

Evidence-Based Medicine: Systemic Corticosteroids for Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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Abstract

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MeSH Words: Humans, Acute Disease, Administration, Oral, Adrenal Cortex Hormones/tu (therapeutic use), Glucocorticoids/ad (administration and dosage), Lung Diseases, Obstructive/dt (drug therapy), Randomized Controlled Trials

Objective

To determine the efficacy of corticosteroids, administered either parenterally or orally, on the outcome in patients with acute exacerbations of Chronic Obstructive Pulmonary Disease (COPD).

Search Strategy

Searches were carried out using the Cochrane Airways Group COPD RCT register. Additional studies were sought in the bibliographies of randomized controlled trials and review articles. Authors of identified randomized controlled

trials were contacted for other published and unpublished studies.

Study Selection

Randomized controlled trials comparing corticosteroids that were administered either parenterally or orally with an appropriate placebo for the treatment of COPD. Other non-corticosteroid interventions such as bronchodilators and antibiotics intervention were standardized for both treatment arms. All clinical studies involving acute asthma were excluded.

Participants were adults with COPD disease and a recent exacerbation defined by any combination of symptoms such as an increase in breathlessness, sputum volume, sputum purulence, cough or wheeze and common cold symptoms. Most subjects were chronic tobacco smokers. The Primary outcome measures were: treatment Failure (e.g. hospital readmission rates or return to emergency department) and mortality.

Data Extraction

Two reviewers independently examined all selected studies. The trials entered were scored according to the Cochrane adequacy of allocation concealment and the Jadad criteria (Jadad, 1996). All studies were assessed for the reliability of the diagnosis of COPD using the following criteria: Was the age of patients over 45 years? Was the smoking history greater than 10 pack years? Were the subjects with a previous physician diagnosis of asthma excluded? Was there evidence of airflow obstruction?

For continuous variables, a weighted mean difference (WMD) or standardized mean difference (SMD), with 95% confidence intervals (CI) was used. For dichotomous outcomes, the odds ratio (OR) with 95% CI, was calculated, and compared with the risk ratio (RR) and risk difference (RD). For time-to-event outcomes such as log hazard ratios, the fixed effects generic inverse variance outcome was used to combine results. Number needed to treat was calculated from the pooled odds ratio and its confidence interval, using the baseline risk in the control group.

Main Results

A total of 921 participants were included in the nine studies contributing to the meta-analysis. The use of corticosteroids varied.

Primary outcomes

There was a significant difference between those treated with corticosteroids versus placebo with a reduction in the treatment failure (definition varied from return to ED/Physician office, change in treatment, hospital admission, intensification of treatment, or death), with an

odds ratio 0.48; (95% CI 0.34 to 0.68). The risk of relapse within 30 days was significantly less

for those treated with corticosteroids. In two large studies, accounting for 45% of the total subjects, (n=415) the hazard ratio for relapse was 0.78 (95%CI 0.63 to 0.97). The reduction in risk of re-admission at 30 days was not statistically significant OR 0.79 (95% CI 0.45 to 1.37). Mortality rates were reported in nine studies (n=910), however there was no statistically significant difference, OR 0.85 (95% CI 0.45 to 1.59). Data about duration of hospitalization was skewed and could not be combined but in one large study there was a significant reduction of 1.2 days of hospitalization (95% CI 0.12 to 2.28). In addition, two other studies demonstrated a 2 day difference in hospitalization stay.

Adverse effects

Subjects treated with corticosteroid were significantly more likely to have an adverse drug reaction with an OR of 2.28 (95%CI 1.56 to 3.34). Overall one extra adverse effect occurred for every 6 people treated (95% CI 4 to 10). Subjects in the corticosteroid treated group had an increased risk for hyperglycemia with an OR 5.48 (95% CI 1.58 to 18.96). The large outpatient based study reported incidences of specific adverse effects and found a significant increased risk of weight gain, appetite and insomnia in the corticosteroid treatment group with non-significant increases for anxiety and depression.

Conclusions

There is evidence to support the early use of oral or parenteral corticosteroids for exacerbations of COPD with a reduction in treatment failure and the need for additional medical treatment. It increases the rate of improvement in lung function and dyspnea over the first 72 hours; however this is an increased likelihood of adverse drug reactions.

Commentary: Clinical Implication

COPD is a leading cause of morbidity and mortality in the United States and worldwide. Preceded only by heart disease, cancer, and cerebrovascular disease, COPD currently ranks as the fourth leading cause of death in the United

States (2). Furthermore, COPD is estimated to become the fifth leading burden of disease worldwide by the year 2020 (3). According to

estimates made by the National Heart, Lung, and Blood Institute, in 2002 the annual cost to the nation for COPD was \$32.1 billion. This included \$18.0 billion in direct health care expenditures, \$6.8 billion in indirect morbidity costs, and \$7.3 billion in indirect mortality costs (4).

Although there is no standardized definition of COPD exacerbation, the pathophysiology of an acute exacerbation is better understood. The partially reversible, progressive airflow obstruction is usually associated with an abnormal inflammatory response to noxious particles and gases, enlargement of mucus secreting glands, and progressive fibrosis of the smaller airways (5). Because inflammation is a hallmark of COPD, several studies have examined the effectiveness of steroids in acute COPD exacerbations.

As acute COPD exacerbations are responsible for more than 1 million Emergency Department visits a year in the United States, proper treatment of an exacerbation is of paramount importance to an emergency clinician (6). This systematic review attempts to answer the question: what is the evidence for using systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease? The authors examined nine studies in which outcomes involving corticosteroids, administered either parenterally or orally, were compared with outcomes with appropriate placebo. The data analysis favors the usage of steroids for acute COPD exacerbation.

The authors specified primary outcomes as treatment failure and mortality, while secondary outcomes were lung function, ABG measurements, symptom and dyspnea scores, quality of life assessments, functional capacity, duration of hospitalization, sputum production, and adverse effects. The outcomes were further divided into early, 0-72 hours, and late, greater than 72 hours.

The review does confirm a significant reduction in treatment failure by 52% with corticosteroids and only 9 patients would need to be treated to prevent one treatment failure within 30 days.

The mortality rate in the studies was 4.4%, but with an odds ratio of 0.85 (95% CI 0.45 to 1.59), there was no significant difference in mortality rates between the corticosteroid treatment and placebo group.

As COPD has proven to be quite costly, reducing hospital admission rates and length of stay could possibly decrease the economic impact of this disease. The review does demonstrate that with an odds ratio of 0.79, corticosteroid usage reduced the readmission/admission rates for COPD treatment by 21%. Taking into account that numerous issues may affect length of hospital stay, such as hospital policy, social conditions, and the presence of co-morbidities needing treatment, the reviewers were not able to pool the data and confirm a significant reduction of length of stay in the corticosteroid treatment group. However, three studies found a significant reduction in duration of stay for the corticosteroid treated group of around one to two days.

A patient's quality of life is extremely important to both the patient and his/her clinician. One can assume that if a patient with COPD subjectively feels dyspneic, he/she is more likely to present to the Emergency Department or an outpatient clinic. There was evidence of an earlier improvement in lung function, ABG measurements, and dyspnea for the corticosteroid treated group; however, this was not proven beyond 72 hours. This early improvement in physiological function may manifest in better quality of life and functional ability for COPD patients. Finally, the data analysis showed an increase in adverse effects with the corticosteroid treatment group. These adverse effects included hyperglycemia, increase in appetite, weight gain, depression, anxiety, and insomnia.

Summary

Corticosteroids should be considered for patients with COPD exacerbation. The evidence demonstrates that treatment with corticosteroids can help reduce inflammation associated with acute COPD exacerbations, especially in the first 72 hours. This is associated with improved lung function, dyspnea, and blood gases, which may result in shorter hospital stays, fewer hospital admissions, fewer follow-up visits, and better quality of life. The clinician should be aware of

the adverse effects associated with this medication, as well as the fact that the dose and

duration of corticosteroid treatment has not been established.

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