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Different Dose Corticosteroid Treatment Protocols for COVID-19 Patients Admitted to Intensive Care: Comparison of the Effects on Efficacy and Mortality

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ABSTRACT

Aim: In the present study, our purpose was to evaluate the efficacy of the pulse-steroid treatment used in COVID-19 associated severe ARDS patients, and also to identify its effects on mortality in different doses.

Study design: Retrospective Study

Method: Patients with severe COVID-19 associated ARDS who had not previously received steroids, but were administered 1 g methylprednisolone (group 1) or 250 mg methylprednisolone (group 2) for 3 days, then 1 mg/kg/day during their hospitalization were retrospectively analyzed. The primary end-point was the discharge rate from the ICU or death. The secondary end-point was the 15th day survival rate.

Results: A total of 48 patients with a mean age of 70.96±11.04 years were included. Twenty-six (54.2%) of them were male, 22 (45.8%) were female. Group 1 included 21 patients, group 2 included 27 patients. There was no difference in terms of demographic characteristics, comorbidities present, and medical findings between the groups on admission, except for the ferritin value which was lower in group 2 (p=0.027). There was no significant difference between groups groups in the 15-day mortality (p=0.134) and length of ICU stay (p=0.329). There was no difference between the groups in terms of discharge rates (p=0.55), need for mechanical ventilation (p=0.381), and complications (p=0.784). The odds ratio regarding the mortality of the patients in the 1 g pulse-steroid group was 3.17 times more likely than the 250 mg pulse-steroid group.

Conclusion: Our results support that pulse-steroid therapy with 250 mg methylprednisolone may be more effective in patients admitted to intensive care units with ARDS due to COVID-19.

Keywords: COVID-19, methylprednisolone, intensive care, pulse-steroid

Introduction

Coronavirus disease 2019 (COVID-19) which is a cause of severe respiratory failure originated in Wuhan, China, and spread all over the world, is still threatening the health of people and a proven pharmacological treatment has not yet been found. Some of the patients who present with augmented inflammatory response to COVID-19, progress to a condition that is consistent with macrophage activation syndrome (MAS) or cytokine storm, especially after the first week of infection. The direct invasion of certain cell types with the virus, such as the endothelial cells of the vessels in the lung or the alveolar wall epithelia or macrophages, can induce an immune response leading to a cytokine storm, and MAS (1). MAS, clinically manifests as excess levels of ferritin (>684 ng/mL), hematocytopenia, hepatic dysfunction (high aspartate aminotransferase and lactate dehydrogenase levels), high levels of triglycerides (>156 mg/dl) and fibrinogen (≤360 mg/dl), and coagulopathy (platelet number ≤181×10–9/liter) and fever (1, 2). This emerges as a clinical manifestation associated with high mortality, acute respiratory distress syndrome (ARDS), and numerous organ dysfunctions in a significant number of patients (1). ARDS develops on average 12.0 days [8.0-15] after the onset of COVİD-19 (2). Therefore, we evaluated the 15-day mortality days of the patients admitted to the intensive care unit.

Although corticosteroids are used widely in severe ARDS during the progression of COVID-19, their effectiveness remains highly controversial. There is a recommendation in the guideline, that was issued by the Ministry of Health of the Republic of Turkey on November 7th, 2020 under the heading "Glucocorticoids in the Treatment of COVID-19 related

Hyperinflammatory Response", stating that administration of higher dose of glucocorticoids (pulse, ≥250 mg/day methylprednisolone) may be considered taking into account the risk factors of the patient (3, 4).

Unfortunately, corticosteroids have many side effects. Some of the mild-and long-term side effects of this group of agents include hyperglycemia, increased cardiovascular risk, and increased risk of bacterial infection (1-6). These complications may be detected and treated early as a result of close monitoring and observation in intensive care units (ICU).

In the RECOVERY study conducted on treatment, they reported that there was a significant decrease in 28-day mortality and hospital stay in the group given dexamethasone at a dose of 6 mg/day for 10 days, in patients who required oxygen therapy, especially those who needed mechanical ventilation (6). In patients who did not receive oxygen therapy, no positive effect was found on both mortality and hospital stay, and steroids were not recommended due to possible side effects (6, 7). Although 6 mg/day dexamethasone is recommended for treatment, the efficacy of pulse steroid therapy has been evaluated in some other studies. In one of these studies, 17 patients were given 1000 mg of methylprednisolone for 3 days, followed by 8 mg of dexamethasone for 3-5 days (8). Although a decrease in dyspnea, an improvement in oxygen saturation and a decrease in C-reactive protein (CRP) were detected in the treatment group, D-dimer increased. Thromboembolic complications developed in 4 patients in the treatment group (8). As well, there is no consensus on which type of corticosteroid should be used in treatment of COVID-19 patients.

The primary aim of this study was to evaluate the efficacy of different doses of pulse-steroid treatments used in severe ARDS patients that develop MAS, who have bilateral lung involvement in thoracic computed tomography (CT). Patients who were admitted to intensive care units and did not receive steroid treatment outside the hospital until respiratory distress developed were included. Our secondary aim was to investigate 15th day mortality rate.

Method

In this study, patients admitted to the general ICU of Karaman Training and Research Hospital, Turkey and who complied with the study criteria were retrospectively included. Karamanoglu Mehmetbey University, Faculty of Medicine, Ethics Committee approval was taken with decision number 01-2021/06.

Inclusion Criteria

A total of 48 patients, who developed MAS due to COVID-19, who met the criteria of severe ARDS were included in the study. Inclusion criteria are as follows:

1. Being over 18 years of age,
2. Not being pregnant or breast feeding,
3. Having a positive polymerase chain reaction (PCR) result for SARS-CoV-2,
4. Having bilateral ground glass image in thoracic computed tomography (CT),
5. Presence of severe hypoxemia (severe ARDS) (PaO2/FiO2 ≤100 mmHg) (9)
6. Not having received steroids before admission to the ICU,
7. Meeting at least 3 of the following items defined as helpful findings to show the development of MAS in the directive that was issued by the Ministry of Health of the Republic of Turkey on November 7, 2020:
   - Ongoing resistant fever,
   - C-reactive protein (CRP) that is continuously high or continues to increase,
   - Ferritin value (>700 µg/L) above the upper limits of normal and continues to increase,
   - D-dimer elevation,
   - Lymphopenia, thrombocytopenia, and neutrophilia,
   - Disruptions in liver function tests [Alanine transaminase (ALT), aspartate aminotranferase (AST), lactate dehydrogenase (LDH)] (3),
8. Procalcitonin value of <0.5 ng/dL, which may rule out bacterial infection, or no bacterial growth in microbiological culture samples,
9. Not being on immunosuppressive agents,
10. Not having uncontrolled diabetes,
11. Having no history of gastrointestinal bleeding,

Grouping and Treatment Protocols

Patients who met the inclusion criteria were divided into 2 different groups based on the pulse-steroid treatment protocol employed as the most frequently applied protocols, and depending on the decision of the intensivist regarding the usage duration of the treatment.

The groups were as follows

Group 1: 3 days of 1 gram methylprednisolone, then maintenance with 1 mg/kg/day methylprednisolone

Group 2: 3 days of 250 mg methylprednisolone, then maintenance with 1 mg/kg/day methylprednisolone.

On the basis of hospital protocols, steroid treatments were applied to all patients intravenously at 06.00 a.m. in the morning. Also, pantoprazole 40 mg was administered intravenously twice a day, and enoxaparin 1 mg/kg was administered subcutaneously starting as of the first day of the treatment, which is the treatment protocol applied to all COVID-19 patients in our hospital. When the PCR test was positive, Favipiravir was initiated to patients as an antiviral treatment at a dose of 1600 mg twice a day on the first day, and as 600 mg twice a day on other days, for 10 days orally or via a naso-gastric catheter.

Complete blood count (CBC), CRP, ferritin, troponin, D-dimer, LDH, glucose and procalcitonin levels, length of stay in the ICU, complications (myocarditis, pulmonary emboli, hyperglycemia) and mortality were recorded.

Statistical Analysis

In statistical analysis, firstly analysis was carried out for normality and the homogeneity of variances. The Shapiro-Wilk test and skewness values and Withitsz-scores have been used to check normality assumptions. The Levene test was used for the homogeneity of variances. Secondly, the descriptive statistics including mean and standard deviations for quantitative measurements, and frequencies and percentages for qualitative measurements are summarized. Thirdly, various statistic altests have been conducted to determine whether there were any significant differences between the measurements forth quantitative variables and the distributions of each level for the qualitative variables. A two-way mixed measures analysis of variances has been performed on repeated measures and an independent factor.

Due to the insignificant interaction terms between repeated and independent measures, analysis of variances has been carried out only for the results of repeated measures for the sake of simplicity. Student's t (parametric) and Mann-Whitney U tests (non parametric) have been carried out to compare two groups for each variable where appropriate. In order to investigate the association between categorical variables, Chi Square and Fisher Exact tests have been applied. Binomial proportion tests were used to compare the distributions of each level for binary variables. In addition, the odds ratios have been calculated to determine the possibility for each level of binary variables corresponding to a base line group of another binary variable. The significance value is set as 0.05 for two-sided testing. The 95% confidence intervals have been added where appropriate. All statistical analyses have been performed via IBM SPSS (Version 26 for Windows), Jamovi (1.2.17) and R software (4.0.2).

Results

Totally 48 patients with the mean age of 70.96±11.04 years were included in the study and 26 (54.2%) of them were male. Half of the patients had at least one comorbidity; most common ones were hypertension (30%) and diabetes mellitus (27.1%) (Table 1).

There was no any significant difference between group 1 and group 2 for age, gender, present comorbidities, sepsis existence and laboratory values. Ferritin levels of group 2 were higher (655.38±362.99 vs 756.53±393.71 ng/mL; p=0.027) (Table 1).

There was no significant difference between groups for the in the 15-day mortality (p=0.134) and length of ICU stay (p=0.329). Chronic diseases was significantly higher in group 2 (p=0.042) (Table 2).

Table 1. Demographic and clinical characteristics of the patients

	Attribute	Total (n=48,%)	Group 1 (n=27,%)	Group 2 (n=21, %)	p
Demographic	Age (years)(mean±SD)	70.96±11.04	70.59±12.22	71.43±9.58	0.798
	Male gender	26 (54.2%)	15 (57.7%)	11 (42.3%)	0.557
Comorbidities	Malignancy	2 (4.2%)	0 (0%)	2 (100%)	0.500
	Respiratory disorder	6 (12.5%)	2 (33.3%)	4 (66.7%)	0.687
	Cardiovascular disorder	8 (16.7%)	3 (37.5%)	5 (62.5%)	0.727
	Hypertension	14 (30%)	5 (35.7%	9 (64.3%)	0.424
	Diabetes mellitus	13 (27.1%)	5 (38.5%)	8 (61.5%)	0.581
Laboratory values	Lactate dehydrogenase (U/L)	553.74±239.60	591.76±298.82	504.84±119.86	0.283
	C-reactive protein (mg/L)	104.58±52.16	113.67±57.09	92.87±43.57	0.172
	White blood cell count (×1000/MCL)	16.30±8.40	15.43±7.06	17.41±9.93	0.436
	Lymphocyte (K/uL)	2.25±6.97	1.5±4.05	0.67±0.86	0.480
	Lymphocyte (%)	8.67±13.96	8.48±12.64	8.91±15.81	0.789
	D-dimer (ng/mL)	3210.21±2123.8	3536.07±2357.55	2791.22±1745.59	0.232
	Ferritin (ng/mL)	655.38±362.99	756.53±393.71	525.32±276.65	0.027*
	Troponin (ng/L)	698.92±1319.28	642.15±995.94	771.9±1670.55	0.247
	Procalcitonin (ng/mL)	1.65±3.47	2.41±4.45	0.67±0.86	0.603
	Glucose (mg/dl)	188.06±47.37	193.16±41.49	181.17±54.68	0.397
	PaO2/FiO2 (mmHg)	69.1±18.5	71.1±17.7	66.5±19.6	0.328

Values were given as mean±standart deviation

Table 2. Comparison of primary outcomes between groups

Characteristics	Group 1 (n=27, %)	Group 2 (n=21, %)	p
Length of intensive care unit admission (days) (mean±SD)(n:20)	18.0±12.53	13.24±4.29	0.329
Days to death from the intensive care unit admission (days) (mean±SD)(n:28)	7.53±3.39	9.67±3.5	0.134
Intensive care unit mortality	19 (70.3 %)	9 (42.8%)	0.055
Need for invasive mechanical ventilation	22 (81.5%)	19 (90.5%)	0.381
Complications	8 (29.7%)	7 (33.3%)	0.784
Presence of comorbidities	10 (37%)	14 (66.7%)	0.042

CRP measurements in group 1 at 1st day and 3rd day were higher (p < 0.001). The mean CRP values on 3rd day were lower than the values on day 1 (91.0 ± 53.1 vs 159.4 ± 95.7; p=0.003). However, the changes in CRP values were not significantly different in the following measurements in group 1 (5th day and 7th day). On the other hand, the decrease in CRP levels in group 2 on 3rd day (p = 0.003) and on 5th day (p = 0.022) were found to be significant. For group 2, the difference in CRP levels were not significant at 5th and 7th days (p=0.585, p=0.282) (Table 3).

The mortality rate was significantly higher in patients who developed complications when compared to those who did not (p =0.007) (Table 4).

The rate of death was lower in group 2 (42.9% vs. 70.4%; OR, 3.17; 95% CI, 0.95 to 10.5) (Table 5). Complications related to corticosteroid treatment were hyperglycemia (11.1%, 23.8%), myocarditis (7.4%, 4.8%), pulmonary embolism (3.7%, 4.8%), sepsis (11.1%, 9.5 %) respectively and there was no statistical difference between the groups (Table 5).

Discussion

In this study, we aimed to evaluate the therapeutic effect of different doses of methylprenisolone in patients admitted to the intensive care unit due to COVID-19. We found that the rate of mortality was 3.17 times higher in the patient group who received pulse-steroids of 1 g methylprednisolone than 250 mg methylprednisolone group. In addition, inflammatory markers, such as ferritin and CRP, were lower especially in the first week in the group who were treated with pulse-steroids of 250 mg methylprednisolone. However, high-dose methylprednisolone did not show any significant benefit in terms of length of hospital stay, need for mechanical ventilation, and the mortality rates.

The Turkish Ministry of Health recommends the usage of anti-inflammatory agents in case of severe COVID-19 cases (4,8,10). Corticosteroids have taken their place as widely used anti-inflammatory agents in the treatment of COVID-19 in many healthcare centers with their easy availability and low-cost nature. After recent researches, corticosteroid use in COVID-19 as an anti-inflammatory agent is included in the literature nowadays. Corticosteroids are well known to be beneficial in stopping the inflammatory storm by suppressing pro-inflammatory gene expression and reducing cytokine levels, if used at the appropriate time (11-15). Parallel to this, it was reported in a study on the COVID-19 pandemic that methylprednisolone improved symptoms and pulmonary damage in severe and rapidly progressing ARDS but, it did not improve survival rates (13). In our study, we did not find a significant difference in the 15-day mortality and length of ICU stay rates of high-dose steroids.

There are studies not recommending the use of steroids as anti-inflammatory agents before COVID-19 and during the pandemic period, and there are also studies reporting beneficial results (16). It was reported in a letter that methylprednisolone use (1-2 mg/kg/day for 5-7 days) in 26 patients who had severe COVID-19 was associated with better radiographic findings and shorter durations of supportive oxygen treatments (17). In another study that included 463 hospitalized patients mortality rate decreased with a rate of 41.8% in those who received steroid treatment compared to those who did not receive steroid treatment (18). Some studies recommend steroids in the inflammatory phase of the ARDS because of their possible beneficial effects (19-21). Pinzon et al. (5), ambispective cohort study with high dose dexamethasone and methylprednisolone, had lower mortality and less hospital stay in the methylprednisolone group. This seems to correspond to the dose-dependent effect of methylprednisolone, which resulted in

Table 3. The laboratory parameters of patients after steroid treatment

	Group 1 (n=27)							Group 2 (n=21)						
	1 day	3 day	1-3 day	5 day	3-5 day	7 day	5-7 day	1 day	3 day	1-3 day	5 day	3-5 day	7 day	57 day
	Mean±SD	Mean±SD	*P* value	Mean±SD	*P* value	Mean±SD	*P* value	Mean±SD	Mean±SD	*P* value	Mean±SD	*P* value	Mean±SD	*P* value
LDH (Lactate Dehydrogenase) (U/L)	529.2±224.5	548.3±135.1	0.449	713.6±668.2	0.254	561.5±324.1	0.184	490.5±163.0	520.3±147.8	0.217	473.0+162.8	0.183	551.7±180.6	0.065
C-reactive Protein (CRP) (mg/L)	159.4±95.7	91.0±53.1	<0.001	105.9±62.1	0.585	98.5±82.7	0.982	144.6±60	92.4±55.6	0.003	54.9±46.5	0.022	93.3±149.6	0.282
Fibrinogen (gr/L)	4.8±0.9	4.5±0.9	0.292	3.9±1.2	0.087	4.0±1.5	0.894	4.9±1.2	4.5±1.2	0.147	4.1±1.2	0.166	4.2±1.5	0.585
White Blood Cell (WBC) count (×1000/MCL)	11.5±6.1	13.8±7.7	0.489	18.2±11.4	0.026	15.5±7.8	0.547	14.0±9.8	15.8±7.4	0.146	18.6±10.4	0.054	19.1±14.1	0.446
Lymphocyte (K/ul)	1.3±2.9	1.6±5.0	0.009	1.9±5.3	0.060	0.9±0.7	0.661	0.6±0.2	0.6±0.3	0.932	3.6±10	0.303	1.3±2.5	0.252
Lymphocyte (%)	10.2±13.0	7.9±14.0	0.047	8.5±13.1	0.830	10.9±16.7	0.210	5.9±3.3	5.1±2.7	0.128	8.6±16.8	0.222	5.0±2.8	0.890
D-Dimer (ng/mL)	2866.0±3465.4	3025.2±2711.1	0.524	4344.2±2986.6	0.239	4942.4±3499.5	0.792	1798.5±2202.6	1869.8±1277.9	0.116	3412.3±2705.1	0.052	3900.5±2975	0.831
Ferritin (ng/mL)	768.6±449.7	640.2±436.6	0.084	689.5±524.4	0.619	633.8±502.9	0.388	535.8±267.6	579.2±395.3	0.486	465.7±251.6	0.042	448.6±269.7	0.413
Troponin (ng/L)	568.8±2054.0	281.5±542.6	0.324	809.2±2412.1	0.297	1075.6±3411.5	0.759	132.1±236.5	543.1±1910.3	0.094	619.1±1252.1	0.355	1390.0±4163.9	0.709
Procalcitonin (ng/mL)	0.7±1.5	0.6±1.4	0.872	3.0±11.3	0.396	2.3±5.7	0.656	0.7±1.3	0.4±0.8	0.189	0.2±0.3	0.197	0.4±0.7	0.512
Glucose (mg/dl)	188.2±72.8	191.9±67	0.411	179.6±53.6	0.928	212.9±68.1	0.121	187.9±80.2	199.5±71.0	0.151	144.9±71.2	0.010	207.0±112	0.099

Table 4. Comparison of survivors and non-survivors

Characteristics	Non-survivors (n=28, %)	Survivors (n=20, %)	p
Need for invasive mechanical ventilation	28 (100%)	13 (65%)	<0.001
Presence of diabetes mellitus	9 (32.2%)	5 (25%)	0.591
Complications	13 (46.5%)	2 (10%)	0.007
Presence of comorbidities	14 (50%)	10 (50%)	0.000

Table 5. The effect of corticosteroid use on intensive care unit outcome and the factors associated with mortality

Characteristics	Group 1 (n=27,%)	Group 2 (n=21,%)	Odds Ratio	p	Confidence Interval (95%)
Intensive care unit mortality	19 (70.4)	9 (42.9)	3.17	0.055	0.958 - 10.5
Need for invasive mechanical ventilation	22 (81.5)	19 (90.5)	0.463	0.381	0.080 – 2.67
Sepsis	3 (11.1)	2 (9.5)	1.19	0.841	0.18 – 7.84
Myocarditis	2 (7.4)	1 (4.8)	1.60	0.704	0.135 – 18.9
Pulmonary Emboli	1 (3.7)	1 (4.8)	0.769	0.884	0.045 – 13.1
Hyperglycemia	3 (11.1)	5 (23.8)	0.400	0.727	0.083 – 1.91

a more significant reduction in the inflammatory response (CRP, LDH, and D-dimer). The RECOVERY trial and the other studies examined the effect of dexamethasone on the clinical symptoms of hospitalized COVID-19 patients (6,22). The RECOVERY study showed a lower 28-day mortality rate with dexamethasone use, particularly in patients receiving supplemental oxygen and invasive mechanical ventilation.(6). In our study, we found a significant decrease in CRP and lymphocyte counts on the 3rd day in the group administered 1 g methylprednisolone. However, there was no difference between mortality rate, hospital stay and need for ventilator. The fact that the levels of these markers were higher in group 1, may be considered the reason why complications were higher in this group.

Corticosteroids have many side effects. Some of the moderate and long-term side effects are increased hyperglycemia (22,23,24), increased cardiovascular risk, and bacterial infection risk. No significant differences were detected between the groups in terms of complications. Complications were more commonly seen in group 1, although not at statistically significant levels. Only hyperglycemia was proportionally higher in group 2. Hyperglycemia may be associated with higher diabetes in group 2. There was a relationship between the complications and outcomes. In case of complications, the probability of mortality increased.

This study had several limitations, including the small sample size in the groups and as a single-center retrospective study. The groups consisted of only patients admitted to ICU, limited data on complications were available, and laboratory data features were included. Randomized controlled trials with larger sample sizes are needed to evaluate the effectiveness of different methylprednisolone doses in COVID-19 ARDS.

Conclusion

In the present study, the efficacy and effects of two different pulse-steroid treatment protocols on mortality were evaluated in severe COVID-19 patients with MAS and ARDS. We found no significant difference in mortality and length of hospital stay between patients treated with 250 mg and 1 g methylprednisolone. For this reason, we support the use of pulse-steroid treatment with 250 mg methylprednisolone rather than a pulse of 1 gr when pulse steroid treatment is considered.

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AUTHOR CONTRIBUTIONS:

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