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A randomized, controlled multicentric study of inhaled budesonide and intravenous methylprednisolone in the treatment on acute exacerbation of chronic obstructive pulmonary disease

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ABSTRACT

Background: Almost all international guidelines recommend corticosteroids for management of exacerbations of chronic obstructive pulmonary disease (COPD), because it leads to improved outcomes of acute exacerbations of chronic obstructive pulmonary disease (AECOPD). Nevertheless, due to its side effects, there are still concerns regarding the use of systemic corticosteroid (SC). Inhaled corticosteroids (IC) can be used as an alternative to SC, while reducing the risk of occurrence of side effects.
Purpose: To measure the clinical efficacy and side effects of nebulized budesonide and systemic methylprednisolone in AECOPD.
Methods: Valid data from 410 AECOPD patients in 10 hospitals was collected. Patients were randomly divided into 2 groups; budesonide group, treated with nebulized budesonide (2 mg 3 times/day); and methylprednisolone group, treated with intravenously injected methylprednisolone (40 mg/day). COPD assessment test (CAT), arterial blood gas analysis, hospitalization days, adverse effects, fasting blood glucose, serum creatinine, alanine aminotransferase levels, and blood drug were measured and analyzed in both groups.
Results: Symptoms, pulmonary function and arterial blood gas analysis were significantly improved after treatment in both groups ($P < 0.05$), with no significant differences between them ($P > 0.05$), while incidence of adverse events in the budesonide group was lower ($P < 0.05$). No significant differences in CAT score, days of admission, blood gas analysis results and physiological and biochemical indexes were found between the two groups. Patients treated with methylprednisolone showed a higher degree of PaO_2 level improvement.

Abbreviations: COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbations of chronic obstructive pulmonary disease; SC, systemic corticosteroid; IC, inhaled corticosteroids; CAT, COPD assessment test; FBG, fasting blood glucose; WBC, white blood cell count; ALT, alanine aminotransferase; SCr, serum creatinine.

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Conclusion: Results show that inhalation of budesonide (2 mg 3 times/day) and systemic methylprednisolone (40 mg/day) had similar clinical outcome in AECOPD. In conclusion, inhaled budesonide is an alternative to systemic corticosteroids in AECOPD treatment.

1. Introduction

COPD is a common and frequently-occurring disease that progresses continuously. Most of the patients with moderate or severe COPD may experience at least 1 episode of acute exacerbation per year [1]. Moreover, frequency of acute exacerbation and severity of this disorder are directly associated with mortality [1–5]. Several guidelines and studies have recommended the systemic application of corticosteroids during the AECOPD [1,6–9]. However, majority of COPD patients are aged people, and more likely to have decreased immunity [10–13].

For patients with frequent exacerbations of COPD, high dose of corticosteroids is a common clinical practice to control the inflammation. Nevertheless, such treatment profile can induce side effects, such as osteoporosis, skin thinning, abnormal glucose tolerance, and myodystrophy. Those side effects present on COPD patients are generally long-term and severe [14–16].

Consequently, due to its side effects, it of high relevance to find alternative treatments to systemic application of corticosteroids. Several studies suggest that inhalation of corticosteroids, such as budesonide, can be effective for AECOPD treatment [17–19].

Those preliminary results are promising, but evidence from large-scale, multi-center, randomized controlled trials is still lacking. Furthermore, no standard drug dose inhalation has been established. Due to that, great discrepancies in dose and application method may be found in different clinical settings.

The present study was a prospective, single-blind study involving 10 participating general hospitals, to determine the clinical efficacy and side effects of nebulized budesonide, when compared to intravenous administration of methylprednisolone in AECOPD patients. After valid data from 410 out of 471 AECOPD patients was obtained, treatment efficacies, including the CAT score, blood-gas analysis parameters, blood biochemical analysis parameters (fasting blood glucose, alanine aminotransferase, and serum creatinine), hospital stay, time to disease recurrence, and side effects of inhalation of budesonide and intravenous injection of methylprednisolone were compared.

2. Material and methods

2.1. Patients

The present study recruited 471 patients with AECOPD, between March 2012 and April 2015, from 10 general hospitals. The patients were divided into two groups; 233 received budesonide inhalation treatment (budesonide group), and 238 were treated with intravenous injection of methylprednisolone (methylprednisolone group). Forty-two patients were dropped out during the study, 17 were lost to follow up after discharge, and 28 patients were excluded because key data was not available. As a result, 410 patients were considered to have completed the study with valid data. Among those 410 patients with valid data, 220 were part of the budesonide group and 190 were part of the methylprednisolone group. Patients in the budesonide group were treated with inhalation of budesonide (2 mg, 3 times/day), using a pulse air atomizer or a ventilator connected to an air atomizer, while patients in the methylprednisolone group were treated with intravenous injection of methylprednisolone (40 mg methylprednisolone in 100 mL normal saline for injection, 1 time/day). Additional treatments required for AECOPD patients, such as anti-infection and bronchodilator therapy, were performed according to clinical guidelines, with no variations between the groups. Data from drug treatments and methods used was recorded in the clinical observation form.

The present study was approved by the Ethics Committee of the First People's Hospital of Hefei (the leading hospital of the study) and the Ethics Committee of all participating hospitals.

2.2. Inclusion criteria

The inclusion criteria for the patients were all of the following: 1) age between 60 and 80 years old; 2) to meet the diagnostic criteria of COPD: a) the COPD diagnosis must be based on the comprehensive consideration of the clinical presentations, exposure to risk factors, signs, and other laboratory examination results; b) to show the major COPD symptoms (chronic cough, expectoration, and/or dyspnea) and the exposure to risk factors; c) to exhibit incomplete reversible airflow, this is, if the FEV_1/FVC is <70% after application of a bronchodilator, the patients will be diagnosed with incomplete reversible airflow limitation; and 3) met the AECOPD diagnostic criteria: a) to possess a history of COPD (the patient has been clearly diagnosed with COPD; with typical clinical COPD presentations, and the pulmonary functions during the hospitalization confirmed COPD); b) to display unusual continuous exacerbation that required a change in the routine medication; c) to show cough, expectoration, dyspnea, and/or wheeze exacerbated, and to have an increased amount of expectoration, or to have a short-term change in the sputum, which can be accompanied with evident aggravation of inflammatory (infection) symptoms (such as fever).

2.3. Exclusion criteria

The exclusion criteria for the patients were all of the following: 1) to possess serious disease that required invasive mechanical ventilation (patients with excessive respiratory secretion that are not able to use non-invasive mechanical ventilation, or with the $PaCO_2$ >70 mmHg) (the $PaCO_2$ level was accessed according to the safety profiles of the study); 2) to have a history of acute exacerbation or to have received systemic application of corticosteroids within the past month (patients in the stable phase receiving the standard dose with the quantitative inhaled corticostroid (ICS) device were not considered to meet the exclusion criteria); 3) with diabetes or other cardiac, cerebral, renal, or liver diseases that required hospitalization; 4) to have a history with pneumothorax, pulmonary embolism, pneumonia, or other respiratory diseases; and 5) to have been included in this study before.

2.4. Study design

2.4.1. Randomization

The present study was a prospective, randomized, single-blind, multi-center, parallel study. A random number table was generated