Effect of Corticosteroids therapy on mortality in the COVID-19 patients- A systematic review and Meta-analysis

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Abstract

Background and Purpose: Corticosteroid therapy is still controversial to use for treatment of coronavirus disease-2019 (COVID-19). The results of multiple randomized clinical trials (RCTs) and observational studies are very diverse and contradictory, which arising difficulty in the clinical decision-making. The objective of this study is to investigate the effect of corticosteroids on mortality by systematic review and meta-analysis. External Approach: A systematic search was performed on different databases namely Medline/PubMed, Cochrane and Google scholar on 10 February 2022, according to PRISMA guidelines. The 28-days mortality was considered as outcome of study. A pooled estimate was calculated with random effects and fixed effects models. Cochran's Q test and the I2 statistic were conducted for statistical heterogeneity. Key Results: 38 studies were included, having sample size of 87,781 patients. Amongst them, 16437 patients received corticosteroid therapy (intervention group) while 71344 patients were standard (noncorticosteroids) therapy (control group). 12.68% (2084) mortality observed in the intervention group while 5.93% (4227) mortality observed in the control group. The overall pooled estimate showed a significantly (OR2.305;95%CI: 2.1810 to 2.4370) increased mortality in intervention group. A pooled fold change estimation showed significantly increased in the mortality in methylprednisolone (OR 1.206;95%CI: 1.0770 to 1.3500) and dexamethasone (OR 1.388;95% CI:1.1870 to 1.6220) therapy. Conclusion and Implication: In conclusion, corticosteroid therapy produced a negative prognosis as depicted by increased mortality among COVID-19 patients. The possible reasons might be delay in virus clearance and secondary infection due to initiation of the corticosteroids at high dose in the early stage of infection.

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Running title: Role of corticosteroid therapy in COVID-19 patients

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Key Results:

38 studies were included, having sample size of 87,781 patients. Amongst them, 16437 patients received corticosteroid therapy (intervention group) while 71344 patients were standard (noncorticosteroids) therapy (control group). 12.68% (2084) mortality observed in the intervention group while 5.93% (4227) mortality observed in the control group. The overall pooled estimate showed a significantly (OR2.305;95%CI: 2.1810 to 2.4370) increased mortality in intervention group. A pooled fold change estimation showed significantly increased in the mortality in methylprednisolone (OR 1.206;95%CI: 1.0770 to 1.3500) and dexamethasone (OR 1.388;95% CI:1.1870 to 1.6220) therapy.

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In conclusion, corticosteroid therapy produced a negative prognosis as depicted by increased mortality among COVID-19 patients. The possible reasons might be delay in virus clearance and secondary infection due to initiation of the corticosteroids at high dose in the early stage of infection.

Keywords: COVID-19, SARS-CoV-2, Coronavirus, infection, methylprednisolone, dexamethasone, corticosteroids, mortality, death, fatality

1. Introduction:

World Health Organization (WHO) reported 505,817,953 confirmed COVID-19 cases and 6,213,876 fatality from COVID-19till April 22, 2022 (1). COVID-19 infection can cause infection without any symptoms, moderate upper respiratory tract sickness, severe pneumonia condition, respiratory failure and even death (2). In severe COVID-19 infection, symptoms deteriorate and become hypoxic after four to seven days and can advance to acute respiratory distress syndrome (ARDS) between eight and twelve days (3). Immune-mediated cascades including increased proinflammatory cytokines levels and cytokine storm, rather than virus-induced damage, are equally important in the pathophysiology of multiple organ damage and mortality (4). Therefore, corticosteroid therapy was proposed to suppress the immune-mediated cascades and cytokine storm-related complications and mortality in COVID-19 (5,6). Therefore, numerous of observational studies and randomized controlled trials (RCT) to investigate the effect of corticosteroids therapy in COVID-19 have been initiated and reported.

Recently, the RECOVERY study reported the rationale for the corticosteroid therapy in severe COVID-19 patients (7). As per initial results from the RECOVERY study, dexamethasone reduced 28-daysfatality in severe COVID-19 patients (7). Multiple randomized trials have been found that systemic corticosteroids therapy improve clinical results and lowers fatality in COVID-19 hospitalized patients thoseneedof oxygen

supplement(7–16). Based on results from these clinical trials, WHO advised to utilization of corticosteroids for the management of severe COVID-19 patients (17). Furthermore, the recent global Surviving Sepsis Guideline suggests to use steroids in the severe COVID-19 patients those on mechanical ventilation support with ARDS (18).

In contrary, the Centers for Disease Control and Prevention (CDC), United States has not been specifically advice either for or against the utilization of corticosteroids in COVID-19. for immunological regulation (20). It has been reported that corticosteroids usage causes the delay in viral RNA clearance in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MARS)(19). A recent study also indicated that corticosteroid therapy started at high dose or early stage (less than three days) of infection in critical COVID-19 patients delayed viral clearance and increased the risk of 28-days mortality (20). The possible cause might be weakening of the immune response by corticosteroid therapy. The weakening of patients' immune systems from corticosteroid therapy leads to rarely occurring fungal infections (e.g. aspergillosis, mucormycosis), relapsing of dormant infections (e.g. herpesvirus infections, strongyloidiasis, hepatitis B virus infection, tuberculosis) and respiratory failure (21–25). Recent study reported that corticosteroids use in SARS patients has been associated to significant consequences such as avascular necrosis, diabetes and psychosis. (19,26)

The results of multiple RCTs and observational studies are very diverse and contradictory, which arising difficulty in the clinical decision-making. Furthermore, these studies were performed with limited sample size. Therefore, there is need to review available studies with greater statistical power for concrete conclusion in relation to utilization of corticosteroids in the COVID-19 patients. The objective of this study is to assess relationship between corticosteroids therapy usage and mortality in the COVID 19 patients by a systematic review and meta-analysis of RCT and observational cohort studies.

2. Methods:

2.1 Data sources and search strategy:

A systematic review was conducted as per the PRISMA guideline. This systematic review and meta-analysis was registered to PROPERO (CRD42022304323). A comprehensive search was performed in PubMed/Medline, Cochrane and Google Scholar databases on 10 February 2022 by two persons independently (D.P.; K.P.). All the probable combination of key words were included in the study such as "corticosteroid therapy" "methylprednisolone" "dexamethasone" "Prednisolone" "COVID-19" "SARS-CoV-2 infection" "Corona infection" "Mortality" "fatality" "death". The cross-references from the screened studies were explored for more articles. The same study selection criteria were utilized for articles identified via forward/backward search.

2.2 Study selection criteria:

The studies were included on basis of the inclusion and exclusion criteria. The inclusion criteria considered in the selection of studies were adult COVID-19 patients (aged 18 years or above), infection of COVID-19 confirmed through rapid antigen test or RT-PCR, the corticosteroid therapy given in at least one arm of the treatment. The exclusion criteria considered for selection of studies were review articles, case reports, editorials, and studies having only in-vitro or preclinical data and published in other than English language,.

2.3 Data Extraction:

The title and abstract of the articles included via keyword search were screened as per the study selection criteria. Full-text content screening was performedfor highly relevant studies. Full text and corresponding supplementary information of the following items were collected and recorded from the eligible studies; first author name, publication year, country, study design, types of steroid used, sample size, number of patient in intervention and control group, mortality in intervention and control group. MS Office Excel worksheet was utilized to collect the extracted information from included studies.

2.4 Study Quality Assessment:

The quality of the included studies was assessed using nine quality assessment criteria adapted from Littell et al. (24): (1) Was the research problem clearly mentioned? (2) Were the inclusion and exclusion criteria clearly mentioned? (3) Were the subjects in the study representative of the pathological population? (4) Were the principaloutcome of the study clearly mentioned? (5) Was a control group included? (6) Were effect of corticosteroid therapy clearly mentioned (7) Were diagnosis method of COVID-19 clearly defined (8) Was a sample size justification via power analysis provided? (9) Were potential confounders properly controlled in the analysis? Each of the nine criteria was scored on a scale of zero to two, depending on whether the criterion was unmentioned or unmet (0), partially met (1), or completely met (2). The possible total score ranged from zero to 18. The study quality score was used to quantify the strength of existing evidence but was not used in the study selection.

2.5 Meta-Analysis:

Associations between corticosteroidtherapy used in COVID-19patients and prevention of mortality in COVID-19 patients were analyzed using meta-analysis. A meta-analysis was performed for the obtained odd ratio values and 95% confidence interval (CI) from the articles. A pooled estimate was calculated for the effect of corticosteroid therapy on mortality and graphically summarized in a forest plot using Microsoft Exceland Graphpad Prism software. Random effects and fixed effects models were used for meta-analysis. Cochran's Q test and the I^2 statistic were performed to assess the statistical heterogeneity.

3. Result:

3.1 Study selection:

The flowchart represents the search and selection strategy for the study. The initial search resulted total 1361 studies, PubMed (n=65), Cochrane Library (n=276), Google Scholar (n=1000) and articles identified through forward/backward search (n=20). 29 articles were excluded as duplicate and 1270 articles were excluded from title and abstract screening. From remaining articles, 24 articles were excluded due to lacking of mortality data in screening full-text content. A total 38 studies were considered in the systematic review (Figure-1).

3.2 Basic Characteristics of the Selected Studies:

The studies were conducted in China (n = 10)(25–34), Spain (n=7)(2,35–40), The United States of America (n = 6)(41–46), Italy (n=4)(47–50), Iran (n=3)(51–53), France (n=3)(9,54), Brazil (n=2)(55,56), Japan (n=1)(57), Turkey (n=1)(58), Netherlands (n=1)(59). The majority of studies were retrospective cohort studies (28/38) while10 studies were randomized controlled trials (Table-1).

A total 22 studies were demonstrated the beneficial effects of the corticosteroid therapy on the mortality in the COVID-19 patients(2,9,44–47,49,51,53,55,56,58,25,59,60,27,35,36,38,39,42,43). 14 studies were reported the increased in the corticosteroid therapy received COVID-19 patients(26,28,50,52,57,29,31–34,37,48,49)while 2 studies reported the neutral effects of the corticosteroid therapy on the mortality in the COVID-19 patients (41,54).

Four types of corticosteroid were used as single or multiple steroids individually including Methylprednisolone (n=24), Dexamethasone (n=5), Hydrocortisone (n=1), Prednisone (n=1), corticosteroid used individually including Methylprednisolone and Dexamethasone in the study (n=6) unknown corticosteroid (n=1) (Table-1).

In this review, total sample size was 87646 patients. Amongst them, 16437 patients were in the intervention group (Received corticosteroid therapy) while 71344patients were in the control group (Received standard treatment). A total 6374 patients were died in both groups. Among them, 2084 (12.68%) patientswere died in the intervention group and 4227(5.92%) patients were died in the control group. 28.93% and 25.24% mortality was observed in the methylprednisolone and standard treatment groups, respectively whereas 31.64% and 25.01% mortality was observed in the dexamethasone and standard treatment groups, respectively (Table-1).

3.3 Study Quality assessment:

Study quality assessment showed the scores ranged between 13 and 18 with an average score of 15.26. The mean score of study quality assessment with standard deviation is 1.696±0.55 for all the studies. All the studies scored high on the clarity of the research question (2.00 ± 0.00), subject representative of the pathological population (2.00 ± 0.00), and the diagnosis method of the COVID-19 (2.00 ± 0.00). In addition, corticosteroid therapy administered through intranasal, oral and intravenous routes at different doses. The lowest scoring category was the employment of a power analysis (0.3 ± 0.72). Sample size justification via power analysis was conducted by only four studies. (Table-2)

3.4 Meta-Analysis:

Collectively, 87646 patients from 38 studies were included in the meta-analysis. A pooled fold change estimation of 2.305 (95% CI: 2.1810to 2.4370) was calculated for mortality in corticosteroid therapy versus standard therapy. P-value = 0.0001 was obtained from a meta-analysis. Heterogeneity (I^2 values) was observed to be 65.50.Figure-2 represents the forest plot of the primary meta-analysis of the pooled fold change estimation values along with the 95% CI from corticosteroid therapy.

A pooled fold change estimation of 1.206 (95%CI: 1.0770 to 1.3500) was calculated for mortality in methylprednisolone therapy versus standard therapy. P-value = 0.0001 was obtained from a meta-analysis. Heterogeneity (I^2 values) was observed to be 72.78. Figure-3 represents the forest plot of the primary meta-analysis of the pooled fold change estimation values along with the 95% CI from methylprednisolone therapy.

A pooled fold change estimation of 1.388 (95% CI: 1.1870 to 1.6220) was calculated for mortality in dexamethasone therapy versus standard therapy. P-value = 0.0001 was obtained from a meta-analysis. Heterogeneity (I^2 values) was observed to be zero.Figure-4 represents the forest plot of the primary meta-analysis of the pooled fold change estimation values along with the 95% CI from dexamethasone therapy.

The graphical representation of the x-axis of the plot is the pooled fold change estimation, and 95% of the included studies and the blue triangle with the line represent the effect size of mortality in COVID-19 patients.If the pooled fold change estimation value is more than 1, it favors the increased mortality in the intervention treatment group as compared to standard treatment group while less than 1, favor the beneficial effect of intervention group on the prevention of the mortality in COVID-19 patients as compared to standard treatment group.

4. Discussion:

The treatment approach for severe COVID-19 patients is facing dual challenges. First one is to suppress the hyper-inflammatory responses and cytokine storm while other one is the viral clearance (27). This foremost theory hypothesizes that corticosteroids could be used to alleviate the "cytokine storm" and its lethal consequences. In a systematic review of twenty-two studies, Judith VP et al quantified the effect of corticosteroids on death rate in COVID-19 patients. (17) The results showed that corticosteroids therapy significantly reduced short-term mortality in the COVID-19 patients. (17) Furthermore, meta-analysis of 7 RCTs involving 1703 disparagingly ill COVID-19 patients also revealed that systemic corticosteroids therapy reduced 28-day mortality when compared to standard care (28). The RECOVERYtrial found that dexamethasone therapy reduced 28-day mortality in individuals requiring oxygen therapy or mechanical ventilation as compared to standard care. (7)

Our systematic review and meta-analysis comprised 28 cohorts and 10 RCTs for investigating the outcome of corticosteroids treatment on the mortality in COVID-19 patients. Despite the fact that the several randomized trials found that corticosteroids medication was related to decreased mortality in COVID-19 patients, we were unable to find the similar result in our meta-analysis, having sample size 89053 patients. Our study found that corticosteroids therapy didn'tavert mortality in the COVID-19 patients, but it has increased the death in the COVID-19 patients as compared to usual care. Furthermore, we also found that both methylprednisolone and dexamethasone showed the higher mortality in the COVID-19 patients as compared to usual care. However, there was no significant difference found in the mortality with respect to treatment of

specific corticosteroid including methylprednisolone and dexamethasone.

The possible reasons may be considered for increasing the mortality with corticosteroid therapy like initiation of corticosteroid therapy in early stage of viral infection and higher dosage of corticosteroids, which delay the viral clearance and secondary infections. Consistent toour findings, the results of other meta-analysis on steroid treatment in COVID-19 patients showed the delay in viral clearance and enhance the mortality as compared to standard therapy (29). Similar manner, another propensity score-based analysis study found that corticosteroids use significantly increased the period of hospital stay and majority of patients progress to more deteriorated critical conditions compared to the standard therapy (30). Similarly, Li et al. described a significantly longer hospital stay in COVID-19 patients who treated with corticosteroids compared to standard care treatment(31). Furthermore, patients who received corticosteroids for more than five days required a extended course of chemotherapeutic agents as compared to patients who received short-term treatment for 3–5 days (31). Multi-organ malfunction is much more likely in critically sick COVID-19 patientswho underwent corticosteroid treatment, according to Lu et al., and each ten-mg increase in dosage was linked with an extra four percent mortality risk(32). Furthermore, another meta-analysis found that giving corticosteroids to patients with influenza increased death and hospital-acquired infections(33). In a comprehensive evaluation of influenza pneumonia, glucocorticoid medication was found to be related with an increased risk of death, length of stay in the critical care unitand risk of secondary infections(33). According to a meta-analysis of SARS, MERS and COVID-19, systemic glucocorticoids are not useful in lowering mortality (34). In meta-analysis of observational studies and RCT, Tlayjeh et al. reported that corticosteroids therapy was not associated with a reduction in short-term mortality but may be associated with a delay in viral clearance in patients hospitalized with COVID-19. (35) Similarly, WangJ also reported that corticosteroid use in COVID-19 patients delayed viral clearance and didn't improve survival (36) .

5. Conclusion:

In conclusion, corticosteroid therapy did not lower the but increased the mortality in COVID-19 patients. The possible reasons for the increase in the mortality might be delay in virus clearance and secondary infection due to initiation of corticosteroid therapy atthe early stage of the infection and at the high dose. There is need to conduct further clinical studies for developmentof the standard guideline to use corticosteroids in COVID-19 with considering factors such as initiation of the therapy with monitoring the virus load, dosage, route of administration and duration of the therapy as well as confounding antibiotics.

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