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Pulse dose glucocorticosteroid therapy in COVID-19 pneumonia patients in an intensive care unit

İlkay Ceylan[1], Halil Erkan Sayan[1], Korgün Ökmen[1], Gürcan Güler[1], Ebru Karakoç[2]

[1]Department of Anesthesiology and Reanimation, University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey
[2]Department of Anesthesiology and Reanimation, Faculty of Medicine in Eskişehir Osmangazi University, Eskişehir, Turkey

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Corresponding author:
İlkay Ceylan.
E-mail: ceylanilkay@yahoo.com;
ORCID: 0000-0003-3306-3107

Abstract

Introduction: Coronavirus pneumonia occurs with severe lung tissue damage and rapid activation of cytokines and chemokines, called "cytokine storm," and simultaneously with a high risk of thrombosis and thromboembolism. There is no specific therapy for new coronavirus infection (COVID-19) also for cytokine storm. Therefore it is necessary to search for effective anti-inflammatory treatment. The aim of this study is to investigate the efficacy of pulse-dose glucocorticosteroid use in the treatment of COVID-19 patients hospitalized in the intensive care unit.

Material and methods: The efficacy of pulse dose glucocorticosteroid therapy with 250-1000 mg for three days methylprednisolone 1 mg/kg for 5-7 days more in 144 patients in an intensive care unit with severe coronavirus pneumonia was studied in a retrospective analysis of 55 patients in the standard dose glucocorticosteroid (1 mg/kg/day methylprednisolone) group. The study's primary endpoint was mortality in ICU, and the secondary endpoint was the effects on inflammatory markers. The treatment groups' disease severities were initially the same.

Results: Pulse dose glucocorticosteroid therapy did not reduce overall intensive care mortality but also increased it. C-reactive protein and fibrinogen levels decreased statistically significantly from the 1st day of admission, but D-dimer did not change statistically significantly. Neutrophilia was seen after steroid use, but it was significantly higher in the pulse dose group. Recovery in the pulse dose group was slower (median ICU stay was 12 days in the pulse dose group versus 10 days in the standard dose group, p=0.002)

Conclusion: Pulse dose glucocorticosteroid therapy has a rapid anti-inflammatory effect but did not reduce intensive care mortality, also increased intensive care length of stay in our cohort.

Key words: pulse dose glucocorticosteroids, critical care, mortality, thrombosis, D-dimer, COVID-19

Introduction

Severe forms of corona virus disease 2019 (COVID-19) are accompanied by viral pneumonia with total damage of small pulmonary vessels, bronchioles and alveoli. Progressive systemic inflammation plays a significant role in the pathogenesis of COVID-19. Pathological immune system hyperreactivity, manifested by uncontrolled cytokine activation of immune cells and release of cytokines and chemokines by the latter, was called "cytokine storm" [1]. Cytokine storm increases the risk of acute respiratory distress syndrome and can lead to multiple organ failure. Thus, reducing systemic inflammatory response activity is one of the urgent problems of treatment of patients with COVID-19 since this process triggers pathophysiological mechanisms of the coagulation cascade and lung damage [2].

Research on the management of patients with COVID-19 related cytokine storm phenomena prioritizes immunosuppressive preamplifiers from monoclonal antibody groups. IL-6 blockers (tocilizumab and sarilumab) and IL-1 inhibitors (anakinra) are recommended for cytokine storm treatment in severe COVID-19 [3]. The recommendations of the Ministry of Health of the Republic of Turkey using high-dose glucocorticosteroid (GCS) (methylprednisolone 30 mg/kg/day, intravenously) as a proactive anti-inflammatory

therapy [4]. It has been shown that early use of high-dose methylprednisolone at the onset of respiratory insufficiency can slow the progression of the process in patients with COVID-19. At the same time, studies have found no pronounced positive effect of GCS use in the management of patients with viral lung lesions [5]. It was noted that GCS use could cause increased lethality and prolong of the disease and causative prolongation of the viral load period. It should be noted that the vast majority of studies are based on the results of patients with influenza, SARS-CoV1 and MERS-CoV [5].

GCS is one of the most popular anti-inflammatory agents, with a long history of use; the effectiveness of GCS therapy in patients with COVID-19 pneumonia and cytokine storm is of scientific interest and practical significance. This study aimed to evaluate the efficacy of pulse dose steroid therapy with methylprednisolone on inflammatory markers and mortality in ICU patients with COVID-19 pneumonia.

Material and methods

We performed a single center, retrospective study between 12 November 2020 and 31 December 2020. The study included 197 patients hospitalized at the Republic of Turkey Health Sciences University, Bursa Yüksek Ihtisas Training and Research Hospital COVID-19 ICU with a proven diagnosis of coronavirus pneumonia related respiratory failure and cytokine storm. The diagnosis in all cases was confirmed by detection of SARS-CoV-2 RNA by polymerase chain reaction (PCR).

Treatment protocol

Patients whose oxygen saturation was below 90 or whose respiratory rate was above 35/min with a reservoir oxygen mask under a flow of 15 liters/min were diagnosed as COVİD-19 pneumonia related respiratory failure and admitted to the intensive care unit as stated in local guidelines [4]. Initially, standard therapy was prescribed with hydroxychloroquine and favipiravir. In addition, all patients received anticoagulant therapy with LMWH and antithrombotic therapy with ASA from the first day of hospitalization, as stated in local guidelines. If necessary, antibiotic therapy was added to the therapy.

Cytokine storm defined at least two hyperferritinemia, hyperfibrinogenemia, high levels of D-dimer, and CRP with respiratory failure. The treatment decision with one dosage or another was exclusively at the discretion of the treating medical team. The attending physicians decided to treat patients in cytokine storm with high doses of GCS: methylprednisolone 250-500-1000 mg intravenously for 3-5 days with the transition to methylprednisolone 1 mg/kg/day twice a day for 5-7 days or standard dose of GCS with methylprednisolone 1 mg/kg/day for 7-10 days [4]. It was decided to use a pulse or standard dose drugs based on inflammatory markers of cytokine storm rather than oxygenation status (Table 1).

Table 1 COVID-19 Glucocorticosteroid treatment protocol in macrophage activation syndrome or severe respiratory insufficiency recommended by MOH of Republic of Turkey (9 October 2020)

	Standard dose	Pulse Dose
Methylprednisolone*	0,5-1 mg/kg/day (10 days)	>250 mg/day (3-5 days) than 1 mg/kg/day (7 days)
Dexamethasone	6 mg/day (10 days)	
*only methylprednisolone used patients included the study		

We recorded demographic data, acute physiologic and chronic health evaluation APACHE2 score, comorbidities, length of stay in ICU, need for invasive ventilation and intubation, death in ICU and dose of GCS were given. Other specific anti-inflammatory therapies like monoclonal antibodies, plasmapheresis or IVIG were also noted. The duration of follow-up in both groups was until deceased or discharged from ICU.

Neutrophil and lymphocyte count, glomerular filtration rate, creatinine kinase, lactate dehydrogenase, ferritin, international normalized ratio (INR), D-dimer, prothrombin time (PT) and partial thromboplastin time (aPTT), C-reactive protein (CRP) levels were recorded before the initiation of GCS therapy (1st day), 4th and 7th days of GCS therapy. Due to the limited availability of interleukin 1 and 6 diagnostic kits in the hospital, these parameters are not routinely studied. Therefore, they were not included in the study protocol.

Ethics

The study was initiated after obtaining the ethics committee approval no. 2011-KAEK-25 2021/03-28 from TC SBU Bursa Yüksek Ihtisas TRH. The need for informed consent from individual patients from waived due to its retrospective design.

Statistical analysis

Data were analyzed with Statistical Package for the Social Sciences (SPSS) for Windows 22.0 (IBM Corp., Armonk, NY) package program.

The normality of the data was tested using the Shappiro-Wilk test. Quantitative data description is presented as the median and interquartile range (median and 25%; 75%). Qualitative data are presented as absolute and relative values. The significance of differences between groups in qualitative characteristics was assessed using the $\chi 2$ criterion and two-sided Fisher exact test.

A comparison of quantitative characteristics between the groups was performed using the Mann-Whitney test. The critical level of significance for statistical testing hypotheses was taken to be <0.05.

Results

Characteristics of the cohort

We recruited 197 adult patients between the specified dates. The mean age was 64.19±13.28, ranging from 25 to 92 years. 114 were men (57.86%) and 83 were women (42.13%).

Hypertension and diabetes mellitus were present in a (n:98) 49.74% and (n:50) 25.83% of the patients respectively. Other comorbid conditions were infrequent (less than 10%) and did not show any statistically significant differences between groups. The initial characteristics of the examined patients are presented in Table 2.

Study endpoint

We aimed to investigate whether pulse dose steroid was effective in COVID-19 ICU patients or not. In our cohort, pulse dose steroids did not decrease the mortality in ICU; also, standard dose steroids had a better survival ratio in ICU (Table 3). Endotracheal intubation need in whom receiving HFNO and NIV in ICU in pulse dose steroid group was statistically higher ($p<0.01$).

Time course analysis of laboratory markers

We carried out a time course analysis between 1st and 7th day of COVID-19 related cytokine storm pro-inflammatory markers: Ferritin, Lactate dehydrogenase (LDH), D-dimer and

Table 2 Demographic data

			Pulse dose n:144	Standard dose n:53	p
Age ($\bar{X}$±Ss)			63.58±13.02	65,85±14,82	0.30
Sex	Male	n%	88a 61.1%	26a 49.1%	0.12
	Female	n%	56a 38.9%	27a 50.9%	
Comorbidities	Yes	n%	103a 71.5%	44a 83.0%	0.1
	No	n%	41a 28.5%	9a 17.0%	
IMV need in ICU	Yes	n%	78a 54.2%	12b 22.6%	0.01
	No	n%	66a 45.8%	41b 77.4%	
O2 support	NIV	n%	25a 17.4%	2b 3.8%	X2: 8.81, p:0.01
	IMV	n%	34a 23.6%	21b 39.6%	
	HFNO	n%	85a 59.0%	30a 56.6%	
ICU LOS			12.62±6,92	10.08±6,40	0.02
APACHE 2 ($\bar{X}$±Ss)			22.99±5,70	23,53±5,81	0.56

O2: Oxygen; IMV: Invasive Mechanical Ventilation; NIV: Non-invasive Mechanical Ventilation; HFNO: High Flow Nasal Oxygenation Therapy; ICU: Intensive Care Unit; LOS: Length of Stay; APACHE: Acute Physiologic and Chronic Health Evaluation

Table 3 Mortality in groups

			Deceased	**Discharged**	**Total**	***p***
Pulse dose		n %	109a 76,8%	35a 63,6%	144 73,1%	0,06
Standard dose		n %	33a 23,2%	20a 36,4%	53 26,9%	
Pulse steroid dosage	250 mg/d	n %	75a 68,8%	30a 85,7%	105 72,9%	0,1
	500 mg/d	n %	7a 6,4%	0a 0,0%	7 4,9%	
	1000 mg/d	n %	27a 24,8%	5a 14,3%	32 22,2%	

C-reactive protein (CRP), fibrinogen (Fib). Due to the utility in clinical decision making, we also highlight overall time differences in platelets, total neutrophils, total lymphocytes. When we evaluated pro-inflammatory markers, a statistically significant decrease was found in the some parameters in both groups over time (Table 4).

Discussion

We did not find any statistical difference between pulse dose and standard dose steroid groups in survival in COVID-19 patients with severe pneumonia with cytokine storm in the ICU. In addition, we found that patients who received standard doses were discharged from the ICU at a higher rate and stay shorter in ICU. In addition, we found that inflammatory markers decreased compared to baseline values in both groups.

COVID-19 goes through different stages, each of which requires different therapeutic approaches. Each stage requires a different treatment approach. At the stage of advanced viral pneumonia with alveolar damage, the problem is aggravated by the progression of systemic inflammation and the involvement of the pulmonary parenchyma and bronchioles, small vessels, and increased thrombogenesis. In these cases, immune system hyperreactivity is accompanied by excessive cytokine activation, further activation of macrophages and epithelial cells, and permanent cytokines and chemokines called "cytokine storm" [6,7].

Table 4 Pro-inflammatory markers in COVID-19

	Pulse Dose	Standard Dose	*p*
Fibrinogen 1st day	2,42	2,5	0,05
Fibrinogen 4th day	1,79	2,1	0,68
Fibrinogen 7th day	1,79	1,4	0,02
	***p:0,01*	***p:0,01*	
D-Dimer 1st day	2,01	2,14	0,82
D-Dimer 4th day	2,05	2,08	0,19
D-Dimer 7th day	1,94	1,78	0,02
	***p:0,61*	***p:0,12*	
Ferritin 1st day	2,12	2,07	0,06
Ferritin 4th day	1,94	2,15	0,16
Ferritin 7th day	1,94	1,78	0,01
	***p:0,19*	***p:0,13*	
LDH 1st day	2,01	2,21	0,27
LDH 4th day	2,15	2,17	0,09
LDH 7th day	1,84	1,62	0,01
	***p:0,03*	***p:0,01*	
CRP 1st day	2,48	2,6	0,44
CRP 4th day	1,67	1,91	0,44
CRP 7th day	1,85	1,49	0,01
	***p:0.01*	***p:0.01*	
Neutrophil 1st day	1,77	1,94	0,67
Neutrophil 4th day	2,12	2,23	0,49
Neutrophil 7th day	2,1	1,83	0,94
	***p:0.01*	***p:0.1*	
Lymphocyte 1st day	2,42	2,28	0,51
Lymphocyte 4th day	1,81	1,99	0,01
Lymphocyte 7th day	1,77	1,73	0,69
	***p:0.01*	***p:0.01*	

LDH: Lactate Dehydrogenase; CRP: C-Reactive Protein

**Mann Whitney-U test ** Friedman test*

This study is devoted to treating such patients in ICU with COVID-19 pneumonia and cytokine storm. Recommendations suggest using "pro-active anti-inflammatory therapy" in such cases to relieve "cytokine storm" and overcome critical inflammation [8]. WHO has not recommended the use of the most popular anti-inflammatory drugs (GCS) in COVID-19. The guidelines of Turkish MoH specify the possible use of GCS at low doses up to 1 mg/kg/day until November 2020. The published guideline on 11 November stated that pulse/high dose could be used in patients with cytokine storm [4].

Systemic GCS's have always been controversial in treating viral pneumonia. A meta-analysis demonstrated that GCS treatment was associated with longer length of stay, higher probability of bacterial infection, and mortality among patients with coronavirus pneumonia [9]. In addition, whether systemic GCSs delay viral clearance is another topic of priority. The first randomized controlled trial about GCSs and viral clearance observed that patients with early use of hydrocortisone harbored higher plasma SARS-CoV viral load and a long time of viral shedding than those without hydrocortisone [10]. Sijia Li et al. [11] showed that high dose of metyhlprednisolone may delay viral shedding in COVID-19 patients.

However, pulse therapy with high doses of GCS in early therapy of SARS showed a delay in disease progression, better resolution of lung changes with a low risk of side effects [12,13]. Limitations of GCS use are their ability to increase prothrombotic factors, especially in immune inflammation, which occurs in COVID-19 with "cytokine storm" [1,14]. Studies link the risk of VTE during therapy with steroid hormones with the doses of preparations, with the maximum risk increase noted at doses from 1000 to 2000 mg/day [15].

Our study aimed to study the efficacy of GCS pulse therapy (250-500-1000 mg of methylprednisolone for 3-5 days intravenously with 1 mg/kg/day methylprednisolone for 5-7 days) in the treatment of patients in ICU with severe COVID-19 pneumonia compared with the group of patients receiving standard dose GCS (1 mg/kg/day for 7-10 days) therapy. Analysis of the examined patients in both groups showed signs of systemic inflammation with an extreme increase of CRP, ferritin, fibrinogen and D-dimer. Patients in the control group had the same severe course of the disease according to the majority of studied parameters.

Our study failed to confirm the possible effectiveness of PDS therapy in treating COVID-19 pneumonia with cytokine storm in ICU patients. Statistically insignificantly but more significantly in the PDS group, survival in ICU (primary endpoint of the study) decreased. Also, in the study group, there was a significant increase in invasive mechanical ventilation need. Even though reduction of CRP levels on 4th day, which characterized the rapid anti-inflammatory effect of high doses of GCS, increased on 7th day. There was a progression of hypoxia and a significant increase in the need for IMV. Trahmerteg [16] offer that there was a spectrum of reactivity with high prevalence in the extensive panel of autoantibodies in patients with respiratory failure and patients with COVID-19-induced respiratory failure have similar autoantibody profiles as contemporaneous. Therefore, steroid administration alone may not have prevented the progression to respiratory failure.

The second objective of the study was to assess the inflammatory markers of COVİD 19. D-dimer dynamics appeared to be the most problematic. Previous studies have demonstrated that a D-dimer increase above 2.0 µg/ml increases VTE risk in patients with COVID-19 by 51 times [17]. Zhou et al. [18] demonstrated that even D-dimer increase above 1.0 µg/mL significantly increased the risk of thrombosis by 18 times. In our findings the D-dimer decreased in standard dose group rather then pulse dose group on 7th day (p:0.02). It is known that GCS can cause leukocytosis and neutrophilia [19]. In our study, the neutrophil count increased from 1st day to 7th day (p:0.01) during pulse GCS treatment, while there were no changes in the SDS group. Lymphopenia persists in both groups. Thus, despite the rapid decrease of acute inflammation, the use of GCS provokes the growth of neutrophilia and lymphopenia (increases in N/L index), which leads to a statistically significant increase of thrombosis and TE risk, which is indicated by significant growth of D-dimer. Although we did not analyze the N/L index and correlation between changes in N/L index and D-dimer in our study, it has been stated that it is an inflammation marker and a predictor of VTE and TE [20]. The N/L index can predict both COVID-19 severity and unfavorable prognosis [21,22]. At the maximum N/L index increase (4.85-88.09), the risk of death in patients with coronavirus pneumonia increases 15-fold [23]. The N/L index value reflects activation of chronic inflammation and autoimmune endothelial inflammation and may cause the unfavorable course of COVID-19 [24].

Our results showed D-dimer significantly high in the pulse dose group (p:0.02). Our patients in this study received the same dose of anticoagulant (enoxaparin 0.01 IU/kg BID) and antithrombotic (ASA 100 mg/day) therapy. Because this is very difficult to determine, we do not know precisely how many thromboembolic events were seen in patients as the cause of death. Therefore, when choosing pulse steroid therapy as an anti-inflammatory response to "cytokine storm" in patients with COVID-19 pneumonia, D-dimer levels should be considered, strengthening anticoagulant therapy should be necessarily considered.

Limitation

Our study was a retrospective chart analysis from a single center study with a limited sample size. The most important limitation was that the doses given are in the choice of the clinician. Also, we did not study viral elimination, which is the primary concern of using steroids.

Conclusion

If the course COVID-19 pneumonia is persistent and inflammatory markers increase, it may not successfully be cured without anti-inflammatory drugs. Our results showed that PDS therapy could interrupt the cytokine storm. However, the results of our study with COVID-19 did not confirm the improvement of prognosis in ICU. This led to the recommendation of using anti-cytokine drugs rather than GCS, which can also slow down eliminating the virus during COVID-19 treatment.

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