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Research

Methylprednisolone Versus Dexamethasone in Patients with COVID-19 the MEDEX Clinical Trial

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Introduction

The new coronavirus pandemic, also called Covid-19, has the SARS-Cov 2 virus as its causative pathogen. An emerging arbovirus initially identified in the province of Wuhan, China. The inflammatory response resulting from the infection is primarily responsible for lung lesions [1], respiratory compromise [2,3] and other organic dysfunctions that frequently occur in infected patients [1,2]. There is a correlation between levels of pro-inflammatory cytokines and the extent of acute respiratory distress syndrome (ARDS) [1-3].

In this scenario, the role of anti-inflammatory treatments based on systemic corticosteroids has taken a prominent position in clinical research [2-4]. In June 2020, preliminary results of the RECOVERY study demonstrating that the early use of dexamethasone in severe cases is safe and effective in reducing mechanical ventilation time and disease mortality [4-6]. However, the study focused on patients on mechanical ventilation, and the non-use of corticosteroids as a control.

It was also unclear whether treatment for complications from Covid-19, ARDS or Cytokine Release Syndrome (CRS) would be a particular effect of dexamethasone or common to the pharmacological group [7,8]. To answer it, specific studies comparing the effects of dexamethasone with other corticosteroids began to be developed [7,9-11]. However, most were carried out during the first year of the pandemic, when there was little variation in viral strains and before the emergence of more aggressive variants of the pathogen and the disease.

Studies specifically aimed at analyzing the effects of methylprednisolone are limited to retrospective studies, studies with little significant sampling or independent hospital protocols. In this context, and considering that methylprednisolone has been routinely used in intensive care units [12,13] in general for the treatment of acute respiratory syndromes, its real effectiveness also began to be studied against SARS-Cov-2 [13,14].

The aim of the present study was to compare the clinical evolution of patients treated with early administration of methylprednisolone as opposed to dexamethasone, at the hospital level in a high complexity hospital in southern Brazil, a national reference for cases of the disease.

Materials and Methods

Prospective, randomized, controlled, single-center, open-label, comparative clinical trial. The study was carried out in a high complexity hospital in the city of Campo Largo, state of Paraná, Brazil.

The study was approved by the Brazilian National Research Ethics Committee (CONEP). The Research Ethics Presentation Certificate (CAAE) is 47957821.2.0000.5529. The substantiated opinion that approved the study is number 4.867.609. The research was also registered in the International Standard Randomized Controlled Trial Number (ISCTRN), with the test registration number ISRCTN44151777.

The inclusion criteria used were: (1) age 18 years or older; (2) confirmed or suspected infection for Covid-19; (3) chest tomography showing an image compatible with Covid-19; (4) need for hospital admission for treatment.

Exclusion criteria were: (1) known medical history of allergy to methylprednisolone; (2) use of corticosteroids for another condition; (3) patient refusal to participate in the study; (4) being pregnant or breastfeeding; (5) presence of contraindication to the use of corticosteroids.

The study center was Hospital do Rocio, the largest hospital in the state of Paraná and one of the largest in Brazil. The sample size was calculated based on the population served by Hospital do Rocio, also considering the fact that it is one of the national reference hospitals, which is why it receives patients from other states and regions of the country for treatment of the disease. The sample size calculation resulted in a sample of 400 patients. Randomization took place in the ward the day after hospital admission, performed by the research coordinator with notification to the attending physician. Blinding was performed in the statistical analysis of the data.

As the primary outcome, all-cause mortality was adopted at 28 days after randomization. As secondary outcomes, length of hospital stay, need or not for ICU referral, time on mechanical ventilation between randomization and day 28 (for cases that required), ICU length of stay between randomization and day 28, and changes in laboratory pattern between randomization and final outcome.

After obtaining informed consent, patients were allocated to one of the study groups (intervention or control). The control group was treated with the institutional protocol plus 6 mg intravenous dexamethasone daily for 10 days or until hospital discharge. The intervention group was treated with the institutional protocol plus 250 mg of methylprednisolone intravenously for 3 days, followed by a daily dose of methylprednisolone of 1 mg/kg/day for 7 days.

The institutional standard treatment protocol used in both groups consisted of daily follow-up by the attending physician at the inpatient unit (or by the diarist physician at the intensive care unit); monitoring, adjustment of conducts and care of intercurrences by the physician on duty; continuous hemodynamic and ventilation monitoring; monitoring of vital data following the inpatient unit's routine; motor and respiratory physiotherapy; ventilation support measures (invasive or not); hemodynamic support measures, with or without vasopressors, as medically indicated; hydro-electrolytic and acid-base control; medical interventions in general (such as central venous access puncture, closed chest drainage, tracheostomy, among others); use of antimicrobials (antibiotics, antivirals, antifungals, etc. as medically indicated); laboratory routine according to the inpatient unit and/or medical indication.

During the study, all patients who met any of the following criteria were discontinued: (1) withdrawal of informed consent by the patient or legal representative; (2) development of any medical contraindication to the use of methylprednisolone; (3) discarded infection for COVID-19 (defined as two negative tests collected by the institution and whose samples have been evaluated by a duly authorized laboratory using protocols and guidelines established by Brazilian National Health Surveillance Agency – ANVISA); (4) death or discharge before receiving at least two doses of dexamethasone or three doses of methylprednisolone.

Upon admission, laboratory tests were performed, such as blood count, renal function, C-reactive protein (CRP) measurement, among others, for a global assessment of the patient. For the study, laboratory variables of packed cell volume, hemoglo-

Table 1. Quantitative

Variables	Corticoid	n	Mean ± standard devation	Median (IIQ)	Mann & Whitney p	Student's t test
Age (years)	Dexa	194	50,8 ± 12,8	51 (42 - 57)		
	Metil	131	49,3 ± 12,8	47 (40 - 57)	---	0,309
VG D0	Dexa	194	40,0 ± 5,3	40,6 (36,8 - 43,7)		
	Metil	131	41,2 ± 4,3	41,7 (38,7 - 44,2)	---	0,029
Hb DI	Dexa	194	13,7 ± 1,8	13,9 (12,5 - 15)		
	Metil	131	14,1 ± 1,5	14,4 (13,3 - 15,1)	---	0,051
Leuc DI	Dexa	194	9445 ± 4298	8850 (6500 - 12000)		
	Metil	131	11147 ± 7024	10100 (7000 - 13800)	0,015	---
Bast DI	Dexa	194	7,9 ± 3,7	7 (5 - 11)		
	Metil	131	8,7 ± 3,4	8 (6 - 11)	0,029	---
PCR DI	Dexa	194	95,8 ± 67,2	93,2 (32,9 - 137,3)		
	Metil	131	97,9 ± 66,1	93,4 (45,2 - 139,2)	0,729	---
VG DF	Dexa	194	39,8 ± 5,5	40,3 (36,7 - 43,5)		
	Metil	131	41,3 ± 4,4	41,5 (38,7 - 44,1)	---	0,008
Hb DF	Dexa	194	13,5 ± 1,7	13,8 (12,4 - 14,8)		
	Metil	131	14,0 ± 1,5	14 (13 - 15)	---	0,013
Leuc DF	Dexa	194	9129 ± 3831	8300 (6500 - 11000)		
	Metil	131	9235 ± 3323	8700 (6800 - 11600)	0,405	---
Bast DF	Dexa	194	7,1 ± 3,2	6 (5 - 10)		
	Metil	131	7,6 ± 3,1	7 (5 - 9)	0,149	---
PCR DF	Dexa	194	52,6 ± 53,0	29,8 (15,1 - 80)		
	Metil	131	51,1 ± 57,3	26,3 (11,5 - 72,7)	0,451	---

Subtitles. IIQ: interquartile range (Quartile 1 – Quartile 3). DI: date of admission. DF: end date. VG: packed cell volume. Hb: hemoglobina. Leuc: leukocytes. Bast: rods. PCR: C-Reactive Protein. Dexa: dexamethasone. Metil: methylprednisolone.

* Non-parametric Mann-Whitney test, used to analyze Leuc, Bast e PCR variables.

** Student's t test for independent samples, used to analyze the variables age, VG and Hb.

bin, leukocytes, rods and CRP were used. These variables were analyzed at the beginning and at the end of the treatment. Age, sex and presence of the following comorbidities were also evaluated as variables in the present study: diabetes mellitus (DM), systemic arterial hypertension (SAH), chronic obstructive pulmonary disease (COPD) and smoking.

The standardization was carried out in the observation of the researcher, guaranteeing adequate techniques in the collection of information. With these data, a database was built in Microsoft Excel and, before the analysis, it was submitted to quality control.

Results of quantitative variables were described as mean and standard deviation or as median and interquartile range. Categorical variables were described by frequency and percentage. To compare two groups defined by dichotomous variables, in relation to quantitative variables, the Student's t test for independent samples or the non-parametric Mann-Whitney test was used. Categorical variables were analyzed using Fisher's exact test. To assess the correlation between two quantitative variables, Spearman correlation coefficients were estimated. For univariate and multivariate analysis of factors associated with outcomes (need for ICU, mechanical ventilation and death), logistic regression models were adjusted. The Wald test was used to analyze the significance of the variables and the estimated measure of association was the odds ratio (OR). The normality condition of the quantitative variables was evaluated by the Kolmogorov-Smirnov test. Values of $p<0.05$ indicated statistical significance. Data were analyzed using the computer program Stata/SE v.14.1. StataCorpLP, USA.

Results

The total study sample consisted of 325 patients, of which 194 were treated with dexamethasone (control group) and 131 with methylprednisolone (intervention group).

Table 2. Categorical

Variables	Classification	Dexamethasone	Methylprednisolone	p*
Sex	Female	83 (42,8%)	53 (40,5%)	
	Male	111 (57,2%)	78 (59,5%)	0,731
DM	No	184 (94,8%)	120 (91,6%)	
	Yes	10 (5,2%)	11 (8,4%)	0,258
Smoking	No	191 (98,5%)	130 (99,2%)	
	Yes	3 (1,5%)	1 (0,8%)	0,651
SAH	No	161 (83%)	111 (84,7%)	
	Yes	33 (17%)	20 (15,3%)	0,760
COPD	No	191 (98,5%)	127 (96,9%)	
	Yes	3 (1,5%)	4 (3,1%)	0,446

Subtitles. DM: diabetes mellitus. SAH: systemic arterial hypertension. COPD: chronic obstructive pulmonary disease.

* Fischer's exact test.

The two groups had similar characteristics in terms of age and comorbidities (Tables 1 and 2). The median age of patients was 51 years (42 to 57) in the control group and 47 years (40 to 57) in the intervention group (Table 1).

Most patients were male, 59.5% in the intervention group and 53% in the control group (Table 2). Most had no previously known comorbidities (Table 2). There were no statistically significant differences in the epidemiological profile between the two groups of patients for the variables age, sex and comorbidities (Tables 1 and 2).

For the statistical results of each outcome, the following variables were considered: age, sex, DM, SAH, smoking, COPD, laboratory tests on the day of admission and on the day of the outcome.

For the primary outcome, ie, death from any cause within 28 days (Table 3), mortality was 1.54-fold lower in the methylprednisolone-treated group (dexamethasone=8.2%; methylprednisolone=5.3%). For each of the variables, the null hypothesis that there is no association between the variable and death within 28 days was tested, versus the alternative hypothesis that there is an association (Table 3).

As for the need for transfer to the ICU (Table 4), this was 1.18 times lower in the group that received methylprednisolone (dexamethasone=8.92%; methylprednisolone=6.9%). Likewise, for each of the variables, the null hypothesis that there is no association between the variable and the need for ICU was tested, versus the alternative hypothesis that there is an association.

The proportion of patients who required ventilation support by mechanical ventilation was twice as high in the group that received dexamethasone (Table 5), being 3.1% for this group, against 1.5% in the group that received methylprednisolone. For each of the variables, the null hypothesis that there is no association between the variable and the need for MV was tested, versus the alternative hypothesis that there is an association.

In addition, the need for an ICU proved to be an independent risk factor for the outcome of death within 28 days (Table 6 and 8). The proportion of deaths among patients who required ICU was 64% versus 2.3% among those who did not.

The mean ICU stay was also shorter in the group that received methylprednisolone (Table 7), being 1.76 times shorter (dexamethasone=24.9±22.3 days; methylprednisolone=17±7.3 days). However, there was no statistically significant association between quantitative variables and length of ICU (Table 8).

Discussion

The high mortality of Covid-19 infection can be explained by the rapid development of pneumonia and ARDS [1–3,15,16]. Its appearance in the first week of infection demonstrates a very rapid progression of the disease with a consequent immunological dysregulation associated with persistent exacerbated inflammatory processes [2,3].

At the beginning of the pandemic, the administration of corticosteroids was controversial. This is due to the lack of medical consensus regarding the use of corticosteroids in ARDS in general [7,13]. Numerous clinical protocols for the treatment of ARDS have been developed over the last few decades, in many

Table 3. Assessment of the association between type of corticosteroid and death within 28 days

Variable	Classification	n total	Death within 28 days	OR (IC95%)	
			No	Yes	
Age (years)	(mean ± SD)		49,7 ± 12,7	56,3 ± 13,4	1,04 (1,01 - 1,07)
Gender	Female (ref)	136	127 (93,4%)	9 (6,6%)	
	Male	189	175 (92,6%)	14 (7,4%)	1,13 (0,47 - 2,69)
DM	No (ref)	304	281 (92,4%)	23 (7,6%)	
	Yes	21	21 (100%)	0 (0%)	-
Smoking	No (ref)	321	298 (92,8%)	23 (7,2%)	
	Yes	4	4 (100%)	0 (0%)	-
SAH	No (ref)	272	251 (92,3%)	21 (7,7%)	
	Yes	53	51 (96,2%)	2 (3,8%)	0,47 (0,11 - 2,06)
COPD	No (ref)	318	296 (93,1%)	22 (6,9%)	
	Yes	7	6 (85,7%)	1 (14,3%)	2,24 (0,26 - 19,5)
VG DI	(mean ± SD)		40,5 ± 4,9	39,6 ± 5,9	0,97 (0,89 - 1,04)
Hb DI	(mean ± SD)		13,9 ± 1,6	13,4 ± 2,3	0,87 (0,69 - 1,09)
Leuc DI	(median, IIQ)		9600 (6700 - 12400)	8200 (6100 - 14700)	1,01 (0,95 - 1,08)*
Bast DI	(median, IIQ)		7 (5 - 11)	7 (6 - 12)	1,04 (0,93 - 1,17)
PCR DI	(median, IIQ)		91,6 (35,8 - 136)	125,1 (61,2 - 153)	1,004 (0,998 - 1,010)
VG DF	(mean ± SD)		40,5 ± 5,2	38,7 ± 5,1	0,94 (0,88 - 1,01)
Hb DF	(mean ± SD)		13,8 ± 1,6	13 ± 1,8	0,77 (0,61 - 0,99)
Leuc DF	(median, IIQ)		8600 (6700 - 11100)	8700 (6400 - 14000)	1,06 (0,96 - 1,18)*
Bast DF	(median, IIQ)		7 (5 - 10)	8 (5 - 9)	1,00 (0,87 - 1,14)
PCR DF	(median, IIQ)		26,2 (12,4 - 71,7)	133,4 (50 - 185)	1,017 (1,010 - 1,023)
Corticoide	**Dexa (ref)**	**194**	**178 (91,8%)**	**16 (8,2%)**	
	Metil	**131**	**124 (94,7%)**	**7 (5,3%)**	**0,63 (0,25 - 1,57)**

Subtitles. IIQ: interquartile range (Quartile 1 – Quartile 3). DI: date of admission. DF: end date. VG: packed cell volume. Hb: hemoglobina. Leuc: leukocytes. Bast: rods. PCR: C-Reactive Protein. Dexa: dexamethasone. Metil: methylprednisolone.

* OR corresponding to every 1000 more leukocyte units.

of which corticosteroids have a therapeutic role to play [8,13,14].

Likewise, evidence was obtained from clinical research and changed the management of ARDS secondary to Covid-19 in critically ill patients [4,6,9,11]. Initially with dexamethasone [4,6,7] and later with other corticosteroids [9,15,17,18].

The RECOVERY clinical trial [4,5,7] showed lower mortality, shorter hospital stay and better mechanical ventilation outcomes among patients who received doses of dexamethasone when compared to patients who did not receive corticosteroid treatment trial [6,7] also demonstrated better outcomes for patients who required mechanical ventilation after receiving doses of dexamethasone. The two clinical trials had some limitations, one of which was the restriction to patients on mechanical ventilation or oxygen therapy. Another limitation was the lack of data on the efficacy of dexamethasone in non-ICU patients. There were also no comparison data between corticosteroids, as the control group in both clinical trials was standard treatment without any corticosteroids.

As methylprednisolone has been used for a long time in clinical protocols for the treatment of ARDS, questions have arisen about its effectiveness compared to dexamethasone. Consequently, questions also arose about the possibility of using it as a therapeutic arsenal for the prevention of ARDS in Covid-19 infection.

Edalatifard et al. [16] randomized patients with Covid-19 pneumonia to receive methylprednisolone 250 mg daily for three days versus standard care treatment. Clinical improvement was greater in the methylprednisolone group (94.1% versus 57.1%), and the mortality rate was lower in the methylprednisolone group (5.9% versus 42.9%).

Espinosa-Solano et al. [17] carried out a study comparing pulses of methylprednisolone 250 mg for up to 3 days followed by 40 mg daily until completing 5 days of treatment versus standard treatment. The use of methylprednisolone resulted in a lower rate of orotracheal intubation and a shorter hospital stay. Ruiz-Irastorza et al. [19] studied the prolonged application of methylprednisolone pulses and concluded that it is possible to use the medication preventively in patients hospitalized for Covid-19, a finding that was corroborated by Yang et al. [20].

In the present study, we evaluated the differences in outcomes in patients treated with doses of dexamethasone equivalent to those of the RECOVERY(5) (previously considered the gold standard for treatment) or methylprednisolone according to the institution's protocol.

The results showed lower 28-day mortality in the methylprednisolone group (5.3% versus 8.2%, being 1.54 times lower). There are still few studies comparing outcomes of methylpred-

Table 4. Assessment of the association between type of corticosteroid and the need for ICU

Variable	Classification	n total	Need for ICU	OR (IC95%)	
			No	Yes	
Age (years)	(mean ± SD)		50,2 ± 13,0	50,0 ± 9,7	0,99 (0,97 - 1,03)
Gender	Female (ref)	136	125 (91,9%)	11 (8,1%)	
	Male	189	175 (92,6%)	14 (7,4%)	0,91 (0,40 - 2,07)
DM	No (ref)	304	281 (92,4%)	23 (7,6%)	
	Yes	21	19 (90,5%)	2 (9,5%)	1,29 (0,28 - 5,87)
Smoking	No (ref)	321	296 (92,2%)	25 (7,8%)	
	Yes	4	4 (100%)	0 (0%)	
SAH	No (ref)	272	251 (92,3%)	21 (7,7%)	
	Yes	53	49 (92,5%)	4 (7,5%)	0,98 (0,32 - 2,97)
COPD	No (ref)	318	293 (92,1%)	25 (7,9%)	
	Yes	7	7 (100%)	0 (0%)	-
VG DI	(mean ± SD)		40,4 ± 4,9	40,9 ± 5,6	1,02 (0,94 - 1,12)
Hb DI	(mean ± SD)		13,8 ± 1,6	13,9 ± 2,1	1,04 (0,81 - 1,33)
Leuc DI	(median, IIQ)		9350 (6700 - 12400)	10400 (7200 - 14200)	1,03 (0,98 - 1,09)*
Bast DI	(median, IIQ)		7 (5 - 11)	8 (7 - 10)	1,06 (0,95 - 1,18)
PCR DI	(median, IIQ)		90,7 (34,5 - 135,6)	125,1 (85 - 153,8)	1,006 (1,001 - 1,012)
VG DF	(mean ± SD)		40,5 ± 5,2	39,2 ± 4,6	0,96 (0,89 - 1,03)
Hb DF	(mean ± SD)		13,8 ± 1,7	13,2 ± 1,7	0,84 (0,66 - 1,06)
Leuc DF	(median, IIQ)		8550 (6600 - 11100)	8800 (7500 - 11400)	1,08 (0,98 - 1,19)*
Bast DF	(median, IIQ)		7 (5 - 10)	6 (5 - 8)	0,93 (0,81 - 1,06)
PCR DF	(median, IIQ)		25,9 (12,4 - 71,2)	101,3 (68,4 - 163,6)	1,016 (1,010 - 1,023)
Corticóide	**Dexa (ref)**	**194**	**178 (91,8%)**	**16 (8,2%)**	
	Metil	**131**	**122 (93,1%)**	**9 (6,9%)**	**0,82 (0,35 – 1,92)**

Subtitles. IIQ: interquartile range (Quartile 1 – Quartile 3). DI: date of admission. DF: end date. VG: packed cell volume. Hb: hemoglobina. Leuc: leukocytes. Bast: rods. PCR: C-Reactive Protein. Dexa: dexamethasone. Metil: methylprednisolone.

* OR corresponding to every 1000 more leukocyte units.

nisolone with dexamethasone, which are still restricted to observational studies or clinical trials with small samples. Even so, these studies and systematic reviews [7,9] point to a possible advantage of methylprenisolone [8,11,15,16,18,20] in patients at an early stage of infection, results consistent with those of the present study.

The need for an ICU was also lower in patients who received methylprednisolone (6.9% for methylprednisolone versus 8.92% for dexamethasone, 1.18-fold lower). This result is consistent with other studies that have shown that methylprednisolone decreases the risk of progression of Covid-19 disease severity [11,15,19,20]. Despite the small sample size, Ranjbar et al.[18] also found better outcomes in patients treated with methylprednisolone compared with dexamethasone in a clinical trial with 86 patients. The same conclusion was also found by Pinzón et al. [15] in a study with 216 patients.

The duration of ICU stay was also shorter for the group that received methylprednisolone, being 1.76 times shorter (17±7.3 days versus 24.9±22.3). This result is consistent with other clinical trials and observational studies [7,9,11,16–18] in which shorter ICU stays were also observed.

In addition, the proportion of patients who required ventilatory support by mechanical ventilation was half in the group receiving methylprednisolone (1.5% versus 3.1%). The data is consistent with evidence that methylprednisolone administered early can reduce progression to severe cases [11,14,15,19,20].

As advantages of the present study, it is worth mentioning the early administration of corticosteroids at admission and even before the development of ARDS, allowing a better clinical evaluation of the effects of the medication on CLS. Another strong point, also resulting from the early use of corticosteroids, was the collection of data that allow us to verify a protective effect of the medication on the progression of pneumonia by Covid-19, preventing patients from evolving into severe cases. However, this can also be seen as a limitation, as its effects on ICU patients have not been evaluated in detail. Although it was carried out in a single center may be a limitation, it is worth remembering that the hospital in question (Hospital do Rocio) was placed as one of the main national references to receive patients with Covid-19 and received patients from different regions of the country, in different clinical states and contaminated by different viral strains. The limited range of laboratory tests evaluated in the present study also limited their comparison.

Conclusions

In the present study, treatment of Covid-19 with pulse methylprednisolone 250 mg for 3 days, followed by doses of 1 mg/

Table 5. Assessment of the association between type of corticosteroid and the need for mechanical ventilation

Variável	Classification	n total	Need for mechanical ventilation	p*	OR (IC95%)	
			No	Yes		
Variable	(mean ± SD)		50,1 ± 12,9	51,5 ± 8,2	0,767	1,01 (0,96 - 1,06)
	Female (ref)	136	133 (97,8%)	3 (2,2%)		
Age (years)	Male	189	184 (97,4%)	5 (2,6%)	0,801	1,20 (0,28 - 5,13)
Gender	No (ref)	304	296 (97,4%)	8 (2,6%)		
	Yes	21	21 (100%)	0 (0%)	1**	-
DM	No (ref)	321	313 (97,5%)	8 (2,5%)		
	Yes	4	4 (100%)	0 (0%)	1**	-
Smoking	No (ref)	272	264 (97,1%)	8 (2,9%)		
	Yes	53	53 (100%)	0 (0%)	0,362**	-
SAH	No (ref)	318	310 (97,5%)	8 (2,5%)		
	Yes	7	7 (100%)	0 (0%)	1**	
VG D0	(mean ± SD)		40,5 ± 4,9	38,3 ± 7,3	0,204	0,93 (0,83 - 1,04)
Hb D0	(mean ± SD)		13,9 ± 1,6	13 ± 2,9	0,149	0,77 (0,54 - 1,10)
Leuc D0	(median, IIQ)		9400 (6700 - 12400)	10450 (6300 - 13200)	0,850	1,01 (0,91 - 1,13)***
Bast D0	(median, IIQ)		7 (5 - 11)	10 (9 - 13)	0,049	1,20 (1,00 - 1,43)
PCR D0	(median, IIQ)		93,2 (37,5 - 135,8)	124,6 (82,3 - 162)	0,205	1,006 (0,997 - 1,016)
VG D4	(mean ± SD)		40,5 ± 5,1	36,1 ± 4,4	0,026	0,90 (0,82 - 0,99)
Hb D4	(mean ± SD)		13,7 ± 1,6	12,3 ± 1,7	0,020	0,63 (0,43 - 0,93)
Leuc D4	(median, IIQ)		8600 (6700 - 11200)	8150 (3950 - 9400)	0,185	0,84 (0,65 - 1,09)***
Bast D4	(median, IIQ)		7 (5 - 10)	8 (6 - 9)	0,765	1,03 (0,83 - 1,28)
PCR D4	(median, IIQ)		27,8 (12,7 - 73)	135,9 (69,9 - 222)	<0,001	1,018 (1,009 - 1,027)
Corticóide	Dexa (ref)	194	188 (96,9%)	6 (3,1%)		
	Metil	131	129 (98,5%)	2 (1,5%)	0,381	0,49 (0,10 - 2,44)

Subtitles. IIQ: interquartile range (Quartile 1 – Quartile 3). DI: date of admission. DF: end date. VG: packed cell volume. Hb: hemoglobina. Leuc: leukocytes. Bast: rods. PCR: C-Reactive Protein. Dexa: dexamethasone. Metil: methylprednisolone.
* Wald logistic regression model.
** Fisher's exact test.
*** OR corresponding to every 1000 more leukocyte units.

Table 6. Deaths in 28 days in patients who required ICU or mechanical ventilation

Variable	Classification	n total	Death within 28 days		p*
			No	Yes	
Need for ICU	No (ref)	300	293 (97,7%)	7 (2,3%)	
	Yes	25	9 (36%)	16 (64%)	<0,001
Mehcanical	No (ref)	317	301 (95%)	16 (5%)	
Ventilation	Yes	8	1 (12,5%)	7 (87,5%)	<0,001

* Wald logistic regression model, p<0,05

Table 7. ICU time considering the cases that required ICU

Variable	n	mean ± SD	Median (IIQ)
Time in ICU (days)	25	22,0 ± 18,5	18 (9 – 31,5)

IIQ: interquartile range.

Table 8. Assessment of the association between quantitative variables and ICU time

Variables	n	Spearman correlation coefficient	P
Time in ICU x age	25	-0,11	0,598
Time in ICU x VG DI	25	-0,19	0,356
Time in ICU x Hb DI	25	-0,20	0,337
Time in ICU x Leuc DI	25	-0,15	0,470
Time in ICU x Bast DI	25	-0,27	0,196
Time in ICU x PCR DI	25	-0,32	0,124
Time in ICU x VG DF	25	-0,20	0,330
Time in ICU x Hb DF	25	-0,28	0,174
Time in ICU x Leuc DF	25	0,09	0,651
Time in ICU x Bast DF	25	-0,21	0,314
Time in ICU x PCR DF	25	0,09	0,679

Subtitles. DI: date of admission. DF: end date. VG: packed cell volume. Hb: hemoglobina. Leuc: leukocytes. Bast: rods. PCR: C-Reactive Protein.
Spearman's correlation coefficient is a measure of association between two quantitative variables and ranges from -1 to +1. A positive coefficient indicates direct correlation between variables. Negative coefficients indicate an inverse correlation. Correlation coefficients close to zero indicate a weak association and coefficients closer to -1 or +1 indicate a strong association between the two variables.

kg/day for 10 days, compared with dexamethasone 6 mg for 10 days or until discharge, decreased 28-day mortality, as well as ICU need and ICU length of stay. Further randomized controlled trials targeting each outcome are needed to corroborate the conclusions, as well as to adequately assess the laboratory impacts of the treatment.

Conflicts of Interest

The authors declare no conflict of interest.

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