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Early View

Original research article

Effect of high *versus* low dose of dexamethasone on clinical worsening in patients hospitalised with moderate or severe COVID-19 Pneumonia: an open-label, randomised clinical trial

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13. Authors contributions:

Drs Manuel Taboada and Valentín Caruezo had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The authors contributed equally to this study.

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BACKGROUND

Low dose dexamethasone demonstrated clinical improvement in patients with coronavirus disease 2019 (COVID-19) needing oxygen therapy; however, evidence on the efficacy of high dose of dexamethasone is limited.

METHODS

We performed a randomized, open-label, controlled trial involving hospitalized patients with confirmed COVID-19 pneumonia needing oxygen therapy. Patients were randomly assigned in a 1:1 ratio to receive low dose dexamethasone (6 mg once daily for 10 days) or high dose dexamethasone (20 mg once daily for 5 days, followed by 10 mg once daily for additional 5 days). The primary outcome was clinical worsening within 11 days since randomization. Secondary outcomes included 28-day mortality, time to recovery, and clinical status at day 5, 11, 14 and 28 on an ordinal scale ranging from 1 (discharged) to 7 (death).

RESULTS

A total of 200 patients (mean (SD) age, 64 (14) years; 62% male) were enrolled. Thirty-two patients of 102 (31.4%) enrolled in the low dose group and 16 of 98 (16.3%) in the high dose group showed clinical worsening within 11 days since randomization (rate ratio, 0.427; 95% CI, 0.216-0.842; P = 0.014). The 28-day mortality was 5.9% in the low dose group and 6.1% in the high dose group (P = 0.844). There was no significant difference in time to recovery, and in the 7-point ordinal scale at day 5, 11, 14 and 28.

CONCLUSIONS

Among hospitalized COVID-19 patients needing oxygen therapy, high dose of dexamethasone reduced clinical worsening within 11 days after randomization as compared with low dose.

Task-Home Message: The study showed that in hospitalized COVID-19 patients with moderate or severe COVID-19 pneumonia needing oxygen therapy, high dose of dexamethasone reduced clinical worsening within 11 days after randomization as compared with low dose of dexamethasone.

Introduction

Since the emergence of the 2019 novel coronavirus (SARS-CoV-2) infection in Wuhan, China in December 2019, it has rapidly spread across China and many other countries. The most common presenting symptoms by patients with COVID-19 are fever, cough, myalgia, dyspnea, headache, and diarrhea [1]. Many of those admitted to the hospital show fatigue and dyspnea, displaying on radiological imaging bilateral lung and/or multilobe involvement and requiring some type of oxygen support. Although most patients are known to have a favorable outcome, in some of them respiratory failure sets in, and may eventually progress to acute respiratory distress syndrome (ARDS). Eventually, respiratory support such as high flow nasal cannulas (HFNC), noninvasive mechanical ventilation (NIMV) or mechanical ventilation (MV) become necessary [2-4]. The unfavorable outcome of these patients has been related to an exaggerated inflammatory response caused by the SARS-CoV-2.

Recently one meta-analysis [5] that included seven randomized clinical trials showed improved outcomes in moderate or severe coronavirus disease 2019 (COVID-19) patients treated with corticosteroids. However, the doses (high vs low dose) and the type of corticosteroids (dexamethasone vs hydrocortisone vs methylprednisolone) used in these trials were different. The most important clinical trial due to the number of patients investigated was the RECOVERY [6]. The RECOVERY trial used a fixed dose of 6 mg dexamethasone daily for 10 days showing a clear beneficial effect in patients with COVID-19 who were receiving MV at the time of randomization. However, only a modest benefit was observed in less severe ill patients receiving oxygen without MV, whereas no benefits were seen in patients without respiratory support. As a result of the RECOVERY trial, numerous studies with different corticosteroids and higher doses were prematurely stopped [7-9] and low dose of dexamethasone was recommended by the Infectious Diseases Society of America (IDSA [10], the US National Institutes of Health (NIH) [11] and the WHO [12]for the usual care of hospitalized patients with COVID-19 needing oxygen therapy. At present, it is unclear which would be the optimal drug and dose, and when to initiate corticosteroid therapy. Findings from previous studies involving patients with moderate or severe COVID-19 pneumonia have suggested that the use of higher dose of corticosteroids may be associated with better outcomes [7,13].

We performed a randomized, open-label, controlled clinical trial (HIGHLOWDEXA-COVID) to evaluate the efficacy of high dose of dexamethasone (20 mg once daily for 5 days, followed by 10 mg once daily for additional 5 days) versus low dose of dexamethasone (6 mg once daily for 10 days) in patients hospitalized with COVID-19 pneumonia needing oxygen therapy. We hypothesized that high dose of dexamethasone might reduce the risk of clinical worsening defined as worsening of the patient´s condition during treatment (need to increase fraction of inspired oxygen > 0.2, need for fraction of inspired oxygen > 0.5, respiratory rate > 25) or score higher than 4 on the 7-point ordinal scale WHO-CIS.

Methods

Study Design

This is a randomized, controlled, parallel-group, open-label clinical trial aimed to assess the efficacy of high versus low dose of dexamethasone in hospitalized COVID-19 patients with respiratory failure requiring oxygen therapy. Patients were randomized using a web-based system with a 1:1 allocation ratio. The trial was approved January 13, 2021, by the Ethics Committee of Galicia, Spain (CEIm-G, code No. 2020-636), and on January 14, 2021, by the Spanish Agency of Medicines and Health Products (AEMPS, Nº EudraCT 2020-005702-25). The study was conducted in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki, local requirements, and the institutional protocol for the care of hospitalized COVID-19 patients. The authors designed the trial, collected the data, and performed the analysis. All the authors revised the manuscript, testify for its accuracy and the completeness of the data, and approved the decision to submit the manuscript for publication.

Participants

Patients were enrolled if they were at least 18 years old, had SARS-CoV-2 infection confirmed by nasopharyngeal swab polymerase chain reaction, and were receiving supplemental oxygen in order to maintain an oxygen saturation greater than 92% (Level 4 using the World Health Organization 7-point Ordinal Scale for clinical improvement (WHO-CIS)). Scores on the 7-point ordinal scale WHO-CIS were defined as follows: 1. Not hospitalized; 2. Hospitalized, not requiring supplemental oxygen, no longer requires ongoing medical care (independent); 3. Hospitalized, not requiring supplemental oxygen, but in need of ongoing medical care (COVID-19 related or otherwise); 4. Hospitalized, requiring supplemental oxygen; 5. Hospitalized, requiring non-invasive ventilation or high flow nasal cannula; 6. Hospitalized, requiring UCI admission and invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 7. Death. Exclusion criteria were pregnancy or active lactation, known history of dexamethasone allergy or known contraindication to the use of corticosteroids, indication for corticosteroids use for other clinical conditions (e.g. refractory septic shock), daily use of oral or intravenous corticosteroids in the past 15 days, expected death within the next 48 hours, different level of 4 using

the 7-point ordinal scale WHO-CIS, need of supplemental oxygen with fraction of inspired oxygen > 0.5 in order to maintain an oxygen saturation greater than 92%, and consent refusal for participating in the trial. All the patients provided the informed consent before randomization.

Randomisation

Patients were randomly assigned in a 1:1 ratio to receive standard care plus dexamethasone, 6 mg once daily for 10 days (low dose group) or dexamethasone 20 mg once daily for 5 days, followed by 10 mg once daily for additional 5 days (high dose group). Randomization sequence was performed by a computer program in blocks of six and was not stratified. Physicians, patients, and individuals who assessed the outcomes were not blinded for the assigned treatment. All clinical interventions, such as use of antiviral agents, antibiotics, other immunomodulators, anticoagulants, laboratory testing, were left at the discretion of the medical team for both groups in accordance with the hospital's own protocol, previously agreed upon by the Pneumology, Internal Medicine (Infectious Diseases Unit), Anesthesiology, Intensive Medicine, and Hospital Pharmacy departments**.** Patients who suffered clinical worsening could receive high dose of dexamethasone as a rescue therapy. Protocol adherence was assessed daily until day 11.

Procedures

The following data of all patients were collected on Hospital admission: demographic characteristics, coexisting disorders, home treatments, time from initial symptoms to randomization, time from Hospital admission to randomization, laboratory values on randomization (biochemical parameters, leukocytes, lymphocytes, serum ferritin, procalcitonin, Lactate dehydrogenase, D-dimer, C-reactive protein). During the Hospital stay we assessed the patients´ overall outcome, clinical status using the 7-point ordinal scale WHO-CIS, their medication (antibiotic agents, antiviral agents, anticoagulants), the need of respiratory support (nasal cannula, simple mask, high flow nasal cannula, noninvasive mechanical ventilation, invasive mechanical ventilation), the need of ICU admission, and complications (hospital-acquired infection, hyperglycemia, thromboembolic complications, acute kidney injury needing kidney replacement, gastrointestinal bleeding, death).

Outcomes

The goal of the investigation was to evaluate the efficacy of high versus low dose of dexamethasone in patients with respiratory failure by COVID-19. The primary outcome was clinical worsening within 11 days since randomization, defined as worsening of the patient´s condition during treatment (need to increase fraction of inspired oxygen > 0.2, need for fraction of inspired oxygen > 0.5, respiratory rate > 25) or score higher than 4 on the 7-point ordinal scale WHO-CIS. Secondary outcomes included: time to recovery (defined as the first day after enrollment, on which a patient attained category 1, 2, or 3 on the 7-point ordinal scale WHO-CIS), clinical status of patients using the 7-point ordinal scale WHO-CIS at day 5, 11, 14, 28, and 60 days after randomization, adverse drug reactions, number of patients admitted to the ICU, number of patients who needed mechanical ventilation, duration of mechanical ventilation, length of ICU and Hospital stay, number of patients discharged from hospital at day 28, mortality during hospitalization and mortality at day 28 and 60.

Statistical Analysis

We assumed, by clinical experience during the pandemic, that the risk of clinical worsening (primary outcome) within 11 days after randomization in patients with COVID-19 needing oxygen therapy would be 35% in the low dose dexamethasone group and that the risk with high dose would be about 15%. Also, it was decided to set a limit of 5% superiority. We found that a minimum of 98 patients will need to be included in each group of the test to ensure a power of 80% and to be able to conclude with a significance level of 5%.

For primary outcome and the secondary outcomes: recovery, hospital discharge and death at 28 day, Kaplan – Meier survival curves were performed to show time-to-event analysis between the two patterns of treatment. Also, by the Kaplan-Meier analysis, the number of patients in risk at specific time points in each group was estimated. The two treatments strategies were compared with the use of log-rank tests. For the prespecified primary and all prespecified secondary outcomes stated in protocol, a logistic regression model was used to estimate the risk ratios and their 95% confidence intervals. Risk ratios were estimated for the outcomes of complications and adverse events (nosocomial infection, insulin use for hyperglycemia, thrombosis, death at day

28 and death at day 60). To consider the age as an important prognostic factor, estimates of risk ratios were adjusted for the baseline age as a continuous variable.

All P values are two-sided and are shown without adjustment for multiple testing. All analyses were performed according to the intention- to-treat principle.

Finally, we examined whether the treatment effect on the primary outcome varied within subgroups defined as clinical risk factors for poor evolution of COVID-19 such as advanced age, obesity, low PaO2:FiO2 and StO2:FiO2 ratio, and time from symptoms onset to randomization. Although these analysis were not stated in study protocol, we analyzed a low number of subgroups and treatment-effect modification was assessed in separate interaction models for each risk factor to assess heterogeneity between groups. The statistical significance of the interactions will allow to determine if the differences between the subgroups are random or are due to the effect of the treatment studied.

Results

Between January 15 and May 26, 2021, a total of 200 patients were enrolled; 102 patients were randomly assigned to the low dose group and 98 patients to the high dose group (Figure 1). The number of patients randomized weekly during the study period is represented in supplementary table S1. Follow-up was completed on July 5, 2021, and at that time no patient remained hospitalized. Demographic, baseline clinical and biological characteristics of patients, and details of the treatments received during hospitalization in the two groups are summarized in Table 1. One patient in the low dose group and 3 patients in the high dose group did not receive supplemental oxygen during the study period. The mean (standard deviation) age was 64.3 ± 14.3 years and 62% were male. The median time for symptoms onset to randomization was 8 days (interquartile range (IQR): 7-10).

All patients were followed for 11 days according to the study protocol (primary outcome) and for 28 days for secondary outcomes. Follow-up at 60 days was completed in 182 patients (91%).

Thirty-two patients of 102 (31.4%) enrolled in the low dose group and 16 of 98 (16.3%) in the high dose group showed clinical worsening within 11 days since randomization (risk ratio, 0.427; 95% confidence interval (CI), 0.216-0.842; P = 0.014), (Table 2). The Kaplan-Meier curves for the time to clinical worsening are shown in Figure 1A and in supplementary Figure S1. Patients who suffered clinical worsening in the low dose was allowed to receive high dose of dexamethasone. Table 2 describe the event that led to clinical worsening in the 48 patients of the trial. Supplementary Tables 4 and 5 describe the evolution of these 48 patients.

Secondary outcomes are shown in Table 2 and Figure 1-3. The median time to recovery was 7.0 days (interquartile range, 5.0 to 11.0) in the low dose group and 7.0 days (interquartile range, 5.0 to 11.2) in the high dose group (risk ratio, 0.997; 95% CI, 0.961 – 1.035; P = 0.895). The Kaplan-Meier curves for the time to recovery are shown in Figure 1B and in supplementary Figure S2. At 14 days, 78.6% of patients in the high dose group and 77.5% in the low dose group were no longer receiving supplemental oxygen. At 28 days, the percentages were 90.8% and 90.2%, respectively (Table 2).

The median time to home discharge was 9.0 days (interquartile range, 6.7 to 14) in the high dose group and 8.5 days (interquartile range, 6.0 to 13.2) in the low dose group (risk ratio, 0.993; 95% CI, 0.973 – 1.014; P = 0.523). The Kaplan-Meier curves for the time to home discharge are shown in Figure 1C and in supplementary Figure S3. At 14 days, 69.4% of patients in the high dose group and 71.6% in the low dose group were discharged home. At 28 days, the percentages were 86.7% and 88.2%, respectively.

There was no significant difference between the two groups in need of ICU admission, need of mechanical ventilation, in-hospital mortality, and in all-cause mortality at 28 days (Table 2). The Kaplan-Meier curves for the time to death are shown in Figure 1D and in supplementary Figure S4.

There was no significant difference between the two groups in the 7-point ordinal scale at day 5, 11, 14, and 28. (Figure 3, and supplementary Table S2).

In the subgroup analyses performed according to age, sex, obesity, PaO2:FiO2 ratio, SpO2:FiO2 ratio, and time from symptoms onset to randomization, we cannot establish difference for the treatment effect. These results are shown in supplementary Table S3.

Adverse events are shown in Table 2. Both groups had a comparable need for insulin use for hyperglycemia: 47 patients (48%) in the high dose group vs 49 (48%) in low dose group. There was no significant difference in complications and adverse events between the two groups studied (Table 2).

Discussion

In this randomized clinical trial involving 200 hospitalized patients with respiratory failure by COVID-19 needing oxygen therapy, high dose compared with low dose of dexamethasone significantly decreased clinical worsening within 11 days after randomization. In addition, high dose of dexamethasone was not associated with increased risk of adverse events in this population of COVID-19 patients.

Clinical studies in which corticosteroids have been used to treat patients with COVID-19 have a high heterogeneity regarding the type of corticosteroids, the dose, the course for which the medication was given, and which patients are suitable for the drug [6-9, 13-16]. Since the publication of the RECOVERY trial, all studies comparing different corticosteroids and regimens have been discontinued. Since then, the corticosteroids and the recommended dose for COVID-19 needing oxygen therapy is dexamethasone 6 mg [10-12]. However, we do not know if a higher dose can improve outcome of COVID-19 patients. The high dose of dexamethasone used in present trial was chosen based on previous trials showing the benefit of this dose in patients with COVID-19 [7] and non-COVID-19 ARDS [14].

In the present trial we decided to include only hospitalized patients with moderate or severe COVID-19 pneumonia, needing oxygen therapy at the time of randomization. Instead, HFNC, NIMV, MV or ICU patients were not included. Clinical worsening in these patients was chosen as the primary outcome to investigate whether a higher dose of dexamethasone than the one recommended in the RECOVERY trial, administered in an early phase of the disease, when the inflammation is starting and the patient needs oxygen therapy but is not sick enough to need more respiratory support or intensive care, may be more effective in reducing progression to a more severe disease. This primary outcome was also used in trials of other drugs such as remdesivir, tocilizumab or hydroxychloroquine in non-ICU patients with moderate to severe COVID-19 pneumonia [17-23]. Our data suggest that an early intervention with high dose of dexamethasone may have prevented the progression to a more severe respiratory disease, as shown by the lower proportion of clinical worsening in patients who received high dose of dexamethasone compared to those who received the low dose (16.4% vs 31.4%). In a recent multicenter, observational, cohort study in patients with severe respiratory disease admitted in ICU, authors

observed that early use of moderate to high dose of corticosteroids was associated with better outcomes such as shorter length ICU stay, decreased organ dysfunction, fewer days on MV and no increase in medical or infections complications [13]. In a recent trial involving severely ill COVID-19 patients, the administration of high dose of methylprednisolone compared with standard care in the early pulmonary phase of the disease decreased the mortality rate and improved pulmonary involvement, oxygen saturation, and inflammatory markers [15]. The results of these studies [13,15] and the present trial should lead us to believe that ideally, the corticosteroids should be started in the early stages of inflammation to avoid onset of severe inflammation.

Although in present study we observed a decrease on clinical worsening within 11 days in the group of patients who received high doses of corticosteroids (primary outcome), we did not observe differences between the two groups in secondary outcomes such as the time of recovery, clinical status at day 5, 11, 14, and 28, or mortality. This may be explained mainly because in the low dose group, all patients who suffered a clinical worsening, high dose of dexamethasone was administered. Many of these patients, after administration of high dose of dexamethasone, improved, avoiding a further clinical deterioration, or the need of HFNC, NIV, and MV (Supplementary table 4).

The lower mortality rate seen in present study compared with RECOVERY trial might be explained by the type of patients studied, and the higher doses administered. In the RECOVERY trial, patients were divided into those who needed oxygen therapy and mechanical ventilation with a mortality of 29.3% and those who did not need mechanical ventilation with mortality of 23.3%. However, in this last group the authors included patients with different levels of severity disease. In present trial we included only patients who needed oxygen therapy and we excluded patients requiring HFNC, NIMV, or MV. Consequently, this might have excluded patients with comorbidities and high risk of mortality.

The main adverse events related to corticosteroids are hyperglycemia and new infections. Although higher doses of corticosteroids could be associated with more complications, in the present trial the number of adverse events, new infections, and the use of insulin were comparable in both groups, in line with previous studies that did not demonstrate an augmented risk of adverse events with corticosteroids in patients with ARDS and with or without COVID-19 [7,14,23].

This trial has several limitations. First, 31.4% of the patients in the low dexamethasone group received high dose of dexamethasone after clinical worsening (first outcome studied), related to the open-label design and because it was allowed in the study protocol according to the treatment protocol of our hospital. The decision to allow a rescue therapy with high dose of dexamethasone was motivated by ethical concerns regarding the use of a safe and potentially effective drug as reported by previous clinical trials [7,14]. Nevertheless, although rescue therapy did not affect the results of the primary endpoint, it would have biased the results towards the null in the secondary endpoints such as mortality, hospital stay, or side effects. Second, the open-label design and investigator-reported data on adverse events and infections may have led to bias in the description of these events. Third, the trial was underpowered for important secondary outcomes like mortality and the study was limited to demonstrate benefits in secondary outcomes. Fourth, our study did not include critically ill patients or patients with mild disease. Nevertheless, the study results confirm the beneficial effects of high dose of dexamethasone in a well-defined subset of patients, including those with moderate or severe pneumonia needing oxygen therapy who are at risk of developing ARDS, thus becoming critically ill and requiring MV. To our knowledge, this is the first randomized clinical trial evaluating the effect of two doses of dexamethasone in patients with COVID-19 and pneumonia. Another six randomized clinical trials are being carried out comparing high vs. standard doses (6 mg) of dexamethasone in adult patients with COVID-19 and hypoxia (NCT04509973, NCT04545242, NCT04663555, NCT04726098, NCT04395105, IRCT20100228003449N31.

In conclusion, among hospitalized COVID-19 patients needing oxygen therapy, high dose of dexamethasone reduced clinical worsening within 11 days after randomization as compared with low dose of dexamethasone. Further studies are necessary for confirming these preliminary results and to compare different types of corticosteroids, doses, and regimens in different stages of the disease. ClinicalTrials.gov Identifier: NCT04726098

Data sharing

Data collected for the study, included deidentified data and related documents, including the protocol, and statistical analysis plan, will be made available to qualified researchers after publication of the manuscript upon reasonable request via application to the corresponding author (MT) (manutabo@yahoo.es, manuel.taboada.muniz@sergas.es).

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Table 1. Patient Characteristics at Baseline. *

Characteristic	All patients (N = 200)	Low dose Dexamethasone (N = 102)	High dose Dexamethasone (N = 98)
Age – years			
Mean age – years	64.3±14.3	64.8±14.1	63.9±14.5
Distribution – no. (%)			
<50	37 (18.5)	18 (17.6)	19 (19.4)
50-70	91 (45.5)	46 (45.1)	45 (45.9)
>70	72 (36.0)	38 (37.3)	34 (34.7)
Male sex – no. (%)	123 (61.8)	61 (60.4)	62 (63.3)
Median weight (IQR) – Kg	85.0 (74.0 – 95.5)	84.0 (72.0 – 95.5)	87.9 (79.6 – 95.7)
Median body-mass index (IQR) †	31.0 (27.1 – 34.1)	29.8 (27.0 – 34.0)	31.2 (27.8 – 34.2)
Coexisting condition – no. (%)			
Hypertension	96 (48.0)	49 (48.0)	47 (48.0)
Hyperlipidemia	83 (39.8)	44 (43.1)	39 (39.8)
Obesity (BMI ≥ 30 Kg m-2)	106 (53.0)	48 (47.1)	58 (59.2)
Diabetes	38 (19.0)	20 (19.6)	18 (18.4)
Chronic pulmonary disease	14 (7.0)	6 (5.9)	8 (8.0)
Asthma	10 (5.0)	7 (6.9)	3 (3.1)
Cardiovascular disease	27 (13.5)	15 (14.8)	12 (12.2)
History of cancer	10 (5.0)	6 (5.9)	4 (4.1)
Chronic kidney disease	7 (3.5)	4 (3.9)	3 (3.1)
Previous medication use – no. (%)			
ACE inhibitors	28 (14.0)	13 (12.7)	15 (15.3)
Antihypertensive	52 (26.1)	25 (24.8)	27 (27.6)
Anticoagulants	11 (5.5)	7 (6.9)	4 (4.1)
Antiplatelet	26 (13.0)	14, 13.7	12 (12.2)
Inhaled corticosteroids	15 (7.5)	9 (8.8)	6 (6.1)
Statins	64 (32.0)	32 (31.4)	32 (32.7)
Immunosuppressants	4 (2.0)	1 (1.0)	3 (3.1)
Insulin	14 (7.0)	8 (7.8)	6 (6.1)
Median laboratory parameters (IQR) ‡			
Absolute Leukocytes count — cells/mm³	5210 (3975 – 6625)	5190 (3980 – 6542)	5290 (3960 -7077)
Absolute Lymphocyte count — cells/mm³	860 (612 – 1080)	905 (680– 1145)	780 (507 – 1010)
Lactate dehydrogenase — U/liter	384 (284 – 509))	357.00 (242 – 497)	415 (310 – 535)
D-dimer — ng/ml	742 (490 – 1181)	664 (457– 1160)	763 (499 – 1244)
C-reactive protein — mg/liter	7.0 (2.9 – 11.3)	6.1(2.8 – 9.6)	8.3 (4.6– 12.9)
Procalcitonin — ng/ml	0.10 (0.06 – 0.16)	0.09 (0.05 – 0.15)	0.11 (0.07 – 0.17)
Ferritin level — ng/ml	599 (284 – 1226)	539 (293 – 1203)	623 (269 – 1244)
Interleukin-6, pg/ml	13.1 (6.8 – 25.1)	14.5 (7.1 – 33.8)	10.8 (6.4 – 21.6)
Symptoms — no. (%)			
Dyspnea	128 (64.0)	61 (59.8)	67 (68.4)
Cough	155 (77.5)	84 (82.4)	71 (72.4)
Fever	146 (73.0)	76 (74.5)	70 (71.0)
Asthenia	46 (23.0)	21 (20.6)	25 (25.5)
Diarrhea	40 (20.3)	17 (16.8)	32 (24.0)
Disease			
Median temperature (IQR) – ºC	36.6 (36.0 – 37.5)	36.6 (36.0 – 37.5)	36.6 (36.0 – 37.4)
Median respiratory rate (IQR) – bpm	16.0 (15.0 – 17.0)	16.0 (15.0 – 18.5)	16.0 (15.0 – 16.0)
Median oxygen saturation (IQR) – %	92.8 (90.3 – 94.0)	93.0 (90.0 – 94.0)	92.7 (90.0 - 94.0)
Median PaCO2 on admission (IQR)	34.0 (31.3 – 37.2)	34.1 (31.9 – 37.4)	34.0 (31.0 – 37.2)
Median PaO2:FiO2 ratio (IQR)	294.0 (264.9 - 317.7)	295.2 (266.3 – 314.3)	291.4 (262.9 – 321.1)
Median days from symptom onset to randomization (IQR)	8 (7 – 10)	8 (7 – 9)	8 (7 – 10)
Median days from Hospital admission to randomization (IQR)	0 (0 – 0)	0 (0- 0)	0 (0 – 0)
Type of oxygen therapy on randomization — no. (%)			
Nasal cannula	150 (75.0)	80 (79.2)	70 (73.7)
Simple mask	46 (23.0)	21 (20.8)	25 (26.3)
Median FiO2 on randomization (IQR)	0.28 (0.28 – 0.32)	0.28 (0.28 – 0.32)	0.28 (0.28 – 0.32)
Median SpO2:FiO2 ratio on randomization (IQR)	339.3 (300.0 – 350.0)	342.8 (302.3 – 350.0)	335.7 (300.0 – 350.0)
Hospital medical treatments – no. (%)			
Remdesivir	20 (10.0)	11 (10.8)	9 (9.2)
Prophylactic anticoagulant dose	140 (70.0)	76 (74.5)	64 (65.3)
Intermediate anticoagulant dose	53 (26.5)	22 (21.6)	31 (31.6)
High anticoagulant dose	28 (14.0)	16 (15.7)	12 (12.2)
Tocilizumab	24 (12.0)	12 (11.8)	12 (12.2)

Table 1: Patient Characteristics at Baseline

* Plus-minus values are means ± SD. Percentages may not total 100 because of rounding. Abbreviations: PaCO2: partial pressure of carbon dioxide; FiO2: fraction of inspired oxygen; SpO2:FiO2: oxygen saturation to the fraction of inspired oxygen ratio; PaO2:FiO2: partial pressure of arterial oxygen to the fraction of inspired oxygen ratio; ºC: degrees Celsius; bpm: breaths per minute; %: percentage; IQR: interquartile range; ACE: angiotensin-converting enzyme.

† The body-mass index (BMI) is the weight in kilograms divided by the square of the heigh in meters.

‡ Interleukin-6 levels were missing for 14 patients (6 patients in low dose dexamethasone group and 8 patients in high dose dexamethasone group).

There was a significant difference in four laboratory parameters (Absolute Lymphocyte count, Lactate dehydrogenase, D-dimer, Procalcitonin) between patients in the low dose dexamethasone group and those in the high dexamethasone group. There were no significant differences between the groups in any other baseline characteristic.

Table 2. Primary, Secondary Outcomes, and Adverse Events. *

Outcome	All patients N = 200	Low dose Dexamethasone N = 102	High dose Dexamethasone N = 98	Risk Ratio (95% CI)†	P value
Primary outcome					
Clinical worsening within 11 days – no. (%)	48 (24.0)	32 (31.4)	16 (16.3)	0.427 (0.216 – 0.842)	0.014
First event – no. (%)					
Worsening of the patient´s condition	47 (23.5)	31 (30.4)	16 (16.3)		
NIV/HFNC (level 5 on the 7-level ordinal scale)	7 (3.5)	3 (2.9)	4 (4.1)		
MV (level 6 on the 7-level ordinal scale)	15 (7)	6 (5.9)	9 (9.2)		
Death (level 7 on the 7-level ordinal scale)	1 (0.5)	1 (1.0)	0 (0)		
Secondary outcomes					
Recovery – no. (%)					
Day 5	36 (18.0)	16 (15.7)	20 (20.4)	1.350 (0.648 – 2.816)	0.423
Day 11	135 (67.5)	67 (65.7)	68 (69.3)	1.164 (0.625 – 2.170)	0.632
Day 14	156 (78.0)	79 (77.5)	77 (78.6)	1.043 (0.504 – 2.162)	0.909
Day 28	181 (90.5)	92 (90.2)	89 (90.8)	1.000 (0.369 – 2.711)	1.000
Median time to recovery (IQR) – days	7.0 (5.0 – 11.0)	7.0 (5.0 – 11.0)	7.0 (5.0 – 11.2)	0.997 (0.961 – 1.035)	0.895
Admission to ICU – no. (%)	28 (14.0)	13 (12.7)	15 (15.3)	0.995 (0.976 – 1.015)	0.622
Median length ICU stay (IQR) – days	8.0 (6.0 – 14.7)	9.0 (6.5 – 15.0)	7.0 (6.0 – 13.0)	1.020 (0.952 – 1.093)	0.577
Mechanical ventilation requirement – no. (%)	19 (9.5)	9 (8.8)	10 (10.2)	0.995 (0.976 – 1.015)	0.629
Median duration of MV (IQR) – days	9.0 (6.0 – 15.0)	13.0 (8.0 – 15.0)	8.0 (4.7 – 12.2)	0.997 (0.915 – 1.086)	0.945
Discharged from hospital within 28 days – no. (%)	175 (87.5)	90 (88.2)	85 (86.7)	1.021 (0.845 – 1.233)	0.831
Median length Hospital stay (IQR) – days	9.0 (6.0 – 14.0)	8.5 (6.0 – 13.2)	9.0 (6.7 – 14.0)	0.993 (0.973 – 1.014)	0.523
In-hospital mortality, – no. (%)	10 (5%)	6 (5.9)	4 (4.1)	0.997 (0.977 – 1.017)	0.734
Complications and adverse events – no. (%)					
Nosocomial infection	20 (10.0)	10 (9.8)	10 (10.2)	1.081 (0.425 – 2.750)	0.870
Pneumonia	12 (6.0)	7 (6.9)	5 (5.1)		
Catheter-related bloodstream infection	1 (0.5)	1 (0.9)	0 (0.0)		
Bacteremia	5 (2.5)	4 (3.9)	1 (1.0)		
Urinary tract infection	6 (3.0)	1 (0.9)	5 (5.1)		
Insulin use for hyperglycemia	96 (48.0)	49 (48.0)	47 (48.0)	0.997 (0.572 – 1.736)	0.991
Thrombosis	7 (3.5)	6 (5.9)	1 (1.0)	0.169 (0.020 – 1.434)	0.103
Death at day 28	12 (6.0)	6 (5.9)	6 (6.1)	1.129 (0.338 – 3.772)	0.844
Death at day 60 ‡	15 (8.2)	8 (8.3)	7 (8.0)	1.012 (0.333 – 3.080)	0.983

Table 2. Primary, Secondary Outcomes, and Adverse Events.

* Abbreviations: CI: confidence interval; %: percentage; ICU: Intensive care unit; VM: mechanical ventilation; HFNC: high-flow nasal cannula, NIV: non-invasive ventilation, IQR: interquartile range.

† Rate ratios have been adjusted for age with respect to the outcomes studied.

‡ Follow-up at 60 days was completed in 184 patients (92.0%). Data regarding "Death at day 60" were missing for 10 in the low dose dexamethasone group and 6 patients in the high dose dexamethasone group.

Figure 1. Screening, Randomization, and Outcomes.

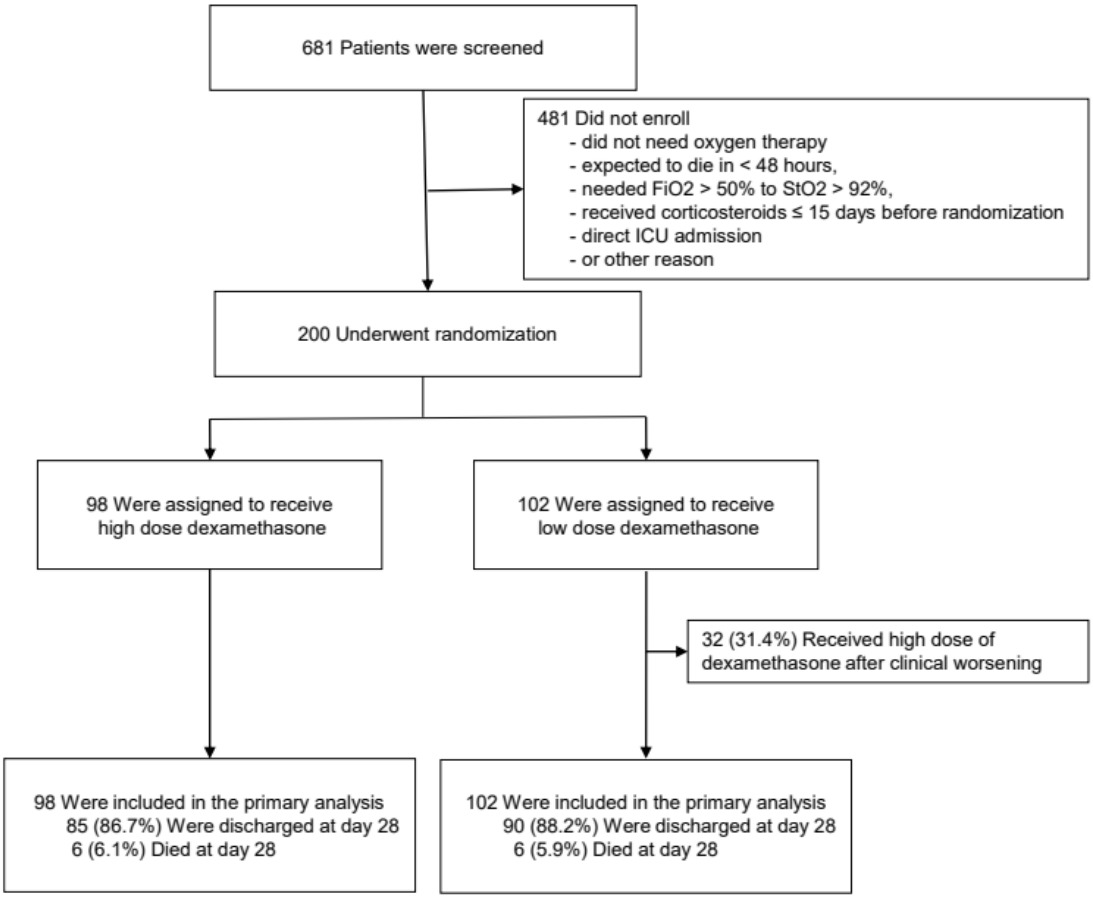


Figure 2. Kaplan-Meier Analysis of Efficacy Outcomes.

Shown are Kaplan-Meier curves for the time-to-event analyses of clinical worsening (primary outcome) (Panel A); recovery, defined as the first day after enrollment, on which a patient attained category 1, 2, or 3 on the 7-point ordinal scale (scores range from 1 to 7, with higher scores indicating worse clinical condition (Panel B); hospital discharge (Panel C); death (Panel D).

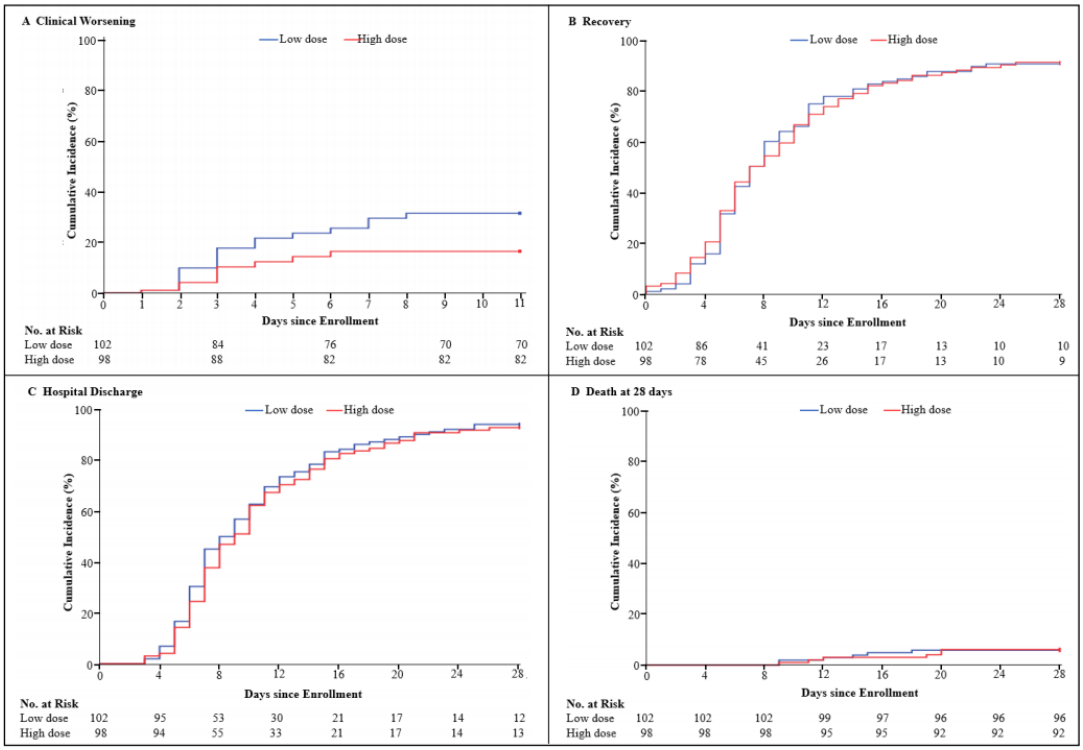
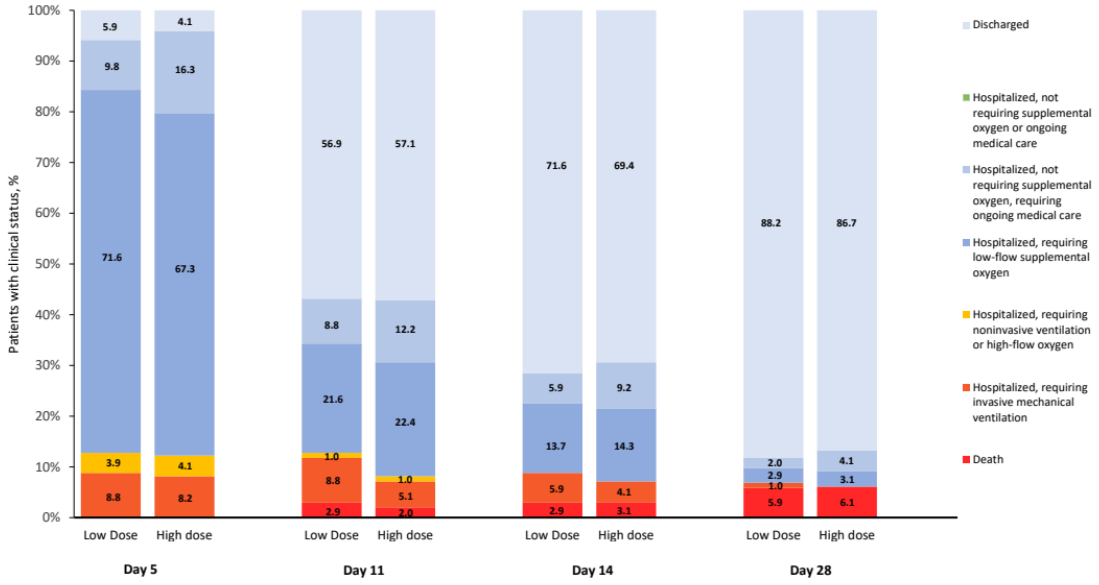


Figure 3: Clinical Status on a 7-Point Ordinal Scale on Study Days 5, 11, 14, and 28 by treatment group

All percentage values in each point category are provided in supplementary appendix, table S 3. At day 5, P = 0.885 for comparison of the distribution of the high dose group vs low dose group. At day 11, P = 0.666 for comparison of the distribution of the high dose group vs low dose group. At day 14, P = 0.870 for comparison of the distribution of the high dose group vs low dose group. At day 28, P = 0.831 for comparison of the distribution of the high dose group vs low dose group.



Supplementary Results

Supplementary Results for the manuscript Entitled:

Effect of high vs low dose of dexamethasone on clinical worsening in patients hospitalized with moderate or severe COVID-19 Pneumonia: an open-label, randomized clinical trial.

This supplement contains supplementary results

Trial registration:
The trial was approved January 14, 2021, by the Spanish Agency of Medicines and Health Products (AEMPS, Nº EudraCT 2020-005702-25)

The trial was approved January 13, 2021, by the Ethics Committee of Galicia, Spain. (CEIm-G, code No. 2020-636).

Registered in clinicaltrials.gov: NCT04726098.
https://clinicaltrials.gov/ct2/show/record/NCT04726098
term=dexamethasone&cond=Covid19&cntry=ES&draw=2&rank=1

Keywords: COVID-19, SARS-CoV-2, acute respiratory distress (ARDS), corticosteroids, dexamethasone, failure respiratory, randomized clinical trial.

Effect of high vs low dose of dexamethasone on clinical worsening in patients hospitalized with moderate or severe COVID-19 Pneumonia: an open-label, randomized clinical trial.

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ClinicalTrials.gov Identifier: NCT04726098, EudraCT Identifier: 2020-005702-25

In ClinicalTrials.gov there is an 8-day delay between the start of recruitment and study registration
These were the dates and the reason for the delay:

1. On December 2, 2020, the trial protocol (Nº EudraCT: 2020-005702-25) was sent to the "Galicia (Spain) Drug Research Ethics Committee" requesting permission to conduct the clinical trial urgently due to the serious situation that was being experienced in Spain with COVID-19.
2. On December 18, 2020, the trial protocol was sent to the "The Spanish Agency of Medicines and Medical Devices" (AEMPS) requesting permission to conduct the clinical trial urgently due to the serious situation that was being experienced in Spain with COVID-19.
3. On January 13, 2021, the "Galicia (Spain) Drug Research Ethics Committee" authorizes to carry out the clinical trial with registration number: : 2020/636.
4. On January 14, 2021, The Spanish Agency of Medicines and Medical Devices" (AEMPS), authorizes to carry out the clinical trial (Nº EudraCT 2020-005702-25).
5. On January 15, 2021, (Friday), starting the third wave (COVID-19) in Spain, we decided to urgently start the recruitment of patients in the trial as well as register them in "clinical trials gov", after having been authorized by the two institutions that oblige in Spain, the "Galicia (Spain) Drug Research Ethics Committee" and the "The Spanish Agency of Medicines and Medical Devices" (AEMPS).
6. On January 15, 2021 (11:15) (Friday) we sent an email to register@clinicaltrials.gov., requesting login information to register the trial.
7. On January 15, 2021 (12.49), (Friday) register@clinicaltrials.gov sent us an email with the login to access clinicaltrials.gov and to register the trial. This email
8. On January 18, 2021 (Monday) we found the email sent by register@clinicaltrials.gov with the Login to access to the clinicaltrials.gov. The message was flagged as spam. During the week of January 18-24, the data from the clinical trial (Study Description, Study Design, Outcome Measures, Eligibility Criteria, other information...) were incorporated in "clinical trials gov" and it was finally registered.
9. The first patient was enrolled on January 15 in the afternoon. Second patient on January 16. Third patient on January 18. Six patients were randomized before January 23. When the trial was registered in clinicaltrials gov, the trial was registered as in the "recruitment phase" and the registered *study start date* in ClinicalTrials.gov was January 15th.

Table of Contents

1. Background

After RECOVERY trial publication, low dose (6 mg dexamethasone for 10 days) was recommended as the usual care treatment in hospitalized patients with respiratory failure by COVID-19 needing oxygen therapy. At present, it is unclear what dose of dexamethasone: low dose: 6 mg daily for 10 days, versus high dose: 20 mg daily for 5 days and 10 mg daily another 5 days, is most beneficial in patients with COVID-19 and respiratory failure.

In this context, our hypothesis was that high doses of dexamethasone would have greater benefits than low doses of dexamethasone in patients with respiratory failure and COVID-19

2. Objectives

To investigate the efficacy of high dose of dexamethasone (20 mg daily 5 days + 10 mg daily 5 days) versus low dose of dexamethasone (6 mg daily 10 days) in patients with respiratory failure by COVID-19

2.1 The primary outcome

The primary outcome was **clinical worsening within 11 days since randomization**, defined by the occurrence of one of the following events, whichever occurred first:

- Death from any cause (**score 7** on the seven-level ordinal scale).
- Admission to ICU and need of invasive ventilation or ECMO (**score 6** on the seven-level ordinal scale).
- Need of non-invasive ventilation or nasal high-flow oxygen therapy (**score 5** on the seven-level ordinal scale)
- Worsening of the condition clinic of the patient during treatment (two of these: need to increase fraction of inspired oxygen inspired>20%, need for fraction inspired oxygenation>50%, increase in respiratory rate>25).

2.2. Secondary outcomes

- Clinical status of patients using the 7-point Ordinal Scale of the World Health Organization for clinical improvement (WHO-CIS) at day 5, 11, 14, 28, and 60 after randomization.
- Time to recovery (time to clinical improvement: defined as the first day after enrollment, on which a patient attained category 1, 2, 3-point ordinal scale WHO-CIS)
- Number of patients admitted to the ICU admission
- Number of patients who needed mechanical ventilation
- Duration of mechanical ventilation
- Duration of ICU admission.
- Length of Hospital stay
- Mortality during hospitalization, at day 28 and at day 60.
- Adverse drug reactions
- Complications during hospitalization:
    - Nosocomial infection:
        Pneumonia,

Catheter-related bloodstream infection,

Bacteremia,

Urinary infection,

Others...

- Insulin use for hyperglycemia
- Gastrointestinal bleeding
- Thrombosis
- Pneumothorax
- Renal replacement therapy

3. Tables and Results

Table S1: Enrolment rate of 200 patients through the 5 months of the trial

Period (weeks)	Number of randomized patients
15 January – 17 January 2021	2
18 January – 24 January 2021	11
25 January- 31 January 2021	45
1 February – 7 February 2021	27
8 February – 14 February 2021	21
15 February – 21 February 2021	17
22 February – 28 February 2021	11
1 March – 7 March 2021	5
8 March – 14 March 2021	4
15 March – 21 March 2021	2
22 March – 28 March 2021	1
29 March – 4 April 2021	3
5 April – 11 April 2021	6
12 April – 18 April 2021	4
19 April – 25 April 2021	5
26 April – 2 May 2021	9
3 May – 9 May 2021	9
10 May – 16 May 2021	11
17 May – 23 May 2021	2
24 may – 26 May 2021	5

Table S2: Distribution of patients´ scores on the 7-point ordinal scale at 5, 11, 14, and 28 days.

Outcomes * *					
Outcome	**All patients N = 200**	**Low dose Dexamethasone N = 102**	**High dose Dexamethasone No = 102**	**Risk Ratio (95% CI)†**	**P value**
Seven-level ordinal scale at 5 days					
Distribution – no. (%) ‡				**0.979 (0.737 – 1.301)**	**0.885**
1:	**10 (5.0)**	**6 (5.9)**	**4 (4.1)**		
2:	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**		
3:	**26 (13.0)**	**10 (9.8)**	**16 (16.3)**		
4:	**139 (69.5)**	**73 (71.6)**	**66 (67.3)**		
5:	**8 (4.0)**	**4 (3.9)**	**4 (4.1)**		
6:	**17(8.5)**	**9 (8.8)**	**8 (8.2)**		
7:	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**		
Seven-level ordinal scale at 11 days					
Distribution – no. (%)				**0.964 (0.818 – 1.137)**	**0.666**
1:	**114 (57)**	**58 (56.9)**	**56 (57.1)**		
2:	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**		
3:	**21 (10.5)**	**9 (8.8)**	**12 (12.2)**		
4:	**44 (22.0)**	**22 (21.6)**	**22 (22.4)**		
5:	**2 (1.0)**	**1 (1.0)**	**1 (1.0)**		
6:	**14 (7.0)**	**9 (8.8)**	**5 (5.1)**		
7:	**5 (2.5)**	**3 (2.9)**	**2 (2.0)**		
Seven-level ordinal scale at 14 days					
Distribution – no. (%)				**1.014 (0.854 – 1.206)**	**0.870**
1:	**141 (70.5)**	**73 (71.6)**	**68 (69.4)**		
2:	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**		
3:	**15 (7.5)**	**6 (5.9)**	**9 (9.2)**		
4:	**28 (14.0)**	**14 (13.7)**	**14 (14.3)**		
5:	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**		
6:	**10 (5.0)**	**6 (5.9)**	**4 (4.1)**		
7:	**6 (3.0)**	**3 (2.9)**	**3 (3.1)**		
Seven-level ordinal scale at 28 days					
Distribution – no. (%)				**1.021 (0.845 – 1.233)**	**0.831**
1:	**175 (87.5)**	**90 (88.2)**	**85 (86.7)**		
2:	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**		
3:	**6 (3.0)**	**2 (2.0)**	**4 (4.1)**		
4:	**6 (3.0)**	**3 (2.9)**	**3 (3.1)**		
5:	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**		
6:	**1 (0.5)**	**1 (1.0)**	**0 (0.0)**		
7:	**12 (6.0)**	**6 (5.9)**	**6 (6.1)**		

***** * Abbreviations: CI: confidence interval; %: percentage; IQR: interquartile range.

‡ Scores on the ordinal scale are follows: 1, not hospitalized; 2, not hospitalized, not requiring supplemental oxygen, no longer requires ongoing medical care (independent); 3, hospitalized, not requiring supplemental oxygen, but in need of ongoing medical care (COVID-19 related or otherwise); 4, hospitalized, requiring supplemental oxygen; 5, hospitalized, requiring non-invasive ventilation or high flow nasal cannula; 6, hospitalized, requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 7, death.

† Rate ratios have been adjusted for age with respect to the outcomes studied.

Table S 3: Subgroup Analyses of Clinical Worsening through Day 11.

Subgroup	No. of Patients	Risk Ratio (95% CI)
Overall	**200**	**0.427 (0.216 – 0.842)**
Sex		
Male	123	0.477 (0.204 – 1.113)
Female	76	0.335 (0.106 – 1.061)
Age		
< 65 years	91	0.594 (0.178 – 1.976)
≥ 65 years	**109**	**0.349 (0.149 – 0.816) ***
Obesity		
Yes	**106**	**0.367 (0.145 – 0.931) ***
No	94	0.504 (0.185 – 1.374)
PaO2:FiO2 ratio		
≤294	**100**	**0.399 (0.166 – 0.959) ***
>294	100	0.407 (0.132 – 1.257)
SpO2:FiO2 ratio		
≤339	**108**	**0.410 (0.177 – 0.948) ***
>339	92	0.285 (0.074 – 1.090)
Days from symptoms onset		
≤8 días	121	0.480 (0.209 – 1.101)
>8 días	79	0.406 (0.120 – 1.370)
≤ 10 días	**164**	**0.437 (0.211 - 0.904) ***
> 10 días	36	0.600 (0.074 – 4.834)

Table S 4: Subgroup of the 32 patients in the low dose group who suffered Clinical Worsening through Day 11.

P.No	First event	Day treatment	Need of MV	Need of ICU	Score level at day 11	Score level at day 14	Death at day 11	Death at day 60
1	Worsening of the patient´s condition	6	No	No	**4**	**4**	No	No
2	NIV/HFO	2	No	Yes	4	3	No	No
3	MV	3	Yes	Yes	6	6	No	No
4	Worsening of the patient´s condition	7	No	No	**4**	**4**	No	No
5	MV	1	Yes	Yes	6	6	No	No
6	Worsening of the patient´s condition	7	No	No	**4**	**4**	No	No
7	Worsening of the patient´s condition	4	No	No	**4**	**4**	No	Yes
8	Worsening of the patient´s condition	3	No	No	**1**	**1**	No	No
9	Worsening of the patient´s condition	3	No	No	**1**	**1**	No	No
10	Worsening of the patient´s condition	2	Yes	Yes	6	6	No	No
11	Worsening of the patient´s condition	7	No	No	**4**	**4**	No	No
12	Worsening of the patient´s condition	8	No	No	**4**	**4**	No	Yes
13	Worsening of the patient´s condition	3	Yes	Yes	6	6	No	No
14	Worsening of the patient´s condition	3	No	No	**4**	**4**	No	No
15	Worsening of the patient´s condition	2	No	No	5	**4**	No	No
16	Worsening of the patient´s condition	7	No	No	7	7	No	Yes
17	Worsening of the patient´s condition	3	No	No	**4**	**4**	No	No
18	Worsening of the patient´s condition	2	No	No	**1**	**1**	No	No
19	Worsening of the patient´s condition	7	No	No	**1**	**1**	No	No
20	Worsening of the patient´s condition	3	No	No	7	7	Yes	Yes
21	Worsening of the patient´s condition	2	No	No	**1**	**1**	No	No
22	MV	2	Yes	Yes	6	6	No	No
23	MV	5	Yes	Yes	6	6	No	No
24	Death	8	No	No	7	7	Yes	Yes
25	Worsening of the patient´s condition	2	No	Yes	**4**	**1**	No	No
26	Worsening of the patient´s condition	2	Yes	Yes	6	**4**	No	No
27	NIV/HFO	3	Yes	Yes	4	1	No	No
28	MV	6	No	Yes	6	6	No	Yes
29	Worsening of the patient´s condition	5	No	No	**4**	**4**	No	Yes
30	Worsening of the patient´s condition	2	No	No	**1**	**1**	No	No
31	MV	3	Yes	Yes	6	6	No	Yes
32	NIV/HFO	4	No	Yes	4	1	No	No

16 patients in the low dose group did not worsen level greater than 4 at day 11 after starting high doses. On day 14, 7 of those patients had a level lower than 4.

Table S 5: Subgroup of the 16 patients in the high dose group who suffered Clinical Worsening through Day 11.

P.N	First event	Day treatment	Need of MV	Need of ICU	Score level at day 11	Score level at day 14	Death at day 11	Death At day 60
1	Worsening of the patient´s condition	3	Yes	Yes	7	7	Yes	Yes
2	NIV/HFO	1	No	Yes	4	3	No	No
3	MV	4	Yes	Yes	6	6	No	No
4	MV	6	Yes	Yes	4	4	No	No
~~5~~	MV	4	Yes	Yes	4	3	No	No
6	Worsening of the patient´s condition	2	No	Yes	4	1	No	No
7	MV	3	Yes	Yes	6	4	No	No
8	MV	5	Yes	Yes	6	6	No	No
9	MV	2	Yes	Yes	6	6	No	No
10	NIV/HFO	3	No	Yes	1	1	No	No
11	Worsening of the patient´s condition	5	Yes	Yes	6	6	No	Yes
12	NIV/HFO	3	No	Yes	4	3	No	No
13	MV	3	Yes	Yes	4	3	No	No
14	Worsening of the patient´s condition	3	No	No	7	7	Yes	Yes
15	MV	2	Yes	Yes	3	1	No	No
16	NIV/HFO	6	No	Yes	5	4	No	No

Figure S1: Kaplan-Meier Analysis of Efficacy Outcomes: clinical worsening.

Shown are Kaplan-Meier curves for the time-to-event analyses of clinical worsening (primary outcome).

Comparaciones globales

	Chi-cuadrado	gl	Sig.
Log Rank (Mantel-Cox)	5,992	1	,014

Prueba de igualdad de distribuciones de supervivencia para diferentes niveles de Dosis de Dexametasona.

Clinical worsening

Nº at risk	D_0	D_3	D_6	D_9	D_{11}
Low dose	102	84	76	70	70
High dose	98	88	82	82	82

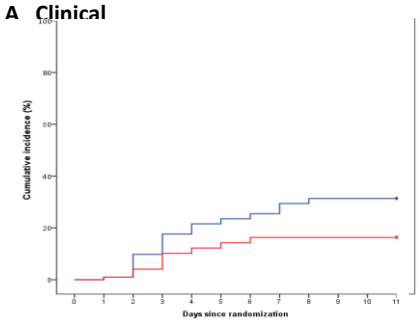

Figure S2: Kaplan-Meier Analysis of Efficacy Outcomes: recovery.

Shown are Kaplan-Meier curves for the time-to-event analyses of recovery, defined as the first day after enrollment, on which a patient attained category 1, 2, or 3 on the 7-point ordinal scale (scores range from 1 to 7, with higher scores indicating worse clinical condition.

Comparaciones globales

	Chi-cuadrado	gl	Sig.
Log Rank (Mantel-Cox)	,000	1	,991

Prueba de igualdad de distribuciones de supervivencia para diferentes niveles de Dosis de Dexametasona.

Recovery

Nº at risk	D_0	D_4	D_8	D_{12}	D_{16}	D_{20}	D_{24}	D_{28}
Low dose	102	86	41	23	17	13	10	10
High dose	98	78	45	26	17	13	10	9

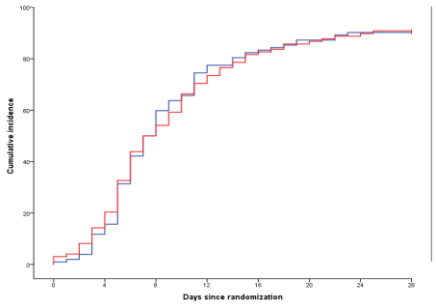

Figure S3: Kaplan-Meier Analysis of Efficacy Outcomes: hospital discharge.

Shown are Kaplan-Meier curves for the time-to-event analyses of hospital discharge.

Comparaciones globales

	Chi-cuadrado	gl	Sig.
Log Rank (Mantel-Cox)	,400	1	,527

Prueba de igualdad de distribuciones de supervivencia para diferentes niveles de Dosis de Dexametasona.

Hospital discharge

Nº at risk	**D_0**	**D_4**	**D_8**	**D_{12}**	**D_{16}**	**D_{20}**	**D_{24}**	**D_{28}**
Low dose	102	95	53	30	21	17	14	12
High dose	98	94	55	33	21	17	14	13

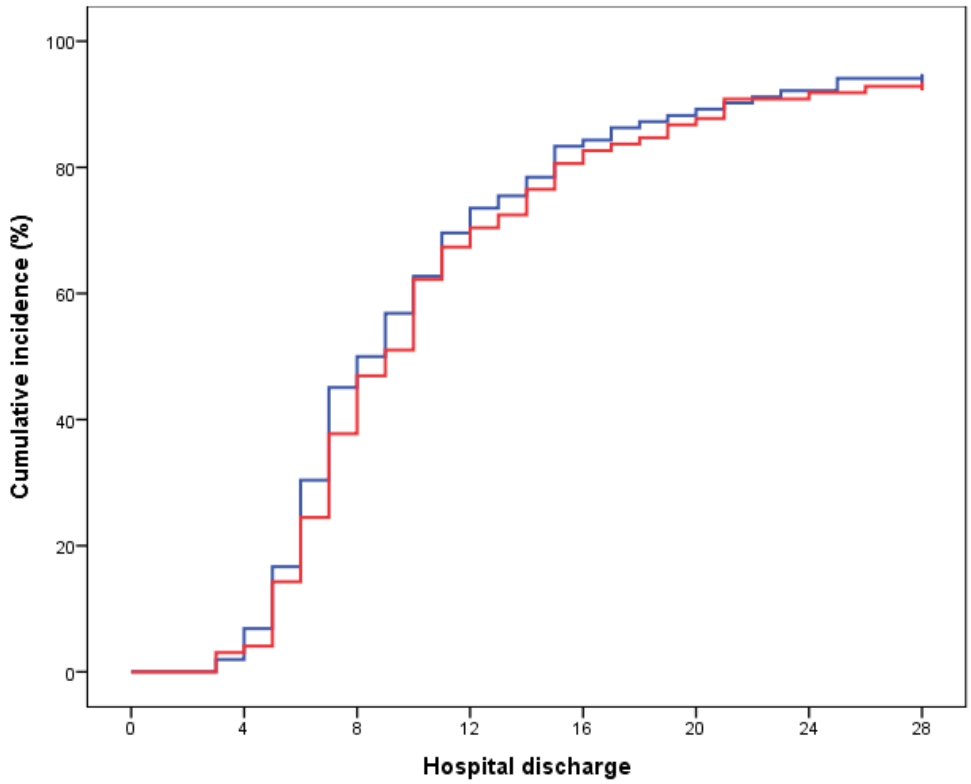

Figure S4: Kaplan-Meier Analysis of Efficacy Outcomes: death.

Shown are Kaplan-Meier curves for the time-to-event analyses of death

Comparaciones globales

	Chi-cuadrado	gl	Sig.
Log Rank (Mantel-Cox)	,003	1	,956

Prueba de igualdad de distribuciones de supervivencia para diferentes niveles de Dosis de Dexametasona.

Death at 28

Nº at risk	**D_0**	**D_4**	**D_8**	**D_{12}**	**D_{16}**	**D_{20}**	**D_{24}**	**D_{28}**
Low dose	102	102	102	99	97	96	96	96
High dose	98	98	98	95	95	92	92	92