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Low-dose compared to high-dose methylprednisolone in patients with Chronic Obstructive Pulmonary Disease exacerbation requiring invasive mechanical ventilation: a proposed randomized controlled trial

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Abstract:

Background: *Chronic obstructive pulmonary disease (COPD) is characterized by obstruction of lung airflow that is not fully reversible. Clinical spectrum of acute exacerbation of COPD ranges from increased cough and sputum to respiratory failure. Systemic corticosteroids are widely used in management of exacerbation of COPD. Nevertheless, for the subgroup of patients requiring invasive mechanical ventilation (MV), dosage, route of administration and duration of treatment are not yet established.*

Aim: *To assess whether 60mg compared to 240mg of daily intravenous (IV) methylprednisolone reduces ventilator-free days (VFD) in individuals aged 40 and over undergoing invasive MV for severe exacerbation of COPD.*

Methods: *Multicenter, randomized, controlled, double-blinded clinical trial with two parallel arms in five ICUs of tertiary centers in Brazil. Patients will be enrolled to daily receive either 60 or 240mg of IV methylprednisolone for 7 days and will be followed up to hospital discharge. Primary endpoint is VFD, i.e., the number of days between extubating and day 28 after study enrollment. A final sample of 250 individuals is estimated in order to detect a 1-day reduction on VFD (80% power at an alfa level of 0.05) among those receiving 60mg of IV methylprednisolone.*

Perspective: *Prevention of adverse effects related to high dose of corticosteroids is expected to reduce length of mechanical ventilation. Anticipated higher efficacy along with decreased side effects and costs might have a dramatic impact on patients' general health and on hospital resources.*

Keywords: *Chronic Obstructive Pulmonary Disease; Disease Exacerbation; Glucocorticoids; Respiratory Failure; Mechanical Ventilation; Ventilator Weaning*

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common respiratory condition characterized by prolonged and persistent respiratory symptoms associated with airflow limitation and hyperinflation (Vogelmeier et al., 2017). It is the third leading cause of death worldwide (Murray & Lopez, 1997; Raherison & Girodet, 2009), and it has also a substantial public health burden leading to repetitive hospitalizations, work absence and increased healthcare costs (Bahadori & FitzGerald, 2007; Ding, Small, Bergstrom, & Holmgren, 2017; Nielsen, Klemmetsby, & Gulsvik, 2008). From 1990 to 2010, there was a 68.9% increase of COPD global prevalence, with the highest numbers in the Americas (Adeloye et al., 2015). Prevalence estimate of COPD in Latin America and in Brazil is of 14.3% and 15.8%, respectively (Menezes et al., 2008).

Clinical course of COPD is characterized by exacerbations, which have short and long-term consequences and often requires additional care beyond

usual standard treatment. Patients experiencing severe acute COPD exacerbations are at greater risk of being admitted to the intensive care unit (ICU) and undergoing invasive mechanical ventilation (MV) (Qureshi, Sharafkhaneh, & Hanania, 2014; Vogelmeier et al., 2017).

Pharmacological management of exacerbation of COPD is based on systemic corticosteroid, antibiotics, short action beta agonists and muscarinic receptor antagonists (Vogelmeier et al., 2017). Oral or parenteral corticosteroids significantly reduce treatment failure and the need for additional medical treatment and shorten hospital stay (Alia et al., 2011; Walters, Gibson, Wood-Baker, Hannay, & Walters, 2009). A large cohort study (Lindenauer et al., 2010) showed that low-dose steroids administered orally were not associated with higher relapse rates than high-dose intravenous therapy for COPD patients admitted to the emergency room or the ward. Neither is overall mortality influenced by corticosteroid doses (Abroug et al., 2014; Kiser, Allen, Valuck, Moss, & Vandivier, 2014). Accordingly, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (Vogelmeier et al., 2017) advise using the equivalent of prednisone 40 mg once daily during 5 to 7 days for the majority of COPD exacerbations.

However, for those patients requiring ventilatory support at the ICU, the effect of steroids dosage on other clinical meaningful outcomes, such as duration of MV and ICU or hospital length of stay, is still controversial (Abroug et al., 2014; Kiser et al., 2014; McCann, Teare, Cochard, & Toney, 2017). Moreover, corticosteroid dose-related side effects have been extensively reported (Abroug et al., 2014; Kiser et al., 2014; Walters et al., 2009). Exogenous glucocorticoid administration is the most common cause of drug-induced myopathy (Pereira & Freire de Carvalho, 2011; Schakman, Gilson, & Thissen, 2008). Corticosteroid-induced hyperglycemia may aggravate this process (Hermans et al., 2007). Higher cumulative dose of steroids has been related to increased number of infections in COPD individuals at ICU (McCann et al., 2017). Since data to guide a particular posology are lacking, clinicians use an intravenous (IV) formulation at a wider dosing range, mostly from 40 to 240mg of methylprednisolone or equivalent daily (Kiser et al., 2017; McCann et al., 2017).

Since low dosage leads to less adverse effects, we hypothesize that low compared to high dose of methylprednisolone decreases length of MV in individuals presenting exacerbation of COPD requiring ventilatory support and ICU admission. We plan a multicenter, randomized, controlled trial to fill this knowledge gap.

MATERIAL AND METHODS

Research question

Among patients with COPD exacerbation requiring invasive ventilatory support, does low dose (60mg daily) of IV methylprednisolone reduce ventilator-free days (VFD) compared to high dose (240mg daily) of IV methylprednisolone?

Hypothesis

Null hypothesis: There is no difference in VFD in patients with acute exacerbation of COPD requiring invasive MV between patients treated with low (60 mg IV methylprednisolone daily) or high (240 mg IV methylprednisolone daily) dose of corticosteroids.

Alternative hypothesis: There is difference in VFD in patients with acute exacerbation of COPD requiring invasive MV between patients treated with low (60 mg IV methylprednisolone daily) or high dose (240 mg IV methylprednisolone daily) of corticosteroids.

Trial Design

Multicenter, randomized, controlled, double-blinded clinical trial with two parallel arms with a 1:1 allocation in five ICUs of tertiary referral centers situated in urban areas in Brazil.

Randomization - sequence generation and allocation concealment

Permuted-block randomization list, with varying block sizes (4, 6 and 8) and stratified by study site, will be automatically generated by a web-based program.

A pharmacist or other research team member not involved in further steps of the trial, is going to assign the enrolled individual to a group based on an allocation sequence previously generated. The research member will be trained to ensure that the sequence is concealed until the assignment of the intervention. This research member won't have any contact with the patients.

Blinding

After randomization, intravenous active and placebo treatments, identical in appearance and containing only the patient's ID number, will be dispensed in a blinded fashion by a central pharmacy. Thus, research subjects, their families, care providers, study members and statistician will be blinded for intervention allocation.

Infrastructure for emergency unblinding will be provided in case attending physician considers a life-threatening event due to intervention. The overall prevalence of steroid hypersensitivity is estimated to be

0.3-0.5%, mainly allergic contact dermatitis (Vatti, Ali, Teuber, Chang, & Gershwin, 2014). To the extent of our knowledge, we found no reports of severe or life-threatening side effects attributed to corticosteroids. Hyperglycemia will be managed with insulin therapy, as usual care.

Eligibility criteria

All following inclusion criteria must be met:
1) Patients who are 40 years or older with COPD, whose diagnosis will be based on history, physical examination, chest radiograph, and previous pulmonary function tests (if available); AND
2) Hospitalization due exacerbation of COPD with acute respiratory failure that requires invasive MV. Exacerbation of COPD is defined as the presence of 2 or more of the following: worsening dyspnea, increase in sputum purulence, or increase in sputum volume; AND
3) Invasive MV is indicated in following circumstances: life-threatening hypoxemia in patients unable to tolerate noninvasive mechanical ventilation; respiratory or cardiac arrest; massive aspiration or persistent vomiting; inability to remove respiratory secretions; severe hemodynamic instability without response to fluids and vasoactive drugs; severe ventricular or supraventricular arrhythmias; or diminished consciousness, psychomotor agitation inadequately controlled by sedation; AND
4) Agreement to participate in the trial – free and informed consent will be obtained from patients' representatives.

All following exclusion criteria must be ruled out:
1) Use of systemic corticosteroids for treatment of COPD exacerbation or another clinical condition in the last 7 days preceding time of randomization; OR
2) History of asthma, bronchiectasis, interstitial lung disease, cystic fibrosis, alpha-1 antitrypsin deficiency or tuberculosis; OR
3) Congestive heart failure requiring use of inotropes, vasoactive drugs or mechanical circulatory support devices; OR
4) Prior history of adverse reaction to corticosteroid therapy; OR
5) Palliative care; OR
6) Prior inclusion on present trial.

Interventions

Within 24 hours after initiation of MV, the patients assigned to each group will receive the study medication as follows:

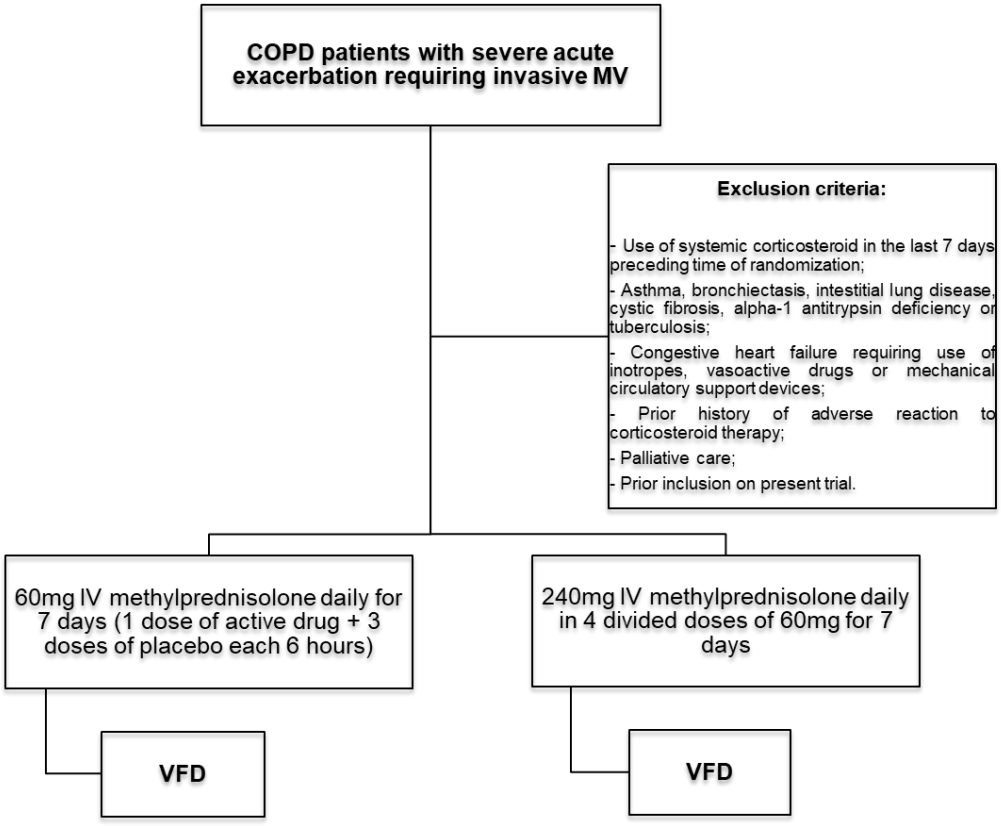

Figure 1. Flowchart of study COPD: Chronic obstructive pulmonary disease, MV: Mechanical ventilation, IV: Intravenous, VFD: Ventilator-free days

A) Low dose corticosteroid: methylprednisolone 60mg (diluted in 50ml of intravenous normal saline) plus 3 doses of placebo every 6 hours (50 mL of intravenous normal saline solution), totaling 60 mg daily; OR
B) High dose corticosteroid: methylprednisolone 60mg (diluted in 50ml of intravenous normal saline) every 6 hours, totaling 240 mg daily.

Corticosteroids will be continued for 7 days. Flowchart of study is showed on figure 1.

ICU team will be free to define co-management of exacerbation of COPD, such as systemic antibiotics, bronchodilators, sedation, neuromuscular blockers, insulin protocol, vasopressors, MV settings and MV withdrawal, according to local protocols and GOLD guidelines (Vogelmeier et al., 2017).

Outcomes

Primary outcome: Ventilator-free days (VFD), i.e., the number of days between extubation and day 28 after study enrollment. VFD is defined as follows:
VFD = 0: If the patient dies before 28 days.
VFD = (28 - x): If the patient is successfully extubated within 28 days, where x is the number of days spent receiving invasive MV.
VFDs 0: If the patient requires MV for 28 days or more.

Secondary outcomes: daily average capillary blood glucose levels; daily average dosage of insulin (ui); new infections during ICU stay (time-frame: 28 days); Medical Research Council (MRC) scale for testing muscle strength on extubation day; ICU length of stay (time-frame: 6 months); ICU-mortality (time-frame: 6 months); In-hospital mortality (time-frame: 6 months)

Sample size calculation and statistical analysis

Previous studies have shown that median duration of MV among COPD patients was 4 days (Alia et al., 2011; Esteban et al., 2002). Using a standard deviation of 3 for high-dose regimen group and 2 for low-dose regimen group, we obtained the initial number of 208 individuals to give us 80% power at an alpha level of 0.05 to detect a 1-day reduction on VFD. Such difference was based on an aforementioned report comparing different doses of steroids on COPD (Kiser et al., 2014). As we expect a highly skewed distribution for VFD variable and, then, use of non-parametric test, we increased this initial amount in 15%. Anticipating a very low rate of dropouts, we selected a final sample size of 250 total patients.

All analyses will follow the intention-to-treat principle. Baseline characteristics will be reported as counts and percentages, mean and standard deviation, or median and interquartile range (IQR), whenever appropriate. We will assess the effects of the intervention on continuous variables with median and IQR using Mann Whitney test, and on categorical variables with risk ratios and 95% confident intervals using the $\chi 2$ test. Hypothesis tests were 2-sided. All analyses will be performed using STATA v.14.2 software (StataCorp, Texas, USA).

Baseline and endpoint data can be recovered from eletronical medical records or patient's archives. In case of unforeseen EMR loss, nursing charts can be reviewed for reference. Therefore, we presume no missing data.

Three interim analysis for futility will be performed throughout the trial. The analysis will be conducted at the recruitment of 60, 120 and 180 patients using the conditional power approach. Trial will be terminated if the conditional power is smaller or equal than 0.2 in any of the analysis considering a 2-sided significance level of 0.05. Recalculation of sample size will also be conducted at second interim analysis.

Implementation

Data on demographic and clinical characteristics of patients will be obtained at baseline. In addition, we will record the need of vasopressors or inotropes, occurrence of new organ failure, need of renal replacement therapy and nutrition support.

Routine ICU assessment and management, as well as urgent intervention, will be left to the discretion of each ICU team and will be prescribed and monitored according to global guidelines.

Study timeline is provided on figure 2. Schedule of study procedures is showed on table 1.

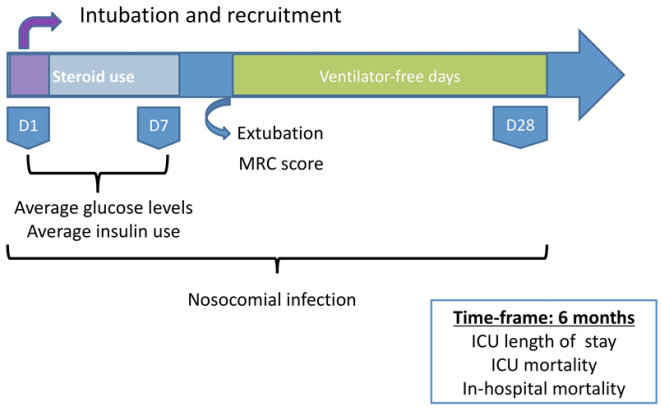

Figure 2. Study timeline indicating primary and secondary endpoints. D: day. MRC: Medical Research Council. ICU: intensive care unit.

Recruitment strategy

Eligible centers must be tertiary. ICU coordinators will be invited to participate in present trial by e-mail correspondence or personal contact. Intensive care national society (AMIB – Associação de Medicina

Intensiva Brasileira) greatly promotes intensivists interaction, which gives opportunity for announcement and expansion of the trial.

We estimate recruitment rate is 25 individuals per ICU yearly, considering a previous Brazilian report (Viana et al., 2017).

	Day 1	Day 7	Extubation day (any time between day 2 and day 28)	Day 28	ICU discharge up to 6 months of admission date	Hospital discharge up to 6 months of admission date
Eligibility screen	X					
Informed Consent	X					
Randomization	X					
Baseline clinical data	X					
Intervention	X	X				
VFD			X	X		
Daily average glucose levels	X	X				
Insulin (ui) per day	X	X				
Nosocomial infection	X	X	X		X	
MRC score			X			
ICU length of stay					X	
ICU mortality					X	
In-hospital mortality						X

Table 1. Schedule of study procedures. VFD: Ventilator-free days, MRC: Medical Research Council, ICU: intensive care unit.

Adherence

In order to ensure sites are trained in study procedures and willing to kept enrollment, and to discuss issues that may arise during recruitment and follow-up, monthly videoconferences will be conduct reuniting all participants sites. Main investigator on each site will be contacted biweekly by email about how study is being carried out. Main investigator will also have full access to principal investigators for solving problems at any moment.

Discontinuation

Discontinuation of the participant can ensue in following circumstances: withdrawal of consent by participant or his/her next-of-kin; abandonment of protocol for any reason; violation of the protocol affecting the patient's safety; or any clinical condition or adverse event that, at the discretion of the attending physician, prevents the continuation of the research participant in the protocol.

Data management

We will provide a system for randomization, capture and data management (eletronic case report form - eCRF) to the participant centers.

An independent data monitoring committee (IDMC) composed by a biostatistician, an expert on clinical trials and an expert on Intensive Care Medicine will meet monthly to evaluate safety and scientific validity of the trial. Ad hoc meetings may be performed if there is an emergence related to safety issues or protocol violation. IDMC will provide analytic reports to the sponsor after each meeting, keeping the groups blinded. Data about protocol violation and severe adverse events (sever hyperglycemia, death) must be provided to the IDMC by the principal investigation in 24 hours. IDMC will also provide the information necessary if emergency unblinding is needed.

Table 2 summarizes implementation and timeline for study protocol.

Date	*Activity*
January 2019	Study coordinator appointed to oversee all aspects of published protocol
March 2019	Data collection form and protocol finalized
March 2019	Application for grants from Brazilian Public Health Ministry (CNPq – Conselho Nacional de Pesquisa)
July 2019	Institutional Review Board approval at first site
August 2019	Recruitment of participants at first center
	Announcement of trial and invitation of centers via AMIB (Associação de Medicina Intensiva Brasileira)
August 2019 – August 2021	Data entry and cleaning
	Interim analysis
September 2021 – December 2021	Data analysis
January 2022 – June 2022	Summary of results to participant centers
	Write up papers for publication
	Presentation at conferences

Table 2. Implementation and timeline of the protocol

DISCUSSION

We propose a study protocol for a Phase III, randomized, double-blinded, multi-center trial to estimate to what extent 60 mg of IV methylprednisolone versus 240mg of IV methylprednisolone impact on number of days off

invasive MV. As far as we know, no well-delineated intervention study has ever addressed corticosteroids dosage in this specific subgroup of COPD patients with severe exacerbation, and that is a common dilemma in ICU practice. We believe, as it was pointed out elsewhere (Kiser et al., 2017), there is sufficient clinical equipoise to justify conduction of present trial.

Based on best available scientific evidence, we understand that it would be unethical to compare methylprednisolone doses of over 240mg daily or to use placebo treatment. Indeed, our proposed comparators are within a common and preferred dosage range used at ICU management of exacerbation of COPD (Kiser et al., 2017). A comparative analysis (Lindenauer et al., 2010) of

glucocorticoid dosing examined outcomes of 79,985 patients admitted to the hospital with an exacerbation of COPD, excluding those requiring intensive care management. The median glucocorticoid dose administered in the first two days was 60 mg for those on oral therapy and 556 mg for intravenous therapy. Lower doses did not lead to greater risk of treatment failure. An observational cohort study (Kiser et al., 2014), among 17,239 patients admitted to an intensive care unit (ICU) with exacerbation of COPD, a dose of methylprednisolone of 240 mg/day or less, compared with a higher dose (methylprednisolone >240 mg/day), was associated with slightly shorter hospital and ICU lengths of stay, as well as lower duration of MV and need for insulin therapy. However, a small retrospective observational study (McCann et al., 2017) failed to demonstrate any relationship between steroid dosage and MV outcomes, and an open-label randomized, placebo-controlled trial (Abroug et al., 2014) assessed length of MV as a secondary endpoint and it was underpowered to detect any effect of corticosteroids in severe exacerbation of COPD.

We select VFD as the main outcome because it evaluates simultaneously reduction on duration of MV and mortality improvement (Schoenfeld, Bernard, & Network, 2002). Otherwise, whether a treatment led to an increased number of deaths, false reduction on time spent on ventilator would be observed. The 28-day landmark implies that, by this time, vast majority of ICU patients will have either been discharged or died. Subconscious or unconscious behaviors to postpone weaning from MV are not supposed to influence this primary endpoint, once ICU team will be blinded to interventions.

Our protocol has several strengths. The randomized, double-blinded design minimizes presence of biases and confounders. Comparison between two active drugs, although of different dosage, prevents refusal to participate in the trial or low adherence to intervention. Nevertheless, the required large sample size increases costs, and that is how we plan an interim analysis for futility. General ICU approach and specific co-management of COPD are not standardized. In order to address this drawback, we recruit tertiary centers, certainly familiar with GOLD guidelines (Vogelmeier et al., 2017) and with other highly recommended practices regarding Critical Care. Still, randomization will be stratified by study site, further improving balance between groups.

The present study has the potential to pinpoint a specific corticosteroid regimen for severe COPD exacerbation and further improve outcomes. Prevention of systemic side effects of high dose of corticosteroids might have a dramatic effect on hospital, ICU and MV exposure time, new acquired infections and COPD patient's general wellbeing. Availability of ICU beds is of monumental value as it can be very scarce in underprivileged areas around the world.

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Conflict of interest and financial disclosure

The authors have no personal or financial conflicts of interest. All authors agree with the submission of this manuscript and declare that all them have approved it.

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