

Efficacy of Nebulised Budesonide *versus* Oral Prednisolone in Acute Severe Asthma

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Abstract

Objective To compare the efficacy of nebulised budesonide with that of oral prednisone in the treatment of acute severe asthma in children.

Methods Children aged 5–12 y with acute exacerbation of bronchial asthma were included. The study (budesonide) group received budesonide respirator solution (800 µg) at intervals of 20 min and a single dose of placebo tablets. The control (prednisolone) group received placebo solution at intervals of 20 min and a single dose of oral prednisolone (2 mg/kg). Both groups received three doses of nebulised salbutamol (0.15 mg/kg). Heart rate, respiratory rate, oxygen saturation, PEFR (Peak Expiratory Flow Rate) and fitness for discharge were assessed.

Results Both groups showed a progressive decrease in tachycardia with treatment, but it was significantly greater in study group ($p=0.0002$). There was significant decrease in tachypnea and improvement in oxygen saturation in both groups, but the difference between the groups ($p=0.334$ and $p=0.814$ respectively) was not significant. There was significant improvement in PEFR values in budesonide group

($p=0.024$). Both groups showed significant improvement in clinical severity scores at the end of 2 h ($p<0.0001$). Budesonide group had significantly higher proportion of patients fit for discharge at 2 h (based on clinical severity scores) ($p=0.0278$).

Conclusions Nebulised budesonide significantly improves PEFR levels and fitness for discharge at 2 h when compared to oral prednisolone in children between 5 and 12 y with acute severe asthma.

Keywords Bronchial asthma · Acute exacerbation · Budesonide · Prednisolone · Children

Introduction

Bronchial asthma is a common chronic inflammatory disorder of airways and is characterized by variable and recurring symptoms of airflow obstruction and bronchial hyper-responsiveness. Acute exacerbations of asthma are one of the most common medical emergencies in children. Adequate oxygenation, inhaled beta 2 agonists, anticholinergic drugs, systemic corticosteroids and sympathomimetics are the current mainstay of therapy for severe disease [1]. Oral and parenteral corticosteroids decrease the need for hospitalization within four hours after therapy among children with acute asthma, improve normalization of lung function and decrease the incidence of relapse [2]. In view of the systemic toxicity, inhaled steroids have long been tried to replace or to supplement oral steroids. Inhaled corticosteroids (ICS) cause immediate improvement in adults with stable asthma [3, 4]. Inhaled corticosteroids suppress airway inflammation, which is responsible for asthma-associated changes of the airway vasculature. These genomic actions are mediated by intracellular receptors, which alter transcription through direct DNA binding or transcription factor inactivation [5]. In addition to these

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genomic actions, the beneficial effects of inhaled steroids as against systemic administration in acute asthma may be due to the local drug delivery causing immediate non-genomic actions like bronchial mucosal vasoconstriction and inhibition of edema formation [6]. These non-genomic actions inhibit the uptake of norepinephrine thereby increasing norepinephrine concentration at the neuromuscular junction, hence inducing vasoconstriction. This enhances the action of inhaled bronchodilators by diminishing their clearance from the airways. Thus, simultaneous administration of inhaled corticosteroids and bronchodilators results in greater effects [5]. Thus, ICS also has systemic action in addition to local action. But, controversy still exists regarding its use in children with acute asthma due to the lack of convincing evidence [7, 8]. The current available literature in this area is equivocal. Beneficial effects have not been consistently proven in the concluded clinical trials [9, 10]. This randomized controlled study was done to compare the efficacy of Nebulised budesonide with that of oral prednisone in the treatment of acute severe asthma in children between 5 to 12 y.

Material and Methods

This randomized double blind, placebo controlled trial was conducted at the Pediatric Emergency Department of a tertiary care teaching hospital in South India from May 2008 through November 2010. Children aged 5–12 y with known asthma presenting with acute severe asthma were included in the study. Diagnosis of ‘asthma’, ‘acute severe asthma’ and ‘life threatening asthma’ in children was based on British Thoracic Society guidelines (Table 1) [11].

Children with first wheezing episode, life threatening asthma, those who received oral steroids in last 7 d, children who were on high dose inhaled steroids (1,000 µg or more of inhaled beclomethasone dipropionate or budesonide per day or 500 µg or more of inhaled fluticasone per day) and those with other concurrent cardiopulmonary disease, immunodeficiency, diabetes mellitus, allergy to corticosteroids, or exposure to Varicella within the previous 21 d were excluded from the study.

The study group or budesonide group received three doses of nebulised salbutamol (0.15 mg/kg) and budesonide respirator solution (800 µg) simultaneously (*i.e.*, mixed together in the same nebulizer chamber) at intervals of 20 min and a single dose of placebo tablets. Both budesonide nebulised solution and salbutamol respiratory solutions are compatible with each other and can be mixed. Similarly the control group or prednisolone group received three doses of nebulised salbutamol (0.15 mg/kg) along with placebo solution simultaneously at intervals of 20 min and a single dose of oral prednisolone (2 mg/kg). The patients as well as the clinicians were blinded regarding the drugs and respirator solution.

Table 1 Definition of a case of bronchial asthma, acute severe asthma and life threatening asthma (British Thoracic Society Guidelines) [11]

Diagnosis of asthma

- More than one of the following symptoms: wheeze, cough, difficulty breathing, chest tightness, particularly if these symptoms:
 - are frequent and recurrent
 - are worse at night and in the early morning
 - occur in response to, or are worse after, exercise or other triggers, such as exposure to pets, cold or damp air, or with emotions or laughter
 - occur apart from colds
- Personal history of atopic disorder
- Family history of atopic disorder and/or asthma
- Widespread wheeze heard on auscultation
- History of improvement in symptoms or lung function in response to adequate therapy

Acute severe asthma in children >5 y is defined by the presence of any one of the following:

1. SpO₂<92 %
2. Respiratory rate >30/min
3. Heart rate >125/min
4. Use of accessory neck muscles

Life threatening asthma in children >5 y means any one of the following in a child with severe asthma:

1. Silent chest
2. Poor respiratory effort
3. Altered consciousness (exhaustion/confusion)
4. Cyanosis
5. Hypotension

Random numbers for two groups were generated using a computer and were placed in opaque sealed envelopes in the Emergency Department (ER). As soon as the child was received in the ER and recruited into the study a random envelope was opened and the child was managed as per the group assigned in the envelope.

The study and control groups were assessed every 20 min for up to one hour. The parameters that were assessed include heart rate, respiratory rate, and oxygen saturation. Peak Expiratory Flow (PEF) maneuver is unpleasant in the emergency situation and can occasionally aggravate the bronchospasm, in addition to delaying the initiation of treatment. Hence PEFR (Peak Expiratory Flow Rate) was assessed at the end of one hour and at four hours. PEFR was measured using “Micropeak Flow Meter”. Fitness for discharge was evaluated at the end of 2 h using the clinical severity scoring [12]. This scoring underlines the fact that careful ongoing clinical evaluation is superior to reliance on pulmonary function and SaO₂ measurements in predicting the need for hospitalization in acute childhood asthma.

The study was approved by the Human Ethics Review Board of authors’ institution, Informed consent was obtained from the parents before enrolling their children into the study.

A log of patients who were missed or excluded or whose parents refused participation was kept so that generalizability of the study could be assessed.

Statistical analysis for the outcomes were done by using Chi square test for fitness for discharge, paired *t*-test for parametric variables in each group and two sample (unpaired) *t*-test for estimating difference in the improvement in parametric variables between the groups. A *p* value of less than 0.05 was considered as significant.

Results

Eighty five asthmatic children aged 5 to 12 y presenting to the Emergency Department with cough, cold and acute onset

breathlessness was initially screened. Wheezing was present in all the 85 children who were initially assessed. Fifteen children with features of life-threatening asthma were excluded from the study. Parents of four children declined consent. Five children with strong clinical suspicion of bronchopneumonia were subject to X-ray and were excluded. The remaining sixty one (61) children were recruited in to the study after obtaining informed consent (Fig. 1).

Thirty one (31) children were randomized into prednisolone group and thirty (30) children into budesonide group and were treated accordingly. The baseline characteristics of both the groups were comparable as shown in Table 2. Only 17 children in prednisolone group and 18 children in budesonide group were able to perform FVC (Forced Vital Capacity) manoeuvre. Hence PEFs were measured only in these

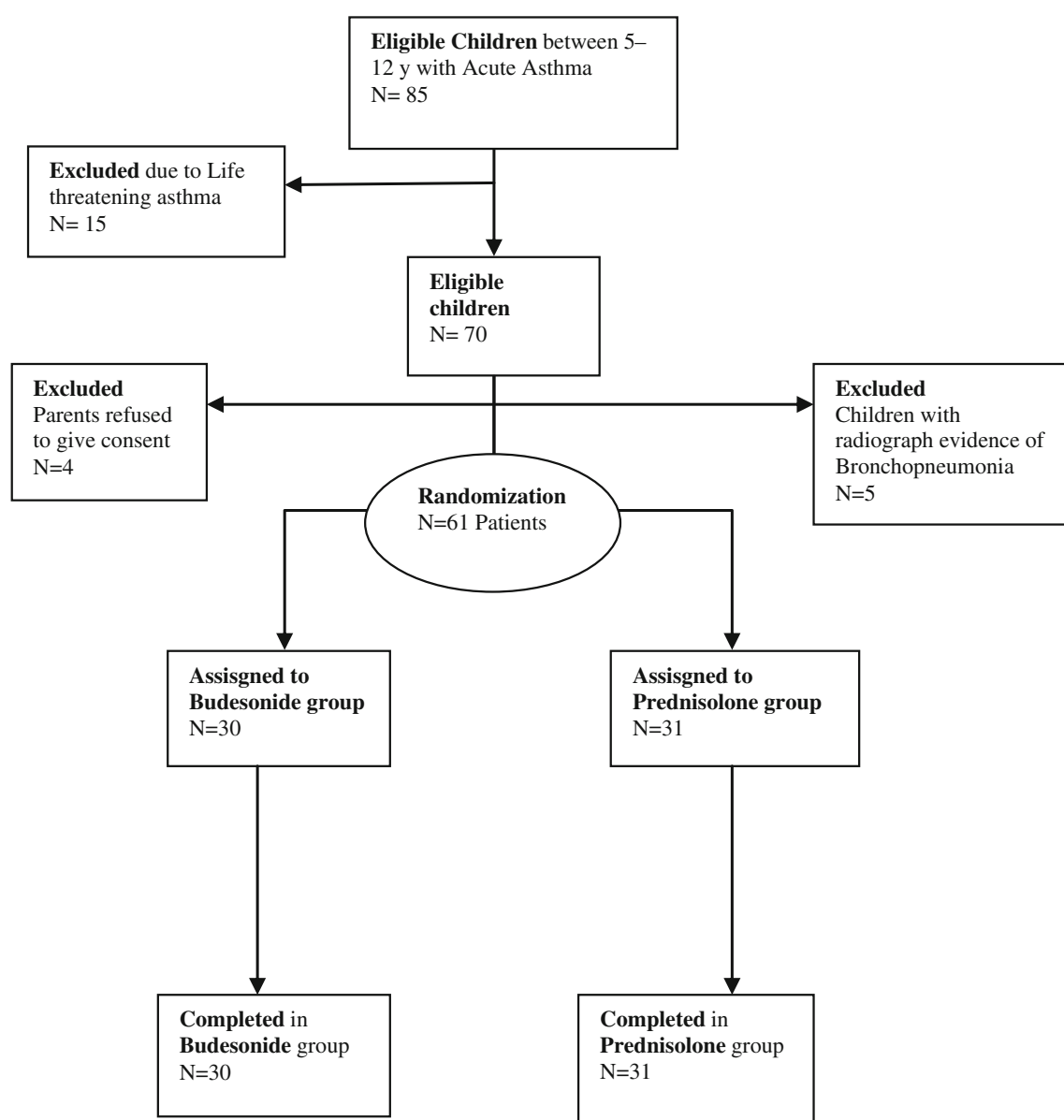


Fig. 1 Study flow diagram

children at the end of one hour and again at 4 h after starting treatment. The fitness for discharge was assessed at the end of 2 h using the clinical severity scoring system shown in Table 3. Children with a score of 0.4 or less were taken as fit for discharge.

Comparison in the outcome measures between the two groups are summarized in Table 4. Children in both groups showed a progressive decrease in tachycardia with treatment but decrease in HR in budesonide group was significantly greater than in prednisolone group ($p=0.0002$). Though there was significant decrease in Tachypnea in both groups, the difference between the groups were not significant ($p=0.334$). Similarly, there was significant improvement in oxygen saturation in both groups, but the difference between the groups was not significant ($p=0.814$). Improvement in PEFR values in budesonide group were significantly higher than with prednisolone group ($p=0.024$).

Both groups showed a statistically significant improvement in clinical severity scores at the end of 2 h ($p<0.0001$). But, the proportion of patients who were fit for discharge at the end of 2 h was significantly higher in budesonide group than in the prednisolone group (p value of $=0.0278$).

Discussion

Inhaled corticosteroids are primarily used as preventive therapy of childhood asthma. Their role in acute severe bronchial asthma is still equivocal. Contrary to other nebulised steroids, budesonide nebulization has demonstrated immediate beneficial effects in children with asthma. A study comparing the bronchial vasoconstrictive efficacy of inhaled glucocorticosteroids showed that inhaled fluticasone propionate and budesonide cause greater vasoconstriction in the airway than beclomethasone dipropionate [13]. Absorption of nebulised budesonide from the lungs is rapid with peak plasma concentrations reached approximately 10 to 30 min

Table 3 Clinical Scoring System [12]

Variable	Score=0	Score=1
Heart rate	<120/min for >5 y <130/min for 2–5 y	>120/min for >5 y >130/min for 2–5 y
Respiratory rate	<50/min 2–5 y <30/min for >5 y	>50/min 2–5 y >30/min for >5 y
Dyspnea	Absent or mild	Moderate or severe
Accessory muscle use	Absent or minimal	Moderate or severe
Wheezing	Absent or end expiratory only	Throughout expiration or expiration + inspiratory

The score was expressed by adding the number of positive values (*i.e.*, score =1) for an individual patient, as a fraction of the total number of variables *i.e.*, 5. The final score ranged from 0 to 1.0, increasing with severity

after the start of nebulization. The pharmacokinetics of budesonide administered by nebulization in children allows for a long duration of local therapeutic effects with minimal systemic exposure [14]. Several studies have showed improved FEV1 within hours of budesonide administration in patients with stable asthma [3, 4]. This prompted researchers to believe that budesonide could be an ideal candidate for acute severe bronchial asthma. The preliminary results obtained from budesonide trials were not disappointing. But in children, in spite of more than a decade of research, it is still unclear whether it is better than oral prednisolone, which is the current standard therapy due to conflicting results.

Several studies have demonstrated a significant benefit of inhaled corticosteroids from two to four hours after administration in patients with asthma. The proposed biologic mechanisms include up-regulation of β_2 -adrenergic receptors, mucosal vasoconstriction, and a decrease in airway edema [15].

A meta analysis of 17 trials from 1996 to 2006 suggested that inhaled corticosteroids present early beneficial effects (1–2 h), when they were used in multiple doses

Table 2 Comparison of baseline characteristics of two groups

Variable	Prednisolone group <i>n</i> =31	Budesonide group <i>n</i> =30	<i>p</i> value
Age	7.14±1.93	7.8±1.93	0.19
Sex (M : F)	15:16	17:13	
Respiratory rate	53.81±8.86	50.67±6.02	0.112
Heart rate	148.19±11.86	143.53±11.66	0.127
O ₂ saturation	93.39±1.022	98.37±1.098	0.940
PEFR (at 1 h) (L/min)	185.88±40.05 (<i>n</i> =17)	180.56±38.15 (<i>n</i> =18)	0.69
Clinical Severity Scoring	0.677±0.17	0.66±0.18	0.69

PEFR Peak expiratory flow rate

Table 4 Comparison in the outcome measures between the groups

Outcome measure	Prednisolone group	Budesonide group	<i>p</i> value
Decrease in Heart rate*	24.77±13.0	36.87±10.86	0.0002
Decrease in Respiratory rate*	20.51±6.73	22.07±5.62	0.334
Improvement in Oxygen Saturation*	1.452±0.89	1.4±0.81	0.814
Increment in PEFR [#]	16.76±11.17	30.28±20.97	0.024
Fitness for discharge [§]	26 %	53 %	0.0278

PEFR Peak expiratory flow rate

*At the end of 60 min

[#] At the end of 4 h

[§] At the end of 2 h

administered in time intervals <30 min over 90–120 min [16].

Schuh et al. reported that children with acute exacerbation of asthma in the Emergency Department improved faster on oral prednisolone than inhaled fluticasone [7]. The possible reasons for the poorer outcome were that it had children with severe disease, who may have had too much inflammation and mucous plugging to be successfully treated with inhaled corticosteroids. The authors attempted to minimise this possibility by excluding children with life threatening asthma.

Nebulised budesonide was found to be as effective as oral steroid in improving lung function and symptom severity in severe exacerbation of childhood asthma [17]. An Indian study found that after three doses of nebulization with budesonide, oxygen saturation, respiratory rate, pulmonary index and respiratory distress scores significantly improved in the budesonide group compared to the prednisolone group. They also found that the proportion of patients who were fit for discharge at the end of 2 h after the third dose of nebulization was significantly higher in the budesonide group than in the prednisolone group [9].

Comparison of oral prednisolone (OCS) with inhaled flunisolide found no clinical difference in the response to ICS or OCS. However spirometry data suggested a more rapid resolution of asthma in the patients receiving OCS [18].

Though the present study showed a significant decrease in Tachypnea and improvement of oxygen saturation from the pre-treatment levels with inhaled budesonide, there was no significant difference in improvement when compared with oral prednisolone. But the increment in PEFr at the end of four hours among those treated with inhaled budesonide was about twice that in those given oral prednisolone. Furthermore, the rate of discharge in the budesonide group was about two times that in the prednisone group.

Conclusions

Nebulised budesonide significantly improves PEFr and fitness for discharge at the end of 2 h when compared to oral prednisolone among children of 5–12 y of age with acute severe asthma.

Contributions CSA and CR were involved in the study design, protocol, data collection and statistical analysis. IS, BS, SP and JH were involved in study design, data collection and interpretation of data. TA reviewed the literature, did statistical analysis and drafted the manuscript which was critically reviewed and approved by all authors. CR will act as the guarantor of the paper.

Conflict of Interest None.

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