Efficacy of Corticosteroid Therapy in Patients With an Acute Exacerbation of Chronic Obstructive Pulmonary Disease Receiving Ventilatory Support

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Background: Randomized trials assessing the effect of systemic corticosteroids on chronic obstructive pulmonary disease (COPD) exacerbations excluded patients who were mechanically ventilated or admitted to the intensive care unit (ICU). Critically ill patients constitute a population of persons who are prone to develop complications that are potentially associated with the use of corticosteroids (eg, infections, hyperglycemia, ICU-acquired paresis) that could prolong the duration of mechanical ventilation and even increase mortality.

Methods: A double-blind placebo-controlled trial was conducted to evaluate the efficacy and safety of systemic corticosteroid treatment in patients with an exacerbation of COPD who were receiving ventilatory support (invasive or noninvasive mechanical ventilation). A total of 354 adult patients who were admitted to the ICUs of 8 hospitals in 4 countries from July 2005 through July 2009 were screened, and 83 were randomized to receive intravenous methylprednisolone (0.5 mg/kg every 6 hours for 72 hours, 0.5 mg/kg every 12 hours on days 4 through 6, and 0.5 mg/kg/d on days 7 through 10) or placebo. The main outcome measures were duration of mechanical ventilation, length of ICU stay, and need for intubation in patients treated with noninvasive mechanical ventilation.

Results: There were no significant differences between the groups in demographics, severity of illness, reasons for COPD exacerbation, gas exchange variables, and corticosteroid rescue treatment. Corticosteroid treatment was associated with a significant reduction in the median duration of mechanical ventilation (3 days vs 4 days; $P = .04$), a trend toward a shorter median length of ICU stay (6 days vs 7 days; $P = .09$), and significant reduction in the rate of NIV failure (0% vs 37%; $P = .04$).

Conclusion: Systemic corticosteroid therapy in patients with COPD exacerbations requiring mechanical ventilation is associated with a significant increase in the success of noninvasive mechanical ventilation and a reduction in the duration of mechanical ventilation

Trial Registration: clinicaltrials.gov Identifier: NCT01281748

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PATIENTS WITH CHRONIC OBstructive pulmonary disease (COPD) have intermittent episodes of acute exacerbation that often require hospitalization. Hospital treatment for COPD exacerbations includes the use of bronchodilators, antibiotics, oxygen, and systemic corticosteroids.[1-3] The efficacy of systemic corticosteroid therapy on the outcomes of acute exacerbations of COPD was recently evaluated in a Cochrane systematic review.[4] Overall, the change in forced expiratory volume in the first second of expiration within the first 72 hours was increased in patients who were given corticosteroids (mean difference, 140 mL; 95% confidence interval [CI], 90-190 mL); there were fewer treatment failures within 30 days (odds ratio, 0.50; 95% CI, 0.36-0.69); and the duration of hospitalization was significantly shorter (mean difference, –1.22 days; 95% CI, –2.26 to –0.18 days). There was no effect on mortality, but 1 extra adverse effect occurred for every 5 patients who were treated, and the risk of hyperglycemia was significantly increased (odds ratio, 4.95; 95% CI, 2.47-9.91).

See Invited Commentary at end of article

Exacerbations of COPD occur in 5% to 15% of patients who are receiving mechanical ventilation in intensive care units (ICUs).[5-8] Because studies evaluating the effect of the use of corticosteroids on the outcomes of exacerbations of COPD have been limited to patients who were ini-

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tially cared for outside the ICU, it is uncertain whether the results are applicable to more severely ill patients. Furthermore, the risks associated with the use of corticosteroids in critically ill patients are unclear, but recent studies of ventilated patients found a strong association between the use of corticosteroids and muscle weakness.[9,10] Because critically ill patients constitute a population of persons who are prone to develop complications potentially associated with corticosteroid therapy (eg, infections, hyperglycemia, ICU-acquired paresis) that could prolong the duration of mechanical ventilation and even increase mortality, we conducted a randomized trial to evaluate the efficacy and safety of systemic corticosteroid therapy in patients with an acute exacerbation of COPD who were receiving ventilatory support.

METHODS

STUDY PATIENTS

All patients who were 18 years or older with known COPD and who were hospitalized because of an exacerbation that required ventilator support in participating ICUs were eligible for entry into the study. Exacerbation of COPD was defined as the presence of 2 or more of the following: worsening dyspnea, increase in sputum purulence, or increase in sputum volume, with acute hypercapnic respiratory failure (pH <7.35, with a $Paco_2$ >45 mm Hg) requiring invasive or noninvasive mechanical ventilation. Patients were excluded if they had a history of (1) asthma or atopy; (2) use of systemic corticosteroids within the preceding month; (3) use of systemic corticosteroids for the treatment of COPD exacerbation for more than 24 hours at the time of randomization; (4) clinical or radiologic evidence of pneumonia; (5) uncontrolled left ventricular failure requiring the use of inotropes or vasoactive drugs, (6) uncontrolled arterial hypertension; (7) uncontrolled diabetes mellitus; (8) a neuromuscular disease; or (9) allergy and or adverse reaction to corticosteroid therapy.

PROTOCOL

The trial was approved by the ethics committee at each center, and written informed consent was obtained from the patients or their surrogates. Randomization was performed by the hospital pharmacy at each center by a random number table with permuted blocks of 4, with stratification according to the type of mechanical ventilation (conventional or noninvasive), and the allocation schedule was concealed with sealed envelopes that were opened sequentially. Pharmacists dispensed the intravenous medications in a blinded fashion. Within 24 hours after ICU admission, the patients were randomly assigned to 1 of 2 groups: corticosteroid group (methylprednisolone: 0.5 mg/kg every 6 hours for 72 hours, 0.5 mg/kg every 12 hours on days 4 through 6, and 0.5 mg/kg/d on days 7 through 10) or placebo group (50 mL of intravenous normal saline solution). The nurses who were administering the medications of study, the physicians who were caring for the patients, and the local investigators and research personnel who collected the data were unaware of the treatment assignments. The physicians who were in charge of the patients were free to prescribe systemic corticosteroids after the third study day if they thought that clinical improvement was not satisfactory, in which case the administration of the study medication was suspended.

The patients in both groups received an inhaled β_2-adrenergic agonist (2.5 mg of salbutamol every 6 hours or 2 puffs from a metered-dose inhaler at least 4 times daily) and inhaled ipratropium bromide (0.5 mg every 6 hours or 2 puffs from a metered-dose inhaler at least 4 times daily). Any patient who was receiving inhaled corticosteroid therapy before randomization was continued on this therapy. Systemic antibiotics were used at the judgment of the treating physicians.

Patients who were treated with noninvasive mechanical ventilation were considered to need tracheal intubation if they met any of the following criteria: a pH of less than 7.20; a pH of 7.20 to 7.25 on 2 separate measures within 1 hour apart; a hypercapnic coma (Glasgow Coma Scale <8 and $Paco_2$ ≥60 mm Hg); a Pao_2 of less than 45 mm Hg despite a maximum tolerated fraction of inspired oxygen; and/or cardiac arrest. Patients with conventional mechanical ventilation were screened each morning to evaluate their recovery from respiratory failure and to see whether they should start being weaned from mechanical ventilation. In patients with noninvasive mechanical ventilation, weaning was considered successful if after at least 3 hours of breathing without ventilator assistance the following criteria were met: an arterial oxygen saturation of 90% or more with a fraction of inspired oxygen of 40% or less, a pH of 7.35 or higher, and a respiratory rate of 35 breaths/min or less.

END POINTS

The primary end points were duration of mechanical ventilation, length of ICU stay, and need for intubation in patients treated with noninvasive mechanical ventilation. The secondary end points were length of hospital stay and ICU mortality. The complications of systemic corticosteroid therapy were assessed with the following criteria: secondary infection (the administration of antibiotics for any proved or suspected infection); gastrointestinal bleeding (the presence of clinically relevant hematemesis or melena with a decrease in hemoglobin level ≥2 g/dL [to convert to grams per liter, multiply by 10]) in the absence of any other source of loss of blood); arterial hypertension (the institution or intensification of antihypertensive therapy because of a systolic pressure >160 mm Hg and/or a diastolic pressure >90 mm Hg); hyperglycemia (the initiation of insulin therapy because of a blood glucose level >120 mg/dL [to convert to millimoles per liter, multiply by 0.0555] in patients without preexisting diabetes mellitus or increased doses of insulin in patients with diabetes mellitus); hospital-acquired pneumonia (the presence of a new persistent or progressive infiltrate on chest x-ray films and at least 2 of the following criteria: [1] fever [body temperature ≥38.5°C] and/or hypothermia [≤35.5°C]; [2] a white blood cell count ≥10 000/μL and/or <3000/μL [to convert to $\times 10^9$/L, multiply by 0.001]; and [3] isolation of potential pathogens from any of the following: semiquantitative culture of purulent tracheal aspirate [$\geq 10^5$ colony-forming units (CFU)/mL]; semiquantitative culture from a bronchoalveolar lavage [$\geq 10^4$ CFU/mL; semiquantitative culture from a protective brush catheter [$\geq 10^3$ CFU/mL]; positive blood culture result; positive pleural fluid culture result; and ICU-acquired paresis [patients with a Medical Research Council score <48 were considered to have ICU-acquired paresis]). Delirium was assessed with the Confusion Assessment Method for the ICU. The following data were recorded on days 1 to 5: arterial blood gas analysis, plasma C-reactive protein level, white blood cell count, maximal blood glucose level, daily dose of insulin, and intrinsic positive end-expiratory pressure (only in patients who were intubated).

STATISTICAL ANALYSIS

Sample size was estimated from our previous observational study.[6] A sample size of 198 patients was estimated to have at

least 80% power at an α error of 0.05 to detect 2 days' difference in the duration of mechanical ventilation, with an SD of 5 days. Data are presented as mean (SD), medians with the 25th and 75th percentiles, or proportions as appropriate. The studied groups were compared on an intention-to-treat basis, and $P < .05$ was considered significant in 2-sided tests. Continuous variables with normal distribution were compared with the independent samples *t* test, and variables with a nonnormal distribution were compared with the Mann-Whitney test. Categorical variables were compared with χ^2 test or the Fisher exact test.

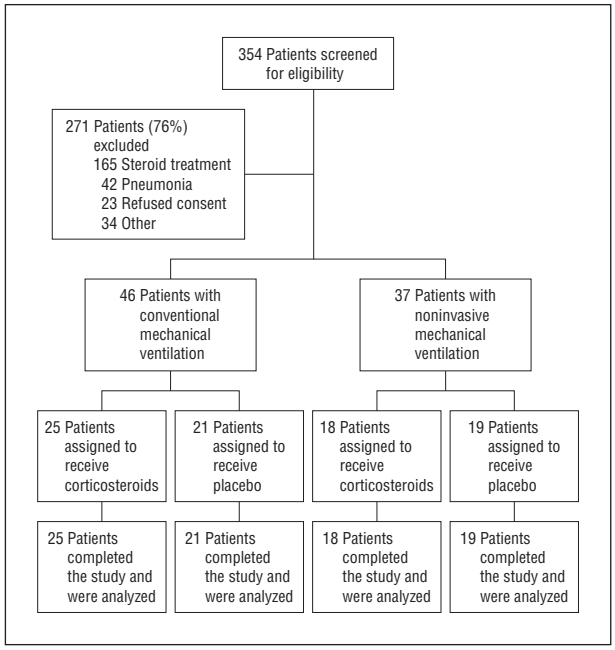

Figure 1. Screening and enrollment.

RESULTS

Patients hospitalized because of acute exacerbations of COPD were prospectively recruited from 8 hospitals in 4 countries (Hospital Universitario de Getafe, Hospital Fundación Alcorcón, Hospital Clinic de Barcelona, Consorci Hospitalari Parc Taulí, and Hospital Príncipe de Asturias in Spain; Hospital ABC in Mexico; Clínica Universitaria Bolivariana in Colombia; and University of Texas Health Science Center in the United States [University Hospital and Audie L. Murphy Veterans Affairs Hospital]). Recruitment began in June 2005 and concluded in July 2009. During the study period, each participating ICU was incorporated into the study at different times, and patients were enrolled during a mean time of 19.6 months (range, 5-49 months).

Of 354 patients who underwent screening for eligibility, 271 (76%) were excluded and 83 were randomly assigned to treatment (**Figure 1**). The low rate of enrollment precluded completion of the original sample size. The most common reason for exclusion was the prior use of corticosteroids. As a whole, 1 of each 2 potentially eligible patients had received corticosteroids either in the previous month or during the 24 hours before randomization. There were no statistically significant differences between the patients included in and those excluded from the study with respect to age (68 [10] years vs 69 [9] years; $P = .43$), sex (men, 79% vs 73%; $P = .26$), severity of illness (Simplified Acute Physiology Score II: 36 [10] vs 38 [10]; $P = .96$), and ICU mortality (11% vs 16%; $P = .25$).

The baseline characteristics of the 2 treatment groups are shown in **Table 1**. There were no statistically signifi-

Table 1. Baseline Characteristics of the 83 Patients According to Treatment Assignment

Characteristic	Placebo Group (n=40)	Corticosteroid Group (n=43)	*P* Value
Age, mean (SD), y	67.6 (10.7)	69.1 (9.7)	.52
Men, No. (%)	34 (85)	32 (74)	.23
SAPS II, mean (SD)	36.3 (10.9)	36.3 (9.8)	.99
Comorbid condition, No. (%)			.07
Diabetes mellitus	9 (22)	15 (35)	
Arterial hypertension	22 (55)	15 (35)	
Neuromuscular disease	1 (2)	1 (2)	
Reason for acute exacerbation of COPD, No. (%)			.72
Respiratory infection	28 (70)	30 (70)	
Cardiac failure	9 (22)	8 (19)	
Sepsis	1 (2)	1 (2)	
Postoperative	1 (2)	0 (0)	
Unidentified cause	0 (0)	4 (9)	
Other	2 (5)	3 (7)	
Initial ventilatory support, No. (%)			.60
Noninvasive	19 (47)	18 (42)	
Conventional	21 (52)	25 (58)	
Blood gases, mean (SD)			
Pa_{O_2}/FI_{O_2}, mm Hg	191.5 (75.9)	197.8 (83.7)	.72
Pa_{CO_2}, mm Hg	68.7 (18.5)	69.9 (19.7)	.78
pH	7.31 (0.10)	7.27 (0.11)	.12
Blood glucose, mean (SD), mg/dL	158.7 (65.7)	193.3 (60.6)	.02
White blood cell count, mean (SD), /μL	10 515 (3645)	12 166 (5268)	.10

Abbreviations: COPD, chronic obstructive pulmonary disease; FI_{O_2}, fraction of inspired oxygen; SAPS II, Simplified Acute Physiology Score II.
SI conversions: To convert blood glucose values to millimoles per liter, multiply by 0.0555; to convert white blood cell count to $\times 10^9$/L, multiply by 0.001.

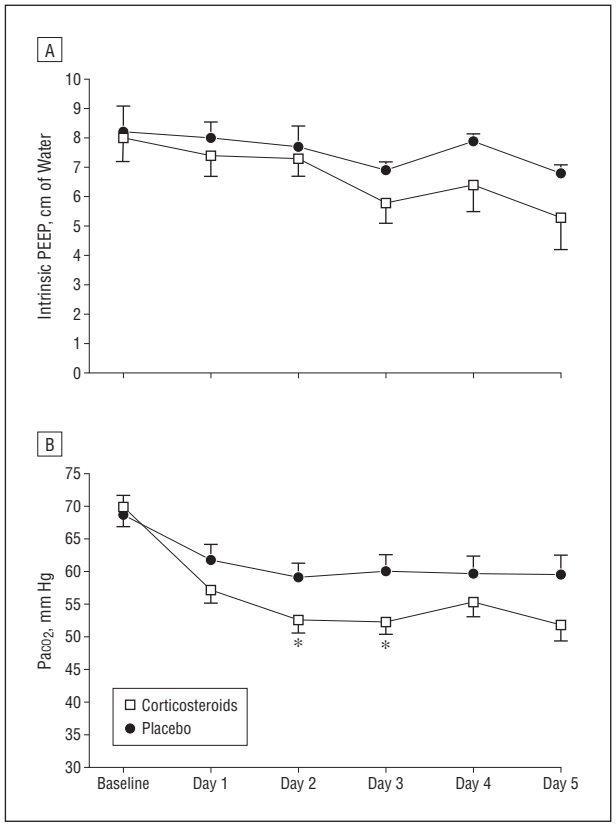

Figure 2. Mean values of intrinsic positive end-expiratory pressure (PEEP) (A) and $Paco_2$ (B) at selected times according to treatment group. The error bars indicate standard errors. *$P<.05$ for comparison with placebo.

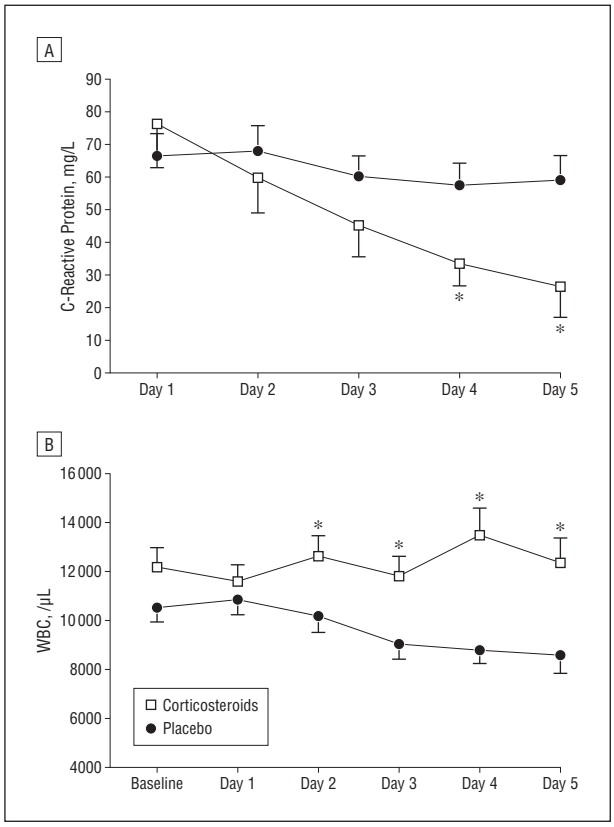

Figure 3. Mean levels of C-reactive protein (A) and white blood cell count (WBC) (B) at selected times according to treatment group. To convert C-reactive protein values to nanomoles per liter, multiply by 9.524; to convert white blood cell count to $\times 10^9$/L, multiply by 0.001. The error bars indicate standard errors. *$P<.05$ for comparison with placebo.

cant differences between the groups with respect to demographics, severity of illness, reasons for COPD exacerbation, and gas exchange variables, but the blood glucose level was significantly higher in the corticosteroid treatment group ($P=.02$), probably because there was a higher prevalence of diabetes mellitus in this group. There were no statistically significant differences between groups in the use of systemic antibiotics (65% of patients in the placebo group and 74% in the corticosteroid group; $P=.35$), selective digestive decontamination (40% vs 25%; $P=.16$), use of inhaled corticosteroids (42% vs 30%; $P=.24$), and corticosteroid rescue treatment (10% vs 9%; $P=.91$).

Intrinsic positive end-expiratory pressure and $Paco_2$ improved over time in both groups (**Figure 2**). Plasma C-reactive protein levels decreased over time in the corticosteroid group and were statistically significantly lower than those in the placebo group on days 4 ($P=.02$) and 5 ($P=.01$); however, the white blood cell count was significantly higher in the corticosteroid group on those days ($P=.02$ on day 2, $P=.01$ on day 3, $P<.001$ on day 4, and $P=.01$ on day 5) (**Figure 3**).

Outcomes are shown in **Table 2**. The treatment with corticosteroids was associated with a statistically and clinically significant 1-day reduction in the median duration of mechanical ventilation (3 days vs 4 days; $P=.04$) and a trend toward a shorter length of ICU stay (6 days vs 7 days; $P=.09$). Furthermore, failure of noninvasive mechanical ventilation was significantly and clinically reduced in patients assigned to corticosteroid treatment (0% vs 37%; $P=.004$). In-ICU mortality was similar in the 2 groups (10% vs 12%; relative risk, 1.16; 95% CI, 0.34-4.03; $P=.81$).

The treatment with corticosteroids was associated with an almost 2-fold increase in the risk of hyperglycemia requiring treatment (46% vs 25%; relative risk, 1.86; 95% CI, 1.00-3.48; $P=.04$). Compared with the placebo group, the corticosteroid group had significantly higher glucose levels and daily insulin doses throughout the 5-day study period (**Figure 4**). There were no reported cases of ICU-acquired paresis (**Table 3**), and there were no statistically or clinically significant differences in Medical Research Council score values between the 2 study groups.

COMMENT

This is the first clinical trial (to our knowledge) in patients receiving mechanical ventilation for a COPD exacerbation that confirmed the benefits of systemic corticosteroid therapy and showed a clinically significant reduction in both the duration of ventilatory support and the failure of noninvasive mechanical ventilation. The results of our study might not have a great impact on the current clinical treatment of ICU patients with COPD exacerbations because most of them are probably treated with corticosteroids,[11-14] but they do provide strong evidence of the beneficial effects of systemic corticosteroid

Table 2. Outcome Measures

Outcome[a]	Placebo Group (n=40)	Corticosteroid Group (n=43)	*P* Value
Duration of mechanical ventilation, d	4 (3-7)	3 (2-6)	.04
NIMV	4 (2-5)	2 (2-3)	.008
CMV	7 (4-11)	5 (3-7)	.09
Length of ICU stay, d	7 (5-12)	6 (4-10)	.09
NIMV	5 (4-9)	4 (3-5)	.04
CMV	10 (7-18)	9 (6-12)	.18
Length of hospital stay, d	15 (11-21)	13 (8-21)	.30
NIMV	15 (9-20)	14 (8-19)	.99
CMV	17 (12-31)	13 (8-22)	.07
In-ICU mortality, No. (%)	4 (10)	5 (12)	.81
NIMV	1/19 (5)	0/18 (0)	>.99
CMV	3/21 (14)	5/25 (20)	.71
Failure of NIMV, No. (%)	7/19 (37)	0/18 (0)	.004
Reintubation within 48 h,[b] No. (%)	5/26 (19)	3/22 (14)	.71

Abbreviations: CMV, conventional mechanical ventilation; ICU, intensive care unit; NIMV, noninvasive mechanical ventilation.
[a] Data are presented as median (interquartile range) unless specified otherwise.
[b] Data are from patients who underwent planned extubation and received CMV either initially or after failure of NIMV.

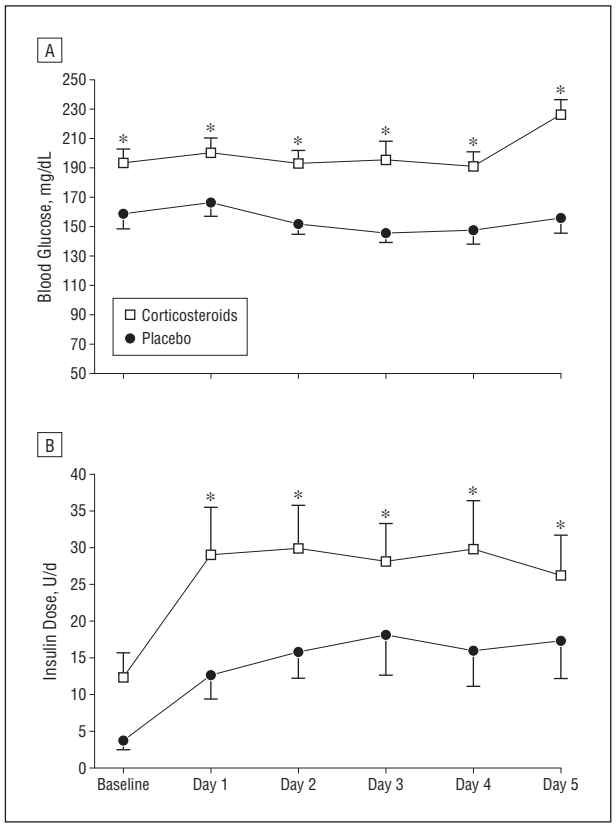

Figure 4. Mean of highest blood glucose level (A) and daily dose of insulin (B) at selected times according to treatment group. To convert blood glucose values to millimoles per liter, multiply by 0.0555. The error bars indicate standard errors. *$P<.05$ for comparison with placebo.

Table 3. Frequency of Adverse Events

Event	No. (%) Placebo Group (n=40)	No. (%) Corticosteroid Group (n=43)	*P* Value
Superinfection	6 (15)	5 (12)	.65
Gastrointestinal bleeding	2 (5)	2 (5)	.60
Arterial hypertension	4 (10)	2 (5)	.42
Hyperglycemia	10 (25)	20 (46)	.04
Ventilator-associated pneumonia	3 (7)	4 (9)	.77
Delirium	3 (7)	1 (2)	.35
ICU-acquired paresis	0	0	. . .

Abbreviation: ICU, intensive care unit.

therapy on clinically relevant outcomes in a patient population that had never previously been enrolled in a clinical trial. Randomized trials assessing the effect of systemic corticosteroid therapy on COPD exacerbations have excluded patients with respiratory failure who required mechanical ventilation or ICU admission[15-17]; moreover, patients were withdrawn from the studies if respiratory acidosis or a need for mechanical ventilation occurred.[15,18,19] Our results show that corticosteroid therapy was associated with an absolute reduction of 1 day in the median duration of mechanical ventilation and a relative reduction of 25%. Because the sample size was small, the study was underpowered for detecting a statistically significant difference in the median length of ICU stay that was reduced by 1 day. The magnitude of the treatment effect on the duration of ventilation and ICU stay is similar to that reported regarding the duration of hospitalization in clinical trials of nonventilated patients with exacerbated COPD. In the study by Davies et al,[20] the median length of hospital stay in patients treated with corticosteroids was significantly shorter than in those receiving placebo (7 days vs 9 days; $P=.03$). Niewoehner et al[21] reported that the average length of hospitalization was significantly longer in the placebo group than in the corticosteroid group (9.7 days vs 8.5 days; $P=.003$). Wood-Baker et al[19] reported a reduction in the length of hospitalization from 9.5 (5.2) days in the placebo group to 8.1 (4.4) days in the corticosteroid group.

Noninvasive mechanical ventilation is an adjunct treatment in COPD exacerbations. Although it significantly reduces the risk of tracheal intubation to more than half com-

pared with usual care in patients with COPD exacerbations, the percentage of patients needing intubation after trying noninvasive mechanical ventilation ranged from 0% to 52% in randomized trials[22-24] and from 14% to 48% in observational studies.[6,25-33] In our study, the percentage of patients needing tracheal intubation in the placebo group (38%) was comparable to that reported in other studies,[26-28] while noninvasive mechanical ventilation failure was absent in the corticosteroid group. The markedly beneficial effect of corticosteroid therapy on the avoidance of tracheal intubation likely caused the reduction of 2 days in the median duration of mechanical ventilation and 1 day in the median length of ICU stay among patients in the noninvasive mechanical ventilation group.

The variability in published outcomes for patients with COPD exacerbations requiring mechanical ventilation suggests that significant heterogeneity exists within populations, so comparison of the different studies is not easy. Observational studies published in the last 10 years have reported median durations of mechanical ventilation ranging from 2 to 12 days,[6,26,29,30,34] median lengths of ICU stay ranging from 3 to 14 days,[6,29,30,34-37] and ICU mortality rates ranging from 10% to 30%.[6,29,30,34-37] More than 75% of patients received invasive mechanical ventilation in all of the aforementioned studies. By contrast, randomized trials performed in the last 10 years in patients with COPD exacerbations requiring mechanical ventilation used noninvasive mechanical ventilation in 50% to 100% of enrolled patients and reported ICU mortality rates ranging from 4% to 23%.[23,24,38,39] In our opinion, the beneficial effect of corticosteroid therapy observed in the present study may be generalized, because the characteristics of our study population and the outcomes are consistent with those reported in other studies. Furthermore, the results may be also applicable to patients excluded from the study since the demographic characteristics, severity of illness, and mortality of these patients were similar to those of included patients. A high percentage of patients screened for inclusion in this clinical trial were excluded. The most common reason for ineligibility was previous treatment with systemic corticosteroids. Other studies have reported rates of exclusion ranging from 75% to 89%,[16,17,20,21] and between 23% and 50% of screened patients had previously taken systemic corticosteroids,[16,17,20,21] findings that are very similar to those reported in the present study. However, to our knowledge, our study is the only one that collected information of excluded patients and showed that they were not different from the study group.

Corticosteroids are very potent inhibitors of inflammation. In our trial, the decline in C-reactive protein levels was faster in patients who were treated with corticosteroids. This finding has been also reported in randomized controlled trials evaluating the efficacy of corticosteroid therapy in patients with community-acquired pneumonia.[40-42] Changes in the immune response may contribute to the reduction in the duration of mechanical ventilation in patients assigned to corticosteroid treatment.

The optimal dose of corticosteroids and the duration of treatment for COPD exacerbations requiring hospitalization remain unknown. Most clinical trials reporting benefits administered corticosteroids for 10 to 14 days,[4] and there is evidence that courses longer than 2 weeks have no advantages.[21] Dosages varied from 30 mg of prednisolone per day[20] to 125 mg of methylprednisolone every 6 hours.[21] We have demonstrated that a tapered course of 10 days, with a high dose during the first 4 days, reduces the duration of mechanical ventilation, although it is possible that a lower dosage could obtain a similar effect.

Corticosteroid treatment was not associated with an increased risk of gastrointestinal bleeding, superinfections, psychiatric disorders, or acquired neruromuscular weakness in our study. Similar findings have been reported in a recent systematic review on the benefits and risks of the use of corticosteroids in patients with severe sepsis and septic shock[43] and in a randomized trial on the use of corticosteroids in patients with persistent acute respiratory distress syndrome.[44] On the contrary, hyperglycemia is a known complication of corticosteroid treatment.[43,44] Hyperglycemia was the major complication of corticosteroid therapy that we identified. However, the disparity in glycemic control had no unfavorable clinical consequences on mortality or neuromuscular abnormality.

A limitation of our study is that the sample size was too small to detect uncommon risks associated with corticosteroid treatment, such as neuropathy causing difficulties in weaning, which would offset the reduction in the duration of mechanical ventilation that was observed in our clinical trial. There are other limitations. The study lasted 5 years because of the lower enrollment rate, which was mainly due to a reduction in ICU admissions of patients with COPD exacerbations and a high rate of exclusion. We do not believe that this limitation affects the study findings. It is also possible that during the study period there were significant changes in the treatment of these patients. In our opinion, the only substantial change could be an increase in the use of noninvasive mechanical ventilation. Our study included a high number of patients treated with noninvasive mechanical ventilation and demonstrated that corticosteroid treatment is beneficial in these patients. We conclude that systemic corticosteroid therapy for patients with COPD exacerbations requiring mechanical ventilation is associated with a clinically significant increase in the success of noninvasive mechanical ventilation and a modest but relevant reduction in the duration of mechanical ventilation.

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Author Contributions: Dr Alía had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design*: Alía, de la Cal, Esteban, Abella, Torres, Gordo, and Anzueto. *Acquisition of data*: Alía, Abella, Ferrer, Molina, Gordo, Elizalde, de Pablo, Huete, and Anzueto. *Analysis and interpretation of data*: Alía, de la Cal, Esteban, Torres, Gordo, Elizalde, and Anzueto. *Drafting of the manuscript*: Alía, de la Cal, Esteban, Molina, Gordo, Elizalde, and Anzueto. *Critical revision of the manuscript for important intellectual content:* de la Cal, Abella, Ferrer, Torres, de Pablo, Huete, and Anzueto. *Statistical analysis*: de la Cal and Gordo. *Obtained funding:* Ferrer. *Administrative, technical, or material support:* Abella, Torres, Gordo, de Pablo, Huete, and Anzueto. *Study supervision*: Alía, de la Cal, Esteban, Torres, and Elizalde.

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INVITED COMMENTARY

Clinical Trials in the Critically Ill

Practical and Ethical Challenges

Chronic obstructive pulmonary disease (COPD) remains associated with substantial morbidity and mortality and has become a leading reason for hospitalization in the United States.[1,2] These acute exacerbations of COPD (AECOPDs) may progress to respiratory failure, necessitating mechanical ventilation (MV).[3] In fact, approximately 10% of patients with AECOPDs require MV.[4] Over the last decade, multiple studies of novel therapies for stable COPD suggest that these treatments help to prevent AECOPDs.[5,6] However, there is a paucity of interventions for the management of AECOPDs. Available treatments for AECOPDs include antibiotics, bronchodilators, noninvasive ventilation, and corticosteroids,[7] but, unfortunately, nearly all studies of ACEOPDs have excluded persons who are at the highest risk for failure, ie, those who are critically ill. Often patients with impending respiratory failure are excluded from clinical trials because of concerns about safety or because of more practical issues. A critically ill patient is less likely to tolerate an adverse event. Alternatively, it is difficult to determine whether outcomes in patients who are enrolled in the intensive care unit (ICU) are driven by their underlying physiology or by the treatment under study. Similarly, the process of obtaining consent is cumbersome and adds to the challenge of enrolling those in the ICU. Therefore, few researchers venture into the ICU for clinical trials. As a consequence, intensivists are often left extrapolating data from non–critically ill patients. However, is it appropriate to administer medical therapy to patients in the ICU when the safety and efficacy of the therapy has not been demonstrated in this population?

In this issue of the *Archives*, Alía et al[8] report an important study investigating the use of corticosteroids in critically ill patients with AECOPDs. They conducted a multicenter, double-blind, placebo-controlled randomized trial comparing corticosteroids with placebo in hopes of documenting the value of these agents in the treatment of AECOPDs and respiratory failure. They found that corticosteroid therapy resulted in shorter time on MV and in the ICU. For patients initially requiring noninvasive ventilation, administration of corticosteroids eliminated the need for rescue MV. The differences that the authors observed (eg, 1 day less in the ICU) are certainly clinically significant. Given the economic burden of AECOPDs, reducing both ICU length of stay and the need for rescue MV can lead to substantial savings.

Despite these findings, Alía and colleagues' study raises several methodological concerns. First, how was blinding maintained? As a secondary end point, adverse effects due to the use of corticosteroids were monitored; however, the adverse effects of these agents are well known. Because investigators were watching for hyperglycemia, a known consequence of corticosteroid administration, physicians may have inadvertently become unblinded. This is of particular concern as the study's primary end points (eg, duration of MV) are, at their root, subjective. Although protocolizing liberation from MV can address ascertainment bias to some degree, the authors provide no description of the placebo and what efforts were made to ensure that researchers remained blinded. Second, the study enrolled fewer than 25% of the planned sample size. This low enrollment derived, in part, from the rigorous exclusion of persons recently exposed to corticosteroids. This difficulty illustrates the trap articulated above. Many physicians have concluded that corticosteroid therapy is efficacious in severely ill patients with AECOPDs by inferring from data obtained in non-ICU AECOPD studies. Widespread use of corticosteroids in clinical practice precluded many patients from being eligible for the clinical trial. The dilemma regarding trials in patients in the ICU is clear: How can we study such questions if we have already altered our clinical practice so that we believe that what works in less sick patients will presumptively work in the ICU? We do not mean to suggest that intensivists should be handcuffed and not use potentially effective therapies simply because we lack clear data from patients in the ICU. The absence of proof is not proof of an absence. However, it is important to acknowledge that treatments that