Randomized Clinical Trial of Intramuscular vs Oral Methylprednisolone in the Treatment of Asthma Exacerbations Following Discharge From an Emergency Department*

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Abstract

Objective: To compare the efficacy of long-acting IM methylprednisolone to tapering oral methylprednisolone in adult asthmatic patients discharged from the emergency department (ED).

Methods: Randomized, double-blind, placebo-controlled trial of a single IM dose of 160 mg depot methylprednisolone vs 8-day tapering of a total dose of 160 mg oral methylprednisolone in adult asthmatic patients (age range, 18 to 45 years) who were discharged from the ED following standardized treatment for an acute exacerbation. The primary end point was relapse, which was defined as the need to seek unscheduled care at a doctor’s office, clinic, or ED for symptoms of persistent or worsening asthma within 10 days of ED discharge.

Results: Of 190 patients enrolled into the study, 180 completed the study and the follow-up at 10 days (96%). The relapse rate was nearly identical for the two treatment groups (IM administration, 14.1% [13 of 92 patients]; oral administration, 13.6% [12 of 88 patients]; difference, 0.5% [95% confidence interval, –9.6 to 10.6%]).

Conclusions: Single-dose IM methylprednisolone administered to adult asthmatic patients at ED discharge appears to be a viable therapeutic alternative to a course of oral methylprednisolone. Clinicians may choose to base the route of administration of corticosteroids on concerns about nonadherence to therapy or on the ability of a patient to afford a prescription for outpatient medication.

Asthma is a common disorder accounting for > 1.5 million emergency department (ED) visits per year in the United States.1 There is sound evidence from a meta-analysis2 to support the administration of corticosteroids to patients who have been discharged from EDs following treatment for asthma exacerbations. Despite the proven benefit of therapy with steroids, the relapse rates for asthmatic patients remain high.3 A single IM dose of a long-acting corticosteroid offers the advantage of a sustained drug level, eliminating the need for a pharmacy visit, and may reduce nonadherence.45
Earlier work has suggested a role for corticosteroids with a depot-repository release given via the IM route in asthmatic patients who have been discharged from the ED. Although these previous studies have reported results ranging from a 20% difference in relapse rate at 7 to 10 days favoring IM administration to a 6% difference favoring oral administration, none achieved statistical significance, and all were accompanied by wide confidence intervals (CIs). Consequently, the question of whether the IM repository administration of corticosteroids is of greater, less, or equal efficacy when compared to oral administration of corticosteroids has not yet been answered.

This randomized clinical trial was designed to test the hypothesis that a single IM dose of depot methylprednisolone would reduce relapse rates at 10 days (ie, the primary end point) and 21 days (ie, the secondary end point) compared to an oral tapering course of methylprednisolone given to asthmatic patients who have been discharged from the ED following treatment for an acute exacerbation.

Materials and Methods

Study Design

The study was a prospective, randomized, placebo-controlled, double-blind trial. The study was approved by the Committee on Clinical Investigation of the Albert Einstein College of Medicine and by the Institutional Review Board of the Montefiore Medical Center.

Study Setting and Population

Patients were enrolled from the EDs of two hospitals with a combined adult ED census of 130,000 patients. Patients were considered to be eligible for study entry if they were 18 to 45 years of age and were expected to be discharged from the ED following treatment for an acute asthma exacerbation. This diagnosis was based on the American Thoracic Society Guidelines for the evaluation of impairment/disability in patients with asthma, and included both clinical symptoms and physical examination findings. Eligibility criteria also required a peak expiratory flow rate (PEFR) of ≤ 70% predicted during the ED visit, and a minimum PEFR of ≥ 40% predicted. PEFR entry criteria were included to define an appropriate study population that was ill enough to merit corticosteroid therapy, but was well enough to be managed as outpatients. Predicted values were calculated in the standard fashion, based on age and height. Patients who had other chronic lung diseases, who had known or suspected bacterial pneumonia, who had received systemic corticosteroid therapy in the past month, who currently used theophylline, mast cell stabilizers, or inhaled anticholinergic agents, who had a current illness precluding use of corticosteroids, or who had an allergy to methylprednisolone were excluded from the study.

Study Protocol

The medication was prepared and block-randomized by a research pharmacist who used a computer-generated set of random numbers to package the medications in balanced blocks of 20 (ie, each block of 20 medication packets contained 10 packets of oral methylprednisolone plus an IM placebo and 10 packets of IM methylprednisolone plus oral placebo). The randomization code was held by the pharmacist and was not broken during the course of the study.

A methylprednisolone acetate suspension was selected as the study drug for its pharmacokinetic properties and its familiarity to physicians. Methylprednisolone acetate for IM injection has a time to maximum concentration of 9.0 h and a half-life of 139 h. The 160-mg IM dose (2 mL) was chosen to
minimize the volume and pain of injection, while still administering an amount that was equivalent to the total dose of oral methylprednisolone tapered over 8 days.

Patients fulfilling the entry criteria were approached by treating physicians or trained research associates for enrollment into the trial. Written, informed consent was obtained from all participants. A data collection instrument was completed by trained research associates. All eligible patients received nebulized β-agonist agents and an IV injection of 1 mg/kg methylprednisolone as standard ED treatment.

At ED discharge, consenting patients were randomized to receive in a double-blind fashion either of the following: (1) an IM depot injection of 160 mg (2 mL) methylprednisolone and an 8-day supply of a tapering oral placebo; or (2) an IM injection of 2 mL isotonic saline solution (ie, the placebo) and an 8-day tapering dose of oral methylprednisolone. The protocol for methylprednisolone tapering was as follows: day 1, 32 mg; day 2, 32 mg; day 3, 24 mg; day 4, 24 mg; day 5, 16 mg; day 6, 16 mg; day 7, 8 mg; day 8, 8 mg (total dose, 160 mg).

The injection was reconstituted and administered by an ED nurse who was not blinded to the treatment but who had no involvement in any aspect of the study. This individual was instructed not to provide the patient, physician, or study personnel with any information about the contents of the syringe. Although the placebo and methylprednisolone injections were similar in appearance, the nurse also was instructed not to allow anyone to see the contents of the syringe. The injection was administered in a private setting with no one else present. The oral methylprednisolone and oral placebo were identical in appearance and were given to patients in identical containers. To the best of our knowledge, allocation concealment was maintained.

Patients were given instructions to begin the oral therapy when they arrived home. Written ED discharge instructions explaining the study and how to take the oral medications were given to all participants in English and Spanish. All participants were discharged from the ED with a prescription for an albuterol metered-dose inhaler. Patients were discharged from the ED receiving inhaled corticosteroids if they were currently receiving this therapy. They were instructed to continue all other medications.

The primary end point of the study was relapse, which was defined as the need to seek unscheduled care at a doctor’s office, a clinic, or ED for symptoms of persistent or worsening asthma within 10 days of ED discharge. The secondary end point was relapse between 11 and 21 days. Relapse rates were determined by phone contact after day 10 and day 21. Additional information obtained on follow-up included self-reported pain of IM injection, which was recorded using a validated verbal numerical rating scale, and the development of bruising, swelling, or continued pain for > 7 days at the site of the injection.

**Statistical Analysis**

An *a priori* sample size calculation indicated that 170 patients would be needed to provide 80% power to detect a difference in relapse rate of at least 13.4% at a 2-tailed α of 0.05. We chose 13.4% as the difference in the relapse rate at 7 to 10 days based on the calculation of weighted mean differences in proportions derived from prior work. The distribution of this difference of 13.4% between the two expected sample proportions (oral administration group, 18.7% relapse rate; IM group, 5.3% relapse rate) was approximated by converting these proportions to normal variables using the arcsine transformation (PASS, version 6.0; NCSS; Kaysville, UT). The data were entered into a database program (Microsoft Excel, version 2000; Microsoft; Redmond, WA) and were imported into a statistical software...
package (SPSS, version 10.0.7; SPSS; Chicago, IL) for statistical analysis. The differences in relapse rates between the two treatment groups at 10 and 21 days were reported as simple proportions bounded by 95% CIs. In addition to our primary efficacy analysis, we also performed an intention-to-treat (effectiveness) and sensitivity analysis, based on best-case and worst-case assumptions about outcomes in each treatment group, including all protocol violations and patients who were lost to follow-up.

Results

One hundred ninety patients were entered into the study over a 60-month period from November 1997 to November 2002. As shown in the diagram of the Consolidated Standards of Reporting trials17 (Fig 1), three patients (all in the oral methylprednisolone/IM placebo group) were removed after study entry due to protocol violations. One patient’s asthma was too severe to be discharged safely from the ED, a second patient did not receive a β-agonist prescription at ED discharge, and a third patient was instructed by the primary physician to discontinue the study medication at day 5. Seven patients (IM administration group, three patients; oral administration group, four patients) were lost to follow-up and were excluded from the primary efficacy analysis. The remaining 180 patients, 92 of whom received IM methylprednisolone plus oral placebo, and 88 of whom received oral methylprednisolone plus IM placebo, completed the protocol and were available for follow-up at 10 days. All patients reached for follow-up at 10 days were successfully contacted again for follow-up at 21 days. No patients who were lost to follow-up at 10 days were available for follow-up at 21 days.

As shown in Table 1, the baseline characteristics of the two study groups were similar except for a smaller percentage of men, fewer previous intubations, and greater use of inhaled steroids in the IM methylprednisolone/oral placebo group. About one patient of three in each group was a smoker.

<table>
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<th>Table 1. Baseline Characteristics by Treatment Group</th>
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As shown in Table 2, the relapse rate in the two groups differed by only 0.5% at 10 days, and by 4.2% at 21 days. Although the 10-day relapse rate favored an oral course of methylprednisolone over an IM course by a very slight margin, the 21-day relapse rate reversed itself to favor the IM route. The relapse rates in the IM and oral administration groups could not be distinguished statistically from one another at 10 or 21 days, nor could the 10-day difference in relapse rates of 0.5% be distinguished statistically from the 21-day difference in relapse rates of 4.2%. The differences between the two groups in gender, number of prior intubations, and inhaled steroid use at baseline (Table 1) was not evident when patients who had experienced a relapse were compared with those who had not.

As shown in Table 3, the frequency of side effects associated with IM injection was low among patients in both treatment groups. However, there was significantly more pain and bruising among patients receiving IM methylprednisolone compared to those receiving IM saline solution placebo.

In addition to our primary efficacy analysis, we performed a combined intention-to-treat and sensitivity analysis, under best-case and worst-case assumptions for the IM and oral administration groups at 10 and 21 days. As shown in Table 4, an intention-to-treat analysis at 10 days under best-case assumptions for the IM and oral administration groups showed 6% and 4% differences, respectively, in relapse rates, favoring IM and oral administration. Under identical assumptions, the 21-day follow-up for the IM and oral administration groups showed a difference in relapse rates of 10% and 0%, respectively, favoring IM and oral administration. None of these differences achieved statistical significance, nor could they be distinguished statistically from one another. Similarly, the results of the efficacy and intention-to-treat analyses were statistically indistinguishable.

**Discussion**

Our findings suggest that a single IM dose of methylprednisolone acetate is a viable therapeutic option for the treatment of asthma patients who have been discharged from the ED. This is consistent with two studies\(^7\,^8\) that were published prior to the initiation of our study, and with two additional studies\(^9\,\,\,10\) that were published while this trial was in progress. The findings of these four studies, compared to one
Hoffman and Fiel\textsuperscript{7} compared 7-day relapse rates among 18 asthmatic patients who had been discharged from an ED who were randomized to either a single 80-mg IM dose of methylprednisolone or a 7-day oral taper of methylprednisolone. These authors reported no relapses in the IM group vs a 20% relapse rate among the orally treated patients. Although the 95% CI (−45 to 5%) surrounding the −20% difference in relapse rate favored IM over oral administration of methylprednisolone, the findings were not statistically significant and were too imprecise to support the conclusion that the IM route was superior.

Lee et al\textsuperscript{8} compared 7-day relapse rates among 52 asthmatic patients who had been discharged from an ED who were randomized to one of the following three arms: 17 patients received a single 10-mg IM dose of dexamethasone; 19 patients received an 8-day oral taper of dexamethasone; and 16 patients received placebo administered both IM and orally. These authors reported a 6% relapse rate among the IM administration patients vs no relapses in the oral administration group (difference in relapse rate, 6%). The 95% CI of −5 to 17% indicated that these findings trended in a direction that was the opposite of the data from the study by Hoffman and Fiel,\textsuperscript{7} but were also neither statistically significant nor sufficiently precise to support the conclusion that the oral route was superior to an IM injection.

Combining relapse rates of Hoffman and Fiel\textsuperscript{7} and Lee et al\textsuperscript{8} in a subset meta-analysis of oral vs IM corticosteroid administration, Rowe et al\textsuperscript{2} reported a pooled odds ratio of 0.82 (95% CI, 0.05 to 13.77), indicating that there was no discernible quantitative or statistical difference between the two routes of administration. Despite the close proximity of the odds ratio to the null of 1.00, the width of the CI bounding this point estimate indicates that either the IM or oral route might still be associated with clinically important, although undetected, differences in relapse rates.

To examine this question further, Schuckman et al\textsuperscript{9} compared relapse rates at 7 to 10 days among 168 asthmatic patients who had been discharged from an ED, and had been randomized either to a single 40-mg IM dose of triamcinolone or to 5 days of prednisone therapy at 40 mg/d without a taper. Of the 154 patients available for analysis, these authors reported a 9% relapse rate in the IM group vs a 15% relapse rate among those allocated to oral administration. Although the 95% CI (−16 to 5%) surrounding the −6% difference in relapse rates slightly favored IM over oral administration, this finding was not statistically significant. Despite the increased precision, which was driven by the larger sample size of the study by Schuckman et al,\textsuperscript{9} the CIs remained too wide to support the inference that the two routes of administration possessed equivalent efficacy. These authors concluded, however, that a single IM dose of dexamethasone appeared to be an “attractive alternative” when compliance with an oral regimen was of concern.\textsuperscript{9} This study was published while ours was in progress.

Chan and colleagues\textsuperscript{10} also investigated this question while our trial was underway. These authors compared 7-day and 21-day relapse rates among 171 asthmatic patients discharged from an ED, who had been randomized to either a single 12-mg IM dose of betamethasone or to 7 days of prednisone. Another and to our study, are summarized in Table 5.
therapy at 50 mg/d, without a taper. At 7 days, these investigators reported a 15% relapse rate among
the IM administration patients vs a 25% relapse rate in the oral administration group. Although the tilt
of the 95% CI (−22 to 2%) surrounding the −10% difference in relapse appeared to strongly favor IM
over oral administration at the 7-day follow-up, this trend reversed itself at 21 days, for a relapse rate
of 37% in the IM administration group vs 31% in the oral administration group (95% CI for the difference
of 6% favoring oral administration, −8 to 20%). These were the highest relapse rates reported in any
study comparing IM with oral administration of corticosteroids. Chan et al.10 analyzed their data
according to an intention-to-treat model, classifying all patients who violated protocol or were lost to
follow-up as relapses. As shown in Table 5, when we reanalyzed the data from the study by Chan et
al.,10 using an efficacy analysis, the relapse rates were slightly reduced but still remained the highest of
any reported. The differences in relapse rates between those allocated to oral administration of
corticosteroids vs IM administration were similar in both the efficacy and intention-to-treat analyses at
7 and 21 days.

A difference of 0.5% in relapse rates at 10 days in our study falls within the CIs of the four previous
clinical trials78910 comparing IM vs oral administration of corticosteroids with end points at 7 to 10 days
(Table 5). Similarly, our finding of a −4.2% relapse rate at 21 days falls well within the CIs of the one
prior trial with an end point at 21 days,10 whether the data are analyzed by efficacy or intention-to-
treat (Table 5).

As shown in Table 5, similar to all four previous clinical trials examining this question, we did not find
that either route of administration was superior to the other. However, a failure to identify a difference
between two treatments does not logically support the inference that no difference exists. Although our
data, taken both in isolation and in the context of Table 5, are consistent with the absence of any
important clinical difference between the two routes of administration, our findings lack sufficient
precision to allow us to conclude that IM and oral administration of steroids are equally efficacious.
Indeed, the limits of the CIs bounding the point estimate of a 0.0.5% difference in relapse rate at our
primary end point of 10 days do not allow us to exclude the possibility that the IM administration of
steroids may be associated with as much as 10% more or, conversely, 11% fewer relapses compared to
the oral administration of steroids. To be able to exclude what might be a clinically important
difference in a relapse rate roughly half this size (10% in one group vs 5% in the other for an absolute
difference of 5%) would require about 950 patients, under traditional assumptions of a 2-tailed α of
0.05 and a 1-tailed β of 0.20 (with a power of 80%).

These considerations notwithstanding, the value of 0.5% residing at the center of its CI remains the
single best estimate of the true difference between the two treatment regimens under comparison.
Thus, pending a much larger study, our findings, which are similar to those of all four previous clinical
trials, are most consistent with the conclusion that an IM injection of depot methylprednisolone is at
least as efficacious as a tapering oral dose of methylprednisolone among asthmatic patients who were
discharged from the ED following treatment for an acute exacerbation. Whether or not the clinician
chooses one modality over another may therefore be determined by concerns about nonadherence to
therapy or by an individual’s economic status and their ability to afford a prescription for an oral
medication.

Inferences that can be drawn from this study are limited in several important respects. (1) Data were
collected by convenience sampling over a 60-month period. Although this may have caused assembly
bias, which might in turn undercut generalizability, the validity of our results should remain intact
because the randomization process, which took place after consenting subjects were enrolled, provides
protection against selection bias, as well as against confounders both known and unknown. An IV dose of methylprednisolone was required in all patients. Although commonly administered to asthmatic patients meeting our entry criteria, this may not be standard practice in all EDs.

Consistent with prior work, we conclude that single-dose IM injection of methylprednisolone administered to adult asthmatic patients at ED discharge appears to be a reasonable therapeutic alternative to an oral course of methylprednisolone.

Footnotes

Abbreviations: CI = confidence interval; ED = emergency department; PEFR = peak expiratory flow rate

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