Treatment with 3-day methylprednisolone pulses in severe cases of COVID-19 compared with the standard regimen protocol of dexamethasone

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ABSTRACT

Since the outbreak of COVID-19, research has been focused on establishing effective treatments, especially for patients with severe pneumonia and hyperinflammation. The role and dose of corticosteroids remain obscure. We evaluated 58 patients with severe COVID-19 during two periods. 24 patients who received methylprednisolone pulses (250 mg/day intravenously for 3 days) were compared with 34 patients treated according to the standard dexamethasone protocol of 6 mg/day. Among non-intubated patients, the duration of hospitalization was shorter for those who received methylprednisolone pulses (9.5 vs 13.5, p<0.001). In a subgroup analysis of patients who required intubation, those treated with the dexamethasone protocol demonstrated a relative risk=1.89 (p=0.09) for dying, in contrast to the other group which showed a tendency towards extubation and discharge from the hospital. A 'delayed' need for intubation was also observed (6 vs 2 days, p=0.06). Treatment with methylprednisolone pulses significantly reduced hospitalization time. Although there was no statistically significant influence on the necessity for intubation, methylprednisolone pulses revealed a tendency to delay intubation and hospital discharges. This treatment could benefit patients in the hyperinflammatory phase of the disease.

Significance of this study

What is already known about this subject?

- Corticosteroids have been useful in the treatment of severe cases of COVID-19, especially for the hyperinflammatory phase of the disease.
- The optimal dose and regimen remain a matter of debate.

What are the new findings?

- High doses of corticosteroids should be considered in the treatment of the hyperinflammatory phase of COVID-19.
- Compared with the standard dose of dexamethasone, methylprednisolone pulses seem to shorten hospitalization time.
- Methylprednisolone pulses could also delay intubation and favor extubation.

How might these results change the focus of research or clinical practice?

- These results, alongside further research that needs to be done, could potentially affect the existing clinical practice concerning the role of corticosteroids in the treatment of COVID-19.

INTRODUCTION

In December 2019, COVID-19 was first reported in Wuhan, the capital of Hubei, China.[1] The high infective capacity of SARS-CoV-2 infection led to its rapid spread around the world, causing a sustained global outbreak.[2] Finally, on March 12, 2020, the WHO declared the COVID-19 outbreak as a Public Health Emergency of International Concern.[3] The clinical spectrum of COVID-19 ranges from asymptomatic, mild pneumonia to critically ill cases of acute serious respiratory failure and multiple organ dysfunction syndromes.[4] The course of the disease has been divided into three phases: a first phase characterized by a local propagation of the virus in the respiratory tract but a limited innate immune response; a secondary pulmonary phase characterized by the propagation and migration of the virus down the respiratory tract along the conducting airways, triggering a more robust innate immune response; and a third hyperinflammatory phase.[5] The hyperinflammatory phase is driven by a dysregulated host innate immune response which is characterized by overproduction of early response proinflammatory cytokines that can lead to multiorgan failure and death.[6] The hyperinflammatory phase is linked to the highest mortality rate.[7] Thus, several studies have postulated that immunomodulators such as tocilizumab, anakinra or corticosteroids at different doses could be useful treatment for patients experiencing severe COVID-19.[8–11]

Corticosteroids were a point of disagreement at the outbreak of the pandemic. Due to the possibility of delayed viral clearance, as well

as the risk of adverse effects, recommendations warned against the use of systemic corticosteroids based on experience during the epidemics of SARS-CoV and Middle East Respiratory Syndrome-CoV.[12] The RECOVERY trial came to establish the use of 6 mg/day of dexamethasone in the standard of care (SOC) treatment in hospitalized patients requiring supplemental oxygenation.[13] In several studies, higher doses of corticosteroids were used, with the question of 'one dose of corticosteroids does not fit for all patients' to remain a hot point of interest.[14]

In this retrospective study, we investigated the effect of 3-day methylprednisolone pulses (MPs) on the prognosis and the need for endotracheal intubation in hospitalized patients with severe COVID-19, in comparison with SOC.

Study population

We conducted a single-center retrospective observational study and analyzed a cohort of 58 patients with severe, proven COVID-19 infection admitted to the First Department of Internal Medicine of General Hospital 'Korgialenio-Benakio Red Cross', Athens, Greece, during two different periods of the pandemic. Period 1 was defined from September to December 2020 and period 2 from January to March 2021. During period 1, 34 patients were treated according to the standard regimen of dexamethasone (6 mg/day), while, in the second period, a total of 24 patients were treated with MPs (250 mg/day intravenously for 3 days), followed by standard dose regimen of 6 mg/day dexamethasone. Both groups received remdesivir and anticoagulation with low molecular weight heparin. Antimicrobial agents were prescribed as needed.

Inclusion and exclusion criteria

All patients older than 18 years old, non-vaccinated, testing positive on reverse transcriptase-PCR assay for SARS-CoV-2 in nasopharyngeal swabs were eligible to participate in the study. Only patients with significant lung involvement (SpO_2/FiO_2 <300 and a CT scan with bilateral and over 50% of the lung parenchyma distribution of opacities, either ground glass or consolidated) were included in the study. We excluded patients on different corticosteroid regimens than the ones described above. Pregnant women, patients who were intubated or died in the first 24 hours after admission, those who died of causes non-related to COVID-19 infection, as well as terminally ill patients or suffering from active malignancies, were also excluded (online supplemental figure 1).

Data collection and variables measured

We carried out a retrospective analysis of epidemiologic and clinical data retrieved from paper and electronic records in our department, regarding all patients meeting the inclusion criteria. Medical charts of patients were retrospectively reviewed and clinical, laboratory and therapeutic parameters were recorded. Data collected included demographic and clinical parameters, date of onset of the COVID-19 symptoms and the oxygen saturation levels were registered. Regarding the medical history, the following details were registered: smoking history, body mass index (BMI), hypertension, chronic heart failure, coronary artery disease, diabetes mellitus (DM) and chronic obstructive pulmonary disease. In addition, the patient's usual home medication regimen and any treatment prescribed in the outpatient setting (before hospitalization) were registered. On admission, all patients had an in-depth laboratory testing. Markers tested included hemogram, renal function, liver function tests, creatine kinase, triglycerides, lactate dehydrogenase, high-sensitivity troponin, C reactive protein, procalcitonin, ferritin, immunofixation electrophoresis, quantitative serum immunoglobulin tests, lymphocyte immunophenotyping, prothrombin time, partial thromboplastin time, D-dimer and fibrinogen. During their hospital stay, we evaluated the need for oxygen supplementation, the maximum oxygen flux required and the need for non-invasive mechanical-assisted ventilation. We also registered all the medications prescribed during hospitalization.

Outcomes

In the present study, the effect of two corticosteroid schemes on the clinical course of patients with severe SARS-CoV-2 infection was investigated. We analyzed differences between the two groups, regarding in-hospital and 30-day mortality, the need for mechanical ventilation and the days of hospitalization. Serious adverse events related to treatment protocols were also recorded.

Statistical analysis

Continuous variables were expressed as mean value and SD or median value and IQR, whereas categorical variables as frequencies and percentages. To investigate the differences between baseline demographic, clinical and immunophenotyping variables between patients with different therapeutic schemes, the t-test and Mann-Whitney U test for independent samples for continuous variables and the χ^2 and Fisher's exact test for categorical variables were applied. Univariate linear regression analyses for estimating the association between different characteristics of our patients and the duration of their hospitalization in the department were performed. Data were analyzed using Stata V.13.0 software (Stata Corporation, College Station, Texas, USA), and significance was set at $\alpha=0.05$. All tests proceeded as two tailed.

RESULTS

Description of study population

All patients admitted to the First Department of Internal Medicine of General Hospital of Athens 'Korgialenio-Benakio Red Cross' during the two different periods of the pandemic in Greece were potentially eligible to be enrolled in the present study. Out of 232 patients, 58 were finally enrolled. A total of 58.6% of them received a 3-day MP scheme, while 41.4% were treated with 6 mg/day dexamethasone. Based on demographic and clinical characteristics, no major difference was noted regarding age, sex, BMI, smoking habits or medical history between the two groups. Baseline demographic characteristics of each treatment group are displayed in tables 1 and 2. Table 3 presents the clinical and laboratory findings on admission day. None of the basic laboratory findings, with the exception of D-dimers (1.2 vs 0.9, p=0.06), was notably different between the study groups.

Table 1 Comparison of basic demographic characteristics among patients who received MP or 6 mg/day dexamethasone

Characteristics	Treatment with SOC	Treatment with MP	P value
Mean (±SD), N/%	N=34 patients	N=24 patients	
Sex			0.15
Female	7/20.6	9/32.5	
BMI (kg/m^2)			0.32*
18.5–24.9	4 (11.7)	6 (25)	
25–29.9	16 (47)	6 (25)	
30–34.9	11 (32.3)	4 (16.6)	
35–39.9	0 (0)	4 (16.6)	
>40	3 (9)	4 (16.6)	
Smoking			0.72*
No	22 (65)	18 (75)	
Past	7 (22)	6 (25)	
Current	5 (13)	0 (0)	
Age (y)	65/12	61/14	0.21

independent-sample t-test and X^2 tests.
*Fisher's exact tests.
BMI, body mass index; MP, methylprednisolone pulse; SOC, standard of care.

Study outcomes

We investigated the effects on prognosis and the need for endotracheal intubation of the administration of MP to hospitalized patients, in comparison with the standard administration of dexamethasone. It was a more reasonable approach to examine the effects separately for the patients who required endotracheal intubation and admitted to the intensive care unit (ICU) and those who had a milder clinical course. Among the non-intubated patients, those who were treated with MP tend to require less days of hospitalization (coefficient=−4.91, p=0.01) (online supplemental figure 2).

Table 2 Medical history of patients who received MP or 6 mg/day dexamethasone

Comorbidities			
	Treatment with SOC	Treatment with MP	P value
Hypertension			
No	17 (50)	17 (73)	0.14
Yes	17 (50)	7 (27)	
Diabetes mellitus			
No	30 (88)	20 (84)	0.68
Yes	4 (12)	4 (16)	
Coronary artery disease			
No	32 (92)	18 (78.9)	0.37
Yes	2 (8)	6 (21.1)	
Atrial fibrillation			
No	32 (96)	23 (95)	1
Yes	2 (4)	1 (5)	
COPD			
No	32 (96)	24 (100)	1
Yes	2 (4)	0 (0)	

X^2 tests.
COPD, chronic obstructive pulmonary disease; MP, methylprednisolone pulse; SOC, standard of care.

Table 3 Clinical and laboratory findings on admission day of patients with severe pneumonia due to SARS-CoV-2 infection

Variables	Treatment with SOC	Treatment with MP	
Mean (±SD), median/IQR	N=34 patients	N=24 patients	P value
SpO_2/FiO_2	264 (±122)	267 (±74)	0.91
Respiratory rate (n/min)	26 (±6)	24 (±8)	0.51
White cell count (10^9 c/L)	6.8/4.7	5.15/5.25	0.33
Lymphocytes (c/μL)	700/500	700/300	0.39
D-dimers (ng/dL)	1.2/0.6	0.9/0.7	0.06
CRP (mg/L)	85.5/72.6	67.9/73.4	0.17
Ferritin (μg/L)	872/878	621/870	0.50
Fibrinogen (mg/dL)	669/205	612/154	0.27
LDH (U/L)	410/188	391/188	0.83
CPK (μg/L)	106/88	162/125	0.18
Troponin (ng/mL)	0.01/0.01	0.01/0.01	0.26
PCT (ng/mL)	0.11/0.11	0.08/0.1	0.37

Fisher's exact tests.
CPK, creatine kinase; CRP, C reactive protein; LDH, lactate dehydrogenase; MP, methylprednisolone pulse; PCT, procalcitonin; SOC, standard of care.

In linear regression analysis (table 4), age, female gender and current smokers (vs non-smokers) seemed to have a negative effect, prolonging the hospitalization period in non-intubated patients (not statistically significant results), while a greater score in the Mini-Mental State Examination test was associated with fewer days in hospital (coefficient=−1.14, p=0.08). No other laboratory or clinical characteristic was found to affect the time until discharge or death.

The analyses were performed for the intubated patients as well; patients with DM had a greater risk of a prolonged need for hospitalization (coefficient: 10, p=0.03). No effect was noted from the study of other variables. Treatment with MP was not associated with lower risk of endotracheal intubation (54.1% vs 52.9%, p=0.92). However, in a subgroup analysis of patients who required endotracheal intubation (n=27 patients), those who received MP (n=11 patients) demonstrated a relative risk=2.03 (p=0.09) for extubation, weaning and discharge from the hospital. They also appeared to have a 'delayed' need for intubation, in contrast to the 6 mg/day dexamethasone group (6 vs 2 days, p=0.06) (table 5).

Table 4 Factors associated with the duration of hospitalization in non-intubated patients

Variables	β-coefficient	95% CIs	P value
MP vs SOC	−4.91	−8.75 to -1.07	0.01
Age	0.07	−0.09 to 0.25	0.37
Female vs male	0.50	−4.06 to 5.08	0.82
Smoking (past vs no)	−2.72	−8.2 to 2.74	0.31
Smoking (current vs no)	7.43	−1.13 to 16.01	0.08
Mini-mental test score	−1.14	−2.39 to 0.10	0.07

Linear regression analysis.
MP, methylprednisolone pulse; SOC, standard of care.

Table 5 Endpoints in the clinical course of patients who required or not endotracheal intubation

	Patients who required endotracheal intubation			Patients who did not require endotracheal intubation		
	SOC	MP		SOC	MP	
	Median/IQR		P value	Mean/SD		P value
Hospitalization days until intubation/discharge	2/5	6/4	0.06	13.5/5	9.5/4.5	<0.001
	N (%)					
Outcome			0.09			0.41
Death	11 (69)	4 (36)		0 (0)	1 (8)	
Discharge	5 (31)	7 (64)		18 (100)	12 (92)	

Mann-Whitney U tests.
IQR, Interquartile Range; MP, methylprednisolone pulse; SOC, standard of care.

In our cohort, there was only one death observed in patients who did not require invasive ventilation. No death was recorded 30 days after discharge for both groups (p=1). In the MP treatment group, no major adverse events such as infections were recorded.

While there were no significant differences regarding the demographic and clinical characteristics of patients suffering from severe COVID-19, the lymphocyte immunophenotyping assay demonstrated a worse pattern of disease during the second period. Results concerning the expression of CD8, NK and CD19 cells were statistically significant (p=0.05, p<0.01, p=0.01 and p<0.01, respectively) (figure 1), as expected from the dominance of the British variant in Greece since January 2021 (online supplemental table 1).

DISCUSSION

Cytokine storm induced by proinflammatory cytokines is related to most severe cases of COVID-19.[15] Corticosteroids, among other immunomodulators, have been studied as a possible treatment option in these cases. After the initial distrust,[12] the RECOVERY trial established the use of 6 mg dexamethasone to be included in the SOC in patients requiring supplemental oxygen.[13] Since then, several studies have confirmed the beneficial effect of systemic corticosteroids in reducing mortality.[16] Although the accurate timing of initiation of corticosteroid administration seems to be universally accepted to be the second week of the disease, the appropriate dosage and regimen remain controversial. In addition, organizing pneumonia as well as acute fibrinous pneumonia have been demonstrated as the main imaging and histopathological pattern respectively in the majority of moderate or severe cases,[17] implying that higher doses of corticosteroids should be considered.[18] As 'one size does not fit all' in the treatment of COVID-19 with corticosteroids,[14] several studies have introduced the usefulness of the MP in severely ill hospitalized patients.[14 16 19–22]

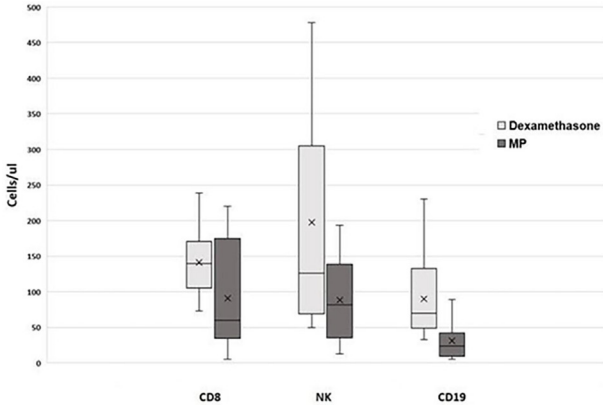

Figure 1 Lymphocyte immunophenotyping assay, regarding the expression of CD8, NK and CD19 cells in patients presented during the two study periods and were treated with different corticosteroid scheme. MP, methylprednisolone pulse.

In this retrospective study, we compared the effects of 3-day 250 mg MP with the standard dose protocol of 6 mg/day dexamethasone in hospitalized patients with severe COVID-19. While there was no statistically significant difference in mortality or the need for intubation between the two groups, patients who were not intubated were hospitalized for less days (p<0.001) and, even for those requiring intubation, there was a 'delay' in intubation time (p=0.06). Less days of hospitalization had financial benefits for the healthcare system and psychological benefits for the individuals, as patients with COVID-19 infection and especially those who are admitted to the hospital have been reported to suffer from high levels of stress and potentially some form of post-traumatic stress disorder.[23] While some studies showed prolonged recovery time for patients treated with MP,[24 25] our results coincide with Ranjbar *et al* who also found that the use of MP resulted in less days of hospitalization.[26]

In addition, MP treatment in our study led to 'delayed' intubation compared with SOC, meaning that more days were required from the day of admission to the day of intubation. We interpret this outcome as a positive one, as in a healthcare system so deeply impacted by the pandemic, 'offering' a few more days could possibly help relieve the ICU system and provide more time for different treatments to act collectively. Among patients who eventually required mechanical ventilation, there was a trend towards extubation and discharge from the hospital for those who received MP (p=0.09). It should also be underlined that there were no major side effects associated with MP treatment, such as serious infections or prolongation of time to recovery. Interestingly, patients with higher Mini-Mental State Examination scores had better outcomes. Experience from infections caused by different strains of coronavirus shows involvement of the central nervous system in various ways.[27] The difference observed in our study could be associated with a lower burden of disease.

The results of lymphocytic phenotypes indicate a more aggressive disease profile throughout the second period of the study, during which all patients were treated with MP, pointing out that in spite of disease severity patients benefit from MP. Despite the fact that several studies have advocated MP as a treatment choice, our study is one of the very few that directly compare short-term treatment with MPs with the standard dose of 6 mg dexamethasone. Fatima *et al* did not report any difference between treatment with MP and dexamethasone,[28] while the study of Ko *et al* was conducted in ICU patients.[29] The results of Ranjbar *et al* were in accordance with our results regarding the days of hospitalization. It should be underlined though that Ranjbar *et al* used a different MP protocol.[26] To the best of our knowledge, no other study has reported 'delayed' intubation and the trend towards extubation and discharge from ICU, in patients treated with MP compared with 6 mg/day dexamethasone. There are several limitations to the study, including its retrospective nature, the limited sample size, as well as the possibility that different disease phenotypes dominated during the two study periods.

CONCLUSION

Despite accumulating data supporting the benefits of corticosteroids in individuals with COVID-19, the optimal dose and duration of corticosteroid therapy in various clinical settings remain unknown. In this study, we assessed the effect of MP compared with the standard dose of dexamethasone. Our research revealed that hospitalized patients during the hyperinflammatory phase of the disease, considered as the most life-threatening, could benefit from the administration of short-term MP without an increase in the risk of severe adverse effects. Additional research is needed to determine the best corticosteroid regimen in order to achieve the desired therapeutic impact while minimizing side effects.

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