

The Effect Of Early Parenteral Administration Of Corticosteroids In Severe Asthma: A Study Not Employing Concomitant Ipratropium Treatment

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Citation

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Abstract

There is studies in the medical literature that supports the use of parenteral corticosteroid and aerosolized anticholinergic treatments in acute asthma. Since study treatments often involve giving both agents, it is not known whether the beneficial effects of corticosteroids are similar in patient given beta adrenergic treatments alone compare to patients given both beta adrenergic and anticholinergic treatments. In this study, the effects of corticosteroid administration was studied in the absence of ipratropium treatment, in a protocol similar to that previously used by the investigators in a prior study that involved both albuterol and ipratropium treatments. Thirty seven adult patients with acute asthma were randomized to either 125 mg of intravenous methylprednisolone(n=19) or to saline(n=18) treatments in a double blinded study. As entry criteria, all patients were required to have significant peak flow reductions despite initial albuterol treatment. Identical regimens of repeated albuterol nebulization were administered to the patients, and peak flow measurements were made serially over 3 hours. Peak flow measurements showed no differences between the 2 groups in terms of change with time. There was also no significant difference in the proportion of patients who were admitted to the hospital for the two groups(steroid n=3, placebo n=2). In conclusion, our study did not show a benefit for parenteral corticosteroid administration in adults treated for acute severe asthma with only beta agonists.

BACKGROUND

This study examined the effect of early corticosteroid administration on airway obstruction in emergency room adults asthmatics. In a prior study by us(1), the benefits of parenteral corticosteroids were observed in the presence of concomitant beta agonist and anticholinergic nebulizer treatment. Thus it could not be ascertained if corticosteroids effects required bronchodilator effects of one or both of these nebulized therapies. More specifically, it was not known if patients who received beta agonists therapy in the absence of ipratropium would also benefit from corticosteroid parenteral therapy. The goal of this study was thus to test the hypothesis that early corticosteroid therapy in severe acute asthma is beneficial in the absence of ipratropium treatment.

METHODS

Asthmatic patients were considered for recruitment from the

Emergency Department if they had a PEFr which was less than 50% predicted or an absolute PEFr value of less than 200 L/min, after having received an initial 2.5 mg albuterol nebulizer treatment twenty minutes previously. Exclusion criteria included 1) age less than 18 years old, 2) inability to perform peak expiratory flow(PEFR) measurements after the initial pre-study albuterol treatment, 3) smoking history of 10 or more pack years of cigarettes, and 4) pregnancy. Asthma was defined as 1) having a history of asthma diagnosed by a physician, 2) having had a bronchodilator prescribed by a physician, and 3) having had episodes of wheezing that improved with beta agonist inhalers.

Patients in the study had all measurements of PEFr performed in the sitting position without nose clips. These were administered by the study physicians using a Wright peak flow meter(model N183JD, Ferraris Medical Ltd, London).. Percent predicted peak flow rates were calculated using the Quanjer prediction equations(2) for smokers/non-

The Effect Of Early Parenteral Administration Of Corticosteroids In Severe Asthma: A Study Not Employing Concomitant Ipratropium Treatment

smokers/ex-smokers which are based solely on age(years), sex, and height(meters). For males the equation for predicted peak flow(L/sec) was $5.48 \times \text{height(meters)} - .041 \times \text{age(years)} + 1.58$. For females predicted peak flow was $3.72 \times \text{height(meters)} - .03 \times \text{age(years)} + 2.24$. The recruited patients were randomized to treatment with either methylprednisolone or normal saline administration. Each treatment designation was placed in sealed, opaque envelopes stored in a locked cabinet. A staff member uninvolved with the patient's care then drew into a syringe either 125 mg of freshly dissolved methylprednisolone sodium succinate(Solumedrol™) or an equal volume of normal saline based on a computer generated random number assignment list. This syringe was then given to the study physician, unaware of its contents, who then administered the contents by bolus intravenous injection to the subject. Immediately thereafter, a nebulization of 2.5 mg albuterol was administered to the subject. Patients then received every 20 minutes, 3 more 2.5 mg albuterol doses and then after a 30 minute period 3 more 2.5 mg albuterol treatments every 30 minutes. Thus during the study period, patients received 5 albuterol aerosol treatments in total at times 0, 20, 40, 60, 90, 120, and 150 minutes.

The primary endpoints of peak expiratory flow rates and percent predicted PEFR, were analyzed by repeated measured analysis of variance, with the time by group interaction being the analysis of interest(3). A pre-planned orthogonal contrast was used to compare the change from baseline to all subsequent peak flow values for the 2 treatment groups(4). The Greenhouse-Geisser adjustment for non-sphericity was applied(5). Peak expiratory flow rates and percent predicted PEFR were logarithmically transformed in order to normalize them for analysis. Heart rates were also analyzed by repeated measures analysis of variance. The proportion of admissions in the two groups were analyzed, using Fisher's exact test. A total of 40 patients was targeted on the basis of the results of a prior related study(1) which suggested that a beneficial corticosteroid effect would be observed with a relatively small number of patients.

RESULTS

A total of 37 patients were recruited between the dates of 11/7/98 and 8/2/00. Nineteen patients were randomized to active treatment and eighteen were randomized to placebo treatment. All patients completed the entire protocol. The baseline characteristics of the 2 groups are shown in Table I. The patients' ages ranged from 18 to 59 years. There were no

significant differences between the baseline characteristics between the 2 groups in terms of medication use, duration of asthma, frequency of asthma events, age, gender, ethnicity, baseline heart rates, and baseline peak flow rates. Most patients were not using long acting bronchodilators or corticosteroids(either inhaled or oral). Seven of the active treatment group patients were current smokers compared to 4 of the placebo treated patients. The methylprednisone patients had a somewhat higher number of lifetime emergency department visits for asthma, but this difference was not significant. The median number of ED visits for asthma in the preceeding month was 1 for both groups. Three patients in the methylprednisolone group had been intubated for asthma, compared to only 1 in the control group. This difference in proportions was not significant.

Figure 1

Table I: Baseline characteristics of the methylprednisolone and saline treated groups

	methylprednisolone group(n=19)	saline group(n=18)
Age(mean and SD)	34.4+/- 9.8	37.3+/-10.0
Gender	15 F, 4 M	10 F, 8 M
Baseline PEFR(L/min)(mean and SD)	158.4+/-43.4	173.5+/-51.1
current inhaled corticosteroid use	3	6
current oral corticosteroids	1	2
current salmeterol use	2	3
current corticosteroid or salmeterol use	4	7
Ethnicity*	2O,1A,3B,7H,6W	1A,3B,8H,6W
history of allergic rhinitis	9	9
current ipratropium use	2	3
median number of lifetime ED visits for asthma	10	3
median number of lifetime asthma admissions	1	2
duration of acute asthma symptoms	24	14
median number of albuterol inhalations in past 24 hours	7.5	6
median number of years with asthma	20	25
percent predicted PEFR(mean and SD) [†]	33.5+/-8.5	35.7+/-9.4
baseline heart rate(mean and SD)	96.4+/-19.3	98.1+/-13.5

*A=Asian, B=African-American, H=Hispanic, O=other or not recorded, W=Caucasion [†] One of the methylprednisolone treated patients was not studied for percent predicted peak flow, due to the missing height data

Four patients in the methylprednisolone group was admitted to the hospital compared to 3 patients in the control group(Fisher's exact test $p>0.5$). One of the methylprednisolone treated patients was advised to be admitted but left against medical advise. Heart rate responses were similar in the 2 groups(data not shown). The absolute values for peak flow rates did not differ between the two groups in terms of their change with time(Figure 1). Likewise the percent predicted peak flow rates were not different between the 2 groups in terms of their change with time(Figure 2). Unblinded methylprednisolone was administered after the protocol period in 6 of the active treatment group and in 3 of the placebo treated group. Five

patients only developed tremor during the second and third hour observation points, while 13 other patients had tremor observed at any observation point in time. Agitation was only observed in one patient.

Figure 2

Figure 1: Absolute expiratory peak flow rate(L/min) responses in steroid(upper frame) and placebo(lower frame) treated groups

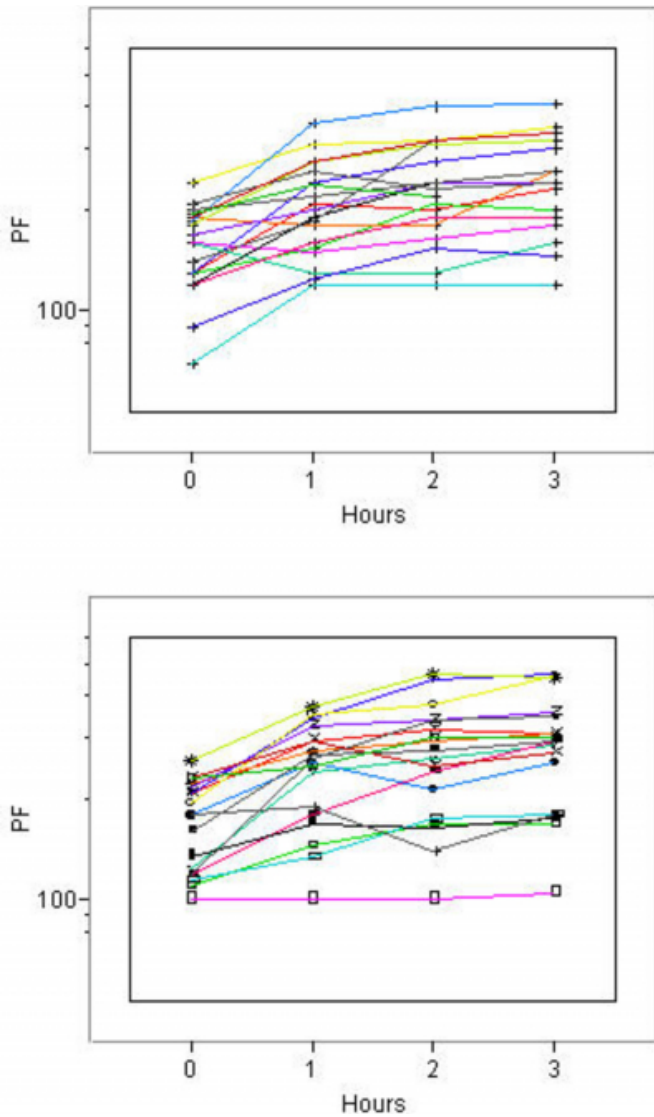
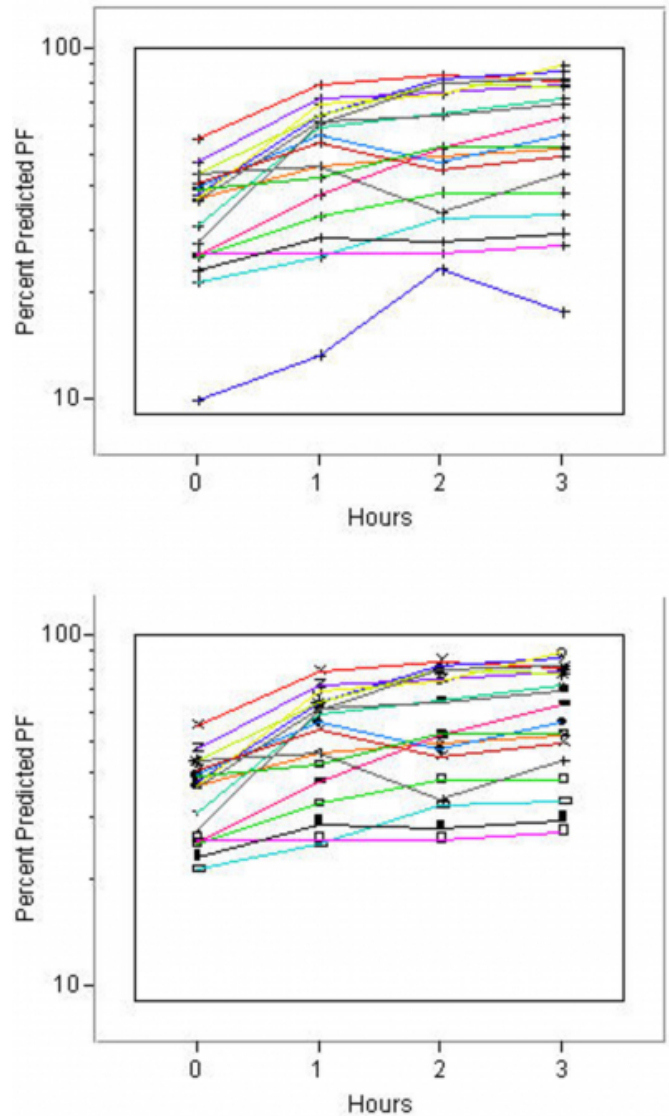


Figure 3

Figure 2: Percent predicted expiratory peak flow rate responses in steroid(upper frame) and placebo(lower frame) treated groups



DISCUSSION

This study details the bronchodilator responses of acute severe asthmatic patients treated with beta agonists in the presence and absence of parenteral corticosteroids. Unlike a prior study performed by us, no addition of the anticholinergic medication ipratropium was employed. There was no benefit observed with methylprednisolone treatment in terms of expiratory flow rates or admissions. The results of this study add to the observations which examine the hypothesis that parenteral corticosteroids have a rapid effect in asthma. In a recent systematic review, Rowe and associates(6) concluded that corticosteroids given within 1 hour decrease hospital admissions for asthma, especially in

patients not previously taking corticosteroids and in patients with more severe asthma. In the systematic reviews on acute corticosteroid effects, no mention is made of the covariate effects of ipratropium.

Our patients had mean percent predicted peak expiratory flow rates less than 40%, and thus certainly had severe disease. Moreover, only a few patients were taking either inhaled or oral corticosteroids. It is conceivable that the number of patients was too small to detect a difference between the 2 groups. However, it is very interesting that an analogous protocol utilizing ipratropium did find a very significant difference on only 65 asthmatic patients using similar entry criterion. This raises the possibility that corticosteroids may have a more clinically significant effect when both beta agonists and anticholinergic agents⁽⁷⁾ are used to attain bronchodilation. The patients recruited in the present study differed from our previous asthma steroid study⁽¹⁾ in that patients were younger by almost a decade, and were only included if smoking history was less than 10 pack years. In our previous study, the smoking threshold for inclusion was less than 20 pack years. These differences may have related to the negative outcome observed in the present study.

The protocol employed in the present study involved a longer observation time frame, which consisted of 3 hours after the screening for initial albuterol treatment response. The total amount of albuterol used during the entire ED stay was 20 mg by nebulizer in a less than 4 hour period of time. This was well tolerated by the patients, with tremor being the only significant side effect noted in 18 of the patients. Tachycardia was not observed in any of the patients and there was no treatment by time effect on heart rates for the overall group (data not shown). This suggests that unlike some high dose albuterol treatment protocols^(8,9), this regimen is well tolerated.

One of the proposed mechanisms of corticosteroid effects in asthma is the effect on muscarinic receptors⁽¹⁰⁾. We suggest that further clinical studies are needed to examine the

hypothesis that corticosteroids preferentially enhance bronchodilator responses in the presence of ipratropium.

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