

Dexamethasone: The First Drug to be Shown to Decrease Mortality in Critically Ill Patients with COVID-19

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Abstract

Background: The precise role of corticosteroids for treatment of coronavirus disease 2019 (COVID-19) is unclear due to lack of randomized trials.

Objective: To review the therapeutic value of corticosteroids for treatment of hospitalized patients with COVID-19 with more emphasis on randomized trials.

Methods: English literature search of electronic databases supplemented by manual search up to June 29, 2020. Search terms included corticosteroids, COVID-19, dexamethasone, methylprednisolone, hydrocortisone, mortality, safety. Randomized trials were the main focus of research, but observational studies were also reviewed.

Results: Preliminary data from the only available randomized trial “The Randomized Evaluation of COVID-19 therapy” (RECOVERY) 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, 95% CI 0.74 to 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 to 0.82 ($P < 0.001$), followed by patients receiving oxygen without mechanical ventilation, RR 0.80, 95% CI, 0.70 to 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 to 1.61 ($P = 0.14$).

Conclusions: Dexamethasone 6 mg daily for up to 10 days should be used for 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.

Keywords: COVID-19, Dexamethasone, Mortality, Mechanical ventilation

Introduction

COVID-19 can elicit a severe inflammatory and pathological immune host response [1]. Therefore, use of corticosteroids as anti-inflammatory and immunosuppressive agents was used as part of treatment of COVID-19 [1]. Available limited data from observational studies yielded conflicting results (Table 1). In one meta-analysis of 4 cohort studies, Lu et al. [2] found that there is a non-significant tendency of corticosteroids to increase mortality with a relative risk 2.0 (95% CI, 0.7 to 5.8). In addition, these authors found no significant effects on

hospital stay or duration of pneumonia [2]. Likewise, in a small cohort of 15 critically ill COVID-19 patients, Zhou et al. [3] found no survival benefit from corticosteroids given as median hydrocortisone equivalent dose of 400 mg/d upon admission to intensive care unit for a mean of 9.5 days. In another cohort of 40 patients with mild COVID-19 (none of them was admitted to the intensive care unit), Liu et al. [4] failed to find any significant effect on progression of the disease after intravenous administration of methylprednisolone 30-80 mg/d for 3 to 5 days. Fadel et al. [5] reported that early treatment with methylprednisolone (0.5-1.0 mg/kg/d in 2 equal doses for 3 days) given within 2

Reference	Design	Corticosteroid regimen	Conclusions
Lu et al. [2]	Meta-analysis of 4 cohort studies	Variable	Trend towards increase mortality, *RR 2.0 (95% CI, 0.7 to 5.8)
Zhou et al. [3]	15 critically ill patients	Median hydrocortisone equivalent dose 400 mg/d for a mean of 9.5 days	No survival benefit
Liu et al. [4]	40 patients with persistent fever or disease progression	Methylprednisolone 30-80 mg/d for 3-5 days	No significant effect on disease progression
Fadel et al. [5]	Early corticosteroids given within 48 h of hospitalization (n=132) vs standard of care (n=81)	Methylprednisolone 0.5-1.0 mg/kg/d in 2 equal doses for 3 days	Lower mortality in the early corticosteroids group vs standard of care group, **OR= 0.45, 95% CI, 0.22 to 0.90; P=0.024).

*RR= relative risk; **OR= odds ratio

Table 1: Observational studies of use of corticosteroids in COVID-19.

days of hospitalization was associated with lower mortality and progression of COVID-19 when compared with a group of patients who received standard of care. Based on the preceding, it is difficult to draw a conclusion regarding the therapeutic role of corticosteroids in COVID-19 due to lack of randomized trials, and large variability in corticosteroid preparation, dosage, timing and duration of administration, and patient severity of the disease.

Drug Profile of Dexamethasone

Dexamethasone is a synthetic corticosteroid with potent anti-inflammatory action. Thus, 0.75 mg of dexamethasone is equivalent to approximately 4 mg of methylprednisolone and 5 mg of prednisone in terms of anti-inflammatory effect [6]. It has long duration of action with biological half-life of 36-72 h compared with 12-16 h in case of prednisone [6]. Dexamethasone almost completely lacks mineralocorticoid activity [7]. The anti-inflammatory mechanism of action of corticosteroids in general consists in reduction of recruitment of white blood cells, including monocytes-macrophages into affected areas (e.g in case of COVID-19 in the lungs), decrease lymphocyte proliferation and inhibition in cytokine production [1]. In addition, corticosteroids have immune-suppressive effects such as decreased cell-mediated immunity and antigen presentation [1].

Overview of the RECOVERY Trial

The RECOVERY trial is the first randomized trial that examined the role of corticosteroids for treatment of a large population (n=6,425) of hospitalized patients with COVID-19 [8]. The authors randomized hospitalized

patients with COVID-19 to 2 groups in a 2:1 ratio, the larger group (n=4,321) received usual care while the smaller group (n=2,104) received low-dose dexamethasone 6 mg/d orally or intravenously for up to 10 days in an open-label fashion [8]. 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 [8]. Its publication after peer review is pending. The primary outcome of RECOVERY is 28-day mortality [8]. Table 2 provides an overview of the design and main findings of the RECOVERY trial. Herein we present the main results, strengths and limitations, and clinical implications of the RECOVERY trial.

Primary Outcomes 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; RR 0.83; 95% CI 0.74 to 0.92; (P<0.001) [8]. 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). Thus, in the latter group of patients, dexamethasone was associated with mortality reduction of 35%, RR 0.65, 95% CI 0.51 to 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 to 0.92 (P=0.002) [8]. Meanwhile, 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 to 1.81 (P=0.14) [8]. Interestingly,

Design	Randomized, open-label, non-placebo controlled, 2 groups 2:1 ratio, multi-center in UK
Patients	Hospitalized with COVID-19, mean age 66.1 years, 36% 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 to 0.92; P<0.001
Effect of dexamethasone on 28-day mortality among patients on mechanical ventilation	*RR; 0.65, 95% CI 0.51 to 0.82; P<0.001
Effect of dexamethasone on 28-day mortality among patients on oxygen only	*RR: 0.80, 95% CI 0.70 to 0.92; P=0.02
Effect of dexamethasone on 28-day mortality among patients without respiratory support	*RR: 1.22, 95% CI 0.93 to 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 to 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 to 1.00; P=0.049
*RR= Rate ratio; **RR=Risk ratio	

Table 2: Overview of the RECOVERY Trial [8].

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) [8]. It should be emphasized that mortality rate in the usual care group, as expected, is highest among patients receiving mechanical ventilation reaching 40.7%. It follows that the absolute mortality benefit of dexamethasone is also highest in this group of patients. In fact, based on these results, the authors estimated that 1 death would be prevented by dexamethasone therapy of around 8 patients requiring invasive ventilation. In patients receiving oxygen only, mortality rate in the usual care group was 25.0%. Hence, in the latter group it is estimated that 1 death would be prevented by dexamethasone treatment of around 25 patients [8].

Secondary Outcomes

The RECOVERY trial included 2 secondary outcomes: duration of hospitalization, and a composite of receipt of mechanical ventilation or death. 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 to 1.19; P=0.002 [8]. Again, the greatest effect of dexamethasone in shortening hospitalization was observed in patients on mechanical ventilation (P for trend =0.002). 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 to 1.00, P=0.049), with significantly greater effects among patients receiving oxygen (P for trend = 0.008) [8].

Strengths of the RECOVERY trial

The RECOVERY trial is overall a well-designed, large, with adequate statistical power including more than 6,000 patients with COVID-19 [8]. Interestingly, no exclusion criteria were reported, except for patients known to have contraindications to dexamethasone [8]. 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 RECOVERY trial readily applicable to all hospitalized patients with COVID-19. In fact, the greatest value of RECOVERY trial is that it is the first randomized trial to provide convincing evidence of mortality reduction among the sickest patients with COVID-19 [8]. Furthermore, the trial was conducted in the middle of the COVID-19 pandemics when no other agent has shown a mortality benefit. Indeed, 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 1960s.

Limitations of RECOVERY Trial

The first limitation of the RECOVERY trial is the open-label design and lack of a placebo group, and therefore may be open for bias [8]. While mortality is clearly a hard outcome, it cannot be excluded that investigator decision to withdraw mechanical ventilation might be influenced by assigned dexamethasone 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 in the setting of COVID-19. Third, frequency of adverse effects of dexamethasone such as hyperglycemia, secondary infection, gastrointestinal bleeding, and psychosis were not reported. Fourth, minimal cross over of dexamethasone therapy occurred, with 7% of patients in the control group received dexamethasone. 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 UK practice on the same day the results were released [8]. The World Health Organization (WHO) has welcomed the preliminary results of the RECOVERY trial [9]. The WHO should update its treatment guidelines of COVID-19 very soon in the light of these results. It should be emphasized, however, that corticosteroids should not be used in patients with milder forms of COVID-19 not requiring oxygen as the results of RECOVERY trial suggest a possible harm.

Conclusions and Current Needs

The RECOVERY trial has shown convincing evidence that dexamethasone in a low dose of 6 mg/d for up to 10 days significantly reduced mortality in patients with severe COVID-19 receiving mechanical ventilation or oxygen. Meanwhile, this trial showed a trend towards increase mortality in patients with milder disease. Several clinical trials are underway to clarify the precise place of corticosteroids in 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. In the meantime, the immune suppressive effect of dexamethasone and corticosteroids in general should be studied e.g. by checking the duration of viral shedding and incidence of secondary bacterial or fungal infections.

Conflict of Interest

The authors do not have any conflict of interest to declare.

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