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Comparison of high-dose, short-term steroid and low-dose long-term steroid use in ARDS caused by COVID-19: Retrospective cohort study

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Ethics Committee Approval
Biruni University's non-interventional clinical research ethics committee (no: 2021/53-05, Date: 16.06.2021)
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All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Given the increasing incidence and mortality caused by coronavirus 2019 (COVID-19) worldwide, beneficial and effective treatment for patients in the early pulmonary phase is still of great importance. Fifteen-day continuous hemodynamic, laboratory, and clinical courses of patients with acute respiratory distress syndrome (ARDS) due to COVID-19 who received short-term high-dose and long-term low-dose systemic methylprednisolone were compared.

Methods: Two hundred and two patients were reported to have ARDS due to COVID-19 in the intensive care unit between June 1, 2020 and February 1, 2021. The patients were divided into two groups: (1) short-term high-dose and (2) long-term low-dose systemic methylprednisolone. Age, gender, Acute Physiology and Chronic Health Evaluation (APACHE II) scores, steroid treatment protocol, intubation duration, length of stay (LOS), Neutrophil/Lymphocyte Ratio, C-reactive protein (CRP), procalcitonin, lactate levels, cytokine filter requirements, the prognosis, and total costs were obtained from their records.

Results: It was determined that elderly patients tended to be given low doses of steroids. No significant differences between the two treatment protocols in terms of other parameters were found. It was determined that high doses of steroids affected only CRP levels ($P<0.05$).

Conclusion: No differences in lactate, PCT levels, NLR, intubation and weaning times, hemoperfusion requirements, hospital stay, and prognosis between administration of different doses and durations of methylprednisolone for the treatment of COVID-19 ARDS were found.

Keywords: Methylprednisolone, COVID-19, ARDS, Prognosis

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Introduction

Since coronavirus 2019 (COVID-19) was appeared in China in late 2019, the number of infected people continues to rise. If the COVID 19 infection is not eradicated by proper and powerful immune responses, pulmonary fibrosis, shortness of breath, decreased O_2 saturation, acute respiratory failure syndrome (ARDS), and mortality owing to the resulting cytokine storm can occur [1].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been found to cause a cytokine storm in COVID-19 patients who are in the intensive care unit (ICU) high plasma levels of inflammatory cytokines have been linked to illness severity and prognosis [2].

Glucocorticoids and immunosuppressive therapy can cause a reduction in respiratory tract inflammation and prevent cytokine storm and ARDS induction in COVID-19 patients. Because no effective specific therapeutic agents for the disease are available, glucocorticoids and immunosuppressive therapy can. lead to a reduction in respiratory tract inflammation and prevent cytokine storm and ARDS induction [3].

The 15-day continuous hemodynamic, laboratory, and clinical course of COVID 19 patients who received short-term (3 days) high-dose (10 mg/kg/day) systemic methylprednisolone versus COVID 19 patients who received low-dose long-term (1 mg/kg/day) systemic methylprednisolone in this retrospective study was compared.

Materials and methods

After receiving approval from Biruni University's non-interventional clinical research ethics committee, this project was started as a retrospective cohort study (Ethics committee no: 2021/53-05; Date: 16.06.2021 ClinicalTrials.gov Identifier: NCT05047874). Patients over the age of 18 who were hospitalized in the General intensive care unit of Biruni University Medical Faculty Hospital with the diagnosis of COVID 19 between June 1, 2020 and February 1, 2021, diagnosed with ARDS, and over the age of 18 were included in the study. In the retrospective study, the sample size was not calculated to screen all patients who met the inclusion criteria. Identification of SARS-CoV-2 by reverse transcription-polymerase chain reaction (RT-PCR) in nasopharyngeal swab or sputum specimens and/or abnormal lung computed tomography (CT) scans with 90% oxygen saturation at rest (bilateral, subpleural, peripheral ground glass opacities) were considered positive-for the diagnosis of COVID-19. If the ARDS was caused by COVID 19, patients who received high flow nasal oxygen (HFNO), non-invasive mechanical ventilation (NIV), or invasive mechanical ventilation (IMV) due to acute hypoxemic respiratory failure associated with SARS-CoV-2 pneumonia [4] were included in the study. In the context of COVID-19, this definition is fully consistent with the pathophysiological logic that supports the Berlin Definition for ARDS (Table 1).

Patients with a diagnosis of steroid allergy or those who developed an allergy during therapy, pregnant or breastfeeding women, patients with active malignancies, and patients receiving any immunosuppressive drug were all excluded from the trial.

Table 1: Characteristics of the pragmatic definition of coronavirus 2019 acute respiratory distress syndrome (COVID-19 ARDS) [4]

Feature of definition	Berlin Criterion	COVID application
Associated with COVID-19	No restriction by pathogen	Limited to patients with SARS-CoV-2 pneumonia
Acute	< 7 days since onset	5–14 days is common; most important factor is that the respiratory failure be from COVID-19
Bilateral opacities	Bilateral opacities consistent with pulmonary edema "may be very mild, patchy, and asymmetric"	COVID-19 pneumonia is generally a bilateral process
Hypoxemic	Positive pressure ventilation with PEEP ≥ 5 cm H2O and PaO2:FIO2<300 (Kigali modification SpO2:FIO2<315 and eliminates PEEP and positive pressure ventilation requirements)	Hypoxemic respiratory failure treated with HFNO, NIV, IMV (FIO2 ≥ 0.35 guarantees SpO2:FIO2<315 regardless of SpO2)
Not primarily cardiogenic / hydrostatic	Clinical assessment and judgment	Respiratory failure primarily due to COVID-19 pneumonia

PEEP: positive end-respiratory pressure, PaO2: partial pressure of oxygen in arterial blood, FIO2: fraction of inspired oxygen, SpO2: oxygen saturation, HFNO: high-flow nasal oxygen, NIV: non-invasive ventilation, IMV: intermittent mandatory ventilation

In the study, information from the file records of 202 patients hospitalized with the diagnosis of ARDS due to COVID 19 in the General intensive care unit of XX University Medical Faculty Hospital between June 1, 2020 and February 1, 2021; patients' age, gender, Acute Physiology and Chronic Health Evaluation (APACHE II) scores, steroid treatment protocol (low dose steroid therapy [1 mg/kg/day] for 15 days or high-dose steroid therapy [10 mg/kg/day] for three days) were tapered off after three days. low dose continued for up to 10 days) intubation time (Day), weaning time (days), hospital stay time (days), prognosis: (death/survival), cost (Turkish Lira), and daily neutrophil lymphocyte ratio for 15 days (NLR), C-reactive protein (CRP), PCT Procalcitonin (PCT), lactate levels, and the need for cytokine filter (HMP) were recorded.

After obtaining ethics committee and chief physician approval, a "data processor" who was not involved in the study anonymized the patients who met the study's inclusion criteria between these dates, and after ensuring that their identity information was hidden, the data in the case registration form was accessed and recorded from the computer records. The primary aim of the study was to compare the 15-day continuous hemodynamics, laboratory findings, and clinical course of COVID 19 patients.

Statistical analysis

The results were presented for categorical variables as numbers and percentages, and for continuous variables as mean (standard deviation (SD)). Comparison of the categorical variables between groups was done using a chi-square or Fisher exact test. For comparison of independent continuous variables between two groups, the Student's t- or Mann–Whitney U test was used depending on whether the statistical hypotheses were fulfilled or not. Similarly, for dependent continuous variables paired samples t- or Wilcoxon signed rank test was used.

SPSS version 21.0 for Windows was used for statistical evaluation (IBM Software, New York, United States), and $P < 0.05$ was considered statistically significant.

Results

The mean age of 202 patients included in the study was 66.64 (14.9) years and 57.4% were male. Over half (67.3%) of the cases were extubated when they were admitted to the first intensive care unit, (ICU) and their mean APACHE II score was

26.32 (12.1). While the mean day of intubation was 2.19 (3.7) days, mean weaning days were 5.86(6.8) days. A total of 78 (38.6%) patients were administered short-term (three days) high-dose (10 mg/kg/day) systemic methylprednisolone, and it was observed that 51 (25.2%) patients needed HMP. The mortality rate was 59.4%, the duration of hospital stay was 10.99 (7.8) days, and the cost was mean 30243,378 (36596.2) TL (Table 2).

Table 2: Descriptive Statistics

		N	Mean (SD) (min–max)
Female		86	42.6%
Male		116	57.4%
Age (year)		202	66.64 (14.9) (25–93)
APACHE-II		202	26.32 (12.1) (2-62)
Intubation Time (Days)		202	2.19 (3.7) (0–25)
Weaning (Days)		202	5.86 (6.8) (0–40)
Arrival Status	Extubated	136	67.3%
	Intubated	66	32.7%
Methylprednisolone	None	124	61.4%
	Yes	78	38.6%
HMP	None	151	74.8%
	Yes	51	25.2%
Prognosis	Death	120	59.4%
	Discharge	82	40.6%
LOS (days)		202	10.99 (7.8) (1–49)
Cost (Turkish Liras)		202	30,243,37 (36,596,2) (208,2–307,721,2)

* HMP: hemoperfusion, LOS: length of stay; APACHE: Acute Physiology and Chronic Health Evaluation, SD: standard deviation

The planned 15-day follow-up of 202 patients included in the study was included in the first 10-day follow-up calculations so as not to cause errors in the calculations due to the deficiencies in the continuous data with the increase in deaths after the 10th day. These 10-day NLR, lactate, PCT, and CRP levels are shown in Figures 1 and 2.

Figure 1: Changes of neutrophil/lymphocyte ratio (NLR) and lactate over time (days)

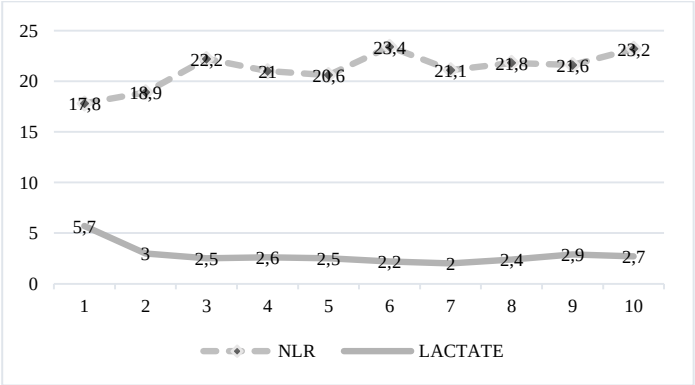
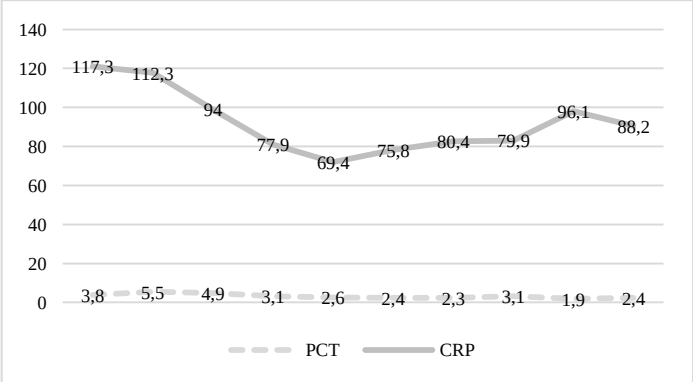


Figure 2: Changes of procalcitonin (PCT) and CRP over time (day)



The comparison of COVID 19 patients (n=78) who were received short-term (three days) high-dose (10 mg/kg/day) systemic methylprednisolone and low-dose (n=124) long-term (1 mg/kg/day) systemic methylprednisolone is shown in Table 3. It was determined that elderly patients tended to be given low-dose steroids. In addition, it was observed that high-dose steroid therapy was preferred mostly in extubated patients, while low-dose long-term steroid therapy was preferred in patients who were intubated (P<0.05). No significant differences between the two treatment protocols in terms of gender, APACHE II, intubation and weaning time, need for hemoperfusion, prognosis, LOS, and costs were found (Table 3).

Table 3: Comparisons between groups

		Group		*P*-value
		High dose (n=78) Mean (SD)	Low dose (n=124) Mean (SD)	
Sex	Female	31	55	0.309
	Male	47	69	
Age (year)		62.7 (14.1)	69.0 (15.0)	0.003
Status of arrival	Extube	61	75	0.006
	Intube	17	49	
APACHE II		25.1 (12.6)	27.0 (11.7)	0.299
Intubation time (Days)		2.5 (3.9)	1.9 (3.5)	0.344
Weaning (Days)		5.5 (6.6)	6.0 (6.9)	0.655
HMP	Yes	15	36	0.083
	None	62	87	
Prognosis	Death	45(57.7%)	75 (60.5%)	0.402
	Discharge	33	49	
LOS (Days)		11.4 (7.4)	10.7 (8.1)	0.530
Cost (Turkish Liras)		27535.1 (25873.8)	31946.9 (41978.2)	0.357

* ANOVA: analysis of variance ** chi square, HMP: hemoperfusion, LOS: length of stay

When changes in laboratory values of high- and low-dose steroid treatments over time were examined, it was found that high-dose steroid only affected CRP levels (table 4), but there was no difference in mortality rate (P=0.402).

Table 4: C-reactive protein (CRP) levels between groups over time

		Mean (SD)	*P*-value
CRP 1st day	Low dose	105.4 (85.4)	0.012*
	High dose	136.2 (81.6)	
CRP 2nd day	Low dose	109.8 (82.8)	0.596
	High dose	116.3 (85.4)	
CRP 3th day	Low dose	99.0 (78.2)	0.267*
	High dose	86.3 (76.0)	
CRP 4th day	Low dose	90.4 (74.6)	0.004*
	High dose	59.3 (59.3)	
CRP 5th day	Low dose	83.9 (73.1)	0.001*
	High dose	48.9 (63.1)	
CRP 6th day	Low dose	95.2 (85.4)	0.001*
	High dose	47.0 (74.8)	
CRP 7th day	Low dose	101.8 (92.2)	0.001*
	High dose	50.2 (77.7)	
CRP 8th day	Low dose	99.3 (84.4)	0.003*
	High dose	53.0 (80.1)	
CRP 9th day	Low dose	142.6 (119.4)	0.081
	High dose	60.4 (95.3)	
CRP 10th day	Low dose	110.5 (95.7)	0.007*
	High dose	59.2 (87.2)	

* one-way analysis of variance (ANOVA)

Discussion

In rheumatic illnesses, methylprednisolone is a glucocorticoid medication that produces a decrease in autoimmune and inflammatory reactions [5]. Previously, some studies have been conducted with the thought that methylprednisolone administration in the hyperinflammatory stage in COVID-19 patients may have possible benefits due to the suppression of the cytokine storm, but the results of these studies are inconsistent. Studies that claim to be useful include a randomized controlled study conducted by Maryam et al. [2] in which they found that giving methylprednisolone in a pulse at the start of the early pulmonary phase of the disease cut the death rate in half, enhanced recovery, and led to a decrease in the length of hospital stay by half [2]. In the same study, they found that methylprednisolone caused an improvement in pulmonary involvement, oxygen saturation, dyspnea, heart rate, respiratory rate, and inflammatory markers, such as CRP and interleukin 6 (IL-6) in patients, and that methylprednisolone could be an effective therapeutic agent for severe COVID-19 patients during

the pulmonary phase. In meta-analyses by Li [6] and Sterne [7] it was found that systemic glucocorticoids are associated with a decrease in all-cause mortality in COVID-19-positive critically ill patients. Investigations that claim to be ineffective include studies by Hu [8] and Rodrigez Molinerio [1] in which it was found that glucocorticoid treatment had no significant effect on the clinical course, side effects, or outcome of COVID-19 pneumonia. In a cohort study by Wang et al. [9], it was shown that patients treated with methylprednisolone had a faster recovery in oxygen saturation and a decrease in CRP and IL-6 levels and were less likely to require invasive ventilation. However, they did not observe significant differences in mortality between the groups. Hu et al. [8] focused on the impact of low-dose glucocorticoid therapy in COVID-19 pneumonia patients and found that glucocorticoid medication had no effect on the clinical course, side effects, or outcome of COVID-19 pneumonia in their retrospective analysis.

In these studies, the dose of methylprednisolone was different, and 1 mg/kg was used as the high dose. The observed differences could be related to disparities in therapy dosage and duration, limited sample sizes, the patients' ages, and disease severity. In reality, patient characteristics, duration of administration, and pulmonary phase are key factors in the effectiveness of corticosteroid therapy. So et al. [10], who reported the sole case report in the literature involving administration of 1000 or 500 mg/day methylprednisolone for three days, theorized that high-dose corticosteroid treatment could prevent tissue damage and hence, cause less lung damage. Five-hundred milligrams per day of methylprednisolone followed by 1 mg/kg once daily and then a reduction by 10 or 20 or 30 mg was administered. They finished with 10 mg/day oral prednisolone. They claimed that giving patients methylprednisolone intravenously led to lowering of their temperature, cause a 100% survival rate, reintubation rates were 0%, and ventilator support could be removed in all cases within seven days. In our study, it was determined that short-term high-dose methylprednisolone only led to a decrease in CRP values and had no effect on lactate, PCT, NLR levels, intubation time, weaning time, hemoperfusion requirement, hospital stay, or prognosis. Our study has limitations in that it is a single-center report with a small number of cases. Because clinical course findings, such as fever, heart rate, inotrope need, and oxygenation level are not available in computerized form and can only be collected from handwritten nursing records, they were not included in the study to avoid a faulty or biased conclusion.

Conclusion

It was discovered that varied doses and durations of methylprednisolone for the treatment of COVID-19 ARDS had no effect on lactate, PCT, NLR levels, intubation time, weaning time, hemoperfusion requirements, hospital stays, and/or prognosis. The time and dosage of glucocorticoids for the treatment of COVID-19 ARDS still require in-depth and systematic investigations to ensure that they limit the inflammatory response in COVID-19 ARDS.

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