.¹ While short-term SCS is effective in controlling asthma exacerbation, high doses of SCS may predispose patients to acute adverse effects, such as gastrointestinal bleeding, hypertension, hyperglycaemia and mental disorders.^{6–8} The slow-acting property of SCS (not until 3–4 h after administration) further compromises their clinical benefits.^{9,10} Moreover, the long-term safety of repeated use of short-course SCS

Table 3 Clinical measures at baseline and at different time points post-treatment in the BUD group ($\bar{x} \pm s$)

	Baseline	0 h	t	P-value	1 h	t	P-value	2 h	t	P-value
CS	4.07 ± 2.85	1.68 ± 1.86	7.928	0.000	0.53 ± 0.68	6.626	0.000	0.00 ± 0.00	5.865	0.000
RR (tpm)	31.35 ± 11.80	26.47 ± 8.67	7.633	0.001	23.88 ± 4.87	6.683	0.003	23.58 ± 3.21	2.131	0.018
HR (bpm)	115.26 ± 16.89	114.58 ± 15.34	0.686	0.602	117.31 ± 14.29	1.606	0.172	118.78 ± 15.29	1.634	0.107
SaO ₂ (%)	93.67 ± 1.41	95.00 ± 1.97	4.408	0.010	96.50 ± 0.99	7.320	0.002	96.67 ± 0.97	5.262	0.015
FEV ₁ (L)	0.65 ± 0.25	0.90 ± 0.29	7.066	0.000	1.00 ± 0.28	8.989	0.000	1.10 ± 0.29	8.825	0.000
FEV ₁ %	46.29 ± 11.80	65.45 ± 14.88	7.323	0.000	73.61 ± 15.14	9.228	0.000	79.95 ± 17.51	9.085	0.000

bpm, beats per minute; BUD, budesonide; CS, clinical score; FEV₁, forced expiratory volume in 1 s; HR, heart rate; RR, respiratory rate; SaO₂, percutaneous oxygen saturation; tpm, times per minute.

Table 4 Clinical measures at baseline and at different time points post-treatment in control group ($\bar{x} \pm s$)

	Baseline	0 h	t	P-value	1 h	t	P-value	2 h	t	P-value
CS	4.00 ± 2.43	1.56 ± 1.89	6.971	0.000	0.67 ± 1.12	8.624	0.000	0.56 ± 1.00	7.568	0.000
RR (tpm)	28.69 ± 8.22	24.38 ± 4.34	3.484	0.001	22.38 ± 3.54	3.361	0.004	21.23 ± 1.49	2.678	0.018
HR (bpm)	117.61 ± 13.59	119.00 ± 13.16	0.582	0.452	120.67 ± 16.42	1.570	0.217	121.22 ± 18.80	0.771	0.280
SaO ₂ (%)	92.67 ± 1.85	96.17 ± 1.10	5.078	0.008	97.67 ± 0.97	8.085	0.002	97.33 ± 1.41	5.702	0.010
FEV ₁ (L)	0.78 ± 0.34	1.11 ± 0.38	7.604	0.000	1.17 ± 0.36	9.827	0.000	1.19 ± 0.32	9.254	0.000
FEV ₁ %	52.95 ± 16.67	76.78 ± 19.37	6.906	0.000	80.44 ± 19.18	7.982	0.000	80.66 ± 17.79	8.263	0.000

bpm, beats per minute; CS, clinical score; FEV₁, forced expiratory volume in 1 s; HR, heart rate; RR, respiratory rate; SaO₂, percutaneous oxygen saturation; tpm, times per minute.

Table 5 Spirometric parameters at baseline and at different time points post-treatment in both groups ($\bar{x} \pm s$)

Parameter	BUD	Control	$t^{\dagger}$	P-value
FEV ₁ (L)				
Increase from baseline at 0 h	0.250 $\pm$ 0.161	0.326 $\pm$ 0.190	1.272	0.212
Increase from baseline at 1 h	0.348 $\pm$ 0.170	0.385 $\pm$ 0.171	1.627	0.106
Increase from baseline at 2 h	0.445 $\pm$ 0.204	0.407 $\pm$ 0.170	0.742	0.459
Δ_{1-0} FEV ₁	0.095 $\pm$ 0.062	0.059 $\pm$ 0.082	2.532	0.013
Δ_{2-1} FEV ₁	0.100 $\pm$ 0.120	0.021 $\pm$ 0.128	3.372	0.001
FEV ₁ %				
Increase from baseline at 0 h	19.16 $\pm$ 11.29	23.83 $\pm$ 14.58	1.086	0.285
Increase from baseline at 1 h	27.32 $\pm$ 13.38	27.49 $\pm$ 13.82	0.296	0.768
Increase from baseline at 2 h	33.66 $\pm$ 14.13	27.72 $\pm$ 13.54	1.956	0.053
Δ_{1-0} FEV ₁ %	8.16 $\pm$ 6.87	3.67 $\pm$ 5.41	5.381	0.000
Δ_{2-1} FEV ₁ %	6.34 $\pm$ 5.20	0.22 $\pm$ 3.71	5.067	0.000

[†] BUD group versus control group.

Δ_{1-0} , difference between 1 and 0 h post-treatment; Δ_{2-1} , difference between 2 and 1 h post-treatment; BUD, budesonide; FEV₁, forced expiratory volume in 1 s.

remains unclear. In certain studies, SCS was linked to systemic adverse effects, which might be accumulative after repeated use in asthmatic children. These included a dose-dependent reduction in serum osteocalcin level in school-age children treated with short-term oral prednisolone (2.5 or 5 mg/day),¹¹ and the diminished responses of serum cortisol to hypoglycaemia and adrenocorticotrophic hormone in asthmatic children treated with short-term SCS (<7 days) for ≥ 4 courses in the previous year.¹²

Compared with SCS, ICS has been shown to be safer and more effective, with a favourable therapeutic index. Direct delivery into the airways makes the rapid action of ICS possible. ICS has been proven to be an effective and safe medication for long-term control of asthma and was recommended as the first-line therapy for persistent asthma both in children and adult. However, there is insufficient data from clinical research to determine if ICS can be used in combination with inhaled SABA as the first-line therapy for the management of acute exacerbation of asthma. In a study comparing the therapeutic outcomes of oral prednisone versus inhaled fluticasone propionate in acute exacerbation of childhood asthma, Schuh *et al.*² randomized a group of children with moderate-to-severe asthma exacerbation to receive oral prednisone (2 mg/kg) or 2000 μ g fluticasone propionate (via metered-dose inhaler plus a spacer) on the basis of nebulized short-acting bronchodilators. They found greater improvement in lung function and a much lower rate of hospitalization after 4 h in the SCS-treated group, suggesting that SCS was more effective than ICS in the management of moderate-to-severe acute exacerbation of asthma in children. In another study with similar study design, Volovitz *et al.*³ randomly allocated paediatric patients to receive a single dose of oral prednisolone (2 mg/kg) or 1600 μ g BUD by turbuhaler, and then the dose of inhaled BUD was tapered off as maintenance therapy for 1 week at home. During the first 4 h of treatment, there was no statistically significant difference between two groups in the improvement of lung

function or clinical symptoms. However, the BUD-treated group experienced better relief in symptoms during the subsequent week. Meanwhile, serum cortisol at baseline and after adrenocorticotrophic hormone stimulation was significantly reduced in children receiving SCS but not in children receiving inhaled BUD. This suggests that high-dose ICS may have similar effect as SCS in the treatment of acute exacerbation of childhood asthma and at the same time with better safety profiles.

Nebulization is the preferred method of inhalation in emergency settings for acute exacerbation of asthma, especially for young children. BUD solution is so far the only Food and Drug Administration (FDA)-approved nebulized ICS for children. However, the efficacy of nebulized BUD in the treatment of acute exacerbation of asthma has been addressed only in a very limited number of randomized, double-blind, placebo-controlled studies.^{13–22} In one study, Devidayal *et al.*²¹ investigated the efficacy of nebulized BUD (800 μ g) versus SCS (oral prednisolone 2 mg/kg) as an add-on therapy to salbutamol (0.15 mg/kg) for the treatment of acute exacerbation of asthma in children aged 2–12 years. Both the nebulized BUD and SCS groups had marked improvement in clinical symptoms and lung function, but the improvement in clinical symptoms was greater in children treated with nebulized BUD. Moreover, the BUD group required less intravenous hydrocortisone and hospital admission than the SCS. These findings suggest that high-dose nebulized BUD may work synergistically with β_2 -receptor agonists resulting in rapid improvement of asthma exacerbation and reduction of the rate of hospitalization. It was concluded that fast-acting high-dose ICS might be more effective than SCS. In another study by Nuhoglu *et al.*,²² high-dose nebulized BUD added to SCS and short-acting bronchodilator provided more benefit to lung function in children with acute exacerbation of asthma. These reports support the use of high-dose ICS for the management of acute exacerbation of asthma. In the present study, we compared combined

use of high-dose nebulized ICS and SABA with nebulized SABA alone as the first-line therapy in acute exacerbation of childhood asthma. It was found that the use of nebulized BUD was associated with better improvement in symptoms and lung function as well as higher complete remission rate, less need of SCS and hospitalization (by 3.6-fold). Our findings are consistent with those of Devidayal *et al.*²¹ All these data support the combined use of high-dose nebulized ICS and SABA as the first-line treatment for acute exacerbation of asthma.

In summary, on the basis of nebulized short-acting bronchodilators, three dosage in the first hour, add-on high-dose nebulized BUD is effective as the first-line treatment of moderate-to-severe acute exacerbation of childhood asthma, with better improvement of symptoms, lung function, less need for SCS and hospitalization. We believe that nebulized high-dose ICS can be recommended to be used with nebulized bronchodilators as first-line treatment of non-life-threatening acute exacerbation of asthma in children.

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