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ORIGINAL ARTICLE

Effect of high-dose methylprednisolone in mechanically ventilated ICU patients with COVID-19: a retrospective observational study

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Abstract

Background: COVID-19 is associated with clinical features that closely resemble acute respiratory distress syndrome and causes hypoxic respiratory failure requiring ventilator support. The primary purpose of this study is to investigate the effects of high-dose methylprednisolone on the respiratory condition of COVID-19 patients on the intensive care unit (ICU) in the absence of early treatment with hydrocortisone

Methods: This retrospective observational study reports on all patients who were hospitalised with COVID-19 and received mechanical ventilation while on the ICU in Rijnstate Hospital. These patients received intravenous methylprednisolone following the 'Meduri protocol'. The primary outcome was defined as improvement of the respiratory conditions expressed by P/F ratio and PEEP.

Results: Seventeen of the 42 COVID-19 patients admitted to our ICU received methylprednisolone, initiated at day 13 (median). The mean length of ICU stay of these patients was 34 days. The average P/F ratio improved significantly from 14.2 kPa (107 mmHg) to 17.9 kPa (135 mmHg) after one week of treatment and from 17.9 kPa to 20.8 kPa (158 mmHg) after two weeks of treatment. This also applies to the positive end-expiratory pressure (PEEP), which decreased significantly to 9 cmH_2O and 7 cmH_2O after one and two weeks of treatment, respectively, compared with 10 cmH_2O before start of the protocol. In our population the 28-day mortality was 18% versus an overall in-hospital mortality of 29% in patients with COVID-19.

Conclusion: In patients with COVID-19 who received mechanical ventilation on the ICU, the use of high-dose methylprednisolone seemed to provide a significant improvement in both oxygenation and ventilation.

Introduction

Currently, the world is experiencing a pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; COVID-19). In turn, COVID-19 was preceded by similar coronaviruses such as SARS and MERS, also known for causing severe respiratory failure.[1,2] Furthermore, the COVID-19 virus is also known to cause hypoxaemic respiratory failure requiring ventilatory support.[3-6] The clinical features of many of these patients suffering from SARS, MERS and COVID closely resemble those of acute respiratory distress syndrome (ARDS): patients require high oxygen ventilation of a low-compliant lung. Early reports suggest that as many as 30% of COVID-19 patients suffer from ARDS.[7] While other studies claim that up to 60% of the COVID-19 patients admitted to the intensive care unit (ICU) are eventually diagnosed with ARDS.[8] Based on the reports, it was hypothesised that this COVID-19 related ARDS is of a vascular endotype, in which endothelial and subendothelial inflammation appears to play a key role in its pathophysiology.[9]

As advised by the European Society of Intensive Care Medicine (ESICM) in 2017[10] and confirmed by a more recent meta-analysis,[11] corticosteroids should be considered in patients with early, moderate to severe ARDS.[10] The initial reports from China and Italy, however, suggested avoiding corticosteroids in patients with COVID-19.[3,6,8]This is in contrast to more recent studies showing a lower mortality in patients treated with methylprednisolone.[12] Due to the conflicting evidence, there was initially no consensus in the expert panel of clinicians in the Netherlands on whether to use corticosteroids as a rescue therapy for the severely affected ICU patient with COVID-19. In the desperate position of progressive oxygenation and ventilatory failure in our most affected patients, we started

treating that specific group of patients with methylprednisolone. Meanwhile, multiple clinical trials started to report the positive effects of corticosteroids on mortality, duration of mechanical ventilation and severity of the illness.[13-15]

In this report we aim to assess the effect and safety of a long, high-dose methylprednisolone treatment in severely affected COVID-19 patients admitted to the ICU, in the absence of early treatment with hydrocortisone. This retrospective observational study reports on all of the 17 patients who received methylprednisolone in the first half of 2020, focusing mainly on their respiratory conditions.

Methods

Patients

For this retrospective observational study we included all COVID-19 patients admitted to the ICU in Rijnstate Hospital who received methylprednisolone as rescue therapy between 30 March and 5 June 2020. In total 42 COVID-19 patients were admitted to the ICU in Rijnstate Hospital in this period; of these 17 patients eventually received methylprednisolone and all were included in this report. Informed consent for retrospective studies was obtained from all patients.

Intervention

Before treatment with methylprednisolone was considered, patients had to meet the following criteria; persistent need of mechanical ventilation with progressive oxygenation and ventilatory failure. This was defined as a P/F ratio <15 kPa, PEEP > 10 cmH_2O and static compliance <50 ml/cm H_20. All patients were screened for active co-infections by serological and deep bronchial cultures before treatment was given. When treatment with methylprednisolone was indicated, we used the Meduri[16] methylprednisolone protocol as seen in *table 1*.

Table 1. Meduri protocol

	Daily dose of methylprednisolone
Day 1 to 14	2 mg/kg/day
Day 15 to 21	1 mg/kg/day
Day 22 to 25	0.5 mg/kg/day
Day 26 to 28	0.25 mg/kg/day
Days 29 and 30	0.125 mg/kg/day

Data collection

The following data were collected from the electronic patient file: baseline parameters such as age, sex, comorbidity, days of ICU admission and date of start methylprednisolone. The following parameters were scored daily during the period from 14 days before start of the Meduri protocol until 14 days after treatment was started: co-infections, SOFA score, inflammation parameters and respiratory parameters such as PEEP and P/F ratio.

Outcome

The primary outcome was defined as improvement in respiratory conditions expressed as P/F ratio and PEEP. For the secondary outcome analysis we looked at inflammation (expressed by CRP), total duration of mechanical ventilation, duration of the ICU admission, in-hospital and 28-day mortality and multi-organ failure (SOFA score).

Statistical analysis

IBM SPSS statistics 25 was used for the statistical analysis. Descriptive statistics were used to compare baseline data. We used the Shapiro-Wilk test to determine whether the variable was normally distributed in our study population. For normally distributed variables we used the mean and 95% confidence interval (CI), for non-normally distributed variables the median and the standard error. For the analysis of our primary outcome parameters paired T-tests were performed as all three were normally distributed.

Results

The baseline characteristics of our study population are shown in *table 2*. A total of 17 patients were treated with the Meduri protocol. All patients were being mechanically ventilated when the methylprednisolone was initiated. The majority of the patients were male (82%), with an average age of 64 years. Cardiovascular comorbidity was present in 29% of the patients, with hypertension (4 patients) and acute coronary syndrome (2 patients) as most frequent diagnosis. Pulmonary comorbidity was present in 35% of our patients, with obstructive lung disease (5 patients) and lung cancer (1 patient) as the most frequently found diagnosis. The mean duration of ICU admission for this group was 34 days, all patients required mechanical ventilation from the day of ICU admission. The median day at which the methylprednisolone was started was day 13 of ICU admission.

Table 2. Baseline characteristics

Gender (male, %)	82%
Age (years, mean, 95% CI)	64 [59-70]
BMI (kg/m2, median, SE)	27,8 [1,3]
Duration of mechanical ventilation (days, mean, 95% CI)	34 [27-42]
Duration of ICU admission (days, mean, 95% CI)	34 [25-43]
28-day mortality	18%
In hospital mortality	29%
Start Meduri (days ICU admission, median, SE)	13 [2.7]
Cardiovascular comorbidity	29%
Pulmonary comorbidity	35%

CI = confidence interval; SE = standard error

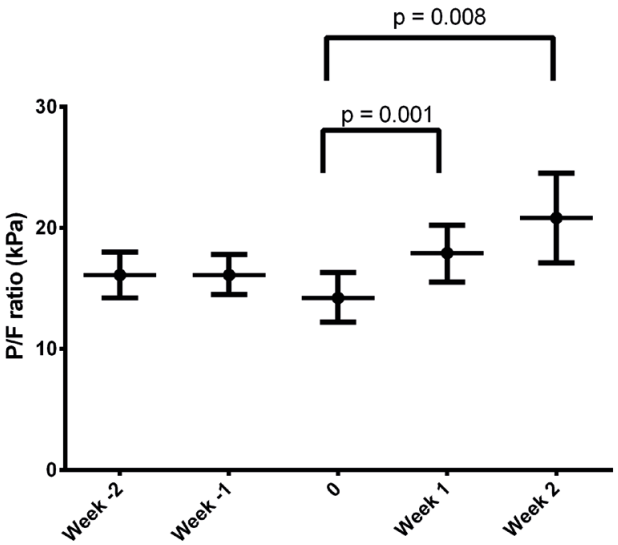

Figure 1. Average P/f ratio (kPa) two weeks before and after start of the Meduri protocol.

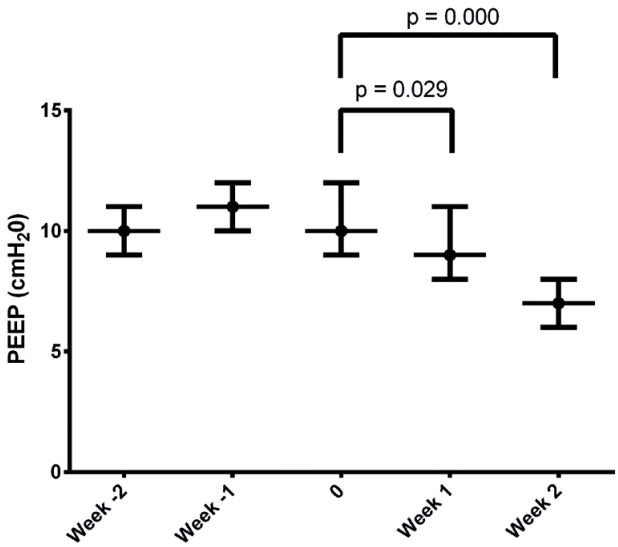

Figure 2. Average PEEP (cmH2O) two weeks before and after start of the Meduri protocol.

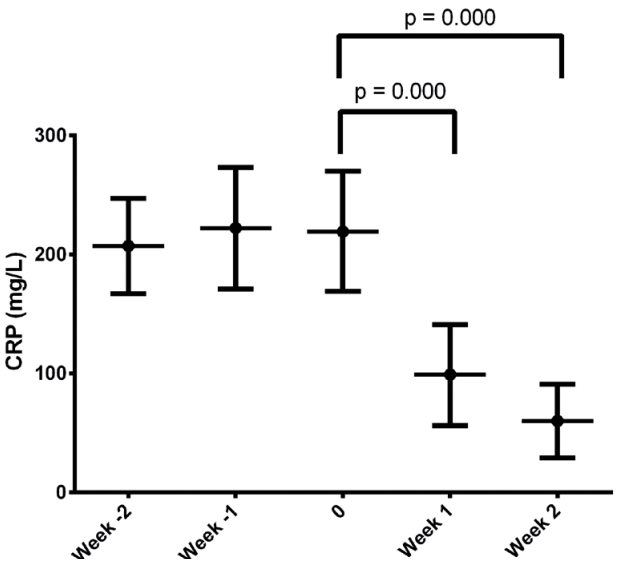

Figure 3. Average CRP (mg/L) two weeks before and after start of the Meduri protocol.

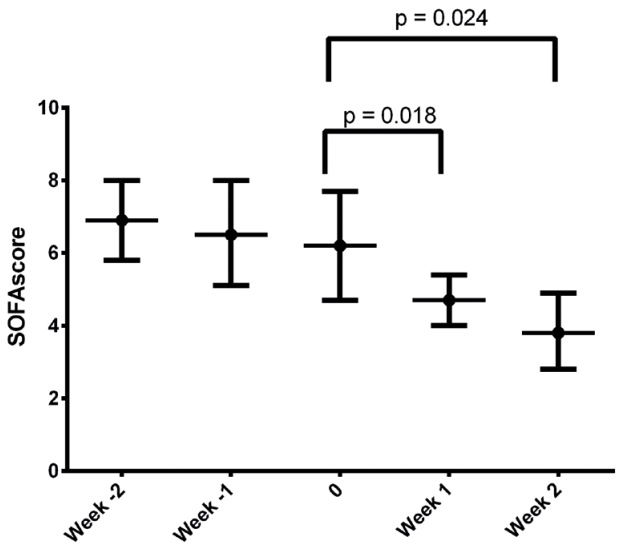

Figure 4. Average SOFA score two weeks before and after start of the Meduri protocol.

In our population, the 28-day mortality was 18% compared with an in-hospital mortality of 29%. A total of five patients in the population died during treatment. Three patients died within five days of starting methylprednisolone: one from massive intracranial bleeding, the other two patients from progressive respiratory failure. One patient died 14 days after steroid induction, also due to progressive respiratory failure caused by COVID-19 and recurrent pneumothorax. Finally one patient died on the general hospital ward after being discharged from the ICU, due to the consequence of recurrent aspiration and pneumonia. Regarding adverse events: no new co-infections were found after start of the treatment with dexamethasone.

Methylprednisolone following Meduri protocol

After treatment with methylprednisolone was initiated, both the ventilation and oxygenation of our patients improved gradually. As shown in *figure 1*, the average P/F ratio improved significantly after one week of treatment, from an average of 14.2 kPa (107 mmHg) to 17.9 kPa (135 mmHg) after one week and eventually to 20.8 kPa (158 mmHg) after two weeks of treatment. Likewise, we reported positive effects for the positive end-expiratory pressure (PEEP). The PEEP needed to maintain adequate ventilation decreased significantly to 9 cmH_2O and 7 cmH_2O after one and two weeks of treatment, respectively, compared with 10 before the start of the protocol (*figure 2*). In the same way, mean level of C-reactive protein

(CRP) improved significantly one week after the start of treatment, from 219 to 99 and eventually declining to a mean of 66 in week 2 (*figure 3*). The SOFA score also improved significantly from 6.2 initially to 4.7 after one week, to 3.8 in week 2 (*figure 4*)

Discussion

In this observational study, we show that conditions of mechanical ventilation (FiO_2 and PEEP level) significantly improved after initiation of high-dose methylprednisolone in 17 patients with pneumonia caused by COVID-19, meeting criteria of severe ARDS. In addition, CRP levels significantly decreased, as did the SOFA scores.

In the early phase of the COVID-19 pandemic in China, corticosteroids were believed to act counterproductively, by increasing viral replication and causing increased duration of viral shedding as reported in SARS and MERS-CoV infected patients[1,2] Corticosteroids thereby increase the risk of nosocomial infections and death.[17] Later on, accumulating evidence supported the role of corticosteroids in preventing immune-mediated damage, such as in severe ARDS.

In agreement with the positive effects of corticosteroids in ARDS, reports from China eventually encouraged the use of steroids in COVID-19 patients on the ICU. Wu and co-authors[14] describe lower mortality if these patients were treated with methylprednisolone, which is in line with evidence from non-viral ARDS.[18-20] The Recovery trial[13] even supports the use of corticosteroids before onset of ARDS-like syndrome in COVID-19 and introduced a 6 mg hydrocortisone once daily regimen as standard of care, inspired by the positive effect of hydrocortisone in non-COVID-19 ARDS as described by Villar et al.[21] Patients requiring oxygen support or mechanical ventilation showed decreased 28-day mortality compared with controls in the Recovery trial. Likewise, in non-mechanically ventilated patients, Salton and co-authors[15] show lower ICU referral, lower mechanical ventilation and lower mortality than in patients not treated with steroids. Although most trials were stopped early after the positive results from the Recovery trial, a recently published meta-analysis by Sterne et al.,[22] including seven randomised trials and over 1700 patients, showed a significantly lower 28-day all-cause mortality in patients who were treated with corticosteroids compared with usual care or placebo. Another meta-analysis[23] confirmed these results.

The relationship between administration of high-dose corticosteroids and improvement in conditions of mechanical ventilation may be explained by decreased pulmonary inflammation, reflected by a significantly lower CRP. This mechanism has been proven in ARDS. [18]
To hypothesise, by relief of pulmonary inflammation, mechanical ventilation conditions improve, which presumably translates to decreased organ failure as displayed in an almost halving of SOFA scores two weeks after initiation of high-dose methylprednisolone. This decrease in SOFA scores may lead to decreased mortality in patients with COVID-19 pneumonia meeting severe ARDS criteria. In our population no significant side effects were found. Comparably, no serious short-term side effects were reported in different dose regimens of corticosteroids in the recently published meta-analysis.[22] However, long-term consequences remain unknown.

Our study has many limitations, especially due to the observational, non-controlled, single-centre design in a small number of patients. However, to our knowledge, there are no trials investigating the potential benefit of a longer, high-dose treatment with corticosteroids for the more severely affected COVID-19 patients who fail to respond to the initial treatment. Our study shows that a long, high-dose treatment with corticosteroids is both effective and safe. The success of other clinical trials such as the Recovery trial with use of dexamethasone for ten days, is an invitation to reduce our steroid dose and duration in the future, especially to decrease side effects. Whether the much shorter and lower dosed corticosteroid treatments used in most of the previously mentioned clinical trials are sufficient for the more affected ICU patients remains to be investigated. As well as whether prolonged therapy with high-dose corticosteroids is effective in patients who show progression of the disease after the initial treatment. In learning more about treating severely ill COVID-19 patients, our observed beneficial effect of high-dose steroids may be biased by other unidentified contributing treatment factors.

Conclusion

In our 17 ICU patients suffering from COVID-19 pneumonia meeting criteria of severe ARDS, administering high-dose corticosteroids seemed to provide a significant improvement in both oxygenation and ventilation, as well as a rapid decline of the inflammation markers. Doing so also proved safe within our small population.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

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