Evaluation of Corticosteroid Dose in Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Alice N. Hemenway[1] and Alexandra M. Terry[1]

Abstract

Background: Several recent studies have shown that both lower doses and shorter durations of systemic corticosteroids have similar efficacy for treatment of acute exacerbation of chronic obstructive pulmonary disease (AECOPD). However, each trial has limitations that constrain direct applicability to a US hospital population. **Objective:** The aim of this study was to determine whether, in a US community hospital, low doses of corticosteroids provide the lowest risk of adverse effects without increasing length of stay or readmission rate. **Methods:** A single-center retrospective cohort was performed using patients meeting criteria for AECOPD. Primary endpoints included length of hospitalization, proportion of patients with >30% increase in blood glucose from baseline, and rate of 30-day readmission; multivariable regression analysis was used for comparison. The 3 inpatient cumulative dose range groups were low: ≤250-mg prednisone equivalents, medium: 251 to 500 mg, and high: ≥501 mg. **Results:** A total of 665 records were evaluated, with 369 records included. As the corticosteroid dose ranges increased, there were more patients with increased blood glucose (33.3%, 54.4%, 59.9%). When holding all other factors constant, there was a statistically significant increase in patients with elevated blood glucose with the medium- and high-dose groups as compared with the low-dose group ($P < .009$, $P < .001$), the average length of stay was 21.3 hours higher in the high-dose group as compared with the low-dose group ($P < .001$), and there were no significant differences in readmission rates between the dose groups. **Conclusions:** The lowest dose range of corticosteroids was associated with the lowest rate of impaired blood glucose without a statistically significant increase in length of stay or readmission rate.

Keywords

pulmonary disease, chronic obstructive, patient readmission, glucocorticoids

Systemic corticosteroids are part of the standard of treatment for acute exacerbation of chronic obstructive pulmonary disease (AECOPD), with recent data supporting the use of lower doses for shorter lengths of time.[1-3] A meta-analysis that compared low doses, defined as 30- to 80-mg prednisone equivalents daily, with high doses, defined as greater than 80-mg prednisone equivalents daily, found no difference in rates of treatment failure.[2] In addition, a Cochrane meta-analysis found that shorter courses of corticosteroids, defined as 3 to 7 days of treatment, performed as well as longer courses of corticosteroids, defined as 10 to 15 days of treatment.[3] These meta-analyses provide information suggesting that both lower doses and shorter courses are as effective as higher doses and longer courses. Both studies evaluated ranges and do not provide consensus on an exact, ideal regimen. The current Global Initiative for Chronic Obstructive Lung Disease guidelines suggest a 5- to 7-day course of corticosteroids for AECOPD, and specifically recommend a regimen of prednisone 40 mg daily for 5 days.[4] The study that supports this specific dose regimen is the REDUCE trial, which was performed in Switzerland and compared a 5- with a 14-day course of prednisone 40 mg.[5] This prospective randomized trial showed a similar rate of exacerbation within 180 days of follow-up, as well as similar time to re-exacerbation between the 2 groups.

There are some concerns when applying the results of the REDUCE trial to a US hospital population. The US average length of stay for AECOPD is 4.8 days.[6] However, in the REDUCE trial, both arms of the study had hospital lengths of stay greater than the US average (9.3 days short course, 10.8 days long course).[5] In addition, all patients in the study received antimicrobials, and the Global Initiative for Chronic Obstructive Lung Disease guidelines only suggest their use in patients with a suspicion of bacterial infection, such as patients with increase in sputum prurulence.[4] In the REDUCE

[1]College of Pharmacy, Rockford Regional Campus, The University of Illinois at Chicago, Rockford, IL, USA

Corresponding Author:
Alice N. Hemenway, Clinical Assistant Professor/Clinical Pharmacist, Department of Pharmacy Practice, College of Pharmacy, The University of Illinois at Chicago, Rockford Regional Campus, 1601 Parkview Road S233, Rockford, IL 61107, USA.
Email: aliceh@uic.edu

trial, additional corticosteroids were allowed, which resulted in a cumulative mean of 379 mg in the short-course group and 793 mg in the long-course group.[5] And finally, in the United States, there is a concern regarding rates of 30-day hospital readmission for patients with AECOPD, which was not assessed by the REDUCE trial.[7] Our study was performed to determine whether, in a US community hospital, low doses of corticosteroids provide the lowest risk of adverse effects without increasing length of stay or readmission rate.

Methods

Patients and Setting

Institutional review board approval was obtained on August 28, 2015. Patients were selected from a report generated from our electronic health record using the International Classification of Diseases, Ninth Revision, code of 491.21 between May 1, 2013, and July 31, 2015. Patients were included in the study if they met clinical criteria for AECOPD defined as 2 of the following: increase in dyspnea, increase in cough frequency, increase in cough strength, or increase in amount or purulence of sputum. They also needed to receive at least 1 dose of a systemic corticosteroid. Patients were excluded if they were admitted to an intensive care unit or the step-down intensive care unit. They were also excluded if they were discharged with hospice, or died during the index admission. Data were collected using a retrospective chart review. A total of 665 charts were reviewed, with 369 included in the final analysis. Data abstraction was performed by the 2 authors using a detailed protocol.

The data were split into 3 groups: low: ≤250-mg prednisone equivalents, medium: 251- to 500-mg prednisone equivalents, and high: ≥501-mg prednisone equivalents. These groups were chosen using the REDUCE trial's planned short-course total of 200-mg prednisone, actual short-course mean total of 379 mg due to the allowance of extra steroids, and the planned long-course total of 560 mg.[5] Less than or equal to 250 mg was chosen as our low-dose group in place of 200 mg because providers at our hospital often give a first dose of methylprednisolone and this inclusion would put our lowest dose over the 200-mg cutoff. Inpatient doses that were documented on the medication administration record were included.

Endpoints and Measurements

This study was undertaken to determine whether a lower dose of corticosteroid was as effective as higher doses, while providing a lower risk of adverse effects. The primary effectiveness outcomes were rates of 30-day hospital readmission and length of stay. The adverse effect measured was an elevation of blood glucose greater than 30% above the patient's baseline. To determine the 30-day readmission rate, we reviewed the electronic health record for any inpatient readmissions to our facility within 30 days. Length of stay in hours was included on the initial report generated from our electronic health record. An increase of blood glucose greater than 30% above baseline was determined by dividing the patient's maximum blood glucose during their hospitalization by the first recorded for the index admission. We chose to use a 30% increase from each patient's baseline based upon data from Islam et al, who found an average increase of ~30% in blood glucose even with low doses of corticosteroids, and higher increases seen with larger doses.[8] Only blood glucose concentrations drawn as part of the patient's metabolic panel were included; point-of-care glucose tests were not used.

Baseline characteristics of age, sex, diagnosis of chronic obstructive pulmonary disease (COPD) verified with spirometry, use of home oxygen, oxygen use (L) at admission, LACE readmission risk score (**L**ength of stay, **A**cuity of admission, **C**omorbid conditions, number of **E**mergency department visits), and Charlson comorbidity score were collected.[9,10] Potential confounders were collected, which included if the patient had concomitant diabetes mellitus, notation of hemoglobin A1c within 6 months of admission to help assess control of diabetes, if antibiotics were given during admission, concomitant diagnosis of pneumonia verified with a chest radiograph, concomitant diagnosis of acute decompensated heart failure (ADHF) verified with a N-terminal pro–B-type natriuretic peptide level greater than their age-adjusted range, and if they were a current smoker.

Statistical Analysis

All statistical tests were run using IBM SPSS version 24 (IBM, Inc, Armonk, New York). The significance level was determined a priori for the univariate and multivariable tests using a Bonferroni adjusted alpha level of $P < .0167$ per outcome. Patient baseline characteristics and potential confounders were described using descriptive and univariate statistical tests (1-way analysis of variance for continuous data and chi-square for categorical data). Binary logistic regression was performed for the rate of readmission within 30 days, which included covariates that could be considered impactful in addition to the dose groups. From those potential covariates, a backward Wald χ^2 process was used to determine the variables included in the final model. A similar process was performed for the rate of blood glucose elevation greater than 30%. For length of stay, multivariable linear regression was performed. A backward process was utilized to determine the variables included in the final model, and collinearity diagnostics were determined. For readmission and length of stay, the covariables included age, sex, confirmed diagnosis of COPD, home oxygen use, amount of oxygen used at admission, LACE, Charlson comorbidity score, antibiotic use during admission, confirmed ADHF, confirmed pneumonia, and whether they were a current smoker. For increase in blood glucose, the covariables

Table 1. Demographic Information.

Baseline characteristics	Total, n (%)	Low	Medium	High	*P*
Total	369	63 (17.1)	114 (30.9)	192 (52.0)	
Age	66	68	66	66	0.67
Female	212 (57.5)	37 (58.7)	59 (51.8)	116 (60.4)	0.33
Confirmed COPD	159 (42.9)	22 (34.9)	34 (29.8)	103 (53.6)	.02
Home oxygen use	97 (26.3)	8 (12.7)	24 (21.0)	65 (33.9)	<.001
Oxygen use at admission	1.6	1.5	1.6	1.7	0.2
LACE	12.2	11.9	12.1	12.3	0.61
Charlson score	3.0	3.1	2.8	3.0	0.42
Confounders					
Concomitant DM	159 (43.1)	26 (41.3)	51 (44.7)	82 (42.7)	0.9
A1c for DM patients	7.2	7.2	7.6	7.0	0.07
Concomitant ADHF	33 (8.9)	12 (19.0)	10 (8.8)	11 (5.7)	.02
Concomitant pneumonia	55 (14.8)	10 (15.9)	12 (10.5)	33 (17.2)	0.19
Current smoker	150 (40.7)	25 (39.7)	46 (40.4)	79 (41.1)	0.99
Antibiotic use	314 (85.1)	51 (81.0)	96 (84.2)	167 (87.0)	0.54

Note. COPD = chronic obstructive pulmonary disease; LACE = Length of stay, Acuity of admission, Comorbid conditions, number of Emergency department visits; DM = diabetes mellitus; ADHF = acute decompensated heart failure.

Table 2. Outcomes.

Outcomes	Total, n (%)	Low	Medium	High	*P*
Total	369	63 (17.1)	114 (30.9)	192 (52.0)	
Blood glucose increased by >30%	198 (53.7)	21 (33.3)	62 (54.4)	115 (59.9)	.001
Readmission within 30 d	83 (22.5)	13 (20.6)	19 (16.7)	51 (26.6)	0.11
Length of stay, h	87.9	77.9	73.6	99.7	.0001

included age, sex, Charlson comorbidity score, and underlying diabetes mellitus in addition to the dose groups.

Results

The baseline characteristics and potential confounders are described in Table 1, with data from univariate statistical tests included. Baseline demographic data were similar, with an increased rate of confirmed COPD in the high-dose group. In addition, the use of home oxygen was greatest in the high-dose group; however, there was no difference in the amount of oxygen used at admission between the groups. The rate of concomitant ADHF was greatest in the low-dose group.

The outcomes are described in Table 2, with results of univariate statistical tests included. Using univariate analysis, there was no statistically significant difference in readmission rates between the 3 groups. There was a statistically significant larger percentage of patients with increased blood glucose in the highest dose group as compared with the lowest dose group, as well as the highest length of stay in the high dose group.

Using binary logistic regression, when holding all other variables constant there was no statistically significant association found between the rates of readmission for either the medium- or high-dose groups when compared with the baseline comparator, the low-dose group (Table 3). When holding all other variables constant, both the medium- ($P < .009$) and high-dose ($P < .001$) groups were associated with a higher rate of an increase in blood glucose of >30% as compared with the low-dose groups (Table 4). When holding all other variables constant, the high-dose group was associated with a longer length of stay as compared with the low-dose group (21.3 hours, $P < .001$, Table 5).

Table 3. Binary Logistic Regression Predicting Readmission From Covariables and Dose Groups.

Predictor	*B*	Wald χ^2	*P*
Age	−0.21	3.961	.047
Home oxygen use	0.588	4.116	.042
LACE	0.245	17.990	<.001
Confirmed ADHF	−0.924	2.939	.086
Dose groups			
Medium	−0.555	1.727	.189
High	−0.009	0.001	.980

Note. LACE = Length of stay, Acuity of admission, Comorbid conditions, number of Emergency department visits; ADHF = acute decompensated heart failure.

Table 4. Binary Logistic Regression Predicting Elevated Blood Glucose From Covariables and Dose Groups.

Predictor	*B*	Wald χ^2	*P*
Age	−0.015	2.930	.087
Charlson score	0.165	5.728	.017
Dose groups			
Medium	0.870	6.902	.009
High	1.179	14.327	<.001

Table 5. Linear Regression Predicting Length of Stay (Hours) From Covariables and Dose Groups.

Predictor	*B*	*t*	*P*
Age	0.419	2.321	.021
LACE	6.580	6.225	<.001
Charlson score	−5.977	−3.822	<.001
Confirmed ADHF	19.456	2.599	.01
Confirmed pneumonia	10.560	1.821	.07
Confirmed smoker	−9.752	−2.097	.037
Dose groups			
Medium	−2.158	−0.348	.728
High	21.313	3.675	<.001

Note. LACE = Length of stay, Acuity of admission, Comorbid conditions, number of Emergency department visits; ADHF = acute decompensated heart failure.

Discussion

All data were collected from our community, regional medical center. The overall severity of our population, as determined by the average Charlson score, is typical for a community medical center.[11] In addition, our readmission rate for AECOPD is similar to other published data; however, one limitation of our study is that we were only able to determine readmission to our own facility.[12] The focus of our study was patients admitted to our medical, cardiac, or surgical floors. Patients admitted to a higher level of care were excluded, and the potential need for higher doses of corticosteroids in this population was not determined in this study.

Our medical center does not currently provide a suggested corticosteroid dose for AECOPD. This leads to a wide range of doses used in the study. This variety helped make our study possible, and these data will help our hospital make an informed decision on the optimal dose. However, the dose range skewed toward the high-dose (>500 mg) group, which could have had implications on our sample size. We did not find a statistically significant difference in readmission rates. However, it is unknown whether this is due solely to there being no difference, or whether data availability contributed. We were also limited in the amount of data available, which was determined by the date we converted to an electronic health record.

This study was performed as a retrospective, single-center trial. Readmission is a multifactorial outcome, with facility differences that can affect readmission rates.[13,14] We decided to limit our study to just 1 site to attempt to control for facility factors related to readmission. We also used the LACE tool to help compare readmission risk for the different groups. However, there are data suggesting that LACE does not determine readmission risk as well in certain populations, such as heart failure.[15] It is unknown how this variability may have affected our readmission outcome data. As the data were collected retrospectively, a list of potential covariables and confounders were collected. Although several of the baseline characteristics were similar, we did find that the high-dose group had a higher percentage of patients who had COPD verified through spirometry, and more use of home oxygen. In addition, the low-dose group had a higher percentage of patients who had a concomitant diagnosis of ADHF. Taken together, it is possible that the higher dose group had a portion of patients with a more reliable diagnosis of COPD. We attempted to control for these group differences by using multivariable regression analysis.

Our study found that the low-dose group was associated with a lower amount of patients who experienced a blood glucose increase of >30% from baseline as compared with both the medium- and high-dose groups. This finding is consistent to those found in some studies, but not others.[5,8,16,17] This potential difference may be due to the way we determined an increase in blood glucose, which differed compared with other studies.[5,16] The use of a 30% increase from each patient's baseline allowed patients to act as their own reference point, and assess impact of the corticosteroids instead of overall control of diabetes.[8] This potentially provided a more even comparison while including both patients with and without diabetes. We also chose to use blood glucose concentrations from their daily metabolic panel which may have provided more consistency between concentrations. Our results may have been affected by additional blood glucose data points in patients with longer length of stays which could have led to a larger chance for a higher blood glucose ratio.

We did not find a statistically significant association between readmission rate and dose group, even when holding possible covariables constant. This is similar to the findings in the REDUCE trial, which did not directly evaluate readmission, but assessed re-exacerbation.[5] It is also consistent with the results of 2 large meta-analyses.[2,3] Our evaluation of differences in length of therapy found that the highest dose group was associated with the longest length of stay, while holding other covariables constant. As our study is a retrospective cohort, we are only able to ascertain an association between lengths of stay and dose group, not determine a direct cause and effect. However, as this was not seen with the low- or medium-dose group, and similar results were seen in the REDUCE trial, we feel confident that using lower amounts of corticosteroids should not lead to an increase in length of stay.[5] Future evaluation of length of stay differences after implementation of a lower dose protocol could

help determine financial benefits of lower doses of corticosteroids beyond savings in medication costs.

Conclusion

When comparing 3 dose ranges of corticosteroids, the lowest dose range (≤250 mg) was associated with the lowest rate of increased blood glucose, and use of this lower dose did not appear to impact length of stay or readmission rate. Further study on the financial benefits of implementing lower doses of corticosteroids, in terms of total medication cost, length of stay, and use of medications to combat adverse effects of higher doses, may be warranted.

Declaration of Conflicting Interests

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References

1. Walters JAE, Tan DJ, White CJ, Gibson PG, Wood-Baker R, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2014;9. doi:10.1002/14651858.CD001288.pub4.
2. Cheng T, Gong Y, Guo Y, et al. Systemic corticosteroid for COPD exacerbations, whether the higher dose is better? A meta-analysis of randomized controlled trials. *Clin Respir J*. 2013;7:305-318.
3. Walters JAE, Tan DJ, White CJ, Wood-Baker R. Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2014;12. doi:10.1002/14651858.CD006897.pub3.
4. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. Global initiative for chronic Obstructive Lung Disease (GOLD). http://goldcopd.org. Accessed March 10, 2017.
5. Leuppi JD, Schuetz P, Bingisser R, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. *JAMA*. 2013;309:2223-2231.
6. Wier LM, Elixhauser A, Pfuntner A, Au DH. Overview of hospitalizations among patients with COPD, 2008. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb106.pdf. Published February 2011. Accessed October 1, 2016.
7. Readmissions Reduction Program (HRRP). Centers for Medicare & Medicaid Services. https://www.cms.gov/medicare/medicare-fee-for-service-payment/acuteinpatientpps/readmissions-reduction-program.html. Published April 18, 2016. Accessed March 10, 2017.
8. Islam EA, Limsuwat C, Nantsupawat T, Berdine GG, Nugent KM. The association between glucose levels and hospital outcomes in patients with acute exacerbations of chronic obstructive pulmonary disease. *Ann Thorac Med*. 2015;10:94-99.
9. van Walraven C, Dhalla IA, Bell C, et al. Derivation and validation of an index to predict early death or unplanned readmission after discharge from hospital to the community. *CMAJ*. 2010;182:551-557.
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373-383.
11. Meltzer D, Manning WG, Morrison J, et al. Effects of physician experience on costs and outcomes on an academic general medicine service: results of a trial of hospitalists. *Ann Intern Med*. 2002;137:866-874.
12. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med*. 2009;360:1418-1428.
13. Park L, Andrade D, Mastey A, Sun J, Hicks L. Institution specific risk factors for 30 day readmission at a community hospital: a retrospective observational study. *BMC Health Serv Res*. 2014;14:40.
14. Anderegg SV, Wilkinson ST, Couldry RJ, Grauer DW, Howser E. Effects of a hospitalwide pharmacy practice model change on readmission and return to emergency department rates. *Am J Health Syst Pharm*. 2014;71:1469-1479.
15. Wang H, Robinson RD, Johnson C, et al. Using the LACE index to predict hospital readmissions in congestive heart failure patients. *BMC Cardiovasc Disord*. 2014;14:97.
16. Baker JM, Pace HA, Ladesich JB, Simon SD. Evaluation of the impact of corticosteroid dose on the incidence of hyperglycemia in hospitalized patients with an acute exacerbation of chronic obstructive pulmonary disease. *Hosp Pharm*. 2016;51:296-304.
17. Kiser TH, Allen RR, Valuck RJ, Moss M, Vandivier RW. Outcomes associated with corticosteroid dosage in critically ill patients with acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2014;189:1052-1064.