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Nebulized budesonide to treat acute asthma in children

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Abstract

Objective: To investigate the efficacy of a single dose of inhaled budesonide as compared to oral prednisone in patients with acute asthma.

Methods: Randomized double-blind, double-dummy and placebo-controlled clinical trial. Forty-nine children aged 2 to 7 years with acute asthma were randomized in three groups after receiving nebulized salbutamol (0.15 mg/kg). Group I received placebo both as tablets and nebulization, group II was treated with a single dose of oral prednisone (1 mg/kg) and inhaled placebo, and group III received a single dose of placebo tablet and nebulized budesonide (2 mg). Patients were evaluated in terms of symptom score and transcutaneous hemoglobin saturation. Nebulized salbutamol was repeated in case of increasing symptom score or lower saturation.

Results: Progressive clinical improvement was observed in all three groups. However, a significant increase in hemoglobin saturation was observed after 2 hours with prednisone, 4 hours with budesonide, and 24 hours with placebo.

Conclusion: A combination of single-dose nebulized budesonide and salbutamol may be as effective as oral prednisone to improve symptom severity, but the latter increases hemoglobin saturation in exacerbation of asthma.

J Pediatr (Rio J). 2004;80(2):106-12: Budesonide, acute asthma, prednisone, inhaled steroids.

Introduction

Traditionally, asthma has been described as presenting reversible bronchoconstriction, bronchial hyperreactivity and increased mucus production. It is only recently that it has been described as an inflammatory disease, provoking a change of treatment strategy. Greater emphasis is now given to anti-inflammatory medicines.[1]

Glucocorticoids are potent anti-inflammatory agents, effective at controlling asthma and suppressing inflammation of the airways. Despite the exact mechanism by which its molecule functions being unclear, important advances have been made which aid in the understanding of its action.[2-4]

Asthma management consensus documents recommend the use of oral corticoids for moderate acute episodes that do not fully respond or relapse after the use of inhaled b2-agonists . In severe crises the use of corticoids is obligatory.[1,5]

In emergency situations asthma patients should be given systemic corticoids as soon as possible, since recovery is faster and there is a lower risk of both hospitalization and of a fatal asthma crisis.[5]

During acute asthma crises, corticoids are generally administered systemically. Inhaled corticoids are effective for chronic asthma treatment while their role in acute crises has not yet been defined.[6]

Few studies have analyzed the action of inhaled corticoids on acute respiratory diseases. Comparisons of oral corticoids with inhaled corticoids has demonstrated that the two routes are similar in terms of efficacy, but that repeat acute episodes are less common when the medication is inhaled.[7,8]

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The objective of this study was to evaluate the efficacy of budesonide suspension, prepared for inhalation in 2 mg single doses, as an auxiliary treatment to inhaled ß2, compared with single-dose oral prednisone for patients in acute asthma crises.

Methods

Forty-nine children were included, all suffering from moderate, acute asthma crises and who sought treatment at the Pediatric Walk-in Clinic at the Hospital de Clínicas of the UFPR.

Moderate acute asthma crises were defined as the presence of audible wheezing, use of accessory muscles retraction, increased respiratory rate and an inability either to walk or to speak more than three to five words per breath.[5]

Inclusion criteria were: acute asthma crisis having lasted at least 6 hours; a previous history of at least three crises; aged between 2 and 7 years, either sex, clinical asthma crises evaluation score equal to or greater than 8.

Exclusion criteria were: concurrent chronic or acute cardiopulmonary disease; systemic corticoid use during the 14 days prior to the crisis or inhaled corticoid use within the previous 72 hours; severe crises or crises requiring immediate hospitalization (including patients requiring intense effort to breath, altered state of consciousness, bradycardia, room air oxygen saturation of less than 88%, risk of respiratory fatigue); previous history of liver or kidney disease, of congenital heart disease or sickle-cell anemia; concurrent stridor; recurring vomiting, worsening clinical status during the evaluation period.

Patients were split into the following three groups at random (Table 1):

- Group I (n = 15): inhaled and oral placebo.
- Group II (n = 17): inhaled placebo and oral corticoid.
- Group III (n = 17): inhaled budesonide and oral placebo.

This is a double-blind, double-placebo controlled, prospective study. On arrival at the Walk-in Clinic, all patients underwent clinical examinations, the clinical severity score was assessed and average transcutaneous hemoglobin saturation was measured with an oximeter by NONIN (Onyx 9500, NONIN MEDICAL INC; MN - USA).

All patients were treated with an inhaled bronchodilator (salbutamol – 0.15 mg/kg diluted in 3.0 ml of isotonic saline solution) using a nebulizer with a PARI LC plus mouthpiece and valve system (PARIJET, Germany), adapted for the hospital oxygen outlet at a flow rate of 6 l/min. The patients remained seated for an approximate inhalation duration of fifteen minutes.

The clinical severity score evaluations (Table 2) and the hemoglobin saturation measurements were repeated fifteen minutes after inhalation and taken as baselines.

Next, depending on randomization group, each patient received either prednisone at 1 mg/kg or a placebo, orally, from a nurse with n o involvement in the study. Randomization was performed on groups of six patients at the point of recruitment. Medication was stored in identical 1, 5 and 20 mg capsules. In the event that any given patient did not ingest the capsules, its contents were diluted in 3 ml of water, tea or gooseberry flavor fruit drink. If vomiting occurred, the medication was re-administered 15 minutes later.

Table 1 - Characteristics of patients on admission

	Placebo (GI) n = 15	**Prednisone (GII) n = 17**	**Budesonide (GIII) n = 17**
Age (months)	49.6±15.6	51.1±18.7	47.3±16.3
Sex (M : F)	9 : 6	8 : 9	8 : 9
n. of previous admissions	1 (7%)	3 (19%)	3 (19%)
Duration of wheezing (h)	26.1±21.1	16.8±9.9	29.7±28.4
Clinical severity score	10.0±1.7	9.7±1.3	9.9±1.4
O_2 saturation (%)	91.0±2.1	91.6±1.5	91.8±2.0
Heart rate	141.9±13.3	136.2±16.4	133.9±19.4
Respiratory rate	44.2±10.6	42.3±8.7	45.6±9.2

Values are shown in mean±SD.

Immediately after ingestion, budesonide inhalation was begun with 4 ml of inhalation suspension at 0.5 mg/ml (2 mg total dose), or with an equal volume of a placebo, at an O_2 flow rate of com 6 l/min.

Patients were kept under observation for 4 hours. Clinical severity scores were calculated and hemoglobin saturation measured at 30 minutes, 60 minutes, 2 hours and 4 hours.

If the patient's severity score did not improve or if hemoglobin saturation worsened then bronchodilator inhalation was repeated.

After 4 hours' observation, hospital discharge was indicated for patients who had exhibited clinical improvement, inhaled bronchodilators were prescribed and they were directed to return in between 24 and 72 hours.

All patients were evaluated by the same examiner. Patients who did not respond to treatment were referred to the doctor on-call at the walk-in clinic and standard hospital practice was followed thereafter.

The study was approved by the Committee for Ethics in Research at the Hospital de Clínicas. All patients and their parents were informed of the nature of the study and gave consent for their participation.

The scale used to calculate the clinical severity score was based on clinical scores previously employed in research into acute asthma within the pediatric population.[9,10]

Scores were calculated based on the following parameters: respiratory rate, wheezing, retraction, dyspnea and hemoglobin saturation. Each parameter could be scored from zero to three, giving a maximum score of 15.

The outcome used to calculate sample size was a change in clinical severity score. The sample size was estimated according to the estimated standard deviation from the placebo group's clinical scores needed to detect a variation of ten percent. Assuming an alpha error of 0.05 and a beta of 0.03 the required sample size was 30 children.

Related samples were submitted to an analysis of variance (ANOVA) and the Wilcoxon non-parametric tests. The Mann-Whitney test was applied to independent samples (using the Primer of Biostatistics software package). Yates' corrected Chi-square test and Fisher's exact test (using Epi-Info) were used for independent and related samples. The minimum level accepted for statistical significance was 5%.

Results

Fifteen of the 49 participating children were recruited into group I, 17 into group II and 17 into group III. Six patients who had initially been included did not complete the study. Forty-four patients attended the 24 hour follow-up evaluation of whom 13 were from group I, 15

Table 2 - Clinical severity score

	0	1	2	3
Respiratory rate (BPM)*	< 30	31–45	46–60	> 61
Wheezing	Absent	End of exhalation	Whole exhalation	Inhaling and exhaling or absent VM
Retraction	Absent	Intercostal retraction	Intercostal or supraesternal retraction	Nasal wing beat
Dyspnea	Absent	Normal activity and speaking	Reduced activity. 5 to 8 words per sentence	Concentrates on respiration. < 5 words per sentence
O_2 saturation	99–100%	96–98%	93–95%	< 93%

* Patients older than 6: RR < 20 BPM, score 0; 21-35, score 1; 36-50 BPM, score 2; > 50 BPM, score 3.

from group II and 16 from group III. At 72 hours 43 patients attended; 13 from group I, 14 from group II and 16 from group III. Just one patient (group I) was excluded from the study because of worsening clinical condition after the 60 minute examination and was referred to the on-call doctor at the pediatric walk-in center. The patient was admitted according to that sector's routine procedures.

As can be seen in Figure 1, all three groups exhibited a similar response to the initial salbutamol dose, with a reduction in the clinical severity score observed at 30 minutes, which suggests a fast-acting ß2-agonist effect. The differences between groups in terms of clinical severity score were not significant at any point of the evaluation.

Hemoglobin saturation progressed differently in each of the groups (Figure 2). The average initial saturation value was 91.0±2.1% for the placebo group and did not increase significantly until the 24-hour point, with an average of 94.6±1.8 ($p < 0.05$).

The prednisone group exhibited a significant hemoglobin saturation improvement compared to their baseline at 2 hours ($p < 0.05$), while the group that used budesonide did so at four hours ($p < 0.01$). There were no significant hemoglobin saturation differences between groups during the period they were under evaluation.

The required number of bronchodilator inhalations was also similar across the three groups, with the placebo group receiving an average of 2.9, the prednisone group 2.7 and the budesonide group 2.5. The greatest number of patients requiring more than three inhalations was found in the prednisone with five patients (29%), compared with three in the placebo group (21%) and two in the budesonide group (11%), although these differences did not reach statistical significance.

In general, the drugs under study were well tolerated. Coughing was observed in two patients using nebulized budesonide, and one patient who was inhaling the placebo. In all three cases the symptom was well tolerated and treatment continued.

Two prednisone group patients and one placebo patient presented vomiting after medication.

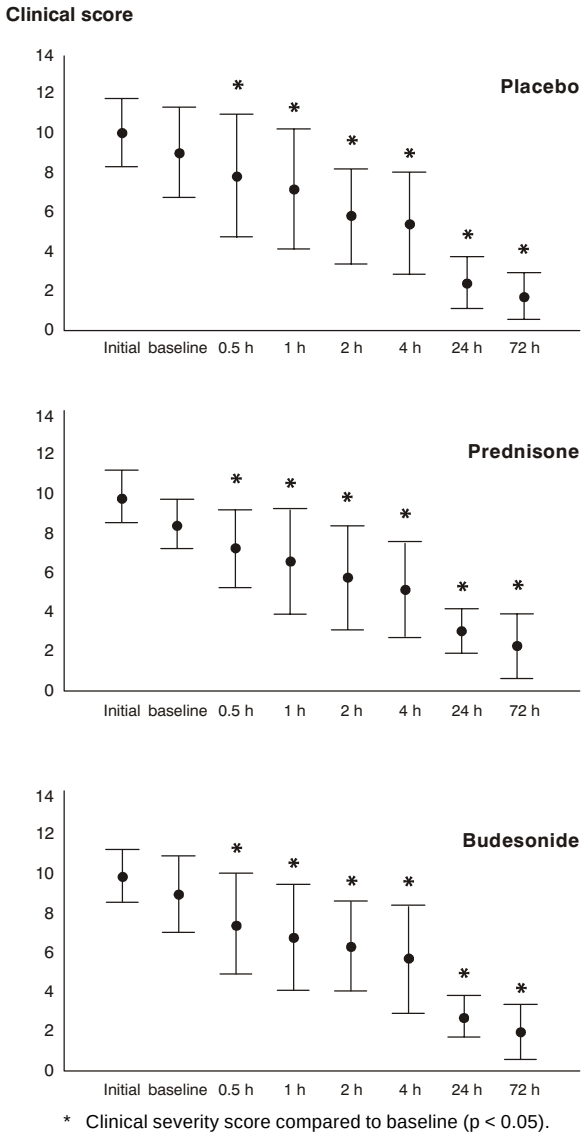

Figure 1 - Variations of clinical severity score (mean±SD) in different evaluations

Discussion

The recognition of asthma as an inflammatory disease has implications for diagnosis, treatment and prognosis. In contrast with chronic asthma, in which inhaled corticoids are considered the first line of defense, there is still discord over their benefit in acute asthma.

National and international asthma treatment consensus documents recommend the use of systemic corticoids for acute asthma crises. Oral corticoids prevent exacerbations from progressing and reduce hospitalization rates, due to improved pulmonary function and arterial oxygen pressure.[5,11-15]

Treatment was evaluated using a clinical severity score and hemoglobin saturation measurement. The importance of clinical scoring systems when indicating hospital admission has been demonstrated by a number of studies.[10,16,17] Oximetry can be useful for continuous assessment of rapid changes during the course of blood oxygenation and also for the evaluation of the effects of treatments given to patients with asthma suffering from varied degrees of bronchial obstruction. This is a method that provides objective data and can be used with patients of any age since it is non-invasive and does not require sedation or patient cooperation.[18]

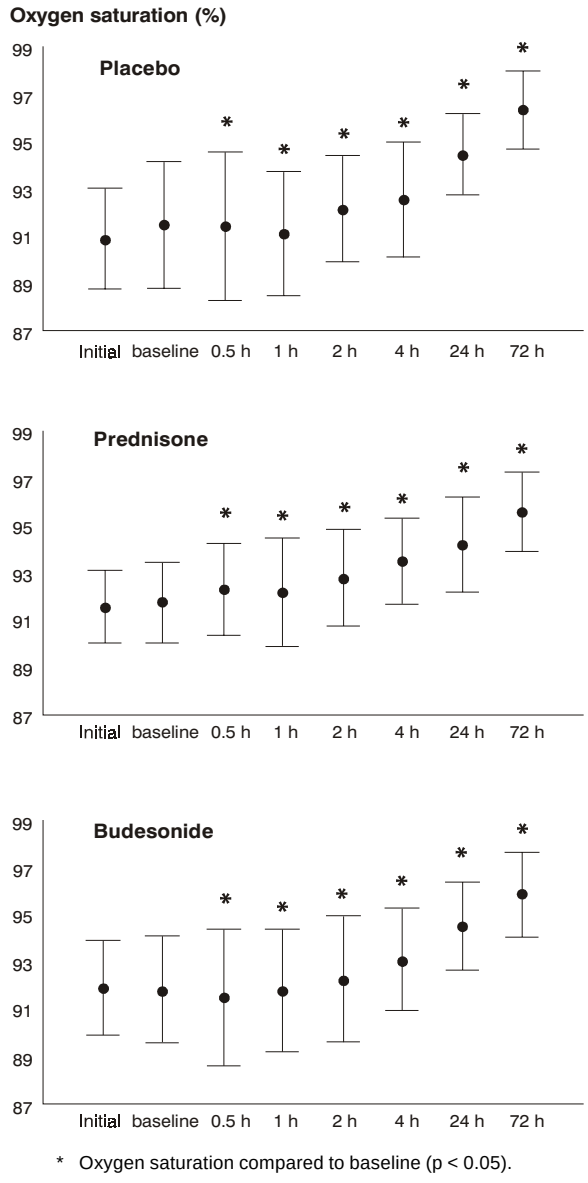

Figure 2 - Variations of oxygen saturation (mean±SD) in different evaluations

This study began with a single inhalation of salbutamol for every patient. The trial protocol then decided whether each patient would receive further doses according to the criteria already described. The average number of bronchodilator inhalations was greatest for the placebo group, but the number of patients requiring more than three inhalation sessions during crises was greatest in the prednisone group, although the difference between the groups was not significant.

Only one patient had to be hospitalized. This was the patient who exhibited the highest clinical score,[14] and the lowest saturation (88%). It is probable that the reduced frequency of hospitalizations is a consequence of exclusion criteria since patients with more severe crises and greater difficulty breathing were not recruited.

There was a progressive improvement in clinical scores over three days in all three groups. There was no significant variation between the groups.

Corticoid use has returned conflicting results in terms of improving clinical score, peak expiratory flow (PEF) and length of hospital stay for patients with acute asthma.[12-14] The diversity displayed by these results may be justified by considerable variation between individuals which would be consistent with the heterogeneous nature of asthmatic patient responses to treatment.[14]

A single dose of prednisolone improves the peak expiratory flow of children hospitalized for acute asthma after 3 hours. No improvement was observed among children less than two years old, but above this age patients who received prednisolone presented reduced clinical severity scores 5 hours after admission and for up to 24 hours, which suggests that a single dose of oral prednisolone may reduce the number of cases requiring hospitalization.[13]

Budesonide treatment for acute wheezing and dyspnea crises in infants is followed by faster clinical improvement and reduced hospital stays when compared with ipratropium bromidetreatment.[19]

It is possible that the only parameter which shows improvement during acute asthma treated with intravenous glucocorticoids is hypoxemia.[20] In this study oxygen saturation increased in all groups, although faster in the prednisone group than the budesonide group, or the placebo group. Younger et al. found no significant differences when analyzing blood gasses after adding intravenous corticoids to the treatment of acute asthma in children.[21]

The authors of another study were not surprised when, despite spirometric clinical benefits resulting from corticoid use they did not observe a parallel increase in FEV_1 or PaO_2 since they already considered that hypoxemia was almost resistant to asthma treatments.[22]

The results of research into inhaled corticoids for acute asthma are highly varied since there is no standardized dose for the drug in acute cases. The studies have different treatment regimen, varied doses and even use different types of glucocorticoid.

An assessment of moderate acute asthma, treated with either prednisolone or budesonide (1,600 µg), associated with inhaled terbutaline, revealed both clinical severity scores and PEF progressing in a similar manner for the first 4 hours of observation and for 7 days after the crises.[23] Similar results have been described with adults with acute asthma after fluticasone propionate had been given.[8]

The majority of studies involving inhaled corticoids for acute asthma compare the treatment with oral corticoids, without including a placebo group. A randomized, double-blind and double placebo controlled multicenter study assessed 135 patients who had attended hospital in

severe acute asthma crisis. The authors did not observe differences in terms of clinical improvement during the first 24 hours, when comparing budesonide with prednisolone.[24]

Devidayal et al., however, observed significant improvements among children with asthma receiving budesonide in hemoglobin saturation, respiratory rate and symptom scores when compared with children given prednisolone.[25]

Another, open, study comparing the effects of nebulized budesonide with those of prednisolone on the pulmonary function over 24 hours of children hospitalized for acute asthma demonstrated the treatments to be equivalent.[26] In a different study however, the improvement in FEV_1 after 24 hours was more evident with inhaled budesonide than with oral prednisolone.[27] Repeated doses of budesonide over 3 days resulted in similar pulmonary and pulmonary function indices to prednisolone in an open study.[28] Schuh et al. obtained different results when assessing children over five years old with severe acute asthma. Patients treated with fluticasone via metered-dose inhaler, exhibited a worse response to treatment when compared with those who were prescribed oral prednisone.[29] After 4 hours of treatment there was a 9.4% increase in FEV_1 in the fluticasone group and of 18.9% in the prednisone group after 4 hours de treatment.

Single dose budesonide in suspension (2 mg) or a placebo were compared with prednisone and frequent salbutamol inhalations for asthmatics. Pulmonary indicators and hospitalization rates were similar, but discharge occurred earlier with budesonide. This suggests that inhaled budesonide may be effective as an adjunct to prednisone in treating acute asthma in infants.[30] In our study the improvement in clinical severity scores across all groups may reflect a response to the bronchodilator drug, used at the correct dosage, via an efficient nebulizer, during the initial phase of recovery.

The early improvement in hemoglobin saturation observed here (within 2 hours for the prednisone group and 4 hours for the budesonide group) was not observed by other authors.[27] There are certain limitations to those studies that have employed nebulized medication for acute asthma. There is no ideal method for estimating the dose that is inhaled by children or infants. Different dosages and treatment schemes were employed in the various different studies of inhaled corticoids and may explain the divergence between their results. The ideal dose for acute asthma crises control has not been defined.

Current evidence does not support the recommendation of inhaled corticoids for the treatment of asthma exacerbation among children.[31]

It was concluded that single-dose inhaled budesonide did not reveal any superiority over the conventional treatment of moderate asthma crises with oral prednisone.

References

1. III Consenso Brasileiro no Manejo da Asma. J Pneumol. 2002;28 Suppl 1:1-28.
2. Barnes PJ. Molecular mechanisms of steroid action in asthma. J Allergy Clin Immunol. 1996;97:159-68.
3. Laitinen LA, Laitinen A. Remodeling of asthmatic airways by glucocorticosteroids. J Allergy Clin Immunol. 1996;97:153-8.
4. Johnson M. Pharmacodynamics and pharmacokinetics of inhaled glucocorticoids. J Allergy Clin Immunol. 1996;97:169-76.
5. Warner JO, Naspitz CK, Cropp GJA. Third International Pediatric Consensus Statement on the Management of Childhood Asthma. Pediatr Pulmonol. 1998;25:1-17.
6. De Blic J, Delacourt C, Le Bourgeois M, Mahut B, Ostinelli J, Caswell C, et al. Efficacy of nebulized budesonide in treatment of severe infantile asthma: a double-blind study. J Allergy Clin Immunol. 1996;98:14-20.
7. Scarfone RJ, Loiselle JM, Wiley II JF, Decker JM, Henretig FM, Joffe MD. Nebulized dexamethasone versus oral prednisone in the emergency treatment of asthmatic children. Ann of Emerg Med. 1995;26:480-86.
8. Levy ML, Stevenson C, Maslen T. Comparison of short courses of oral prednisolone and fluticasone propionate in the treatment of adults with acute exacerbations of asthma in primary care. Thorax. 1996;51:1087-92.
9. Schuh S, Johnson DW, Callahan S, Canny G, Levison H. Efficacy of frequent nebulized ipratropium bromide added to frequent high-dose albuterol therapy in severe childhood asthma. J Pediatr. 1995;126:639-45.
10. Morgenstern GK, Rosário NA, Ferrari FP, Cat R, Carreiro JE, Caleffe LG. Uso de escore clínico para a avaliação da gravidade da crise de asma. J Pediatr (Rio). 1998;74:455-60.
11. Tal A, Levy N, Bearman JE. Methylprednisolone therapy for acute asthma in infants and toddlers: a controlled clinical trial. Pediatrics. 1990;86:350-6.
12. Scarfone RJ, Fuchs SM, Nager AL, Shane SA. Controlled trial of oral prednisone in the Emergency Department treatment of children with acute asthma. Pediatrics. 1993;92:513-18.
13. Storr J, Barrell E, Barry W, Lenney W, Hatcher G. Effect of a single dose of prednisolone in acute childhood asthma. Lancet. 1987;18:879-82.
14. Kattan M, Gurwitz D, Levison H. Corticosteroids in status asthmaticus. J Pediatr. 1980;96:596-9.
15. McFadden Jr ER. Inhaled glucocorticoids and acute asthma. Therapeutic breakthrough or nonspecific effect? Am J Respir Crit Care Med. 1998;157:677-8.
16. Kerem E, Tibshirani R, Canny G, Bentur L, Reisman J, Schuh S, et al. Predicting the need for hospitalization in children with acute asthma. Chest. 1990;98:1355-61.
17. Fischl MA, Pitchenik A, Gardner LB. An index predicting relapse and need for hospitalization in patients with acute bronchial asthma. N Engl J Med. 1981;305:783-9.
18. Holmgren D, Sixt R. Effects of salbutamol inhalations on transcutaneous blood gases in children during the acute asthmatic attack: from acute deterioration to recovery. Acta Paediatr. 1994;83:515-19.
19. Sano F, Naspitz CK, Solé D, Pedersen S. Nebulized budesonide in the treatment of acute episodes of wheeze in infants. J Allergy Clin Immunol. 1998;101:S9.
20. Pierson WE, Bierman CW, Kelley VC. A double-blind trial of corticosteroid therapy in status asthmaticus. Pediatrics. 1974;54:282-8.
21. Younger RE, Gerber PS, Herrod HG, Cohen RM, Crawford LV. Intravenous methylprednisolone efficacy in status asthmaticus in childhood. Pediatrics. 1986;80:225-30.
22. Fanta CH, Rossing TH, McFadden ER Jr. Glucocorticoids in acute asthma. A critical controlled trial. Am J Med. 1983;74:845-51.
23. Volovitz B, Bentur L, Finkelstein Y, Mansour Y, Shalitin S, Nussinovitch 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.
24. Mitchell CA, Alpers JH, Morton SM, Raggoley CJ. Comparison of nebulized budesonide with oral prednisolone in the treatment of severe acute asthma. Eur Respir J. 1995;8:490A.
25. Devidayal, Singhi S, Kurnar L, Jayshree M. Efficacy of nebulized budesonide compared to oral prednisolone in acute bronchial asthma. Acta Paediatr. 1999;88:835-40.

26. Curtis P. Comparison of prednisolone and nebulised budesonide in acute asthma in children: a pilot study. Eur Resp J. 1995;8:S470.
27. Matthews EE, Curtis PD, Mclain BI, Morris LS, Turbitt ML. Nebulized budesonide versus oral steroid in severe exacerbations of childhood asthma. Acta Paediatr. 1999;88:841-3.
28. Nuhõglu Y, Bahceciler NN, Barlan IB, Mujdat-Basaran M. The effectiveness of high-dose inhaled budesonide therapy in the treatment of acute asthma exacerbation in children. Ann Allergy Asthma Immunol. 2001;86:318-22
29. Schuh S, Reisman J, Alshehri M, Dupuis A, Corey M, Arseneault R. A comparison of inhaled fluticasone and oral prednisone for children with severe acute asthma. N Engl J Med. 2000;343: 689-94.
30. Sung L, Osmond MH, Klassen TP. Randomized controlled trial of inhaled budesonide as an adjunct to oral prednisone in acute asthma. Acad Emerg Med. 1998;5:209-13.
31. Hendeles L, Sherman J. Are inhaled corticosteroids effective for acute exacerbation of asthma in children. J Pediatr. 2003;142(2 Suppl):26-33.

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