

Place of Corticosteroids in the Treatment of Coronavirus Disease 2019

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ABSTRACT

Background: The precise role of corticosteroids for the treatment of coronavirus disease 2019 (COVID-19) is unclear due to lack of randomized trials. **Objective:** The objective of the study was to review the therapeutic value of corticosteroids in hospitalized patients with COVID-19. **Methods:** English literature search of electronic databases supplemented by manual search up to July 5, 2020. Search terms included corticosteroids, COVID-19, dexamethasone, methylprednisolone, hydrocortisone, mortality, and safety. Randomized trials were the main focus of research, but observational studies were also reviewed. **Results:** Preliminary data from the only available randomized trial in COVID-19, the “Randomized Evaluation of COVID-19 therapy” (RECOVERY) trial, showed that dexamethasone 6 mg/day for up to 10 days reduced 28-day mortality (the primary outcome) in hospitalized patients with COVID-19 by 17%, adjusted rate ratio (RR) 0.83, and 95% confidence interval (CI) 0.74–0.92 ($P < 0.001$). The highest magnitude of mortality reduction was observed among patients receiving mechanical ventilation, RR 0.65, 95% CI; 0.51–0.82 ($P < 0.001$), followed by patients receiving oxygen without mechanical ventilation, RR 0.80, 95% CI, 0.70–0.92 ($P = 0.002$). However, there was a non-significant trend toward increase mortality in patients not receiving respiratory support, RR 1.22, 95% CI, 0.93–1.61 ($P = 0.14$). A smaller randomized study ($n = 277$) showed that dexamethasone decreased 60-day mortality in mechanically ventilated patients with acute respiratory distress syndrome (ARDS), but without COVID-19. These latter results may be pertinent to COVID-19, in which ARDS is a common complication. **Conclusions:** The dexamethasone treatment protocol of the RECOVERY trial should be implemented for the treatment of patients with COVID-19 receiving mechanical ventilation or oxygen. Meanwhile, corticosteroids should not be used in milder cases that do not require oxygen due to a possible harm.

Key words: Acute respiratory distress syndrome, coronavirus disease 2019, dexamethasone, mechanical ventilation, mortality

INTRODUCTION

Coronavirus disease 2019 (COVID-19) can elicit a severe inflammatory and pathological immune host response.^[1] Therefore, the use of corticosteroids as anti-inflammatory and immunosuppressive agents was used as part of the treatment of COVID-19.^[1] Available data from small observational studies yielded conflicting results. In a cohort of 15 critically ill COVID-19 patients, Zhou *et al.*^[2] found no survival benefit from corticosteroids given on admission to intensive care unit. The median

dose of corticosteroids was hydrocortisone equivalent of 400 mg/day for a mean of 9.5 days.^[2] In another cohort of 40 patients with mild COVID-19 (none of them was admitted to the intensive care unit), Liu *et al.*^[3] failed to find any significant effect on progression of the disease after intravenous administration of methylprednisolone 30–80 mg/day for 3–5 days. Fadel *et al.*^[4] reported that early treatment with methylprednisolone (0.5–1.0 mg/kg/day in two equal doses for 3 days) given within 2 days of hospitalization was associated with lower mortality and progression of COVID-19 when compared with a historical control group of patients

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who received corticosteroids later within 5 days of hospitalization. In one series from the USA, Selvaraj *et al.*^[5] described 21 patients with COVID-19 and hypoxia admitted to the intermediate level of care unit. They received 6 days course of dexamethasone (4 mg tid for 2 days, then 4 mg bid for 2 days, and then 4 mg qd for 2 days). None of patients had escalation of care, and their C-reactive protein levels dropped by 79% on discharge.^[5]

Meta-analyses may provide some insight. In the largest meta-analysis of 16 observational studies including 2407 patients with COVID-19 receiving corticosteroids, Zhang *et al.*^[6] reported that administration of corticosteroids was significantly associated with higher rates of acute respiratory distress syndrome (ARDS) ($P < 0.0003$). In another meta-analysis of five cohort studies, Lu *et al.*^[7] found that there is a non-significant tendency of corticosteroids to increase mortality with a relative risk 2.0 (95% confidence interval [CI], 0.7–5.8). In addition, these authors found no significant effects on hospital stay or duration of pneumonia.^[7] On the other hand, a cohort Chinese study showed that patients with COVID-19 complicated by ARDS had lower mortality with methylprednisolone therapy (dose and duration not reported),^[8] Thus, mortality rates were 46.0% (23 of 50 patients) and 61.8% (21 of 34 patients) in patients who received methylprednisolone treatment and those who did not receive it, respectively; hazard ratio 0.38; 95% CI, 0.30–0.72, $P = 0.003$.^[8]

Due to the observational non-randomized nature of the above studies, it is difficult to draw a conclusion regarding the therapeutic role of corticosteroids in COVID-19. Even when using a control group, there is inability to control for confounding factors (e.g., concomitant medications). Moreover, there is large variability in corticosteroid preparations, dosage, timing and duration of administration, and severity of the disease. Another major limitation inherent to these retrospective studies is indication bias, that is, the sickest patients having the worst prognosis are those who are more likely to receive corticosteroids. Therefore, randomized trials are crucial to determine the status of corticosteroid therapy in COVID-19. The RECOVERY trial (see below) is the first randomized trial that examined the role of corticosteroids, specifically low-dose dexamethasone, for the treatment of a large population ($n = 6.425$) of hospitalized patients with COVID-19.^[9]

DESIGN OF THE RECOVERY TRIAL

In the RECOVERY trial conducted in the UK, the investigators randomized hospitalized patients with COVID-19 to two groups in a 2:1 ratio, the larger group ($n = 4.321$) received usual care while the smaller group ($n = 2.104$) received

usual care plus low-dose dexamethasone 6 mg/day orally or intravenously for up to 10 days in an open-label fashion.^[9] The main results of the RECOVERY trial were announced in a preliminary form on June 16, 2020, just 98 days after the protocol was first drafted.^[9] Its publication after peer review is pending. The primary outcome of RECOVERY is 28-day mortality.^[9] Table 1 provides a summary of the design and main findings of the RECOVERY trial.

PRIMARY OUTCOME OF THE RECOVERY TRIAL

Significantly fewer patients assigned to dexamethasone reached the primary outcome of 28-day mortality compared with usual care, 21.6% and 24.8%, respectively; rate ratio (RR) 0.83; 95% CI 0.74–0.92; $P < 0.001$.^[9] Pre-specified subgroup analysis revealed significant trend ($P < 0.001$) of greatest absolute and proportional mortality reduction in the group of patients receiving mechanical ventilation at randomization ($n = 1.007$).^[9] Thus, in the latter group of patients, dexamethasone was associated with mortality reduction of 35%, RR 0.65, 95% CI 0.51–0.82 ($P < 0.01$). In the subgroup of patients receiving oxygen ($n = 3.883$), dexamethasone was associated with mortality reduction of 20%, RR 0.80, 95% CI 0.70–0.92 ($P = 0.002$).^[9] Conversely, there was a trend toward an increase in 28-day mortality with dexamethasone in the subgroup of patients who were not receiving respiratory support ($n = 1.535$), RR 1.22, 95% CI: 0.93–1.81 ($P = 0.14$).^[9] Interestingly, dexamethasone was associated with reduction in 28-day mortality among patients with symptoms for more than 7 days but not among those with more recent symptom onset (P for trend < 0.001).^[9] It should be emphasized that mortality rate in the usual care group, as expected, was highest among patients receiving mechanical ventilation reaching 40.7%.^[9] It follows that the absolute mortality benefit of dexamethasone was also highest in this group of patients. In fact, based on these results, the authors estimated that one death would be prevented by dexamethasone treatment given to around eight patients requiring invasive ventilation.^[9] In patients receiving oxygen only, mortality rate in the usual care group was 25.0%. Hence, in the latter group, it is estimated that one death would be prevented by dexamethasone treatment of around 25 patients.^[9]

SECONDARY OUTCOMES

The RECOVERY trial included two secondary outcomes: Duration of hospitalization, and a composite of receipt of mechanical ventilation or death.^[9] Thus, dexamethasone was associated with shorter duration of hospitalization than usual care, median 12 days and 13 days, respectively, RR 1.11 (95% CI, 1.04–1.19; $P = 0.002$).^[9] Again, the greatest effect of dexamethasone in shortening hospitalization was observed in patients on mechanical ventilation (P for

Table 1: Overview of the RECOVERY trial^[9]

Design	Randomized, open-label, non-placebo controlled, two groups 2:1 ratio, multicenter in the UK
Patients	Hospitalized with COVID-19, mean age 66.1 years, 36% of woman, 24% with diabetes, 27% with heart disease
Patient groups	Usual standard care ($n=4.321$) versus standard care + dexamethasone ($n=2.104$)
Dexamethasone regimen	6 mg once daily (oral or intravenously) for up to 10 days
Median number of days of dexamethasone therapy	6 days
Primary outcome	28-day mortality
Secondary outcomes	(1) Time to discharge, (2) subsequent receipt of mechanical ventilation or death (composite outcome)
Effect on dexamethasone on all patients who met the primary outcome	Dexamethasone group 454 of 2104 (21.6%), usual care group 1065 of 4321 (24.6%), *RR: 0.83, 95% CI, 0.74–0.92; $P<0.001$
Effect of dexamethasone on 28-day mortality among patients on mechanical ventilation	*RR; 0.65, 95% CI 0.51–0.82; $P<0.001$
Effect of dexamethasone on 28-day mortality among patients on oxygen only	*RR: 0.80, 95% CI 0.70–0.92; $P=0.02$
Effect of dexamethasone on 28-day mortality among patients without respiratory support	*RR: 1.22, 95% CI 0.93–1.61; $P=0.14$
Effect of dexamethasone on the first secondary outcome: Hospital discharge within 28 days	*RR: 1.11, 95% CI, 1.04–1.19; $P=0.002$
Effect of dexamethasone on the second secondary outcome: Subsequent receipt of mechanical ventilation or death	**RR: 0.91, 95% CI, 0.82–1.00; $P=0.049$

*RR: Rate ratio, **RR: Risk ratio. CI: Confidence interval

trend =0.002).^[9] Regarding the second secondary outcome, the number of patients progressing to mechanical ventilation or death was lower among those allocated to dexamethasone, risk ratio being 0.91 (95% CI 0.82–1.00, $P = 0.049$), with significantly greater effects among patients receiving oxygen (P for trend = 0.008).^[9]

STRENGTHS OF THE RECOVERY TRIAL

In general, the RECOVERY trial is a well-designed randomized controlled study with adequate statistical power including more than 6000 patients with COVID-19.^[9] Interestingly, no exclusion criteria were reported, except for patients known to have contraindications to dexamethasone.^[9] Even pregnant and breast-feeding women and patients younger than 18 years old were included. Furthermore, the enrollment of hospitalized patients with various stages of COVID-19 allowed drawing conclusions regarding the differential effect of dexamethasone on mortality as a function of disease severity. Thus, this non-selected patient sample that represents 15% of all UK hospitalized patients makes results of the RECOVERY trial

directly applicable to all hospitalized patients with COVID-19 worldwide. In fact, the greatest value of RECOVERY trial is that it is the first randomized trial to provide convincing high-quality evidence of mortality benefit among the sickest patients with COVID-19.^[9] Moreover, it is fortunate that the RECOVERY trial showed that this decrease in mortality was achieved by dexamethasone, a non-expensive and well-studied drug available since the 1960s.

Limitations of RECOVERY trial

The first limitation of the RECOVERY trial is its open-label design and lack of a placebo group and therefore may be open for bias.^[9] While mortality is clearly a hard outcome, it cannot be excluded that investigator decision to withdraw mechanical ventilation might be influenced by type of assigned therapy. Second, the authors did not measure intermediate outcomes such as viral load and inflammatory markers that could substantiate the results and clarify the mechanism of action of dexamethasone. Third, frequency of adverse effects of dexamethasone such as hyperglycemia, secondary infection, gastrointestinal bleeding, and psychosis was not reported. Fourth, minimal cross-over of dexamethasone therapy occurred, with 7% of patients in the control group received dexamethasone.^[9] However, the

latter limitation should attenuate the mortality benefit of dexamethasone.

CLINICAL IMPLICATIONS OF THE RECOVERY TRIAL

Despite the above limitations, the RECOVERY trial is a breakthrough study with direct implications to clinical practice. The quality of data is sufficiently strong to implement the dexamethasone protocol used in the RECOVERY trial to all patients with COVID-19 receiving mechanical ventilation or oxygen. This implementation should be immediate due to the high mortality rates in patients with severe COVID-19, and absence of any other agent having a clear mortality benefit. Indeed, the RECOVERY protocol was adopted into the UK practice on the same day the results were released.^[9] The World Health Organization (WHO) has welcomed the preliminary results of the RECOVERY trial.^[10] The WHO must update its treatment guidelines of COVID-19 as soon as possible in the light of the RECOVERY trial results. It should be emphasized, however, that corticosteroids should not be used in patients with milder forms of COVID-19 who do not require oxygen as the results of RECOVERY trial suggest a possible harm.

DEXAMETHASONE IN PATIENTS WITH ARDS WITHOUT COVID-19

ARDS is a common complication of COVID-19 ranging from 41% among all patients admitted to the hospital to 71% of patients admitted to the intensive care units.^[8,11] In the preliminary report from the RECOVERY trial, the proportion of patients with ARDS was not indicated. However, it is assumed that it was high, particularly in the group receiving mechanical ventilation. To the author's best knowledge, there is a single randomized controlled trial that evaluated corticosteroids represented by dexamethasone in patients with ARDS on mechanical ventilation but without COVID-19.^[12] In this Spanish study, one group of patients was allocated to dexamethasone + conventional treatment ($n = 139$) and a second group of patients received conventional treatment alone ($n = 138$).^[12] The dexamethasone dose was 2.5–3-fold higher doses than in the RECOVERY trial, 20 mg IV once daily for 5 days followed by 10 mg IV once daily for the following 5 days.^[12] The timing of initiation of dexamethasone was set to be within 30 h after confirmation of the diagnosis of ARDS.^[12] The number of ventilator-free days at 28 days (the primary outcome) was significantly higher in the dexamethasone group compared with the conventional-treatment group, with a between-group difference of 4.8 days (95% CI, 2.57–7.03; $P < 0.001$).^[12] Mortality at 60 days (the secondary outcome) was significantly lower in the dexamethasone group compared with control group, 21% and 36%, respectively, with a between-group absolute difference of –15.3% (95%

CI, –25.9––4.9; $P = 0.0047$).^[12] The number needed to treat with dexamethasone to prevent one death in 60-day period was seven patients.^[12] Interestingly, these results are overall similar to those of the RECOVERY trial in the subgroup of COVID-19 patients receiving mechanical ventilation. Thus, in terms of mortality reduction, the absolute mortality difference at 28 days in the RECOVERY trial was approximately 11.7% (40.7% in control group vs. 29.0% in dexamethasone group), and the number of patients needed to treat with dexamethasone to prevent one death at 28 days was eight patients.^[9]

Although the pathophysiology of ARDS that complicates COVID-19 may not be identical to that associated with other diseases (e.g., pneumonia, sepsis, aspiration, and trauma), the results of the above two trials, taken together, suggest that dexamethasone may reduce mortality in mechanically ventilated patients having ARDS with and without COVID-19.^[9,12]

CONCLUSIONS AND CURRENT NEEDS

The RECOVERY trial has shown convincing evidence that dexamethasone in a low dose of 6 mg/day for up to 10 days significantly reduced mortality in patients with severe COVID-19 receiving mechanical ventilation or oxygen. These results are substantiated by a smaller randomized trial using higher doses of dexamethasone in non-COVID-19 patients with ARDS.^[12] Meanwhile, the RECOVERY trial showed a trend toward increase mortality in patients with milder COVID-19 disease.^[9] Several clinical trials are underway to further clarify the precise place of corticosteroids in the treatment of COVID-19. These trials should determine the optimum corticosteroid preparation, dosage, and timing of administration relative to the disease severity to achieve the maximal therapeutic benefit. Until such trials are available, the current evidence is sufficiently strong to follow the RECOVERY trial protocol of dexamethasone therapy in all patients with COVID-19 who require oxygen or mechanical ventilation.

CONFLICTS OF INTEREST

The author does not have any conflicts of interest to declare.

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