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Research Article

Methylprednisolone on ICU Patients with COVID-19 on Mechanical Ventilation

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Abstract

Objectives: Corticoids were widely used to minimize the inflammatory response. SARS-CoV2 affects the lungs causing inflammation and diffuse alveolar damage. The corticoids could suppress inflammation and inhibit immune response. The primary objective of this study was to evaluate 28-day mortality in patients receiving mechanical ventilation with SARSCoV2. The secondary objectives were to evaluate the risk of bloodstream infections and ventilator-associated pneumonia (VAP), the time of mechanical ventilation, the length of stay in ICU and in the hospital.

Methods: A unicentric prospective randomized double-blinded study was designed. The inclusion criteria were patients over 18 years-old with COVID-19 on invasive mechanical ventilation within 24 hours of meeting criteria of moderate or severe Acute Respiratory Distress Syndrome (ARDS). The patients were randomized into two groups 1:1 by the pharmacist responsible for the unit. The methylprednisolone group consists of initial dose of 1 mg/Kg/day for five days, followed by 0.5 mg/Kg/day for three days and 0.25 mg/Kg/day for two days. The placebo group received intravenous injection of 0.9% saline. The primary outcome was the mortality at 28-days.

Results: 148 patients with SARS were screened, 112 underwent to randomization, 58 to the methylprednisolone group and 54 patients to the placebo group. There was no significant difference in all-cause mortality at 28-days (46.7 in the methylprednisolone group vs 53.3% in the placebo group). Methylprednisolone group had more extubation (67.2 % vs 48.1%, $p = 0.042$) and lower number of tracheostomies (5 vs 14, $p = 0.015$). The median days of mechanical ventilation were lower in the methylprednisolone group (6 days vs 14 days, IC 95%, $p = 0.012$), as well as the mean days in ICU (12.5 days ±10.54 vs 18.76 ± 15.1, $p = 0.043$). There was no significant difference in the length of stay in hospital, bloodstream infections, or VAP incidences.

Conclusion: In patients with COVID-19 with moderate or severe ARDS, the use of methylprednisolone reduced the days on mechanical ventilation, ICU stay and favors early discharge without difference in mortality.

Keywords: COVID-19; Mechanical ventilation; Corticosteroid

Introduction

In December 2019, an illness characterized by pneumoniae associated with new coronavirus (COVID-19) emerged in Wuhan, China, and rapidly spread around the world. The World Health Organization had declared South America as an epicenter of COVID-19 pandemic, and Brazil has become one of the most affected countries of the world [1]. The greatest impact of these disease was on Intensive Care Units (ICU), almost 40% of the COVID-19 patients evaluated with acute respiratory failure [2,3]. The mortality of the patients in mechanical ventilation is high, about 88.1%, according to the cohort described by Richardson and colleagues [4-7].

Due to an expressive mortality a lot of therapies emerged to control the disease. One of these therapies was the use of systemic corticosteroids. Over decades, many clinical trials have tested the effectiveness of corticosteroids in critically ill patients with pneumonia, septic shock, or acute respiratory syndrome, however, due to limited sample size, variable dosing strategies and inconsistent findings, results remained inconclusive [8].

Corticosteroids were widely used during outbreaks of Severe Acute Respiratory Syndromes (SARS) like the Middle East Respiratory Syndrome (MERS-CoV) without improvement [9], and in Influenza pneumonia when the use was associated with a higher mortality [10,11].

COVID-19 affects several organs, manly the lung. The pulmonary histology reveals inflammation and diffuse alveolar damage [12,13]. Acute lung injury is partly caused by the host immune responses. Inflammatory organ injury may occur in severe COVID-19, in a subgroup of patients who have high levels of inflammatory markers, including C-reactive protein, ferritin, interleukin-1 and interleukin-6 [14,15]. Several therapeutics have been proposed to mitigate the inflammatory organ injury in viral pneumonia. The corticoids are one of these therapeutics, it can suppress lung inflammation, but it can also inhibit immune responses and pathogen clearance [16,17]. In case of inhibit immune responses some infectious clinical condition may occur, like invasive fungal disease, cytomegalovirus infection, other viral diseases, and bacterial infections [18].

The primary objective of this study was to evaluate the association between the use of systemic methylprednisolone and 28-days all-cause mortality in patients with acute respiratory syndrome caused by COVID-19 on invasive mechanical ventilation. The secondary objectives were length of stay in the intensive care unit, length of stay in the hospital, hospital mortality, duration of mechanical ventilation, number of extubations, number of tracheostomies, ventilator-associated pneumonia and bloodstream infections.

Methods

A unicentric prospective randomized double-blinded study was designed to evaluate if the effectiveness and safety of methylprednisolone associated with the stand of care was superior to stand of care alone for reduction of 28-days mortality in patients with COVID-19 on mechanical ventilation.

Sample size calculation: based on the previous data, Richard et al. [14] showed a hospital mortality of 88.1% of patients with COVID-19 on mechanical ventilation. Wu C, et al. [12] showed a 25.56% mortality reduction in COVID-19 patients treated with methylprednisolone. For the sample calculation, with power of 80% and an α less than 0.05 assumed, a sample of 112 patients were calculated resulting in 56 patients in the intervention group and 56 patients in the control group randomized 1:1.

The inclusion criteria were patients over 18 years old with COVID-19 on invasive mechanical ventilation within 24 hours of meeting criteria of moderate or severe Acute Respiratory Distress Syndrome (ARDS) defined as the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2:FIO2) of 200 or less, with positive RT-PCR test for COVID-19 at the time of inclusion.

Exclusion criteria were pregnancy or active lactation, known history of methylprednisolone allergy, corticosteroid use in the past 15 days for no hospitalized patients, use of corticosteroids during the present hospital stay, consent refusal, or expected risk of death in the next 24 hours.

The patients were randomized into two groups 1:1 by the pharmacist responsible for the unit. The others health professionals were blind to the medication administered (methylprednisolone or placebo). The pharmacist was notified of the inclusion of the patient, performed randomization, and delivered the medication (methylprednisolone or placebo) to the ICU staff in an injection bottle with only the identification of the patient. The methylprednisolone group consists of initial dose of 1 mg/Kg/day for five days, followed by 0.5 mg/Kg/day for three days and 0.25 mg/Kg/day for two days. The placebo group received intravenous injection of 0.9% saline associated a stand of care. The saline and methylprednisolone solution were indistinguishable to the naked eye.

Written informed consent was obtained from all patients or from a legal responsible if they were unable to provide one. The trial was conducted in accordance with the principles of Good Clinical Practice Guidelines of International Conference and Helsinki Criteria and was approved by the Ethics Committee of

Institute of Medical Assistance to the State Server in São Paulo (IAMSPE) (CAAE 32561120.6.0000.5463).

The primary outcome was the mortality at 28-days. The secondary outcomes were length of stay in the intensive care unit, length of stay in the hospital, hospital mortality, duration of mechanical ventilation, number of extubations, number of tracheostomies, ventilator-associated pneumonia and bloodstream infections.

Diagnosis of infections were made by the attending physician. For the diagnosis of pneumonia associated with mechanical ventilation it was necessary to have more than 48 hours of mechanical ventilation and 2 of the 3 criteria: increase or change of the color of tracheal secretion, decrease the PaO2/FIO_2 ratio or positive culture of tracheal secretion with pathogens >105 CFU/mL. Pulmonary imaging was not included, due to the possibility of worsening of the pulmonary image be related to worsening of inflammatory caused by COVID-19. Bloodstream infections was considered if the patient had one or more positive blood culture collected from peripheral blood and the pathogen was not related to another site of infection.

Patients were followed until the outcome (death or discharge), if the patient was discharged from the hospital before 28 days after randomization, a physician made a telephone contact on the twenty-eighth day after inclusion.

Statistical analyses

The full analysis included all the participants who underwent randomization and received a dose of methylprednisolone or placebo. The analyses were conducted in the per-protocol population, which included participant who received methylprednisolone or placebo.

A preplanned interim analysis for the evaluation of efficacy and safety after 88 patients with full follow-up was scheduled. The stopping rule for safety was $p<0.1$ and for efficacy $p<0.001$ (Haybittle-Peto boundary) [19]. There was no adjustment in the final threshold for statistical significance for sequential analysis.

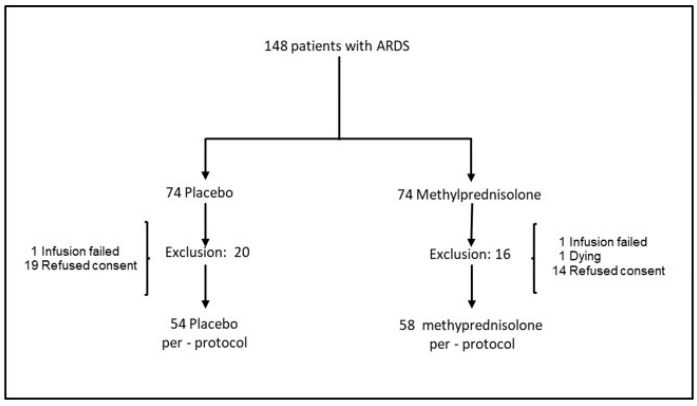
The trial was designed to ascertain whether methylprednisolone reduces the 28-days mortality. The primary comparison between the groups was performed using the X2test. The comparison of the duration of mechanical ventilation, length of stay in the ICU and in the hospital between the two groups was performed using Log Rank test. Adverse events are expressed as counts and percentages and compared between the two groups using the X2-test.

Patients were analyzed according to the randomization groups, and no adjustments for multiplicity were performed. A 2-sided p value of less than 0.05 was considered statistically significant. All analyses were performed using the SPSS software version 24.0.

Results

From July 2020 to March 2021, 148 patients were evaluated in a hospital with medical residence. Of the 148 patients who were screened, 112 underwent randomization, 58 to methylprednisolone group and 54 were assigned to placebo. Two patients (one who was assigned to receive placebo and one who was assigned to receive methylprednisolone) did not received an infusion. One patient was in refractory septic shock and thirty-three without informed consent. The 112 patients who underwent randomization and received at least one infusion of methylprednisolone or placebo were included in the efficacy and safety analyses (Figure 1).

Figure 1: Flowchart of the study.



Baseline characteristics between the groups showed a higher severity in the placebo group (mean SOFA of 7.24 ±2.41 in placebo group and 6.17 ±2.41 in methylprednisolone group, $p = 0.021$), there were more patients with systemic arterial hypertension in the methylprednisolone group, 38 (65.5%) vs 25 (46.3%) in placebo group, $p=0.04$. The other baseline characteristics were well balanced between groups (Table 1).

Table 1: Demographic and baseline characteristics between the two groups

	Placebo N=54	**Methylprednisolone N=58**	**p value**
Age, mean (SD), y	61.48 (10.84)	60.93 (13.15)	0.81
Men (%)	33 (61.1)	30 (51.7)	0.317
BMI *, Kg/m^2 , mean (SD)	31.5 (3.53)	31.75 (9.32)	0.974
SOFA, mean (SD)	7.24 (2.41)	6.17 (2.41)	0.021
SAPS III, mean (SD)	61.24 (12.31)	60.50 (9.94)	0.726
Arterial Hypertension (%)	25 (46.3)	38 (65.5)	0.04
Diabetes mellitus (%)	16 (29.6)	17 (29.3)	0.97
Obesity (%)	24 (44.4)	21 (36.2)	0.374
COPD ** (%)	4 (7.4)	3 (5.2)	0.625
Asthma (%)	1 (1.9)	4 (6.9)	0.196
Renal injury (%)	2 (3.7)	2 (3.4)	0.942
Miocardiopathy (%)	2 (3.7)	4 (6.9)	0.453
Coronariopathy (%)	4 (7.4)	6 (10.35)	0.566
Liver injury (%)	0 (0)	1 (1.7)	0.332
Malignancy (%)	2 (3.7)	2 (3.5)	0.942

* BMI – body mass index

** COPD - chronic obstructive pulmonary disease

Driving pressure was higher in methylprednisolone group, mean of 11.57 ±2.16 in the methylprednisolone group Vs 10.59 ±2.59 in the placebo group, p=0.037, the other respiratory variables were similar between the groups, there was also no difference between the groups regarding the use of antibiotics and vasopressors (Table 2).

Table 2: Respiratory measures, use of antibiotics and vasopressors between the two groups

	Placebo N=54	**Methylprednisolone N=58**	**p value**
Respiratory variables, mean SD			
PEEP* cm H_2O	10.83 $\pm$1.94	10.93 $\pm$1.84	0.785
Driving pressure cm H_2O	10.59 $\pm$2.59	11.57 $\pm$2.16	0.037
PaO_2:FIO_2	189.17 $\pm$33.2	180.78 $\pm$84.2	0.816
$PaCO_2$ mmHg	49.42 $\pm$13.14	49.63 ±24.19	0.980
PaO_2 mmHg	132.5 $\pm$46.7	105.78 ±37,57	0.191
Norepinephrine (mcg/kg/min)**	0.35 $\pm$0.48	0.19 ±0.39	0.053
Additional medication			
Azithromycin	29 (53.7%)	23 (39.65%)	0.184
Clarithromycin	15 (27.77%)	22 (37.93%)	0.316
Oseltamivir	19 (35.18%)	14 (24.13%)	0.22

*PEEP - positive end-expiratory pressure

** Mean dose of norepinephrine on the first day

Primary Outcome

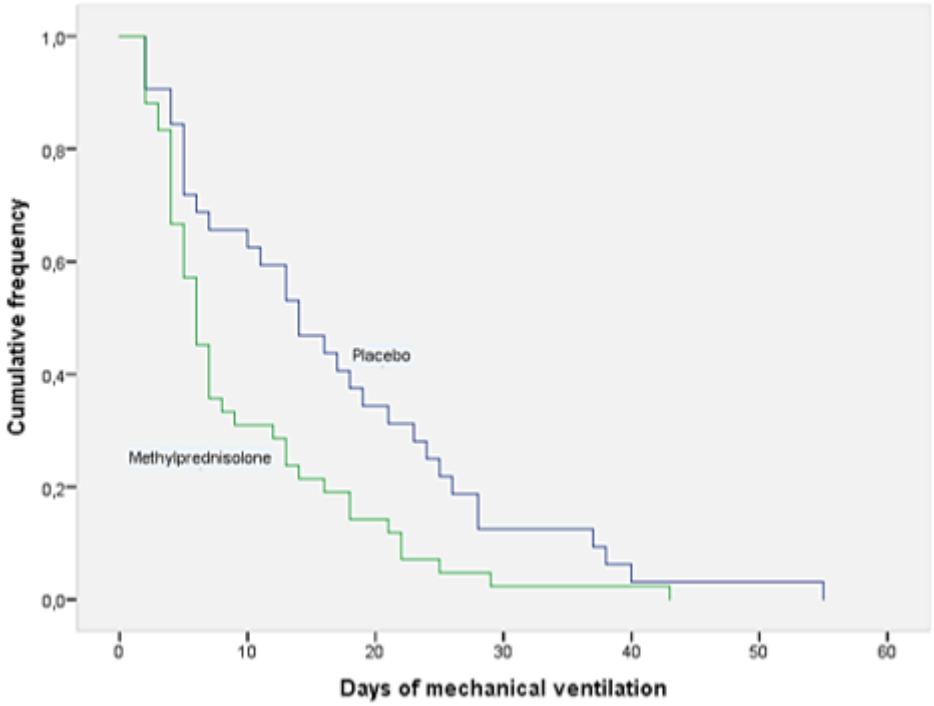
There was no significant difference in all-cause mortality at 28 days (24.1% in the methylprednisolone group vs 29.6% in the stand of care alone group, *p*=0.512).

Secondary Outcome

The mean of the number of days in ICU stay was lower in the methylprednisolone group, (12.5 days ±10.45 in the methylprednisolone group vs 18.76 ±15.1 in the placebo group, p=0.043). There was no significant difference between groups with regard length of hospital stay (25.0 ± 18.96 in the methylprednisolone group vs 28.57 ± 20.39 in the placebo group). Although there is no difference between the hospital stay, the discharge rate in the 28 -days was higher in the methylprednisolone group than in the placebo group, (48.3% in the methylprednisolone group vs 27.8% in the placebo group, p=0.026). There was no significant difference in all-cause hospital mortality (32.8% in the methylprednisolone group and 48.1% in the placebo group, p=0.097).

The median of the days in mechanical ventilation was also significant lower in the methylprednisolone group than in the placebo group, 6 days vs 14 days: IC 95%, p = 0.012, (Figure 2).

Figure 2: The median of the days in mechanical ventilation.



There was significant difference in the number of extubated patients (67.2% in the methylprednisolone group vs 48.1% in the placebo group, p=0.042). The number of extubated patients were counted as extubated for the first time with no extubation failure. The number of tracheostomies was lower in the methylprednisolone group, five patients in the methylprednisolone group and fourteen in the group placebo (p=0.015).

There was no difference in adverse events between the two groups regarding bloodstream infections (10.3% in methylprednisolone group vs 16.7% in placebo group, p=0.326), and pneumonia associated with mechanical ventilation (37.9% in methylprednisolone group vs 51.9% in placebo group, p=0.139). We also did not have any cases of pulmonary aspergillosis due to the use of corticosteroids.

Discussion

In this randomized clinical trial involving 112 patients on mechanical ventilation with moderate or severe ARDS due to COVID-19, the mortality rates were not significant different between the two groups. This data may be explained because the study was under power, the expected mortality used to calculate the sample was 88.1% and the real mortality in this study was lower than 50%. Methylprednisolone was not associated with an increased risk of infectious events in this studied dose and in this critical patient population.

The hospital mortality of this trial was 32.8 % in the methylprednisolone group and 48.1% in the placebo group, this is interesting because data collected by Brazilian Association of Critical Care demonstrated mortality rates of 65.3% for ventilated patients with COVID-19 in Brazilian ICUs. When analyzing the mortality in public ICU, this rate reaches 72.2% [20]. Mortality in the IAMSPE ICU was below the average mortality in public ICUs. This is very important because the use of protective ventilation and prone position when indicated has been shown to be able to reduce mortality in relation to the national average, the IAMSPE did not use disease-modifying therapies like remdesivir, interleukin inhibitors or mesenchymal cell transplantation, for example.

One important point of this trial is that methylprednisolone was able to increase the number of extubations, reduced the duration of mechanical ventilation and the ICU stay. These data are very relevant, because reducing the duration of mechanical ventilation and ICU stay, we also reduce the risk of complications such as ventilator associated pneumonia or the need for procedures such as tracheostomy, among others. Despite this, analyzing the median days of hospitalization there was no significant difference between the groups.

Hospital discharge at 28-days was higher in the methylprednisolone group, this is particularly relevant for the public health service where the source of investment is scarce. In public hospitals, the reduced number of ICU beds makes difficult to provide optimal care to the population, with early hospital discharge, care in public hospitals can be more efficient, and reduces public spending.

This trial has several strengths, the study was double blinded, randomized and the participants were followed until de outcome (death or discharge). All participants were analyzed according to their randomization group. The weakness of the study is the small sample size, and the mortality rate of the study was much smaller than that used for the sample calculation.

Conclusions

In patients with COVID-19 included in this study with moderate or severe ARDS, the use of methylprednisolone reduced the days on mechanical ventilation, ICU stay, favors early discharge, and can have a significant economic impact on both the public and private health.

Author Contributions

Ellen Pierre de Oliveira, Ederlon Alves de Carvalho Rezende, Augusto Yamaguti and José Marconi de Sousa: Study planning; Writing and proofreading the text; Final version approval

Caio Vinicius Gouvêa Jaoude, Vânia Quinato Malacize, Leonardo Costa Lobato, Thaís Guimarães, Ricardo Goulart Rodrigues: Study planning; Writing and proofreading the text.

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