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Use of steroids in COVID-19 patients: A meta-analysis

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ABSTRACT

Background: Emerging reports have shown the benefits of steroids in hospitalized COVID-19 patients as lifesaving drugs. However, the use of steroids in COVID-19 patients is confusing among many physicians.

Aim: The aim of the current study was to find out the exact association of steroids in the deaths of COVID-19 patients.

Methods: The relevant studies were searched in PubMed, Google scholar, and Clinical trials registries till May 25, 2021 and sorted out based on inclusion and exclusion criteria. The quality of studies was assessed using a standard scale. The pooled odds ratio was calculated with a 95% confidence interval. The sensitivity and subgroup analyses were also done. The publication bias was assessed qualitatively. The Rev Man 5 was used for all analyses with a random-effect model.

Results: The quantitative analysis was done with 9922 patients (6265-male and 3657-females) from 21 relevant studies. The pooled estimate results i.e. 0.52 [0.34, 0.80] have shown a significant reduction in deaths of COVID-19 patients in the steroidal group as compared to the non-steroidal group. The sensitivity analyses did not alter our conclusions. In subgroup analysis, methylprednisolone has shown a significant reduction in deaths of COVID-19 patients as compared to the non-steroidal group, however, more clinical evidence is required for dexamethasone and hydrocortisone.

Conclusion: The use of steroids in hospitalized COVID-19 patients is useful to reduce deaths.

1. Introduction

The novel coronavirus (2019-nCoV) spreads from Wuhan City of China to the rest of the world (Singhal, 2020). The first case was reported on November 17, 2019 (Allam, 2020). The Severe acute respiratory syndrome- Coronavirus-2 (SARS-Cov-2) is a positive single-strand ribose nucleic acid (RNA) virus having spike proteins on its surface which attach with the angiotensin-converting enzyme (ACE2) of the host and helps in the entry of the virus (Jha et al., 2021). After entry, it uses the machinery of the host and results in the production of various viral proteins. The transmission of the infection occurs mainly through the inhalational route and symptoms appear between 2 and 14 days after the infection. The symptoms vary among the individuals and overlap with other viral infections. The reverse transcription polymerase chain reaction (RT-PCR) is the most commonly used method for the detection of this infection. Other laboratory blood tests such as C-reactive protein (CRP) level, D-dimer, complete blood count (CBC) is also done to know about inflammatory and coagulation level of the individuals. It has been observed that patients with comorbid conditions like diabetes, obesity, hypertension, etc are more likely to get into serious conditions (Rahman et al., 2021; Yan et al., 2021). Many researchers across the globe are working on the development of new chemical entities (NCEs) against this infection, however, no specific drugs are available in the market for its treatment so far (Singhal, 2020). Various classes of drugs are repurposed for the management of COVID-19 cases including steroids, ravidan, janus activated protein kinase (JAK) inhibitors (Patoulas et al., 2021) and antiandrogens (Mauvais-Jarvis, 2021; Fagone et al., 2020).

Steroids are well-known drugs that are available in the market for the treatment of various diseases like rheumatoid arthritis, multiple sclerosis, crohn’s disease, etc. Various case reports, case series, as well as research articles, have shown the benefits of using steroids in hospitalized COVID-19 patients (Van Paassen et al., 2020; Kalfaoglu et al., 2020;
Steroids turned to be life-saving drugs for serious COVID-19 patients. The regulatory authorities also recommended the use of steroids in serious COVID-19 patients. On September 2, 2020, World Health Organization (WHO) has updated clinical care guidance and recommended the use of corticosteroids in severe and critical COVID-19 patients under medical supervision (WHO, 2020). As per National Institute of Health (NIH) guidelines (updated on November 3, 2020), corticosteroids can be used in severe COVID-19 patients to control systemic inflammation (Fagone et al., 2020). Recently, on April 22, 2021, Indian Council of Medical Research (ICMR) updated the guidelines and recommended the use of steroids like methylprednisolone in hospitalized COVID-19 patients if not contraindicated (ICMR, 2021). It has been observed that the life of serious COVID-19 patients was saved using steroids but the exact role of steroids in COVID-19 patients is still an open question to answer. Thus, we have conducted a meta-analysis of available clinical evidence on the use of steroids in COVID-19 patients.

2. Methodology

The study was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. The study is registered with the International prospective register of systematic reviews Prospective register of systematic reviews (PROSPERO), registration number CRD42021259891.

2.1. Search strategy

A search was done in PubMed, Google scholar, and Clinical trial registry for observational, randomized, and non-randomized controlled studies, cohort studies, and comparative cross-sectional studies with the following search strategies. Steroids OR corticosteroids OR corticoids OR dexamethasone OR prednisone OR methyl prednisolone OR dexamethasone sodium phosphate OR hydrocortisone OR betamethasone OR beclomethasone OR budesonide OR formoterol AND COVID-19 OR SARS-CoV-2 OR severe acute respiratory syndrome OR Novel coronavirus. The references of included studies were screened to boost the search.

2.2. Study selection

The inclusion criteria are as follows a) confirmed COVID-19 cases b) participants should be on steroidal therapy c) comparator group without steroidal therapy d) death should be one of the outcomes of study e) all age groups f) both male and female participants. Studies were excluded if a.) study participants were not on steroidal therapy. b.) if there is no comparator group. c.) case reports, case series, narrative review, systematic review, meta-analysis d.) studies of poor quality as per standard scale. Two authors (MT and AK) separately screened all the titles and abstracts for eligibility criteria. Finally, the full-text articles were separately screened by two authors (MT and AK). In the case of conflicts over the inclusion, the third author (AKD) was consulted.
2.6. Statistical analysis

The overall estimate was calculated as an odds ratio with 95% confidence intervals using a random effect model. The heterogeneity among studies was calculated using Cochrane Q and I square statistics. The publication bias was analyzed qualitatively using a funnel plot.

2.5. Sensitivity analysis

The sensitivity analysis was done to check the effect of high or low sample size on the outcome.

2.4. Data extraction

The data was extracted from studies by two authors (MT and AK) in an excel sheet. The information such as name of the first author with publication year, name of the country where the study was conducted, study design, the total number of subjects, subjects in the steroid group, number of deaths in steroid group, subjects in the non-steroid group, number of deaths in non-steroidal group was extracted from full-text articles.

2.3. Quality assessment

The quality assessment was done using Newcastle-Ottawa Scale (NOS). The assessment was done by two reviewers (MT and AK) separately. The studies were categorized into three categories i.e., good, fair, and poor quality.

2.2. Search results and study characteristics

A total of 21 studies contains 9922 COVID-19 cases. Out of 9922 COVID-19 cases, 4018 were on steroids whereas 5904 were in the non-steroid group. The overall estimate was 0.52 [0.34, 0.80] which indicates a significant decrease in deaths of COVID-19 patients in the steroidal group as compared to the non-steroidal group (Fig. 2). The funnel plot was not found to be symmetrical in shape which indicates involvement of publication bias (Fig. 3).

3. Results

3.1. Search results and study characteristics

The 631 studies were found after the initial search. After removing duplicates and primarily screening of titles, 34 articles were retrieved, of which 21 articles (Villar et al., 2020; Salton et al., 2020; Petersen et al., 2020; Horby et al., 2021; Steroid SARI, 2020; Tomazini et al., 2020; Potlali et al., 2021; Rashad et al., 2021; Jamaati et al., 2021; Edalatifard et al., 2020; Ramiro et al., 2020; Tang et al., 2021; Pontali et al., 2021; Corral-Gudino et al., 2021; Angus et al., 2020; Dequin et al., 2020; Liu et al., 2020; Ranjbar et al., 2021; Jeronimo et al., 2021; Fadel et al., 2020; Nelson et al., 2021; Ooi et al., 2020) were found to be appropriate for quantitative analysis as presented in Fig. 1. The full-text or secondary screening with bibliography searching of the literature did not yield any additional article for inclusion. Out of the 21 studies, 13 studies were randomized control trials, 01 was retrospective, cohort, multi-centered quasi study each and the remaining 5 were clinical trials (CT). A total of 9922 patients (male: 6265, female: 3657) were found. The study characteristics are compiled in Table 1.

3.2. Quality assessment

All randomized controlled trials (RCTs), clinical trials (CTs), cohort studies with one protocol assessed for methodological quality using Newcastle-Ottawa Scale (NOS) were found to be of good and fair quality, based on the scores of the study in the selection, comparability, and outcome subscales. Out of 21 studies, 15 were of good quality, and remaining 6 were of fair quality (Table 2).
after exclusion of both studies with high sample size which also indicates a significant decrease in the deaths of COVID-19 patients in the steroidal group as compared to the non-steroidal group (Fig. 4). The conclusion was also not affected after the removal of the study with a low sample size (Fig. 5). Finally, we have also excluded all the outliers with high and low sample sizes and found no effect on the conclusion of the study (Fig. 6).

3.5. Heterogeneity

The I² (90%) and chi² statics has shown high heterogeneity. However, after the removal of outliers, heterogeneity among studies was also reduced from 88% to 59%.

3.6. Sub-group analysis

The sub-group analysis was done to check the effects of individual steroids in the deaths of COVID-19 patients. The pooled OR 0.65 [0.35, 1.20] with dexamethasone indicates a non-significant reduction in deaths of COVID-19 patients as compare to the non-steroidal group (Fig. 7). Similar non-significant results were also observed with hydrocortisone (Fig. 8). However, with methyl-prednisolone, a significant

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Table 2

| References             | Selection | Comparability | Exposure | Total Score | Quality of the Study |
|------------------------|-----------|---------------|----------|-------------|---------------------|
| Villar et al. (2020)   | **        | *             | ***      | 6           | Fair                |
| Salton et al. (2020)   | ****      | **            | ***      | 9           | Good                |
| Steroid SARI (2020)    | ***       | *             | **       | 6           | Good                |
| Petersen et al. (2020) | ***       | *             | ***      | 7           | Good                |
| Horby et al. (2021)    | ***       | *             | ***      | 7           | Good                |
| Tomazini et al. (2020) | ***       | *             | ***      | 7           | Good                |
| Rashad et al. (2021)   | **        | **            | **       | 6           | Fair                |
| Jamaati et al. (2021)  | **        | *             | **       | 5           | Fair                |
| Edalatifard et al. (2020) | **     | *            | ***      | 6           | Fair                |
| Ramiro et al. (2020)   | ***       | **            | **       | 7           | Good                |
| Tang et al. (2021)     | **        | *             | **       | 5           | Fair                |
| Pontali et al. (2021)  | ****      | **            | **       | 8           | Good                |
| Corral-Gudino et al. (2021) | **    | *            | **       | 7           | Good                |
| Angus et al. (2020)    | ***       | *             | **       | 6           | Good                |
| Dequin et al. (2020)   | ***       | *             | ***      | 7           | Good                |
| Liu J et al. (2020)    | ***       | *             | **       | 6           | Good                |
| Ranjbar et al. (2021)  | ***       | **            | **       | 7           | Good                |
| Jeronimo et al. (2021) | ****      | **            | **       | 8           | Good                |
| Fadel et al. (2020)    | ***       | **            | **       | 7           | Good                |
| Nelson et al. (2021)   | ***       | **            | **       | 7           | Good                |
| Ranjbar et al. (2021)  | ***       | **            | **       | 7           | Good                |
| Ooi et al. (2020)      | **        | *             | ***      | 6           | Fair                |

Fig. 2. Pooled analysis results using a random effect model (forest plot).

Fig. 3. Funnel plot for qualitative analysis of publication bias.
A 0.32 [0.23, 0.45] reduction in mortality was observed in the steroidal group as compared with the non-steroidal group (Fig. 9).

4. Discussion

Steroids are found to be life saving drugs in the management of COVID-19. It enters the cytoplasm and acts on the nuclear receptors which results in the synthesis of specific mRNA causes protein synthesis which lead to responses. It downregulating the hyper activation of the components of both innate (neutrophils) and acquired (T and B lymphocytes) immune system and the cytokine storm that characterizes severe case of covid-19 (Vanderbeke et al., 2021; Kalfaoglu et al., 2020; Sunkara and Dewan, 2021). The current meta-analysis was performed to check the association of the use of steroids in the deaths of COVID-19 patients. The available meta-analysis results are contradictory and also contain a smaller number of patients. Thus, further analysis is required to help physicians to make better clinical decisions. The meta-analysis results of Sterne et al. (2020), have reported the role of corticosteroids in the decrease of deaths of COVID-19 serious patients. Sarma et al. (2020) have also conducted a meta-analysis to find out the role of steroidal therapy in mechanically ventilated COVID-19 patients and reported a reduction of mortality of mechanically ventilated patients as well as decreased the requirement of mechanical ventilation. Chaudhuri et al. (2021) have reported higher survival rates in acute respiratory distress syndrome (ARDS) patients treated with corticosteroids (longer duration) as compared to a shorter duration. Pulakurthi et al. (2021) meta-analysis results have reported a significant reduction in deaths of COVID-19 patients who were on steroidal therapy as compared to patients who were on non-steroidal therapy. Pasin et al. (2021) conducted a meta-analysis and concluded that steroids should be used only in the patients who are critically ill and require ventilation and should be avoided in the patients who do not require any oxygen. However, the meta-analysis results of Sarkar et al. (2021) have shown the use of systemic glucocorticoid did not result in a significant reduction of mortality.
as well as no significant reduction in duration of hospital stay of COVID-19 patients was observed. Wang et al., (2021) meta-analysis results have reported that the patients who were on steroid therapy have delayed the viral clearance time, thus, there was no significant difference in the use of steroids. Cano et al. (2021) meta-analysis results have also reported no effect (harmful or beneficial) between high and low-dose steroidal therapy. We have found a significant decrease in deaths of COVID-19 patients who are on steroids as compared to non-steroidal patients. The sensitivity analysis results also did not alter the findings of the study. The subgroup analysis results have shown a significant association of methyl-prednisolone in the reduction of deaths of COVID-19 patients, however, results with dexamethasone and hydrocortisone were found to be non-significant. Overall, to get a clear picture of individual steroids, more evidence is required.

**Limitations**

The study has the following limitations. The search for relevant articles has been performed on limited search engines. The articles which were published in the English language were only considered.

**Conclusion**

The steroids play a significant role in the decrease of demises of hospitalized COVID-19 patients.

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