Review

Short-term versus longer duration of glucocorticoid therapy for exacerbations of chronic obstructive pulmonary disease

Zhao Ma a, *, Wei Zhang b

a Department of Pharmacy, Hangzhou Third Hospital, Hangzhou 310009, China
b Hangzhou Institute for Food and Drug Control, Hangzhou 310022, China

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ABSTRACT

Background: Systemic glucocorticoid has been shown to improve the outcome of acute exacerbation of chronic obstructive pulmonary disease (COPD). However, the optimal duration remains controversial.

Objectives: To investigate whether a short-term (seven days or fewer) systemic glucocorticoid treatment in patients with COPD exacerbation is non inferior to longer duration (more than seven days) treatment in clinical outcome.

Methods: We searched PubMed, EMBASE, CENTRAL databases, China Clinical Trials, CNKI, The Chinese biomedical literature database (CBM) and wanfang database to identify randomized controlled trials using systemic glucocorticoid in COPD. At least two review authors independently assessed each potentially eligible trial for its inclusion in the review and its quality. Glucocorticoid is given for a period of seven days or fewer versus systemic given for more than seven days. We retrieved time from building to Apr 20, 2016, and supplemented by manual retrieval into literature references. By adopting the combination of keywords and free word retrieval methods, we performed a routine meta-analysis to evaluate the effects of glucocorticoid on FEV1, FEV1/FVC, PaO2, clinical symptoms, relapse, treatment failure, mortality and side-effects between the two treatment groups.

Results: Our search yielded 9 studies involving 874 patients. Six studies were fully published and three were published as abstracts. We obtained data for one study published as abstracts from authors. Short-term treatment varied between three and seven days and longer duration 10 to 15 days, at equivalent daily doses of glucocorticoid. Mean ages of participants ranged from 60 to 90 years. The FEV1, FEV1/FVC, PaO2 and clinical symptoms between the two treatment groups did not differ significantly by treatment duration. There was no significant difference of relapse, treatment failure, mortality and side-effects between the two treatment groups.

Conclusion: These data show that short-term glucocorticoid is as effective as and possibly safer than longer duration.

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* Corresponding author.
E-mail address: mazhao@stu.xjtu.edu.cn (Z. Ma).

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth commonest cause of death worldwide, posing a large socioeconomic burden. And COPD are associated with significant morbidity and mortality [1]. So, it is must therefore be promptly and rigorously treated. In spite of many patients have respiratory symptoms persisting using bronchodilators and inhaled corticosteroids, systemic glucocorticoid therapy is an integral part of the management of COPD exacerbations [2,3]. Moreover, International guidelines and systematic reviews confirm the role of glucocorticoid, namely can improve lung function, alleviate symptoms of shortness of breath, and improve the treatment success [4].

However, randomized clinical trials addressing the use of systemic glucocorticoid are relatively sparse and heterogeneous in their designs and settings [5]. Notably, the optimal dose and duration of treatment remains unknown. Most importantly, prolonged use of glucocorticoid increase blood pressure, septic shock even mortality in COPD, so glucocorticoid exposure should be minimized [6].

This therapeutic dilemma prompted the initiation of the present multicentre trial aiming to demonstrate non-inferiority of a short course of systemic glucocorticoid as compared to a standard course. A recent Cochrane [7] review of 5 studies including a total of 519 patients with exacerbated COPD found no significant differences in clinical outcome between short-term and longer duration of glucocorticoid treatment. But due to report researches were fewer and some outcomes unable to statistics. Therefore our article integrated the above reasons and we referred four latest articles that want to assess whether a short-term (seven or fewer days) of this treatment was as good as a longer duration (longer than seven days) and caused fewer side effects.

2. Methods

2.1. Study design and patients

This was a randomized controlled trials which included consecutive COPD patients who were admitted to the hospital for an exacerbation. (One study was not blinded to participants or investigators. Incomplete data were adequately addressed in six studies, but risk of bias was judged high in two studies. Allocation concealment was adequate in five studies and others were unclear. Five studies were assessed as free of selective reporting, but risk of bias was unclear in four studies).

The definition of an acute exacerbation could include any combination of an increase in breathlessness, sputum volume, sputum purulence, cough or wheeze and age older than 40 years. We excluded studies that included patients with asthma, uncontrolled hypertension or diabetes mellitus, previously diagnosed bronchiectasis, need for mechanical ventilation, and other lung diseases. Systemic glucocorticoid was given for a short-term (seven or fewer days) versus systemic glucocorticoid given for a longer duration (longer than seven days). Co-interventions were required to be standardised across groups.

2.2. Search methods

We searched PubMed, EMBASE, CENTRAL databases, Chinal Clinical Trials, CNKI, The Chinese biomedical literature database (CBM) and wanfang database to identify randomized controlled trials using systemic glucocorticoid in COPD. At least two review authors independently assessed each potentially eligible trial for its inclusion in the review and its quality. Glucocorticoid is given for a period of seven days or fewer versus systemic given for more than seven days. We retrieved time from building to Apr 20, 2016.

2.3. Measurements

The measurements at admission (baseline and endpoint) included pulmonary function tests (FEV1, FEV1/FVC measured using Sensormedics Vmax 22D spirometer), arterial blood gases (PaO2), symptom scores (shortness of breath, cough, sputum production measured using visual analog scores on a 10-point scale), relapse, treatment failure and mortality (re-admission for index episode, return to emergency department, unscheduled physician visit for the index episode), adverse effects. A sputum sample was collected for bacteriologic analysis.

2.4. Statistical analysis

Data were pooled using Review Manager 5.3. We used a fixed-effect model, and when heterogeneity could not be explained, we performed a sensitivity analysis using a random-effects model.

3. Results

Our search yielded 9 studies involving 874 patients [8–16]. Six studies were fully published and three were published as abstracts. We obtained data for one study published as abstracts from authors (Fig. 1). We have provided the primary information of the nine included studies in Table 1. We graded the risk of bias in each domain as high, low or unclear risk. The standard components in the risk of bias assessment tool include: adequacy of sequence generation; allocation concealment; blinding; completeness of outcome data; possibility of selective outcome reporting; and other potential bias (Table 2).

3.1. Lung function

FEV1 was measured and reported in six studies on 403 participants (Fig. 2). Short-term and longer duration group also can improve FEV1 situation. It affirmed that the glucocorticoid on COPD can improve lung function. Moreover, there was no significant difference in the improvement of FEV1 between the two treatment groups (MD 0.00 l; 95% CI –0.00 to 0.01); and no statistical heterogeneity was observed. (Chi2 = 2.47, df = 5 (P = 0.78; I2 = 0%).

FEV1/FVC was measured in two studies on 173 participants (Fig. 3). It showed no statistically significant differences between groups (MD 0.68%; 95% CI –0.03 to 1.40).
3.2. Arterial blood oxygen partial pressure

Response of arterial oxygen tension (PaO₂) was reported in six studies on 497 participants (Fig. 4), and showed no statistically significant difference between groups (MD 1.04 mmHg; 95% CI –0.32 to 2.40).

3.3. Clinical symptoms improvement

In two studies no differences were noted in clinical symptoms when measured between systemic glucocorticoid for short-term and longer duration (n = 170; mean difference (MD) –0.70, 95% CI –1.89 to 0.48), and no statistical heterogeneity was observed (Chi² = 1.54, df = 1 (P = 0.21); I² = 35%) (Fig. 5).

3.4. Relapse, treatment failure and mortality

Relapse was measured as a new acute exacerbation or hospital admission for COPD in four studies. No significant difference was reported between systemic glucocorticoid use short-term and longer duration (n = 615; OR 1.01, 95% CI 0.71 to 1.43), and no statistical heterogeneity was observed. The outcome was downgraded for imprecision and was rated as having moderate quality because the confidence intervals for the pooled effect included important benefit and potential harm (Fig. 6).

Five studies on 594 participants reported treatment failure as an outcome (Fig. 7). No significant difference was noted in the likelihood of treatment failure between systemic glucocorticoid for short-term and longer duration (n = 594; odds ratio (OR) 0.80, 95% confidence interval (CI) 0.42 to 1.54), and no statistical heterogeneity was observed. The outcome was downgraded for imprecision and was rated as having moderate quality because the confidence intervals for the pooled effect included important benefit and potential harm.

Three studies on 473 participants reported treatment failure as an outcome (Fig. 8). No significant difference was reported between

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Total number</th>
<th>Age (year)</th>
<th>Intervention</th>
<th>Outcomes</th>
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<tr>
<td>Wang, 2015</td>
<td>137</td>
<td>68.3 ± 8.8</td>
<td>IV methylprednisolone 40 mg, days 2–5: oral prednisolone 40 mg per day</td>
<td>FEV₁, PaO₂, Side-effects, treatment failure, Relapse, Mortality</td>
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<td>Chen, 2015</td>
<td>70 (35/35)</td>
<td>63.6 ± 4.7</td>
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<td>FEV₁, PaO₂, Side-effects</td>
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<td>Liu, 2014</td>
<td>81 (48/33)</td>
<td>70.23 ± 11.56</td>
<td>Oral Prednisone 30 mg per day for 5 days</td>
<td>FEV₁, PaO₂, Side-effects, The clinical symptoms</td>
</tr>
<tr>
<td>Lv, 2014</td>
<td>86 (43/43)</td>
<td>74.3 ± 2.1 Female average age</td>
<td>IV methylprednisolone 40 mg, days 2–5: oral prednisolone 30 mg, days 6–14: placebo</td>
<td>PaO₂, Side-effects, FEV₁/FVC</td>
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<tr>
<td>Leuppi, 2013</td>
<td>311</td>
<td>69.8 ± 11.3/69.8 ± 10.6</td>
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<td>Sirichana, 2008</td>
<td>41 (23/18)</td>
<td>72.45 ± 9.62/73.39 ± 9.16</td>
<td>5-day group received prednisolone 30 mg/d for 5 days</td>
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<td>Chen, 2004</td>
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<td>prednisolone 30 mg/d 7 days + placebo 7 days</td>
<td>FEV₁, FVC, Side-effects, FEV₁/FVC, PaO₂, Side-effects, Treatment failure, Relapse</td>
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<td>Sayner, 2001</td>
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<td>methylprednisolone, 0.5 mg/kg IV 6-hourly for 3 days, followed by normal saline solution as placebo treatment IV twice daily for the following 3 days and once daily for the final 4 days</td>
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<td>Wood-Baker, 1997</td>
<td>25 (12/13)</td>
<td>69.3 ± 5.5/71.1 ± 9.7</td>
<td>methylprednisolone, 0.5 mg/kg IV 6-hourly for the first 3 days, followed by 0.5 mg/kg 12-hourly for 3 days and 0.5 mg/kg once daily for 4 more days</td>
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Fig. 1. Study flow diagram.

Table 1

Primary information of included studies.

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3.5 Safety evaluation  

Side-effects were reported in nine studies on 901 participants (Fig. 9). Including Stress ulcer of digestive tract, Oral fungal infections, hyperglycemia, hypertension, gastrointestinal tract bleeding, sleep disturbance, fractures and depression, ischaemic...
heart disease. No difference was noted in the likelihood of another adverse event between systemic glucocorticoid for short-term and longer duration (OR 0.68; 95% CI 0.47 to 0.97).

4. Discussion

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline for COPD updated in 2009 recommends low dose systemic glucocorticoid (30 mg–40 mg prednisone/day) for outpatient but does not recommend the systemic glucocorticoid dose for inpatients [17]. The GOLD guideline revised in 2011 recommends low dose systemic glucocorticoid for both outpatients and inpatients [18]. However, it is based on evidence D [18]. Few randomized controlled clinical trials have directly compared high-, medium- and low dose regimens. GOLD 2014 [1] indicate Guidelines for the management of COPD specify a duration of treatment
ranged from 7 days to 10 days, but NICE [19] pointed out the duration from 7 days to 14 days, and McKenzie [20] demonstrated the duration from 10 days to 14 days. Thus, it is important to define the optimum duration of corticosteroid treatment and to take into account limiting potential adverse effects. Until 2014, Walters JAE [7] pointed out that the longer duration did not show superiority to the short-term regimen. Our research increased four latest published articles on this basis and the results are consistent with Walters JAE. Furthermore, we consummated the improvement of FEV1, FEV1/FVC, PaO2, relapse, treatment failure and mortality indexes. It fully confirmed a short-term (seven or fewer days) of this treatment is as good as a longer duration (longer than seven days) and caused fewer side effects.

In our current study, for lung function, first of all, the two indexes were all improved no matter short-term or longer duration group. It affirmed that the glucocorticoid on COPD can improve lung function. Secondly for short-term group, the effect was no less than the longer duration group. For arterial blood oxygen partial pressure, there was no statistically significant difference between the two groups. The improvement of the arterial blood oxygen partial pressure was consistent with the amelioration of FEV1. It was agree with the physiology viewpoint. For the clinical symptoms improvement, it affirmed the glucocorticoid for COPD with acute exacerbation can improve shortness of breath symptoms score. There was no statistical significance between short-term and longer duration group. But symptom score had some disadvantages: (1) The design criteria of symptoms score is not very detailed enough. (2) The subjectivity is strong and test error is great. For relapse, treatment failure and mortality, short-time and longer range group had no statistical significance, but the longer use glucocorticoid, the side effects are greater. Due to repeated exacerbations COPD, the frequency of short-term systemic glucocorticoid therapy is increasing [21]. The cumulative dose of glucocorticoids also leads to the occurrence of side effects. Although the risk of side effects caused by intermittent use of glucocorticoid is small, but it can also lead to osteoporosis with many times therapy [22] and significantly increased risk of steroid myopathy [23]. These hormones related complications caused the quality of life decreased significantly and the medical costs higher [24]. The side-effects and dangers of treatment with systemic glucocorticoid are well known. These patients are at enhanced risk for osteoporosis, the cumulative dose of glucocorticoids strongly correlated with vertebral fracture risk due to loss of bone mineral density [25]. Glucocorticoids contribute to muscle catabolism in COPD [26], and the cumulative dose has been found to correlate with muscle weakness [27].

Otherwise, Walters JAE article also introduced the other two indexes. FVC was reported in three studies (Wood-Baker 1997; Sayiner 2001; Sirichana 2008) and compared at two follow-up time points. There was no significant difference in early response of FVC between the two treatment groups (MD 0.01 L; 95% CI -0.20 to 0.22) or response at completion of treatment (MD-0.12 L; 95% CI -0.33 to 0.09). For hospitalization, three studies on 421 participants (Wood-Baker 1997; Chen 2004; Leuppi 2013) gave results for duration of it. There was no statistical significance difference in number of hospitalization days between groups (MD -0.61: 95% CI -1.51 to 0.28). This again confirmed a short-term treatment is as good as a longer duration.

Our study had some limitations. First of all, we referred four latest articles, but they were all from Chinese literature. Although from a variety of channels we got the documents of methodological quality evaluation, only Chen 2015 incomplete outcome data was high risky, but it did not obviate the national region of bias.

Second, adverse events among the trials were not classification discussion, such as hyperglycemia, hypertension, gastrointestinal bleeding, insomnia, oral infection etc. In Sayiner and Leuppi articles, a short-term group and longer duration group respectively appeared 2 cases and 74 cases hyperglycemia. In Ling Liu article, longer duration group appeared gastrointestinal stress ulcer. The number is the twice of a short-term group. And it appeared one case oral cavity fungal infection in longer duration group. In Xiaobing Wang article, the number of pharyngeal discomfort in longer duration group is the fifth of short-term group, and each group appeared one case of insomnia phenomenon. In Chen 2004 article, each group appeared one case of upper gastrointestinal bleeding. In a word, adverse reactions in each study were different. Because the sample size of these adverse events in each research was difference and quantity was too small to bring a conclusion. So separating those indexes will make little sense. Therefore, more clinical trials on COPD patients were needed.

Third, apart from the intervention, these referred articles had rigorously standardise COPD medication, particularly inhaled steroids and bronchodilators, and the use of antibiotics during the initial treatment phase. Due to different doses of these drugs, it may also affect test results and make it biases. In most articles, the fixed combined use of long-acting beta agonists, inhaled steroids, and tiotropium was beyond generally accepted treatment recommendations. For example, in Leuppi trial, patients were treated with broad-spectrum antibiotics for 7 days and inhaled tiotropium 18 μg once daily, and antibiotic treatment regardless of sputum...
purulence or procalcitonin levels. But they aimed at eliminating all possible confounding factors so that any potential difference in outcome could be attributed to the different glucocorticoid treatment regimes [8]. In Sayiner trial, it showed glucocorticoid treatment together with the optimal bronchodilator therapy resulted in more marked improvements in PaO₂, FVC, and FEV₁ levels in COPD patients who were administered systemic steroids for 10 days as compared to 3 days [9]. In TORCH trial, inhaled long-acting beta-agonists combined with inhaled glucocorticoids reduce exacerbation rate, improve health status, and preserve lung function [28]. Similarly, in the UPLIFT study, tiotropium was shown to improve lung function and quality of life as well as reduce COPD exacerbations [29]. These results are reassuring in view of the treatment plan chosen in those study protocols. Also, published guidelines recommend antibiotic use in patients with altered sputum characteristics [17], but there is a large scope for discretion as to the choice of the antibiotic and the duration of treatment [30]. In the present study, an unbalanced distribution of antibiotic use in the two treatment arms has to be avoided, especially as physicians are likely to prescribe antibiotics more frequently in patients with slow improvement, which could be the case in the short treatment arm. Thus, antibiotic treatment bias could compromise our non-inferiority design and obscure the true treatment effects from systemic corticosteroids. However, we wanted to minimise any treatment bias that might have led to falsification of the effects of systemic glucocorticoid.

On the whole, in our current study, we found that the longer duration did not show superiority to the short-term regime in the FEV₉, FEV₁/FVC, PaO₂ and clinical symptoms improvement. The meta-regression did not show a positive correlation between the risk reduction of relapse, treatment failure, mortality and side-effects.

Acknowledgments

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References
