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Effects of two different dexamethasone dosing regimens on ventilator-free days and long-term mortality in COVID-19 patients with moderate-to-severe ARDS: the REMED randomized clinical trial

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Abstract

Background Dexamethasone 6 mg in patients with severe COVID-19 has been shown to decrease mortality and morbidity. The effects of higher doses of corticosteroid, that would further increase anti-inflammatory effects, are uncertain. The objective of our study was to assess the effect of 20 mg dexamethasone vs. 6 mg dexamethasone intravenously in patients with moderate-to-severe acute respiratory distress syndrome (ARDS) and COVID-19.

Methods In a multicenter, open-label, randomized trial conducted in nine hospitals in the Czech Republic, we randomized adult patients with ARDS and COVID-19 requiring high-flow oxygen, noninvasive or invasive mechanical ventilation to receive either intravenous high-dose dexamethasone (20 mg/day on days 1–5, 10 mg/day on days 6–10) or standard-dose dexamethasone (6 mg/d, days 1–10). The primary outcome was 28-day ventilator-free days. The five secondary outcomes were 60-day mortality, C-reactive protein dynamics, 14-day WHO (World Health Organization) Clinical Progression Scale score, adverse events and 90-day Barthel index. The long-term outcomes were 180- and 360-day mortality and the Barthel index. The planned sample size was 300, with interim analysis after enrollment of 150 patients.

Results The trial was stopped due to a lack of recruitment, and the follow-up was completed in February 2023. Among 234 randomized patients of 300 planned patients, the primary outcome was available for 224 patients (110 high-dose and 114 standard-dose dexamethasone; median [interquartile range (IQR)] age, 59.0 [48.5–66.0] years; 130 [58.0%] were receiving noninvasive or invasive mechanical ventilation at baseline). The mean number of 28-day ventilator-free days was 8.9 (± 11.5) days for high-dose dexamethasone and 8.0 (± 10.7) days for standard-dose

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dexamethasone, with an absolute difference of + 0.81 days (95% CI − 2.12–3.73 days). None of the prespecified secondary outcomes, including adverse events, differed between the groups.

Conclusions Despite not reaching its prespecified enrollment, there was no signal to either benefit or harm high-dose dexamethasone over standard-dose dexamethasone in patients with COVID-19 and moderate-to-severe ARDS.

Trial registration Trial registration: ClinicalTrials.gov Identifier: NCT04663555. Registered 10 December 2020, https://clinicaltrials.gov/study/NCT04663555?term=NCT04663555&rank=1 and EudraCT: 2020–005887-70.

Keywords COVID-19, ARDS, Dexamethasone, Randomized clinical trial, Ventilator-free days, Long-term outcomes

Background

Administration of dexamethasone 6 mg/day to patients with COVID-19 pneumonia in need of oxygen therapy or noninvasive or mechanical ventilation improved mortality in the RECOVERY trial [1]. However, this dose was reduced, especially in patients with more severe disease [2]. As shown before the COVID-19 pandemic in patients with acute respiratory distress syndrome (ARDS), the administration of higher doses of dexamethasone reduced mortality [3]. Therefore, several trials testing higher doses of corticosteroids in patients with COVID-19 have been conducted [4–10]. Although no significant difference in mortality was found, two trials showed that the administration of high-dose dexamethasone may be associated with reduced morbidity [6, 10]. Additionally, a prospective preplanned meta-analysis of eight trials concluded that higher doses of corticosteroids probably increase the number of days without invasive mechanical ventilation or circulatory support while having little or no effect on mortality [11]. Finally, a Cochrane systematic review of 10 randomized controlled trials on COVID-19 revealed that systemic corticosteroids probably slightly reduce short all-cause mortality (up to 30 days) but are very uncertain about the effect on all-cause mortality (up to 120 days). Furthermore, the probability of clinical improvement (discharged alive on day 28) may slightly increase, while the risk of clinical worsening (new need for invasive mechanical ventilation or death) may slightly decrease. Four randomized controlled trials (RCTs) comparing high-dose dexamethasone (≥ 12 mg) to low-dose dexamethasone (6–8 mg) were also assessed, and low-certainty evidence that high-dose dexamethasone may reduce all-cause mortality (up to 30 days) was reported, but the evidence was very uncertain about the effect of high-dose dexamethasone on all-cause mortality (up to 120 days) [12]. Here, we add to the literature by reporting the results of the REMED trial, which compared the administration of high-dose dexamethasone vs. standard-dose dexamethasone to COVID-19 patients admitted to the intensive care unit (ICU) with moderate-to-severe ARDS with respiratory support requirements exceeding facemask oxygen. Long-term (1 year) mortality and morbidity are reported as crucial aspects of our study.

Methods

Trial design

This trial was an investigator-initiated, prospective, stratified, open-label, multicenter, randomized controlled trial performed in nine centers in the Czech Republic. The trial protocol and consequent amendments were approved by the State Institute for Drug Control and Multicentre Ethics Committee of University Hospital Brno and institutionally at each trial site. The REMED trial was registered prior to the beginning of the trial and first patient enrollment. The trial protocol was published in the form of a structured summary [13] and the full version [14] (eSupplement 1) prior to premature termination of the study. The statistical analysis plan (SAP) was approved by the Steering Committee before the first patient was enrolled (eSupplement 1). The trial was overseen by an independent external Data and Safety Monitoring Committee (DSMC) who reviewed a preplanned interim analysis.

The decision-making capacity of the patients was assessed individually by investigators using the Glasgow Coma Scale (GCS), a simple tool used worldwide [15]. Fully conscious and oriented patients were asked to provide written prospective informed consent. For patients lacking capacity, a deferred consent policy was applied. Next-of-kin were informed about the patient's enrollment and the nature of the study and signed a confirmation of this effect. After patients regained capacity, they were approached to provide consent to continue participation in the trial. The full details are listed in eSupplement 1.

Patients

Patients were screened and randomized between February 12, 2021, and March 9, 2022. One center (General University Hospital in Prague) enrolled only one patient who was subsequently transferred to another study center and analyzed within this cohort.

Eligible patients were (1) ≥ 18 years, (2) admitted to the ICU within the last 24 h, (3) had confirmed COVID-19 infection, (4) required intubation/mechanical ventilation or high-flow nasal cannula (HFNC) therapy, and (5) presented with moderate or severe ARDS based on

the Berlin criteria (partial pressure of arterial blood oxygen to fraction of inspired oxygen (PaO_2:FIO_2) ratio ≤ 200 mmHg) [16]. When HFNC therapy was used, the ratio of PaO_2 to FIO_2 applied by HFNC therapy was used as a pragmatic surrogate.

The exclusion criteria were (1) known hypersensitivity or allergy to dexamethasone, (2) ARDS fulfilled for more than 14 days prior to enrollment, (3) pregnancy or breastfeeding, (4) unwillingness to comply with contraception for at least one week after the last dexamethasone dose, (5) expected death in the next 24 h, (6) ceiling of treatment decision in place, (7) any contraindication of corticosteroids, (8) current hematological or generalized solid malignancy, (9) cardiac arrest before ICU admission, (10) participation in another interventional trial in the last 30 days, or (11) a history of endogenous or exogenous immunosuppression. Patients who had received dexamethasone treatment exceeding 8 mg per day (or the equivalent dose of another corticosteroid) during the present hospital stay due to COVID-19 for more than one day were excluded. Patients who received dexamethasone ≤ 8 mg per day (or an equivalent dose of another corticosteroid) for > 5 days before enrollment were also excluded. After the regulatory authority was granted specific therapies related to COVID-19, such as interleukin-6 receptor antagonists or Janus kinase inhibitors, such patients could be admitted to the trial. The full details are listed in the trial protocol (eSupplement 1).

Procedures

Patients were randomized at a 1:1 ratio to one of the two treatment arms. The randomization was performed through the electronic case report form (eCRF) using a stratified permuted block randomization method (Fig. 1). The allocation sequences were prepared by a statistician independent of the study team. Allocation to the treatment arm of an individual patient was not available to the investigators before completion of the whole randomization process. The following four stratification factors were applied: age (< 65 or ≥ 65 years), Charlson Comorbidity Index (< 3 or ≥ 3) [17], C-reactive protein (CRP) (< 150 or ≥ 150 mg/L) and trial center. Randomization through the eCRFs was possible every 24 h. The trial was open label to both participants and study staff. A blinded preplanned statistical analysis was performed according to the SAP (eSupplement 1).

Interventions

Patients in the intervention group received once-daily intravenous dexamethasone 20 mg/day over Days 1–5

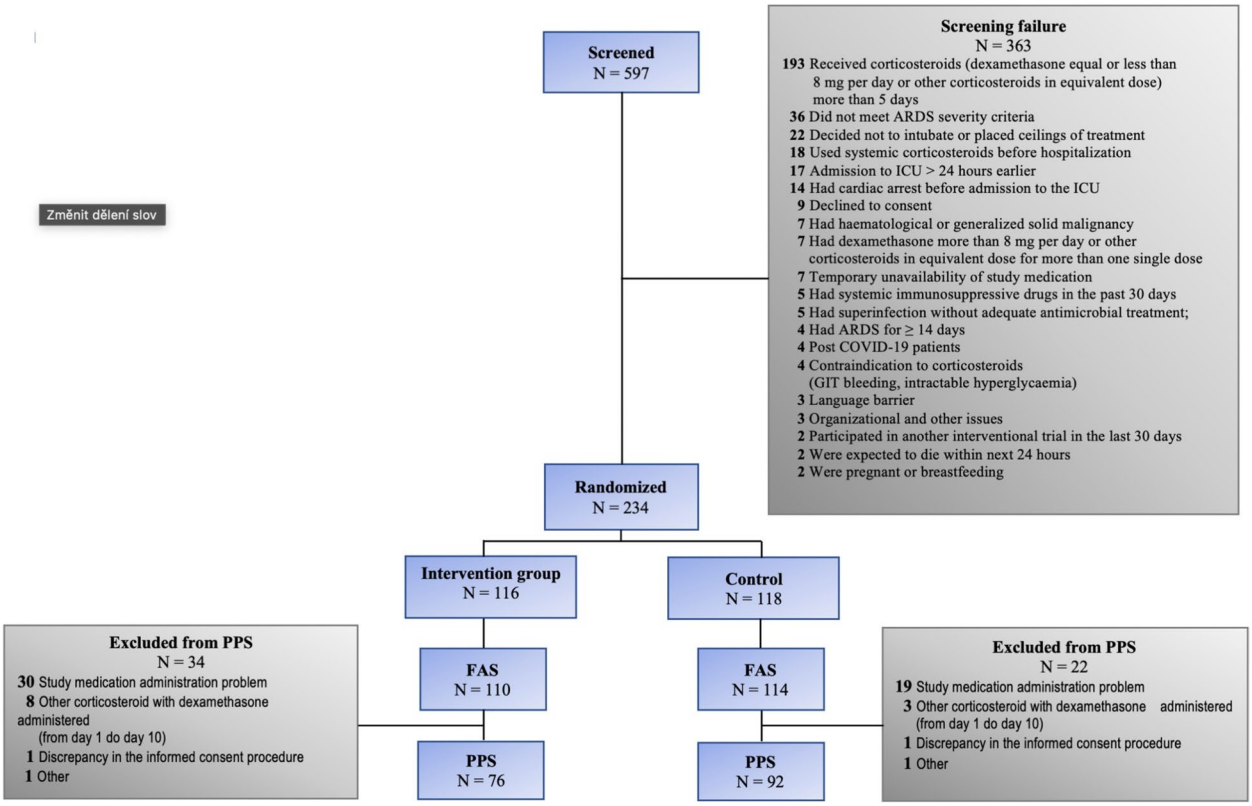

Fig. 1 Patient screening and randomization flowchart in the REMED trial

and then 10 mg/d over Days 6–10. Patients in the control group received once-daily intravenous dexamethasone (6 mg/day) for 10 days. All other interventions were at the discretion of the treating clinicians, except for the restricted concomitant medication listed in the trial protocol (eSupplement 1).

Data collection and monitoring

Patient data were recorded in the eCRF over days 1–28 (or until ICU discharge) and at 60, 90, 180 and 360 days of follow-up. Follow-up data were obtained either at an outpatient visit or by a structured phone call performed by a study nurse. Trial data and processes were monitored using a preplanned monitoring plan at each center by independent monitors (eSupplement 1). Adverse effects were recorded in the eCRFs and reported to the sponsor (eSupplement 1).

Outcomes

The primary outcome of the study was the number of ventilator-free days (VFDs) on day 28 after randomization [18]. When appraising VFDs, only invasive ventilation was considered. The outcome definitions are provided in eSupplement 1. The secondary outcomes were 60-day all-cause mortality, CRP dynamics from days 1 to 14 (relative increase or decrease), the World Health Organization Clinical Progression Scale (WHO-CPS) score on day 14 [19], adverse events related to the use of corticosteroids until day 28 or hospital discharge, and independence at 90 days after randomization, as assessed by the Barthel index (BI) [20]. Exploratory objectives were long-term effects at Days 180 and 360.

Predefined subgroup analysis

A preplanned subgroup analysis was performed regarding the primary outcome variable in the following subgroups:

- Age (age < 65 vs. ≥ 65).
- Sex (male vs. female).
- BMI (< 30 vs. ≥ 30).
- Comorbidities (Charlson Comorbidity Index < 3 vs. ≥ 3).
- P/F ratio (< 100 vs ≥ 100) The P/F ratio was evaluated as PaO2 [mmHg]/FiO2 = PaO2 [kPa]*7.50/FiO2 [%]*100.
- Length of dexamethasone treatment before enrollment (≤ days vs. 3–5 days).
- ECMO procedure during the study (yes vs. no).
- Corticosteroids other than the study medication administered from day 11 to day 28 (yes vs. no).
- CRP at baseline (< 150 mg/L vs. ≥ 150 mg/L).
- Trial center.

No adjustments of p values due to multiplicity were planned.

Sample size

The sample size was calculated to detect a difference of 3 VFDs at 28 days (primary efficacy endpoint) between the two treatment arms with a two-sided type I error of 0.05 and a power of 80%. Based on data from a multicenter randomized controlled trial in COVID-19 ARDS patients in Brazil [21] and a multicente observational study from French and Belgian ICUs in COVID-19 patients with moderate-to-severe ARDS [22], investigators assumed a standard deviation of VFDs at 28 days of 9 days. Under these assumptions, the required sample size was 150 patients per treatment arm (300 patients in total, including an expected drop-out rate of 5%).

Statistical analysis

Statistical analyses were performed according to the SAP. All patients with available data for analysis of the primary outcome were analyzed. A sensitivity analysis of the primary outcome was performed on a per-protocol subset excluding patients with at least one major protocol violation. There was no significant difference in the results using the different analysis sets. In the primary outcome analysis, the number of VFDs within the 28-day period was analyzed using a linear model adjusted for stratification variables. To control the overall level of type I error, a P value of 0.01 for interim analysis and 0.04 for the final analysis were applied.

The primary outcome was analyzed in prespecified subgroups. Mortality was summarized as the percentage of nonsurvivors in each treatment group. Treatment groups were compared by Fisher's exact test and by logistic regression adjusted for age, site, invasive mechanical ventilation at baseline and P:F ratio. A Kaplan–Meier analysis was also performed. Comparisons between groups in continuous parameters were performed using the Wilcoxon test, and categorical parameters were compared by Fisher's exact test. All analyses were performed using SAS software, version 9.4.

Study termination

Due to a fall-off in recruitment in the spring of 2022, the DSMB recommended an unplanned second interim analysis. Consequently, patient enrollment was prematurely stopped on March 9, 2022 due to futility in the primary outcome. The original sample size (study protocol) was calculated to detect a difference of 3 VFDs at 28 days between the two treatment arms with a two-sided type I error of 0.05 and a power of 80%. With a total of 234 patients enrolled and 222 patients included in the analysis of the primary endpoint, the power of the test to

detect the expected difference between treatment arms was 69.6%.

Results

Patients

Between February 12, 2021 and March 9, 2022, 597 patients were screened and 234 patients were randomized. Patients were allocated to high-dose (116 patients) or standard-dose (118 patients) groups using stratified randomization. In the full analysis set, 224 patients (median [interquartile range (IQR)] age, 59.0 [48.5–66.0] years; 147 [65.6%] men) were included, of whom 114 were enrolled in the intervention group and 110 in the standard-dose group (Fig. 1). The 360-day follow-up was completed on February 23, 2023. Patient demographic characteristics were similar (Table 1). Unfortunately, data regarding vaccination status were not collected.

Treatment and interventions

Corticosteroids were administered before study inclusion to 30 patients allocated to high-dose dexamethasone and to 33 patients allocated to standard-dose dexamethasone. The respiratory support required at baseline was similar in both groups, as was the use of antiviral agents and anti-inflammatory agents (Table 1). Among the 234 randomized patients, the primary endpoint was evaluable in 110 (94.8%) patients in the high-dose dexamethasone group and 114 (96.6%) in the standard-dose group.

Primary outcome

The mean number of VFDs at 28 days after randomization was 8.9 days (standard deviation (SD), 11.50 days) in the high-dose dexamethasone group and 8.0 days (SD, 10.65 days) in the standard-dose group. The difference between groups adjusted for stratification factors was 0.81 days [95% confidence interval (CI) − 2.12–3.73 days], P = 0.5872 (Table 2 and Fig. 2). Comparing the primary outcome with the predefined per-protocol subgroup analysis, there were no significant differences except for the administration of corticosteroids after the intervention period. We observed a significant correlation between VFDs and the administration of corticosteroids other than interventional medication from days 11 to 28, with an adjusted mean difference of 5.55 (95% CI − 10.98–22.9) (Fig. 3).

Secondary outcomes

WHO clinical progression scale at 14 days

At 14 days, the median WHO-CPS was 7.0 (IQR, 5.0–8.0) in the high-dose dexamethasone group and 7.0 (IQR, 5.0–8.0) in the standard-dose dexamethasone group (Table 2).

Mortality from any cause at 60 days after randomization

At 60 days, 49 (44.5%) of 110 patients in the high-dose dexamethasone group and 45 (39.5%) of 114 patients in the standard-dose dexamethasone group died (Table 2).

Independence at 90 days after randomization

At 90 days, the median score for independence assessed by the Barthel Index was 100 (IQR, 95–100) in the high-dose dexamethasone group and 100 (IQR, 90–100) in the standard-dose dexamethasone group (Table 2).

Changes in inflammatory marker (CRP) levels from day 1 to day 14

From day 1 to day 14, the median CRP decrease was − 11.6 (IQR, − 84.9–127.0) mg/l in the high-dose dexamethasone group and − 43.7 (IQR, − 113.4–44.1) mg/dl in the standard-dose dexamethasone group (p = 0.079) (Table 2).

Adverse events

Overall, 52 (44.8%) of 110 patients in the high-dose group and 48 (40.7%) of 114 patients in the standard-dose group experienced at least one serious adverse event (SAE). Four (3.4%) patients in the high-dose group and one (0.8%) in the standard-dose group suffered pulmonary embolism. Septic shock was reported in 11 patients (9.5%) in the high-dose group and five (4.2%) in the standard-dose dexamethasone group. Other SAEs related to corticosteroids are listed in Table 2.

Long-term outcomes

All-cause mortality at 180 and 360 days

At 180 days, 49 (44.5%) of 110 patients in the high-dose group died, while 49 (43.0%) of 114 patients in the standard-dose group died (Table 2). At 360 days, 51 out of 110 patients (46.4%) died in the high-dose group, compared with 49 (43.0%) of 114 patients in the standard-dose group (Table 2).

Independence at 180 and 360 days

At 180 days, the median score for independence assessed by the Barthel Index was 100 (IQR, 100–100) in the high-dose group and 100 (IQR, 100–100) in the standard-dose dexamethasone group (Table 2). At 360 days, the median independence score was 100 (IQR, 95–100) in the high-dose group and 100 (IQR, 90–100) in the standard-dose group (Table 2).

Discussion

Although terminated prematurely due to a fall-off in the recruitment of critically ill patients with COVID-19, the REMED randomized clinical trial revealed no significant benefit of high-dose dexamethasone on 28-day VFDs in

Table 1 Demographic and baseline characteristics

	High dose (*N* = 110)	**Standard dose (*N* = 114)**
Age, median (IQR), years	59 (49–66)	59 (48–66)
Sex, *n* (%)		
Male	77 (70.0)	70 (61.4)
Female	33 (30.0)	44 (38.6)
Weight, median (IQR), kg	100 (90–115)	97 (89–120)
BMI, median (IQR), kg/m^2	33.27 (28.41–37.18)	33.13 (28.96–37.18)
Charlson Comorbidity Index, median (IQR)	2.0 (1.0–3.0)	2.0 (0.0–3.0)
Coexisting conditions, *n* (%)		
Diabetes	29 (26.4%)	27 (23.7%)
Hypertension	69 (62.7%)	66 (57.9%)
Chronic kidney disease	3 (2.7%)	3 (2.6%)
Ischemic heart disease	8 (7.3%)	6 (5.3%)
Congestive heart failure	6 (5.5%)	3 (2.6%)
CRP, median (IQR), mg/l	130.0 (87.3–211.0)	143.5 (95.0–212.0)
Systolic BP, median (IQR), mmHg	125 (115–138)	128 (114–138)
Heart rate, median (IQR), bpm	83 (70–93)	80 (68–91)
Respiratory rate, median (IQR), rpm	20 (16–25)	20 (16–25)
FiO_2, median (IQR)	0.75 (0.60–0.90)	0.70 (0.55–0.90)
PaO_2, median (IQR), mmHg	69.0 (57.5–82.5)	71.3 (58.2–86.3)
Type of respiratory support, n (%)		
High-flow nasal cannula (HFNC)	49 (44.5)	44 (38.6)
Flow rate, median (IQR), L/min	60.0 (50.0–60.0)	60.0 (50.0–60.0)
Invasive ventilation (IPPV)	55 (50.0)	66 (57.9)
Noninvasive ventilatory support (NIVS)	6 (5.5)	4 (3.5)
Therapies in use at randomization, *n* (%)		
Beta blockade	31 (28.2)	20 (17.5)
Statin	24 (21.8)	26 (22.8)
Metformin	22 (20.0)	16 (14.0)
Angiotensin II receptor blocker	16 (14.5)	23 (20.2)
ACE inhibitor	39 (35.5)	34 (29.8)
Therapies in use related to COVID-19, *n* (%)		
Corticosteroids	30 (27.3)	33 (28.9)
Antiviral agents	12 (10.9)	14 (12.3)
Remdesivir	12 (10.9)	11 (9.6)
Anti-SARS-CoV-2 MAbs	1 (0.9)	3 (2.6)
IL-6 receptor antagonists	1 (0.9)	5 (4.4)
Janus kinase inhibitors	1 (0.9)	1 (0.9)
Other anti-inflammatory agents	3 (2.7)	2 (1.8)

IQR, Interquartile range; BMI, body mass index; CRP, c-reactive protein; BP, blood pressure; FiO_2, fraction of inspired oxygen; HFNC, high-flow nasal cannula; NIVS, noninvasive ventilatory support; ACE, angiotensin-converting enzyme, anti-SARS-CoV-2 MABs, monoclonal antibodies against severe acute respiratory syndrome coronavirus 2; IL-6, interleukin-6

adult patients with moderate-to-severe ARDS compared to standard-dose dexamethasone.

Regarding secondary and long-term outcomes, no significant differences were observed between the groups. Subgroup analysis also revealed no heterogeneity in the treatment effect. The frequency of SAEs was comparable among the groups. The REMED trial had several strengths, including stratified randomization, a multicenter setting, a strict prespecified protocol and long-term follow-up with reporting of 360-day outcomes. The protocol was accepted for publication before inclusion of the first patient.

The results of the REMED trial are consistent with those of other trials comparing high-dose to

Table 2 Primary, secondary and long-term outcomes

Outcome	High dose (*N* = 110)	Standard dose (*N* = 114)	p-value [a]	Adjusted p-value [b]
Primary outcome				
VFD on Day 28, mean (SD)	8.9 (11.50)	8.0 (10.65)	0.5913	0.5872
Death or on ventilator on Day 28, *n* (%)	65 (59.1)	69 (60.5)		
Ventilator free on Day 28, *n* (%)	45 (40.9)	45 (39.5)		
Secondary outcomes				
Mortality on Day 60, *n* (%)	49 (44.5)	45 (39.5)	0.4175	0.3664
Serious adverse events (SAEs) [c]				
Number of subjects with at least one SAE, *n* (%)	52 (44.8)	48 (40.7)	0.5973	
Number of different SAEs, *n*	21	20		
Total number of SAEs, *n*	73	62		
SAEs related to corticosteroids, *n*	20	15	0.6982	
Pulmonary embolism, i (%)	4 (3.4)	1 (0.8)		
Septic shock, *n* (%)	11 (9.5)	5 (4.2)		
Sepsis, *n* (%)	3 (2.6)	3 (2.5)		
Pneumonia, *n* (%)	1 (0.9)	2 (1.7)		
Hospital acquired pneumonia, *n* (%)	-	1 (0.8)		
Stercoral peritonitis, *n* (%)	-	1 (0.8)		
Superinfection bacterial, *n* (%)	1 (0.9)	-		
Urinary tract infection, *n* (%)	-	1 (0.8)		
Deep vein thrombosis, *n* (%)	-	1 (0.8)		
CRP change from Day 1 to Day 14, median (IQR)	−11.6 (−84.9–127.0)	−43.7 (−113.4–44.1)	0.0790	
WHO clinical progression scale on Day 14, median (IQR)	7 (5–8)	7 (5–8)		
Independence at 90 days after randomization assessed by Barthel Index, median (IQR)	100.0 (95.0–100.0)	100.0 (90.0–100.0)	0.4132	
Long-term outcomes				
Mortality on Day 180, *n* (%)	49 (44.5)	49 (43.0)	0.7852	0.8038
Mortality on Day 360, *n* (%)	51 (46.4)	49 (43.0)	0.6815	0.6867
Independence at 180 days after randomization assessed by Barthel Index, median (IQR)	100.0 (100.0–100.0)	100.0 (100.0–100.0)	0.8497	
Independence at 360 days after randomization assessed by Barthel Index, median (IQR)	100.0 (95.0–100.0)	100.0 (90.0–100.0)	0.5325	

VFD, ventilator-free days; SD, standard deviation; SAE, serious adverse event; CRP, C-reactive protein; IQR, interquartile range, WHO, World Health Organization

[a] p value of Wilcoxon or Fisher's exact test (not adjusted)

[b] Linear model for the primary endpoint adjusted for age, site, and IPPV and P/F at baseline or logistic regression adjusted for age, invasive mechanical ventilation and P/F at baseline

[c] Safety set used for the evaluation of SAEs: intervention group, *N* = 116; control group, *N* = 118

n(%) = number and percentage of patients

standard-dose dexamethasone [4, 10], which revealed no significant benefit of higher doses in COVID-19 patients. The largest trial comparing high-dose dexamethasone to standard-dose dexamethasone was the COVID STEROID 2 trial, which included 1000 adult patients who were treated with 12 mg/day dexamethasone or 6 mg/day dexamethasone for up to 10 days [4]. No statistically significant difference was noted in the primary outcome, i.e., the number of days alive without life support at 28 days. However, a preplanned secondary Bayesian analysis reported high probabilities of benefit and low probabilities of clinically important harm in the higher-dose group [23]. Long-term follow-up evaluations of 180-day mortality and health-related quality of life revealed no statistically significant differences, but the results suggested a potential benefit from the higher dose [24]. In the COVIDICUS trial, 546 patients were assigned either to a high-dose dexamethasone regimen identical to that used in the REMED trial or to standard-dose dexamethasone (or placebo prior to communication of the RECOVERY trial results). No difference was reported in the time to death from any cause up to day 60 [5]. The

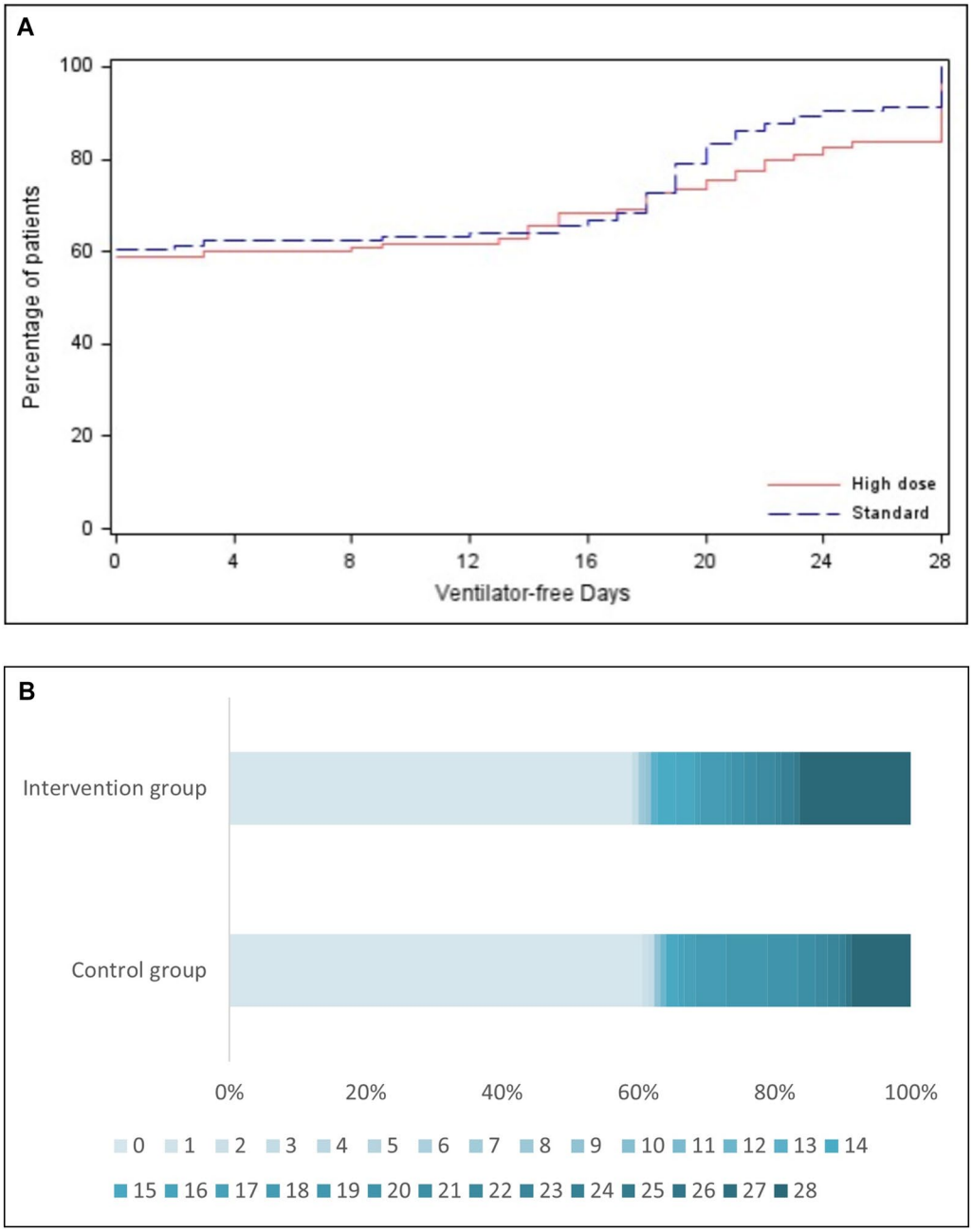

Fig. 2 Distribution of the primary outcomes. **A** Cumulative distribution of ventilatory support-free days. **B** Number of ventilator-free days according to the horizontal stacked bar chart

HIGHLOWDEXA-COVID single-center trial compared an identical high-dose dexamethasone regimen to a standard-dose dexamethasone regimen in 200 patients with COVID-19 pneumonia requiring oxygen therapy; the administration of high-dose dexamethasone was associated with a significant reduction in clinical worsening over the first 11 days [10]. Other published reports have compared different doses of dexamethasone, but they were either stopped early and hence included fewer patients than in the REMED trial [6–8], suffered from methodological limitations [8, 9], were not performed in the ICU [7–9] or were not multicenter [9].

The inclusion criteria in the REMED trial regarding ventilatory support and the criteria for moderate or severe ARDS were stricter than those in other reported studies. For example, COVID-19 STEROID 2 required at

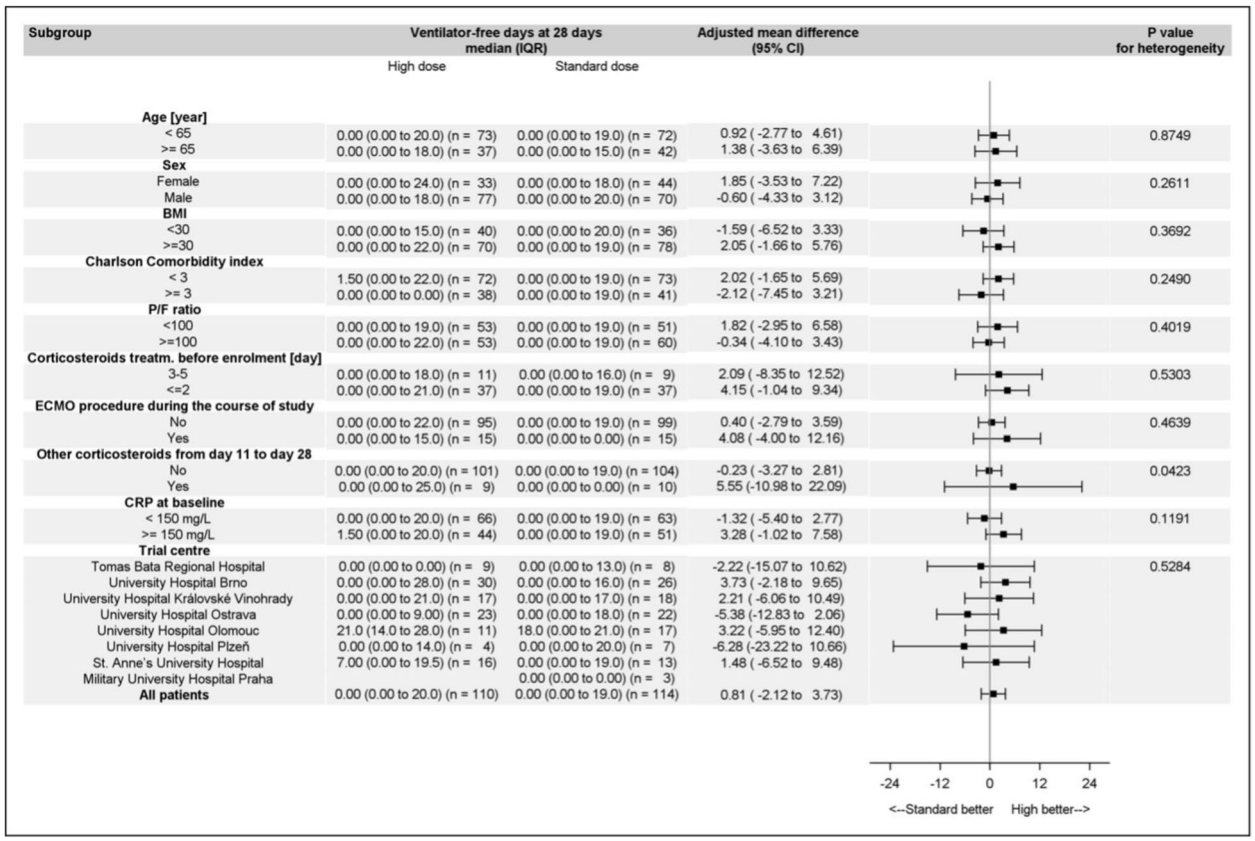

Fig. 3 Forest plot of the median number of ventilator-free days at 28 days and the adjusted mean difference in the 10 predefined subgroups. IQR, interquartile range; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; P:F, PaO_2/:fraction of inspired oxygen; ECMO, extracorporeal membrane oxygenation. FAS, full analysis set; PPS, per-protocol set. [a]Adjusted for age, invasive mechanical ventilation and P/F at baseline

least 10 L/min of oxygen or mechanical ventilation without the need to fulfill ARDS criteria [4], COVIDICUS includes patients with generally defined acute hypoxemic respiratory failure [5], while the HIGHLOWDEXA-COVID-19 study requires only the need for oxygen therapy due to COVID-19 pneumonia [10]. The population in our trial should be regarded as more severely ill, as suggested by a higher overall mortality than in the aforementioned trials. Long-term follow-up was also longer in REMED patients (360-day mortality and independence) than in COVID-19 patients (160-day mortality and health-related quality of life), COVID-19 patients (60 days) and HIGHLOWDEXA-COVID patients (28 days).

Limitations

Our study has several limitations. First, the trial was stopped early after 234 of the anticipated 300 patients had been enrolled. Of these, 222 patients were included in the analysis of the primary endpoint with the power to detect a difference between treatment arms of 69.6%. Second, the trial used an open-label design, so the awareness of group allocation could influence the primary outcome. Third, the sample size estimation was calculated to detect the difference in 3 ventilator-free days at 28 days between the two treatment arms, with a two-sided type I error of 0.05 and a power of 80. Fourth, the dynamic changes in delivered care during the pandemic, especially for therapies related to COVID-19, supportive care and overwhelming healthcare systems in the first and second waves, could have affected the results. Fifth, all centers were located in the Czech Republic; hence, the generalizability of the results could be limited.

Conclusions

In this randomized controlled trial, the administration of higher doses of dexamethasone to COVID-19 patients with moderate-to-severe ARDS did not result in a statistically significant difference in the number of ventilator-free days at 28 days compared to the standard dose. Serious adverse events were similar between the groups. However, the trial was stopped early due to a reduction in

critically ill patients, suggesting careful interpretation of the results.

Abbreviations

ARDS	Acute respiratory distress syndrome
BI	Barthel index
BMI	Body mass index
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
DSMC	Data and Safety Monitoring Committee
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
ESICM	European society of intensive care medicine
GCS	Glasgow coma scale
HFNC	High-flow nasal cannula
ICU	Intensive care unit
IPD	Individual patient data
IQR	Interquartile range
PaO_2FIO_2	Partial pressure of arterial blood oxygen to fraction of inspired oxygen
P:F	PaO_2:Fraction of inspired oxygen
RCT	Randomized controlled trial
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
VFDs	Ventilator-free days
WHO	World Health Organization
WHO-CPS	World Health Organization Clinical Progression Scale

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-024-02215-6.

Additional file 1

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Author contributions
JM and JS conceived the study and wrote the original protocol. JM led the protocol and proposal development and selected and contracted the sites. FD, MB, JZ, MK, JK, and MS contributed to the study design and to the development of the proposal. JS, JMac, MK, FD, PK, OK, LD, JH, MF, TG, LČ, JZ, JP, PN, and MB are the principal investigators and study managers of each site responsible for conducting the study and reviewed the original draft. RD, JK, and JV are clinical research specialists. AS is the trial statistician and analyst. All authors critically revised the manuscript for intellectual content and approved the final version of the manuscript.

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Availability of data and materials
The collected data will be shared with other ongoing clinical trials on the same topic for an individual patient data (IPD) meta-analysis or shared upon relevant requests. A deidentified participant-level dataset will be made available 6 months after publication of the results of the study at www.mendeley.com.

Declarations

Ethics approval and consent to participate
The trial protocol and consequent amendments were approved by the State Institute for Drug Control and Multicentre Ethics Committee of University Hospital Brno (Ref. No. 11/21MEK) and institutionally at each trial site.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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