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Effects of Nebulized Budesonide as an Adjunct to Standard Treatment of Asthma Exacerbations: A Randomized, Double-Blind, Placebo-Controlled Trial

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This study was done to determine the effects and outcome of inhaled budesonide in addition to standard management of asthma exacerbations in pediatric age groups. A randomized, double-blind, placebo controlled trial was done in a tertiary care urban hospital. Sixty six children aged 5 to 15 years with moderate to severe asthma exacerbations were eligible. All patients received a single dose of prednisolone 1mg/kg orally as first dose of systemic corticosteroids and then salbutamol (0.15mg/kg) and ipratropium bromide (500mcg) was nebulized every 20 minutes for 3 doses and then hourly for 2 hours as a part of standard treatment of asthma exacerbations. The intervention was 2mg (4mL) of budesonide or 4mL of normal saline which was nebulized immediately after the 1st dose of nebulized salbutamol and ipratropium bromide. The baseline characteristics of the budesonide group (n=33) and placebo group (n=33) were similar, but at 1 hour, 2 hour and 3 hour PEFR, respiratory rate, pulse rate, SaO_2 and asthma score were significantly improved in the budesonide group compared to placebo group ($p<0.01$). The positive immediate effect of nebulized budesonide added to standard treatment of asthma exacerbations is an encouraging finding for further investigations of its routine use in the treatment of asthma exacerbations in children.

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Key words: Nebulized budesonide, Asthma exacerbations, Children

Introduction

Asthma is a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyper responsiveness, and an underlying inflammation. Asthma exacerbations are acute or sub acute episodes of progressively worsening shortness of breath, cough, wheezing, chest tightness or some combination of these symptoms[1]. Asthma is common in people of all ages in countries throughout the world. The global prevalence of asthma ranges from 1 to 18% of the population in different countries[2]. In Bangladesh the prevalence of asthma is 6.9%. The prevalence of asthma in children (5-14 years) is higher than in adults[3]. All patients with asthma are at risk for acute exacerbations[4]. In the United States, over 60% of childhood asthmatics experience exacerbations at least once per year[5]. Risk factors for asthma exacerbations are acute viral respiratory infections, aeroallergen exposure, airborn pollutants, tobacco smoke and psychological stress[6]. Recommendations for treatment of asthma exacerbations include the use of selective b2-agonists, ipratropium bromide (IB), and systemic corticosteroids (SCS)[1].

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Intravenous (IV) and oral corticosteroids (CS) appear to have equivalent effects[7]. Systemic corticosteroids improve pulmonary function and reduce hospitalizations, but require 4-6 hours to reach peak effect[7,8].

This time delay is due to changes in gene transcription and altered protein synthesis (genomic effect)[9]. Many studies published in last 15 years have shown therapeutic early effects (after minutes of its administration) of inhaled corticosteroids (ICS) suggesting a different mechanism of action of topical character (nongenomic effect)[10]. Studies also show that asthmatics present a significant increase in airway mucosal blood flow in comparison with healthy subjects (24 to 77% higher in asthmatics), and that inhalation of fluticasone (880μg) or budesonide (400μg) decreases blood flow in both groups[11,12,13,14,15,16,17]. Evidence suggests that ICS decrease airway blood flow by modulating sympathetic control of vascular tone, potentiating no-adrenergic neurotransmission in the airway vasculature[14,15]. After release from sympathetic terminals, norepinephrine must be taken up by postsynaptic cells for inactivation by intracellular enzymes. Because uptake of norepinephrine is inhibited by CS, this could lead to an increased norepinephrine concentration at the neuromuscular junction explaining the CS-induced vasoconstriction[18]. Furthermore, this decrease of airway blood flow is likely to enhance the action of inhaled bronchodilators by diminishing their clearance from the airway[19]. Thus, simultaneous administration of ICS and bronchodilators could be of clinical significance[18].

Inhaled corticosteroids are recommended for long-term control of persistent symptoms.[1] However, recent data indicate that ICS used in the acute setting may have an additive effect to SCS[20,21,22,23], perhaps due to a more rapid effect on topical plasma membrane-based vasoconstriction[24]. A recent Cochrane systematic review of ICS use in acute asthma calls for further study in this area[25].

Budesonide inhalation suspension (BUD) is the only nebulized corticosteroid approved for use in children in the United States[26]. Studies of BUD in children with asthma exacerbations report a more rapid improvement in oxygen saturation, respiratory rate, heart rate, peak expiratory flow rate (PEFR), and asthma scores, when compared to or combined with SCS[21,22,23]. Children treated with BUD are reported to be suitable for discharge from the hospital earlier[21,23]. No dose-related adverse effects were apparent among the patients treated with budesonide for short duration. There were no differences in the incidence, severity, or types of adverse events reported among the BUD and placebo groups[27]. If budesonide nebulisation improve the clinical condition of asthma exacerbations more rapidly and reduce hospital admission or stay it would highly be cost effective[28].

Our hypothesis was that adding a single, 2-mg dose of inhaled budesonide to standard treatment of asthma exacerbations provides early and greater clinical improvement in children compared to standard therapy alone. If adding ICS to standard treatment of asthma exacerbations improves symptoms more rapidly, it would be an important adjunct to standard treatment of asthma exacerbations.

Methods

This double-blind, placebo-controlled, randomized clinical trial was done on children (5 to 15 years) with asthma exacerbations in the Department of Paediatrics, Mymensingh Medical College Hospital, from 1st November 2011 to 31st October 2012.

Inclusion criteria: i) Children with age range from 5 to 15 years, ii) Children of either sex with asthma exacerbations having asthma score 8 or greater (Table I), iii) Capable of measuring PEFR.

Exclusion criteria: i) Any evidence of respiratory tract infection or suppurative lung disease, ii) Any history or evidence of cardiac, renal or hepatic dysfunction, iii) History of use of steroid within last seven days, iv) Having altered level of consciousness, v) Have been enrolled in the study previously.

Operational definition

i) Asthma: At least two prior episodes of wheezing and dyspnea requiring bronchodilator therapy[26].

ii) Asthma exacerbations: An asthma exacerbation was defined as an episode of wheezing for which the patient needed an emergency visit to a hospital or a physician[29].

Table I: Asthma severity score[30]

Variables	Asthma Scoring		
	1 Point	2 Points	3 Points
Respiratory rate			
2-3 years	≤34	35-39	≥40
4-5 years	≤30	31-35	≥36
6-12 years	≤26	27-30	≥31
>12 years	≤23	24-27	≥28
O_2 saturation (%)	>95 on room air	90-95 on room air	<90 on room air or with supplemental oxygen
Wheeze	Normal or end expiratory wheeze	Expiratory wheeze	Inspiratory and expiratory wheeze, diminished breath sounds, or both
Retractions	None or intercostals	Intercostal and substernal	Intercostal, substernal, and supraclavicular
Dyspnea	Speaks in sentences or coos and babbles	Speaks in partial sentences or utters short cries	Speaks in single words or short phrases or grunts

They were distributed randomly by lottery, 33 patients fall in nebulized budesonide with standard therapy group and the rest 33 in Placebo (nebulized normal saline) with standard therapy group i.e., Placebo group.

Sample size was calculated by following formula[31]:

$$n = \frac{P_1(1-P_1)+P_2(1-P_2)}{(P_1-P_2)^2} \times (Z_\alpha + Z_\beta)^2$$

Where,
n= sample size for each group
P_1=Proportion of patients developing outcome in control group
P_2=Proportion of patients developing outcome in treatment group
$Z\alpha$ =Z-value (two tails) at a definite level of significance e.g. 1.96 at 5% level of significance
$Z\beta$= Z-value (one tail) at a definite power e.g. 1.64 at 95% power (when β=0.05)
Here
P_1=33.3%=0.333 [Devidayal et al.[21] found good response in 33.3% patients in prednisolone group i.e. >70% PEFR (% of predicted)]
P_2=73.3%=0.733 we expected that there would be a 40% (effect size) absolute improvement for those on the study therapy[32] (i.e. 73.3% of the subjects will have a successful outcome).
So,

$$n = \frac{0.333(1-0.333)+0.733(1-0.733)}{(0.333-0.733)^2} \times (1.96+1.64)^2$$

=32.98
So sample size is=33×2=66
There was no drop out.

This study was approved by the research ethics committee at Mymensingh Medical College Hospital, and informed consent was obtained from all participants prior to enrollment.

Every patient received standard asthma exacerbations therapy while the guardian was approached for consent to participate in the study. This therapy included prednisolone 1mg/kg orally

and nebulized salbutamol (0.15mg/kg), nebulized ipratropium bromide (500mcg) and supplemental oxygen to maintain an oxygen saturation >92%. Then they were divided randomly into experimental group or placebo group by lottery. The randomization sequence remained concealed to all study personnel until the conclusion of the study and beginning of data analysis. To maintain blinding the study medications (Budisonide nebulizer solution or Normal saline) were administered by a physician other than the investigators. He placed the study medication into shielded nebulization chamber in the absence of the investigators. Immediately after the 1st dose of nebulized salbutamol and IB, 2mg/4ml of budesonide was nebulized[26,33] to experimental group and 4ml of normal saline (NS) was nebulized to placebo group .

Just after giving the nebulized budesonide or NS, 2nd dose of salbutamol and ipratropium bromide was nebulized and 20 minutes after the start point of 2nd dose, 3rd dose of salbutamol and ipratropium bromide was nebulized and then they were nebulized hourly for two hours[1].

Measures

PEFR, respiratory rate, pulse rate, SaO_2 and asthma score were obtained at study entry and then hourly upto 3 hours. Additional baseline data collected included patient demographics, clinical asthma history, and prior treatments.

Peak expiratory flow rate was measured by using a peak flow meter. The best of three successfully performed maneuvers was accepted.

Data were analyzed by SPSS 14.0 (Statistical package for social sciences). Initially the base line characteristics between the two groups were compared. Then the changes in the PEFR, pulse rate, respiratory rate, SaO_2 and asthma score were compared at 1, 2 and 3 hours after administration of study drug. Unpaired Student's 't' tests were used to compare means between two groups. Chi-square analysis was done to compare distribution of age, sex, family history of asthma, medication and presenting symptoms and signs. Confidence interval was set at 95% level. Results were considered to statistically significant at P value <0.05.

Results

A total of 66 consecutive children who presented to the pediatric wards with asthma exacerbations were considered for the study. Thirty three patients were assigned to the budesonide group and another thirty three patients were assigned to the placebo group.

In the budesonide group, 20 patients were male and 13 patients were female. On the other hand in the placebo group 19 patients were male and 14 patients were female. The baseline demographic and clinical characteristics of the two groups were similar (Table II & III).

Both study groups improved with treatment. However, in budesonide group the improvement in PEFR, respiratory rate, pulse rate, SaO_2 and asthma score was significantly more ($p<0.05$) (Table IV).

There were no adverse events in children in both groups.

Table II: Baseline characteristics of patients (n=66)

Parameters	Budesonide Group (n = 33) mean±SD	Placebo Group (n=33) mean±SD	P value*
Age (years)	8.44±2.16	8.38±2.11	0.945 NS
Height (inch)	48.18±4.21	48.27±4.32	0.851 NS
Weight (kg)	21.33±4.95	21.03±4.97	0.811 NS
Duration of asthma (years)	2.38±0.82	2.35±0.81	1.000 NS
Asthma score	11.36±1.41	11.25±1.21	0.0541 NS

* Unpaired student's "t" test; NS= not significant

Table III: Presenting symptoms and signs (n=66)

Parameters	Budesonide Group (n = 33)		Placebo Group (n=33)		P value*
	No.	(%)	No.	(%)	
Breathlessness during					
Talking	24	72.70	25	75.80	0.778 NS
Resting	09	27.30	08	24.20	
Physical exhaustion					
Yes	03	9.10	02	06.10	0.642 NS
No	30	90.90	31	93.90	
Speaks in					
Sentences	00	00	00	00	
Partial sentences	26	78.80	27	81.80	0.757 NS
Wards	07	21.20	06	18.20	
Wheeze					
Expiratory	28	84.80	29	87.90	0.720NS
Expiratory and inspiratory	05	15.20	04	12.10	
Retractions					
Intercostal	02	06.10	04	12.10	
Intercostal and substernal	30	90.90	29	87.90	0.431 NS
Intercostal, substernal and supraclavicular	01	03.0	00	0.00	
Pulse (per minute) 100-160	33	100	33	100	a
PEFR (% of predicted value) 40-60	33	100	33	100	a
SaO_2					
94-90%	30	54.50	25	45.50	0.093 NS
<90%	03	27.30	08	72.70	

*Chi-square test; NS= not significant; a = No statistics computed because both group had same value.

Table IV: Out come (at 1hr, 2hr & 3hr) compared with base line (Mean±SD)

Parameters		PEFR (% of predicted value)	Respiratory rate/min	Pulse rate/min	SaO_2 (%)	Asthma score
At base line	Group A	49.50±1.55	39.94±7.77	122.91±11.01	91.00±1.85	11.36±1.41
	Group B	50.79±3.69	39.82±6.64	124.12±8.3	91.09±1.59	11.25±1.21
	*P value**	*0.068NS*	*0.946NS*	*0.616NS*	*0.831NS*	*0.054 NS*
1 hour	Group A	76.63±1.38	24.97±3.25	102.18±6.58	95.15±0.71	7.36±1.03
	Group B	69.30±1.13	27.82±4.10	109.09±5.48	94.12±0.89	9.18±1.01
	*P value**	*<0.01***	*<0.01***	*<0.01***	*<0.01***	*<0.01***
2 hour	Group A	77.42±1.23	23.55±2.77	88.42±5.36	95.55±0.71	5.91±0.52
	Group B	71.42±1.09	25.27±3.35	96.85±5.24	94.45±0.83	7.30±1.05
	*P value**	*<0.01***	*<0.01***	*<0.01***	*<0.01***	*<0.01***
3 hour	Group A	78.58±1.06	22.42±1.79	83.64±3.86	95.94±0.35	5.42±0.50
	Group B	72.36±0.99	24.48±2.74	93.52±4.56	94.76±0.66	6.36±0.70
	*P value**	*<0.01***	*<0.01***	*<0.01***	*<0.01***	*<0.01***

Group A: Budesonide group; Group B: Placebo group

*Unpaired Student's "t" test; NS = not significant, ** = significant.

Discussions

In this study children with moderate-to-severe asthma exacerbations found significant improvement in the PEFR, respiratory rate, pulse rate, SaO_2 and asthma score when nebulized budesonide was added to standard therapy of asthma exacerbations including SCS. Some studies comparing ICS to SCS in asthma exacerbations reported improvements in asthma scores[21,34] or pulmonary function tests (PFTs)[21,29,35,] and reduced length of hospital stay[29,36] in children with ICS. In a Cochrane systematic review, Edmonds et al.[25] concluded that the use of ICS for asthma exacerbations in the emergency department (ED) was associated with small improvements in peak expiratory flows and forced expiratory volumes and a decreased risk of hospitalization. To date, the role of ICS as an adjunct to standard treatment of asthma exacerbations has been unclear. The Cochrane review included two studies in which ICS were given in addition to SCS. Sung et al.[23] conducted a trial in children with asthma exacerbations using prednisolone plus BUD and found that the use of budesonide with prednisolone was associated with some interesting tendencies with improved Pulmonary Index Score (PIS) at 1 hour and a more rapid discharge rate from the hospital. Nuhoglu et al.[22] reported an increase in peak expiratory flow rate in pediatric patients with moderate asthma exacerbations treated with methylprednisolone plus BUD when compared to treatment with methylprednisolone plus placebo. Upham et al.[26] found that budesonide added to standard treatment of asthma exacerbations did not improve asthma score or other short-term ED based outcome. In their study they did not measure PEFR. Abdullah et al.[28] found that the addition of budesonide nebulization to standard treatment of asthma exacerbations decrease the admission rate of children with severe asthma exacerbations.

Limitations of the study

Spirometry was not done. Duration of hospital stay and subsequent follow up not done. The study was of short duration. This was a single centered study.

Conclusion

The effect of nebulized budesonide in addition to systemic steroids, nebulized salbutamol and nebulized IB in improving the PEFR, respiratory rate, pulse rate, SaO_2 and asthma score in children with asthma exacerbations is an encouraging this finding needs further investigations of its routine use in the treatment of asthma exacerbations in children.

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