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Original article

Clinical outcomes of corticosteroids for COVID-19 patients at the National Center for Global Health and Medicine during the first wave of infections

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ARTICLE INFO

Article history:
Received 29 April 2021
Received in revised form
3 November 2021
Accepted 4 November 2021
Available online 26 November 2021

Keywords:
COVID-19
Corticosteroids
SARS-CoV 2
Japan

ABSTRACT

Background: Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2, has been a significant concern worldwide since its outbreak in December 2019. Various treatments are being researched and developed, and there are reports that dexamethasone has reduced the mortality rate and improved the clinical course of critically ill patients with COVID-19. In this study, we examined the clinical efficacy of corticosteroid therapy for patients with COVID-19 in our hospital during the first wave of infections.

Methods: We retrospectively reviewed the medical records of patients with COVID-19 who were treated with or without corticosteroid therapy at the National Center for Global Health and Medicine in Japan between February and April 2020. The primary outcome was improvement in the patients' clinical course using a seven-category ordinal scale. We collected data on patient characteristics, treatment, and clinical course, and compared them between two groups: the steroid-using group and the non-steroid-using group.

Results: Between February and April 2020, 110 patients were diagnosed with COVID-19. Despite poor conditions during admission into the steroid group, there were no statistical differences in clinical course between both groups, as measured using the scale. There were no statistical differences between the two groups in the number of days to fever resolution or negative polymerase chain reaction results.

Conclusions: There was no difference in the clinical course between both groups. Because of the difference in background, corticosteroids may potentially make the clinical course of severely ill patients similar to that of mildly ill patients.

Abbreviations: COVID-19, coronavirus disease 2019; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; WHO, World Health Organization; PCR, polymerase chain reaction.

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https://doi.org/10.1016/j.resinv.2021.11.001

1. Introduction

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2, has become a serious global concern since its emergence in December 2019 [1]. In severe cases of COVID-19 pneumonia, 15% of patients progress to acute respiratory distress syndrome (ARDS), which necessitates admission to the intensive care unit (ICU) and leads to high mortality rates [2,3]. The effects of steroids on severe pneumonia in patients with COVID-19 have been verified worldwide. The RECOVERY study found that the use of dexamethasone is associated with lower 28-d mortality rates in patients requiring oxygen support [4], and the CoDEX Randomized Clinical Trial has shown that the addition of dexamethasone to standard therapy statistically increased the number of ventilation-free days to over 28 d in patients with COVID-19-associated moderate to severe ARDS [5]. Based on these results, the World Health Organization (WHO) guidelines recommend the use of corticosteroids for patients with severe COVID-19 [6].

In our hospital, hydrocortisone and methylprednisolone were used to treat COVID-19 from the early stages of infection according to the dosing regimen used for ARDS and severe pneumonia [7,8]. The purpose of our study was to evaluate the clinical efficacy of these corticosteroids against COVID-19 in our hospital.

2. Patients and methods

2.1. Study population

To compare the efficacy of corticosteroids against COVID-19, we retrospectively reviewed the medical records of patients with COVID-19 who were admitted to the National Center for Global Health and Medicine in Japan between February and April 2020. We collected data on patient characteristics, treatment, and clinical course, and categorized them into two groups: the steroid-using group (steroid group) and the non-steroid-using group (non-steroid group). Furthermore, we checked the medical records of the steroid group and selected cases that were administered according to ARDS and severe pneumonia protocols. The doses were as follows: hydrocortisone administered intravenously at 200 mg, followed by continuous infusion at 10 mg/h for 7 d for severe pneumonia [7], along with methylprednisolone for the treatment of ARDS that was tapered and completed within 28 d [8]. Patients who were given doses that deviated from the standard used to treat severe pneumonia and ARDS were excluded.

Severity was defined as follows: on the seven-category ordinal scale, a score of 1–3 indicated “mild,” 4 indicated “moderate,” and 5 to 7 indicated “severe.” The seven-category ordinal scale is shown in Table 1.

This study was approved by the Ethical Review Committee of the National Center for Global Medicine and Research Hospital (NCGM-G-004162-00) in April 2021. This study was conducted in compliance with the Declaration of Helsinki (revised Fortaleza, 2013) and the Ethical Guidelines for Medical Research Involving Human Subjects (partially revised on February 28, 2017). The patients who participated in this study were required to provide informed consent.

2.2. Detection of COVID-19

The diagnosis of COVID-19 was established with polymerase chain reaction (PCR)-based methods using nasal and pharyngeal swab specimens.

2.3. Outcome

The primary outcome was a 2-point improvement from the lowest value during hospitalization on the seven-category ordinal scale (Table 1). When the minimum value was 2, improvement was defined as a change from 2 to 1. Observation was terminated if the patient improved and was transferred to a general hospital or hotel, extracorporeal membrane oxygenation was introduced, or death occurred. We compared the different clinical courses within the study population using the seven-category ordinal scale. The clinical course was also compared in moderately and severely ill patients (seven-category ordinal scale, 4 points or more).

The secondary outcomes were mortality at day 28, days to fever resolution, and days to negative PCR results. Fever resolution was defined as a body temperature of 37 °C or lower sustained for at least 24 h. PCR specimens were collected at intervals of at least 24 h after symptom resolution until the results were negative.

2.4. Statistical analysis

To evaluate the differences in the clinical characteristics between the patients, Fisher's exact test was performed. A two-sided test was used, and the significance level was set at $p < 0.05$. We also performed Gray's test to compare the cumulative incidence of a 2-point improvement between both groups. EZR Ver. 1.41 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [9] was used for the statistical analyses.

3. Results

3.1. Patient characteristics

We identified 110 patients diagnosed with COVID-19 between February and April 2020. The differences in patient characteristics are shown in Table 2. There were some differences in the characteristics of the patients at the time of admission. The median (range) age was 67 (54–71) y in the steroid group and 46 (33–56) y in the non-steroid group, with patients being significantly older in the steroid group ($p < 0.001$). Hypertension was also more common in the steroid group ($p < 0.001$). There were no apparent differences in sex, cardiovascular disease, diabetes, malignancy, autoimmune disease, body mass index, smoking history, or use of immunosuppressive drugs.

Clinical manifestations were significantly worse in the steroid group at baseline, with more febrile patients and significantly more patients requiring oxygen (scores of 4–7 on

Table 1 – Seven-category ordinal scale.

point	Status
1	discharge (alive)
2	hospital admission, not requiring supplemental oxygen, no admission requirement[a]
3	hospital admission, not requiring supplemental oxygen
4	hospital admission, requiring supplemental oxygen
5	hospital admission, requiring high-flow nasal cannula or noninvasive mechanical ventilation
6	hospital admission, invasive mechanical ventilation
7	death

[a] "no admission requirement" includes isolation periods with up to two negative polymerase chain reaction tests at least 24 h apart in the first wave in Japan, or the need for continued hospitalization for non-coronavirus disease conditions, such as rehabilitation.

the seven-category ordinal scale) (Table 3). The treatment details for each group are listed in Table 4.

To match the clinical status of the patients as closely as possible, we focused on patients with a score of 4–7 on the seven-category ordinal scale who required oxygen on admission. The baseline values for the steroid and non-steroid groups are presented in Tables 5 and 6. Due to the small number of patients, statistical tests were not performed. Even when the criterium was narrowed down to 4 to 7 points, nine patients in the steroid group and one patient in the non-steroid group underwent invasive positive pressure ventilation, suggesting higher severity in the steroid group (Table 6).

Table 2 – Characteristics of coronavirus disease patients in this study (n = 110).

	Steroid (n = 22)	Non-steroid (n = 88)	*p*-value[a]
Age (y), median (range)	67 (54–71)	46 (33–56)	<0.001
Sex			
Female	4	26	0.42
Male	18	62	
Comorbidity			
Hypertension	16	17	<0.001
Cardiovascular disease	3	3	0.93
Diabetes	7	12	0.06
Malignancy	0	0	1
Autoimmune disease	0	2	1
BMI >25	11	37	0.63
Smoking			
Never	11	53	0.47
Current/Former	11	35	
Immunosuppressive agent	1	0	0.20

BMI, Body Mass Index.
[a] Fisher's exact test.

Table 3 – Clinical manifestations and physical signs of coronavirus disease patients.

	Steroid use (n = 22)	Non-steroid (n = 88)	p-value
Initial Symptoms			
Fever (%)			
<37.0	0	28 (32)	<0.001
>37.0	22 (100)	60 (68)	
Cough (%)	16 (73)	62 (70)	
Dyspnea (%)	15 (68)	26 (30)	
Dysosmia/dysgeusia (%)	1 (4.5)	23 (26)	
Diarrhea (%)	8 (36)	23 (26)	
7-category ordinal scale on admission			
4–7 (%)	18 (81)	11 (7)	<0.001
1–3 (%)	4 (19)	77 (93)	

3.2. *Primary outcome*

The cumulative probabilities showed the number of days to a 2-point improvement from the lowest value in the seven-category ordinal scale using Kaplan-Meier analyses (Fig. 1A). There were no statistically significant differences between the steroid and non-steroid groups (p = 0.27). The results were similar when the baseline was analyzed in patients with a score of 4–7 on the seven-category ordinal scale (p = 0.56) (Fig. 1B).

3.3. *Secondary outcome*

The 28-d mortality rates in the steroid and non-steroid groups were 2/22 (9%) and 0/88 (0%), respectively (p = 0.039). The number of days to fever resolution and the number of days to negative PCR results in patients who scored 4 to 7 on the

Table 4 – Details of treatment given during hospitalization.

	Steroid (n = 22)	Non-steroid (n = 88)
Types of steroids		
Methylprednisolone	14	
Hydrocortisone	8	
Antiviral treatment		
Remdesivir or placebo	5	9
Favipiravir	4	3
Lopinavir/Ritonavir	2	5
Hydroxychloroquine	12	20
Ciclesonide	1	5
Tocilizumab	0	0
PMX-DHP	7	0
Respiratory Support		
Nasal Cannula	21	15
Non-invasive ventilation	4	0
Invasive ventilation	10	1
ECMO	2	1

PMX-DHP: Direct hemoperfusion therapy using a polymyxin B-immobilized fiber column, ECMO: extracorporeal membrane oxygenation.

Table 5 – Characteristics of coronavirus disease patients with a score of 4–7 in the seven-category ordinal scale on admission.

	Steroid (n = 18)	Non-steroid (n = 11)
Age (y), median (range)	69 (45–91)	61 (31–85)
Sex		
Female	4	2
Male	14	9
Comorbidity		
Hypertension	13	6
Cardiovascular disease	2	1
Diabetes	6	4
Malignancy	0	0
Autoimmune disease	0	1
BMI >25	8	6
Smoking		
Never	11	3
Current/Former	7	8
Immunosuppressive agent	1	0
Seven-category ordinal scale		
7	0	0
6	4	0
5	2	0
4	12	11

BMI, Body Mass Index.

seven-category ordinal scale are shown in Fig. 2A and B. No significant difference was found between the two groups.

4. Discussion

In this study, we compared the difference in clinical course between the steroid group and non-steroid group using the seven-category ordinal scale. There was no statistically significant difference between the two groups.

Although the steroid group was considered to have greater disease severity based on clinical status and age, the clinical course of its patients was similar to that of the non-steroid group, which had a higher proportion of patients with mild forms of COVID-19. Based on these results, we presume that steroid administration may have the potential to equalize the clinical course of groups of patients with different disease severities. The mortality rate was statistically significantly higher in the steroid group. We did not adjust for background factors because of the small sample size, which may have affected the difference in the known severity of the patients. Contrary to expectations, there was no significant difference in the number of days until fever resolution, and there was no delay in viral excretion in the steroid group compared to the non-steroid group, suggesting that the risk of prolonged infection due to steroid use is low.

In our study, the patients in the steroid group were older (67 vs. 46 y, $p < 0.001$) and included a greater number of hypertensive patients ($p < 0.001$). In addition, more patients had a fever on admission ($p < 0.001$), and more patients had a score of 4–7 on the seven-category ordinal scale (patients requiring oxygenation or mechanical ventilation) ($p < 0.001$), indicating that the severity was higher in the steroid group. Nevertheless, there was no significant difference in the primary endpoint, which was the cumulative incidence of days to two-point improvement from the lowest score in the seven-category ordinal scale, between the steroid and non-steroid groups. Thus, we believe that steroids have the potential to equalize the clinical outcomes of severely and mildly affected COVID-19 patients.

There was no difference in the clinical course between the two groups, even when the baseline was narrowed down to moderate to severe disease with a score of 4–7 on the seven-category ordinal scale. Similarly, for patients with moderate to severe disease, more patients in the steroid group scored 5 to 6 points, while more patients in the non-steroid group scored 4 points, suggesting that the clinical courses of patients in the two groups may have been similar despite differences in severity.

From these results, we estimate that corticosteroids have the potential to improve the clinical course of patients with severe forms of COVID-19 to a course similar to that of patients with mild forms of the disease. Since there was no significant difference in the clinical course of patients with or without mild disease, we conclude that steroids may not affect the clinical course of patients with mild forms of COVID-19.

We started using corticosteroids when the infection spread in Japan in February 2020; this treatment had not yet been established at the time. We treated patients with moderate to severe COVID-19 with corticosteroids as a clinical practice during the early phase of infection spread in Japan. Since cytokine release syndrome [10,11] and ARDS [2,3] have been reported to develop in patients with moderate to severe COVID-19, hydrocortisone and methylprednisolone were administered based on the results of a previous study

Table 6 – Treatment regimen and prognosis of coronavirus disease patients with points of 4–7 in the seven-category ordinal scale on admission.

	Steroid (n = 18)	Non-steroid (n = 11)
Types of Steroids		
Methylprednisolone	12	
Hydrocortisone	6	
Antiviral treatment		
Remdesivir	2	1
Favipiravir	3	1
Lopinavir/Ritonavir	2	2
Hydroxychloroquine	10	6
Ciclesonide	1	2
tocilizumab	0	0
PMX-DHP	6	0
Respiratory Support		
Nasal Cannula	18	11
Non-invasive ventilation	4	0
Invasive ventilation	9	1
ECMO	2	1

PMX-DHP: Direct hemoperfusion therapy using a polymyxin B-immobilized fiber column, ECMO: extracorporeal membrane oxygenation.

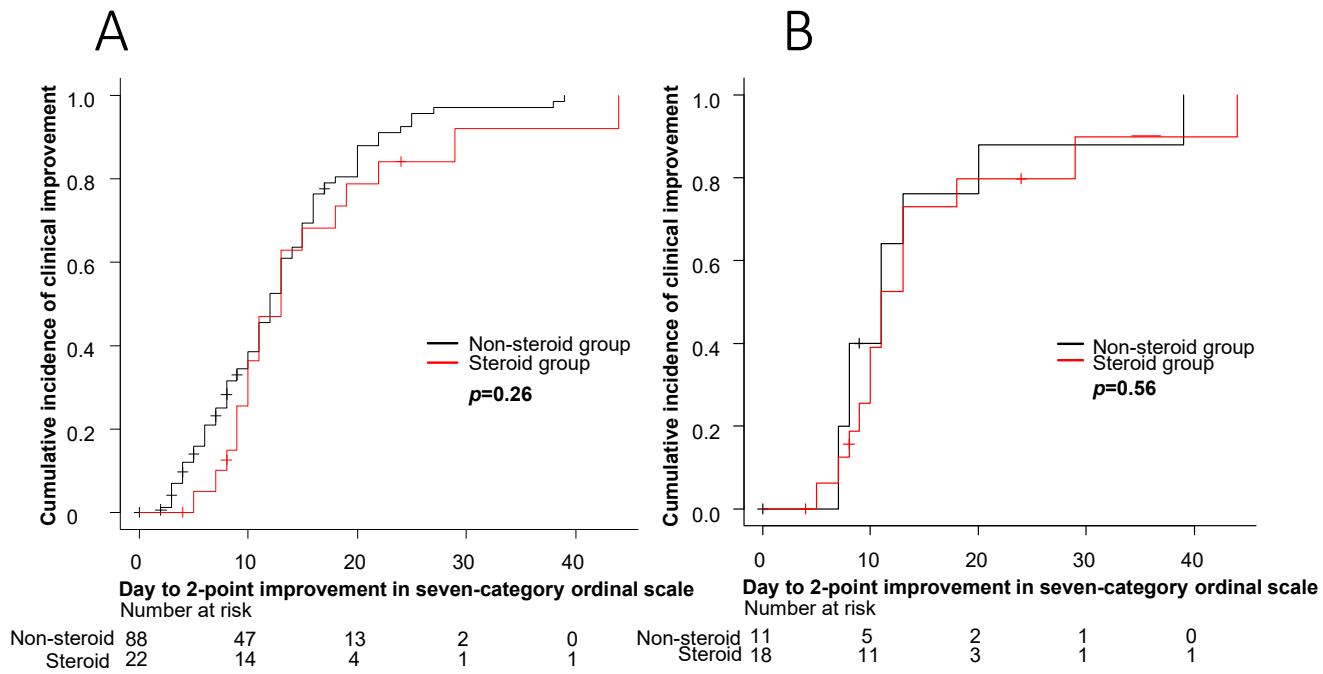

Fig. 1 – Cumulative probabilities showing days to a two-point improvement from the lowest value in the seven-category ordinal scale. (A) all patients, (B) patients with a score of 4–7 in the seven-category ordinal scale on admission.

[7,8]. At the beginning of the infection spread in Japan, even patients with mild disease were admitted to the hospital if their PCR results were positive. As a result, many patients with less severe forms of the disease were admitted. Corticosteroids were administered at the discretion of the physician in charge, and, as a result, patients with moderate to severe disease forms tended to receive corticosteroids, while patients with mild disease forms did not. In this cohort, however, there was no significant difference in the clinical course between the two groups, nor was there a significant difference in the number of days until negative PCR test results were obtained.

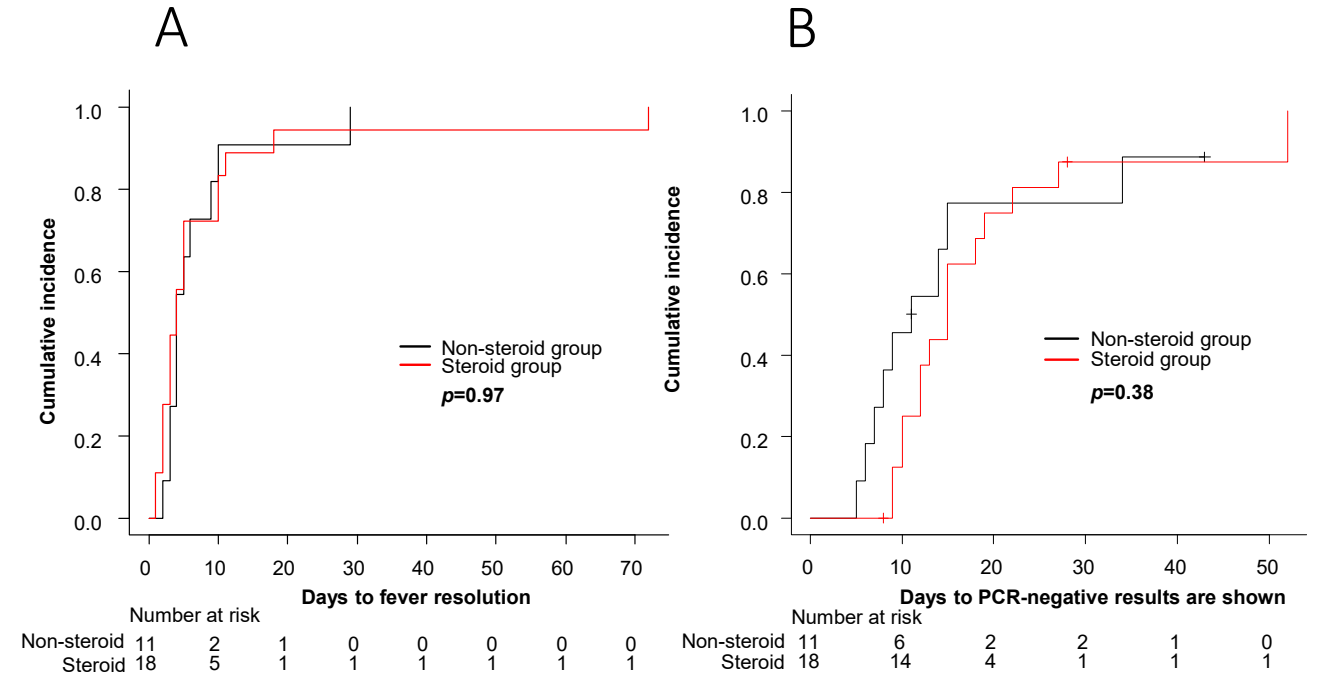

Fig. 2 – Number of days to fever resolution (A) and the number of days to negative polymerase chain reaction test results (B) are shown.

This suggests that a short course of hydrocortisone or methylprednisolone can improve the prognosis of patients with moderate to severe forms of COVID-19 requiring oxygenation to that of patients with mild forms of the disease without markedly delaying viral excretion.

The severity of the disease in patients diagnosed with COVID-19 was mostly mild (81%), but it was severe in 14% of the patients, with symptoms such as dyspnea, respiratory frequency, and hypoxia, while 5% of the patients were critical [12]. Diabetes, hypertension, obesity, smoking history, and cardiovascular disease have been reported as risk factors for severe disease [13–17]. In this study, we also showed that hypertension was more common in the steroid group, which is generally considered a more severely affected population.

Previous studies have reported that the host immune response may be associated with disease severity [10,11,18] and that the efficacy of corticosteroids for cytokine-release syndrome has been investigated since the spread of the infection. The RECOVERY trial has shown that in severe cases of COVID-19, dexamethasone administration was associated with a reduction in 28-d mortality rates [4]. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group has reported that systemic corticosteroids, including dexamethasone, hydrocortisone, and methylprednisolone, reduced mortality at 28 d [19]. Therefore, corticosteroids are now recommended in the WHO guidelines for patients with severe COVID-19 [6].

The optimal dose and duration of corticosteroid therapy for COVID-19 is still under debate: the REACT working group concluded that there is no evidence that high doses of corticosteroids have a better effect than do low doses [19]. However, Edalatifard found that methylprednisolone pulses (250 mg/day intravenously for 3 d) could improve the clinical course and mortality of hospitalized patients with severe COVID-19 [20]. As for the timing of administration, some studies have also shown that methylprednisolone pulses in the late stages of COVID-19 can lead to an improved prognosis [21,22]. Regarding the duration of treatment, Jeronimo et al. found that a short course of methylprednisolone given to patients with COVID-19 did not reduce mortality rates [23].

Recently, Chen et al. found that corticosteroids in combination with tocilizumab in patients with an increased inflammatory phenotype may reduce progression to the composite outcome of mechanical ventilation or death [24]. Further studies are needed to determine the optimal dose, duration, and target of corticosteroids and their combination with other anti-inflammatory drugs.

There were several limitations to this study. First, this was a single-center study with a limited sample size. Second, because this was a retrospective study, there was a bias in the background between the two groups. Unfortunately, the small sample size did not allow us to adjust for the background factors between the two groups.

5. Conclusion

In conclusion, the steroid group did not differ from the non-steroid group in terms of the outcome in the first wave of infections. Because of the difference in the severity of the background of the two groups, we estimate that corticosteroid therapy may improve the prognosis of patients with moderate to severe COVID-19. Further studies on corticosteroid therapy for COVID-19 are warranted.

Funding

No funds, grants, or other support was received.

Conflict of Interest

Yoshie Tsujimoto received research grants from Roche Diagnostic Inc. Masayuki Hojo received Honoraria from AstraZeneca, GlaxoSmithKline, Novartis Pharma, and Boehringer Ingelheim. Chie Morita, Manabu Suzuki, Shinyu Izumi, Akinari Tsukada, Keita Sakamoto, Masao Hashimoto, Jin Takasaki, and Norio Ohmagari have no conflict of interest.

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.

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