DOI: 10.4149/BLL_2021_126

Bratisl Med J 2021; 122 (11)
793 – 798

CLINICAL STUDY

Efficacy of pulse steroid therapy in patients critically ill with COVID-19

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ABSTRACT
OBJECTIVES: The aim of this study was to determine the efficacy of pulse steroid therapy administered to patients critically ill with COVID-19 progressing into severe pneumonia.
METHODS: A total of 600 patients included in this retrospective study were divided into three groups. Group 1 (control group): 200 patients who did not receive steroid treatment, Group 2: 200 patients who received dexamethasone 1x8 milligram (mg) or methylprednisolone 1x80 mg, Group 3: (pulse steroid therapy group): 200 patients who received 1 g methylprednisolone followed by 1x80 mg methylprednisolone. Demographic and laboratory data were recorded.
RESULTS: Mortality rates in groups 1, 2 and 3 were 77 %, 53.55 %, and 58.5 %, respectively. The ratios of intubated patients in groups 1, 2 and 3 were 70 %, 45.5 % and 56 %, respectively. The numbers of patients whose D-dimer values were above 2,250 ng/mL (cut-off value for D-dimer in this study) in groups 2, 1 and 3 were 65, 107, and 105, respectively.
CONCLUSION: Pulse steroid therapy does not shorten the duration of hospital stay, does not reduce the need for intubation and increases the risk of thrombosis by significantly increasing the level of D-dimer among patients critically and severely ill with COVID-19 *(Tab. 4, Fig. 3, Ref. 20)*. Text in PDF *www.elis.sk*
KEY WORDS: COVID-19, pulse steroid therapy, thrombosis, d-dimer, corticosteroid.

Introduction

The novel coronavirus disease induced by SARS-CoV2 virus is named COVID-19 and was announced as a pandemic by the World Health Organization on March 11, 2020. The diagnosis is based on polymerase chain reaction (PCR) test and computed tomography (1). Various antiviral (favipiravir, remdesivir, hydroxychloroquine), and anti-inflammatory drugs (steroids, tocilizumab, anakinra), as well as anticoagulants and fibrinolytics are used in the treatment of COVID-19 disease (2, 3).

The characteristics of COVID-19 progressing into severe pneumonia are increased oxygen need and increased c-reactive protein (CRP). This situation is interpreted as a result of a possible cytokine storm syndrome (CSS) (4). A progressive inflammatory process with a progressing decrease in the number of lymphocytes and increase in the number of neutrophils plays an important role in the pathogenesis of COVID-19. Thus, neutrophil/lymphocyte ratio (NLR) has an important place in the prognosis.

Pathological hyperactivity in the immune system characterized by cytokines and chemokines that are excessively secreted from immune system cells due to the uncontrolled activation caused by cytokines in inflammation focused on immune cells is called cytokine storm syndrome. High levels of interleukins (IL) such as IL-1 β, IL-1RA, IL-6, IL-8, IL-9, IL-10, IL-17, vascular endothelial growth factor (VEGF), tumor necrosis factor alpha (TNF-α), pro-inflammatory chemokines and cytokines were observed in COVID-19 patients. CSS increases the risks of acute respiratory distress syndrome (ARDS) and multiple organ failure (5). Excessive hypercoagulability and microvascular thrombosis seen in the pulmonary vascular bed due to CSS in COVID-19 patients are also responsible for morbidity and mortality.

One of the treatment modalities commonly used in CSS are glucocorticosteroids (GCC). A systematic review including 25 protocols and 41 studies has shown that GCCs are used in different doses and protocols in CSS induced by COVID-19 (6). However, glucocorticosteroids may increase the risk of insulin resistance, cardiovascular disease, and bacterial infection (7, 8, 9). The most dangerous side effect of GCCs are thrombotic and thromboembolic complications that may cause multiple organ failure, which is included in the pathogenesis of COVID-19 disease and a bad prognosis criterion. Especially heparin with low molecular weight and anticoagulants should be added to the treatment protocol in the treatment of patients with COVID-19 progressing into severe pneumonia to prevent these complications. Steroid-induced myopathy is another side effect of a 3–4-week corticosteroid treatment (10). Myopathy and severe muscle atrophies become a major problem in a prolonged treatment of COVID-19 (11).

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The aim of this study was to determine the efficacy of pulse-steroid therapy administered to patients hospitalized in an intensive care unit (ICU) with COVID-19 progressing into severe pneumonia or ARDS.

Method

This retrospective, single-center study included patients who were hospitalized in the intensive care unit of our hospital between April 1, 2020 and February 1, 2021, who were aged older than 18 years, tested positive with the COVID-19 polymerase chain reaction test (COVID-19 PCR), and had pneumonia involvement in at least 4 lung lobes on radiological imaging. The approval of the local ethical committee was obtained for the study. The permission to access the data of the patients was obtained from the surviving patients and relatives of deceased patients.

The data of 1,271 patients who were treated in the intensive care were screened. A total of 600 patients included in the study were divided into three groups. Group 1 (control group): 200 patients who did not receive steroid treatment, Group 2: 200 patients who received dexamethasone 1x8 milligram (mg) or methylprednisolone 1x80 mg, Group 3: 200 patients who received 1 g methylprednisolone followed by 1x80 mg methylprednisolone. Patients who tested negative with the COVID-19 PCR test, were treated with steroids for a shorter period than 4 days, received another anti-inflammatory or anti-cytokine drug (tocilizumab, anakinra) or intravenous immunoglobulin during the steroid treatment in the first four days of the intensive care stay, received methylprednisolone with a dose different from the pulse steroid therapy dose of 1 g for 3 days were excluded from the study. Blood, urine, and sputum cultures of all patients included in the study were collected on the first day of hospitalization. Accordingly, patients who had a secondary infection other than COVID-19 during the hospitalization in the intensive care were excluded from the study. All patients included in the study received the same antiviral treatment consisting of favipiravir in the maximal tolerable dose of 2x1,600 mg and maintenance dose of 2x200 mg.

The age, sex, comorbidities, length of stay in ICU, state of leaving the ICU (dead or alive), need for non-invasive ventilation (NIV) or intubation during the intensive care stay, need for additional anti-cytokine drugs such as tocilizumab or anakinra after the first 4 days of steroid treatment, and the fact whether there was bacteria reproduction in the blood and sputum culture during the intensive care stay were recorded. C-reactive protein (CRP), D-dimer, ferritin, neutrophil count, lymphocyte count, neutrophil/lymphocyte ratio, platelet count, glucose, creatinine values in the blood samples taken from the patients in Group 2 and Group 3 before the administration of steroid treatment and on the 4th day of the steroid treatment were recorded. The same laboratory values of the Group 1 were recorded based on the blood samples taken on the first day of the intensive care admission and on the 4th day of the intensive care stay.

Statistical methods

Data obtained were statistically analyzed using SPSS (Ver: 25) computer program. Mean, standard deviation, and median values were used to present descriptive analyses. Categorical variables were compared using Pearson Chi-Square Test. The changes in the values measured were examined between the groups using repeated measures analysis. ROC analysis was performed to determine the cut-off value for significant values of D-dimer and NLR parameters. The results with a p value below 0.05 were considered statistically significant.

Tab. 1. Demographic parameters and some clinical features.

		Number	%
Gender	Female	247	41.17
	Male	353	58.83
Comorbidity	Absent	114	19.00
	Present	486	81.00
Ventilation support	Mask or nasal O2	151	25.17
	Non-invasive ventilation	106	17.67
	Intubation	343	57.17
Additional anti-cytokine use	Absent	566	94.33
	Present	34	5.67
Bacterial growth	Absent	427	71.17
	Present	173	28.83

Results

Of the participants, 247 were female and 353 were male. While 486 had a comorbidity, 144 did not have any comorbidities. Of the patients, 343 needed an intubation while 106 needed NIV. While 34 patients needed anti-cytokine drugs after a 4-day steroid treatment, 566 did not need it. Bacterial reproduction was observed in 173 patients under steroids while no reproduction was observed in 427 patients (Tab. 1).

The mean age of the patient group without steroid treatment (Group 1) was 73.77 ± 10.18 years, and the mean duration of hospital stay in living patients was 12.87 ± 5.84 days. The mean CRP value was 136.25 ± 94.64 mg/L on the 1st day and 155.78 ± 102.65 mg/L on the 4th day. The mean D-dimer value was 2550.16 ± 3187.02 ng/mL on the 1st day and 3504.33 ± 3595.43 ng/mL on the 4th day. The mean NLR value was 17.84 ± 16.42 on the 1st day and 30.65 ± 44.05 on the 4th day.

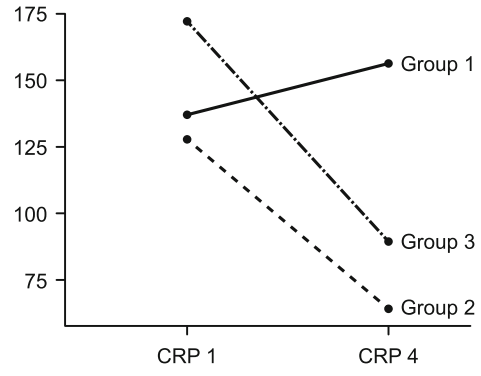

Fig. 1. Comparing the CRP changes between groups.

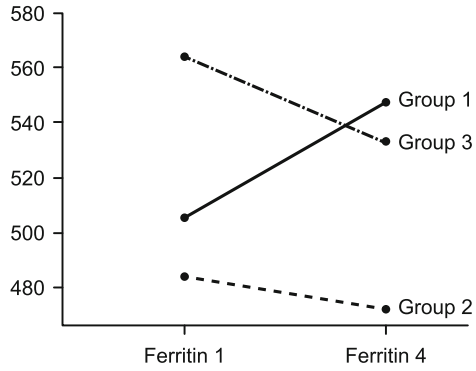

Fig. 2. Comparing the ferritin changes between groups.

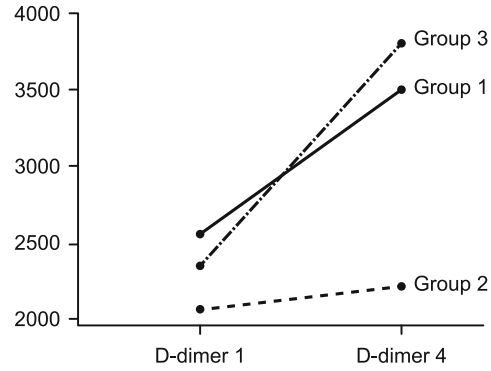

Fig. 3. Comparing the d-dimer changes between groups.

The mean age of the patients in Group 2 was 7133 ± 11.10 years, and the mean duration of hospital stay in living patients was 11.54 ± 5.98 days. The mean CRP value of the patients in Group 2 was 127.13 ± 87.48 mg/L on the 1st day and 63.72 ± 53.29 mg/L on the 4th day. The mean D-dimer value was 2052.98 ± 2454.38 ng/mL on the 1st day and 2199.94 ± 2540.79 ng/mL on the 4th day. The mean NLR value was 19.59 ± 16.46 on the 1st day and 24.47 ± 24.84 on the 4th day.

The mean age of the patients in Group 3 who received 1 g of methylprednisolone followed by 1x80 mg of methylprednisolone for 3 days was 66.87 ± 12.24 years, and the mean duration of hospital stay in living patients was 12.06 ± 6.85 days. The mean CRP value of the patients in Group 3 was 171.19 ± 110.47 mg/L on the 1st day and 89.39 ± 71.49 mg/L on the 4th day. The mean D-dimer value was 2339.91 ± 2772.75 ng/mL on the 1st day and 3806.64 ± 4029.60 ng/mL on the 4th day. The mean NLR val-

Tab. 2. Comparing the changes in laboratory parameters between groups.

	Group 1		Group 2		Group 3		p
	Mean	SD	Mean	SD	Mean	SD	
Creatinine* (mg/dL)	1.74	±1.79	1.42	±1.22	1.14	±1.04	**0.044**
Creatinine** (mg/dL)	1.81	±1.73	1.31	±1.21	1.33	±1.41	
CRP* (mg/L)	136.25	±94.64	127.13	±87.48	171.19	±110.47	**< 0.001**
CRP** (mg/L)	155.78	±102.65	63.72	±53.29	89.39	±71.49	
Ferritin* (µg/L)	505.03	±233.77	483.86	±208.54	563.50	±278.94	**< 0.001**
Ferritin** (µg/L)	546.70	±207.64	471.80	±199.18	532.42	±191.91	
D-dimer* (ng/mL)	2550.16	±3187.02	2053.98	±2454.38	2339.91	±2772.75	**0.001**
D-dimer** (ng/mL)	3504.33	±3595.43	2199.94	±2540.79	3806.64	±4029.60	
Platelet*	243.09	±122.27	253.28	±103.00	257.28	±93.35	**0.005**
Platelet**	234.37	±123.13	275.22	±122.87	278.60	±129.11	

Repeated Measurement Analysis, p < 0.05: significant, Crp: c-reactive protein SD: standard deviation, *: day 1 parameters, **: day 4 parameters

Tab. 3. Comparing the demographic and some clinical features between groups.

		Group 1		Group 2		Group 3		p
		n	%	n	%	n	%	
Gender	Female	93	46.50	89	44.50	65	32.50	**0.009**
	Male	107	53.50	111	55.50	135	67.50	
Comorbidity	Absent	33	16.50	27	13.50	54	27.00	**0.001**
	Present	167	83.50	173	86.50	146	73.00	
State of leaving the ICU	Alive	46	23.00	93	46.50	83	41.50	**< 0.001**
	Dead	154	77.00	107	53.50	117	58.50	
Ventilation support	Mask-Nasal O_2	46	23.00	64	32.00	41	20.50	**< 0.001**
	NIV	14	7.00	45	22.50	47	23.50	
	Intubation	140	70.00	91	45.50	112	56.00	
Additional anti-cytokine use	Absent	196	98.00	197	98.50	173	86.50	**< 0.001**
	Present	4	2.00	3	1.50	27	13.50	
Bacterial growth	Absent	141	70.50	134	67.00	152	76.00	0.134
	Present	59	29.50	66	33.00	48	24.00	

Chi-square test, n: Number, ICU: intensive care unit, NIV: non-invasive ventilation, p < 0.05: significant

ue was 19.71 ± 16.71 on the 1st day and 31.43 ± 52.04 on the 4th day.

Glucose, creatinine, CRP, ferritin, D-dimer, neutrophil, lymphocyte, NLR and platelet values measured on the 1st and 4th days were compared between three groups. There was a significant difference between the groups in terms of creatinine, CRP (Fig. 1), ferritin (Fig. 2), D-dimer (Fig. 3), and platelet values ($p < 0.05$). When comparing the creatinine values on the 1st and 4th days, the creatinine value increased from 1.74 mg/dL to 1.81 mg/dL in Group 1, decreased from 1.42 mg/dL to 1.31 mg/dL in Group 2, and increased from 1.14 mg/dL to 1.33 mg/dL in Group 3 ($p < 0.05$).

Tab. 4. Comparing the D-dimer and NLR values according to the cut-off values between groups.

		Group 1		Group 2		Group 3		Total	
		n	%	n	%	n	%	n	%
D-dimer*	< 2250	93	46.50	135	67.50	95	47.50	323	53.83
	> 2250	107	53.50	65	32.50	105	52.50	277	46.17
NLR*	< 9.75	42	21.00	49	24.50	28	14.00	119	19.83
	> 9.75	158	79.00	151	75.50	172	86.00	481	80.17

NLR: neutrophil/lymphocyte ratio, *: day 4 parameters

The mean platelet value in Group 1 was 243.09 x10³ on the 1st day and 234.37 x10³ on the 4th day. The mean platelet value in Group 2 was 253.28 x10³ on the 1st day and 471.80 x10³ on the 4th day. The mean platelet value in Group 3 was 257.28 x10³ on the 1st day and 278.60 x10³ on the 4th day ($p < 0.05$).

The intergroup analyses of the laboratory parameters on the 1st and 4th days are presented in Table 2.

The three groups were compared in terms of sex, comorbidity, the state of leaving the intensive care, type of ventilation support, necessity of additional anti-cytokine drugs, and bacterial reproduction. The ratios of male and female sexes were found to be 46.5 % and 53.3 % in Group 1, respectively, 44.5 % and 55.5 % in Group 2, respectively, and 32.5 % and 67.5 % in Group 3, respectively. The presence of comorbidity was 83.5 % in Group 1, 68.5 % in Group 2, and 73 % in Group 3. While 77 % of the patients in Group 1 died, the mortality rate was 53.55 % in Group 2 and 58.5 % in Group 3. As to the type of ventilation support, 70 %, 45.5 % and 56 % of patients in groups 1, 2 and 3 were intubated, respectively. The number of patients who needed the administration of tocilizumab or anakinra after the 4-day treatment was higher in Group 3 as compared to other groups (Tab. 3).

The predictability of D-dimer and NLR values relative to mortality was examined with ROC analysis, and the cut-off value was determined for significant results. Considering the D-dimer cut-off value of 2,250 ng/mL, sensitivity specificity, PPD and NPD were 38.62 %, 74.77 %, 72.28 %, and 41.71 %, respectively. Regarding the NLR cut-off value 9.75, sensitivity, specificity, PPD and NPD were 74.60 %, 36.94 %, 66.82 % and 46.07 %, respectively. When the groups were compared based on these cut-off values for D-dimer and NLR values on the 4th day of the treatment, the numbers of patients whose D-dimer values were above 2,250 ng/mL in groups 2, 1 and 3were 65, 107, and 105, respectively. The number of patients with the NLR value above 9.75 was 158 in Group 1, 151 in Group 2, and 172 in Group 3 (Tab. 4).

Discussion

Although corticosteroids are commonly used in the treatment of COVID-19, there are ongoing discussions on the necessary dose to be applied and pulse-steroid practices with these drugs. The groups in this retrospective study were tried to be homogenized as much as possible. The differences between two treatment groups receiving corticosteroids at different doses (Group 2 and Group 3) and the control group (Group 1) without a corticosteroid treatment were revealed. It is believed that the results obtained in this study will change the perspective of clinicians about pulse steroid therapy in COVID-19 patients.

The increase in thrombin production and decrease in fibrinolysis due to endothelial cell dysfunction induced by severe infections like COVID-19 are observed (12). The increase in blood viscosity and hypoxia-dependent transcription due to hypoxia induced by COVID-19 also increases the risk of thrombosis (13). The most important indicator of thromboembolic events that are already considered an important cause of mortality in the currently known pathogenesis of COVID-19 in the clinical follow-up is the increase in D-dimer. The D-dimer values increased the most in Group 3, i.e., in the group that was administered with pulse-steroid therapy during the 4-day follow-up in this study. This is the most important result of this study.

Despite the absence of a statistically significant difference, NLR values increased in all three groups while the lowest rate of increase was seen in Group 2 ($p > 0.05$). The decrease in the CRP values in Group 2 and Group 3 are considered the most definite effect of corticosteroids. However, there are no major differences in the response to CRP suppression in terms of using low dose of steroid and pulse steroid treatment, while both doses suppress the CRP values to the same extent and time in clinical usage.

The fact that there was no significant difference between the groups in terms of the duration of hospital stay of surviving patients shows that pulse steroid treatment does not shorten the duration of hospital stay in patients severely or critically ill with COVID-19. The mortality rate and need for invasive or non-invasive ventilation were higher in Group 3 than in Group 2 ($p < 0.05$). Another remarkable result of this study is that the need for anti-cytokine treatment (tocilizumab or anakinra) after the first 4 days was found at a higher rate in the pulse steroid therapy group although a similar achievement of suppressing CRP was reached in both treatment groups ($p < 0.05$. The reason for this situation is that in this clinic, the decision for using pulse steroid treatment was generally taken in patients with higher basal CRP levels. This is the reason why the CRP levels were high among the patients who were administered with pulse-steroid treatment on the 1st day. A limitation of this study is that the homogenization was not sufficient among the groups in terms of CRP due to this administration. Therefore, it is normal that the need for anti-cytokine in the continuation of the treatment is higher in Group 3. Although bacterial reproduction

was higher in Group 3 in the continuance of the treatment, this was not statistically different from the other groups ($p > 0.05$).

There are single-center studies and reviews with limited numbers of patients with different results regarding the corticosteroid treatment modalities applied to COVID-19 patients in the literature (14, 15, 16, 17). It can be indicated that the common features of these studies is stating the "need for more relevant studies", different doses of corticosteroids, and heterogeneous groups.

In the case series by Edalatifard et al including 68 patients, a group was administered with methylprednisolone therapy at a dose of 250 mg/day for 3 days and the mortality rate was lower and recovery duration was shorter in this group as compared to the control group (18). The contradicting result with the current study is the decrease in the D-dimer level in the methylprednisolone group. Although different doses of steroids were used for Group 2 and Group 3, there was an increase in D-dimer levels in both groups. The dose of corticosteroid used in the study by Edalatifard et al was between the doses of corticosteroid administered to the patients in Group 2 and Group 3 in this study. However, the patient group included in their study had some differences as compared to the present study. The patient groups in the study by Edalatifard et al consisted of patients in an early pulmonary involvement phase of COVID-19. The patients in the present study were more critically ill patients with pulmonary involvement that had already progressed at least into 4 lung lobes. Considering the effect of the severity of infection on the D-dimer level, it can be concluded that the changes in D-dimer in both studies are related to the patient population.

There are many studies on using D-dimer and NLR parameters for assessing the prognosis and predicting mortality in patients with COVID-19 in the literature, and both parameters have an important place in the follow-up of critical patients (19, 20). The D-dimer and NLR cut-off values were determined relative to mortality predictability, and the numbers of patients with values above these cut off values were analyzed in this study. Accordingly, the highest number of patients with values exceeding the cut off value determined for D-dimer (2,250 ng/mL) was in Group 1 while 52.5 % of the patients in Group 3 and 32.5 % of the patients in Group 2 had values above this cut-off value. The highest ratio of the patients with values exceeding the cut-off value determined for NLR belonged to Group 3. The results regarding both values used for the prognosis and mortality predictions were worse in the pulse steroid therapy group.

In the study by Mareev et al conducted on 34 patients, the steroid group received methylprednisolone for 3 days at a dose of 1 g/day and were maintained on dexamethasone at a dose of 8 mg/day, and this group was compared with the control group who did not receive steroids (15). The results of this study using a dose similar to that used in Group 3, were similar to the present study. In the study by Mareev et al, there was a significant increase in D-dimer, NLR, neutrophil count and platelet count and a significant decrease in CRP in the corticosteroid group ($p < 0.05$). A significant difference was found between the groups in terms of the changes in creatinine, ferritin, CRP, D-dimer, and platelet count in this study ($p < 0.05$). It would not be appropriate to put an interpretation on creatinine due to the insufficient homogenization in the groups in terms of creatinine value. However, the analysis results obtained with other parameters mainly support the study by Mareev et al. It was also emphasized in their study that using high dose of corticosteroid increases the risk of thrombosis.

This study has some limitations. The first limitation is that this is a retrospective study. There might be a selection bias due to the retrospective design of the study. Another limitation is that the homogenization was insufficient in terms of creatinine and CRP among the groups due to the high number of parameters examined.

Conclusion

In conclusion, it has been found in this study that pulse steroid therapy does not shorten the duration of hospital stay, does not reduce the need for intubation and increases the risk of thrombosis by significantly increasing the level of D-dimer among patients hospitalized in the intensive care unit for being critically or severely ill with COVID-19. Although positive results were obtained with pulse-steroid treatment when administered in early pulmonary involvement of COVID-19, starting the pulse-steroid treatment in patients with a progressed pulmonary involvement needs to be seriously questioned. We do not recommend starting a pulse steroid treatment routinely in the patients severely ill with COVID-19 in ICU.

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Received April 25, 2021.
Accepted May 4, 2021.