Efficacy and Safety of Corticosteroid Administration in Moderate to Severe COVID-19: A Meta-analysis

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Abstract

Background. Adding to the current available evidence on the efficacy of exogenous corticosteroids as an adjunct to standard of care in improving the clinical outcomes of COVID-19 patients. This meta-analysis examined the experimental and clinical data supporting this therapeutic intervention in improving clinical outcomes.

Objectives. This meta-analysis aimed to assess the efficacy of corticosteroids in improving outcomes in COVID-19 patients.

Search methods. Literature searches of electronic databases (PubMed, Cochrane Library, Science Direct, Google Scholar) were performed to identify relevant studies.

Data Collection and Analysis. Meta-analysis was performed using Review Manager (RevMan) software, version 5.4.1. Intervention effects were expressed in terms of mean differences and risk ratios for continuous and dichotomous variables, respectively. Fixed-effect or random-effects model was adopted according to heterogeneity.

Main Results. A total of seven studies were included in the quantitative synthesis. Analysis of pooled data showed a 12% reduced risk of mortality in COVID patients given corticosteroids (RR 0.88, 95% CI 0.81 to 0.95). Patients who were administered with corticosteroids also had 22% decreased risk of requiring invasive ventilation support (RR 0.78, 95% CI 0.64 to 0.95). Number of adverse events were similar between the two groups (RR 1.10, 95% CI 0.49 to 2.46).

Conclusion. Adjunct corticosteroid therapy provided improvements in clinical outcomes such as decreased deaths and decreased need for invasive ventilation support. There was no sufficient evidence of a significant adverse effect, hence it is relatively safe and beneficial to use in COVID19 patients.

Keywords. *Corticosteroids, COVID-19, meta-analysis, clinical outcomes*

Introduction

Coronavirus Disease 2019 (COVID 19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was declared a Public Health Emergency of International concern on January 30, 2020 by the World Health Organization.[8] The spectrum of disease associated with this ranges from asymptomatic or mild self-limiting infection to rapidly progressing life threatening disease, severe pneumonia, acute respiratory distress syndrome (ARDS), multisystem organ failure, and death. There are many pharmacologic therapies that are being used or considered for treatment of COVID-19 and one of which is corticosteroids.

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In the early days of the SARS-CoV-2 pandemic, recommendations cautioned against the use of systemic corticosteroids based on experience in both SARS and MERS, due to risk of worsening clinical status, delayed viral clearance, and adverse events.[12-15] Guidelines on COVID-19 are also inconsistent about the use of corticosteroids. Rigorous data on the efficacy of corticosteroids have been limited and the pandemic has been a potent stimulus for clinical research addressing this controversy. As COVID- 19 pandemic spreads across the world, clinicians struggled to weigh potential benefits of corticosteroids against the potential harms associated with this drug.

According to the studies by Zhang, Siddiqi and Sanders, COVID-19 is biphasic. The first phase is caused directly by viral replication, while in the second phase, the symptoms and respiratory failure are due to inflammatory response.[9-11] The entire phenomenon is named Cytokine Release Syndrome (CRS), or Systemic Inflammatory Response Syndrome (SIRS), or Secondary haemophagocytic lymphohistiocytosis (SHLH).[8] The anti-inflammatory and immunosuppressive activity of

corticosteroids causing a reduction of pro-inflammatory cytokines, chemokines, and molecules of cellular adhesion and of other enzymes that are involved in the inflammatory response provides a pathophysiologic basis for its use in the management of cytokine and chemokine storm during COVID-19.

Despite the recommendations of the World Health Organization and Infectious Disease Society of America regarding the use of systemic corticosteroids in patients with severe and critical COVID-19 based on randomized controlled trials demonstrating reduction in mortality, many clinicians remained hesitant to start corticosteroids due to concerns regarding adverse effects.[16,17]

As of July 24, 2020, there were 55 studies on corticosteroids for the treatment of COVID-19 registered at ClinicalTrials.gov.[18] Other published systematic review and meta-analyses included different types of studies resulting to significant heterogeneity. With the recent published large scale clinical trials, this study aims to generate reliable data on the efficacy and safety of corticosteroid to guide clinical management of COVID-19. To add to the growing data, the researchers aim to collate the most recent available data to establish whether corticosteroids are beneficial in improving clinical outcomes in COVID-19 patients.

Outcome measures

The primary outcome measure is Mortality rate. Secondary outcome measures include the need for mechanical ventilation and adverse events

General Objective:

The researchers aimed to assess the efficacy of administering corticosteroids in improving clinical outcomes in COVID-19 patients

Specific Objectives:

1. Determine the efficacy of corticosteroid administration in terms of mortality and need for invasive ventilation support
2. Determine if there is significant difference in the number of serious adverse events between patients given the experimental intervention and those provided with standard of care (SOC) only

Significance of the Study. Critically-ill patients afflicted with COVID-19 often have poorer outcomes, hence effective therapies for critically-ill patients with COVID-19 are needed. The role of corticosteroids as adjunct for treatment will be evaluated in association with mortality.

For the WHO and DOH, as the central health agencies, the results of this study will aid in their policy making and amendments of the clinical practice guidelines for the use of corticosteroids in moderate to severe COVID-19, thus improving the overall quality of healthcare.

For the medical practitioners, this study addresses concerns regarding safety of corticosteroid use and thus will strengthen their confidence in its use in COVID 19.

For researchers, the results of this study can help stimulate the generation of future researches on corticosteroid use in COVID-19. Additional areas of future investigation include the optimum time to start, as well as the duration of the giving of corticosteroids in these patients.

Methodology

Criteria for considering studies for this review

Types of studies Randomized controlled clinical trials

Types of participants Adult patients more than 18 years of age, male and female with moderate to severe COVID at presentation with impaired gas exchange PaO2/FiO2 <300, and biochemical evidence of hyperinflammatory state, elevated serum C-Reactive Protein (CRP), D-dimer, ferritin, or IL-6 levels.

Types of interventions Interventions are regarded as any type of corticosteroid preparation, whereas controls are standard of care (SOC) or placebo.

Types of outcome measures

1. Primary outcomes: Mortality rate
2. Secondary outcomes: need for invasive ventilatory support; adverse events such as secondary infections and need for insulin for glucose control

Search methods for identification of studies The researchers conducted a systematic literature search through PubMed, Cochrane Library, Science Direct and Google Scholar, using the following key terms: COVID-19, corticosteroids, mortality. No restrictions were applied based on language or publication status. The bibliographies of the retrieved articles were also checked for additional references.

Data collection and analysis

Selection of studies The authors searched abstracts and titles for potentially eligible studies. Upon obtaining the full-text reports of these studies, the same authors performed study selection based on the following criteria:

1. Randomized controlled trials;
2. Studies evaluating corticosteroids in COVID-19 patients;

Data extraction and management The characteristics of the studies and outcome data were extracted from eligible studies. The information extracted were as follows: (1) name of first author, publication year; (2) number of cases; (3) interventions; (4) control group; (5) outcomes.

Assessment of risk of bias in included studies Methodological quality for clinical trials was evaluated by the researchers using Cochrane risk bias tool. Each journal article was critically appraised for validity in terms of sequence generation, allocation concealment, blinding of patients, personnel and outcome assessors, treatment of incomplete outcome data and the risk of selective reporting. Each domain was judged as being 'low risk', 'high risk' or 'unclear risk' (See Appendix).

Measures of treatment effect Data were analyzed using the Review Manager software (RevMan version 5.4.1).

Table I. Summary characteristics of included studies

Author	Year	Study Design	Outcome	Intervention used (n)	Control (n)
Angus[6]	2020	RCT	28-day mortality	Hydrocortisone 50/ 100mg Q6 (248)	SOC (101)
Dequin[3]	2020	RCT	21-day mortality	Hydrocortisone 200/ 100/ 50mg OD (76)	Placebo (73)
Gudino[7]	2020	RCT	Mortality	Methylprednisolone 20/ 40mg Q12 (56)	SOC (29)
Horby[2]	2020	RCT	28-day mortality	Dexamethasone 6mg OD (2104)	SOC (4321)
Jeronimo[5]	2020	RCT	28-day mortality	Methylprednisone 0.5mg/kg Q12 (194)	Placebo (199)
Tomazini[4]	2020	RCT	28-day mortality	Dexamethasone 10/ 20mg OD (151)	SOC (148)
Villar[1]	2020	RCT	60-day mortality	Dexamethasone 10/ 20mg OD (139)	SOC (138)

n – number of patients given intervention; SOC – standard of care

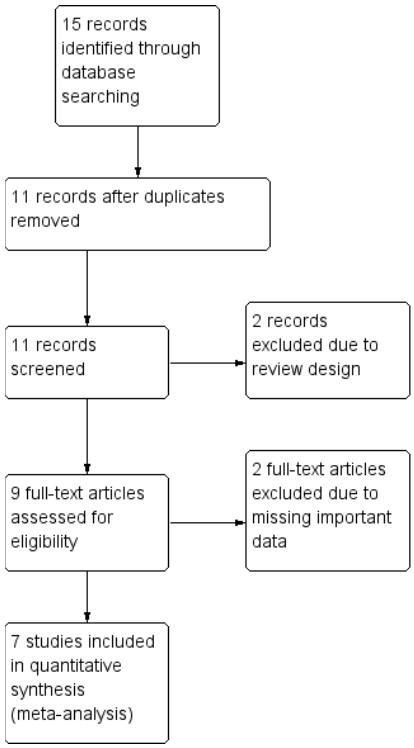

Figure 1. Study flow diagram

Analysis was done in accordance with the Cochrane Collaboration Handbook. A p-value of less than 0.05 for the observed effect size was considered statistically significant.

Assessment of heterogeneity The heterogeneity of intervention effects was appraised visually by observing the overlapping of results in the forest plots. Lack of overlapping was interpreted as indicative of possible heterogeneity. The authors further estimated heterogeneity quantitatively using, I^2 statistics. I^2 is the proportion of total variation observed between the trials attributable to difference between trials. I^2 of more than or equal to 50% indicates significant heterogeneity. Random effects model was used for pooled data with significant inconsistencies, otherwise, fixed effect model was applied.

Data synthesis Mantel-Haenzel test was used for dichotomous outcomes, while inverse variance was used for continuous data.

Results

Results of the search A total of 15 articles were identified from PubMed, Google Scholar, Cochrane Library and Science Direct. Eleven articles were gathered after duplicates and irrelevant studies were removed. Among the 11 articles screened, 2 were removed due to review article design. The remaining articles were assessed for eligibility; 2 articles were removed due to missing important data. After examination of the full texts, seven studies were found to meet all of the inclusion criteria and were entered into the meta-analysis. The entire selection process is illustrated in Figure 1.

Description of studies A total of 8007 patients were included in the seven studies.[1-7] There were 2998 patients in the experimental group, and 5009 patients in the control group. The summarized characteristics of included studies are listed in Table I.

Effect of interventions Fixed effects model was used to compare differences between the groups due to low heterogeneity.

The observed risk for mortality was lower in the group of patients given corticosteroids. Analysis of pooled data showed a 12% reduced risk of mortality in COVID patients given corticosteroids (RR 0.88, 95% CI 0.81 to 0.95; participants = 8007; studies = 7; I^2 = 26%) (Figure 2).

On the contrary, serious adverse events were observed to be higher in the corticosteroid group. However, this observed value was not statistically significant (RR 1.10, 95% CI 0.49 to 2.46; participants = 827; studies = 3; I^2 = 42%) (Figure 3). Lastly, patients administered with corticosteroids had approximately 22% decreased risk of requiring invasive ventilation support (RR 0.78, 95% CI 0.64 to 0.95; participants = 5745; studies = 3; I2 = 21%) (Figure 4). The summary of effects of intervention is shown in Table II

Discussion

From the initial conception of COVID-19 as a pure infectious disease, accumulated data have helped to understand the important role of the host inflammatory response hence the suggested beneficial effect of anti-inflammatory therapy such as corticosteroids.

This meta-analysis of 7 randomized clinical trials included 8007 patients with moderate to severe COVID-19. These

studies showed clear association between giving of steroids and mortality. These studies showed reproducible, significant difference in subjective or objective data. Meta-analysis studies are inherently prone to confounders due to variability in included articles, especially if low quality studies were chosen hence correctional analysis for heterogeneity by employing fixed effect model in the treatment of data was done. Geographic and population differences and differences in study designs were regarded as possible confounders in the study.

This study included more recent randomized controlled trials, latest is the Metcovid trial published in August 2020, hence addressing the risk of selective reporting or of publication bias in the prospective meta-analysis published by WHO. Two randomized trials included in the meta-analysis by WHO was also excluded since full text study was not readily available and the Steroid-SARI trial was assessed to have some concerns on risk of bias, identified as one of limitations in the WHO meta-analysis.

In addition to mortality, secondary outcomes such as need for invasive ventilatory support and serious adverse outcomes were also analyzed in this study. Patients who were administered with corticosteroids also had 22% decreased risk of requiring invasive ventilation support

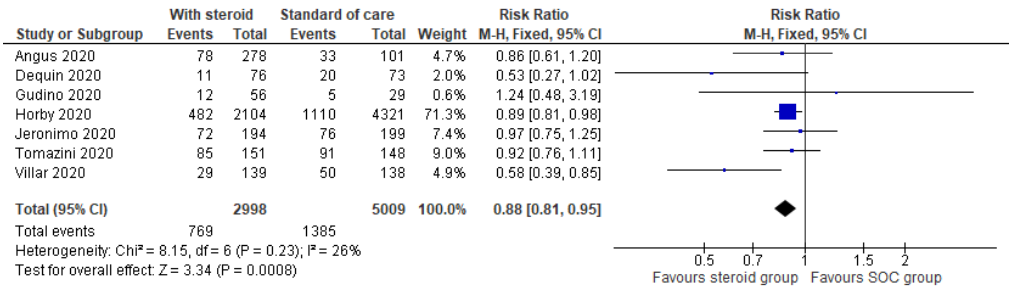

Figure 2. Forest plot of comparison: Efficacy of adjunct steroid regimen in COVID-19, outcome: Adjunct steroid therapy vs Mortality

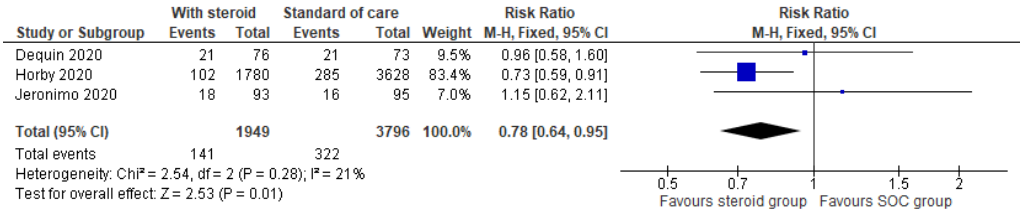

Figure 3. Forest plot of comparison: 1 Efficacy of adjunct steroid regimen in COVID-19, outcome: Steroid treatment vs need for MV support

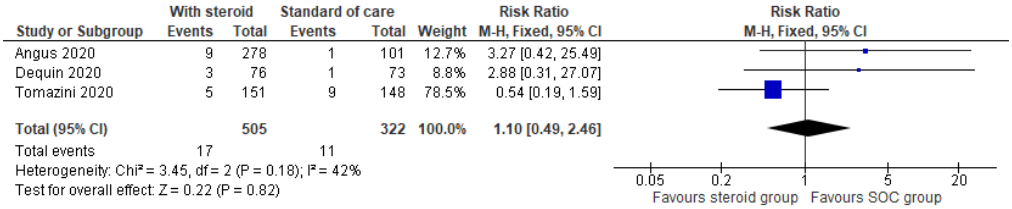

Figure 4. Forest plot of comparison: Efficacy of adjunct steroid regimen in COVID-19, outcome: Steroid treatment vs Risk of serious adverse events.

Table II. Summary of Effect Measures: Efficacy of adjunct steroid in COVID-19

Outcome or subgroup	Studies	Participants	Statistical Method	Effect Estimate
Steroid administration vs mortality	7	8007	Risk Ratio (M-H, Fixed, 95% CI)	0.88 (0.81, 0.95)
Steroid vs need for invasive ventilation	3	5745	Risk Ratio (M-H, Fixed, 95% CI)	0.78 (0.64, 0.95)
Steroid administration vs adverse events	3	827	Risk Ratio (M-H, Fixed, 95% CI)	1.10 (0.49, 2.46)

(RR 0.78, 95% CI 0.64 to 0.95). The number of adverse events were similar between the two groups.

This meta-analysis provides further evidence to support data of previous randomized controlled trials suggesting that corticosteroid use in COVID 19 are beneficial and relatively safe, building another body of evidence that will make health workers confident in its use.

Limitations

There was some degree of inconsistencies in the findings among the included studies. These inconsistencies are better known as heterogeneity of data, which is not uncommon in a meta-analytic study. This is due to the fact that many patients' demographic and clinical factors affect the measurement or development of outcome. More RCTs that investigate the association between these variables are needed which will not only address heterogeneity, but also increase the generalizability of the study, ultimately further increasing the quality of evidence. The trials only recruited adults hence the effect of corticosteroids in children remains unclear.

Conclusion

Based on the interpretation of pooled data, adjunct corticosteroid therapy provides improvements in clinical outcomes such as decreased deaths and decreased need for invasive ventilation support. There was no sufficient evidence of a significant adverse effect, hence it is relatively safe and beneficial to use in COVID19 patients.

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APPENDIX

A. Risk of bias with support for judgement (Angus, et al[6])

Bias	Authors' judgement	Support for judgement
Random sequence generation		Randomize patients to multiple interventions within multiple domains. Assignment was done using computer-generated random numbers
Allocation Concealment		A randomization table determined the order of inclusion for patients in the treatment arms
Blinding of participants and personnel		Open-label study
Blinding of outcome assessment		Even if clinical staff aware of assigned intervention, no information were provided about aggregate patient outcome
Incomplete outcome data		All participants who consented to take part in the study were accounted for until the end of the study
Selective Reporting		The outcomes reported were all pre-specified in the methodology section
Other bias		Insufficient information to assess whether an important risk of bias exist

Low risk High Risk Unclear Risk

B. Risk of bias with support for judgement (Dequin, et al[3])

Bias	Authors' judgement	Support for judgement
Random sequence generation		Randomization was performed by computer-generated random numbers
Allocation Concealment		Allocation sequences were generated in a 1:1 ratio using a blocking schema
Blinding of participants and personnel		Interventions were provided in industrially prepared packaging (No blinding to intervention)
Blinding of outcome assessment		No blinding for outcome assessment. But since primary outcome is death, there is very little risk of systematic bias
Incomplete outcome data		All randomized patients were included in the final analysis
Selective Reporting		All clinical outcomes mentioned were reported in the results
Other bias		Insufficient information to assess whether an important risk of bias exist

Low risk High Risk Unclear Risk

C. Risk of bias with support for judgement (Gudino, et al[7])

Bias	Authors' judgement	Support for judgement
Random sequence generation		Randomization was performed by computer-generated random numbers
Allocation Concealment		Allocation sequences were generated in a 1:1 ratio
Blinding of participants and personnel		Blinding to intervention not specified
Blinding of outcome assessment		Blinding to intervention not specified
Incomplete outcome data		Intention-to-treat analysis was done. Patients were analyzed according to the group to which they were randomized
Selective Reporting		All clinical outcomes mentioned were reported in the results
Other bias		Insufficient information to assess whether an important risk of bias exist

Low risk High Risk Unclear Risk

D. Risk of bias with support for judgement (Horby, et al[2])

Bias	Authors' judgement	Support for judgement
Random sequence generation		Randomization was performed with the use of a Web-based system
Allocation Concealment		Concealment of the trial-group assignment was done
Blinding of participants and personnel		Patients and local members of the trial staff were aware of the assigned treatments
Blinding of outcome assessment		Blinding to intervention not specified
Incomplete outcome data		Intention-to-treat analysis was done.
Selective Reporting		All clinical outcomes mentioned were reported in the results
Other bias		Insufficient information to assess whether an important risk of bias exist

Low risk High Risk Unclear Risk

E. Risk of bias with support for judgement (Jeronimo, et al[5])

Bias	Authors' judgement	Support for judgement
Random sequence generation		An independent statistician prepared an electronically generated randomization list with 14 blocks
Allocation Concealment		Allocation list was accessible only to non blinded pharmacists in the study
Blinding of participants and personnel		Participants are unaware of the interventions given to them.
Blinding of outcome assessment		Those who analyzed the outcome data were unaware of the interventions given to each participants
Incomplete outcome data		No missing outcome data
Selective Reporting		All clinical outcomes mentioned were reported in the results
Other bias		Insufficient information to assess whether an important risk of bias exist

Low risk High Risk Unclear Risk

F. Risk of bias with support for judgement (Tomazini, et al[4])

Bias	Authors' judgement	Support for judgement
Random sequence generation		Randomization was performed through an online web-based system using computer-generated random numbers and blocks of 2 and 4
Allocation Concealment		No allocation concealment
Blinding of participants and personnel		Open-label study – no allocation blinding was done to the participants and outcome assessors
Blinding of outcome assessment		Group treatment was disclosed to the investigators
Incomplete outcome data		Randomized patients were accounted for until the end of the trial
Selective Reporting		All clinical outcomes mentioned were reported in the results
Other bias		Insufficient information to assess whether an important risk of bias exist

Low risk High Risk Unclear Risk

G. Risk of bias with support for judgement (Villar, et al[12])

Bias	Authors' judgement	Support for judgement
Random sequence generation		Randomization sequence was done through a computer-generated random-number table
Allocation Concealment		Allocation was done using blocks of ten opaque, prenumbered, sealed envelopes
Blinding of participants and personnel		Although dexamethasone was not administered in a masked manner, the risk of assessment bias is very low because one of the outcomes of interest (mortality) is objective
Blinding of outcome assessment		No blinding for outcome assessment. But since primary outcome is death, there is very little risk of systematic bias
Incomplete outcome data		No missing outcome data
Selective Reporting		All clinical outcomes mentioned were reported in the results
Other bias		Insufficient information to assess whether an important risk of bias exist

Low risk High Risk Unclear Risk