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Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19

The CoDEX Randomized Clinical Trial

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Key Points

Question

In patients with coronavirus disease 2019 (COVID-19) and moderate or severe acute respiratory distress syndrome (ARDS), does intravenous dexamethasone plus standard care compared with standard care alone increase the number of days alive and free from mechanical ventilation?

Findings

In this randomized clinical trial that included 299 patients, the number of days alive and free from mechanical ventilation during the first 28 days was significantly higher among patients treated with dexamethasone plus standard care when compared with standard care alone (6.6 days vs 4.0 days).

Meaning

Intravenous dexamethasone plus standard care, compared with standard of care alone, resulted in a statistically significant increase in the number of days alive and free of mechanical ventilation over 28 days.

Abstract

Importance

Acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19) is associated with substantial mortality and use of health care resources. Dexamethasone use might attenuate lung injury in these patients.

Objective

To determine whether intravenous dexamethasone increases the number of ventilator-free days among patients with COVID-19–associated ARDS.

Design, Setting, and Participants

Multicenter, randomized, open-label, clinical trial conducted in 41 intensive care units (ICUs) in Brazil. Patients with COVID-19 and moderate to severe ARDS, according to the Berlin definition, were enrolled from April 17 to June 23, 2020. Final follow-up was completed on July 21, 2020. The trial was stopped early following publication of a related study before reaching the planned sample size of 350 patients.

Interventions

Twenty mg of dexamethasone intravenously daily for 5 days, 10 mg of dexamethasone daily for 5 days or until ICU discharge, plus standard care (n =151) or standard care alone (n = 148).

Main Outcomes and Measures

The primary outcome was ventilator-free days during the first 28 days, defined as being alive and free from mechanical ventilation. Secondary outcomes were all-cause mortality at 28 days, clinical status of patients at day 15 using a 6-point ordinal scale (ranging from 1, not hospitalized to 6, death), ICU-free days during the first 28 days, mechanical ventilation duration at 28 days, and Sequential Organ Failure Assessment (SOFA) scores (range, 0-24, with higher scores indicating greater organ dysfunction) at 48 hours, 72 hours, and 7 days.

Results

A total of 299 patients (mean [SD] age, 61 [14] years; 37% women) were enrolled and all completed follow-up. Patients randomized to the dexamethasone group had a mean 6.6 ventilator-free days (95% CI, 5.0-8.2) during the first 28 days vs 4.0 ventilator-free days (95% CI, 2.9-5.4) in the standard care group (difference, 2.26; 95% CI, 0.2-4.38; $P = .04$). At 7 days, patients in the dexamethasone group had a mean SOFA score of 6.1 (95% CI, 5.5-6.7) vs 7.5 (95% CI, 6.9-8.1) in the standard care group (difference, −1.16; 95% CI, −1.94 to −0.38; $P = .004$). There was no significant difference in the prespecified secondary outcomes of all-cause mortality at 28 days, ICU-free days during the first 28 days, mechanical ventilation duration at 28 days, or the 6-point ordinal scale at 15 days. Thirty-three patients (21.9%) in the dexamethasone group vs 43 (29.1%) in the standard care group experienced secondary infections, 47 (31.1%) vs 42 (28.3%) needed insulin for glucose control, and 5 (3.3%) vs 9 (6.1%) experienced other serious adverse events.

Conclusions and Relevance

Among patients with COVID-19 and moderate or severe ARDS, use of intravenous dexamethasone plus standard care compared with standard care alone resulted in a statistically significant increase in the number of ventilator-free days (days alive and free of mechanical ventilation) over 28 days.

Trial Registration

ClinicalTrials.gov Identifier: NCT04327401

Introduction

Three months after the emergence of the coronavirus disease 2019 (COVID-19)[1] caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the World Health Organization declared it a pandemic.[2] Estimates have suggested that up to 12% of patients hospitalized with COVID-19 have required invasive mechanical ventilation,[3,4] with the majority developing acute respiratory distress syndrome (ARDS).[5] Diffuse alveolar damage with hyaline membranes,[6] hallmarks of ARDS, have been found on pulmonary histological examination of patients with COVID-19. Furthermore, an uncontrolled inflammatory state is frequent with COVID-19[7,8] and may contribute to multiorgan failure in these patients. Corticosteroids might exert an effect in controlling this exacerbated response.[9]

Several trials evaluated the role of corticosteroids for non–COVID-19 ARDS with conflicting results.[10,11] Observational studies of other viral diseases suggested that corticosteroids might increase viral load in patients with SARS-CoV[12] and Middle East respiratory syndrome (MERS).[13] A meta-analysis identified an association between corticosteroids and higher mortality among patients with influenza.[14] Findings from a randomized clinical trial involving patients with COVID-19 indicated that the use of dexamethasone decreased mortality in hospitalized patients requiring supplemental oxygen or mechanical ventilation.[15]

The COVID-19 Dexamethasone (CoDEX) randomized clinical trial was conducted to evaluate the efficacy of intravenous dexamethasone in patients with moderate to severe ARDS due to COVID-19. The hypothesis was that dexamethasone would increase the number of days alive and free from mechanical ventilation during the first 28 days.

Methods

Study Design and Oversight

We conducted an investigator-initiated, multicenter, randomized, open-label, clinical trial in 41 intensive care units (ICUs) in Brazil. The trial protocol (Supplement 1) and the statistical analysis plan were submitted for publication before the first interim analysis[16] (Supplement 2). The study was approved at the Brazilian Health Regulatory Agency, the Brazilian National Commission for Research Ethics, and all ethics committees at the participating sites. Written or oral informed consent was obtained before randomization from each patient's legal representative. The trial was overseen by an external and independent data and safety monitoring committee (DSMC).

Patients

Patients were enrolled who were at least 18 years old, had confirmed or suspected COVID-19 infection (eMethods in Supplement 3), and were receiving mechanical ventilation within 48 hours of meeting criteria for moderate to severe ARDS with partial pressure of arterial blood oxygen to fraction of inspired oxygen (Pao_2:FIO_2)ratio of 200 or less. An ARDS diagnosis was made according to the Berlin Definition criteria.[17] Exclusion criteria were pregnancy or active lactation, known history of dexamethasone allergy, corticosteroid use in the past 15 days for nonhospitalized patients, use of corticosteroids during the present hospital stay for more than 1 day, indication for corticosteroid use for other clinical conditions (eg, refractory septic shock), use of immunosuppressive drugs, cytotoxic chemotherapy in the past 21 days, neutropenia due to hematological or solid malignancies with bone marrow invasion, consent refusal, or expected death in the next 24 hours (Figure 1). During the study period we refined some of the inclusion and exclusion criteria. Full details are provided in Supplement 3.

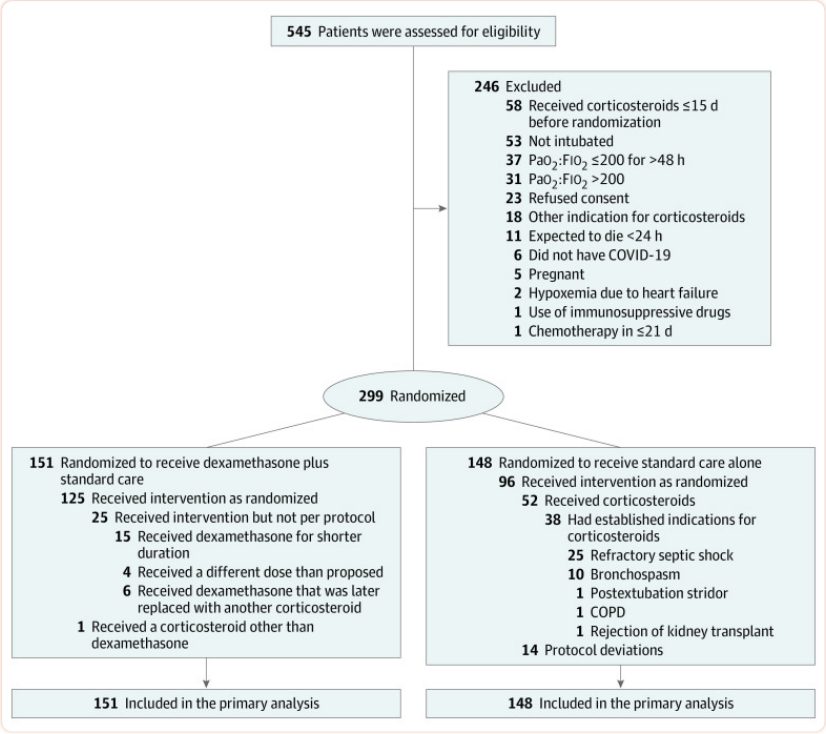

Figure 1.

Flow of Patients in the Coronavirus Dexamethasone (CoDEX) Trial

Abbreviations: COVID-19, coronavirus disease 2019; Pao_2:FIO_2 partial pressure of arterial oxygen to the fraction of inspired oxygen ratio, COPD, chronic obstructive pulmonary disease.

Trial Procedures

Randomization was performed through an online web-based system[18] using computer-generated random numbers and blocks of 2 and 4, unknown to the investigators, and was stratified by center. The group treatment was disclosed to the investigator only after all information regarding patient enrollment was recorded in the online system (eMethods in Supplement 3).

Eligible patients were randomly assigned in a 1:1 ratio to receive dexamethasone 20 mg intravenously once daily for 5 days, followed by 10 mg intravenously once daily for additional 5 days or until ICU discharge, whichever occurred first, plus standard care. Patients in the control group received standard care only. Physicians, patients, and individuals who assessed the outcomes were not blinded for the assigned treatment. Each study center was encouraged to follow the best practice guidelines and their institutional protocol for the care of critically ill patients with COVID-19. All clinical interventions, such as use of antibiotics, ventilatory strategy, laboratory testing, and hemodynamic management were left at the discretion of the ICU team for both groups.

Protocol adherence was assessed daily until day 10. Unjustified corticosteroid use or use for treating ARDS or COVID-19 in the control group was not recommended and considered a protocol deviation. The use of non-study corticosteroids was permitted in the control group for usual ICU indications, such as bronchospasm and refractory septic shock.[19] Additionally, any dexamethasone dosage change or early interruption in the intervention group was considered a protocol violation.

Clinical and Laboratory Data

Data on demographic characteristics, physiological variables, corticosteroid use before randomization, timing from ARDS diagnosis to randomization, insulin use for hyperglycemia, and other clinical and laboratory data were collected. Use of neuromuscular blocking agents, prone positioning, and extracorporeal membrane oxygenation (ECMO) were collected daily through day 14. Use of mechanical ventilation and other oxygen supportive therapies (high-flow nasal cannula, noninvasive positive pressure ventilation, and use of supplemental oxygen) were collected daily through 28 days. Diagnosis of new infections were reported daily through day 28. Individual patient data on infections were adjudicated by a blinded investigator (eMethods in Supplement 3). Patients were followed up for 28 days after randomization or until hospital discharge, whichever occurred first.

Outcomes

The primary outcome was ventilator-free days during the first 28 days, defined as the number of days alive and free from mechanical ventilation for at least 48 consecutive hours.[20] Patients discharged from the hospital before 28 days were considered alive and free from mechanical ventilation at 28 days. Nonsurvivors at day 28 were considered to have no ventilator-free days. More details on the definitions are provided in the eMethods section of Supplement 3.

Prespecified secondary outcomes were all-cause mortality during 28 days, clinical status of patients at day 15 using a 6-point ordinal scale adapted from the World Health Organization R&D Blueprint expert group[21] —(1) not hospitalized, (2) hospitalized, not requiring supplemental oxygen, (3) hospitalized, requiring supplemental oxygen, (4) hospitalized, requiring noninvasive ventilation or nasal high-flow oxygen therapy, (5) hospitalized, requiring invasive mechanical ventilation or ECMO, and (6) death; ICU-free days during the first 28 days; mechanical ventilation duration at 28 days; and Sequential Organ Failure Assessment (SOFA) scores, which range from 0 to 24, with higher scores indicating greater dysfunction, at 48 hours, 72 hours, and 7 days. For post hoc analyses, we evaluated the components of ventilator-free days during the first 28 days, the cumulative proportions of the 6-point ordinal scale at 15 days, and the outcome of discharge from hospital alive within 28 days. For patients who died, the number of ventilator-free days was 0; for patients who were alive, the ventilator-free days were the days they did not require mechanical ventilation.

Statistical Analysis

No reliable data were available at the trial design to allow for an accurate sample size calculation. Therefore, we used data from a multicenter randomized trial of non–COVID-19 ARDS in Brazil[22] for our sample size calculation. We originally estimated a 2-sided α level of .05 and power of 80% to detect a difference of 3 ventilator-free days between groups; assuming a mean of 8 (SD, 9) ventilator-free days in the control group, 290 patients had to be enrolled. Before the first interim analysis, without any study data review and after discussing the protocol with the DSMC, the study steering committee decided to increase the sample size to 350 patients based on necessary adjustments regarding the uncertainty about the normality of the distribution of ventilator-free days. Thus, the original sample size was increased by 15% based on the Pitman asymptotic relative efficiency[23] to preserve study power.

Two preplanned interim analyses for efficacy and safety evaluation after 96 and 234 patients with complete follow-up were programmed. The stopping rule for safety was $P < .01$ and for efficacy $P < .001$ (Haybittle–Peto boundary).[24] There was no adjustment in the final threshold for statistical significance for sequential analysis.

To estimate treatment effects on the primary outcome, a generalized linear model was used with 0-1 inflated beta-binomial distribution, with center as random effect and adjusted for age and the Pao_2:FIo_2 ratio at randomization. The effect size was estimated as mean difference and its respective 95% confidence interval.

The all-cause mortality rate at 28 days was analyzed using a mixed Cox model, with centers as the random effects. The treatment effect on the SOFA score at 48 hours, 72 hours, and 7 days after randomization was analyzed by a linear mixed model with patients as random effects adjusted for the baseline SOFA score. For the clinical status of patients, if the proportional odds assumption was met, a mixed ordinal logistic regression was used. All secondary outcomes were adjusted for age and the Pao_2:FIo_2 ratio to increase statistical power and improve the efficiency of the analysis. Further details on model assumptions and model fit are provided in the eMethods section of Supplement 3. Adverse events are expressed as counts and percentages and compared between groups using the χ^2 test.

All patients were included in the primary analysis. There was no loss to follow-up, and data on the primary outcome, mortality within 28 days, clinical status at day 15, ICU-free days at 28 days, and mechanical ventilation duration were available for all patients. Missing values on individual SOFA components were imputed as normal (eMethods in Supplement 3). We assessed the consistency of the primary analysis results through prespecified sensitivity analyses considering the per-protocol population, patients who received corticosteroids vs patients who did not (as-treated population), patients with confirmed COVID-19, and patients with confirmed or probable COVID-19 (eMethods in Supplement 3).

We performed prespecified subgroup analysis on the primary outcome testing interactions for age (<60 and ≥60 years), Pao_2:FIo_2 ratio (≤100 and >100), symptoms duration at randomization (≤7 and >7 days), Simplified Acute Physiology Score III (SAPS III) (<60 and ≥60), position at randomization (prone or supine), and use of vasopressor at randomization (eMethods in Supplement 3).

Patients were analyzed according to their randomization groups, and no adjustments for multiplicity were performed. Thus, the results of secondary outcomes and subgroup analyses should be interpreted as exploratory. A 2-sided *P* value of less than .05 was considered statistically significant. All analyses were performed using the R software version 4.0.2 (R Core Team).

Early Trial Termination

On June 25, 2020, the DSMC discussed the implications of the results of the dexamethasone group in the RECOVERY (Randomized Evaluation of COVID-19 Therapy) trial,[15] stating that given the study results,[15] it was no longer ethical to continue the trial, which led to the recommendation to stop the trial. This recommendation was accepted by the CoDEX Steering Committee on June 25, 2020 (eMethods in Supplement 3).

Results

Patients

From April 17 to June 23, 2020, 299 patients were randomized. Of the enrolled patients, 151 were randomly assigned to receive dexamethasone and 148 to the control group (Figure 1).

Baseline characteristics were well balanced between groups (Table 1; eTable 1 in Supplement 3), including severity of ARDS and the use of rescue therapies at randomization. Remdesivir was not available in Brazil during the trial period. Only 1 patient received lopinavir-ritonavir treatment. Other therapeutic strategies such as tocilizumab and convalescent plasma were limited and not widely available.

Table 1.

Baseline Characteristics[a]

Characteristic	No. (%)	
	Dexamethasone (n = 151)	Control (n = 148)
Age, mean (SD), y	60.1 (15.8)	62.7 (13.1)
Sex		
Women	61 (40.4)	51 (34.5)
Men	90 (59.6)	97 (65.6)
SAPS III[b]	69.4 (12.6)	71.1 (12.6)
SOFA, median (IQR)[c]	9 (7-10.5)	8 (7-11)
Time since symptom onset, median (IQR), d	9 (7-11)	10 (6-12)
Mechanical ventilation prior to randomization, median (IQR), d	1 (0-2)	1 (0-1)
COVID-19 status[d]		
Positive	144 (95.4)	142 (95.9)
Probable	7 (4.6)	5 (3.4)
Negative	0	1 (0.7)
Comorbidities and risk factors		
Hypertension	91 (60.3)	107 (72.3)
Diabetes	57 (37.8)	69 (46.6)
Obesity	46 (30.5)	35 (23.7)
Heart failure	11 (7.3)	12 (8.1)
Chronic kidney failure	7 (4.6)	9 (6.1)
Current smoker	6 (4.0)	7 (4.7)
Corticosteroids before randomization	7 (4.6)	3 (2)
Moderate or severe ARDS prior to randomization, h		
≤24	136 (90.1)	138 (93.9)
>24-≤48	15 (9.9)	9 (6.1)
Vasopressor use	99 (65.6)	101 (68.2)
Intravenous sedation	150 (99.3)	147 (100)
RASS[e]	−4.8 (0.8)	−4.6 (1.1)
Neuromuscular blockade use[f]	87 (57.6)	94 (63.5)
Prone position	33 (21.8)	33 (22)
Additional medication		
Hydroxychloroquine	36 (23.8)	28 (18.9)
Azithromycin	104 (68.9)	109 (73.6)

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; Fio_2, fraction of inspired oxygen; IQR, interquartile range; Pao_2, partial pressure of arterial oxygen; Pao_2:Fio_2, partial pressure of arterial oxygen to the fraction of inspired oxygen ratio; PEEP, positive end expiratory pressure; RASS, Richmond Agitation–Sedation Scale; SAPS III, Simplified Acute Physiology Score III; SOFA, Sequential Organ Failure Assessment.

SI conversion factor: To convert creatinine from mg/dL to μmol/L multiply by 88.4.

[a]Continuous variables are presented as mean (SD) unless otherwise indicated. The Pao_2 is from the arterial blood gas immediately prior to randomization.

[b]The Simplified Acute Physiology Score III ranges from 0 to 217, with higher scores indicating a higher risk of death. It is calculated from 20 variables at admission of the patient. A score of 70 corresponds to a mortality risk of 70.9% in South America and 46.6% in North America.

[c]Sequential Organ Failure Assessment scores were measured in 6 organ systems (cardiovascular, hematologic, gastrointestinal, renal, pulmonary and neurologic), with each organ scored from 0 to 4, resulting in an aggregated score that ranges from 0 to 24, with higher scores indicating greater dysfunction. An initial SOFA score up to 9 predicts a mortality risk of less than 33%. An unchanged or increasing score in the first 48 hours predicts a mortality rate of 60% when the initial score is 8 to 11.

[d]Patients with initial negative COVID-19 test result had the diagnosis probability evaluated by a blinded committee (eMethods in Supplement 3)

[e]Richmond Agitation–Sedation Scale, which ranges from −5 to 4, with more negative scores indicating deeper sedation and more positive scores indicating increasing agitation, and with 0 representing the appearance of calm and normal alertness. It was calculated at the time of randomization.

[f]Neuromuscular blockade was defined as continuous infusion of neuromuscular blocking agents at the time of randomization.

[g]From the day of randomization.

Interventions

Only 1 patient in the intervention group did not receive any dexamethasone. The rate of dexamethasone use within 10 days was 94.8 per 100 patient-days (eTable 2 in Supplement 3). The median duration of dexamethasone treatment was 10 days (interquartile range [IQR], 6-10 days). In the standard care group, 52 patients (35.1%) received at least 1 dose of corticosteroids, of whom 38 (73.1%) had other established clinical indications for corticosteroid use. The use of corticosteroids in 14 patients (9.4%) was considered a protocol deviation, and the rate of corticosteroid use within 10 days was 16.5 per 100 patient-days (eTable 3 in Supplement 3).

Primary Outcome

The mean number of days alive and free from mechanical ventilation during the first 28 days was significantly higher in the dexamethasone group than in the standard care group (6.6; 95% CI, 5.0-8.2 days vs 4.0; 95% CI, 2.9-5.4 days; difference, 2.26; 95% CI, 0.2-4.38; $P = .04$) (Table 2; eFigure 1 in Supplement 3). The cumulative frequency of ventilator-free days according to study group is shown in Figure 2.

Table 2.

Study Outcomes

Outcomes	Mean (95% CI)		Effect statistic	Between-group effect			
				Adjusted[a]		Unadjusted	
	Dexamethasone (n = 151)	Standard care (n = 148)		Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Primary outcome							
Days alive and ventilator free at 28 d							
Mean (95% CI)	6.6 (5.0 to 8.2)	4.0 (2.9 to 5.4)	MD	2.26 (0.2 to 4.38)[b]	.04	2.55 (0.46 to 4.6)	.02
Median (IQR)	0 (0 to 17)	0 (0 to 3)					
Secondary outcomes							
6-Point ordinal scale at day 15, median (IQR)[c]	5 (3 to 6)	5 (5 to 6)	OR	0.66 (0.43 to 1.03)	.07	0.62 (0.41 to 0.94)	.03
28-Day results							
All-cause mortality No. (%)	85 (56.3)	91 (61.5)	HR	0.97 (0.72 to 1.31)	.85	0.86 (0.64 to 1.15)	.31
ICU free, d	2.1 (1.0 to 4.5)	2.0 (0.8 to 4.2)	MD	0.28 (−0.49 to 1.02)	.50	0.14 (−0.92 to 1.27)	.78
MV duration, d	12.5 (11.2 to 13.8)	13.9 (12.7 to 15.1)	MD	−1.54 (−3.24 to 0.12)	.11	−1.46 (−3.10 to 0.57)	.18
SOFA score[d]							
48 h	8.1 (7.6 to 8.6)	8.4 (7.8 to 8.9)	MD	−0.11 (−0.86 to 0.63)	.76	−0.24 (−1 to 0.51)	.53
No. of patients	151	147					
72 h	7.7 (7.2 to 8.3)	8.3 (7.8 to 8.9)	MD	−0.38 (−1.13 to 0.37)	.32	−0.6 (−1.37 to 0.16)	.12
No. of patients	145	144					
7 d	6.1 (5.5 to 6.7)	7.5 (6.9 to 8.1)	MD	−1.16 (−1.94 to −0.38)	.004	−1.38 (−2.21 to −0.55)	.001
No. of patients	127	120					

Abbreviations: ICU, intensive care unit; HR, hazard ratio; IQR interquartile range, MD, mean difference; MV, mechanical ventilation; OR, odds ratio; SOFA, Sequential Organ Failure Assessment.

[a]All models are adjusted for age and baseline at Pao_2:Fio_2 ratio with random intercept by site.

[b]Average marginal effect from generalized additive model with 0-inflated beta-binomial distribution adjusted for age and baseline Pao_2:Fio_2 ratio with random intercept by site. For the primary model coefficients see eTable 5 in Supplement 2.

[c]See the Methods section for the definitions of the 6-point ordinal scale. The distribution of values among the categories in the dexamethasone and control groups was 6 (35.8% vs 43.9%), 5 (31.8% vs 36.5%), 4 (4.6% vs 2.7%), 3 (16.6% vs 11.5%), 2 (0% vs 0%), and 1 (11.3% vs 5.4%).

[d]Measured in 6 organ systems (cardiovascular, hematologic, gastrointestinal, renal, pulmonary and neurologic), with each organ scored from 0 to 4, resulting in an aggregated score that ranges from 0 to 24, with higher scores indicating greater dysfunction. An initial SOFA score up to 9 predicts a mortality risk of less than 33%. An unchanged or increasing score in the first 48 hours predicts a mortality rate of 60% when the initial score is 8 to 11. Missing values on individual SOFA components were imputed as normal (eMethods in Supplement 2).

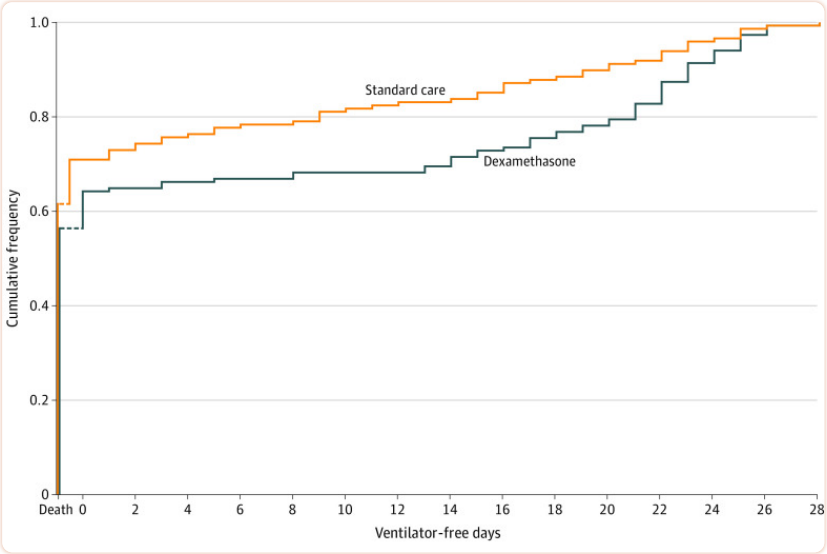

Figure 2.

Ventilator-Free Days at 28 Days

The dashed lines represent patients who died (assigned 0 ventilator-free days), and solid lines show the cumulative frequency of patients who were receiving mechanical ventilation all 28 days (at the 0 ventilator-free days tick mark) and then the cumulative frequency of patients who no longer required the ventilator for an increasing number of days.

Secondary Outcomes and Adverse Events

There was no significant difference in all-cause mortality at 28 days (56.3% in the dexamethasone group vs 61.5% the standard care group; hazard ratio, 0.97; 95% CI, 0.72 to 1.31; $P = .85$), in the 6-point ordinal scale at day 15 (median, 5; IQR, 3-6 for the dexamethasone group vs median, 5; IQR, 5-6 for standard care group; odds ratio [OR], 0.66; 95% CI, 0.39 to 1.13; $P = .07$), ICU-free days at 28 days (mean, 2.1; 95% CI, 1.0 to 4.5 days for the dexamethasone group vs mean, 2.0; 95% CI, 0.8 to 4.2 days for the standard care group; difference, 0.28; 95% CI, −0.49 to 1.02; $P = .50$), and mechanical ventilation duration (12.5; 95% CI, 11.2 to 13.8 days for the dexamethasone group vs 13.9, 95% CI, 12.7 to 15.1 days for the standard care group; difference, −1.54; 95% CI, −3.24 to −0.12; $P = .11$). The mean SOFA score at 7 days was significantly lower in the treatment group (6.1; 95% CI, 5.5 to 6.7 for dexamethasone vs 7.5; 95% CI, 6.9 to 8.1 for standard care; difference, −1.16; 95% CI, −1.94 to −0.38; $P = .004$) (Table 2).

Both groups had a comparable need for insulin use for hyperglycemia: 47 patients (31.1%) in the dexamethasone group vs 42 (28.4%) in the standard care group. The number of new diagnoses of infection until day 28 was 33 (21.9%) vs 43 (29.1%). Twelve patients (7.9%) in the dexamethasone group had bacteremia vs 14 (9.5%) in the standard care group. Five patients (3.3%) had serious adverse events vs 9 (6.1%) (Table 3; eTable 4 in Supplement 3).

Table 3.

Adverse Events

	No. (%) of patients		Absolute difference (95% CI)
	Dexamethasone (n = 151)	Standard care (n = 148)	
Serious adverse events[a]	5 (3.3)	9 (6.1)	2.8 (−2.7 to 8.2)
New diagnosis of infection until day 28[b]	33 (21.9)	43 (29.1)	7.2 (−3.3 to 17.7)
Ventilator-associated pneumonia	19 (12.6)	29 (19.6)	7.0 (−2.0 to 16.0)
Catheter-related bloodstream infection	10 (6.6)	8 (5.4)	−1.2 (−7.3 to 4.8)
Catheter-associated urinary tract infections	1 (0.7)	0	
Other	6 (4)	7 (4.7)	0.7 (−2.5 to 4.2)
Bacteremia[c]	12 (7.9)	14 (9.5)	1.5 (−5.5 to 8.6)
Insulin use for hyperglycemia[d]	47 (31.1)	42 (28.4)	−2.7 (−13.8 to 8.3)

[a]Adverse events in the study groups. In the dexamethason group, 1 event occurred for each of the following outcomes: acute myocardial infarction, deep vein thrombosis, gastrointestinal perforation, unspecified hyperglycemia, and pneumothorax. Except for 2 myocardial infarctions in the standard care group, 1 event occurred for the following outcomes: bronchospasm, cardiogenic shock, deep vein thrombosis, diabetic ketoacidosis, unspecified hyperglycemia, ischemic hepatitis, nephropathy in transplanted kidney, pneumothorax, and pulmonary embolism.

[b]All investigator-reported infections were adjudicated by an infectious disease specialist using unidentified patients records, microbiological data, and radiological images. Seven patients had 2 episodes each.

[c]Comprises all bloodstream infections plus other infections with bacteremia.

[d]Data on insulin use for hyperglycemia were collected daily during ICU stay until day 14.

Subgroup and Exploratory Analyses

In subgroup analyses, tests for interaction were not statistically significant for subgroups defined by age (P = .21), Pao_2:FIo_2 ratio (P = .73), SAPS III (P = .75), time since symptom onset (P = .12), position at randomization (P = .89), and vasopressor use at randomization (P = .81) (eFigure 2 in Supplement 3).

The post hoc analyses showed no significant difference of the intervention in the components of the primary outcome or in the outcome of discharged alive within 28 days (eTable 6 in Supplement 3). Patients in the dexamethasone group had significantly lower cumulative probability of having died or being mechanically ventilated at day 15 (categories 5-6 on the 6-point scale) than the standard care group (67.5% vs 80.4%; OR, 0.46; 95% CI, 0.26 to 0.81; P = .01) (eTable 6 and eFigure 3 in Supplement 3). In the sensitivity analyses for

the primary outcome of ventilator-free days, the treatment effect was not significantly different in the as-treated analysis. The mean number of ventilator-free days was 5.8 (95% CI, 4.6 to 7.3) among 203 patients in the dexamethasone group vs 4.1 (95% CI, 2.6 to 5.5) among 96 patients in the standard care group, for a mean difference of 2.38 (95% CI, −0.6 to 3.32; *P* = .16). In the per-protocol analysis, the mean number of ventilator-free days among dexamethasone group was 6.4 (95% CI, 5.1 to 8.1) among 125 patients vs 4.1 (95% CI, 2.6 to 5.5) among 96 patients in the standard care group for a difference of 2.36 (95% CI, −0.15 to 4.56; *P* = .06). The main results remained statistically significant among patients with confirmed COVID-19 in the dexamethasone group, which had a mean number of ventilator-free days of 6.8 (95% CI, 5.4 to 8.4) among 144 patients vs 3.9 (95% CI, 2.7 to 5.1) among 142 patients in the standard care group for a difference of 2.7 (95% CI, 0.8 to 4.74; *P* = .01). Among the patients with confirmed or probable COVID-19, the mean number of ventilator-free days was 6.6 (95% CI, 5.3 to 8.2) among 151 patients vs 4.1 (95% CI, 2.9 to 5.2) among 147 patients for a difference of 2.38 (95% CI, 0.48 to 4.33; *P* = .02) (eTable 7 in Supplement 3).

Discussion

In this randomized clinical trial involving 299 adults with moderate or severe ARDS due to COVID-19, dexamethasone plus standard care compared with standard care alone significantly increased the number of days alive and free of mechanical ventilation during the first 28 days. Dexamethasone was not associated with increased risk of adverse events in this population of critically ill COVID-19 patients.[15]

This trial included only patients with COVID-19 and moderate or severe ARDS and provided laboratory, physiological, and adverse events data on the use of corticosteroids in this population. The ventilator-free days criterion was chosen as the primary outcome because it comprises both mortality and ventilation duration in surviving patients. The number of days alive and free from mechanical ventilation at 28 days was significantly lower than reported in other trials of non–COVID-19 ARDS,[10,11,25] but consistent with COVID-19 ARDS studies, confirming the disease severity.[26] The difference between groups of 2.26 days was lower than the effect size of 3 days used in the sample size calculation. This reduction is relevant in the context of a pandemic, in which an inexpensive, safe, and widely available intervention like dexamethasone increases even modestly the number of ventilator-free days and may reduce the risk of ventilatory complications, ICU length of stay, and burden to the health care system.

Mortality rates were high and not significantly different between groups, in contrast with the RECOVERY trial of dexamethasone in patients hospitalized for COVID-19[15] and a trial of dexamethasone in patients with non-COVID-19 ARDS.[11] The high mortality rate might be explained by several factors. The patients had a high risk of death as shown by the low mean Pao_2:Fio_2 ratio and mean SAPS III score of 70, which represents a mortality risk of 70.9% in South America.[27,28] In a previous randomized clinical trial, moderate to severe ARDS not caused by COVID-19 had an elevated mortality rate in Brazil of 52%,[22] and recent data collected by Brazilian Association of Critical Care demonstrated mortality rates of 66% to 70% for ventilated patients with COVID-19 in Brazilian ICUs.[29] This may be explained by the pandemic and its burden to the health care system, especially in a country with limited resources like Brazil. However, even in high-income countries the mortality rate in ventilated patients with COVID-19 might range from 54% to 88%.[30,31,32] This mortality rate may be similar to that of other low and middle-income countries and is important to consider when translating the scientific evidence to clinical practice. In this sense, the results of this trial expand those of the RECOVERY trial[15] by showing that corticosteroids were effective even when the baseline mortality rate was high.

The dexamethasone dose was chosen based on a previous[11] trial showing the benefit of dexamethasone to patients with non–COVID-19 ARDS. Previous data suggest that high doses of corticosteroids (the equivalent of 30 mg/d of dexamethasone) in viral pneumonia may be associated with unfavorable outcomes.[33] However, there are no currently available data from patients with COVID-19 to determine if higher doses are harmful.

In the present study, 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 non-COVID-19 ARDS.[10,11,19]

This trial has several strengths. Bias was controlled by ensuring allocation concealment, all patients were analyzed according to their randomization group, and follow-up was complete. Also, adverse events data regarding corticosteroid use among patients with COVID-19 were provided, along with detailed data on ventilatory parameters, ARDS treatment, and laboratory and physiological variables.

Limitations

This study has several limitations. First, it was an open-label trial due to time constraints of producing placebo in a pandemic scenario with an urgent need for reliable and randomized data. Second, 35% of the patients in the control group received corticosteroids during the study period, possibly related to the open-label design, the disease severity of the patients, and other diverse indications for corticosteroid use in critical care.[19] However, the use of corticosteroids in the control group would have biased the results toward the null, and the study identified a benefit of the intervention on the primary outcome. Third, the open-label design and investigator-reported data on adverse events and infections may have led to bias in the description of these events. Fourth, the trial was underpowered for important secondary outcomes like mortality and the study was interrupted before the original sample size was obtained due to external evidence of benefit, and the obtained sample size was limited to demonstrate benefits in secondary outcomes.

Conclusions

In patients with COVID-19 and moderate or severe ARDS, use of intravenous dexamethasone plus standard care, compared with standard care alone, resulted in a statistically significant increase increase in the number of ventilator-free days (days alive and free of mechanical ventilation) over 28 days.

Notes

Supplement 1.

Trial Protocol and Summary of Changes

Click here for additional data file.(1.4M, pdf)

Supplement 2.

Statistical Analysis Plan

Click here for additional data file.(321K, pdf)

Supplement 3.

eMethods

eReferences

eTable 1. Additional data on baseline characteristics

eTable 2. Dexamethasone use in the dexamethasone plus standard of care group

eTable 3. Corticosteroids use in the standard of care group

eTable 4. New diagnosis of infection and adverse events at 28 days

eTable 5. Primary model coefficients

eTable 6. Exploratory study outcomes

eTable 7. Sensitivity analysis for the primary outcome

eFigure 1. Distribution of ventilator-free days according to study group

eFigure 2. Subgroup analysis

eFigure 3. Ordinal-scale results distribution over time

Click here for additional data file.(952K, pdf)

Supplement 4.

Data Sharing Statement

Click here for additional data file.(8.6K, pdf)

Notes

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