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Original Article

Comparison of methylprednisolone pulse vs conventional dexamethasone for adult cases of COVID-19 requiring oxygen; a Japanese retrospective cohort study

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ABSTRACT

Background: Although dexamethasone is an effective treatment in cases of coronavirus disease 2019 (COVID-19) requiring oxygen, the efficacy of methylprednisolone pulse is unclear. We compared the characteristics and outcomes of methylprednisolone pulse to those of dexamethasone.

Methods: We conducted a retrospective cohort study on adult COVID-19 cases requiring oxygen and no invasive mechanical ventilation treated with methylprednisolone pulse (1 g/day for 3 days) or dexamethasone (6 mg/day orally or 6.6 mg/day intravenously for ≥5 days). The primary outcome was intensive care unit (ICU) admission. The secondary outcomes were hospital mortality, length of hospital stay (LoS), duration of oxygen requirement, and requirement for hospital transfer, vasopressor(s), intubation, extracorporeal membrane oxygenation (ECMO), and continuous renal replacement therapy (CRRT).

Results: Twenty two cases of methylprednisolone pulse and 77 cases of dexamethasone were included. Mask ventilation was more common in the methylprednisolone pulse group (P < 0.001). The proportion of ICU admissions was similar between both groups (P = 0.635). The secondary outcomes of hospital mortality and the requirement for hospital transfer, vasopressor(s), intubation, and CRRT were similar between groups. No cases received ECMO. Median LoS (P = 0.006) and duration of oxygen requirement (P = 0.004) were longer in the methylprednisolone pulse group.

Conclusions: The proportion of ICU admissions was similar between the methylprednisolone pulse and the dexamethasone group. However, more cases in the methylprednisolone pulse group required mask ventilation than in the dexamethasone group, suggesting that some cases benefited from methylprednisolone pulse.

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an emerging infection with over 571 million confirmed cases and over 6.3 million deaths reported worldwide [1]. To combat this threat, treatments such as dexamethasone, remdesivir, baricitinib, and tocilizumab are recommended according to disease severity [2]. Dexamethasone is especially effective in cases of COVID-19 requiring oxygen. In the RECOVERY trial, 6 mg per day (mg/day) of dexamethasone reduced the incidence of death more effectively than usual care in cases of COVID-19 requiring oxygen therapy [3]. However, the efficacy of steroids other than dexamethasone has not been established, with alternative steroid options and doses remaining unclear. Previous studies have focused on the efficacy of methylprednisolone in COVID-19 cases [4–7]; however, the dose of methylprednisolone and the outcomes have varied among studies. For non-methylprednisolone pulse, the incidence of clinical deterioration in the group that received 1 mg per kilogram per day (/kg/day) of methylprednisolone was similar to the control group that received 0.9% normal saline [4]. A composite endpoint that included hospital mortality and intensive care unit (ICU) admission was similar between the methylprednisolone pulse group and the standard care group [5]. In contrast, all-cause mortality in the group that received 2 mg/kg/day of

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methylprednisolone was similar to the group that received 6 mg/day of dexamethasone [6]. Hospital mortality in cases that received 40 mg/day or more of methylprednisolone was higher than in cases that received less than 40 mg/day of methylprednisolone [7]. For methylprednisolone pulse, well-documented research about efficacy in cases of COVID-19 is lacking. Although the subgroup analysis in a systematic review reported an association between steroid dose and COVID-19 mortality, the referenced study did not conduct a comparison between dexamethasone and methylprednisolone, the dose of which was 250 mg/day for 3 days [8].

COVID-19 overwhelms the healthcare setting in many aspects. In 2019, the hospitalization cost per case of COVID-19 was $24,826 USD, around 1.8 times higher than the cost of influenza-related inpatient care [9]. The alarm has been sounded in the COVID-19 pandemic about the distress and burnout of healthcare workers, especially those working on the frontlines [10,11]. We need to decrease the burden on hospitals and healthcare workers without decreasing the level of care for COVID-19 patients.

Therefore, we conducted this study to determine which treatment, between methylprednisolone pulse and dexamethasone, prevented worsening of the disease and was associated with a shorter length of stay (LoS).

2. Patients and methods

We conducted a retrospective cohort study comparing methylprednisolone pulse and dexamethasone therapy in COVID-19 cases requiring oxygen and no invasive mechanical ventilation (IMV) using preexisting data at Tokyo Medical University Hospital (TMUH) in Tokyo, Japan, between April 2020 and October 2021. TMUH is a 904-bed tertiary university hospital and a facility for treating COVID-19 cases, from those requiring no oxygen to cases requiring IMV or extracorporeal membrane oxygenation (ECMO). Adults with COVID-19 were included in our study if they required oxygen therapy and received either methylprednisolone pulse or dexamethasone therapy. Based on the attending physician’s judgment, methylprednisolone pulse was administered to cases with rapidly worsening respiratory failure or severe respiratory failure at presentation. The exclusion criteria were cases under the age of 18 years, infection with SARS-CoV-2 after hospitalization to rule out the possibility that the underlying illness contributed to an extended LoS, refusal to participate in the study, and having received methylprednisolone pulse or dexamethasone under the condition of no required oxygen therapy or IMV.

The diagnosis of COVID-19 was made based on the identification of SARS-CoV-2 by reverse transcription polymerase chain reaction, loop-mediated isothermal amplification, and antigen test via nasopharyngeal swab or saliva. Methylprednisolone pulse was defined as 1 g/day of methylprednisolone for 3 days. The methylprednisolone pulse group included cases that had received prior dexamethasone use for COVID-19. Cases receiving methylprednisolone pulse that were admitted to the ICU during pulse therapy or received dexamethasone after methylprednisolone pulse were included in the methylprednisolone pulse group. The dexamethasone group included cases that received 6 mg/day orally or a 6.6 mg/day infusion of dexamethasone for 5 days or more. The doctor in charge decided whether to discontinue methylprednisolone pulse or dexamethasone based on improved oxygenation and the Japanese discharge criteria at the time. Supplemental oxygen devices included cannula, mask, and Oxymizer.

We analyzed the total number of COVID-19 admissions between April 2020 and October 2021 and the patients’ baseline characteristics, including sex, smoking history, age, body mass index (BMI), vaccination against SARS-CoV-2, underlying disease(s), oxygen device at commencement of methylprednisolone pulse or dexamethasone, laboratory data, and treatment medicine. Underlying diseases included diabetes mellitus, hematological malignancy, hypertension, chronic heart failure, asthma, emphysema, chronic kidney disease on hemodialysis, and infection with human immunodeficiency virus. Oxygen devices included cannula, mask, Oxymizer, and supplemental oxygen therapy, high-flow nasal therapy (HFN), non-invasive positive pressure ventilation (NPPV). Laboratory data were collected within 48 h before the administration of methylprednisolone pulse or dexamethasone. Treatment data included duration of steroid treatment and prior use of dexamethasone, remdesivir, favipiravir, anti-coagulant, or azithromycin.

The primary outcome was ICU admission. The secondary outcomes were hospital mortality, LoS, duration of oxygen requirement, the requirement for hospital transfer, vasopressor(s), intubation, ECMO, and continuous renal replacement therapy (CRRT), and complications, including bacterial infection (bacterial pneumonia, empyema, urinary tract infection, or catheter-related bloodstream infection), pneumothorax, pulmonary embolism, deep vein thrombosis, gastrointestinal bleeding, and delirium during the admission period. The P value between the methylprednisolone pulse group and the dexamethasone group was calculated.

Statistical analysis was performed using SPSS version 26 (IBM Corporation, Armonk, NY, USA). The continuous variable in normal distribution is presented as mean and standard deviation. The continuous variable in non-normal distribution is presented as median and interquartile range. Assessment of normality was performed using the Shapiro–Wilk test. Group comparisons were performed using the two-sample t-test and Welch’s test for normally distributed continuous variables and the Mann–Whitney U test for non-normally distributed continuous variables. Differences in proportions among the methylprednisolone pulse and dexamethasone groups were calculated and compared using the chi-square test and Fisher’s exact test. A significance threshold of 0.05 was adopted for all statistical analyses. This study was approved by the TMUH institutional review board (approval no. T2020-0161); after obtaining this approval, we disclosed this study to patients via the TMUH homepage and provided the option to refuse participation in this study. This study was performed in accordance with the Declaration of Helsinki of 1964 and its later amendments.

3. Results

Five hundred and eighty-six cases of COVID-19 were admitted to TMUH between April 2020 and October 2021. The number of adult cases requiring oxygen and no IMV was 22 in the methylprednisolone pulse group and 83 in the dexamethasone group. One case receiving dexamethasone acquired SARS-CoV-2 after admission, and five cases received dexamethasone for less than 5 days; therefore, they were excluded. The clinical backgrounds of the methylprednisolone pulse group and dexamethasone group are shown in Table 1. Sex, smoking history, age, BMI, and underlying disease(s) were similar between both groups. Vaccination history for SARS-CoV-2 was absent in 9.1% of the included cases. The proportion of non-vaccinated cases was higher in the dexamethasone group than in the methylprednisolone pulse group (P = 0.033). There were no twice-vaccinated cases. Although supplemental oxygen via oxygen device at methylprednisolone pulse or dexamethasone commencement was similar among both groups (P = 0.122), mask use was more common in the dexamethasone group than in the methylprednisolone pulse group (P < 0.001). Lower lymphocyte count, higher platelet count, and higher lactate dehydrogenase (LDH) level was observed more frequently in the methylprednisolone pulse group than in the dexamethasone group (P = 0.048, P = 0.030, P = 0.002, respectively). The median duration of steroid therapy in the methylprednisolone pulse group was significantly longer than in the dexamethasone group (14.0 days vs. 7.0 days; P < 0.001). Steroids were gradually reduced in all cases in the methylprednisolone pulse group. Dexamethasone had previously been administered to 31.8% of the methylprednisolone pulse group. Favipiravir and azithromycin were more common in the methylprednisolone pulse group than in the dexamethasone group (P = 0.012, P = 0.021, respectively).
Table 1
Demographic and clinical backgrounds of the participants.

| Characteristics            | Methylprednisolone pulse n = 22 | Dexamethasone n = 77 | P value |
|----------------------------|---------------------------------|----------------------|---------|
| Male – no. (%)             | 18 (81.8)                       | 66 (85.7)            | 0.438   |
| Age, mean (SD)             | 57.3 (14.2)                     | 57.8 (15.4)          | 0.894   |
| BMI, mean (SD)             | 25.9 (4.3)                      | 26.0 (4.9)           | 0.941   |
| Vaccination to SARS-CoV-2  | 0 (15.0)                        | 1 (1.4)              | 0.033   |
| Underlying disease – no. (%) | Diabetes mellitus                | 8 (36.4)             | 0.911   |
|                            | Hematologic malignancy          | 0 (0.0)              | 0.603   |
|                            | Hypertension                    | 12 (54.5)            | 0.451   |
|                            | Chronic heart failure           | 2 (9.1)              | 0.682   |
|                            | Asthma                          | 0 (0.0)              | 0.466   |
|                            | Emphysema                       | 1 (4.5)              | 0.600   |
|                            | Hemodialysis                    | 2 (9.1)              | 0.568   |
|                            | Human                           | 0 (0.0)              | 0.466   |
| Oxygen device at pulse or dexamethasone start – no. (%) | 19 (86.4) | 74 (96.1) | 0.122 |
| Supplementation oxygen     | 10 (45.6)                       | 71 (92.2)            | <0.001  |
| Cannula                    | 7 (31.8)                        | 3 (3.9)              | 0.222   |
| Mask                       | 2 (9.1)                         | 0 (0.0)              | 0.048   |
| Oxygenizer                 | 3 (13.6)                        | 3 (3.9)              | 0.122   |
| Laboratory data, median (IQR) | Neutrophil/μL                  | 4616 (3563–6111)     | 0.580   |
|                            | Lymphocyte/μL                   | 673 (469–934)        | 0.048   |
|                            | Platelet, × 10^12/μL            | 209 (184–269)        | 0.030   |
|                            | LDH, U/L                        | 483 (401–599)        | 0.002   |
|                            | Cr                              | 0.75 (0.62–1.29)     | 0.365   |
|                            | CRP                             | 9.40 (5.66–13.22)    | 0.726   |
|                            | D-dimer                         | 1.52 (1.31–1.98)     | 0.166   |
| Treatment – no. (%)        | Duration of stroid treatment, median (IQR) | 14.0 (10.0–25.0)   | <0.001  |
|                            | prior dexamethasone             | 7 (31.8)             | -       |
|                            | Remdecevir                      | 10 (45.5)            | 0.744   |
|                            | Favipiravir                     | 8 (36.4)             | 0.012   |
|                            | Anti-coagulant                  | 21 (95.5)            | 0.600   |
|                            | Azithromycin                    | 9 (40.9)             | 0.021   |

Abbreviations: CI, confidence interval; SD, standard deviation; BMI, body mass index; HFN, high flow nasal; NPPV, non-invasive positive pressure ventilation; IQR, interquartile range; LDH, lactate dehydrogenase; Cr, creatinine; CRP, C-reactive protein.

Primary and secondary outcomes are presented in Table 2. The proportion of ICU admissions was similar among the methylprednisolone pulse and dexamethasone groups requiring supplemental oxygen or HFN/NPPV. The LoS and duration of oxygen requirement in the methylprednisolone group were longer than in the dexamethasone group. The frequency of complications was similar between both groups. Prior research exists regarding the efficacy of methylprednisolone labeled as “high-dose” or “pulse-dose” for COVID-19. Yaqoob et al. reported that 1 g/day of methylprednisolone did not decrease hospital mortality compared to no steroid use in a single-center retrospective study in the United States [12]. Cruz et al. reported in three patient groups that receiving less than 250 mg/day, 250 mg/day or more, or 500 mg/day of methylprednisolone was not associated with increased hospital mortality compared to 1 mg/kg/day of methylprednisolone at a single center in Spain [13]. In contrast, Pinzon et al. reported that the proportion of ICU admissions after steroid treatment was lower for cases treated with 250–500 mg/day of methylprednisolone than 6 mg/day of dexamethasone in an ambispective cohort study in Colomb [14]. Jamil et al. reported that the proportion of patients requiring IMV was higher in the 500 mg/day of methylprednisolone group than in the 6 mg/day of dexamethasone group in a retrospective cohort study in Pakistan [15]. Although the dosage of methylprednisolone varies between studies, several studies report using methylprednisolone labeled as high-or

Table 2
Primary and secondary outcomes.

| Outcome                        | Methylprednisolone pulse n = 22 | Dexamethasone n = 77 | P value |
|--------------------------------|---------------------------------|----------------------|---------|
| Primary outcome                | 4 (18.2)                        | 14 (18.2)            | 0.635   |
| Secondary outcome              |                                 |                      |         |
| Hospital mortality – no. (%)   | 1 (4.5)                         | 3 (3.9)              | 0.614   |
| Length of hospital stay, median (IQR) | 23.5 (13.5–30.5)              | 11.0 (8.0–20.0)      | 0.906   |
| Duration of oxygen requirement (IQR) | 12.0 (8.25–27.75)             | 6.0 (4.0–13.0)       | 0.004   |
| Hospital transfer (%)          | 4 (18.2)                        | 11 (14.2)            | 0.438   |
| Vasopressor – no. (%)          | 2 (9.1)                         | 8 (10.4)             | 0.610   |
| Intubation – no. (%)           | 4 (18.2)                        | 14 (18.2)            | 0.625   |
| ECMO – no. (%)                 | 0 (0.0)                         | 0 (0.0)              |         |
| CRRT – no. (%)                 | 1 (4.5)                         | 3 (3.9)              | 0.614   |

Abbreviations: ICU, intensive care unit; IQR, interquartile range; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy.

Table 3
Complication during treatment of COVID-19.

| Complication                        | Methylprednisolone n = 22 | Dexamethasone n = 77 | P value |
|-------------------------------------|---------------------------|----------------------|---------|
| Any bacterial infection             | 3 (13.6)                  | 12 (15.6)            | 0.562   |
| Bacterial pneumonia                 | 1 (4.5)                   | 4 (5.2)              | 0.693   |
| Empyema                             | 0 (0.0)                   | 2 (2.6)              | 0.222   |
| Urinary tract                       | 1 (4.5)                   | 3 (3.9)              | 0.641   |
| Pulmonary embolism                  | 1 (4.5)                   | 0 (0.0)              | 0.222   |
| Death caused by blood stream infection | 1 (4.5)                  | 6 (7.8)              | 0.512   |
| Pneumothorax                        | 0 (0.0)                   | 1 (1.3)              | 0.778   |
| Deep vein thrombosis                | 0 (0.0)                   | 0 (0.0)              | 0.359   |
| Gastrointestinal bleeding           | 1 (4.5)                   | 0 (0.0)              | 0.222   |
| Delirium                            | 1 (4.5)                   | 2 (2.6)              | 0.534   |

Primary and secondary outcomes are presented in Table 2. The proportion of ICU admissions was similar among the methylprednisolone pulse and dexamethasone groups requiring supplemental oxygen or HFN/NPPV. The LoS and duration of oxygen requirement in the methylprednisolone group were longer than in the dexamethasone group. The frequency of complications was similar between both groups. Prior research exists regarding the efficacy of methylprednisolone labeled as “high-dose” or “pulse-dose” for COVID-19. Yaqoob et al. reported that 1 g/day of methylprednisolone did not decrease hospital mortality compared to no steroid use in a single-center retrospective study in the United States [12]. Cruz et al. reported in three patient groups that receiving less than 250 mg/day, 250 mg/day or more, or 500 mg/day of methylprednisolone was not associated with increased hospital mortality compared to 1 mg/kg/day of methylprednisolone at a single center in Spain [13]. In contrast, Pinzon et al. reported that the proportion of ICU admissions after steroid treatment was lower for cases treated with 250–500 mg/day of methylprednisolone than 6 mg/day of dexamethasone in an ambispective cohort study in Colomb [14]. Jamil et al. reported that the proportion of patients requiring IMV was higher in the 500 mg/day of methylprednisolone group than in the 6 mg/day of dexamethasone group in a retrospective cohort study in Pakistan [15]. Although the dosage of methylprednisolone varies between studies, several studies report using methylprednisolone labeled as high-or.
pulldose. The efficacy is unclear because the number of cases and the quality of past studies is insufficient. We found that methylprednisolone pulse did not improve the proportion of ICU admissions compared to dexamethasone in cases requiring oxygen and no IMV, and LoS in the methylprednisolone pulse group was longer than in the dexamethasone group. ICU admission in the methylprednisolone pulse group that had received prior dexamethasone therapy was similar to the dexamethasone group in our study. Therefore, there may be no measurable benefit to switching from dexamethasone to methylprednisolone pulse.

Because prolonged LoS due to COVID-19 increases the burden on hospitals and healthcare workers, we need to decrease LoS without harming patients with COVID-19. Several studies have reported the risk of an extended LoS for COVID-19 cases with certain characteristics, such as ICU admission, remdesivir use, death in hospital, male sex, diabetes, and chronic kidney or liver disease [16–20]. However, these factors were similar between the methylprednisolone pulse and dexamethasone groups in our study. In contrast, favipiravir and azithromycin were administered more often in the methylprednisolone pulse group than the dexamethasone group. In a multicenter randomized trial, LoS was similar among the favipiravir group and the lopinavir/ritonavir group [21]. In the RECOVERY trial, the time to being discharged alive was similar among the azithromycin group and the usual care group [22]. Therefore, favipiravir and azithromycin have minimal impact on LoS. Laboratory data analysis revealed that low lymphocyte count and high LDH level were risk factors for increased severity or death due to COVID-19 [23,24]. These factors in addition to methylprednisolone pulse in our study might have contributed to prolonged LoS.

Few studies exist regarding LoS for methylprednisolone pulse therapy among patients with COVID-19. Although a retrospective cohort study reported that the LoS of their methylprednisolone pulse group was similar to their non-methylprednisolone pulse group, the increased hospital mortality rate in the non-methylprednisolone pulse group might have led to shortened LoS [25]. In our study, the duration of steroid therapy in the methylprednisolone pulse group was longer than in the dexamethasone group despite the similar incidence of hospital mortality. Because all cases in the methylprednisolone pulse group required steroid tapering, the process of tapering might have led to a prolonged LoS. Moreover, although supplemental oxygen use was similar between both groups, cannula use was more common in the dexamethasone group than in the methylprednisolone group. Lower lymphocyte count and higher LDH were observed in the methylprednisolone pulse group compared with the dexamethasone group. In addition, the duration of oxygen requirement in the methylprednisolone group was longer than in the dexamethasone group. Therefore, the methylprednisolone pulse group might have included more severe cases requiring supplemental oxygen than the dexamethasone group.

Our study has some limitations. First, it was a retrospective study in a single Japanese center. The relatively small case number may lead to an underestimation of the efficacy of methylprednisolone pulse. Second, 9.1% of the data about vaccination history for SARS-CoV-2 was missing, and no cases were twice-vaccinated; therefore, these results might not be applicable to fully vaccinated cases. Third, we excluded critical cases requiring IMV because we intended to investigate the efficacy of methylprednisolone pulse in preventing the worsening of COVID-19; therefore, an additional study will be needed for critical cases. Fourth, favipiravir and azithromycin were more frequently administered in the methylprednisolone pulse group than in the dexamethasone group. However, the proportion of ICU admissions according to the efficacy of favipiravir was not evaluated [26,27]. Similarly, azithromycin did not improve the requirement for IMV or the clinical status [22,28]. Fourth, we did not investigate SARS-CoV-2 variants. Although the cases of methylprednisolone pulse were distributed sporadically throughout the observation period, 88.3% of dexamethasone use occurred in 2021. Alpha variants of SARS-CoV-2 spread after February 2021 in Japan [29]. Therefore, the dexamethasone group might have included more cases with variants than the methylprednisolone group. Fifth, adults with COVID-19 were included in our study if they required oxygen therapy but did not require IMV. Because mask use was more common in the methylprednisolone pulse group than in the dexamethasone group, it is possible that the methylprednisolone pulse group contained more severe cases. Although this study classified patients by the requirement for supplemental oxygen without IMV, there may be groups for which methylprednisolone pulse is effective when accompanied by more intense oxygen therapy.

Finally, although the proportion of transferred patients was similar between the groups, no evaluation of the time required to coordinate hospital transfers was performed. Therefore, LoS may have been influenced by the need for more days to coordinate hospital transfers in the methylprednisolone pulse group.

5. Conclusion

In cases of COVID-19 requiring oxygen and no IMV, the proportion of ICU admissions was similar between the methylprednisolone pulse group and the dexamethasone group. However, mask ventilation was more prevalent in the methylprednisolone pulse group than in the dexamethasone group, suggesting that these cases benefited from methylprednisolone pulse.

Ethics approval and consent to participate

This study was approved by the Tokyo Medical University institutional review board (approval no. 2020-0161). Written informed consent was obtained from all subjects for the publication of this report. This study was performed in accordance with the Declaration of Helsinki of 1964 and its later amendments.

Authorship statement

All authors meet ICMJE authorship criteria. Yusuke Watanabe, Itaru Nakamura, and Hidehiro Watanabe contributed to the study conception and design. Yusuke Watanabe performed data collection and analysis. Satoko Sato, Hiroaki Fujita, and Takehito Kobayashi collected the data. The first draft of the manuscript was written by Yusuke Watanabe, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability

The dataset supporting the conclusions of this article is included in the article.

Declaration of competing interest

None.

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