Efficacy of Nebulized Fluticasone Propionate in Adult Patients Admitted to the Emergency Department due to Bronchial Asthma Attack

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Abstract

Background: Locally delivered steroids by inhalers or nebulizers have been shown in small trials to be effective in acute asthma attack, but evidence-based data are insufficient to establish their place as routine management of adult asthma attacks.

Objectives: To determine the efficacy of nebulized compared to systemic steroids in adult asthmatics admitted to the emergency department following an acute attack.

Methods: Adult asthmatics admitted to the ED were assigned in random consecutive case fashion to one of three protocol groups: group 1 – nebulized steroid fluticasone (Flixotide Nebules®), group 2 – intravenous methylprednisolone, group 3 – combined treatment by both routes. Objective and subjective parameters, such as peak expiratory flow, oxygen saturation, heart rate and dyspnea score, were registered before and 2 hours after ED treatment was initiated. Steroids were continued for 1 week following the ED visit according to the protocol arm. Data on hospital admission/discharge rate, ED readmissions in the week after enrollment and other major events related to asthma were registered.

Results: Altogether, 73 adult asthmatics were assigned to receive treatment: 24 patients in group 1, 23 in group 2 and 26 in group 3. Mean age was 44.4 ± 16.8 years (range 17–75 years). Peak expiratory flow and dyspnea score significantly improved in group 1 patients compared with patients in the other groups after 2 hours of ED treatment (P = 0.021 and 0.009, respectively). The discharge rate after ED treatment was significantly higher in groups 1 and 3 than in group 2 (P = 0.05). All 73 patients were alive a week after enrollment. Five patients (20.8%) in the Flixotide treatment arm were hospitalized and required additional systemic steroids. Multivariate analysis of factors affecting hospitalization rate demonstrated that severity of asthma (odds ratio 8.11) and group 2 (OD 4.17) had a negative effect, whereas adherence to chronic anti-asthma therapy (OD 0.49) reduced the hospitalization rate.

Conclusions: Our study cohort showed the advantage of nebulized steroid fluticasone versus systemic corticosteroids in adult asthmatics managed in the ED following an acute attack. Both these and previous results suggest that nebulized steroids should be used, either alone or in combination with systemic steroids, to treat adults suffering acute asthma attack.

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The place of glucocorticosteroids in acute asthma settings has been studied for more than half a century. The benefit of systemic steroids was established in the acute setting of the emergency department, although their delayed effect (6–12 hours after infusion or ingestion) resulted in some controversy [1,2]. Systemic steroids have their proven place in the treatment of acute asthma attacks according to most professional guidelines [3,4]. Inhaled corticosteroids conform to accepted rules of reasonable efficacy in acute asthma treatment despite some controversy in the literature. A few studies have shown the benefit of inhaled (nebulized) steroids in children with acute asthma attacks [5-7], establishing the role of inhaled steroids in acute pediatric asthma. However, studies undertaken to determine the efficacy of locally delivered steroids by inhalation or nebulization in adult patients with acute asthma attacks yielded equivocal results [8-10]. A possible explanation for the beneficial effect of inhaled steroids in acute asthma is the more rapid bronchial mucosal vasoconstriction, with inhibition of edema formation in the local delivery route compared to systemic steroid administration [11].

We designed a randomized open-label three-treatment arm comparative study to determine the efficacy of nebulized steroid Flixotide Nebules® (fluticasone propionate) versus either systemic steroids given intravenously or a combination of both protocols in patients admitted to the ED following an acute asthma attack and treated with standard short-acting bronchodilator inhalations. Fluticasone propionate was selected as a very potent steroid formulation with a strong topical anti-inflammatory effect.

Patients and Methods

The study was conducted in the emergency department of Kaplan Medical Center, Rehovot, Israel. The study population comprised patients admitted to the ED following an acute asthma attack and meeting the following inclusion criteria: age between 18 and 75 years, history of atopic or idiosyncratic asthma with any grade of severity, acute asthma attack as a main reason for the recent ED admission, and written informed consent. Exclusion criteria were history of severe congestive heart failure, end-stage renal failure, advanced liver cirrhosis, pregnancy, reasons other than acute asthma for ED admission, patients with tracheostomy, patients brought to the ED already mechanically ventilated or endotracheal intubation done on admission to ED, and patients with severe asthma treated chronically with systemic steroids. All eligible patients who signed an informed consent form were assigned in random consecutive case fashion to one of three protocol arms.

ED = emergency department
OD = odds ratio

All three groups were treated with salbutamol (Ventolin®, Glaxo-Wellcome, UK) by nebulization, 0.5 ml plus 1 ml of ipratropium bromide (Apovent®, Curex®, Luxemburg Pharmaceuticals Ltd, Canada) plus 2 ml of NaCl 0.9% every 20 minutes during the first hour in the ED. Nebulized bronchodilators were continued according to the patients' clinical status. Steroids were given in concordance with the protocol arms. Group 1 patients (the Flixotide group) received inhalation of Flixotide Nebules® (fluticasone propionate) (Glaxo Wellcome, Australia) 2 ml (0.5 mg) by nebulization within the first 30 minutes after admission. Group 2 patients (the Solumedrol® group) received intravenous infusion of Solumedrol (methylprednisolone) 125 mg within the first 30 minutes after admission. Group 3 patients (combined group) were treated by both routes of steroids. Each patient received oxygen at a rate of 5 L/min. Management in the ED was provided by the local staff, who decided independently regarding admission to the internal medicine ward or the intensive care unit, discharge home from the ED, and additional treatment including invasive or non-invasive ventilation.

Several clinical parameters were registered for every patient on admission to the ED and after 2 hours of ED treatment: peak expiratory flow rate, heart rate, pulse oxymetry, and baseline dyspnea index score. PEFR was measured with a mini-Wright peak flow meter (Armstrong Industries, Inc, Northbrook, IL, USA). Heart rate monitoring was done by continuous electrocardiography (Protocol Mennen Medical 740, Rehovot, Israel). Oxygen saturation was measured non-invasively by pulse-oximetry (Nellcor N-180, Pleasanton, CA, USA). Baseline dyspnea index was evaluated by the study team according to a 0 to 3 scoring system, with 0 signifying no dyspnea, 1 indicating mild, 2 moderate, and 3 severe dyspnea [12].

Patients who were admitted to hospital wards or discharged home continued their arm's steroid management: inhalation of Flixotide Nebules 2 ml (0.5 mg) twice daily, intravenous or oral steroids (i.v. Solumedrol 125 mg two to three times daily or prednisone 60 mg per os) in tapered fashion, or both regimens together for a week after admission to the ED. Continuous asthma medications and rescue short-acting bronchodilators were also administered.

The primary end-point was the hospital admission/discharge rate. Secondary end-points were objective (PEFR, oxygen saturation, heart rate) and subjective parameters (BDI) collected during ED treatment. The severity of asthma was determined by GINA (Global Initiative for Asthma) guidelines according to data received directly from the participants and their previous asthma history. Patients' follow-up charts provided information on the type of asthma and the prescribed continuous or rescue anti-asthma medications. Information on the time that elapsed between the start of the asthma attack and ED admission was obtained on enrolment. The results of PEFR follow-up at home were obtained from the study participants by phone monitoring a week after randomization. Additional ED admissions due to asthma were registered during the first week after randomization. Data on group 1 (Flixotide) patients requiring additional systemic steroids were collected. Major events such as death, mechanical ventilation, and subsequent hospitalizations within 1 week from enrolment were also registered.

PEFR = peak expiratory flow rate
BDI = baseline dyspnea index

Statistic analysis

For the population characteristics and the variance in treatment outcomes between the three study groups, chi-square and one-way ANOVA tests were used. For variables in which the standard deviations were considered higher, the non-parametric Kruskal-Wallis test was used. In addition, logistic regression models were estimated for the dependent variable: admission yes = 1, admission no = 0. The independent variables in the equation were those with statistical significance variance between the three study groups, and those clinically known as associated with the dependent variable. Statistical significance was set when $P \leq 0.05$

Results

Demographic results

The study population consisted of 73 asthma patients. Mean age was 44.4 ± 16.8 years (range 17–75 years). This population comprised 35 males (48%) and 38 females (52%). Almost all patients (99%) used rescue anti-asthma medications (short-acting bronchodilators), but only 25 (34%) adhered to prescribed continuous medications. Asthma severity was mild in 25 (34.3%), moderate in 44 (60.2%) and severe in 4 (5.5%). Most of the patients had allergic asthma (85%). The mean time from onset of the asthma attack to admission to the ED was 42 ± 32 hours (range 1–168 hours). No significant difference was found between the study groups [Table 1].

ER treatment results

Twenty-four participants were randomly assigned to group 1 (Flixotide group), 23 to group 2 (Solumedrol group) and 26 to group 3 (combined group). Objective and subjective parameters on ED admission were similar in the three groups [Table 2]. Peak expiratory flow and BDI significantly improved in group 1 patients compared to the other groups after 2 hours of ED treatment [Table 2]. Analysis of differences between objective parameters before and 2 hours after ED therapy revealed a statistically sig-

Table 1. Demographic and baseline parameters

Parameter	Group 1	Group 2	Group 3	*P*
Age (yr)	37.9 ± 16.8	47 ± 14.6	48.2 ± 17.2	NS
Male gender (%)	45.8	39.1	57.7	NS
Allergic asthma (%)	75.0	87.0	92.3	NS
Time to ED admission (hr)	40.6 ± 36.6	37.9 ± 22.0	47.1 ± 36.2	NS
Moderate asthma (%)	45.8	69.6	65.4	NS
Severe asthma (%)	8.3	4.3	3.8	NS
Rescue therapy (%)	100	95.7	100	NS
Chronic asthma medications (%)	29.2	37.9	47.1	NS

Table 2. Objective and subjective evaluation parameters on admission to ED and after 2 hours of ED treatment

Parameter	Group 1 On admission / after 2 hrs	Group 2 On admission / after 2 hrs	Group 3 On admission / after 2 hrs	*P* On admission / after 2 hrs
Mean PEFR (% of predicted)	42.4 ± 27.5 / 51.7 ± 26.4	35.2 ± 21.3 / 39.3 ± 27.9	38.9 ± 18.0 / 47.4 ± 17.7	0.288 / 0.021
Mean oxygen saturation (%)	95.5 ± 2.6 / 98.2 ± 1.5	96.5 ± 3.0 / 97.5 ± 2.2	95.5 ± 2.4 / 97.5 ± 2.2	0.343 / 0.46
Mean heart rate (beats/min)	104.9 ± 18.8 / 98.3 ± 16.1	103.6 ± 22.0 / 95.4 ± 13.0	99.1 ± 15.0 / 97.6 ± 13.0	0.51 / 0.76
BDI score 0 (%)	4.2 / 70.8	0 / 39.1	0 / 69.2	
BDI score 1 (%)	45.8 / 16.7	17.4 / 13.0	50.0 / 23.1	
BDI score 2 (%)	37.5 / 12.5	43.5 / 47.8	34.6 / 7.7	
BDI score 3 (%)	12.5 / 0	34.8 / 0	15.4 / 0	0.19 / 0.009

Table 3. PEFR, blood oxymetry and HR differences before and after ED therapy

Parameter	Group 1	Group 2	Group 3	*P*
PEFR (% of improvement)	+9.3 ± 1.1	+4.1 ± 6.5	+8.5 ± 0.3	< 0.0001
Oxygen saturation (%)	+1.7 ± 2.1	+1.0 ± 2.3	+2.0 ± 2.5	< 0.0001
Heart rate (beats/min)	-6.7 ± 17.0	-8.2 ± 17.9	-1.5 ±13.9	0.57

nificant improvement in PEFR and oxygen saturation in group 1 and group 3 compared with group 2 [Table 3].

Study end-points

The rate of hospitalization was significantly higher in group 2 than in groups 1 and 3 ($P = 0.05$) [Table 4]. All patients requiring in-patient treatment after ED intervention were admitted to internal medicine wards. None of the study cohort was admitted to the intensive care unit. One patient required invasive mechanical ventilation during his hospitalization. No serious adverse events were registered during follow-up. All participants were alive, as determined by phone monitoring after one week. Only one study participant (in group 3) was readmitted to the ED due to asthma within a week after randomization. Five patients (20.8%) in group 1 necessitated an additional systemic steroid course to alleviate an asthma attack, and all were hospitalized after ED treatment.

Multivariate analysis of factors that influence the hospitalization rate in our cohort showed that severity of asthma (odds ratio 8.11) and group 2 protocol (OR 4.17) had a negative effect, whereas adherence to chronic anti-asthma therapy (OR 0.49) reduced the hospitalization rate.

Table 4. End-points according to study groups

	Group 1	Group 2	Group 3	*P*
Hospitalization rate (%)	20.8	47.8	19.2	0.05
ED readmission during 7 days (%)	0	0	3.8	0.4
PEFR (after 1 week) (% of predicted)	83.8 ± 21.6	64.7 ± 17.3	72.5 ± 19.1	0.08

Discussion

The results of our study showed the advantage of nebulized steroid fluticasone versus systemic corticosteroids in adult asthmatics managed in the ED following an acute asthma attack. Notwithstanding the relatively small cohort, a significant reduction in hospitalization rate and short-term improvement in PEFR, oxygen saturation and BDI score were demonstrated in patients receiving nebulized steroids compared to participants treated with systemic steroids alone.

There are a few possible explanations for the advantages of locally delivered as compared to systemic steroids. The reasons for the gradual onset of systemically delivered steroid activity are likely related to the fact that the mechanism of action of corticosteroids requires ligand-dependent activation of glucocorticoid receptor transcriptional functions. The initial cellular interaction is likely to be immediate, but the ultimate expressions of the desired physiological, or therapeutic, consequences lag far behind because of the need to induce and secrete new proteins [11].

Glucocorticoids inhibit the transcription of some of the interleukins (IL-1, IL-3, IL-4, IL-6, and IL-8), tumor necrosis factor-alpha, granulocyte-macrophage colony-stimulating factor, and the synthesis of either cytokine receptors or the inducible form of nitric oxide synthase. One possibility is that the molecular and cell biology of these compounds changes as a function of the route of delivery. Another is that the locally delivered steroids amplified a non-immunological anti-inflammatory event such as vasoconstriction. Because vascular congestion, edema formation, and plasma exudation are important pathophysiological elements in bronchoconstriction associated with acute asthma, it is possible that the nebulized or inhaled steroids cause significant vasoconstriction that modifies these factors in a clinically important way [12].

Equivocal results of studies on inhaled and nebulized steroids conducted in previous decades [1,8] may be explained by the lack of highly potent local steroids with good lung deposition. Investigations that were performed in this field during the last decade have added more to our knowledge. Rowe et al. [13] showed additional clinical improvement when systemic and inhaled steroids were combined after emergency room treatment due to acute asthma attack. Rodrigo [14] demonstrated higher efficacy and earlier improvement after inhaled fluticasone compared to intravenous hydrocortisone for hospitalized asthma patients. Two different studies concluded that high dose inhaled steroids are effective, at least as much as systemic steroids, in managing either in-patients with acute asthma attack or following discharge from hospital [15,16]. A Turkish study published 2 years ago demonstrated that nebulized budesonide is highly effective

IL = interleukin

either alone or in combination with systemic steroids in patients hospitalized due to acute asthma [10].

On the other hand, the Canadian Asthma Exacerbation Study Group [17] reported that inhaled steroid dose-doubling cannot change the natural history of an imminent acute asthma attack. In their Cochrane review Edmonds and collaborators [18] concluded that inhaled corticosteroids reduce the hospital admission rate in adult asthma patients, although they emphasized that there is insufficient evidence of inhaled corticosteroid effect other than that of systemic steroids on the bronchial wall in patients with acute asthma attack.

Due to the lack of large-scale trials investigating the place of inhaled and nebulized steroids in acute asthma settings, there are no clear recommendations on the use of local steroids in the ED to treat adult asthma attack [3,4]. Evidence-based guidelines for asthmatic children in acute settings are better established [6,7].

In our study, treatment with nebulized high dose steroid fluticasone showed clear advantages versus systemic steroids in our adult asthmatic cohort managed in the ED. Faster clinical improvement and a higher discharge-to-home rate were the most prominent findings of this study. According to our present and previous reports, we believe that nebulized steroids (fluticasone, budesonide or other specialized formulations) might be used alone or in combination with systemic corticosteroids to treat adult asthmatics with an acute attack. Initial anti-inflammatory treatment with nebulized steroids might be amplified by systemic steroids in accordance with the clinical picture in patients admitted to the ED following an acute asthma attack. The benefit of local versus systemic steroids is reflected in lower hospitalization rate, better adverse event profile and less expensive treatment. Large double-blind or multi-center studies are required to re-confirm our results and clarify the place of nebulized steroids in acute asthma treatment.

References

1. Fanta CH, Rossing TH, McFadden ER. Glucocorticoids in acute asthma: a critical controlled trial. *Am J Med* 1983;74:845–51.
2. McFadden ER. Dosage of corticosteroids in asthma, a clinical commentary. *Am Rev Respir Dis* 1993;147:1306–10.
3. American Thoracic Society. Standards for the diagnosis and care of patients with COPD and asthma. *Am Rev Respir Dis* 1987;136:225–44.
4. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2006. Available from: http://www.ginasthma.org
5. Sung L, Osmond MH, Klassen TP. Randomized, controlled trial of inhaled budesonide as adjunct to oral prednisone in acute asthma. *Acad Emerg Med* 1998;5:209–13.
6. Volovitz B, Soferman R, Blau H, Nussovitch M, Varsano I. Rapid induction of clinical response with short-term high-dose starting schedule of budesonide nebulizing suspension in young children with recurrent wheezing episodes. *J Allergy Clin Immunol* 1998;101:464–9.
7. 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.
8. Guttman A, Afilato M, Colacone A, Kreisman H, Dankoff J. The effect of combined intravenous and inhaled steroids (beclomethasone dipropionate) for the emergency treatment of acute asthma. The Asthma ED Study Group. *Acad Emerg Med* 1997;4:100–6.
9. Rodrigo G, Rodrigo C. Inhaled flunisolide for acute severe asthma. *Am J Respir Crit Care Med* 1998;157:698–703.
10. Ediger D, Coşkun F, Kunt Uzaslan E, et al. Clinical effectiveness of nebulised budesonide in the treatment of acute asthma attacks. *Tuberk Toraks*. 2006;54(2):128–36.
11. McFadden ER Inhaled glucocorticoids and acute asthma. *Am J Respir Crit Care Med* 1998;157:677–8.
12. Maklei DA, Wells CK. Evaluation of methods for rating dyspnea. *Chest* 1988;93:580–6.
13. Rowe BH, Bota GW, Fabris L, Therrien SA, Milner RA, Jacono J. Inhaled budesonide in addition to oral corticosteroids to prevent asthma relapse following discharge from the emergency department: a randomized controlled trial. *JAMA* 1999;281(22):2119–26.
14. Rodrigo GJ. Comparison of inhaled fluticasone with intravenous hydrocortisone in the treatment of adult acute asthma. *Am J Respir Crit Care Med* 2005;171(11):1231–6.
15. Lee-Wong M, Dayrit FM, Kohli AR, Acquah S, Mayo PH. Comparison of high-dose inhaled flunisolide to systemic corticosteroids in severe adult asthma. *Chest* 2002;122(4):1208–13.
16. Nana A, Youngchaiyud P, Charoenratanakul S, et al. High-dose inhaled budesonide may substitute for oral therapy after an acute asthma attack. *J Asthma* 1998;35(8):647–55.
17. FitzGerald JM, Becker A, Sears MR, et al; Canadian Asthma Exacerbation Study Group. Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. *Thorax* 2004;59(7):550–6.
18. Edmonds ML, Camargo CA, Saunders LD, Brenner BE, Rowe BH. Inhaled steroids in acute asthma following emergency department discharge (Cochrane review). *Cochrane Database Syst Rev* 2000;3.

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