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Original Research Article

To evaluate the efficacy of nebulized budesonide compared to oral prednisolone in the management of moderate exacerbation of acute asthma

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ABSTRACT

Background: Corticosteroids are extremely effective drugs and are used extensively in the management of asthma. Inhaled corticosteroids may offer some benefit in patients with mild to moderate obstruction in acute exacerbation and also offer the advantage of administration directly to the lungs. Hence this study was done to evaluate the efficacy of nebulized budesonide as compared to oral prednisolone in the management of moderate exacerbation of acute asthma.
Methods: A total of 80 children attending pediatric emergency of SMGS Hospital Jammu aged 1 to 18 years with a moderate exacerbation of asthma despite three salbutamol nebulizations were enrolled and randomized into two groups. First group recieved nebulized budesonide (800 mcg) at hourly intervals for three doses followed by twice a day (n=37) while second group recieved oral prednisolone 2 mg/kg/day in two divided doses (n=43). Both groups continued to receive oxygen inhalation and nebulized salbutamol (0.15 mg/kg/dose) initially at hourly intervals for 3 doses followed by 6 hourly. The pattern of response as observed by the pulmonary scores in the two groups was compared.
Results: The pulmonary scores were significantly improved at 1, 2 and 6 hours after starting treatment in the budesonide group as compared to prednisolone group ($p < 0.01$) although the difference was not significant after 12 hours. Oxygen saturation also showed a significant early improvement.
Conclusions: This early demonstrable significant improvement in the clinical parameters of the inhaled budesonide group apparently suggests that inhaled budesonide may be efficacious in treating moderate exacerbations of asthma.

Keywords: Asthma, Budesonide, Exacerbation, Pulmonary score

INTRODUCTION

Asthma is defined as a chronic inflammatory condition of the lung airways resulting in episodic airflow obstruction. It causes considerable morbidity affecting approximately 14% boys and 10% girls during childhood with 5-8% having an attack of asthma in preceding 10 months.[1] Asthma exacerbations are defined as episodes of progressively worsening dyspnea, cough, wheezing, or combination of any of these symptoms. These are characterized by a decrease in expiratory airflow. The primary treatment for exacerbations is the repetitive administration of beta-2 agonists and systemic corticosteroids. The exacerbations are treated depending upon their severity. Initially beta-2 agonists are used alone and corticosteroids are added in case the response is not prompt and sustained.[2] Corticosteroids are extremely effective drugs and are used extensively in the management of asthma. These help in reducing airway inflammation that is pathognomic of the patients with

asthma. Corticosteroids act on almost all mechanisms of inflammation which include modulation of cytokine and chemokine production, inhibition of eocasanoid synthesis, marked inhibition of accumulation of eosinophils, basophils and other leucocytes in lung tissue and decreased vascular permeability.[3] Systemic corticosteroids including both parenteral and oral steroids have been used in acute asthma exacerbations. The use of systemic corticosteroids may have some disadvantages especially in children. Parenteral administration of any drug to a child is cumbersome, time-consuming and painful. On the other hand, orally administered steroids may be refused by children or vomited out and hence may result either in a significant delay or failure in therapy.[4]

Prednisolone is one of the commonly used oral steroid in asthma. It has the advantage of having a very high glucocorticoid effect and only a weak mineralocorticoid effect. The bio-availability of oral prednisolone is variable and estimated to be about 50-80 %. It is metabolized in the liver. Prednisolone has a significant anti-inflammatory effect in asthma. It has multimodal action that includes a reduction in the numbers of various cells like eosinophils, mast cells, T cells and modulation of interleukin 4, interleukin 5, and interferon gamma cytokine expression in the bronchial mucosa resulting in reduced inflammation of the airways.[5] On the other hand budesonide is a locally active steroid given by inhalational route. It has very less systemic effects due to extensive first pass metabolism.[6] It has also got a proven safety record in chronic asthma over the years in all age groups.

Current literature suggests that inhaled corticosteroids may offer some benefit in patients with mild to moderate obstruction in acute exacerbation and also offer the advantage of administration directly to the lungs.[7-9] Hence this study was carried out to compare the efficacy of inhaled budesonide versus oral prednisolone in patients of moderate asthma exacerbations who fail to show prompt and complete improvement after initial treatment with oxygen and three doses of inhaled beta agonist.

METHODS

We conducted a prospective randomized comparative trial in children between 1 and 18 years with a diagnosis of acute exacerbation of Asthma attending emergency of SMGS hospital Jammu. A written informed consent was obtained from the caregiver of the participant.

Inclusion criteria

- The presence of asthma exacerbation was accepted if there was: (a) Appearance or increased frequency of cough, wheezing, dyspnea or any combination of these. (b) At least a twofold increase in mean daily bronchodilator requirement for last 24 hours.
- Pulmonary score more than or equal to 4 after three doses of nebulized salbutamol given over one hour.
- Age between 1 and 18 years.

Exclusion criteria

- Presence of any other congenital or acquired pulmonary/ cardiac disease, diseases affecting compliance of chest wall, moderate/Severe Anemia.
- Presence of red flag signs a) Alterd sensorium (drowsy or very agitated), b) Shock, c) Cyanosis, d) Excessive use of accesory muscles or state of exhaustion (vocalization limited to 1-2 words, e) Excessive diaphoresis, f) Silent chest on auscultation, g) SaO_2 on room air <92%, h) ABG: rate of rise of pCO_2 >5mm Hg/hr, pCO_2 >40 mmHg, pO_2 <60 mm Hg, metabolic acidosis/Severe attack of acute Asthma Exacerbation (Pulmonary Score more than or equal to 7).
- History of systemic Corticosteroids use in past 48 hours.

Therapy protocol

The participants were randomized into two groups.

Group I

These patients continued to recieve oxygen inhalation 5-6 litre/min, inhaled salbutamol 0.15 mg/kg diluted 1:2 times with normal saline every hour for 3 hours followed by 6 hourly and inhaled corticosteroids in the form of nebulised budesonide 800 µgm every hour for 3 times and in case of response, was followed by 800 µgm 12 hourly for 3 to 5 days.

Group II

These Patients continued to recieve oxygen inhalation 5-6 litre/min, inhaled salbutamol 0.15 mg/kg diluted 1:2 times with normal saline every hour for 3 hours followed by 6 hourly, and oral prednisolone 2 mg/kg/day rounded off to nearest 5 mg in two divided doses for 3 to 5 days.

Evaluation of Patient before and after treatment was done. Patients having inadequate or no response to the above treatment were treated with continuous salbutamol nebulization (0.30 mg/kg/h), Ipratropium nebulisation, intravenous (IV) hydrocortisone/other steroids and IV aminophylline. Inadequate or no response to the above was an indication for one dose of IV magnesium sulphate (50 mg/kg). The need for injectable steroids was also recorded in either of the groups and outcome compared.

Respiratory status evaluation

This was done before instituting treatment and after 1 hour, 2 hours, 4 hours, 6 hours, 12 hours and 24 hours of starting treatment. The parameters used for evaluation of respiratory status were as follows: respiratory rate (RR),

heart rate (HR), pulsus paradoxus, accessory muscle usage, wheezing, and oxygen saturation (SaO_2). The above assessment was also used to calculate pulmonary score. Respiratory rate was counted by observing abdominal and thoracic wall movements for 1 min when the child was at rest. Heart rates and SaO_2% were monitored with the help of a hand-held pulse oximeter. Pulsus paradoxus was measured with a sphygmomanometer and stethoscope.

Statistical analysis

The data was collected and analyzed with the help of computer software MS Excel and SPSS 12.0 for windows. Mean Score and standard deviation was calculated and reported. Baseline comparability between the groups was evaluated using Chi squre 't' test. Statistical significance between pulmonary scores was assessed by the use of student 't' test. A p- value of <0.05 was considered as statistically significant. All p- values reported are two tailed. The analysis was undertaken according to intent to treat principle.

RESULTS

During the study period from november 2009 to december 2010 a total of 214 patients suffering from acute attack of asthma attended the pediatric emergency. 80 patients found eligible for study were randomized into two groups. Group I comprised of 37 patients and group II comprised of 43 patients. All the 80 children who were randomized, completed the study and had all the evaluations performed.

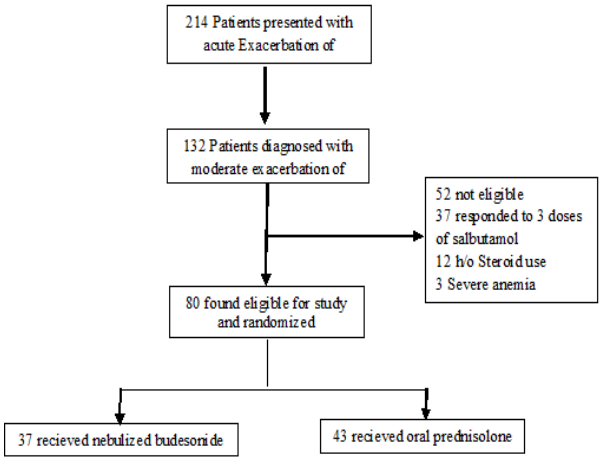

Figure 1: Number of participants.

General characteristics were comparable between the two groups (Table 1). Number of children in different age groups were comparable between the two groups. The two groups were also comparable for other baseline characteristics including anthropometry and clinical characteristics.

The mean heart rates, respiratory rates, SaO_2 and pulmonary scores did not show any significant difference between the two groups. After initiation of treatment the pulmonary scores decreased in both the groups. The decrease was significantly more in group I than in group II at 1 hour (4.2±0.9 Vs 5±0.7), 2 hours

Table 1: Baseline characteristics, anthropometry, vital signs and pulmonary scores in the two study groups.

	Group I (n=37)	Group II (n=43)		p-value
M/F	25/12	27/15	0.13*	0.71
No. of patients (years)				
1 to 5	18	24		
6 to 10	10	11		
>10	9	8		
Mean age (years)±SD	6.22±3.7	5.59±3.6	0.76**	0.45
Mean weight (kg)±SD	19.19±9.2	18.88±10.9	0.13**	0.89
Mean height (cms)±SD	109.5±20.6	106.5±20.3	0.65**	0.52
Mean BMI kg/sq m±SD	15.09±1.8	15.33±2.2	-0.51**	0.61
Mean duration of disease (years)±SD	3.65±2.9	3.49±2.5	0.27**	0.79
Mean no. of ep. in last 6 months±SD	1.3±1.1	1.2±0.8	0.21**	0.83
Heart rate (HR)/min	126±9.5	127±7.5	-1.01	0.31
Respiratory rate (RR)/min	47±8.2	45±7.2	1.43	0.16
SaO_2%	93±1.2	93±1.1	0.72	0.48
Pulmonary score	5.4±0.7	5.3±0.7	0.63	0.53

*=Chi square; **=t test; ***=p by fisher exact test; p>0.01(non-significant for all characteristics)

4 hours (3±0.8 Vs 3.7±0.7) and 6 hours (2.5±1 Vs 3.1±0.8) after starting treatment. The difference was not significant at 12 hours (1.8±1 vs 2.3±0.7) and 24 hours (1.1±1 Vs 1.7±0.8). Similarly, other outcome variables

like Respiratory rate and oxygen saturation also showed significant improvement in group I as compared to group II.

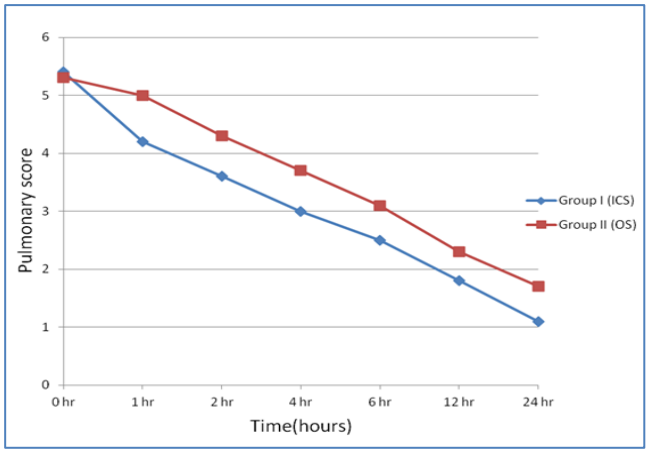

Figure 2: Comparison of the mean pulmonary scores between the two groups after starting treatment.

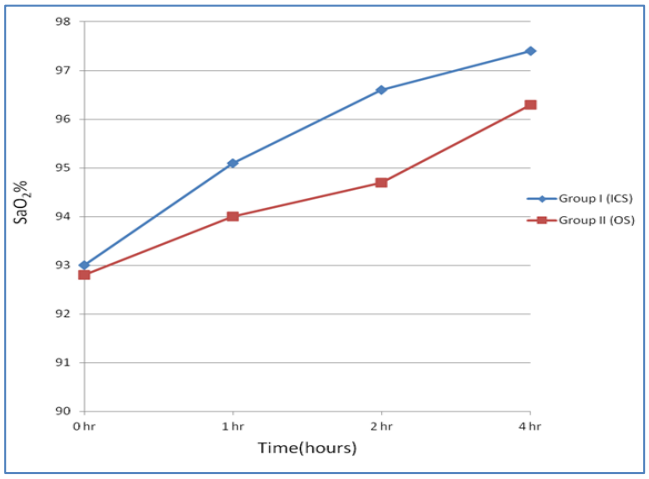

Figure 3: Comparison of the mean arterial saturation of O_2 between the two groups after starting treatment.

DISCUSSION

The results indicate that patients who were not on corticosteroid therapy prior to the attack experienced an early and significant improvement in all the clinical parameters including the pulmonary score when treated with budesonide as compared to prednisolone. The differences in pulmonary score ceased to be significant after some time. This is supported by the fact that the rapid effects of inhaled corticosteroids are initiated by specific interaction with membrane bound or cytoplasmic corticosteroid receptors or non-specific interaction with the cell membrane and the effects are much more rapid occuring in seconds to minutes.[10] Budesonide nebulisation was well tolerated in all age groups without any major side effects. These findings suggest that inhaled corticosteroids may be helpful in an earlier recovery in acute exacerbation although further deliberations are needed.

In the past many studies have conclusively proven repetitive or continuous administration of short acting bronchial agonists (SABA's) to be the most effective means of reversing airflow obstruction.[11-13] However, corticosteroids are needed in Patients who are suffering from moderate or severe exacerbation and in patients who do not show complete response to SABA therapy. These medications speed the resolution of airflow obstruction and reduce the rate of relapse and reduce hospitalizations.[14,15] Oral prednisolone has effects equivalent to those of intravenous methyl prednisolone and is usually preferred as the administration is easier.[16,17]

There is no consensus on the dose and dosing schedule of inhaled budesonide in exacerbations of asthma. The dose schedule of budesonide has been varying in previous studies with doses of 500 to 1000 mcg/dose and a cumulative dose of 2000 to 3000 mcg. In the absence of recommended dosing schedule of inhaled corticosteroids in exacerbations of asthma the dose of budesonide (800 mcg) selected for this study with a cumlative dose of 2400 mcg was similar to some of the previous studies.[18] Inhaled budesonide has also been shown to decrease the airway blood flow and hence it may diminish the clearance of bronchodilators from airways thus enhancing their action.[19] This vasoconstriction peaks between 30 and 60 minutes after the administration of inhaled corticosteroids thus to maximize the effect of bronchodilators, inhaled corticosteroids should administered along with bronchodilators in a similar repetitive dose fashion.[20]

Many studies have been carried out in the past comparing inhaled corticosteroids to placebo and have demonstrated earlier clinical improvement in terms of favourable reduction in pulmonary scores, improvement in oxygen saturation and decreased hospitalization rate in inhaled steroid group.[21-24] Similar rapid beneficial effects of inhaled steroids as compared to oral steroids have also been observed in other previous studies comparing inhaled corticosteroids with systemic corticosteroids.[4,25-27] But there is a marked heterogeneity in the doses of inhaled corticosteroids and study protocols used in these studies. Hence larger trials are warranted to confirm the efficacy of inhaled corticosteroids and arrive at an optimum dose and dosing schedule in patients of acute exacerbation of asthma.

There were some limitations in the present study that merit discussion. No objective measure of lung function test was applied in the present study as most of the children enrolled in the study were too young for such measurements. Even in older children only 65 percent of children 5-18 years of age can complete FEV1/PEF measurements during an acute exacerbation, and for children less than 5 years old, the manoeuvres are almost impossible.[28] Further teaching of these manoeuvres to a

child for the first time during an exacerbation might waste precious time during management. Hence pulmonary score shown to have an excellent correlation with these measurements and easily clinically applicable was used in our study.[29]

CONCLUSION

We conclude that though the therapeutic effects of inhaled budesonide and oral corticosteroids are observed to be almost similar, there was an early demonstrable significant improvement in the clinical parameters of the inhaled budesonide group in our study. Further as the administration of inhaled budesonide is non-invasive, convenient, painless and an easy procedure for both, the treating physician as well as the patient, apparently suggest that inhaled budesonide may find place in the management protocol of moderate exacerbations of asthma in children. However, in the modern era of evidence based medicine larger trials are warranted to derive optimum dosing schedule and to confirm its efficacy so that it can be incorporated into future management guidelines.

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

REFERENCES

1. Liu AH, Covar RA, Spahn JD, Leung DYM. Childhood Asthma. In: Kliegman, Behrman, Jenson, Stanton, eds. Nelson textbook of paediatrics 18th ed. International ed; 2007:chapter-143.
2. Expert panel report-3. Guidelines for diagnosis and management of Asthma-summary report 2007. J Allergy Clin Immunol. 2007;120:S94-138.
3. Schleimer RP. Glucorticoids,their mechanism of action in allergic diseases. In: Allergy:principles and practice. 5th ed.1998;6:638-60.
4. Scarfone RJ, Loiselle JM, Wiley JF 2nd, Decker JM, Henretig FM, Joffe MD. Nebulized dexamethasone versus oral prednisone in the emergency department of Asthmatic Children. Ann Emerg Med. 1995;26:480-6.
5. Bentley AM, Hamid Q, Robinson DS, Schotman E, Meng Q, Assoufi B, et al. Prednisolone treatment in Asthma. Reduction in the numbers of eosinophils, T cells, tryptase-only positive mast cells, and modulation of IL-4, IL-5, and interferon-gamma cytokine gene expression within the Bronchial mucosa Am. J. Respir. Crit. Care Med. 1996;153(2): 551-6.
6. Pedersen S, Steffensen G, Ekman I, Tonnesson M, Borga O. Pharmacokinetics of Budesonide in Children with Asthma. Eur J Clin Pharmacol. 1987;31:579-82.
7. Rowe BH, Spooner C, Ducharme F, Bretzlaff J, Bota G. Corticosteroids for preventing relapse following Acute Exacerbations of Asthma (Cochrane review). In: The Cochrane Library, Version 4. Oxford: Update Software; 2003.
8. Hendeles L, Sherman J. Are Inhaled Corticosteroids effective for Acute Exacerbations of Asthma in Children? J Pediatr. 2003;142:S26-33.
9. Rodrigo GJ. Rapid effects of inhaled corticosteroids in acute asthma: an evidence-based evaluation. Chest J. 2006;130:1301-11.
10. Kumar SD, Brieva JL, Danta I, Wanner A. Transient effect of inhaled fluticasone on airway mucosal blood flow in Subjects with and without Asthma. Am J Respir Crit Care Med. 2000;161:918-21.
11. Camargo CA Jr, Spooner CH, Rowe BH. Continuous versus intermittent beta-agonists in the treatment of acute Asthma. Cochrane Database Syst Rev. 2003b;(4):CD001115.
12. Karpel JP, Aidrich TK, Prejant DJ, Guguchev K, Gaitan-Salas A, Pathiparti R. Emergency treatment of acute Asthma with albuterol metered-dose inhaler plus holding chamber: how often should treatments be administered? Chest. 1997;112(2):348-56.
13. McFadden E Jr. Acute severe Asthma. Am J Respir Crit Care Med. 2003;168(7):740-59.
14. Edmonds ML, Camargo CA Jr, Pollack CV Jr, Rowe BH. Early use of Inhaled Corticosteroids in the emergency department treatment of acute Asthma. Cochrane Database Syst Rev 2003;(3):CD002308.
15. Rowe BH, Edmonds ML, Spooner CH, Diner B, Camargo CA Jr. Corticosteroid therapy for acute Asthma. Respir Med. 2004;98(4):275-84.
16. Harrison BD, Stokes TC, Hart GJ, Vaughan DA, Ali NA, Robinson AA. Need for intravenous hydrocortisone in addition to Oral Prednisolone in Patients admitted to hospital with severe Asthma without ventilatory failure. Lancet. 1986;1(8474):181-4.
17. Ratto D, Alfaro C, Sipsey J, Glovsky MM, Sharma OP. Are intravenous Corticosteroids required in status Asthmaticus? JAMA. 1988;260(4):527-9.
18. Devidayal, Singhi S, Kumar L, Jayshree M. Efficacy of Nebulized Budesonide compared to Oral Prednisolone in Acute Bronchial Asthma. Acta Paediatr. 1999;88:835-40.
19. Kelly L, Kolbe J, Mitzner W, Spannhake EW, Bromberger-Barnea B, Menkes H. Bronchial blood flow affects recovery from constriction in dog lung periphery. J Appl Physiol. 1986; 60:1954-9.
20. Mendes ES, Pereira A, Danta I, Duncan RC, Wanner A. Comparative Bronchial vasoconstrictive efficacy of inhaled Glucocorticosteroids. EurRespir J. 2003;21:989-93.
21. Sung L, Osmond NH, Klassen TP. Randomized, controlled trial of inhaled Budesonide as an adjunct o oral prednisone in acute Asthma. Acad Emerg Med. 1998;5:209-13.
22. Singhi S, Banerjee S, Nanjundaswamy H.Inhaled Budesonide in acute Asthma. J Paediatr Child Health. 1999;35(5):483-7.

23. Estrada-Reyes E, Del Rio-Navarro BE, Rosas Vargas MA, Nava Ocampo AA. Co-administration of Salbutamol and fluticasone for emergency treatment of Children with moderate acute Asthma. Pediatr Allergy Immunol. 2005;16:609-14.
24. Sekerel BE, Sackesen C, Tuncer A, Adalioglu G. The effect of Nebulized Budesonide treatment in Children with mild tomoderate Exacerbations of Asthma. Acta Paediatr. 2005;94:1372-7.
25. Volovitz B, Bentur L, Finkelstein Y,Mansour Y, Shalitin S, Nusssinovitch M, et al. Effectiveness and safety of Inhaled Corticosteroids in controlling acute Asthma attacks in Children who were treated in the emergency department: a controlled comparative study with Oral Prednisolone. J Allergy Clin Immunol. 1998;102:605-9.
26. Matthews EE, Curtis PD, McLain BI, Morris LS, Turbit ML. Nebulized Budesonide versus oral steroid in severe Exacerbations of Childhood Asthma. Acta Paediatr. 1999;88(8):841-3.
27. Milani GKM, Rosario Filo NA, Riedi CA, Figueiredo BC. Nebulized Budesonide to treat acute Asthma in Children. J Pediatr (Rio J). 2004;80:106-12.
28. Gorelick MH, Stevens MW, Schultz T, Scribano PV. Difficulty in obtaining peak expiratory flow measurements in children with acute asthma. Pediatr Emerg Care. 2004;20(1):22-6.
29. Becker A, Nelson N, Simons F. The Pulmonary Index: Assessment of a clinical Score for Asthma. Am J Dis Child. 1984;38:574-6.

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