Comparison of High-Dose Inhaled Flunisolide to Systemic Corticosteroids in Severe Adult Asthma*

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Objective: To investigate whether, after 48 h of IV treatment with corticosteroids, the use of high-dose inhaled flunisolide is as effective as systemic corticosteroids in adults hospitalized for a severe asthma exacerbation.

Design: Randomized, double-blind, placebo-controlled study.

Setting: Inpatient, an urban teaching hospital medical ward; outpatient, asthma clinic affiliated with the hospital.

Participants: Forty patients aged 18 to 55 years with asthma exacerbation requiring hospitalization.

Interventions: Inhaled flunisolide via metered-dose inhaler (250 μg per activation) eight puffs bid compared to systemic corticosteroids alone, following eight doses of IV corticosteroids.

Measurements and results: Peak expiratory flow rate (PEFR), FEV₁, and symptom scores were recorded on day 1 (at presentation to the emergency department) and day 7, at an outpatient follow-up visit. From day 1 to day 7, mean PEFR increased from 190 to 379 L/min in the flunisolide group, and from 207 to 347 L/min in the systemic corticosteroids group (p = 0.95; 95% confidence interval [CI], –66.3, ∞). Mean FEV₁ increased from 1.6 to 2.3 L in the flunisolide group, and from 1.4 to 2.1 L in the systemic corticosteroids group (p = 0.33; 95% CI, –21.7, ∞). Changes in symptom scores were –0.7 in the flunisolide group and –0.9 in the systemic corticosteroids group (p = 0.39; 95% CI, –0.4, ∞). Hospital readmission rates on day 7 were zero for both groups.

Conclusions: High-dose inhaled corticosteroids are as effective as systemic corticosteroids during a 7-day period following admission to the hospital for severe asthma.

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Key words: acute asthma; asthma exacerbation; corticosteroids; emergency department; flunisolide; glucocorticoids; hospitalization; inhaled corticosteroids; severe asthma

Abbreviations: BIMC = Beth Israel Medical Center; CI = confidence interval; ED = emergency department; ICS = inhaled corticosteroids; LOS = length of hospital stay; MDI = metered-dose inhaler; PEFR = peak expiratory flow rate; SS = systemic corticosteroids

According to widely accepted guidelines, systemic corticosteroids (SS) are standard treatment for patients with severe asthma exacerbations who require hospitalization.¹–³ The role of inhaled cortico-

steroids (ICS) in the treatment of asthma requiring hospitalization is unclear. Standard recommendations do not mention their use in the acutely ill hospitalized patient. Several investigators have examined the role of ICS in the treatment of asthma in the emergency department (ED) and report beneficial effects.⁴–¹² A meta-analysis suggests that ICS are potentially efficacious in the ED treatment of asthma.¹¹ The purpose of our study is to compare the early use of ICS to SS in patients who are hospitalized for severe asthma following unsuccessful ED treatment. We hypothesize that ICS would be well tolerated and as effective as oral corticosteroids following an initial period of IV corticosteroid use. ICS may be advantageous in the hospitalized asthmatic for several reasons. For one, their early use...
could reduce the need for prolonged, tapering regimens of oral corticosteroids, which are widely used. This would curtail the incidence of side effects. In addition, compliance with ICS on an outpatient basis may be improved by introducing the medication at a time when patient education is likely to be particularly valuable.\textsuperscript{13}

**Materials and Methods**

All adult patients aged 18 to 55 years admitted from the ED to the inpatient medical service of Beth Israel Medical Center (BIMC) for an acute asthma exacerbation (International Classification of Disease code 493.91) were eligible for the study. The decision to hospitalize a patient on the inpatient medical service for an acute asthma exacerbation was made by senior BIMC ED staff. Implicit to study design is that the investigators had no involvement with the treatment or admission decision for any patient in the ED. Admission criteria employed by the ED were as follows. After 6 h of frequent wheezing, dyspnea, shortness of breath, accessory muscle use, and a peak expiratory flow rate (PEFR) ≤ 50% predicted, patients became eligible for the study only at the time they actually arrived on the inpatient medical service. In addition to the age criteria mentioned above, hospitalized patients were eligible for the study, provided they met the following inclusion criteria: (1) PEFR < 50% predicted while in the ED, (2) ability to perform technically acceptable spirometry, and (3) willingness to participate in the study, with written informed consent. Exclusion criteria included pregnancy, lactation, active substance abuse, history of severe mental illness, refusal of consent to enter the study, intubation for asthma during the present admission in the ED, current use of systemic corticosteroids, severe coexisting medical or neurologic illness, known sensitivity to any study medication, and inability to attend an outpatient visit at 7 days following admission to the hospital for geographic reasons. The Committee of Scientific Activities and Institutional Review Board of BIMC approved this study.

For the first 48 h after admission, all study patients were treated according to preexisting hospital guidelines, as follows: (1) inhaled albuterol via a nebulizer every 4 h until the patient could be trained with a metered-dose inhaler (MDI) and spacer (Fig 1). Thereafter, they received inhaled albuterol, four puffs q4h as needed, using an MDI with spacer (Aerochamber; Monaghan Medical Corporation; Plattsburgh, NY); and (2) methylprednisolone, 40 mg IV q6h, for a total of eight doses. No patients received methylxanthines, cromolyn, ipratropium, leukotriene inhibitors, or any other asthma medications. Patients were enrolled within 12 h of admission to the inpatient service. They were randomized in double-blind fashion to receive, in addition to standard treatment as above, flunisolide, eight puffs bid via spacer (250 \( \mu \)g per actuation), or placebo MDI, eight puffs bid via spacer. All patients were started on study medication within 12 h of admission to the inpatient service. After 48 h (following eight doses q6h of 40 mg IV methylprednisolone), the methylprednisolone was discontinued and patients were started on either oral prednisone or placebo tablets. In double-blinded fashion, the patients receiving active flunisolide (the ICS group) were administered placebo tablets. The placebo tablets bore resemblance to prednisone precisely in terms of taste, color, and size. Patients took all eight placebo tablets once a day until their follow-up appointment 7 days from admission to the hospital. The patients receiving placebo MDI (the prednisone group) were administered in double-blinded fashion eight 5-mg prednisone tablets qd until their follow-up appointment 7 days from admission into the hospital. Double-blind randomization was performed by the BIMC pharmacy by random computer-generated assignment, without any involvement of the investigators. The placebo MDI and flunisolide MDI both contained a mint-flavored additive. The taste of the inhaled medication was therefore identical between the two preparations.

Outcome variables included PEFR, FEV\textsubscript{1}, and symptom scores. These measurements were recorded for each patient before randomization on day 1 and on day 7 at an outpatient follow-up visit. Hospital readmission rate, ED revisit rate, and length of hospital stay (LOS) were also assessed. PEFR was measured in the ED using a mini-Wright peak flowmeter (Armstrong Industries; Northbrook, IL). PEFR and FEV\textsubscript{1} were measured by study investigators using a Puritan Bennett Renaissance Spirometer (Mallinckrodt; St. Louis, MO). Compliance with study medications was measured by pill count and MDI weight.

The decision to discharge the patient from the hospital was made by the medical team caring for the patient. Study investigators had no influence on discharge decisions. Discharge criteria were a PEFR > 50% of predicted normal and clinical improvement of wheezing, dyspnea, and shortness of breath. The ICS group was discharged home on the following regimen: flunisolide MDI, eight puffs bid with spacer; albuterol MDI, two puffs with spacer q4h as needed; and placebo tablets daily. The prednisone group was discharged home on the following regimen: placebo MDI, eight puffs bid with spacer; albuterol MDI, two puffs with spacer q4h as needed; and prednisone, 40 mg/d. Patients were scheduled for outpatient follow-up 7 days after admission to the hospital.

**Statistical Analysis**

The statistical calculations for this study were computed on a Microsoft Excel spreadsheet program (Excel 97; Microsoft; Richmond, WA). Homogeneity of the baseline characteristics of both groups was evaluated using the \( \chi^2 \) statistic.\textsuperscript{14} Resultant \( p \) values ≥ 0.05 (5% significance level) support the null hypothesis, or the homogeneity of the groups. In addition, \( t \) and normal statistics were used to obtain approximate 95% confidence intervals (CIs) for the baseline patient characteristics.\textsuperscript{15} 95% CIs that include the zero point also indicate support for the null hypothesis, or the homogeneity of the two groups.

Outcome differences for the three continuous response variables (PEFR, FEV\textsubscript{1}, and symptom scores) were analyzed using the nonparametric Wilcoxon rank-sum statistic.\textsuperscript{14} In the cases of PEFR and FEV\textsubscript{1}, the data tested were the percentage increases from day 1 to day 7 values. In the case of symptom scores, the data tested were the absolute decreases from day 1 to day 7 values. In all three cases, the null hypothesis was the equality of the medians for the ICS and prednisone groups. For the Wilcoxon rank-sum statistic, \( p \) values ≥ 0.05 validate the null hypothesis, or equivalent outcomes of both groups. Furthermore, one-sided 95% CIs were calculated for the prednisone median minus the ICS median for each of the outcome variables using the Wilcoxon rank-sum statistic. CIs that include zero indicate support for the null hypothesis. In addition, a secondary chart review was performed to record the LOS for both groups. These data were analyzed using the \( \chi^2 \) statistic. Resultant \( p \) values ≥ 0.05 lend support to the null hypothesis that the mean LOS is similar for both groups.
Results

Forty patients met the inclusion criteria, and all 40 patients were enrolled in the study. Twenty-one patients were randomized to the ICS group, and 19 patients were randomized to the prednisone group. One patient in the prednisone group completed only four doses of methylprednisolone in the hospital. One patient in the ICS group did not attend the follow-up appointment. This patient was interviewed by telephone, reported no readmission, and was able to measure PEFR at the time of the interview. Subsequently, the patient brought the MDI and pill bottle in for assessment.

Baseline demographics and disease intensity characteristics were similar in both groups (Table 1). PEFR, FEV₁, and symptom scores were comparable at baseline and improved to similar extent in both groups (Table 2). No patients in either group were readmitted for asthma exacerbation to the hospital or ED during the study period. Pill count and MDI weights showed that all patients were compliant with study medications.

From day 1 to day 7, mean PEFR increased from 190 to 379 L/min in the ICS group, and from 207 to 347 L/min in the prednisone group (p = 0.95; 95% CI, –66.3, ▲) [Table 2]. Mean FEV₁ increased from 1.6 to 2.3 L in the ICS group, and from 1.4 to 2.1 L in the prednisone group (p = 0.33; 95% CI, –21.7, ▲). Mean symptom scores declined from 1.4 to 0.7 in the ICS group, and decreased from 1.3 to 0.4 in the
prednisone group \( (p = 0.39; 95\% \text{ CI}, -0.4, \infty) \). For all outcome variables, \( p \) values \( \geq 0.05 \) generated by the Wilcoxon rank-sum test support the null hypothesis that both groups are equivalent. Ninety-five percent CIs include the origin (zero) and similarly support the null hypothesis that outcome variables are equivalent for the ICS and prednisone groups.

None of the patients in either group were readmitted for an acute asthma relapse by day 7 of the study. The mean \( \pm \text{SD} \) LOS was 2.3 \( \pm 0.5 \) days for the prednisone group and 2.7 \( \pm 0.9 \) days for the ICS group \( (p = 0.34; 95\% \text{ CI}, -0.82, 0.11) \). The high \( p \) value obtained from the \( t \) statistic indicates strong support for the equivalence of the LOS for both groups.

**Discussion**

National Asthma Education and Prevention Program guidelines for the diagnosis and management of asthma recommend that patients with asthma of sufficient severity to require hospitalization be administered SS.\(^1\) They also recommend that the patient be discharged on oral corticosteroids at a recommended dose of 20 mg bid for 3 to 10 days.\(^1\) In addition, they recommend ICS should be started before the course of systemic corticosteroids is completed.\(^1\) The reason provided is that ICS have a gradual onset of action. Furthermore, the early implementation of ICS affords patients adequate time to learn appropriate technique. In this study, we sought to demonstrate that oral corticosteroids following discharge from the hospital for asthma exacerbation are unnecessary, provided ICS are used.

Our study shows that the outcome following hospitalization for asthma exacerbation was identical whether high-dose ICS were used or prednisone, 40 mg orally qd, was used following hospital dis-

### Table 1—Baseline Patient Characteristics*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ICS Group</th>
<th>Prednisone Group</th>
<th>( p ) Value ((\chi^2))</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>21</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female/male sex, No.</td>
<td>15/6</td>
<td>16/3</td>
<td>0.33</td>
<td>-0.38, 0.13</td>
</tr>
<tr>
<td>Present age, yr</td>
<td>34.6 (9.9)</td>
<td>36.9 (10.5)</td>
<td>0.72</td>
<td>-4.09, 8.74</td>
</tr>
<tr>
<td>Age of onset, yr</td>
<td>18.6 (12.9)</td>
<td>20.3 (11.8)</td>
<td>0.28</td>
<td>-8.41, 6.15</td>
</tr>
<tr>
<td>Asthma duration, yr</td>
<td>16.7 (9.5)</td>
<td>19.0 (10.7)</td>
<td>0.87</td>
<td>-3.99, 10.03</td>
</tr>
<tr>
<td>Intubations, No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>4</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>17</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED visits past 3 mo</td>
<td>1.7 (1.4)</td>
<td>1.5 (1.3)</td>
<td>0.97</td>
<td>-0.98, 1.03</td>
</tr>
<tr>
<td>Hospital admissions past year</td>
<td>0.6 (0.8)</td>
<td>0.3 (0.6)</td>
<td>0.44</td>
<td>-0.71, 0.93</td>
</tr>
<tr>
<td>Last admitted, mo</td>
<td>4.3 (1.9)</td>
<td>4.8 (3.9)</td>
<td>0.83</td>
<td>-2.41, 4.36</td>
</tr>
<tr>
<td>Smoking status, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>43</td>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>37</td>
<td>53</td>
<td>0.78</td>
<td>-0.35, 0.26</td>
</tr>
<tr>
<td>Present</td>
<td>14</td>
<td>26</td>
<td>0.34</td>
<td>-0.12, 0.35</td>
</tr>
<tr>
<td>Home ICS use, % patients</td>
<td>67</td>
<td>63</td>
<td>0.82</td>
<td>-0.39, 0.21</td>
</tr>
<tr>
<td>ICS frequency/d</td>
<td>2.0 (0)</td>
<td>2.2 (0.8)</td>
<td>0.2</td>
<td>-0.30, 0.66</td>
</tr>
<tr>
<td>ICS actuations/d</td>
<td>13.6 (6.5)</td>
<td>14.7 (8.4)</td>
<td>0.62</td>
<td>-5.03, 7.34</td>
</tr>
<tr>
<td>Daily albuterol use, % patients</td>
<td>90</td>
<td>71</td>
<td>0.15</td>
<td>-0.06, 0.42</td>
</tr>
<tr>
<td>Total albuterol use, % patients</td>
<td>95</td>
<td>95</td>
<td>0.82</td>
<td>-0.14, 0.13</td>
</tr>
<tr>
<td>PEFR, L/min</td>
<td>190 (80.0)</td>
<td>207 (81.5)</td>
<td>0.66</td>
<td>-33.62, 67.73</td>
</tr>
<tr>
<td>FEV(_1), L</td>
<td>1.6 (0.6)</td>
<td>1.5 (0.6)</td>
<td>0.28</td>
<td>-0.52, 0.22</td>
</tr>
<tr>
<td>Symptom scores</td>
<td>1.4 (0.7)</td>
<td>1.3 (0.6)</td>
<td>0.72</td>
<td>-0.54, 0.30</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD) unless otherwise indicated. All \( p \) values \( \geq 0.05 \) lead to the acceptance of the null hypothesis, or the homogeneity of the two groups. 95% CIs that include zero also indicate support for the null hypothesis of equivalence of the two groups.\(^1\)

†Refers to the use of any ICS (triamcinolone, beclomethasone, fluticasone, etc.) at home prior to study entry.

### Table 2—High-Dose Inhaled Flunisolide vs SS in Severe, Acute Adult Asthma*

<table>
<thead>
<tr>
<th>Variables</th>
<th>ICS Group</th>
<th>Prednisone Group</th>
<th>( p ) Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEFR, L/min</td>
<td>190 (80)</td>
<td>379 (130)</td>
<td>0.95</td>
<td>-66.3, \infty</td>
</tr>
<tr>
<td>FEV(_1), L</td>
<td>1.6 (0.6)</td>
<td>2.3 (0.8)</td>
<td>0.33</td>
<td>-21.7, \infty</td>
</tr>
<tr>
<td>Symptom scores</td>
<td>1.4 (0.7)</td>
<td>0.7 (0.9)</td>
<td>0.30</td>
<td>-0.40, \infty</td>
</tr>
<tr>
<td>Readmission</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD). All \( p \) values \( \geq 0.05 \) demonstrate the acceptance of the null hypothesis, or the equality of the two groups. 95% CIs that include the origin (zero) also support the null hypothesis, or the equivalence of the two groups.
charge. Both patient groups were treated with eight doses of methylprednisolone q6h for a total of eight doses following hospital admission for asthma exacerbation. By double-blinded randomized assignment, one group was then treated with high-dose ICS while the other group was treated with prednisone, 40 mg qd. The duration of treatment in both groups was for 7 days from the day of hospital admission. We could detect no difference in outcome between the ICS and the prednisone group in terms of improvement in FEV1, PEFR, symptom scores, ED revisit rate, or rehospitalization rate. We observed no intolerance to ICS in hospitalized patients, such as cough or wheezing, following inhalation of the drug. The two groups were similar from demographic and disease severity standpoints, and so we believe that the patient randomization was successful.

This study has several methodologic limitations. From a statistical point of view, it is underpowered, and the results should therefore be considered preliminary. The study examines outcomes over 1 week following hospital admission, which is a relatively short time. Of interest is whether this result would prevail over a longer period of observation. We selected the 1-week duration as a reasonable estimate of when a patient may see their outpatient provider following hospital discharge. Optimally, the study should have included an arm in which no treatment was administered after discharge. Is it possible that ICS or oral corticosteroids may be completely unnecessary following hospital discharge? Perhaps the eight doses of methylprednisolone used in the hospital would have sufficed to bridge the patient to the outpatient visit? We feel that the predominant evidence holds that there is benefit to corticosteroids following hospital discharge and, therefore, did not include a no-treatment arm for ethical reasons. Likewise, this study was not designed to examine whether the dose of IV corticosteroids was optimal. We acknowledge that our choice of methylprednisolone every 6 h for a total of eight doses was arbitrary, but it falls within accepted guidelines. It is possible that fewer or lower doses may have been equally effective.

In addition, our choice of outcome variables was relatively simplistic. Daily peak flow, and symptom diaries as well as more sophisticated pulmonary function tests may serve as better outcome measures. From the point of clinical operations, we believe that the simple parameters we report are sufficiently robust to support the conclusion that there was no clinically important outcome difference. Patients were asked to record peak flows and symptom scores thrice daily. Our patients had difficulty keeping these records on a reliable basis. Review of the data suggested to us that it was of doubtful quality, and so we chose not to report it. Other investigators report problems with patient self-assessment.

A final methodologic issue relates to compliance with the study medication. Patients were required to bring back their pill bottles and MDIs. Based on pill count and MDI weights, the patients appeared to be very compliant. However, we are well aware of the pitfalls of pill count and MDI weight. We did not use microprocessor counters on our MDIs, nor did we attempt to measure prednisone use via laboratory studies.

ICS are known to be highly effective in the treatment of asthma. Typically, they are used in the outpatient setting, probably because of the widespread perception that their onset of action is relatively slow and therefore inappropriate for the treatment of severe, acute asthma. In fact, ICS have been studied in the emergency treatment of the acutely ill asthmatic. Rodrigo and Rodrigo5 studied high-dose flunisolide with salbutamol in acute, severe ED asthma, and showed impressive improvement in pulmonary function and decreased hospitalization rates when compared to salbutamol alone. In both their clinical trial and in a separate meta-analysis, Rodrigo and Rodrigo4,5 observed that improvement in pulmonary function occurred within 2 to 3 h of treatment with ICS. Several articles have compared ICS with SS in the ED treatment of acute asthma. Our study is not directly comparable to treatment in the ED, examining as it did the period following admission to the hospital from the ED. Our results combined with data of ED trials suggest the real possibility that SS may be unnecessary in the treatment of the hospitalized asthmatic. This hypothesis is unproven and will require additional study. In support of this theory, Bilancia et al22 found that after a 2-day course of IV methylprednisolone, there was no statistically significant difference between a cohort of hospitalized asthmatics treated with oral methylprednisolone and those treated with high-dose inhaled fluticasone propionate. Both groups had comparable rates of treatment failures, percentages of PEFR increase, and mean diurnal variation in PEFR reduction.

Another issue that warrants further investigation is determining the dose of ICS necessary for the treatment of acute, severe asthma. The available studies, including our own, have used several preparations, delivery systems, and dosing levels. These studies only share in common the attribute that the dosing levels are far higher than standard recommendations. Most studies have used a spacer or nebulizer system to deliver ICS, as the acutely ill...
asthmatic may have difficulty in coordinating the use of a solo MDI device. The availability of dry-powder inhalers may reduce the need for inhalation aids. In conclusion, high-dose ICS appear to render unnecessary oral prednisone in the postdischarge period. Furthermore, ICS appear to be well tolerated in patients with acute asthma exacerbation, at least with the formulation and delivery system used in this study.

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