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Dexamethasone in COVID-19 Care: Dosage and Utilization Insights

Shamim L, *et al*. Dexamethasone in COVID-19 Care

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Abstract

COVID-19 is a contagious disease caused by SARS-CoV-2. It was declared a global pandemic on March 11, 2020 by the WHO. An excessive inflammatory response is a severe respiratory manifestation of COVID-19, which becomes predominant in later stages. Due to its immunosuppressive and anti-inflammatory properties, dexamethasone is the first systemic glucocorticoid used to treat severe COVID-19 patients. This editorial reviews the efficacy and safety of high-dose *vs* low-dose dexamethasone in patients with COVID-19. Findings indicate that using low-dose dexamethasone is beneficial and emphasize the need for additional research on the use of high-dose dexamethasone. While the study provides a robust evidence base, it is limited by the lack of long-term data, focus on specific outcomes, and heterogeneity of the included studies. Future research should focus on the long-term effects of dexamethasone and its impact across varying disease severities and patient populations to refine treatment strategies and improve patient care.

Key Words: COVID-19; Severe Acute Respiratory Syndrome; corticosteroid; dexamethasone

Core Tip: This letter evaluates a meta-analysis comparing high-dose and low-dose dexamethasone in the treatment of COVID-19 patients. The study reveals no significant differences in adverse effects and mortality between the dosing regimens. In line with the current guidelines, the study favors using low-dose dexamethasone but highlights the call for additional research on high-dose dexamethasone's benefits. The study includes limitations such as a lack of long-term data and heterogeneity of the included studies. It is crucial to address these gaps in the future to optimize treatment strategies for COVID-19.

INTRODUCTION

The disease known as Coronavirus disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2)[1]. It is among the most deadly viruses in the history of humans, causing more than 6.8 million deaths globally since its discovery in December 2019[2]. COVID-19 was declared a global pandemic by the WHO on March 11, 2020[3]. There are multiple stages of COVID-19, and each stage indicates the appropriate course of treatment. Stage 1 is the initial phase of early viral infections, including gastrointestinal or respiratory infections, fever, and lymphopenia. The second stage refers to the pulmonary stage. Multisystemic inflammatory syndrome (MIS) occurs in stage 3, and as a pathogenic characteristic, it is frequently associated with a cytokine storm. There is also the involvement of other mechanisms in the late stage of COVID-19, including neutrophil extracellular traps (NET), edema and vascular leak, bradykinin storm, prothrombotic events, endothelins, and coagulation and complement cascade activation[4]. The clinical picture of COVID-19 shows the dominance of MIS and systemic inflammation over the original viral infection in advanced stages[4].

SYSTEMIC CORTICOSTEROIDS FOR COVID-19

Systemic corticosteroids are currently recommended by The National Institutes of Health COVID-19 treatment guidelines for COVID-19 patients who require respiratory support[5]. Systemic corticosteroids are the drugs available for treating inflammatory diseases, classified into mineralocorticoids and glucocorticoids. Dexamethasone is the first glucocorticoid to be used in severe COVID-19 patients with clinical benefits[6]. Dexamethasone is an anti-inflammatory and immunosuppressive agent. Inhibition of pro-inflammatory gene that encodes for cell adhesion molecules (CAM), cytokines, chemokines, and acute inflammatory response is the main anti-inflammatory effect of dexamethasone[7]. The primary causes of mortality related to COVID-19 such as cytokine storm induced by SARS-CoV-2, multiorgan failure, and severe acute respiratory distress syndrome (ARDS) can be suppressed by dexamethasone[8]. In a RECOVERY study, it was found that dexamethasone showed a reduction in 28-day

mortality among COVID-19 patients requiring respiratory support when 6 mg of it was administered for up to 10 days.

In contrast, no benefit was shown in patients who did not require respiratory support[9]. We aim to evaluate the role of dexamethasone in the treatment of COVID-19 and various dose regimens and offer evidence-based recommendations for dexamethasone to improve patient care. The meta-analysis conducted by Sethi I *et al*. focuses on the safety and efficacy of low-dose *vs* high-dose dexamethasone by investigating the impact of various dosing regimens of dexamethasone on the outcomes of COVID-19 patients.

Sethi I *et al.* [10] conducted a meta-analysis on the dosage and utilization of dexamethasone in the management of Covid-19. PRISMA guidelines were followed to conduct the systematic review and meta-analyses. Keywords related to corticosteroid dosing and COVID-19 were used to conduct a thorough literature search from databases such as MEDLINE, Google Scholar, and PubMed up to March 2024. Only randomized controlled trials (RCTs) were included, including dexamethasone-treated covid-19 patients. The exclusion criteria included single-arm, non-randomized controlled trials, case reports, observational studies, and non-English articles. Initial screening involved reviewing the abstract and the title, after which the independent reviewers assessed the full text. Data extraction included participant demographics, study specifics, details of intervention, and outcomes. The Cochrane Risk of Bias Tool and Newcastle-Ottawa Scale were used to assess the potential biases and the quality of the study. A narrative synthesis approach was employed with meta-analyses utilizing a random-effect model where necessary. Forest plots were used to quantitatively synthesize and present the adverse events, hospital stay durations, and mortality outcomes.

Nine randomized controlled trials were analyzed in the study to compare the safety and efficacy of low-dose *vs* high-dose dexamethasone involving 2,740 COVID-19 patients. Negligible differences in 28-day and 60-day all-cause mortality were found between the two dosing regimens. There was a slight reduction in average hospital stay

when low-dose dexamethasone was administered to patients compared to high-dose dexamethasone administration. The reduction achieved no statistical significance. The rate of occurrence of the adverse effects, including infections, thrombosis, arrhythmias, and myocardial infarction, showed no significant differences and were similar between both groups. The overall findings of the study support the use of low-dose dexamethasone and highlight the need for further research on high-dose dexamethasone and its potential benefits.

Similarly, Snow *et al*. and Kow *et al*. also conducted a meta-analysis and found no significant mortality benefit from high-dose dexamethasone compared to low-dose treatment. However, both studies noted a higher risk of hyperglycemia with a higher dose[11-12]. This aligns with Sethi *et al*.'s emphasis on the need for further investigation into high-dose dexamethasone, suggesting that its risks might outweigh the benefits without improving clinical outcomes.

The article covered a wide range of studies by offering an in-depth analysis. It provides a robust evidence base by synthesizing data from multiple studies and clinical trials. The patient cohort was directly compared by evenly dividing it between low-dose and high-dose treatments. The authors maintained a balanced perspective by considering both the potential risks and the advantages related to dexamethasone therapy.

The lack of long-term data on the dexamethasone usage is one significant limitation. Most of the studies included in the review are short-term, which may not fully reflect dexamethasone's potential side effects and long-term effects. Studies of varying quality were included in the review, which may impact the overall conclusion. The generalizability of the findings can be limited, and biases can be introduced by differences in methodologies, sample size, and study design. Studies with different patient populations were involved with disease severity of varying degrees. This variation makes it difficult to apply findings consistently to every patient group. The vaccination status of the patients was not discussed, which may influence the effectiveness of dexamethasone.

Moreover, the study focuses on hospitalized COVID-19 patients, which may have overlooked the effects of dexamethasone on less severe or non-hospitalized patients. Hospital stay duration and mortality were mainly assessed in the study, while other potential outcomes, such as functional recovery and quality of life, were not evaluated. Due to the emergence of new studies and treatment guidelines, some of the conclusions and data in the study may become outdated, given the evolving nature of COVID-19. To ensure the study remains accurate and relevant, there is a need for continuous updates to the review.

CONCLUSION

Low-dose dexamethasone has become the standard treatment for COVID-19 patients requiring oxygen support, showing reduced mortality. It is more safe and effective than higher doses. The risk of adverse events like hyperglycemia may rise with higher dosages, even if they might be just as effective as low doses in lowering mortality. The research by Sethi I *et al.* provides valuable insights into the dosage of dexamethasone in COVID-19 patients. The evidence-based and comprehensive approach of the research is commendable. However, limitations such as heterogeneous patient population, rapidly evolving field, variability in study quality, and lack of long-term data must be acknowledged. Future research should address these limitations, assuring that treatment plans can be continuously improved and refined.

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