Multidisciplinary Respiratory Medicine 2021; volume 16:781

pagepress

SHORT REPORT

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Identification of patients with COVID-19 who are optimal for methylprednisolone pulse therapy

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ABSTRACT

Background: Corticosteroids have been reported to reduce the mortality rates in patients with coronavirus disease 2019 (COVID-19). Additionally, the role of high-dose methylprednisolone pulse therapy in reducing mortality in critically ill patients has also been documented. The purpose of this study is to identify patients with COVID-19 who are suitable for methylprednisolone pulse therapy.

Methods: This was a retrospective study that included patients with COVID-19 receiving methylprednisolone pulse therapy (≥250 mg/day for 3 days) with subsequent tapering doses at our hospital between June 2020 and January 2021. We examined the differences in background clinical factors between the surviving group and the deceased group.

Results: Out of 156 patients who received steroid therapy, 17 received methylprednisolone pulse therapy. Ten patients recovered (surviving group) and seven patients died (deceased group). The median age of the surviving and deceased groups was 64.5 years (range, 57-85) and 79 years (73-90), respectively, with a significant difference (p=0.004). Five of the deceased patients (71%) had developed serious complications associated with the cause of death, including pneumothorax, pneumomediastinum, COVID-19-associated pulmonary aspergillosis, cytomegalovirus infection, and bacteremia. On the other hand, out of the 10 survivors, only one elderly person had cytomegalovirus infection and the rest recovered without complications.

Conclusion: Administration of methylprednisolone pulse therapy with subsequent tapering may be an effective treatment in patients with COVID-19 up to the age of early 70s; however, severe complications may be seen in elderly patients.

Key words: Coronavirus disease 2019; corticosteroids; pulse steroid therapy; methylprednisolone; complications.

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Contributions: SR, NN, contributed to the acquisition of data and prepared the manuscript. All the authors contributed to the interpretation of data, read and approved the final manuscript.

Conflict of interest: None declared.

Funding: No funding received for this study.

Availability of data and materials: Data are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate: The Institutional Review Board of St. Luke 's International Hospital approved this retrospective study (20-R074).

Introduction

Coronavirus disease 2019 (COVID-19) was first reported in late December 2019, and has since then spread rapidly worldwide. The RECOVERY trial has demonstrated that corticosteroids improve the 28-day mortality rate of patients with COVID-19 who are on oxygenation or invasive mechanical ventilation [1], and subsequent meta-analysis also supported the efficacy of steroids [2]. Moreover, high-dose methylprednisolone pulse therapy has been shown to be more effective in patients with more severe respiratory failure than in those in the RECOVERY trial. Edalatifard *et al*. reported the efficacy of intravenous methylprednisolone pulse therapy (250 mg/day for 3 days) in a single-blinded randomized controlled trial. In that study, 49 out of 62 patients (79%) were on oxygen mask or non-invasive mechanical ventilation at baseline [3]. We have also previously reported good outcomes in seven patients with COVID-19 who received methylprednisolone pulse therapy (500-1,000 mg/day for 3 days); 6 out of 7 patients (86%) were intubated at the initiation of methylprednisolone pulse treatment [4]. With limited and restricted access to novel therapeutic agents, such as expensive monoclonal antibodies and molecular targeted drugs, methylprednisolone pulse therapy may serve as a realistic treatment option, as it is relatively affordable and popular. The aim of this study was to ascertain the type of patients best suited to receiving methylprednisolone pulse therapy. Clinical factors of patients with COVID-19 pneumonia who received methylprednisolone pulse therapy were evaluated and comparisons were made between the surviving and deceased groups.

Methods

Among 156 patients with COVID-19, who received corticosteroids at our hospital between June 2020 and January 2021, 17 patients received methylprednisolone pulse therapy (≥250 mg/day for 3 days). Subsequent dose tapering was performed in all patients: methylprednisolone (0.5 to 1.0 mg/kg/day) was initiated after pulse therapy and reduced by 5 to 10 mg according to respiratory status every 3 to 7 days. Ten patients recovered and were discharged (surviving group), and seven patients died (deceased group). To compare the differences between the two groups, the Mann-Whitney *U* test was utilized for nonparametric continuous variables, and Fisher's exact test was conducted for categorical variables. Statistical significance was set at $p<0.05$. Statistical analyses were performed using R software (version 4.0.4; R Foundation for Statistical Computing, Vienna, Austria). The institutional review board approved this study (20-R074), and the need for written informed consent was waived because of the retrospective design.

Results

The clinical characteristics of the surviving group compared with those of the deceased group are listed in Table 1. The median age of surviving group was 64.5 years (range, 57–85), which was significantly lesser than that of deceased group at 79 years (73–90) (p=0.004, Table 1 and Figure 1). None of the patients had been treated with corticosteroids or had autoimmune disease prior to admission. The number of comorbidities per patient was found to be lower in the surviving group than that in the deceased group (1.5 *versus* 3). There were no significant differences in the laboratory data on the day of administration of pulse therapy between the two groups (*data not shown*). In arterial blood gas analyses performed immediately before the administration of methylprednisolone pulse therapy, the partial pressure of arterial oxygen (PaO_2) / fraction of inspiratory oxygen (FiO_2) ratio was higher in the surviving group than in the deceased group (210 versus 147). Eight patients (80%) in the surviving group and seven patients (100%) in the deceased group had received corticosteroids after admission and before administration of pulse therapy: methylprednisolone (0.5 to 1.0 mg/kg/day) was administered to 13 patients, and dexamethasone (6.6 mg/day) was administered to two patients. Among the surviving and deceased groups, the median duration between the onset of symptoms and admission was 6 days and 4 days, respectively. The median duration between symptom onset to intubation was 10.5 days and 7.5 days, respectively, and that between symptom onset to administration of first dose of pulse therapy was 9 days and 7 days, respectively. The median duration of corticosteroid treatment of the surviving group was significantly less, *i.e*., 13.5 days (interquartile range [IQR], 10–16), while that of deceased group was 32 days (22.5-41.5) (p=0.008). In the surviving group, the median number of days from onset to discharge was 30 and that from onset to death was 37 days. In the surviving group, nine patients (90%) had no severe complications and an 85-year-old patient had cytomegalovirus (CMV) infection as a severe complication. Five patients in the deceased group (71%) developed serious complications, such as pneumothorax, pneumomediastinum, COVID-19-associated pulmonary aspergillosis (CAPA), CMV infection, and bacteremia, which were associated with the cause of death.

Discussion

This study revealed that the patients with COVID-19 receiving methylprednisolone pulse therapy up to their early 70s survived but the patients in their late 70s and older died, suggesting that the younger surviving group may have benefited from the pulse therapy, while the older deceased group did not seem to benefit from it.

At the start of the pandemic, corticosteroids were not recommended for COVID-19 because of concerns raised about pro-

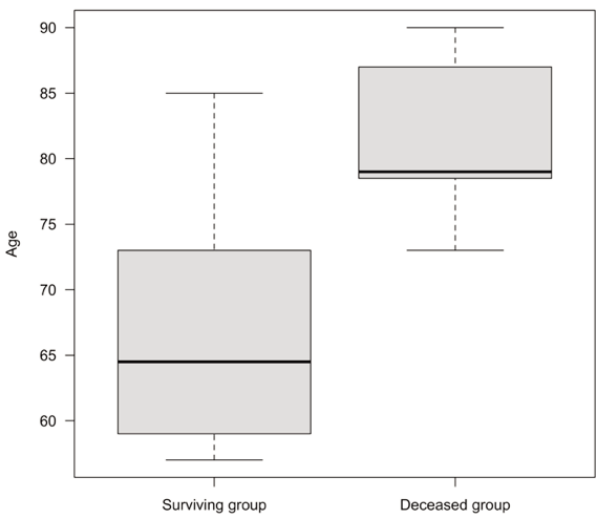

Figure 1. Age differences between the surviving and the deceased groups.

longed viral excretion and negative evidences in other coronavirus diseases [5]. However, RECOVERY trial showed that dexamethasone improved the 28-day mortality rates in patients with COVID-19 who were on oxygenation [1]. This overwhelmingly large-scale trial resulted in the suspension of other ongoing randomized controlled trials that were expected to evaluate corticosteroids other than the 6 mg/day administration of dexamethasone. Consequently, the optimal type, dosage, starting time, and duration of corticosteroids and their administration for COVID-19 were still unclear. Ko *et al.* reported in a retrospective study that methylprednisolone (1.0 mg/kg/day for more than 3 days) compared to dexamethasone (6 mg/day for more than 7 days) improved all-cause mortality rates within 50 days in patients with severe COVID-19 who needed intensive care (16.4% *vs* 26.5%, respectively) [6]. This study suggested that the efficacy of corticosteroids was not specific to dexamethasone, but was rather based on the anti-inflammatory effects of the corticosteroids. Weight-adjusted high-dose methylprednisolone could strongly suppress the inflammation. On the contrary, Jeronimo et al. reported that methylprednisolone (0.5 mg/kg twice daily for 5 days) did not reduce the 28-day mortality rates in COVID-19 patients with oxygen demand in a double-blinded, randomized, placebo-controlled trial [7]. However, more critically ill patients were included in this study compared to the RECOVERY trial, which may explain the lack of efficacy of the corticosteroid dose and duration. Even with these clinical situations, the exploratory analyses showed that the mortality rates were reduced in patients over 60 years of age. Therefore, identification of patients with COVID-19 who are optimally suited for higher doses of corticosteroids is the need of the hour.

In a retrospective study from Spain, mortality rates were not different between administration of methylprednisolone 1

Table 1. Clinical characteristics of the patients in the surviving and the deceased groups.

	Surviving	Deceased	p*
n	10	7	
Age (range)	64.5 (57-85)	79 (73-90)	0.004
Sex, male	7 (70)[#]	4 (57)	0.644
Body mass index, kg/m^2	23.3 (21.9-28.2)	22.8 (19.1-25.4)	0.364
Smoking history	4 (40)	3 (43)	1
Comorbidities			
Number of comorbidities per patient	1.5 (0.3-2.8)	3 (2.5-3.0)	0.313
Hypertension	3 (30)	5 (71)	0.153
Dyslipidemia	1 (10)	2 (30)	0.537
Diabetes mellitus	3 (30)	3 (43)	0.644
Chronic kidney disease	4 (40)	3 (43)	1
Coronary artery disease	2 (20)	0 (0)	0.485
Asthma	1 (10)	1 (14)	1
Chronic obstructive pulmonary disease	1 (10)	1 (14)	1
Interstitial pneumonia	2 (20)	1 (14)	1
Malignancy	2 (20)	1 (14)	1
Respiratory condition at the time of pulse administration			
PaO_2/FiO_2 ratio	210 (151-242)	147 (129-244)	0.491
Nasal cannula	4 (40)	3 (43)	1
Face mask	4 (40)	1 (14)	0.338
High flow oxygen therapy	1 (10)	0 (0)	1
Intubation	1 (10)	3 (43)	0.25
Methylprednisolone pulse therapy			
Standard doses of steroids before first pulse	8 (80)	7 (100)	0.485
Pulse administration more than once	1 (10)	3 (43)	0.25
Tapering of steroids after pulse	10 (100)	7 (100)	
Treatment and outcome			
Do-not-resuscitate/do-not-intubate	0 (0)	3 (43)	0.051
Invasive mechanical ventilation	6 (60)	4 (57)	1
Onset to admission, days	6 (4.25-7.75)	4 (3-6.5)	0.402
Onset to initiation of oxygenation, days	7 (4-8)	6 (5-7.5)	0.765
Onset to intubation, days	10.5 (7.75-11.75)	7.5 (7-8.5)	0.33
Onset to the first pulse administration, days	9 (8.25-10.75)	7 (7-8.5)	0.324
Onset to discharge/death, days	29.5 (22-34.5)	37 (29-46.5)	0.305
Cumulative doses of methylprednisolone, mg	2112 (1892-3051)	3089 (2745-3737)	0.118
Duration of steroids, days	13.5 (10-16)	32 (22.5-41.5)	0.008
Complications	1 (10)	5 (71)	0.035
Pneumothorax or pneumomediastinum	0 (0)	3 (43)	
COVID-19-associated pulmonary aspergillosis	0 (0)	3 (43)[§]	
Cytomegalovirus infection	1 (10)	1 (14)	
Bacteremia	0 (0)	1 (14)	

*Mann-Whitney *U* test or Fisher's exact test; [#]n (%) or median (interquartile range); [§]two suspected cases with positive *Aspergillus* galactomannan antigen tests.

mg/kg/day and administration of methylprednisolone as pulse therapy [8]. However, these groups were classified by the initial doses administered, with 22.5% of the 1 mg/kg/day group later receiving pulse therapy as salvage. The pulse therapy group also included 20.1% patients being administered relatively low doses of less than 250 mg/day. Therefore, although this study claimed that 1 mg/kg/day of methylprednisolone reduced mortality, the above limitations could not overrule the need for pulse therapy. There are several other reports demonstrating the efficacy of methylprednisolone pulse therapy, but they had limitations related to the target patient population.

The median age of the surviving and deceased groups in this study was 64.5 years and 79 years, respectively (p=0.004). In a single-blinded randomized controlled trial from Iran that included 68 patients, the mean age of the patients was 55.8 ± 16.4 years [3]. In a single-center retrospective cohort study from Russia that included 34 patients, the median age was 59 years (interquartile range, 52–67 years) [9]. In our previous case series, which included seven patients, the median age was 69 years (range 41–77), similar to that of the surviving group in this study [4]. Although there were no inclusion criteria for age in these studies, there were very few patients aged in their late 70s and beyond. The efficacy and risks of methylprednisolone pulse therapy in patients of this age group have not been sufficiently investigated yet. It is well established that increasing age is one of the predictive factors for severe disease in patients with COVID-19 [10]. In our study, we observed that severe complications could have a negative influence on the outcomes of the patients who received methylprednisolone pulse with subsequent tapering of the dose, and that often resulted in death.

Pneumothorax and pneumomediastinum, CAPA, and CMV infections were significant severe complications found in our study. Pneumothorax and pneumomediastinum result in poor prognosis among patients aged >70 years [11]. CAPA is frequently found in patients with COVID-19 who receive corticosteroids and causes an increase in mortality rates [12]. There are few reports that have showed an association between COVID-19 and CMV infection. However, severe disease and long-term use of immunosuppressants, as seen in our cases, are known to reactivate CMV [13,14]. In the surviving group, only one 85-year-old patient, the oldest, had CMV infection; the patient recovered with ganciclovir treatment. The remaining relatively younger patients of this group had no complications after methylprednisolone pulse therapy.

Methylprednisolone pulse therapy could be effective in patients with severe COVID-19 who are refractory to standard corticosteroids and are consequently recommended the use of novel but expensive anti-inflammatory agents, such as monoclonal antibodies and molecular targeted drugs. In this study, it was difficult to evaluate the tolerance of methylprednisolone pulse therapy according to age, owing to the small number of patients. However, the boxplot in Figure 1 clearly shows that patients up to the age of early 70s were successfully treated, whereas patients in their late 70s and older often failed to respond to treatment due to severe complications, such as pneumothorax, pneumomediastinum, CAPA, CMV infection, and bacteremia. Therefore, we consider it reasonable to avoid methylprednisolone pulse and subsequent tapering therapy in patients in their late 70s and older. Further research is needed to determine the optimal type, dosage, start time, and the duration of corticosteroid treatment in patients with severe COVID-19. The safety and efficacy of high-dose corticosteroids should be demonstrated in randomized trials or big data analyses.

Conclusion

Based on the data shown in this study, we suggest that methylprednisolone pulse and subsequent tapering therapy may be an effective treatment in patients up to their early 70s, while eliminating the need for using novel anti-inflammatory agents that are usually expensive. However, the possibility of complications, such as pneumothorax, pneumomediastinum, CAPA, CMV infection, and bacteremia, should be born in mind for older patients.

Abbreviations

COVID-19: coronavirus disease 2019;
CMV: cytomegalovirus;
CAPA: COVID-19-associated pulmonary aspergillosis;
PaO_2: partial pressure of arterial oxygen;
FiO_2: fraction of inspiratory oxygen.

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Received for publication: 11 May 2021. Accepted for publication: 15 June 2021

Multidisciplinary Respiratory Medicine 2021; 16:781
doi:10.4081/mrm.2021.781