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A comparative study between methylprednisolone versus dexamethasone as an initial anti-inflammatory treatment of moderate COVID-19 pneumonia: an open-label randomized controlled trial

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Abstract

Background The most appropriate anti-inflammatory treatment for moderate COVID-19 pneumonia remains uncertain. We aimed to compare the effectiveness of a high-dose methylprednisolone versus a high-dose dexamethasone in hospitalized moderate COVID-19 pneumonia, regarding the WHO clinical progression scales, mortality, and the length of hospitalization.

Methods In this open-labeled randomized controlled trial, we enrolled patients with age > 18 years old who were diagnosed moderate COVID-19 pneumonia confirmed by real-time PCR, evidence of pneumonia by chest imaging and resting oxygen saturation between 90 and 94%. Patients were randomized at a 1:1 ratio to receive methylprednisolone 250 mg/day or dexamethasone 20 mg/day over the first three days. Then the patients in both groups received dexamethasone 20 mg/day on days 4–5, and 10 mg/day on days 6–10. Primary outcome was assessed by a 10-point WHO clinical progression scales ranging from uninfected (point 0) to death (point 10) on the fifth day of treatment. Secondary outcomes including 90-day mortality, length of hospitalization, rate of intensive care unit (ICU) transfer and complications were determined.

Results Of 98 eligible patients, the mean age was 76.0 ± 13.3 years. The median date of illness at the time of randomization was 3 days (interquartile range 2, 5). Baseline clinical characteristics and severity did not differ between groups. The WHO clinical progression scales were similar between methylprednisolone and dexamethasone group at 5 and 10 days of treatment [4.84, (95% confidence interval(CI), 4.35–5.33) vs. 4.76 (95% CI, 4.27–5.25), $p=0.821$ and 4.32 (95% CI, 3.83–4.81) vs. 3.80 (95% CI, 3.31–4.29), $p=0.140$, respectively]. Both groups did not differ in-hospital mortality, length of hospitalization, and rate of ICU transfer. There were also no differences in steroid-related complications between groups until 90 days of follow-up.

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Conclusions In patients with moderate COVID-19 pneumonia, initial anti-inflammatory treatment with 250 mg/day of methylprednisolone for three days does not yield better outcomes over high-dose dexamethasone.

Trial registration This study was registered at Thai Clinical Trials Registry on October 17, 2021, with the identifier TCTR20211017001.

Keywords COVID-19, Moderate pneumonia, Corticosteroids, Randomized controlled trial

Background

During the outbreak of the COVID-19, the public health system is overburdened with cases. Severe and critical cases have a higher mortality rate and a greater demand for medical resources [1]. In the large cohort of severe COVID-19 patients during the early pandemic, 40% developed dyspnea within seven days, and 14% progressed to severe and critical illness [2]. Therefore, controlling disease progression is crucial to reduce the mortality and resolve the medical resource crisis. A hyperinflammatory response causes disease progression called a cytokine storm, resulting in multiple organ and failures [3]. Hence, immunosuppressants, particularly systemic corticosteroids, are essential, as evidenced by many studies.

A Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial reported that low-dose dexamethasone (DXM) reduced time to recovery and mortality, especially in patients who needed oxygen support [4]. Subsequently, several studies were conducted using high-dose corticosteroids in moderate to critical cases and demonstrated additional benefits such as reduced systemic inflammation and ventilator days. Based on the COVID-19 dexamethasone (CoDEX) randomized clinical trial (RCT) [5], the regimen of high-dose DXM (20 mg/day) for five days, then 10 mg/day for five more days for moderate COVID-19 pneumonia (90–94% oxygen saturation on room air) was implemented as the guideline in our institute. In our practice, we found that some cases still deteriorated from hypoxemia to respiratory failure within a few days, and the laboratory markers indicated that inflammation was uncontrolled. The increased severity can be attributed to the rapid onset of organizing pneumonia caused by SARS-CoV-2. This condition has been observed in autopsies as early as the first week of infection. It typically necessitates treatment with high doses of corticosteroids, sometimes administered as initial “pulse” doses followed by extended therapy [6].

Some studies showed that high-dose methylprednisolone (MP) three to 5 days had provided better clinical improvement, decreased inflammatory markers, and had a lower proportion of patients who progressed to severe acute respiratory distress syndrome (ARDS) when compared with DXM [7, 8]. In a cohort study, Pinzón et al. compared high-dose MP for three days and oral prednisolone for 14 days against another regimen. The findings

suggest that high-dose MP of 250 to 500 mg daily for three days effectively manages severe cases of COVID-19 pneumonia [7]. Corticosteroids can influence the inflammatory process at the genomic level or through faster-acting non-genomic pathways. The latter requires high doses of corticosteroids, and the response is dose-dependent. In vitro studies indicate that MP elicits a more robust response than DXM [9]. Mechanistically, MP exhibits a greater lung tissue-to-plasma ratio and is more efficient at penetrating tissue than other forms in experimental animals than dexamethasone, demonstrating higher potency in lung injury [10]. Furthermore, high-dose MP therapy did not increase adverse events in severe and critical cases, especially those concerning bacterial infection.

In moderate COVID-19 pneumonia as defined by the World Health Organization (WHO) [11], no RCT has been conducted to compare high-dose MP therapy with high-dose DXM. We hypothesized that the initial treatment with MP 250 mg daily compared with high-dose DXM based on the previous study of the CoDEX randomized clinical trial [5] for moderate COVID-19 pneumonia would improve clinical outcomes in moderate COVID-19 pneumonia patients.

Our objective was to compare the effectiveness of a high-dose MP versus a high-dose DXM in hospitalized moderate COVID-19 pneumonia, regarding the WHO clinical progression scales, mortality, and the length of hospitalization.

Methods

Study design and participants

This study was conducted as an open-label RCT. The trial involved the participation of two medical centers, namely Ramathibodi Hospital and Chakri Naruebodindra Medical Institute. This study was approved by the Human Research Ethics Committee, Faculty of Medicine, Ramathibodi Hospital, Mahidol University on October 11, 2021 (code COA.MURA2021/855) and registered at Thai Clinical Trials Registry on October 17, 2021, with identifier TCTR20211017001 before the first participant was enrolled. Our study adhered to CONSORT guidelines.

The study population included patients who hospitalized with moderate COVID-19 pneumonia within 48 h. To diagnose COVID-19 pneumonia, the following conditions were met: (1) identification of SARS-CoV-2 using

reverse transcription polymerase chain reaction or antigen test kit in nasal swabs and sputum samples, and (2) abnormal chest X-ray (CXR) compatible with pneumonia (mostly bilateral, interstitial opacities and peripheral or subpleural ground glass opacities, predominant in mid to lower lung zones). Moderate COVID-19 pneumonia was defined as a case of COVID-19 pneumonia with a resting oxygen saturation of 90-94% [11].

Inclusion and exclusion criteria

Study participants were required to meet the inclusion criteria: (1) aged over 18 years old, (2) hospitalized within 48 h of symptoms, (3) confirmed the diagnosis with moderate COVID-19 pneumonia as described above, and (4) provided informed consent. Individuals were excluded from the study if they met the exclusion criteria: (1) use of non-invasive or invasive mechanical ventilation (MV), (2) high risk for corticosteroids administration including other concomitant infection (bacteria, mycobacteria or fungi) and poor glycemic control, (3) Immunocompromised status including receiving immunosuppressive agents or chemotherapy, end-stage liver disease, end-stage renal disease without renal replacement therapy and Human Immunodeficiency Virus (HIV) infection with CD4 cell count less than 200 cell/mm², (4) pregnant women, (5) history of active psychiatric problems, (6) current systemic corticosteroids use more than 20 mg per day of prednisolone or equivalent dose, (7) having

other coexisting causes of hypoxemia, and (8) denied to participate the study.

Randomization

Participants in the study were randomly assigned to the experimental and control groups in a ratio of 1:1. A computer-generated random list was prepared using permuted balanced blocks of four in a random sequence. A computer-based randomization system ensured that treatment assignments were concealed until a patient was enrolled in the study.

Study protocol and outcomes

During the first three days, participants in the experimental group received intravenous 250 mg of MP daily, while the control group received 20 mg of DXM daily. Subsequently, all participants were given oral or intravenous 20 mg of DXM daily on days 4 and 5, followed by 10 mg of DXM daily on days 6 to 10, as shown in Fig. 1. The participants in both groups received the same standard care for COVID-19 according to the practical protocol developed by Ramathibodi Hospital and Chakri Naruebodindra Medical Institute, except for corticosteroids therapy.

Clinical and demographic data, COVID-19 vaccination, blood samples, and CXR were obtained before enrollment in the study. All participants were followed up daily for clinical assessment and data collection until

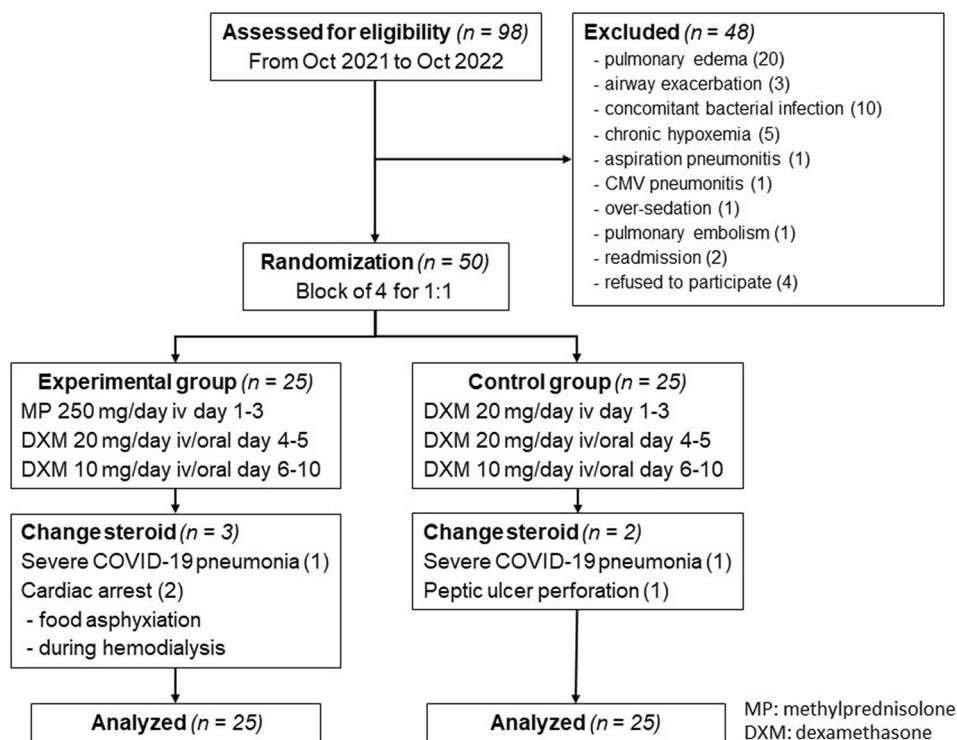


Fig. 1 The Consolidated Standards of Reporting trials flow diagram of the study

discharge or at least 28 days in the hospital. On day 5 and 10, participants were assessed for their clinical status, oxygenation, CXR, and blood samples, especially inflammatory markers namely the complete blood count, C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer, and sequential organ failure assessment (SOFA) score. We utilized the WHO clinical progression scales to compare the two groups' clinical status. These scales are a 10-point system that ranges from 0, representing no clinical or virological signs of infection (i.e., uninfected), to 10, indicating death [12]. More details regarding the WHO clinical progression scales are shown in the supplementary file. We obtained a license to use this scale from the WHO permission team. The investigators (J.L. or T.T.) assessed each patient's WHO Clinical Progression Scales.

A primary outcome was to compare the WHO clinical progression scales on day 5 between both groups. Secondary outcomes included the difference in the WHO clinical progression scales on day 10, oxygenation improvement, transfer to the ICU, respiratory failure, complications, length of hospitalization, mortality rate, inflammatory markers, and SOFA score between the two groups.

For safety concerns, participants were terminated from the corticosteroids regimen of the assigned group if they met the criteria for termination: (1) developing severe COVID-19 pneumonia that required a higher dose than the assigned regimen (resting oxygen saturation less than 90% at room air or the need for a non-invasive or invasive MV), (2) having a contraindication for high-dose corticosteroids which was a hyperglycemic crisis and suspicion of superimposed bacterial or opportunistic infection, and (3) progression of COVID-19 pneumonia (worsening hypoxemia, radiological progression, and an increase of inflammatory markers) after the first three days, and the primary physician refused to reduce the corticosteroids dose per protocol.

All participants were followed up in the outpatient department or telemedicine care for 90 days to assess clinical status at days 14 and 28 and long-term complications at 90 days.

Sample size calculation

Due to no previous study comparing the two corticosteroid regimens at this time, the target sample size was based on the most relevant clinical trial. According to the RCT by Ranjbar et al. [8], in comparison between the first group that received methylprednisolone and the second group receiving dexamethasone, the WHO Clinical Progression Scale on day 5 after treatment was 4.02 ± 1.64 and 5.21 ± 1.73 , respectively. A target sample size of 60 participants was calculated in a 1:1 ratio, with a 95% confidence interval (CI) (first type alpha error) and 80%

power. The sample size was calculated using the n4Studies program [13].

Statistical analysis

Continuous variables were described as mean \pm standard deviation or median (interquartile range, IQR), and categorical variables data were described by number (%). Statistical differences were evaluated using student *t*-tests or Mann-Whitney *U*-tests, as appropriate, for continuous variables and Pearson Chi-square tests or Fisher's exact tests for categorical variables. The difference in the WHO clinical progression scales at days 5 and 10 was evaluated using multilevel mixed-effects linear regression and is described by a 95% confidence interval and a *p*-value. All analysis was performed using STATA version 17 and $p < 0.05$ was considered statistically significant.

Results

Patients

There were 98 eligible patients enrolled between October 18, 2021, and October 31, 2022, from the two centers, 42 patients were excluded due to other causes of hypoxemia as the reasons for admission, four patients refused to participate the study, and two patients were experienced secondary COVID-19 diagnoses and readmitted. We stopped the recruitment at September 2022 and had a sample size lower than expected due to a subsided outbreak during the study period. Of fifty patients who underwent randomization, 25 were assigned to the experimental group and 25 to the control group. Three patients in the experimental group and two in the control group had changed the corticosteroids regimen from protocol; two developed severe COVID-19 pneumonia, two suffered cardiac arrests, and one had a peptic ulcer perforation. Overall were follow-up until 90 days and analyzed as intention-to-treat analysis. Based on the per-protocol analysis, the results for the outcomes did not differ from the intention-to-treat analysis. The flow diagram of the study is summarized in Fig. 1.

Of all patients, the mean age was 76.0 ± 13.3 years old, and 24 (48%) were female. The proportion of patients enrolled from each center was similar between the two groups. The median date of admission and date of illness at the day of enrollment were 2 (IQR, 1, 3) and 3 (IQR, 2, 5) days, respectively. All patients were categorized on WHO ordinal scale at 5 (hospitalized; oxygen by mask or nasal cannula). Baseline characteristics of the underlying diseases, COVID-19 vaccine status, and severity are summarized in Table 1.

There were no significant differences in coexisting conditions, the severity of hypoxemia [Partial pressure of arterial oxygen (PaO₂)/Fraction of inspired oxygen (FiO₂) ratio], SOFA score, and inflammatory markers between the two groups. In addition, no significant differences in

Table 1 Baseline characteristics and severity of COVID-19 in the MP group and DXM group

Characteristics	MP group (n = 25)	DXM group (n = 25)	p-value
Age (years); mean ± S.D.	75.4 ± 12.7	76.5 ± 14.1	0.770
Sex (female)	11 (44%)	13 (52%)	0.571
BMI (kg/M ²); mean ± S.D.	25.9 ± 6.5	23.0 ± 6.0	0.106
Obesity (BMI ≥ 30)	5 (20%)	3 (12%)	0.702
Hypertension	21 (84%)	21 (84%)	1.000
Diabetes mellitus	14 (56%)	16 (64%)	0.564
HbA1C(mg%); mean ± S.D.	6.5 ± 1.8	6.4 ± 1.5	0.843
Poorly controlled (HbA1C ≥ 9)	2 (8%)	1 (4.2%)	1.000
Chronic heart disease	7 (28%)	4 (16%)	0.306
Chronic lung disease	4 (16%)	9 (36%)	0.107
CKD stage 4–5 or ESRD	4 (16%)	2 (8%)	0.667
Old cerebrovascular accident	3 (12%)	1 (4%)	0.609
Status bedridden	3 (12%)	6 (24%)	0.463
COVID-19 vaccines (2 weeks apart)			
No vaccine	10 (40%)	6 (24%)	
1 dose	1 (4%)	2 (8%)	
2 doses	10 (40%)	13 (52%)	
3 doses	4 (16%)	4 (16%)	0.645
Included mRNA vaccine	9 (36%)	8 (32%)	0.765
DOI (days); median (IQR)	3 (2–5)	3 (2–6)	0.687
Severity of COVID-19			
Day 1 PaO ₂ /FiO ₂ ratio; mean ± S.D.	317.6 ± 34.1	326.4 ± 35.1	0.372
Day 1 SOFA score; median (IQR)	2 (1–3)	1 (1–2)	0.213
Day 1 CRP(mg/L); median (IQR)	33 (14.0–63.8)	22.5 (6–63)	0.734
High CRP ≥ 50	9 (36%)	7 (28%)	0.544
Day 1 ALC(cells/mm ³); median (IQR)	1050 (800–1050)	974 (614.5–1574.7)	0.831
Low ALC < 1000	12 (48%)	13 (52%)	0.777
Day 1 LDH(IU/L); mean ± S.D.	275.3 ± 96.2	255.1 ± 104.8	0.480
Day 1 D-dimer(mcg/mL); median (IQR)	869 (483–1489)	1218 (573–1639)	0.222

Data are presented as n (%), mean (standard deviation or S.D.) or median (interquartile range or IQR). MP: methylprednisolone; DXM: dexamethasone; BMI: body mass index; HbA1C: hemoglobin A1C; CKD: chronic kidney disease; mRNA: messenger ribonucleic acid; DOA: Date of admission; DOI: Date of illness; WHO: world health organization; PaO₂: arterial oxygen tension; FiO₂: inspiratory oxygen fraction; SOFA score: Sequential organ failure assessment score; CRP: C-reactive protein; ALC: absolute lymphocyte count; LDH: lactate dehydrogenase

receiving essential treatments between the two groups namely, antiviral treatments, anticoagulants, and immunomodulators. (Table 2).

Primary outcome

The mean of WHO clinical progression scale at day 5 was 4.84 (95% CI, 4.35–5.33) versus 4.76 (95% CI, 4.27–5.25) in the MP group and DXM group, respectively ($p=0.821$).

Table 2 Summary of treatments in the MP group and DXM group

Treatments	MP group (n = 25)	DXM group (n = 25)	p-value
Antiviral			
Favipiravir only	5 (20%)	10 (40%)	
Remdesivir only	12 (48%)	11 (44%)	
Both favipiravir and remdesivir	7 (28%)	4 (16%)	
Monupiravir only	1 (4%)	0 (0%)	0.325
Extended steroids (> 10 days)	3 (12%)	3 (12%)	1.000
Anticoagulant	12 (48%)	9 (36%)	0.390
Immunomodulators			
None	22 (88%)	22 (88%)	
Tocilizumab	1 (4%)	1 (4%)	
Baricitinib	2 (8%)	2 (8%)	1.000

Data are presented as n (%). MP: methylprednisolone; DXM: dexamethasone

No significant difference in the primary outcome was observed between the two groups (Fig. 2).

Secondary outcomes

The mean WHO clinical progression scores on day 10 were lower in the group receiving DXM than in the MP group. The scores were 3.80 (95% CI, 3.31–4.29) for the DXM group and 4.32 (95% CI, 3.83–4.81) for the MP group, but this difference was not statistically significant ($p=0.140$) (Fig. 2). Although all secondary outcomes, including clinical improvement, oxygenation improvement, and inflammatory parameters, did not show a significant difference, the percentage of patients with a lower PaO₂/FiO₂ ratio on the 5th and 10th days of treatment was lower in the DXM group according to Table 3, but this also did not reach statistical significance.

The majority of patients in both groups had the PaO₂/FiO₂>300 at day 5, 18 (75%) in MP group and 16 (64%) in DXM group; and at day 10, 18 (75%) in MP group and 20 (83.3%) in DXM group. CRP levels, as well as LDH, D-dimer and SOFA scores, were not significantly different between the two groups at day 5 and day 10 (Table 3).

Clinical improvements were similar between the two groups at 14-day and 28-day follow-ups. In both groups, there were the same rates of ICU transfer (12%), the development of respiratory failure (8%), and in-hospital mortality (8%). In addition, there were no significant differences between the MP group and the DXM group in the length of hospitalization (13 days versus 11 days, $p=0.227$), 28-day mortality (12% versus 8%, $p=1.000$), and 90-day mortality (16% versus 12%, $p=1.000$).

Table 4 shows no statistically significant difference of complications occurred during hospitalization and until 90 days follow-up. There was a trend towards fewer patients with septic shock in the MP group compared to the DXM group (0% versus 16%, $p=0.110$). Regarding the causes of septic shock in the DXM group, two

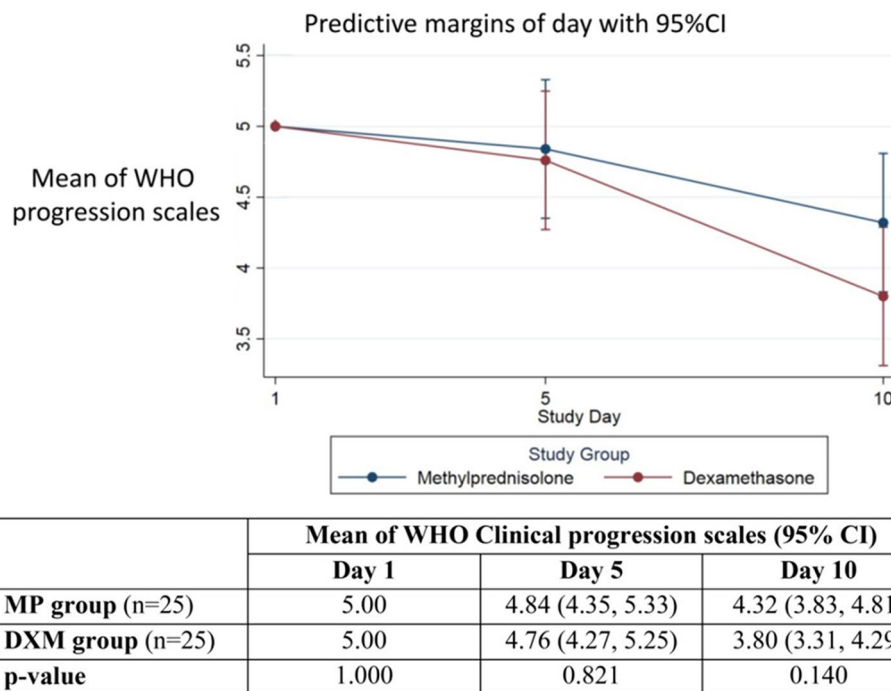


Fig. 2 Diagram of the mean (95% confidence interval) of WHO clinical progression scales at day 1, day 5, and day 10 in the MP group and DXM group and *p*-value by multilevel mixed-effects linear regression. Data are presented as mean (95% confidence interval or 95%CI) and *p*-value. MP: methylprednisolone; DXM: dexamethasone

patients had septic shock from hospital-acquired pneumonia, one from urinary tract infection, and one from peptic ulcer perforation. One patient in the DXM group was diagnosed with a hyperglycemia crisis 22 days after admission.

Discussion

In this open-label RCT, we compared high-dose MP with high-dose DXM for the first three days, followed by the same DXM regimen until ten days in patients with moderate COVID-19 pneumonia. The WHO progression scales on day 5 did not differ significantly between the two groups. The mean WHO clinical progression scores on day 10 were lower in the group receiving DXM than the MP group, but this difference was not statistically significant. There were no significant differences in secondary outcomes, such as clinical improvement in the hospital until 28 days after enrollment, oxygenation improvement, inflammatory markers, respiratory failure, ICU transfer, and mortality. Although the percentage of patients with a lower PaO₂/FiO₂ ratio on the 5th and 10th days of treatment was lower in the DXM group, according to Table 3, this also did not reach statistical significance. Also, superimposed bacterial or opportunistic infections and hyperglycemic crises are not significantly different.

Systemic corticosteroids are well-known and readily available anti-inflammatory medications that much

evidence has shown to be effective in COVID-19 patients. Based on the RECOVERY trial, a medium-dose regimen (6 mg of DXM once daily) was beneficial only for COVID-19 patients who received respiratory support or had inflammation that required control [4]. Subsequently, several studies reported that a high-dose to pulse regimen was also beneficial in COVID-19 patients with severe and critical illnesses and appeared to improve outcomes more than a medium-dose regimen [5, 7, 8, 14, 15]. Based on the evidence, three main factors should be considered to predict the advantage of systemic corticosteroids: (1) degree of inflammation, (2) dose of corticosteroids, and (3) drug tissue concentration.

Firstly, COVID-19 patients who manifest severe to critical illness or meet hyperinflammatory response conditions will deteriorate as these conditions indicate that anti-inflammatory treatment is required to mitigate the inflammatory process. This is important not only in the early phase of COVID-19 pneumonia but also ARDS in the terminal phase of infection to lessen inflammation and tissue injury [16]. In the early stage of COVID-19 pneumonia, the timing of administration is determined by the benefit of inflammation control over the risk of prolonged viral shedding, which has to be discussed. Studies by Raef Fadel et al. and Pablo Monedero et al. have shown that early (within 48 h) corticosteroids use in moderate to critically ill patients results in lower mortality, shorter stays in ICU, decreased organ dysfunction,

Table 3 Secondary outcomes in the MP group and DXM group

Secondary outcomes	MP group (n=25)	DXM group (n=25)	p-value
Day 5 PaO₂/FiO₂ratio ; mean ± S.D.	355.6 ± 79.1	338.9 ± 82.9	0.474
Hypoxemia PaO ₂ /FiO ₂ ratio > 300	75%	64%	
PaO ₂ /FiO ₂ ratio > 200–300	16.7%	32%	
PaO ₂ /FiO ₂ ratio 100–200	8.3%	4%	0.478
Day 10 PaO₂/FiO₂ratio ; mean ± S.D.	369.0 ± 77.7	388.6 ± 72.3	0.370
Hypoxemia PaO ₂ /FiO ₂ ratio > 300	75%	83.3%	
PaO ₂ /FiO ₂ ratio > 200–300	25%	16.7%	0.477
Day 5 CRP(mg/L) ; median (IQR)	7.2 (5.4–17.8)	7.8 (5.5–24.3)	0.667
Normalized CRP < 10 mg/dl	13 (54.2%)	13 (52%)	0.879
Day 10 CRP ; median (IQR)	6 (2.9–13.7)	6 (3.4–18.0)	0.844
Normalized CRP < 10 mg/dl	16 (66.7%)	14 (58.3%)	0.551
Day 5 LDH(IU/L) ; mean ± S.D.	264 ± 87.3	240.4 ± 95.7	0.368
Day 10 LDH ; mean ± S.D.	254.9 ± 91.8	237.2 ± 82.0	0.484
Day 5 SOFA score ; median (IQR)	1 (1–2.5)	1 (1–2)	0.883
Day 10 SOFA score ; median (IQR)	1 (0.5–2)	0 (0–2)	0.103
Day 5 D-dimer(mcg/mL) ; median (IQR)	846.5 (470–2492)	1021 (474–1996)	0.976
Day 10 D-dimer ; median (IQR)	1043 (594.5–1712)	1189 (576.5–3880.5)	0.446
Being alive with SaO₂ ≥ 96% room air			
Day 14	16 (64%)	18 (72%)	0.544
Day 28	21 (84%)	21 (84%)	1.000
Being alive without mechanical ventilation			
Day 14	23 (92%)	23 (92%)	1.000
Day 28	22 (88%)	22 (88%)	1.000
Being alive without hospitalization			
Day 14	16 (64%)	18 (72%)	0.544
Day 28	21 (84%)	20 (80%)	1.000
Transfer to intensive care unit	3 (12%)	3 (12%)	1.000
Acute respiratory failure	2 (8%)	2 (8%)	1.000
Length of hospitalization (days)			
Excluded hospital death; median (IQR)	13 (10–18)	11 (9–13)	0.227
Hospital mortality	2 (8%)	2 (8%)	1.000
28-day mortality	3 (12%)	2 (8%)	1.000
90-day mortality	4 (16%)	3 (12%)	1.000

Data are presented as n (%), mean (standard deviation or S.D.) or median (interquartile range or IQR). MP: methylprednisolone; DXM: dexamethasone; PaO₂: arterial oxygen tension; FiO₂: inspiratory oxygen fraction; CRP: C-reactive protein; LDH: lactate dehydrogenase; SOFA score: Sequential organ failure assessment score; SaO₂: Oxygen saturation

and fewer days on MV [15, 17]. Secondly, the anti-inflammatory effect of corticosteroids depends on their dose categorized by mg of prednisolone equivalent dose per day: low-dose (≤ 7.5 mg), medium-dose (> 7.5 mg and ≤ 30 mg), high-dose (> 30 mg), very high-dose (> 100 mg), and pulse therapy (≥ 250 mg) [18]. Corticosteroids have a dual action pathway: they inhibit inflammation through genomic and non-genomic pathways. The treatment regimen, which involved a prednisolone equivalent dose exceeding 100 mg, demonstrated significant non-genomic potency, contributing to rapidly suppressing the inflammation. It was proven in a triple-blind RCT by Keivan Ranjbar et al. that a very high-dose regimen was more effective than a medium-dose one (as in the RECOVERY trial) for patients with moderate COVID-19 pneumonia [8]. Additionally, it does not increase the risk

of infections that most studies have reported. Thirdly, MP might have contributed to better outcomes because of its tendency to concentrate in lung tissue more than DXM [18–22]. In COVID-19, however, no clinical trial has been established to support this issue.

Regarding the results from our study, there was no difference in overall clinical outcomes between the two corticosteroids groups. The main reason explaining our results could be that our patients' disease progression was less severe than in the previous studies. A significantly lower incidence of respiratory failure, ICU transfer, and the mortality rate was observed in our study, when compared the the previous study [5].

The population in our study includes both vaccinated and unvaccinated individuals. Over half of the patients already had vaccinations. A recent study reported that

Table 4 Summary of complications in the MP group and DXM group

Complications	MP group (n=25)	DXM group (n=25)	p- val- ue
Pulmonary complications			
HAP or VAP	0 (0%)	1 (4%)	1.000
AFOP	3 (12%)	2 (8%)	1.000
Lobar atelectasis	1 (4%)	2 (8%)	1.000
Tracheostomy	0 (0%)	1 (4%)	1.000
Systemic complications			
Acute kidney injury	4 (16%)	7 (28%)	0.306
Septic shock	0 (0%)	4 (16%)	0.110
Hyperglycemic crisis	0 (0%)	1 (4%)	1.000
90-day opportunistic infections	0 (0%)	0 (0%)	-
90-day long term oxygen therapy	0 (0%)	0 (0%)	-

Data are presented as n (%). MP: methylprednisolone; DXM: dexamethasone; HAP: hospital acquired pneumonia; VAP: ventilator associated pneumonia; AFOP: acute fibrinous organizing pneumonia

patients in the unvaccinated group were more likely to develop pneumonia, require supplemental oxygen, and have a longer time from symptom onset to hospital discharge than the vaccinated group [23]. Thus, it's crucial to explicitly address and control the effect of prior vaccination on the progression and treatment response of COVID-19. We performed additional sensitivity analyses to compare the mean differences (M.D.) and their 95% CI, along with p-values for WHO scores on day 5 and day 10, both unadjusted and adjusted for prior vaccination status, between the two groups. Both unadjusted and adjusted M.D. of WHO scores on day 5 and day 10 are small and not statistically significant (p-values 0.79 and 0.61, respectively), suggesting no meaningful difference between the groups (Supplementary Table 1 in supplementary file).

Additionally, the clinician had gained experience and knowledge, and the omicron variant, less virulent than the delta variant, was predominant in the study period. Because of less inflammation, the power of different potencies may not be visible. In comparable studies, multicenter RCTs were conducted in moderate COVID-19 pneumonia, similar to ours. Those studies compared pulse therapy to a medium-dose regimen (6 mg of DXM), with no significant differences in the outcomes [24, 25]. Hence, a medium dose of corticosteroids may be enough for anti-inflammatory treatment in moderate COVID-19 especially patients requiring oxygen therapy without invasive MV.

Despite the overall negative results of our study, we cannot exclude any potential benefits in specific subgroups of patients with more severe illnesses and more inflammatory responses. A recent clinical cohort study by Takuhiro Moromizato et al. found that pulse MP at 500 to 1,000 mg per day was significantly associated with

a lower in-hospital mortality rate among patients receiving invasive MV but not those without invasive MV [26]. Therefore, pulse therapy could be a rescue therapy when critically ill patients require invasive MV. However, this should be demonstrated through a randomized controlled trial.

One of the strengths is this trial is the homogeneity of the sample, in that all patients were categorized into group 5 of the WHO clinical progression scales and had balanced baseline characteristics regarding age and comorbidities. Moreover, most patients were strictly followed and analyzed according to protocol.

Limitations

This study's limitation is that it was conducted at only two centers, which may limit the generalizability of the findings to other settings and populations. The sample size was lower than expected due to a subsided outbreak during the study period. However, the sample size was slightly less than expected (50 out of 60 patients or 83%), and the results' trend was evident. The omicron variant, less virulent than the delta variant, was predominant in the study period, which could have influenced the outcomes and might not have applied to periods dominated by more virulent variants like Delta. Recently, several variants of SARS-CoV-2, such as BA.2.86 and JN.1, have emerged, resulting in reduced disease severity, as evidenced by ICU admissions per 1000 hospitalizations decreasing since the peak in July 2021 [27]. This development prompts investigation into the necessity of high-dose steroids for this patient group.

Regarding the blinding, each patient's WHO clinical progression scale was not blinded and assessed by the investigators in both centers (J.L. and T.T.) Nevertheless, the WHO Clinical Progression Scale depends on the requirement of oxygen therapy, mechanical ventilation, and ambulatory status. It relies on the decision of the primary physician, who was not involved in the studies.

The patients were followed up to 90 days. Considering the potential long-term effects of COVID-19 and corticosteroid use, multicenter prospective trials with extended follow-up would be valuable and provide more robust and generalizable data.

Conclusion

In patients with moderate COVID-19 pneumonia, initial anti-inflammatory treatment with 250 mg per day of MP for three days was not more effective than the high-dose DXM regimen.

Abbreviations

DXM	Dexamethasone
MP	Methylprednisolone
WHO	World Health Organization
RCT	Randomized controlled trial

CXR	Chest X-ray
MV	Mechanical ventilation
HIV	Human Immunodeficiency Virus
CRP	C-reactive protein
LDH	Lactate dehydrogenase
SOFA	Sequential organ failure assessment
IQR	Interquartile range
PaO ₂	Partial pressure of arterial oxygen
FiO ₂	Fraction of inspired oxygen
CI	Confidence interval

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12890-024-03364-4>.

Supplementary Material 1

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Author contributions

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Data availability

The data can be requested from the corresponding author.

Declarations

Ethics approval and consent to participate

This study was approved by the Human Research Ethics Committee, Faculty of Medicine, Ramathibodi Hospital, Mahidol University on October 11, 2021 (code COA.MURA2021/855) and registered at Thai Clinical Trials Registry on October 17, 2021, with identifier TCTR20211017001. Every patient is provided with informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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