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Original Research Article

Inhaled budesonide versus oral prednisolone in the treatment of acute exacerbation of moderate bronchial asthma: an open label randomized clinical trial

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ABSTRACT

Background: Recently published studies have suggested that inhaled corticosteroids may offer benefit over systemic steroids in bronchial asthma. This research was carried out to study the efficacy of inhaled budesonide and to compare the efficacy of inhaled budesonide with oral prednisolone in the treatment of acute moderate asthma in children.
Methods: This was an open label randomized clinical trial. Children in the age group of 1-12 years with acute exacerbation of asthma presenting to pediatric emergency from November 1, 2015 to October 31, 2016 who fail to show prompt improvement after initial treatment with oxygen and three doses of inhaled salbutamol, were enrolled. Children in group B (n=35) and group P (n=35) received inhaled budesonide and oral prednisolone, respectively, in addition to oxygen inhalation and salbutamol as per the study protocol. Outcome was measured in terms of pulmonary score at the beginning, at 6 hours, and at 24 hours of starting the treatment. The analysis was undertaken according to intent to treat principle.
Results: Baseline characteristics (sex, age, weight, height, body mass index) were comparable in the 2 groups. Mean heart rate, respiratory rate, pulmonary score at 6 and 24 hours, mean SpO_2 at 24 hours were significantly showing normalizing trend ($p<0.05$) and mean hospital stay was significantly reduced [2.60 (±0.60) vs 3.11 (±0.80); $p<0.05$] in group B as compared to group P.
Conclusions: Outcome measures of clinical improvement were better in inhaled budesonide group than oral prednisolone group in acute moderate exacerbation of bronchial asthma.

Keywords: Asthma, Steroids, Inhaled, Budesonide, Prednisolone

INTRODUCTION

Acute asthma exacerbation is a medical emergency characterized by progressive increase in shortness of breath, cough, wheezing or chest tightness and by a decrease in expiratory airflow. Traditionally, systemic corticosteroids have been used in acute exacerbations of bronchial asthma. However, systemic corticosteroids have disadvantages, particularly in children. Parenteral administration can be labor-intensive, time-consuming for staff and painful to child. Orally administered steroids may be refused by children or vomited out, which can result either in significant delay in steroid therapy or in the patient not receiving steroids at all. Most of these problems may be overcome with the use of inhaled corticosteroids, which also offer the advantage of administration directly to lungs. Recently published studies suggested that inhaled corticosteroids may offer benefit in patients with mild to moderate obstruction.[1-4] The recent guidelines recommend the use of systemic

corticosteroids in mild and moderate cases of acute asthma who do not show prompt and complete response to oxygen inhalation and β2 agonists.[5] Inhaled budesonide is a potent non-halogenated steroid which has high local activity and little systemic effect.[6] There are only a few studies on use of inhaled corticosteroids in such children reported in India and none of these studies has been carried out in this region. Hence this study was carried out to compare the efficacy of inhaled budesonide with oral prednisolone in children with acute asthma exacerbations who fail to show improvement after initial treatment with oxygen and three doses of inhaled β2 agonist salbutamol.

METHODS

This open label randomized clinical trial (RCT) was carried out in pediatric ward and pediatric intensive care unit (PICU) of a teaching referral hospital in eastern India. The study was conducted over a period of 9 months (November 1, 2015 to October 31, 2016) among children aged 1-12 years with acute exacerbation of moderate asthma. This RCT was approved by the institutional ethical and scientific committees and informed consent was obtained from the parents before enrolling the children in the study.

Inclusion criteria

Children with wheeze requiring bronchodilator therapy on ≥3 prior occasions or wheezing <3 occasions with history of atopic dermatitis or parental history of asthma and satisfying the criteria were enrolled: 1. The presence of asthma exacerbation which was accepted, if there was: (a) Appearance or increased frequency of cough, wheezing, dyspnea or any combination of these (b) At least a two-fold increase in mean daily bronchodilator requirement for last 24 hours. 2. Pulmonary score ≥ 4 after 3 doses of nebulized salbutamol given over 1 hour. 3. Age between 1 to 12 years.

Exclusion criteria

The patients excluded from study were having- 1. Congenital or acquired pulmonary/cardiac disease. 2. Moderate/severe anemia 3. Children with severe respiratory distress identified with presence of red flag signs/severe asthma: (a) Altered sensorium (drowsy or agitated), (b) Shock, (c) Cyanosis, (d) Excessive diaphoresis, (e) Silent chest on auscultation, (f) SaO_2 on room air <92%, (g) Excessive use of accessory muscles or state of exhaustion (vocalization limited to 1-2 words), (h) Severe attack of acute asthma exacerbation (pulmonary score ≥7). 4. History of systemic corticosteroid use in past 48 hours.

Sample size was calculated as per pilot sample method. Randomization was performed by computer generated random numbers. Patients satisfying the inclusion criteria were randomized in 2 groups.

Group B: Inhaled budesonide group

These children continued to receive oxygen inhalation at 5 liter/min, inhaled salbutamol 0.15 mg/kg diluted 1:2 times with normal saline every hour for 3 hours and then at 6 hourly intervals. In addition, they received inhaled budesonide 800 µgm every hour for 3 hours and in case of response, was followed by 800 µgm 12 hourly for 3-5 days.

Group P: Oral prednisolone group

These children continued to receive oxygen inhalation at 5 liter/min, inhaled salbutamol 0.15 mg/kg diluted 1:2 times with normal saline every hour for 3 hours and then at 6 hourly intervals. In addition, they received oral prednisolone 2 mg/kg/day in two divided doses for 3-5 days.

The response to the treatment was evaluated by monitoring the parameters; Respiratory rate (RR), heart rate (HR), Oxygen saturation (SPO_2), Accessory muscle usage and wheezing.

The above parameters were also used to calculate pulmonary index score (Table 1).[7] All the parameters (RR, HR, SPO_2, wheezing and accessory muscle usage) were monitored hourly along with side effects, if any. Outcome was measured in terms of PIS and evaluated at admission, and at 6 and 24 hours of starting the treatment. Evaluation before and after treatment was done by a single investigator to reduce inter-observer bias. The pulmonary index score (PIS) has an excellent correlation with pulmonary function test results and with hospital admission rates in children with varying severity of asthma. Duration of hospital stay was also recorded and compared between the groups.

Table 1: Pulmonary index score.[7]

Score	Respiratory rate/min (age <6 years)	Respiratory rate/min (age >6 years)	Wheezing	Accessory muscle use
0	<30	<20	None	No apparent activity
1	31-45	21-35	Terminal expiratory	Questionable increase
2	46-60	36-50	Entire expiration	Increase apparent
3	>60	>50	Inspiration and expiration/ silent chest	Maximal activity

A PIS of 0-3, 4-6 and ≥7 denotes mild, moderate and severe respiratory distress respectively.

Statistical analysis

Chi-square test or Fisher's exact test was used for categorical variables and student t test or Mann-Whitney U test for continuous variables depending on underlying data distribution. Statistical significance between pulmonary scores was assessed by student ´t´ test. The analysis was undertaken according to intent to treat principle. A p value of <0.05 was considered as statistically significant. The entire data was statistically analyzed using statistical package for social sciences (SPSS version 16.0, IBM Corporation, USA) for MS windows.

RESULTS

A total of 70 children were enrolled out of 81 children with acute exacerbation of moderate asthma during the study period. Among enrolled children, 35 were allocated to inhaled Budesonide group and 35 were allocated to oral prednisolone group (Figure 1).

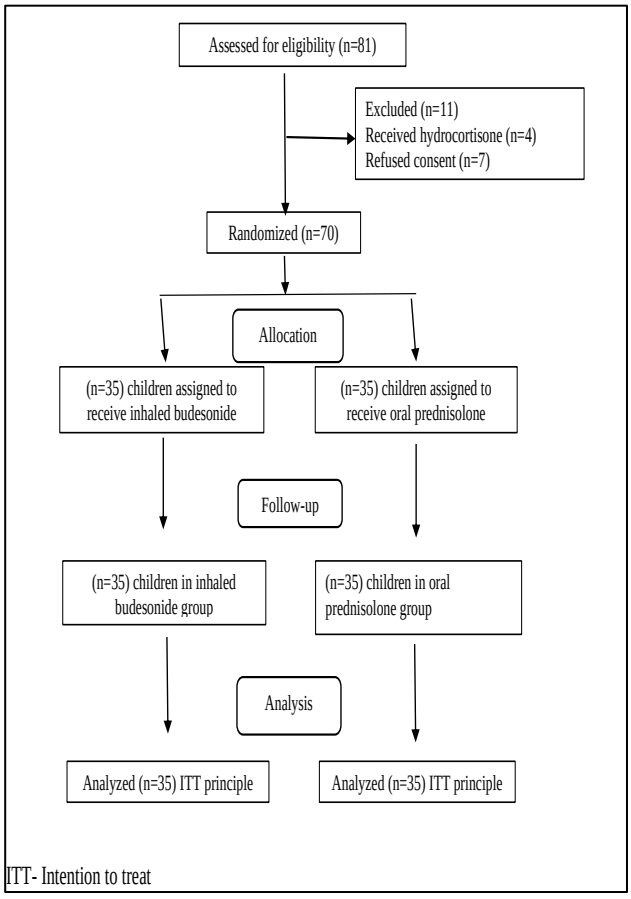

Figure 1: CONSORT diagram.

The baseline characteristics were comparable in both the groups and are shown in Table 2.

Table 2: Baseline characteristics among the 2 groups.

Variable	Group B (Budesonide) n=35 (%)	Group P (Prednisolone) n=35 (%)	P value
Age in years, mean (±SD)	5.14 (±3.74)	4.71 (±3.06)	>0.05
Height in cm, mean (±SD)	98.43 (±21.14)	99.17 (±19.79)	>0.05
Weight in kg, mean (±SD)	16.17 (±7.41)	16.05 (±6.11)	>0.05
BMI in kg/m^2, mean (±SD)	16.14 (±2.54)	16.07 (±2.43)	>0.05
Gender-Male	21 (60)	21 (60)	>0.05
Parental asthma	7 (20)	6 (17.1)	>0.05
Atopic dermatitis	2 (5.7)	2 (5.7)	>0.05
Allergic rhinitis	5 (14.3)	5 (14.3)	>0.05

SD-Standard deviation, BMI-Body mass index

Mean heart rate (HR) at admission was comparable in both the groups; however mean HR at 6 and 24 hours was significantly showing normalizing trend in budesonide group as compared to prednisolone group (p=0.001 and 0.005 at 6 hours and 24 hours respectively) as shown in Table 3.

Table 3: Comparison of heart rate among the groups.

Heart rate/min	Group B (budesonide) n=35	Group P (prednisolone) n=35	P value
At admission mean (±SD)	127.30 (±3.39)	127.4 (±4.69)	0.92
At 6 h, mean (±SD)	109 (±4.46)	116 (±5.3)	0.001
At 24 h, mean (±SD)	104.49 (±4.64)	109.5 (±4.05)	0.005

SD- Standard deviation

Mean respiratory rate (RR) at admission was comparable in both the groups; however mean RR at 6 and 24 hours was significantly showing normalizing trend in budesonide group as compared to prednisolone group (p=0.002 and 0.001 at 6 and 24 hours) shown in Table 4.

Mean SpO_2 at admission and at 6 hours was comparable in both the groups; however mean SpO_2 at 24 hours was significantly showing normalizing trend in budesonide

group as compared to prednisolone group (p=0.007) as shown in Table 5.

Table 4: Comparison of respiratory rate among the groups.

Respiratory rate/min	Group B (Budesonide) n=35	Group P (Prednisolone) n=35	P value
At admission, mean (±SD)	46.29 (±8.73)	45.17 (±2.65)	0.47
At 6 h, mean (±SD)	30.3 (±3.37)	33.74 (±3.85)	0.002
At 24 h, mean (±SD)	24.31 (±2.44)	27.14 (±2.99)	0.001

SD- Standard deviation

Table 5: Comparison of SpO_2 among the groups.

SpO_2	Group B (Budesonide) n=35	Group P (Prednisolone) n=35	P value
At admission, mean (±SD)	92.6 (±1.24)	92.88 (±0.63)	0.24
At 6 h, mean (±SD)	96.37 (±1.55)	96.06 (±1.59)	0.41
At 24 h, mean (±SD)	96.09 (±1.67)	94.74 (±1.52)	0.007

SD- Standard deviation

Mean PIS at admission was comparable in both the groups; however mean PIS at 6 and 24 hours was significantly showing normalizing trend in Budesonide group as compared to prednisolone group (p=0.02 and 0.001 at 6 and 24 hours) as shown in Table 6.

Table 6: Comparison of pulmonary index score (PIS) among the groups.

Pulmonary index score	Group B (budesonide) n=35	Group P (prednisolone) n=35	P value
At admission, mean (±SD)	5.46 (±0.74)	5.2 (±0.83)	0.17
At 6 h, mean (±SD)	2.43 (±1.04)	2.91 (±1.12)	0.02
At 24 h, mean (±SD)	1.6 (±0.74)	2.26 (±0.56)	0.001

SD- Standard deviation

The mean duration of hospital stay was 2.6 and 3.11 days in budesonide group and prednisolone group respectively. The hospital stay was significantly less in budesonide group than prednisolone group (p=0.003) as shown in Table 7.

Table 7: Duration of hospital stay among the groups.

Duration of hospital stay	Group B (Budesonide) n=35	Group P (Prednisolone) n=35	P value
Days, mean (±SD)	2.6 (±0.6)	3.11 (±0.8)	0.003

DISCUSSION

Global initiative for asthma (GINA) guidelines recommend a short course of systemic steroids for patients with acute severe asthma.[8] Expert panel report-3 (EPR-3) guidelines for the diagnosis and management of Asthma recommend that systemic corticosteroids be given to patients who have moderate or severe exacerbations and patients who do not respond completely to initial short-acting beta agonist (SABA) therapy.[5] These medications speed the resolution of airflow obstruction and reduce the rate of relapse and may reduce hospitalizations.[9] This RCT was conducted to evaluate the efficacy of inhaled budesonide with oral prednisolone in the treatment of acute exacerbation of moderate asthma in children. Our study has shown that a trial of inhaled Budesonide can be safely used in acute exacerbation of moderate asthma in children aged 1-12 years before starting systemic corticosteroids. Authors have observed that the children who received inhaled budesonide showed normalization of vital parameters (HR, RR, SpO_2, PIS) earlier than those who received oral prednisolone. Authors also observed that the children who received inhaled budesonide were discharged earlier than those who received oral prednisolone. No adverse effects were noticed in either of the groups during the study period. Our results are comparable to studies by Devidayal and Matthews et al, wherein they have also observed that the vital parameters normalized earlier in inhaled budesonide group that oral prednisolone group.[10,11] Chen et al observed that nebulized high-dose budesonide resulted in clinical improvement in children with moderate-to-severe acute exacerbation of asthma, suggesting that nebulized high-dose can be used as first-line therapy for non-life-threatening acute exacerbation of asthma in children.[12] Singhi et al showed aerosolized budesonide therapy together with nebulized salbutamol early in the emergency room treatment of acute moderate exacerbations of asthma helped in early recovery and decreased the need for hospitalization.[13] The limitation of the study was that only clinical assessment was done to measure the outcome. Spirometry was not possible in majority of the study population. Other limitations were that the long-term effects of the drugs could not be

ascertained besides a small sample size where the participants were not blinded.

CONCLUSION

This study has emphasized that the use of inhaled budesonide can be effectively used in acute exacerbation of moderate asthma in children aged 1-12 years. As inhaled budesonide was more effective and safer, oral prednisolone should not be used for treatment of acute exacerbation of moderate bronchial asthma.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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