

IMMEDIATE EFFECT OF NEBULIZED BUDESONIDE IN ASTHMATIC CHILDREN : A RANDOMIZED CONTROLLED STUDY IN A TERTIARY HOSPITAL

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Summary

Very little is known about the immediate response of nebulized corticosteroid in addition to systemic steroids plus nebulized salbutamol in the early management of acute asthma in children. This study was aimed to observe any immediate effect of nebulized budesonide in the management of acute asthma in children. A total of 106 asthmatic patients aged between 5-12 years were investigated in a prospective single-blind, placebo controlled fashion. All subjects were entered in a randomized manner into one of two groups, Group-I (Study Group) and Group-II (Control Group). After the Paediatric Asthma Severity Score (PASS) and the Peak Expiratory Flow Rates (PEFR) had been measured in all patients at the beginning of the study, 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 hydrocortisone (5 mg/kg/dose, intravenous). After this initial treatment, nebulized budesonide (1 mg/dose) was administered to patients in Group-I. One hour later, the PASS and the PEFR were measured once more and at discharge, the durations of hospital stay (in days) were recorded for comparison between two groups. There were 53 patients in Group-I (mean age: 7.99±2.12) and 53 patients in Group-II (mean age: 7.45±2.13). Both the groups were comparable for age ($p=0.212$) and sex ($p=0.242$) and inhaled steroid prophylaxis rate ($p=0.233$). No statistically significant difference was detected between the two groups with respect to the decrease in PASS ($p=0.851$). Yet, there were statistically significant differences between the two groups with respect to the increase in PEFR ($p=0.006$) and durations of hospital stay in days ($p=0.004$). The positive immediate effect of nebulized budesonide in addition to systemic steroids and nebulized salbutamol in improving the PEFR as well as durations of hospital stay in asthmatic children is an encouraging finding for further study of its routine use in the paediatric emergency department.

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Key words

Budesonide; Salbuamol; Hydrocorisone; Acute asthma; Children.

Introduction

Asthma is one of the most common conditions seen in the paediatric 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 of acute asthma in children [2,3].

With this background, this study was aimed to observe whether addition of one high dose of nebulized budesonide to three doses of nebulized salbutamol and one dose of systemic steroids would further improve the peak expiratory flow rate (PEFR) and the clinical response which was evaluated by Pediatric Asthma Severity Score (PASS) in the pediatric population with acute asthma [4].

Materials & methods

Patients who attended the inpatient Department of Paediatrics ward of Chittagong Medical College Hospital, Chittagong due to an acute attack of asthma over a twelve month period were evaluated for the study.

All patients met the National Guidelines, Asthma Association, Bangladesh criteria for asthma⁵ in which asthma was defined as a clinical syndrome characterized by paroxysmal coughing, wheezing and dysnoea and caused by the hyperresponsiveness

of the trachea-bronchial system to different stimuli, resulting in airway obstruction. Physical examination and paediatric Asthma Severity Score (PASS) were performed. Children with moderate to severe acute asthma attack indicated by PASS one or more were included in the study [5].

Inclusion criteria

1. Having a clinical diagnosis of moderate to severe acute asthma indicated by a Paediatric Asthma Severity Score (PASS) one or more.
2. Age between 5-12 years.
3. Being able to perform peak flow meter.

Exclusion criteria

1. First episode of wheezing.
2. History suggestive of chronic bronchitis or emphysema.
3. Clinical features suggestive of pneumonia.
4. History of congestive heart failure.
5. Requirement of ICU supports judged by the attending physician.
6. Failure to use peak expiratory flow meter.
7. Failure to get consent for participation in the study.

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 prospective single blind randomized controlled fashion. After the patients' demographic data (age, gender, present asthma treatment) was recorded, subjects fulfilling the above mentioned criteria were entered in the study and randomized into two groups, Group-I (study group) and Group-II (control group) by random number table with blinding of the randomization using sealed opaque envelopes.

After the PASS and PEFr had been measured in all patients, both groups received three consecutive doses of nebulized salbutamol (0.15 mg/kg/dose) and one dose of intravenous Hydrocortisone (5 mg/kg/dose) along with all supportive cares. Soon after the initial treatment, nebulized budesonide (1 mg/dose) was administered to patients in Group-I and placebo (nebulized normal saline) was administered to patients in Group-II. One hour later, each patient was followed-up for single time and the PASS and the PEFr were measured once more. The further treatment of all patients was going on according to standard asthma management and at discharge, the durations of hospital stay (in days) were recorded for comparison between two groups (Fig I).

Clinical evaluation

Physical examination findings were evaluated by Paediatric Asthma Severity Scoring system. In this system presence and severity of wheezing, work of breathing and prolonged expiration were evaluated (table 1).

Peak expiratory flow rate

Peak Expiratory Flow Rate (PEFR) was measured by using a peak flow meter. The best of three successfully performed maneuvers was accepted.

Statistical analysis

All the collected data was checked and verified for its consistency. The data was compiled, analyzed and then tabulated according to key variables. Data was analyzed using SPSS/Win v. 15 employing necessary statistical tools (by expert programmer-cum-data analyst). Chi-square tests were performed for larger sets of numbers and Student's t-tests were performed to compare mean value of 2 sets of continuous variables. A p-value of < 0.05 at 95% CI was considered significant.

Results

A total of 106 children who presented to the paediatric ward with an acute exacerbation of asthma were considered for the study. There were no dropouts from the study.

53 patients were in Group-I (nebulized budesonide group). The mean age was 7.99 ± 2.12 years (range 5-12 years). There were 27 girls and 26 boys in this group. 24 patients were having Inhaled Corticosteroids (ICS) prophylaxis (45.3%). There were 53 patients in Group-II (placebo). The mean age was 7.47 ± 2.13 years. There were 21 girls and 32 boys. 18 patients were having ICS prophylaxis (34%). There was no difference between the two groups with respect to age ($p=0.212$), gender ($p=0.242$) and inhaled steroid prophylaxis rate ($p=0.233$).

The mean value of baseline PEFr in Group-I was 147.55 ± 6.77 . Mean PEFr after the treatment was 228.30 ± 17.18 . None of the patients knew their best PEFr, therefore, percent of the best value was not used in the study. The mean increase in PEFr was 80.75 ± 19.98 in the nebulized budesonide group. The mean value of baseline PEFr in Group-II was 150.18 ± 10.65 . Mean PEFr after the treatment was 220.75 ± 18.38 . The mean increase in PEFr was 70.57 ± 17.37 for the placebo group. There was a statistically significant difference between the two groups with respect to the increase in PEFr ($P=0.006$).

of the trachea-bronchial system to different stimuli, resulting in airway obstruction. Physical examination and paediatric Asthma Severity Score (PASS) were performed. Children with moderate to severe acute asthma attack indicated by PASS one or more were included in the study [5].

The mean value of baseline PASS was 4.26±0.44 in Group-I and 4.19±0.39 in Group-II. After the treatment, the mean PASS was 1.08±0.27 in Group-I and 1.02±0.24 in Group-II. The mean decrease in PASS was 3.19±0.56 in Group-I and 3.17±0.47 in Group-II. There was no statistically significant difference between the two groups with respect to PASS (P = 0.851).

In Group-I, the mean hospital stay was 1.47±0.57 days (range 1-3 days) and in Group-II, the mean hospital stay was 1.87±0.78 days (range 1-4 days). There was a statistically significant difference between the two groups with respect to the durations of hospital stay (p=0.004).

Table 1 : Pediatric asthma severity score (PASS)

	0	1	2
Wheezing	None	Moderate	Severe
Work of breathing (use of accessory muscles)	None	Moderate	Severe
Prolonged expiration	None	Moderate	Severe

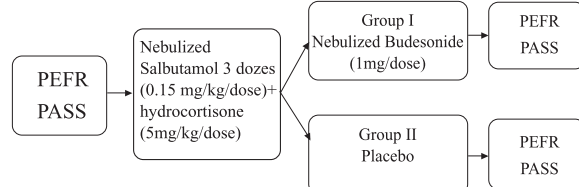


Fig 1 : the study design PEFR: Peak Expiratory Flow Rate, PASS: Paediatric Asthma Severity Score

Table II : Statistics of paediatric asthma severity score (PASS) among the study groups (with t – test significance)

Paediatric Asthma Severity Score (PASS)	N	MEAN	±SD	MEDIAN	RANGE	SIGN
PASS (Before Treatment)	Group I 53	4.26	0.44	4.00	5 - 5	t = 0.923
	Group II 53	4.19	0.39	4.00	4 - 5	P = 0.358
	TOTAL 106	4.23	0.42	4.00	4 - 5	Not Significant
PASS (After Treatment)	Group I 53	1.08	0.27	1.00	1 - 2	t = 1.150
	Group II 53	1.02	0.24	1.00	0 - 2	P = 0.253
	TOTAL 106	1.05	0.25	1.00	0 - 2	Not Significant
PASS Decrease	Group I 53	3.19	0.56	3.00	2 - 4	t = 0.189
	Group II 53	3.17	0.47	3.00	2 - 4	P = 0.851
	TOTAL 106	3.18	0.51	3.00	2 - 4	Not Significant

Table III : Statistics of peak expiratory flow rate (PEFR) among the study groups (with t – test significance)

Peak Expiratory Flow Rate (PEFR)	N	MEAN	±SD	MEDIAN	RANGE	SIGN
PEFR (Before Treatment)	Group I 53	147.55	6.77	150.00	140-160	t = 1.524
	Group II 53	150.18	10.65	150.00	120-180	P = 0.131
	TOTAL 106	148.87	8.98	150.00	120-180	Not Significant
PEFR (After Treatment)	Group I 53	228.30	17.18	230.00	160-270	t = 2.184
	Group II 53	220.75	18.38	220.00	200-270	P = 0.031
	TOTAL 106	224.53	18.11	220.00	160-270	Not Significant
PASS Decrease	Group I 53	80.75	19.98	80.00	0 - 120	t = 2.802
	Group II 53	70.57	17.37	70.70	40 - 110	P = 0.006
	TOTAL 106	75.66	19.32	80.00	0 - 120	Highly Significant

Table IV : Statistics of duration of hospital stay among the study groups (with t-test significance)

	N	MEAN	±SD	MEDIAN	RANGE	SIGN
Duration of Hospital Stay (Days) GROUP I	53	1.47	0.57	1.00	1-3	t = 2.963
	53	1.87	0.78	2.00	1-4	P = 0.004
	TOTAL 106	1.67	0.71	2.00	1-4	Highly Significant

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 [6-8]. Previous studies have shown that oral corticosteroids can decrease the need for hospital admission [9,10]. However, despite these medication, many children still require admission to hospital.

Nonrandomized trials have shown an acute benefit of inhaled budesonide in asthma [11-13]. Budesonide has a very rapid onset of action due to its acute anti-inflammatory effect [13,14] and may therefore have an additive effect in decreasing admission rates when used as an adjunct to systemic steroids.

The single blinded, 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 PEFR and a more rapid discharge rate in children with moderate to severe asthma exacerbation but had no additional effect in improving in 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 sixty adult emergency room patients with acute asthma¹⁵. All patients received nebulized salbutamol and IV methyl prednisolone. In addition to this therapy, the experimental group received beclomethasone dipropionate via a metered dose inhaler (MDI) 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 application¹⁶ 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 PEFr and a more rapid discharge rate in the ones who had received budesonide. This difference might be due to the type and form of inhaled steroid that has been used [15,16].

One study investigated children in this respect. It was conducted by Sung et al [17]. 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 prednisolone 1 mg/kg orally and nebulized salbutamol (0.15 mg/kg) every 30 minutes for three doses and then every hour for four 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 PIS. 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 PASS and a more rapid discharge rate but we observed an additional improvement in PEFr which was not investigated in that 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 [3].

In that 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 3 doses. The investigators reported that children in the intervention group showed greater improvements in PEFr. The results were similar to ours with respect to showing the additional of inhaled budesonide to salbutamol in increasing the PEFr in children but we observed a more rapid discharge rate which was not investigated in that study.

Conclusion

The immediate effects of nebulized budesonide in addition to systemic steroids and nebulized salbutamol in improving the PEFr and duration of hospital stay in asthmatic children are encouraging for further study of its routine use in the paediatric emergency department.

Disclosure

All the authors declared no competing interest.

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