



# Effect of 12 mg vs 6 mg of dexamethasone on the number of days alive without life support in adults with COVID-19 and severe hypoxemia: the COVID STEROID 2 randomized trial

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**Article Type:** Randomized Controlled Trial

**Ratings:** *Methods*—3.5/5, *Usefulness*—3.5/5

## Methods

**Design and Setting** A multicentre, blinded, randomized controlled trial conducted in 26 hospitals across Europe and India.

**Subjects** hospitalized adult patients with COVID-19 requiring 10L/min of oxygen, noninvasive positive pressure ventilation, or mechanical ventilation.

**Intervention** 12 mg of dexamethasone compared to 6 mg of dexamethasone, daily, for up to 10 days.

**Outcomes** Primary outcome was the number of days alive without life support at 28 days.

Secondary outcomes included the number of days alive without life support at 90 days, mortality at 28 days and 90 days, number of days alive out of hospital at 90 days, and serious adverse reactions.

## Introduction

**Background** Previous studies have demonstrated a benefit with 6 mg daily of dexamethasone in patients with severe COVID-19 and hypoxemia [1]; however, the potential benefits of higher-dose corticosteroids remain unclear.

**Objectives** Assess the effects of 12 mg daily of dexamethasone relative to 6 mg daily in patients with COVID-19 and severe hypoxemia.

## Main results

Of the 1000 patients randomized in the study, 982 were included, with primary outcome data available for 971 (491 intervention, 480 control). A daily regimen of 12 mg of dexamethasone did not show a statistically significant difference in the number of days alive without life support at 28 days (22.0 vs. 20.5; 95% CI 0–2.6,  $p=0.07$ ). For the secondary outcomes, the intervention did not produce a statistically significant difference in the number of days alive without life support at 90 days (84.0 vs. 80.0; 95% CI – 1.6 to 10.4,  $p=0.15$ ), mortality at 28 days (27.1% vs. 32.3%; 95% CI – 11.5 to 2.3,  $p=0.10$ ), mortality at 90 days (32.0% vs. 37.7%; 95% CI – 12.1 to 2.4,  $p=0.09$ ), number of days alive out of hospital at 90 days (61.5 vs. 48.0; 95% CI – 1.3 to 9.5,  $p=0.09$ ), or serious adverse reactions (11.3% vs. 13.4%; 95% CI – 7.3 to 3.1,  $p=0.27$ ).

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## Appraisal

### Strengths

- well designed protocol,
- large sample size,
- high percentage of eligible patients included (1000 out of 1414),
- allocation concealment and blinding of patients, clinicians, and trial investigators,
- high percentage of follow-up,
- large number of hospitals (26) and countries (4) included.

### Limitations

- trial may have been underpowered to detect a statistical significance in the study outcomes,
- sample size estimation for the primary outcome was based on large expected relative differences,
- trial design allowed for patients to receive up to four days of corticosteroid therapy prior to enrollment, potentially reducing the duration and effect of the intervention.

### Context

The RECOVERY trial demonstrated a significant increase in 28-day survival among hypoxic COVID-19 patients receiving 6 mg daily of dexamethasone [1].

The CoDEX trial studied a higher dose of steroids, using 20 mg of dexamethasone for five days followed by 10 mg for five days in COVID-19 associated ARDS. This trial found a significant increase in the number of days alive and free of mechanical ventilation at 28 days [2].

Some local critical care physicians support prescribing doses greater than 6 mg for certain COVID-19 cases. These typically involve younger patients or those with contraindications to other immunomodulatory therapies.

## Bottom line

The COVID STEROID 2 randomized controlled trial did not identify a significant benefit for higher-dose corticosteroids in COVID-19 patients with severe hypoxemia. Following the results of this trial, a pre-planned Bayesian analysis demonstrated a high probability of benefit with the intervention [3]. Further studies with sufficient power should be performed to better identify the effects of high dose corticosteroids and delineate which COVID-19 patient populations may benefit from higher-dose corticosteroids.

The results of this trial alone do not support the daily use of 12 mg of dexamethasone over 6 mg of dexamethasone in patients with severe hypoxemia secondary to COVID-19.

### Declarations

**Conflict of interest** The authors have no conflicts to declare.

### References

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