Dexamethasone vs Methylprednisolone In treating Covid-19 Pneumonia: A Meta-Analysis of Randomized Trials

Fatma A. Abdelfattah\textsuperscript{a}, Ahmed M. Abd El-Hamid\textsuperscript{a}, Abeer A. Emara\textsuperscript{b}, Emad F. Ibrahim\textsuperscript{b}

Abstract:

Background: Systemic corticosteroids have demonstrated definite mortality benefit in management of COVID 19 in various studies. Still certain questions regarding the appropriate dose, duration and timing of corticosteroids remain unanswered. For this reason, the study was planned to determine the efficacy and safety of methyl prednisolone in management of COVID 19 from publicly available evidence. Objectives: To compare between dexamethasone and methylprednisolone in treating Covid-19 pneumonia patients with respiratory failure. Study design: Meta-analysis was used to address this concern. Settings: Meta-analysis-based study following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) guidelines. Methods: Online databases (PubMed, Embase, BioMed, and the Cochrane Central Register of Controlled trials) were used for randomized studies ever performed in humans in any clinical setting. Results: Ten studies were identified for inclusion in this study, involving a total of 1812 patients. The risk of bias was low. Meta-analysis found that methylprednisolone result in significant decrease in hospital length of stay, ventilatory need and mortality. Conclusion: Our meta-analysis found that methylprednisolone has the potential to improve the prognosis of patients with severe COVID-19 pneumonia, in comparison to dexamethasone. Keywords: corticosteroids; COVID-19 pneumonia; methylprednisolone; dexamethasone; meta-analysis.
Introduction
Since December 2019, Coronavirus disease 19 (COVID-19) pandemic continues to be one of the leading causes of morbidity and mortality worldwide (1,2). It is now well documented that the pathogenesis of COVID-19 has 3 stages, namely, the viral stage, the pulmonary stage, and the hyperinflammatory stage (3,4). The hyper-inflammatory stage is of major concern as it is associated with increased morbidity and mortality (5,6). Therefore, many anti-inflammatory and antioxidant agents have been tried for the management of COVID-19 with varying success (7,8). To date, systemic corticosteroids are the only class of drugs successfully used for treatment of COVID-19 and has demonstrated definite mortality benefit in various studies (9,10). The mortality benefit with use of corticosteroid is evident in COVID-19 patients requiring oxygen therapy or mechanical ventilation in the late pulmonary or hyperinflammatory stage of the disease (9). The acute respiratory distress syndrome (ARDS) due to viral pneumonitis is one of the leading causes of mortality among patients with COVID-19 (11). ARDS occurs in 33% of hospitalized patients with COVID-19 and 75% of those who required ICU admission (12). The average mortality rate among COVID-19 patients with ARDS is 39% (ranging from 13% to 73%) (11).

Although systemic steroids have shown a mortality benefit in COVID-19, there is no consensus on the doses and types of steroids therapy in these patients (12). Data regarding the role of dose and type of steroids in COVID-19 are still unclear. Therefore, we performed this meta-analysis to evaluate the effect of dexamethasone versus methylprednisolone on the clinical outcomes of patients with COVID-19 pneumonia and respiratory failure.

Materials and Methods
This study adheres to the preferred reporting items for systematic reviews and meta-analysis (PRISMA). No patient consent was required as all analysed data were collected from previously published literature. This study was approved by the Research Ethics Committee (REC) Of Benha University {M.S. 7.12.2021}. This study was conducted over a period of 6 months from from December 2021 to June 2023.

Data sources and search strategy
We performed a comprehensive search for published studies indexed in PubMed/MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Web of Science from inception to February 2023. We also performed a manual search for additional relevant studies using references of the included articles. The following search terms were used (“methylprednisolone” or “dexamethasone” or “glucocorticoids” or “steroids”), and (“COVID” or “COVID-19”). The search was not limited by language, study design, or country of origin. Table 1 describes the full search terms used in each database searched.

Types of studies, participants, intervention, and comparator:
All double/ multiple arm studies (randomized and observational cohort studies) reporting the use of methyl prednisolone in management of COVID-19 along with dexamethasone were included. The study inclusion was not restricted by year of publication, site of study or dose of the drugs. Case series, case reports, review articles and non-English language publications were excluded. All human subjects of both gender with a diagnosis of COVID-19 (RT-PCR confirmed or clinically diagnosed) and treated in hospital were included. The intervention in all included studies was the administration of methyl prednisolone in COVID-19 patients along with dexamethasone. The timing of therapy in relation to disease onset was not a limiting factor. The
Comparators were dexamethasone for management of COVID 19. As there is no universally accepted usual care for management of COVID 19, the standard care followed in different studies as per local guideline without use of systemic corticosteroid is considered as usual care.

Outcome measures
The primary outcome is all-cause mortality: death in COVID 19 patients due to any cause within the available period of follow up in the studies (maximum up to 30 days). The secondary outcome measures are the need for invasive ventilation or intensive care unit (ICU) admission and length of stay.

Information source and search strategy:
PubMed, the Cochrane library, International Clinical Trials Registry Platform (ICTRP) including ClinicalTrials.gov and Pre-print server medRxiv were searched for articles reporting the use of methylprednisolone in management of COVID 19 along with dexamethasone from inception till 2023. Using PICO method, a combination of subject terms and keywords were used for appropriate adjustments of vocabulary and grammar between different databases. We used the search term (COVID 19) “AND” (methyl prednisolone) “OR” (dexamethasone) for literature search in PubMed. The reference list of all relevant articles obtained from electronic search were also reviewed for additional studies.

Data extraction and management:
A pre-designed data extraction format including relevant information was used for data recording. Two review authors (RRM, BRM) independently extracted and assessed the data for quality following Cochrane Collaboration’s guidelines. Any disagreement between them was resolved by the third author (BMP).

Assessment of risk of bias in included studies:
Risk of bias for study validity was accessed for all the studies included in the meta-analysis using Risk of Bias in Non-Randomized Studies - of Interventions (ROBINS-I) for observational studies”. Three authors (RRM, BRM, BMP) independently accessed the risk of bias in each study, and any disagreement was resolved by discussion.

Data analysis:
Cochrane Program Review Manager 5.3 software was used for the meta-analysis. Systematic review was conducted for all the studies reporting the use of methyl prednisolone in management of COVID 19 versus dexamethasone. Studies reporting all-cause mortality as outcome measures were included in the meta-analysis. Odds ratios (ORs) were calculated and combined for estimation of pooled effect by using random effect model in accordance with Cochrane Handbook for Systematic Reviews of Interventions. Heterogeneity among eligible studies was checked by using I2 statistics. I2 > 50% was considered to be statistically significant. For studies reporting only the interquartile range (IQR) for continuous measure outcomes, we assumed that the mean and median were equal. We calculated the SD from IQR by dividing the IQR by 1.35 [11].

Assessment of publication bias and Grade of evidence:
We used funnel plot for visual assessment of asymmetry due to publication bias. For certainty assessment of the evidence, Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiler software (V 3.6.1) was used.

Exclusion criteria:
Studies were excluded if they were case studies, letters to editors, or meta-analyses, or involved paediatric patients. Nevertheless, if their outcomes were not of interest or contained absent or deficient data. Lastly, if the study authors were inaccessible or did not reply if extra data from their trials were requested.

Results
Description of studies
The search of all database and additional sources from the references of relevant publications retrieved 798 studies. Among
them, 21 studies were selected for full text review after removing duplicates and studies not meeting the inclusion criteria. Finally, a total of 10 studies were included in the systematic review and meta-analysis. Eleven studies were excluded after full text review due to the following: the study was a case series with systematic review, studies reporting use of only low dose methyl prednisolone and study, the comparator arm could not be identified. The PRISMA flowchart of study selection is depicted in figure 1.

Out of 10 studies, 7 studies were observational cohort studies (5 retrospective, 1 prospective, 1 misperceive studies), 1 was a randomized controlled trial (RCT), 1 was Quasi experimental, interventional study and 1 was institutional review board approved cohort study.

Though most of the studies included COVID-19 cases of severity ranging from moderate to critical, there were few mild cases in the studies by (13).

The basic demographic profile, co-morbidities and other treatment received were comparable across the groups in all the studies. The lowest dose of methyl prednisolone administered was 1:2 mg/kg/day and the highest was 500 mg/day in two studies. The dose of dexamethasone was 6:8 mg/kg/day. Almost all patients received the pulse dose methyl prednisolone for at least 3 days in the intervention group. In most of the studies, the total duration of methyl prednisolone therapy was up to 7 days except in the study by, where the methyl prednisolone therapy for 3 days was followed by oral methyl prednisolone (50 mg/day) for 14 days (13).

The triple-blinded RCT by Ranjbar et al reported in hospitalized hypoxic COVID-19 patients, methylprednisolone demonstrated better results compared to dexamethasone (14).

Study and patient characteristics
A total of 1812 COVID-19 patients were included in the meta-analysis. Among them, 779 patients received methyl prednisolone, 1033 patients received dexamethasone. The characteristics of patients and studies included in the meta-analysis are summarized in table 1.

Risk of bias in the included studies
The risk of bias for primary outcome was accessed for all the studies included in the meta-analysis. Across all the included studies, 3 important confounding domains were identified, i.e., non-uniformity of COVID-19 patient severity, use of additional treatment modalities and presence of comorbidities). All other studies had overall moderate to serious risk of bias. The domains like, bias due to confounding, bias in selection of participants into the study were identified having moderate to serious risk of bias due to retrospective nature of the included studies. The overall predicted direction of bias for the primary outcome (all-cause mortality) was assessed to be unpredictable. The result of the risk of bias assessment of all studies are summarized in figure 2, and 3.
A meta-analysis of randomized trials

Figure 1. PRISMA flowchart of study selection process

Figure 2. A: Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies B: Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.
Mortality
This meta-analysis indicated that there is a statistically significant mortality benefit with use of methylprednisolone treatment of COVID-19, it shows that dexamethasone resulted in increase in mortality in COVID-19 patients than methylprednisolone.

The result of subgroup analysis is summarized in figure 3.

The forest plot diagram shows that dexamethasone resulted in increase in mortality in COVID-19 patients than methylprednisolone, with RR 2.04 and high heterogeneity (95% CI; RR 2.04 [1.73, 2.40]; $I^2 = 84\%; p < 0.0001$).

Need for invasive ventilation:
This outcome was reported in 8 studies comparing methyl prednisolone group and dexamethasone. It shows that dexamethasone resulted in increase in invasive ventilation in COVID-19 patients than methylprednisolone, with RR 1.69 and high heterogeneity (95% CI; RR 1.69 [1.44, 1.99]; $I^2 = 88\%; p < 0.0001$). The result analysis is summarized in figure 4.

Length of stay
This outcome was reported in 9 studies comparing methylprednisolone group versus dexamethasone. It shows that dexamethasone resulted in increase in hospital length of stay in COVID-19 patients than methylprednisolone, with MD 1.04 [-0.72, 2.81] and high heterogeneity (95% CI; MD 1.04 [-0.72, 2.81] $I^2 = 89\%; p < 0.0001$). The result analysis is summarized in figure 5.
<table>
<thead>
<tr>
<th>Study type</th>
<th>Intervention</th>
<th>Number of patients</th>
<th>Age</th>
<th>ICU length of stay</th>
<th>ICU transfer</th>
<th>Ventilator need</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatima et al 2020 (15)</td>
<td>Dexamethasone</td>
<td>35</td>
<td>57.91</td>
<td>42.8% (n = 15)</td>
<td>20% (n = 7)</td>
<td>17.1% (n = 6)</td>
<td>16.4%</td>
</tr>
<tr>
<td>Ko et al 2020 (16)</td>
<td>Methylprednisolone</td>
<td>65</td>
<td>54.86</td>
<td>33.8% (n = 22)</td>
<td>12.3% (n = 8)</td>
<td>15.3% (n = 10)</td>
<td>26.5%</td>
</tr>
<tr>
<td>May et al 2021 (17)</td>
<td>Dexamethasone</td>
<td>42</td>
<td>10.52 ± 5.47</td>
<td>20.5%</td>
<td>13.8%</td>
<td>17.8%</td>
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<tr>
<td>Mora-Luján et al 2021 (18)</td>
<td>Methylprednisolone</td>
<td>44</td>
<td>7.43 ± 3.64</td>
<td>7.34 ± 3.64</td>
<td>68</td>
<td>88</td>
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<tr>
<td>Pinzón et al 2021 (19)</td>
<td>Dexamethasone</td>
<td>111</td>
<td>63 (58–69)</td>
<td>16</td>
<td>22</td>
<td>17.1%</td>
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<tr>
<td>Plessis et al, 2021 (20)</td>
<td>Methylprednisolone</td>
<td>105</td>
<td>64 (60–68)</td>
<td>4.8%</td>
<td>2.9%</td>
<td>9.5%</td>
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</tr>
<tr>
<td>Ramzy 2021 (21)</td>
<td>Dexamethasone</td>
<td>83</td>
<td>47% over 60 years</td>
<td>14.3+13.1</td>
<td>43.5%</td>
<td>26.5%</td>
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<tr>
<td>Ranjabar et al, 2021 (22)</td>
<td>Methylprednisolone</td>
<td>104</td>
<td>42% over 60 years</td>
<td>13.44+14.8</td>
<td>45.7%</td>
<td>16.4%</td>
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<tr>
<td>Choi et al, 2022 (23)</td>
<td>Control steroid</td>
<td>14</td>
<td>72 (64–76 yr.)</td>
<td>14 (12–24 d)</td>
<td>428.6%</td>
<td>5 (35.7%)</td>
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<tr>
<td>Okano et al, 2023 (24)</td>
<td>Pulse steroid</td>
<td>30</td>
<td>70 (65–76 yr.)</td>
<td>7 (9–16 d)</td>
<td>6 (20%)</td>
<td>7 (23.3%)</td>
<td></td>
</tr>
<tr>
<td>Okano et al, 2023 (24)</td>
<td>Steroid without pulse (NP)</td>
<td>22</td>
<td>73 (59–77)</td>
<td>6 (3–13 d)</td>
<td>10</td>
<td>45.5%</td>
<td></td>
</tr>
<tr>
<td>Okano et al, 2023 (24)</td>
<td>Steroid with pulse (P)</td>
<td>48</td>
<td>63 (56–74)</td>
<td>9 (5–14d)</td>
<td>36 (75.0%)</td>
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<td></td>
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</tbody>
</table>

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Confidence interval (CI); Mantel and Haenszel (M-H); risk ratio (RR)

**Figure 5.** Length of stay.

Confidence interval (CI); Mantel and Haenszel (M-H); risk ratio (RR)

**Figure 6.** ICU transfer the forest plot diagram.

Figure 6 shows that dexamethasone resulted in increase in ICU transfer of COVID-19 patients than methylprednisolone, with RR 2.66 and high heterogeneity (95% CI; RR 2.66 [2.17, 3.24]; \( I^2 = 94\% ; \ p < 0.0001 \)).

**Discussion**

This is meta-analysis comparing dexamethasone and methylprednisolone regimens in patients with COVID-19 and showed that methylprednisolone result in significant decrease in hospital length of stay, ventilatory need and mortality.

Since the RECOVERY trial showed a mortality benefit with steroid therapy due to its anti-inflammatory and immunomodulatory effects (25). Steroid therapy (equivalent dose of 6 mg dexamethasone [DEXA]) became a standard treatment in most hospitals for COVID-19 patients requiring oxygen support. A recent meta-analysis (26) revealed consistent results with a significant reduction in mortality among patients with severe COVID-19, especially when administered earlier. This meta-analysis showed a statistically significant mortality benefit and decreased need for mechanical ventilation or ICU admission with the use of methyl prednisolone in comparison to dexamethasone for management of COVID 19 patients.

Our result is also in conformity with the result of the RCT (27) which include 68 patients with COVID-19, the PDS group (received methylprednisolone therapy at a dose of 250 mg/day for 3 days) had a lower mortality rate and shorter recovery duration as compared to the control group.

The rationale of using PDS therapy is to get a quicker and stronger anti-inflammatory response, thus reducing the need for a prolonged course of steroids (28).

A retrospective study from Japan has also suggested the beneficial effect of pulse/semi-pulse dose methyl prednisolone in shortening the duration of mechanical ventilation for severe COVID 19 patients in comparison to usual care alone (29).
Though the study done in 2021 reported significant improvement in recovery time and need for mechanical ventilation or ICU care with use of pulse dose methyl prednisolone in comparison to low dose dexamethasone, our meta-analysis supports that observation (29).

Several limitations of this study should be acknowledged. First, because the literature lacks RCTs, our meta-analysis included mostly observational studies. Future RCTs are warranted to confirm our findings. Second, even though the random-effects model was used in our analysis, there was significant heterogeneity noted in all the outcomes. This might be driven by differences in patient characteristics, inconsistent follow-up duration, the difference in the location of the patients (hospital ward vs. ICU), use of other drugs for COVID-19 treatment, and lack of standardized dosages and type of the steroids used in the included studies. Lastly, the lack of patient-level data did not allow to control for possible variations in baseline characteristics or optimal dosage of steroids and duration of treatment because other medications used for COVID-19 might have been different and not standardized between patients, which might introduce potential bias.

**Conclusion**

Our meta-analysis found that methylprednisolone has the potential to improve the prognosis of patients with severe COVID-19 pneumonia, in comparison to dexamethasone.

**Conflicts of Interest**

The authors declare no conflicts of interest.

**Data availability statement**

All data were available to all authors of the manuscript.

**References**


