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The use of methylprednisolone in patients with Coronavirus disease 2019 (COVID-19) requiring intensive care hospitalization: a longitudinal observational study

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Abstract : The use of methylprednisolone in patients with Coronavirus disease 2019 (COVID-19) requiring intensive care hospitalization: a longitudinal observational study.

Background : For a long time, the use of corticosteroids in critically ill patients with coronavirus disease 2019 (COVID-19) has been a controversial treatment. However, given the conflicting evidence on this topic, we studied the effects of methylprednisolone on critically ill patients and - share here our experience on laboratory findings and the Pa02/FiO2 ratio (ratio of partial oxygen concentration on arterial blood gas sample to fraction of inspired oxygen).

Methods : In a population of 68 patients hospitalized in the intensive care unit due because of COVID-19 infection, 28 patients with severe respiratory failure received methylprednisolone on a fixed 12-day regimen (125 mg IV for 2 days, followed by 2x0.5 mg/kg IV twice daily for 5 days, and then a decreasing regimen for 4 days until discontinuation). After day 5 and day 10, we analyzed the levels of CRP (C-reactive protein), lymphocytosis, D-dimer, LDH (lactate dehydrogenase) and PaO_2/FiO_2 ratio of our patients.

Results : We observed a significant decrease in median CRP levels between day 0 (start of methylprednisolone treatment) and day 5 (p=0.001), and between day 0 and day 10 (p=0.005). No decrease was seen between day 5 and 10 (p=0.352). The same increase in PaO_2/FiO_2 was recorded between day 0 and day 5 (p=0.009), and between 0 and day 10 (p=0.019). For D-dimer, only a significant difference was found between day 0 and day 10 (p=0.018). No significant difference could be observed for lymphocytosis and LDH levels between the beginning of the treatment and day 5 or day 10.

Conclusion : There is a strong and sustained significant decrease in CRP levels and a tilt in the PaO2/FiO2 ratio after starting methylprednisolone. A slower, but also significant decrease was found for D-dimer. Further research and control group analyses are needed to confirm that this effect is due to corticostreoid treatment. However, this indicates that methylprednisolone may play a very important role in the treatment of the severely ill COVID-19 patients requiring ICU admission.

Keywords : COVID-19 virus; 6-Methylprednisolone; respiratory distress syndrome; acute respiratory distress.

Introduction

SARS-CoV-2 is an RNA virus belonging to the Coronaviridae family. The pathophysiology and cause of organ dysfunction related to Coronavirus disease 2019 (COVID-19) infection are still under extensive research.

COVID-19 virus can be found in various tissues of the body (1). Pathological analysis of lung tissue from a patient who died of COVID-19 disease revealed severe alveolar damage and endothelial damage with coagulopathic features in the pulmonary micro-vasculature (2, 3). IL-6 (Interleukine-6) elevation may play a role in endothelial activation and precipitation of immune-mediated pulmonary thrombosis (4). Since the emergence of COVID-19, several treatment plans for patients with severe respiratory symptoms requiring admissions to an intensive care unit have been proposed.

There is evidence that the use the IL- 6 inhibitor (a specific cytokine) tocilizumab in a population of patients hospitalized with severe COVID-19 infection reduces the risk of mechanical ventilation. It may also reduce the risk of poor outcome and the risk of secondary infections (5).

A recent study by Leisman et al. found that interleukine-6 titers were lower in patients with COVID-19 than in other patients with critical

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illnesses such as sepsis, ARDS of other origin and cytokine release syndrome. As a result of this finding, the role of cytokine storm as a cause of organ dysfunction is therefore questioned (6). Given this new information, we may also question the role of corticosteroids in the treatment of a Covid-19 infection.In the early WHO recommendations, corticosteroids and its derivatives were not administered to patients for fear of suppressing the immune system and causing viral load shedding with a potentially fatal outcome (7).

However, the general opinion has changed due to many new studies published recently (8, 9). As proven with acute respiratory distress syndrome (ARDS), corticosteroids have the ability to reduce the inflammatory response (8). They could prevent the progression to fibrosis, which leads to irreversible lung damage (10, 11).

With this in mind, we would like to share our experience with the use of methylprednisolone on critically ill patients with respiratory distress due to a COVID-19 infection, as well as its effect on laboratory findings and PaO_2/FiO_2 ratio (the ratio of partial oxygen concentration on arterial blood gas sample and fraction of inspired oxygen on ventilator or noninvasive ventilation).

Methods

Ethical approval and registration

The study design was approved by Ethics Committee of AZ Delta Hospital (Roeselare, Belgium) under the clinical trial number B1172020000002 on April 18, 2020. All patients (or their representatives) gave permission to access their medical records through the informed consent procedure.

Patient population

We conducted a longitudinal, observational, single-center study of COVID-19 patients who received methylprednisolone during their stay at the ICU (Intensive Care Unit) of a large Belgian supraregional hospital with 1403 accredited beds. The study took place between April and June 2020.

Inclusion/exclusion criteria

Only patients (a) admitted to the intensive care unit because of severe respiratory distress, (b) diagnosed with SARS-CoV-2 by a positive PCR and (c) who received methylprednisolone were included.

There were three exclusion criteria. The first was inclusion in a prospective study involving interleukin mediators. The second was not receiving the full methylprednisolone regimen at survival. The last was admission for a primary reason other than respiratory distress.

Conduct of the study

Patients did not receiv methylprednisolone until 7 days after the onset of their symptoms. Patients received 125 mg methylprednisolone - IV for 2 days, then 0.5mg/kg IV twice daily for 5 days, then a tapering regimen for 4 days until discontinuation). Due to the lack of specific COVID-19 corticosteroids regimens at the time of this trial (during the first COVID-19 wave in Europe), this regimen was established after seeking expert opinion from other supraregional centers and based on previous ARDSregimens.Demographic data, intubation days, noninvasive ventilation assistance, and survival were collected from all patients in this study. In addition, we monitored laboratory results for PaO_2/FiO_2 ratio, CRP levels, D-dimer, lymphocytosis and LDH on days 0, 5 and 10. For the PaO_2/FiO_2 ratio, we determined the lowest partial oxygen concentration on the ABG (arterial blood gas) on each day, with the corresponding oxygen fraction at that time. The SOFA (Sequential Organ Failure Assessment Score) was calculated at the start of methylprednisolone treatment.

Measurements and data processing

Data was extracted from the electronic medical records and computed using Microsoft Excel 2016 version. Data computed by Excel were imported into the SPSS statistical software (IBM software). Descriptive statistics were plotted as frequency and percentages.

Primary and secondary endpoints

Primary endpoints of our study were the PaO_2/FiO_2 ratio and CRP levels. Secondary endpoints were lymphocytosis, D-dimer and LDH.

Statistical analysis

We used the Shapiro-Wilk test to test for normality, noting that our data were non-normally distributed. Therefore, the nonparametric Wilcoxon signed Rank statistical test was used to determine a significant difference in the median values (IQR) of our variables.

Median values for CRP, D-dimer, LDH, PaO_2/FiO_2 ratio and lymphocytosis were calculated at day 0 (start of methylprednisolone), day 5 and day 10 of the methylprednisolone regimen. An observation is said to be statistically significant if the P-value is less than or equal to 0.05.

Results

From April 2020 to June 2020, 68 patients were admitted to the ICU with positive PCR for SARS-CoV-2. Of these, 44 received methylprednisolone and 28 patients were included in the numerical analysis (Fig. 1).The main reason for exclusion from the numerical analysis when methylprednisolone was administered was not receiving the correct study regimen (aberrant methylprednisolone dosing or longer continuation). The primary reasons for exclusion from methylprednisolone therapy at any dose were admission to the ICU with symptoms less than 7 days old or admission for a reason other than respiratory distress. The median age of the patients was 66 years with a male-to-female ratio of 2.11 (Table 1). The median SOFA score at methylprednisolone initiation was 4, the median BMI (Body Mass Index) was 26 and 7 patients (25%) had diabetes mellitus (all type 2).

Overall survival to hospital discharge was 61.5% (16 of 28 patients survived to hospital discharge), 14 patients (50%) required intubation and mechanical ventilation, 18 patients (64.3%) received non-invasive ventilation (continuous positive airway pressure – CPAP), 2 patients (7.1%) were placed on VV-ECMO (one survived) (Table 2).

We observed a significant (p= <0.05) decrease in median CRP levels between day 0 and 5, and between day 0 and 10 (Table 3). The difference in median CRP levels between day 5 and 10 was not significant (p= 0.352). For median lymphocytosis, there was only a significant decrease between day 5 and 10 (not between day 0 and 10). The median LDH value was significantly lower between day 0 and 5, but not between day 0 and 10 or between day 5 and 10. For the median D-dimer value, there was only a significant decrease between day 0 and 10 (p= 0.018).

The calculated median PaO_2/FiO_2 value increased statistically significantly increased between day 0 and 5, and between day 0 and 10, but not between day 5 and 10. In 4 of 28 patients, we observed a strong upward movement of CRP levels on day 14 (methylprednisolone treatment was stopped on day 12).

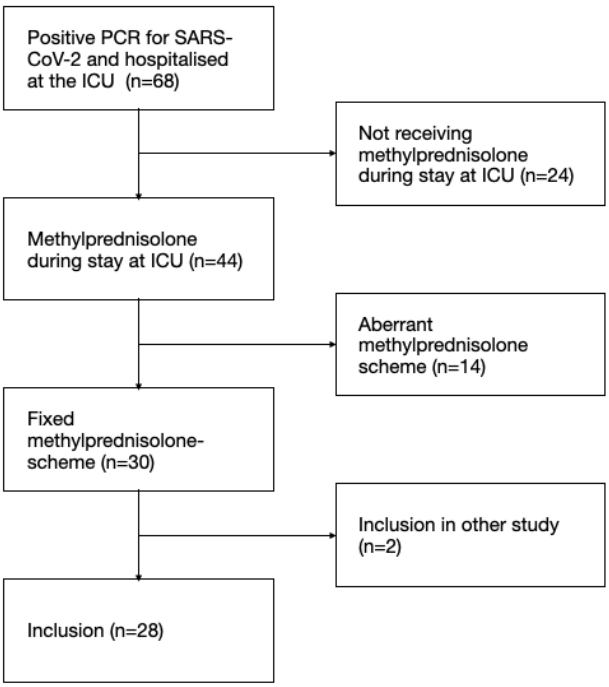

Figure 1. — Flow chart of patient population.

Table 1

General characteristics

Characteristics			
Gender	Male	19	67.9%
	Female	9	32.2%
BMI	Median (SD)	26 (3.9)	
Age	Median (SD)	66 (10.5)	
Type 2 Diabetes Mellitus			
	Yes	7	25%
	No	21	75%
SOFA-score when starting methylprednisolone	Median (SD)	5 (3.2)	

Table 2

Clinical outcomes

Clinical outcomes			
Survival to hospital discharge			
	Yes	16	61.5%
	No	12	38.5%
NIV (CPAP)			
	Yes	18	64.3%
	No	10	35.7%
Intubation			
	Yes	14	50%
	No	14	50%
VV-ECMO			
	Yes	2	7.1%
	No	26	92.9%

Table 3

Comparison of biochemical outcomes and PAO_2/FIO_2-ratio after initiation of methylprednisolone

PaO_2/FiO_2	**Days**	**Median (IQR)**	**Wilcoxon Signed Rank**	**P-Value**
	PaO_2/FiO_2 day 0	84.40 (70.28 - 108.86)	2.603	**0.009****
	PaO_2/FiO_2 day 5	119.87 (82.48 - 171.65)		
	PaO_2/FiO_2 day 0	84.40 (70.28 - 108.86)	2.354	**0.019****
	PaO_2/FiO_2 day 10	102.65 (81.15 - 195.73)		
	PaO_2/FiO_2 day 5	119.87 (82.48 - 171.65)	1.412	0.158
	PaO_2/FiO_2 day 10	102.65 (81.15 - 195.73)		
Lymphocytosis	**Days**	**Median (IQR)**	**Wilcoxon Signed Rank**	**P-Value**
	Lymphocytosis day 0	0.640 (0.450 - 1.080)	1.308	0.191
	Lymphocytosis day 5	0.790 (0.4300 - 1.250)		
	Lymphocytosis day 0	0.640 (0.450 - 1.080)	1.733	0.083
	Lymphocytosis day 10	0.985 (0.475 - 2.213)		
	Lymphocytosis day 5	0.790 (0.4300 - 1.250)	2.120	**0.034****
	Lymphocytosis day 10	0.985 (0.475 - 2.213)		
D-dimer	**Days**	**Median (IQR)**	**Wilcoxon Signed Rank**	**P-Value**
	D-dimers day 0	2627.50 (1280.75 - 3582.50)	1.334	0.182
	D-dimers day 5	1508.50 (754.25 - 6312.50)		
	D-dimers day 0	2627.50 (1280.75 - 3582.50)	2.366	**0.018****
	D-dimers day 10	1630 (490 - 4797)		
	D-dimers day 5	1508.50 (754.25 - 6312.50)	1.363	0.173
	D-dimers day 10	1630 (490 - 4797)		
CRP	**Days**	**Median (IQR)**	**Wilcoxon Signed Rank**	**P-Value**
	CRP day 0	216.40 (150 - 251)	4.372	**0.000****
	CRP day 5	27.20 (14.08 - 45.28)		
	CRP day 0	216.40 (150 - 251)	2.792	**0.005****
	CRP day 10	15.70 (4.90 - 84.30)		
	CRP day 5	27.20 (14.08 - 45.28)	0.931	0.352
	CRP day 10	15.70 (4.90 - 84.30)		
LDH	**Days**	**Median (IQR)**	**Wilcoxon Signed Rank**	**P-Value**
	LDH day 0	467 (396 - 600.50)	2.482	**0.013****
	LDH day 5	397.50 (314.50 - 541.25)		
	LDH day 0	467 (396 - 600.50)	1.820	0.069
	LDH day 10	389.50 (353.50 - 519.25)		
	LDH day 5	397.50 (314.50 - 541.25)	1.274	0.203
	LDH day 10	389.50 (353.50 - 519.25)		

Discussion

In the results shown above, the most notable trend is the sharp decrease in the median CRP levels of the population. This decrease is rapid (within 5 days) and significant between day 0 and day 10, however no significant decrease could be found between day 5 and 10, which could imply a rapid and long-lasting effect of methylprednisolone on CRP levels. This same reasoning could be used for the tilt of the median PaO_2/FiO_2 ratio. For lymphocytosis, the difference between day 5 and 10 does not seem to be clinically relevant.

For LDH, only a significant decrease was observed between day 0 and day 5, but it disappeared by day 10. This could imply only a short but not lasting effect of the methylprednisolone. In contrast, for D-dimer, only a significant difference was found

between baseline and day 10, which could imply a slower but lasting decline in D-dimer levels after the start of the treatment.

As presented above, we observed a strong upward movement of CRP levels on day 14 in 4 of 28 patients. This could be indicative of a 'rebound' effect after the immunosuppressive effect of methylprednisolone has ended (after day 12). Further research is needed to examine this effect, so caution should be exercised when discontinuing steroids. This effect has not been clearly described in other major trials of methylprednisolone.

We acknowledge several weaknesses of our study. First, we are aware that this is a small pilot study without a control group and that larger randomized controlled studies are underway to examine this effect in more detail.. For this reason, we cannot compare pO_2/FiO_2 ratio and biochemical markers with a natural course in a control group. The patients who received methylprednisolone were the most severely ill and a comparison with a less ill group (who did not receive methylprednisolone) would create a distorted picture. Two recently published large trials of corticosteroids use in COVID-19 compared PaO_2/FiO_2 ratio and ventilator dependence, but not as a primary outcome. In the MetCovid trial, the proportion of patients with a PaO_2/FiO_2 ratio <100 through day 7 of treatment was not significantly different between the control and methylprednisolone groups (secondary outcome) (12). In the REMAP-CAP trial, a clear distinction in days without respiratory support was found after hydrocortisone treatment (13). None of these trials used the same methylprednisolone regimen.

Secondly, we began administering methylprednisolone starting in mid-April 2020 to patients with severe respiratory disorders without a clear inclusion protocol (only exclusion criteria for methylprednisolone administration were clearly defined). With stricter inclusion criteria, we could have a clearer idea of which patients could potentially benefit of a methylprednisolone therapy.

Conclusion

We observed a strong, significant and sustained decline in CRP levels and a tilt in the PaO_2/FiO_2 ratio throughout methylprednisolone treatment. A slower but also significant decline was observed in D-dimer (on day 10 of treatment). No (long-term) effect was seen on lymphocytosis and LDH levels. Therefore, methylprednisolone could play a very important role in the treatment of the critically ill COVID-19 patients requiring ICU admission.

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