Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial

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Summary

Background The role of oral corticosteroids in treating patients with exacerbations of chronic obstructive pulmonary disease (COPD) remains contentious. We assessed in a prospective, randomised, double-blind, placebo-controlled trial the effects of oral corticosteroid therapy in patients with exacerbations of COPD requiring hospital admission.

Methods We recruited patients with non-acidotic exacerbations of COPD who were randomly assigned oral prednisolone 30 mg once daily (n=29) or identical placebo (n=27) for 14 days, in addition to standard treatment with nebulised bronchodilators, antibiotics, and oxygen. We did spirometry and recorded symptom scores daily in inpatients. Time to discharge and withdrawals were noted in each group. We recalled patients at 6 weeks to repeat spirometry and collect data on subsequent exacerbations and treatment. Hospital stay was analysed by intention to treat and forced expiratory volume in 1 s (FEV₁) according to protocol.

Findings FEV₁ after bronchodilation increased more rapidly and to a greater extent in the corticosteroid-treated group: percentage predicted FEV₁ after bronchodilation rose from 25·7% (95% CI 21·0–30·4) to 32·2% (27·3–37·1) in the placebo group (p=0·0001) compared with 28·2% (23·5–32·9) to 41·5% (35·8–47·2) in the corticosteroid-treated group (p=0·0001). Up to day 5 of hospital stay, FEV₁ after bronchodilation increased by 90 mL daily (50·8–129·2) more rapidly in the corticosteroid-treated group. Groups did not differ at 6-week follow-up.

Interpretation These data provide evidence to support the current practice of prescribing low-dose oral corticosteroids to all patients with non-acidotic exacerbations of COPD requiring hospital admission.

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were eligible for entry into the study if they had a history of increased breathlessness and at least two of the following symptoms for 24 h or more: increased cough frequency or severity, increased sputum volume or purulence, and increased wheeze. We included patients who were aged 40–80 years, had a history of at least 20 pack-years of cigarette smoking, and had physiological evidence of airflow limitation with initial FEV<sub>1</sub> less than 70% predicted and FEV<sub>1</sub>/forced vital capacity ratio less than 75%.<sup>2</sup>

We excluded patients if they had a personal or family history of asthma or atopy, uncontrolled left-ventricular failure, clinical or radiological evidence of pneumonia, received oral corticosteroids within 1 month of presentation, or if arterial blood pH on admission was less than 7·26. All patients gave written informed consent to participate, and the study was approved by the district ethics committee.

Study design

One investigator (LD) took a detailed medical history and examined patients at admission. The investigational protocol was started within 3 h of presentation to the accident and emergency department. Patients received standard treatment with nebulised β-agonist (5 mg salbutamol) and an anticholinergic (500 µg ipratropium bromide) every 6 h, controlled oxygen therapy, and oral or intravenous antibiotics at the judgment of the admitting physician. Any patient who was receiving inhaled corticosteroid therapy before randomisation was continued on this therapy. In addition, we randomly assigned patients 30 mg prednisolone every day for 14 days or identical placebo. Randomisation was done by the hospital pharmacy according to a table of random numbers. Packages of treatment were numbered in advance and used consecutively. All patients, investigators, respiratory physicians, technicians, and other hospital staff were masked to treatment status until the end of the study. Study duration was from the time of admission to the time of discharge and included a follow-up visit 6 weeks after admission.

On admission, we took blood samples for full blood count, including absolute eosinophil count, and arterial blood gas measurement. Sputum was collected for microscopy, culture, and sensitivity. Spirometry was done daily from admission, before, and 15 min after 5 mg nebulised salbutamol, by a dry-blow spirometer that met the American Thoracic Society and British Thoracic Society standards.<sup>14</sup> At least three forced expiratory manoeuvres were obtained on each occasion until two were within 5%. We compared airflow measurements with European Steel and Coal Company predicted values.<sup>15</sup> We obtained a daily symptom score, which was calculated from a diary completed by the patient. Questions were asked about breathlessness, sputum production, wheeze, mobility, sleep quality, cough, and general well-being. Patients were asked to score each of the symptoms from 0 (much better than usual) to 5 (much worse than usual). We also collected data about potential side-effects of oral corticosteroids (mood swings, heartburn, and overt gastrointestinal bleeding), and tested patients’ urine daily for glucose.

On day 5, static lung volume was measured by helium dilution, and transfer factor by single-breath method (Benchmark respirometer, PK Morgan, Rainham, Kent, U.K.). We did skin tests to eight common allergens. Also on day 5, we used the St George’s respiratory questionnaire to assess patients’ usual health status.<sup>14</sup> Patients were asked, “Ignoring this admission, how has your health been over the last 6 months?” and were shown a 200 mm visual analogue scale with markings every 20 mm from 0 (could not have been worse) to 10 (perfect health) and asked to point to the number that they felt best answered the question.

The respiratory physicians in charge of the patients, who were not investigators, were free to withdraw patients from the study at any time if they felt clinical improvements were not satisfactory. We automatically withdrew any patient whose arterial blood pH fell below 7·26 and treated them with oral corticosteroids and supportive therapy as required. Patients were free to withdraw at any time if they were not satisfied with their progress. The physicians in charge also decided the time at which patients reached medical fitness for discharge, and it is this date that we used. In some patients, the actual time to discharge was delayed because of social and transport arrangements. On the day of discharge, a second visual analogue score was recorded for the answer to, “How do you feel today compared to the day of admission?” from 0 (very much worse) to 10 (very much better).

At 6 weeks after admission, we recalled patients to repeat spirometry before and after 5 mg nebulised salbutamol and to complete a second St George’s respiratory questionnaire and visual analogue scale score of health perception over the past 6 months. We collected data about treatment at follow-up and whether patients had required treatment for further exacerbations from their family physician or the hospital since discharge.

Statistical analysis

We calculated that a sample size of 27 in each group would give us 80% power to detect a difference of 0·05 L per day in mean slope between the groups, with an SD of 0·0625. All data were analysed with Minitab version 1 and SPSS version 8.0. We calculated means (SE), and used Student’s t test, ANOVA, and ANCOVA to compare normally distributed data, and Wilcoxon’s rank and χ<sup>2</sup> tests to compare non-normal data.

Results

We screened 246 patients for the study, and 60 met the inclusion criteria (figure 1). The most common reason for exclusion was previous treatment with oral corticosteroids before attending the accident and emergency department. Of the four patients refusing consent, three declined because they refused oral corticosteroids after being told of possible side-effects and one because she did not wish to participate in a clinical trial.

29 patients were randomly assigned active treatment and 27 were assigned placebo. Six patients were withdrawn from the study: five in the placebo group (on days 1, 2, 3, 6, and 13) and one in the corticosteroid-treated group (day 11). Only one patient (on placebo) was...
Patients withdrawn because of respiratory acidosis. During week 1 of the study, patients in the placebo group were significantly more likely to be withdrawn than those in the active-therapy group (p=0·034). Patients withdrawn from the study had significantly lower percentage predicted FEV\(_1\) on admission than those completing study. *p=0·008.†p=0·004.

Table 1: Baseline characteristics of patients

Long-term oxygen therapy, and two (4%) inhaled long-acting \(\beta\)-agonists. At study entry there were no differences in previous treatment between groups.

34 patients had purulent sputum on admission, although only 11 yielded positive cultures (seven \(P\) aeruginosa, two \(S\) pneumoniae, one \(M\) catarrhalis, and one \(P\) aeruginosa). 52 patients were treated with oral or intravenous antibiotics. The mean percentage predicted residual volume measured on day 5 of admission was 181·4% (SE 6·8), total lung capacity 112·3% (2·0), and single-breath diffusing capacity 65·3% (3·4), and there were no differences between groups. No patient had a positive skin test. There were no deaths during admission. 28 patients on oral corticosteroids and 22 on placebo completed the study to the time of discharge, but two died before the 6-week follow-up visit. Characteristics did not differ between groups on admission (table 2).

By the time of discharge, percentage predicted FEV\(_1\) before bronchodilation had risen from 21·4% (95% CI 16·5–26·3) to 31·0% (26·3–35·7) in the placebo group (p<0·0001) and from 27·4% (22·5–32·3) to 38·4% (32·9–43·9) in the corticosteroid-treated group (p<0·0001). Percentage predicted FEV\(_1\) after bronchodilation rose from 25·7% (21·0–30·4) to 32·2% (27·3–37·1) in the placebo group (p<0·0001) and 28·2% (23·5–32·9) to 41·5% (35·8–47·2) in the corticosteroid-treated group (p<0·0001). Changes in FEV\(_1\) after bronchodilation were significantly greater in the corticosteroid-treated group (figure 2) and these changes were similar to values before bronchodilation. Until day 5, FEV\(_1\) after bronchodilation increased in the corticosteroid-treated group by 90 mL per day (50·8–129·2) compared with that in the placebo group of only 30 mL per day (10·4–49·6; p=0·039). With FEV\(_1\) after bronchodilation on admission as a covariate, the increase until day 5 in the corticosteroid-treated group remained significantly greater than that in the placebo group (p=0·048). Improvement plateaued earlier in the corticosteroid-treated group; by day 5, patients receiving corticosteroids had increased FEV\(_1\), after bronchodilation to 92% of that achieved at discharge, compared with only 85% in the placebo group (p=0·041). Changes in forced vital capacity were similar to those seen in FEV\(_1\).

**Table 2: Demography of patients on admission**
Visual analogue scale scores during the admission period rose significantly in the two groups by a mean of 2.6 (0.5 to 5.7) in the placebo group and 3.4 (2.8–4.0) in the corticosteroid-treated group (both p<0.0001). Decreases in symptom scores were seen in the two groups. The greatest symptom changes were found in sleep quality, breathlessness, mobility, and general well-being, with a trend towards greater improvement in the corticosteroid-treated group. In both groups, the most striking changes in symptom scores were seen between days 0 and 1, and days 1 and 2, with a further improvement from day 2 to discharge (p=0.01, p=0.005, p<0.0001). There were no reports of change in mood. Three patients in the corticosteroid-treated group and two in the placebo group complained of heartburn, but there were no episodes of overt gastrointestinal bleeding. Six patients in the corticosteroid-treated group developed transient glycosuria.

Length of hospital stay was analysed by intention to treat for all 56 patients in the study. The median length of stay in patients treated with oral corticosteroids (7 days) was significantly shorter than in those receiving placebo (9 days; p=0.027; figure 3).

At 6 weeks, percentage predicted FEV₁, after bronchodilation was 39.6% (95% CI 32.5–46.7) in the corticosteroid-treated group and 33.2% (27.9–38.5) in the placebo group, which were not significantly different to discharge values. There was no change in St George’s respiratory questionnaire or visual analogue scale scores for health perception in the past 6 months in the two groups. 16 patients had required treatment for further exacerbations of COPD, nine in the oral corticosteroid group and seven in the placebo group. 11 patients had received further antibiotics or oral corticosteroids from their family physicians, and five had required further hospital admission, during which they had also received antibiotics or oral corticosteroids. There was no difference in exacerbation rate, admission rate, or treatment received between the two groups. None of age, current smoking or ex-smoking, eosinophil count, or concurrent treatment predicted whether further exacerbations might occur within this 6-week period.

Discussion

Any treatment that can hasten the resolution and lower the costs of exacerbations of COPD is welcomed. Data from randomised trials in outpatients suggest that oral corticosteroids can increase the rate of resolution of the attack, but data have only been seen in short-term treatment of inpatients and the impact on health costs was unclear. We found significant differences in the rate of improvement of FEV₁, before and after bronchodilation, compared with placebo, which suggests that the effect of oral prednisolone was more than an indirect effect on bronchomotor tone. Hospital stays were shorter for patients treated with prednisolone than for those on placebo.

Oral prednisolone is widely prescribed for exacerbations of COPD and was the most common reason for patients’ ineligibility. Similar difficulties have been seen in other studies. Ethical constraints prevented us from extending our study to acidotic patients, although we have no reason to suppose they would have differed in changes in FEV₁. Likewise, we were obliged by our ethics committee to offer an open trial of oral corticosteroids to all patients withdrawn. Thus, we presented hospital stay on an intention-to-treat basis, but restricted data for FEV₁ to the according-to-protocol analysis. This approach weighs against the corticosteroid-treated group because the sickest patients probably dropped out first, which would lead to a subsequent improvement in the rate of recovery in the placebo group.

We took measurements after high doses of nebulised β-agonist to follow the patients’ progress. Data in similar patients suggest that nebulised β-agonist or anticholinergics are probably equally effective bronchodilators during recovery from an exacerbation. Even at discharge, our 56 patients remained significantly obstructed, with a mean percentage predicted FEV₁ after bronchodilation of 37.5% (SE 2.0).

Spirometry was done more often than in the outpatient study and the rate of change of FEV₁ after bronchodilation was three times greater in the corticosteroid-treated group than in the placebo group. Maximum improvement in FEV₁ after bronchodilation was seen by day 5 in the corticosteroid-treated group, whereas time to plateau in the placebo group was significantly longer. Since the improvement reached a plateau at day 4 in the corticosteroid-treated group, the 90 mL per day value (calculated at day 5) may underestimate the rate of improvement. Similar changes were seen for forced vital capacity.

Symptom changes showed a similar time course in each group, and like the outpatients’ showed a trend towards greater improvement in the corticosteroid-treated group that did not reach significance. This may reflect the non-parametric nature of such data, or the need for greater numbers in the trial. Both groups showed significant improvements over the admission period that did not match the changes in FEV₁, with substantial changes in general well-being, sleep quality, and mobility within 48 h of admission, and much smaller changes in perceived cough, wheeze, and sputum production.

Our patients were not only physiologically more severely affected than in other studies, but had a worse health status than patients admitted with exacerbations in other UK studies. Although we reported similar improvements in health during admission in the two groups, this similarity did not change during the 6 weeks of follow-up; spirometry was similar at discharge. At 6 weeks the St George’s respiratory questionnaire did not register any change from that completed at 5 days, which suggested that either the score changes less in more severe patients, or recovery from an exacerbation takes longer than 6 weeks to register. Although improvement in FEV₁ after bronchodilation was maintained at 6 weeks, patients...
treated with corticosteroids had similar morbidity at follow-up to those receiving placebo, which suggests that with treatment at 30 mg the initial benefit does not extend beyond the early stages of recovery from an exacerbation.

Neither the mechanism of the effects of oral prednisolone nor the selection of patients most likely to benefit is clear. Despite the absence of any effect on several cytokines in stable patients, other data suggest that eosinophils and neutrophils are increased in exacerbations of COPD. No simple clinical, biochemical, or physiological marker, including duration of disease, current smoker or ex-smoker, presence or absence of acute infection, eosinophil count, and baseline FEV₁, reliably distinguished those patients who responded from those who did not. Prescription of oral corticosteroids for all patients may therefore be the most practical solution.

Our data support the current practice of prescribing low-dose oral prednisolone to patients with non-acidotic exacerbations of COPD who require admission to hospital. Benefits in spirometric improvement are clearly seen within the first 5 days and are matched by an improvement in symptoms of well-being, mobility, and sleep quality. However, the benefits do not extend beyond hospital discharge and shorter courses may be equally effective.

Contributors
P M A Calverley and R M Angus had the original idea for the study, which was developed and planned by all contributors. L Davies recruited the patients, did the clinical assessments, organised the investigations, and analysed the data. All investigators contributed to the writing and critical revision of the paper.

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References