EFFECT OF SYSTEMIC GLUCOCORTICOIDs ON EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE


ABSTRACT

Background and Methods Although their clinical efficacy is unclear and they may cause serious adverse effects, systemic glucocorticoids are a standard treatment for patients hospitalized with exacerbations of chronic obstructive pulmonary disease (COPD). We conducted a double-blind, randomized trial of systemic glucocorticoids (given for two or eight weeks) or placebo, in addition to other therapies, for exacerbations of COPD. Most other care was standardized over the six-month period of follow-up. The primary end point was treatment failure, defined as death from any cause or the need for intubation and mechanical ventilation, readmission to the hospital for COPD, or intensification of drug therapy.

Results Of 1840 potential study participants at 25 Veterans Affairs medical centers, 271 were eligible for participation and were enrolled; 80 received an eight-week course of glucocorticoid therapy, 80 received a two-week course, and 111 received placebo. About half the potential participants were ineligible because they had received systemic glucocorticoids in the previous 30 days. Rates of treatment failure were significantly higher in the placebo group than in the two glucocorticoid groups combined at 30 days (33 percent vs. 23 percent, P=0.04) and at 90 days (48 percent vs. 37 percent, P=0.04). Systemic glucocorticoids (in both groups combined) were associated with high costs and relatively poor outcomes. In addition to antibiotics, oxygen, and bronchodilators, most hospitalized patients receive systemic glucocorticoids. Less severely ill patients often receive oral glucocorticoids as outpatients.

Systemic glucocorticoids improve outcomes in patients with acute asthma, but their clinical efficacy in the treatment of COPD is less clear. Two small trials suggested that several days of therapy with systemic glucocorticoids improved the forced expiratory volume in one second (FEV₁) during exacerbations of COPD. Another trial found that a single dose of methylprednisolone did not improve spirometric results over the succeeding five hours. None of these trials were explicitly designed to evaluate clinical outcomes. The role of systemic glucocorticoids in patients with stable COPD is similarly unclear.

Conclusions Treatment with systemic glucocorticoids results in moderate improvement in clinical outcomes among patients hospitalized for exacerbations of COPD. The maximal benefit is obtained during the first two weeks of therapy. Hyperglycemia of sufficient severity to warrant treatment is the most frequent complication. (N Engl J Med 1999;340:1941-7.) ©1999, Massachusetts Medical Society.
Study Design

We designed this study to assess the equivalence of two approaches to the treatment of COPD. Systemic glucocorticoids are the standard therapy for hospitalized patients with COPD, even though they have adverse effects. Therefore, the withholding of glucocorticoids may be viewed as an experimental intervention associated with no glucocorticoid-related complications. The planning committee settled on a 7.5 percent absolute difference in the rate of treatment failure as the clinically meaningful upper limit. In other words, withholding glucocorticoids would be considered the preferred treatment if the results showed a difference in the failure rate (the rate with placebo minus the rate with active treatment) of 7.5 percent or less. The secondary objective was to assess the equivalence of two different periods of therapy (two and eight weeks). The follow-up period lasted for six months from the time of enrollment. A detailed description of the rationale for the study, its design, the protocol, and the planned analyses is provided elsewhere.

Study Population

All patients admitted to participating Veterans Affairs medical centers for exacerbations of COPD were potential subjects. The principal inclusion criteria were a clinical diagnosis of exacerbation of COPD, an age of 50 years or more, a history of 30 pack-years or more of cigarette smoking, and either an FEV₁ of 1.50 liters or less or an inability to undergo spirometry because of dyspnea. The principal exclusion criteria were a diagnosis of asthma, use of systemic glucocorticoids within the preceding 30 days, coexisting medical conditions that made survival for at least 1 year unlikely, and inability to give informed consent. We obtained base-line data on respiratory disease and other pertinent aspects of the medical history by means of a questionnaire.

Treatments

We randomly assigned patients within 12 hours after presentation to one of three treatment groups. The first group received eight weeks of glucocorticoid therapy, consisting of intravenous methylprednisolone (Solu-Medrol, Pharmacia & Upjohn, Kalamazoo, Mich.) (given in a dose of 125 mg every 6 hours for 72 hours) followed by once-daily oral prednisone (60 mg on study days 4 through 7, 40 mg on days 8 through 11, 20 mg on days 12 through 43, 10 mg on days 44 through 50, and 5 mg on days 51 through 57). The second group received two weeks of glucocorticoid therapy, consisting of intravenous methylprednisolone (125 mg every 6 hours for 72 hours), followed by oral prednisone (60 mg on days 4 through 7, 40 mg on days 8 through 11, and 20 mg on days 12 through 15), with placebo capsules on study days 16 through 57. The third group received placebo, consisting of an equivalent volume of intravenous 5 percent dextrose solution (every 6 hours for 72 hours), followed by placebo capsules on days 4 through 57. Randomization was stratified according to hospital with a permuted-block scheme; 40 percent of the patients were assigned to the placebo group, 30 percent to the eight-week glucocorticoid group, and 30 percent to the two-week glucocorticoid group.

The Veterans Affairs Cooperative Studies Clinical Research Pharmacy Coordinating Center distributed the study medications. Designated research pharmacists dispensed the intravenous medications in a blinded fashion. All patients received the same number of identical-appearing study capsules in blister packs. We assessed compliance on the basis of capsule counts.

The patients remained hospitalized for at least three days for intravenous therapy, after which they received capsules of prednisone or placebo for eight weeks. Hospital staff decided the date of discharge after three days of intravenous therapy. All the patients received a broad-spectrum antibiotic for seven days. For the entire six-month period, the patients were required to use an inhaled β-adrenergic agonist (two puffs from a metered-dose inhaler or a nebulizer treatment at least four times daily), inhaled ipratro-
to identify variables that predicted treatment failure within six months. All reported P values are two-tailed.

RESULTS

Enrollment began in November 1994 and concluded in October 1996, one year ahead of schedule. On the basis of interim analyses, the Veterans Affairs Cooperative Studies Evaluation Committee recommended termination of enrollment at that time.

Study Population

A total of 1840 potential patients at 25 Veterans Affairs medical centers were screened for the study, of whom 271 were found to be eligible and were enrolled. The enrollment rate was lower than had been projected, largely because of a substantial decline in admissions for COPD throughout the Veterans Affairs medical system and an unexpectedly high rate of exclusion because of recent use of systemic glucocorticoids. Among the patients who were screened, 49.9 percent had taken systemic glucocorticoids in the previous 30 days. Other common reasons for exclusion included unwillingness or inability to participate (23.2 percent), a history of less than 30 pack-years of smoking (14.6 percent), and coexisting medical conditions expected to limit survival (18.4 percent).

Discontinuation of Study Drugs and Compliance

Study drugs were discontinued for reasons other than a primary end point in 10 patients assigned to placebo (9 percent), 10 assigned to two weeks of
glucocorticoids (12 percent), and 5 assigned to eight weeks of glucocorticoids (6 percent). Follow-up data were complete for 19 of these 25 patients. All available data were included in the analyses. On the basis of counts of returned study capsules, the compliance rate was 89 percent in the placebo group, 85 percent in the two-week glucocorticoid group, and 87 percent in the eight-week glucocorticoid group.

Primary Outcomes

Figure 1 shows Kaplan–Meier estimates of rates of first treatment failure for the three study groups, and Table 2 shows the reasons for treatment failure at 30, 90, and 182 days. At least one treatment failure occurred in approximately half the patients. Intensification of therapy was the most common reason for treatment failure, accounting for 70 percent of the total failures at 30 days, 62 percent at 90 days, and 58 percent at 182 days. When therapy was intensified, physicians administered open-label systemic glucocorticoids in more than 75 percent of cases.

The trial did not demonstrate equivalence of outcomes at any time. When the upper limits of one-sided confidence intervals are used to compare failure rates between groups, the results show that the withholding of glucocorticoids may have increased treatment-failure rates by as much as 20 percent at 30 days, 21 percent at 90 days, and 12 percent at 182 days. All values exceeded the limit of 7.5 percent set by the protocol.

As compared with placebo, glucocorticoids significantly reduced the rate of first treatment failure at 30 days (23 percent vs. 33 percent, \( P=0.04 \)) and 90 days (37 percent vs. 48 percent, \( P=0.04 \)) (Table 2). Treatment-failure rates did not differ significantly at six months (51 percent in the combined glucocorticoid groups vs. 54 percent in the placebo group, \( P=0.58 \)). The duration of glucocorticoid therapy (two weeks or eight weeks) had no significant effect on the rate of treatment failure at any time.

Length of Hospitalization

The average length of the initial hospitalization was significantly longer in the placebo group than in the combined glucocorticoid groups (9.7 vs. 8.5 days, \( P=0.03 \)). After the initial hospitalization, patients in the placebo group spent an average of 2.0 days in the hospital because of COPD, as compared with 1.9 days for patients in the glucocorticoid groups (\( P=0.98 \)). Glucocorticoid-treated patients, on average, spent more time in the hospital for reasons other than COPD than did patients receiving placebo (4.4 vs. 1.2 days, \( P=0.07 \)).

Spirometric Findings

FEV\textsubscript{1} improved significantly faster in the patients who received systemic glucocorticoids than in those who received placebo (Fig. 2). The maximal difference, approximately 0.10 liter, was evident by the first day after enrollment. By the end of two weeks, FEV\textsubscript{1} did not differ significantly between the active-treatment and placebo groups.
Eleven of the patients in this group were rehospitalized for infection; 9 of the 11 patients in each group for whom data were available. The asterisks denote \( P<0.05 \) for the comparison with placebo. The bars indicate standard errors.

**Table 2. Cumulative Primary Outcomes According to Treatment Assignment.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (N=111)</th>
<th>Glucocorticoids for 2 wk (N=80)</th>
<th>Glucocorticoids for 8 wk (N=80)</th>
<th>( P ) value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>3 (3)</td>
<td>0</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Intubation</td>
<td>3 (3)</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Readmission for COPD</td>
<td>5 (5)</td>
<td>4 (5)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Intensification of therapy</td>
<td>26 (23)</td>
<td>13 (16)</td>
<td>13 (16)</td>
<td>0.04</td>
</tr>
<tr>
<td>Total</td>
<td>37 (33)</td>
<td>19 (24)</td>
<td>18 (22)</td>
<td></td>
</tr>
<tr>
<td>90 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>4 (4)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Intubation</td>
<td>3 (3)</td>
<td>3 (4)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Readmission for COPD</td>
<td>13 (12)</td>
<td>8 (10)</td>
<td>6 (8)</td>
<td></td>
</tr>
<tr>
<td>Intensification of therapy</td>
<td>33 (30)</td>
<td>17 (21)</td>
<td>20 (25)</td>
<td>0.04</td>
</tr>
<tr>
<td>Total</td>
<td>53 (48)</td>
<td>30 (38)</td>
<td>29 (36)</td>
<td></td>
</tr>
<tr>
<td>182 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death†</td>
<td>4 (4)</td>
<td>2 (2)</td>
<td>3 (4)</td>
<td></td>
</tr>
<tr>
<td>Intubation</td>
<td>3 (3)</td>
<td>3 (4)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Readmission for COPD</td>
<td>17 (15)</td>
<td>12 (15)</td>
<td>13 (16)</td>
<td></td>
</tr>
<tr>
<td>Intensification of therapy</td>
<td>36 (32)</td>
<td>22 (28)</td>
<td>24 (30)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>60 (54)</td>
<td>39 (49)</td>
<td>42 (52)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

*\( P \) values are for comparisons of the placebo group with the combined glucocorticoid groups, by the log-rank test.

†Only deaths that were counted as primary outcomes are listed. The total numbers of deaths during six months of follow-up were 11 in the placebo group and 13 in the combined glucocorticoid groups.

### Complications

Table 3 shows the reported complications for each treatment group over the six months. A greater proportion of patients in the glucocorticoid groups than in the placebo group had hyperglycemia requiring treatment (15 percent vs. 4 percent, \( P=0.002 \)). Twenty-two of the 24 episodes in the glucocorticoid groups occurred during the first 30 days of follow-up. Sixteen of the 24 glucocorticoid-treated patients with hyperglycemia were known to have diabetes. The patients who received glucocorticoids also had more adverse events classified as "other" (\( P=0.04 \)); these included 41 separate symptoms or conditions, most of which were not thought to be caused by glucocorticoids. Reported rates of secondary infection did not differ significantly among the three groups, but the eight-week glucocorticoid group had the highest proportion of patients with serious infections. Eleven of the patients in this group were rehospitalized with a primary diagnosis of infection; 9 of the 11 had pneumonia. Only four patients in the placebo group and one in the two-week glucocorticoid group were rehospitalized for infection.

### Subgroup Analyses

As specified by the protocol, we performed subgroup analyses for the following variables: base-line FEV\(_1\), theophylline use before randomization, hospitalization for exacerbation in the previous year, and history of hospitalization for exacerbation in the previous year. None of the comparisons showed significant differences among the three groups.

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**Table 3. Complications of Treatment during the Six-Month Follow-Up Period.**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Placebo (N=111)</th>
<th>Glucocorticoids for 2 wk (N=80)</th>
<th>Glucocorticoids for 8 wk (N=80)</th>
<th>( P ) value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>4 (4)</td>
<td>14 (18)</td>
<td>10 (12)</td>
<td>0.002</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>5 (5)</td>
<td>0</td>
<td>3 (4)</td>
<td>0.21</td>
</tr>
<tr>
<td>Secondary infection</td>
<td>19 (17)</td>
<td>12 (15)</td>
<td>18 (22)</td>
<td>0.73</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (4)</td>
<td>6 (8)</td>
<td>4 (5)</td>
<td>0.33</td>
</tr>
<tr>
<td>Psychiatric disorder</td>
<td>3 (3)</td>
<td>5 (6)</td>
<td>2 (2)</td>
<td>0.47</td>
</tr>
<tr>
<td>Other adverse events†</td>
<td>16 (14)</td>
<td>18 (22)</td>
<td>21 (26)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*\( P \) values are for comparisons of the placebo group with the combined glucocorticoid groups, by the chi-square test.

†This category includes 41 different symptoms or conditions.
nalization because of COPD in the previous two years, a history of cough, a history of wheezing, a history of sputum production, and a history of chest colds. Multiple logistic regression indicated that a base-line value for FEV₁ that was less than the median value of 0.73 liter predicted a higher rate of treatment failure at 182 days (odds ratio, 1.8; 95 percent confidence interval, 1.1 to 3.1), as did theophylline use before randomization (odds ratio, 2.3; 95 percent confidence interval, 1.3 to 4.0). Only prior hospitalization because of COPD had a significant interaction with the treatment assignment (P = 0.01). Treatment with glucocorticoids was associated with a more favorable outcome in the group of 184 patients who had previously been hospitalized because of COPD than in the group of 87 with no history of hospitalization because of COPD (odds ratio, 4.6; 95 percent confidence interval, 1.4 to 14.8). In the group of previously hospitalized patients, the failure rate at six months was 66.7 percent for those who received placebo and 49.5 percent for those who received glucocorticoids.

**DISCUSSION**

We found that the withholding of systemic glucocorticoids was not equivalent to active treatment for hospitalized patients with COPD. Glucocorticoids were marginally superior to placebo in reducing rates of treatment failure at 30 and 90 days, but not at 6 months. Glucocorticoid therapy also shortened the initial hospital stay by an average of 1.2 days. This difference may be an underestimate, because the protocol required a hospital stay of at least three days and because some patients assigned to receive placebo also received open-label glucocorticoids. Glucocorticoid-induced improvements in FEV₁ provide a plausible basis for the better clinical outcomes. The magnitude of the early effect of treatment on FEV₁, approximately 0.10 liter, is similar to that found in a previous study. More patients received open-label glucocorticoids as the study progressed, so we may have underestimated the true differences at later times.

Hyperglycemia of sufficient severity to require therapy was the major complication of glucocorticoids that we identified. This finding may be due in part to the higher proportions of patients with diabetes in the glucocorticoid groups than in the placebo group, but hyperglycemia is a known complication of glucocorticoid therapy. We also noted a trend toward longer hospital stays for causes other than COPD in both glucocorticoid groups. Careful review of these data revealed an unusual number of infections requiring hospital readmission in the eight-week glucocorticoid group. Controlled trials of treatment for other diseases have shown an increased risk of serious infection in patients receiving systemic glucocorticoids.

Osteoporosis was not evaluated in this trial, but even relatively brief courses of systemic glucocorticoids cause reductions in trabecular bone mineral density. The cumulative effects of long-term therapy confer a substantial risk of painful vertebral fractures and other long-term complications.

Intensification of pharmacologic therapy accounted for more than half of all treatment failures at six months and an even higher proportion during the early weeks of follow-up in our study. Open-label glucocorticoids were administered in most of these cases. Thus, the principal consequence of withholding glucocorticoids in patients receiving placebo was to delay their administration to about half of these patients. The other half recovered and received no glucocorticoids during the full six months of follow-up.

The overall exposure to glucocorticoids among patients hospitalized for COPD would be substantially decreased if the drug were withheld until it was evident that other therapy had failed. The disadvantages of this option are a delay in the administration of effective therapy to patients with severe dyspnea and a prolongation of the average hospital stay by slightly more than a day.

Recent use of systemic glucocorticoids disqualified half the patients screened for this study, and these patients might have had different responses to glucocorticoids. We designed this study specifically for hospitalized patients, reasoning that the effect of treatment would be most evident in the sickest patients. However, systemic glucocorticoids are also frequently used for outpatient treatment of COPD, and the clinical profiles of nonhospitalized patients may be different.

We conclude that systemic glucocorticoids decrease the rate of treatment failure by about 10 percentage points for up to 90 days when used for patients hospitalized with exacerbations of COPD. A two-week regimen was as effective as an eight-week regimen; this result was consistent with those of small trials involving patients with acute asthma. In addition, subgroup analyses suggest that the treatment benefit may be restricted largely to patients who have previously been hospitalized because of COPD.
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REFERENCES