Optimal glucocorticoid dose and the effects on mortality, length of stay, and readmission rates in patients diagnosed with acute exacerbation of chronic obstructive pulmonary disease (AECOPD)

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ABSTRACT

The burden of acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is staggering on a national and global level. Yet, surprisingly, there is a profound lack of treatment standardization with glucocorticoids in the treatment of AECOPD. In this review, we bring attention to specific literature that use a cut-off of 60 mg prednisone equivalent per day when distinguishing between high-dose and low-dose glucocorticoid treatment. We hope this review encourages future research to begin incrementally lowering the cut-off dose of 60 mg to discover if mortality, length of hospital stays, and readmission rates change between high-dose and low-dose glucocorticoid treatment. The final hope would be to establish an optimal glucocorticoid dose to treat AECOPD and eliminate treatment ambiguity.

INTRODUCTION

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), an acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is defined as an event that worsens a patient's existing respiratory distress beyond the patient's normal variation of breathing status throughout the day or night, warranting a change in the patient's medical management.[1] The national and global epidemiological burden of COPD and COPD exacerbations is staggering, warranting standard treatment guidelines with proven mortality benefit to patients with COPD and subsequent exacerbations.

Per the latest estimates from the WHO in the year 2005, more than 3 million people died from COPD representing 5% of all deaths globally.[2] In the USA, according to the Center for Disease Control and Prevention (CDC), 44.3 per 100 000 men and 35.6 per 100 000 women over the age of 18 died from COPD in 2014.[3] The prevalence of COPD in some states even reached as high as 12.3% in 2014.[3] The WHO predicts that by the year 2030, COPD will become the third leading cause of death worldwide.[2] This health crisis does not come without economic burden. In 2010, the estimated healthcare cost in the USA was US$50 billion to manage COPD.[4] The increasing severity of COPD in addition to the hospital length of stay were responsible for the majority of the costs, at roughly US$30 billion dollars.[4]

The average number of exacerbations annually is 1–2 per person, with the frequency increasing as the disease worsens.[5] There is a plethora of risk factors that contribute to AECOPD that include genetic and environmental. Older age, percentage of predicted forced expiratory volume in 1 se (FEV1), duration of COPD, a productive cough, antibiotic or systemic corticosteroid use for COPD in the prior year, hospitalization for COPD in the prior year and theophylline use at baseline are predictors for higher risks of COPD exacerbations.[6] Bacterial and viral infections are responsible for the majority of COPD exacerbations while air pollution and other airway inflammatory environmental causes represent about 15%–20% of exacerbations.[5] There are also well-documented instances of significant comorbidities that may also play a role in the frequency and severity of COPD exacerbations. Comorbid conditions such as myocardial ischemia, heart failure, aspiration, or even pulmonary embolism. However, it is unclear whether these comorbid conditions are the cause of the exacerbation or a coincidental finding.

ROLE OF STEROIDS

Glucocorticoid treatment is the gold standard for treatment of patients with AECOPD, regardless of the route of administration (oral vs intravenous). In fact, oral administration was found to not be inferior to intravenous steroid administration with regard to treatment failure and length of hospital stay.[7] However, it is well documented that glucocorticoid administration versus placebo reduces mortality, length of hospital stays, and exacerbation recurrence after 1 month.[8] But at what cost to the patient?

Glucocorticoids are well-known for their vast array of side-effects both in the short term and over an extended course. Some documented side effects include emotional lability, psychosis, skin atrophy, myopathy, peptic ulcer

disease, increased appetite and subsequent weight gain, as well as Cushing's syndrome.[9] They also can induce hyperglycemia in patients with diabetes, or osteoporosis in at-risk patients and must be used with caution by the prescribing physician.[10] Longer term risks particularly include avascular necrosis, however, case reports have been published of osteonecrosis occurring at even low-doses.[11]

While the side effects are commonly at higher doses rather than lower doses, the optimal dose and duration of systemic glucocorticoids in the treatment of AECOPD is largely at the discretion of the physician. The GOLD guidelines advise using the equivalent of prednisone 40 mg once daily for COPD exacerbations in accordance to literature that demonstrated no greater treatment failure with low-dose glucocorticoid therapy versus high-dose glucocorticoid therapy.[1 12] However, the GOLD guidelines do not discuss the effects on mortality rate, length of hospital stay, and readmission rates when this dose is administered instead of high dose. As a result, an extensive literature search was performed to look for data that confirmed the benefits of steroid use versus placebo at low doses, in addition to examining the consequences of low-dose steroid treatment versus high-dose steroid treatment when managing AECOPD in an attempt to begin the conversation of optimal glucocorticoid dosing.

STEROID DOSING STUDIES

An extensive literature review was performed using PubMed keyword search for 'AECOPD', 'Treatment', 'Mortality', 'Length of Hospital Stay', and 'Readmission' and relevant papers that studied AECOPD in non-ICU admitted patients within the last 10 years were chosen and reviewed. Of the 16 papers collected and reviewed, three were chosen for their work in examining mortality, length of hospital stay, and readmission rates between low-dose steroid treatment versus placebo and low-dose steroid treatment versus high-dose steroid treatment in patients with AECOPD (table 1). For purposes of standardizing comparisons, these three papers were also chosen because of the glucocorticoid doses that were in accordance with our definition of low-dose steroid treatment as less than 60 mg prednisone equivalent per day and high-dose steroid treatment as greater than 60 mg prednisone equivalent per day. This cut-off was chosen with reasonable appropriation to the GOLD recommendation of 40 mg prednisone equivalent per day, but also aligned with clinical observations in our own practice, due to the profound lack of a clear definition of high-dose and low-dose steroid treatment boundaries in the literature review and review of the GOLD guidelines.

With regard to mortality, Aksoy *et al* established that low-dose steroids improve mortality in a subset of patients with AECOPD, specifically those with eosinophilic AECOPD versus those with placebo treatment.[13] This study followed the Reduction in the Use of Corticosteroids in Exacerbated COPD (REDUCE) trial published in 2013 that showed mortality is not reduced with 14 days of low-dose prednisone treatment as opposed to 5 days of low-dose prednisone treatment.[14] Furthermore, this followed the study by Wang *et al* published in 2011 that demonstrated that low-dose steroid treatment actually led to the lowest mortality rates compared with high-dose steroid treatment and placebo groups.[15]

With regard to length of hospital stay, Wang *et al* did not find any statistically significant difference between high-dose and low-dose steroid treatment groups in 2011.[15] The REDUCE trial in 2013 did find that low-dose steroids shortened the median length of stay by 1 day compared with the placebo group.[14]

With regard to readmission rates, the REDUCE trial did not find any statistically significant difference in readmission rates between those with 5 days of low-dose treatment versus those with 14 days of low-dose treatment.[14] However, Aksoy *et al* did find that readmission rates were significantly lower with low-dose steroid treatment versus placebo.[13] No studies exist that have examined high dose versus low-dose steroid treatment and readmission rates.

CONCLUSION

Low-dose glucocorticoid treatment, defined as 60 mg of prednisone equivalent or less, shows definitive mortality benefit, reduction of hospital length of stay and lower readmission rates versus placebo in the treatment of patients with AECOPD. Furthermore, a 5-day course shows no reduction in mortality when compared with a 14-day course. Lastly, low-dose glucocorticoid treatment shows reduced mortality rates in addition to similar hospital length of stay when compared with high-dose glucocorticoid treatment. With such variation in glucocorticoid administration, nationally and globally in the treatment of AECOPD, mostly at the discretion of the attending physician, we propose standardization of exacerbation treatment protocols. Based on the publications reviewed above, it is reasonable to encourage that future studies aim to discover the optimal dosing of glucocorticoid treatment using incremental cut-offs lower than 60 mg prednisone equivalent per day. This data can then be compared with see if mortality, length of stay and readmission rates change in reference to low-dose treatment versus high-dose treatment at a 60 mg cut-off.

It is important to recognize that this review was not without limitations. The selection of 60 mg as a cut-off dose for high-dose and low-dose steroids was chosen based on reasonable appropriation to the GOLD criteria, but a higher dose commonly administered during our own observation and practice. Because of the lack of a true definition for high-dose and low-dose steroid treatment, it limited the selection of a cut-off dose to a subjective process. Furthermore, only three of 16 papers were able to be reviewed because of the 60 mg cut-off for high and low doses of steroid treatment. The other 13 papers with similar points of measurement (mortality, hospital length-of-stay and readmission rates) had to be excluded due to the use of other cut-off doses for high-dose and low-dose treatment. Standardization of treatment protocols is imperative to even defining high-dose and low-dose steroid treatment. Only once a cut-off dose can be unanimously agreed on, then optimal dosing of glucocorticoid treatment using incremental cut-offs lower than 60 mg prednisone equivalent per day can be determined. The final hope is this data will further open the door for future meta-analyses that can confidently compare mortality, hospital length-of-stay and readmission rates between different cut-off doses and

Table 1 Published literature that examined low-dose glucocorticoid treatment versus placebo and low-dose glucocorticoid treatment versus high-dose treatment.

Name of publication	Author of publication	Year of publication	Patients (n)	Dose of steroid used	Mortality	Length of stay	Readmission rate
A revised treatment approach for hospitalized patients with eosinophilic and neutrophilic exacerbations of chronic obstructive pulmonary disease	Aksoy *et al*[15]	2018	2727	40–60 mg/day for 5–7 days (low dose vs placebo)	45% mortality in eosinophilic AECOPD without steroids versus 0.6% with steroids (p=0.001). 71% mortality in neutrophilic AECOPD without steroids versus 1.4% with steroids (p=0.19).	Not discussed	30% readmission in eosinophilic AECOPD not taking steroids versus 81% taking steroids (p<0.001). 70% readmission in neutrophilic AECOPD versus 19% taking steroids (p<0.001).
Short term versus conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease, the REDUCE randomized clinical trial (reduction in the use of corticosteroids in exacerbated COPD)	Leuppi *et al*[14]	2013	314	Intervention: prednisone, 40 mg/day, for 5 days followed by placebo for 9 days {n=157) or prednisone, 40 mg/day for 14 days {n=157). Day 1 treatment was intravenous methylprednisolone; all other treatments were oral (low dose vs placebo)	Differences in mortality between 5-day and 14-day treatment course (7.7% and 8.4%) were not significant.	Patients under short-term treatment had a shorter hospital stay with a median of 8 days compared with 9 days in the conventional treatment group (p=0.04).	Differences in readmission for exacerbation between 5 day and 14 days (35.9% and 36.8%) were not significant.
Systemic steroids in acute exacerbation of COPD—from guidelines to bedside	Wang *et al*[13]	2011	164	Patients receiving more than 60 mg/day were designated to the high-dose group; those receiving less than or equal to 60 mg/day to the low-dose group and those who did not receive any steroids during admission to the NIL group (high dose vs low dose)	The mortality rate in the low-dose group was the lowest among the three groups (6.5%, 0%, 7.8% in hig dose, low dose and NIL, respectively); (low dose vs high dose and NIL groups, p=0.042 and 0.063).	There were no statistical differences in hospital stay between the three groups.	Not discussed

AECOPD, acute exacerbations of chronic obstructive pulmonary disease.

ultimately determine the optimal steroid dose for treatment of AECOPD.

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