Maláska et al. Trials (2021) 22:172
https://doi.org/10.1186/s13063-021-05116-9

Trials

LETTER Open Access

Effect of dexamethasone in patients with ARDS and COVID-19 – prospective, multi-centre, open-label, parallel-group, randomised controlled trial (REMED trial): A structured summary of a study protocol for a randomised controlled trial

Jan Maláska[1*], Jan Stašek[1], František Duška[2], Martin Balík[3], Jan Máca[4], Jan Hruda[5], Tomáš Vymazal[6], Olga Klementová[7], Jan Zatloukal[8], Tomáš Gabrhelík[9], Pavel Novotný[10], Regina Demlová[11], Jana Kubátová[11], Jana Vinklerová[11], Adam Svobodník[11], Milan Kratochvíl[12], Jozef Klučka[12], Roman Gál[1], and Mervyn Singer[13] on behalf of the REMED Study Group

Abstract

Objectives: The primary objective of this study is to test the hypothesis that administration of dexamethasone 20 mg is superior to a 6 mg dose in adult patients with moderate or severe ARDS due to confirmed COVID-19. The secondary objective is to investigate the efficacy and safety of dexamethasone 20 mg versus dexamethasone 6 mg. The exploratory objective of this study is to assess long-term consequences on mortality and quality of life at 180 and 360 days.

Trial design: REMED is a prospective, phase II, open-label, randomised controlled trial testing superiority of dexamethasone 20 mg vs 6 mg. The trial aims to be pragmatic, i.e. designed to evaluate the effectiveness of the intervention in conditions that are close to real-life routine clinical practice.

Participants: The study is multi-centre and will be conducted in the intensive care units (ICUs) of ten university hospitals in the Czech Republic.

Inclusion criteria: Subjects will be eligible for the trial if they meet all of the following criteria:
1. Adult (≥18 years of age) at time of enrolment;
2. Present COVID-19 (infection confirmed by RT-PCR or antigen testing);
3. Intubation/mechanical ventilation or ongoing high-flow nasal cannula (HFNC) oxygen therapy;
(Continued on next page)

* Correspondence: malaska.jan@fnbrno.cz
[1]Department of Anaesthesiology and Intensive Care Medicine, University Hospital Brno and Masaryk University, Faculty of Medicine, Jihlavská 20, 625 00 Brno, Czech Republic
Full list of author information is available at the end of the article

(Continued from previous page)

4. Moderate or severe ARDS according to Berlin criteria:
   • Moderate – PaO_2/FiO_2 100–200 mmHg;
   • Severe – PaO_2/FiO_2 < 100 mmHg;
5. Admission to ICU in the last 24 hours.

Exclusion criteria: Subjects will not be eligible for the trial if they meet any of the following criteria:
1. Known allergy/hypersensitivity to dexamethasone or excipients of the investigational medicinal product (e.g. parabens, benzyl alcohol);
2. Fulfilled criteria for ARDS for ≥14 days at enrolment;
3. Pregnancy or breastfeeding;
4. Unwillingness to comply with contraception measurements from enrolment until at least 1 week after the last dose of dexamethasone (sexual abstinence is considered an adequate contraception method);
5. End-of-life decision or patient is expected to die within next 24 hours;
6. Decision not to intubate or ceilings of care in place;
7. Immunosuppression and/or immunosuppressive drugs in medical history:
   a) Systemic immunosuppressive drugs or chemotherapy in the past 30 days;
   b) Systemic corticosteroid use before hospitalization;
   c) Any dose of dexamethasone during the present hospital stay for COVID-19 for ≥5 days before enrolment;
   d) Systemic corticosteroids during present hospital stay for conditions other than COVID-19 (e.g. septic shock);
8. Current haematological or generalized solid malignancy;
9. Any contraindication for corticosteroid administration, e.g.
   • intractable hyperglycaemia;
   • active gastrointestinal bleeding;
   • adrenal gland disorders;
   • presence of superinfection diagnosed with locally established clinical and laboratory criteria without adequate antimicrobial treatment;
10. Cardiac arrest before ICU admission;
11. Participation in another interventional trial in the last 30 days.

Intervention and comparator: Dexamethasone solution for injection/infusion is the investigational medicinal product as well as the comparator. The trial will assess two doses, 20 mg (investigational) vs 6 mg (comparator). Patients in the intervention group will receive dexamethasone 20 mg intravenously once daily on day 1–5, followed by dexamethasone 10 mg intravenously once daily on day 6–10. Patients in the control group will receive dexamethasone 6 mg day 1–10. All authorized medicinal products containing dexamethasone in the form of solution for i.v. injection/infusion can be used.

Main outcomes: Primary endpoint: Number of ventilator-free days (VFDs) at 28 days after randomisation, defined as being alive and free from mechanical ventilation.

Secondary endpoints: a) Mortality from any cause at 60 days after randomisation;
b) Dynamics of inflammatory marker (C-Reactive Protein, CRP) change from Day 1 to Day 14;
c) WHO Clinical Progression Scale at Day 14;
d) Adverse events related to corticosteroids (new infections, new thrombotic complications) until Day 28 or hospital discharge;
e) Independence at 90 days after randomisation assessed by Barthel Index.
The long-term outcomes of this study are to assess long-term consequences on mortality and quality of life at 180 and 360 days through telephone structured interviews using the Barthel Index.

Randomisation: Randomisation will be carried out within the electronic case report form (eCRF) by the stratified permuted block randomisation method. Allocation sequences will be prepared by a statistician independent of the study team. Allocation to the treatment arm of an individual patient will not be available to the investigators before completion of the whole randomisation process. The following stratification factors will be applied:
• Age <65 and ≥ 65;

(Continued on next page)

(Continued from previous page)

• Charlson Comorbidity index (CCI) <3 and ≥3;
• CRP <150 mg/L and ≥150 mg/L
• Trial centre.
Patients will be randomised in a 1 : 1 ratio into one of the two treatment arms. Randomisation through the eCRF will be available 24 hours every day.

Blinding (masking): This is an open-label trial in which the participants and the study staff will be aware of the allocated intervention. Blinded pre-planned statistical analysis will be performed.

Numbers to be randomised (sample size): The sample size is calculated to detect the 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 power of 80%. Based on data from a multi-centre randomised controlled trial in COVID-19 ARDS patients in Brazil and a multi-centre observational study from French and Belgian ICUs regarding moderate to severe ARDS related to COVID-19, investigators assumed a standard deviation of VFD at 28 days as 9. Using these assumptions, a total of 142 patients per treatment arm would be needed. After adjustment for a drop-out rate, 150 per treatment arm (300 patients per study) will be enrolled.

Trial Status: This is protocol version 1.1, 15.01.2021. The trial is due to start on 2 February 2021 and recruitment is expected to be completed by December 2021.

Trial registration: The study protocol was registered on EudraCT No.:2020-005887-70, and on December 11, 2020 on ClinicalTrials.gov (Title: Effect of Two Different Doses of Dexamethasone in Patients With ARDS and COVID-19 (REMED)) Identifier: NCT04663555 with a last update posted on February 1, 2021.

Full protocol: The full protocol (version 1.1) is attached as an additional file, accessible from the Trials website (Additional file 1). In the interest of expediting dissemination of this material, the standard formatting has been eliminated; this Letter serves as a summary of the key elements of the full protocol.

Keywords: COVID-19, Randomised controlled trial, Protocol, ARDS, Dexamethasone, Ventilator-free days

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-021-05116-9.

Additional file 1.

Acknowledgements

The authors thank Dita Budňáková, Ľubica Horváthová, Karolína Grodová, Jarmila Havlová and Iva Knápková for the help and wonderfull assistance during preparation of the protocol and Lenka Dobrovolná for administrative assistance.

REMED Study Group:

University Hospital Brno: Helena Antoni, Petr Suk, Tomáš Korbička, Jan Hudec; *University Hospital Královské Vinohrady*: Michal Fric, Václav Zvoníček, Tomáš Tencer, Martin Kolář, Petr Kafka; *General University Hospital in Prague*: Michal Otáhal, Jan Rulíšek, Marek Flaksa, Eva Svobodová; *University Hospital Ostrava*: Peter Sklienka, Filip Burša, Marcela Káňová, Jan Varady, Filip Haiduk; *St. Anne's University Hospital*: Vladimír Šrámek, Pavel Suk, Marek Fencl, Ivan Čundrle, Pavel Štětka, Marek Lukeš, Miloš Chobola; *University Hospital Motol:* Jan Beroušek, Zuzana Přikrylová, Jiří Bureš, Jaromír Vajter, Vlasta Vlasáková, Michal Garaj; *University Hospital Olomouc*: Lenka Doubravská; *University Hospital Plzeň*: Jiří Pouska, Jakub Kletečka; *Tomáš Baťa Regional Hospital*: Tomáš Graus, Tereza Šobáňová, Radovan Turek; *Military University Hospital Praha*: Tomáš Tyll, Aleš Rára;

Supported by the national budget through MEYS, RI CZECRIN (LM2018128) and from ERDF Project CZECRIN_4 PATIENTS (CZ.02.1.01/0.0/0.0/16_013/0001826) and by MH CZ - DRO (FNBr, 65269705) and Endowment fund Donatio Intensivistam (VAT No 0907206).

Authors' contributions

JM and JS conceived the study and wrote the original protocol draft. JM led the protocol and proposal development, selected and contracted sites. RG selected and contracted sites. FD, MB, JZ, MK, JK, MS contributed to study design and to development of the proposal. JMac, JH, TV, OK, TG, PN reviewed the original draft. RD, JK, JV are clinical research specialists. AS is the trial statistician and analyst. All authors read and approved the final manuscript.

Funding

REMED is an investigator-initiated clinical trial. Funding will be granted from the project research infrastructure Czech Clinical Research Infrastructure Network CZECRIN (LM 2018128), University Hospital Brno and Endowment fund Donatio Intensivistam (VAT No 0907206). Trial funders have no role in the study design, collection, analysis and interpretation of data nor in writing the manuscript.

Availability of data and materials

The sponsor, the trial site and study staff will handle the subject's personal and trial data according to the effective legislation regarding data protection. Collected data will be shared with other ongoing clinical trials on the same topic for individual patient data (IPD) meta-analysis or shared upon relevant requests. A de-identified participant-level dataset will be made available 6 months after publication of the results of the study at www.mendeley.com

Ethics approval and consent to participate

The trial was approved by the Ethics Committee for Multi-Centric Clinical Trials University Hospital Brno on January 28, 2021 Identifier: 11/21-MEK.
This trial will be conducted following the applicable legislation and requirements for good clinical practice according to ICH E6(R2). Compliance with this standard provides public assurance that the rights, safety and well-being of trial participants are protected and that the clinical trial data are credible. All potential amendments will be submitted to the relevant Ethics committee and Regulatory authority for approval.

Informed consent procedure

The investigator assesses the patient's ability to decide, and the extent of potential consciousness impairment based on Glasgow Coma Score and other appropriate clinical measures (at the discretion of the trial centre).

Fully conscious and oriented patients (GCS 15)

Patient with decision-making capacity will go through the standard procedure (informative interview with the investigator, written information for the patient, the possibility to ask questions, and adequate time to discuss with family and decide). If the patient wishes to participate, he/she will provide written prospective informed consent.

Patients with limited ability to decide (GCS 13 or 14)

Some patients may be limited in their decisional capacity due to their acute health status and/or medication. Generally, if a patient understands simplified information and can communicate verbally, the simplified procedure of obtaining informed consent will be applied. The shortened (one-page) information sheet and consent form for signature will be used. As soon as the patient regains full decisional capacity, he/she will be approached to provide consent for continuation of his/her participation in the trial. Patients will be informed about the option to withdraw from the trial. Patients who decide to terminate their involvement can permit the sponsor to use the data collected, or they can ask for deletion of all data collected. Both options will be presented to them.

If the patient does not regain decisional capacity, the initial consent will remain valid.

Patients lacking the capacity to decide (GCS 12 or less)

It is expected that a significant proportion of screened patients will lack capacity to provide informed consent due to severely altered consciousness, severe respiratory distress, or sedation necessary to facilitate mechanical ventilation. In this situation, the deferred consent policy will be applied. Such a patient will be enrolled after an independent physician witnesses (in writing) that the patient cannot give his/her consent and fulfils eligibility criteria.

A patient's close person (spouse/partner, close relative, caregiver) will be informed about the patient's enrolment and the nature of the study. If possible, and compliant with the epidemiological restrictions by the government, the patient's close person will meet the investigator for an informative interview, to obtain the information leaflet, and to sign a confirmation that he/she was informed about the patient's participation in the trial.

As soon as the patient regains decisional capacity, he/she will be approached to provide consent for continuation of his/her participation in the trial. Patients will be informed about the option to withdraw from the trial. Patients who decide to terminate their involvement can permit the sponsor to use data collected, or can ask for deletion of all data collected to date. Both options will be presented to them.

If the patient does not regain decisional capacity, the initial consent by an independent physician will remain valid.

Vulnerable population

Beside patients with diminished decision capacity, other specifically vulnerable participants (children, pregnant women, prisoners, refugees, institutionalized patients, patients with severe mental illnesses, etc.) will not be enrolled in this clinical trial.

Consent for publication

Not applicable

Competing interests

Investigators declare no financial or non-financial competing interest regarding the focus of this trial.

Author details

[1]Department of Anaesthesiology and Intensive Care Medicine, University Hospital Brno and Masaryk University, Faculty of Medicine, Jihlavská 20, 625 00 Brno, Czech Republic. [2]Department of Anaesthesia and Intensive Care, University Hospital Královské Vinohrady and Charles University, 3rd Faculty of Medicine, Šrobárova, 1150 100 34 Praha, Czech Republic. [3]Department of Anaesthesia and Intensive Care, 1st Faculty of Medicine, General University Hospital in Prague and Charles University, U Nemocnice 499/2, 128 08 Praha, Czech Republic. [4]Department of Anaesthesiology and Intensive Care Medicine, Faculty of Medicine, University Hospital Ostrava and University Ostrava, 17. listopadu 1790, 708 52 Ostrava-Poruba, Czech Republic. [5]Department of Anaesthesiology and Intensive Care Medicine, Faculty of Medicine, St. Anne's University Hospital and Masaryk University, Pekařská 664/53, 656 91 Brno, Czech Republic. [6]Department of Anaesthesiology and Intensive Care Medicine, 2nd Faculty of Medicine, University Hospital Motol and Charles University, V Úvalu 84/1, 150 06 Praha 5, Czech Republic. [7]Department of Anaesthesiology and Intensive Care Medicine, Faculty of Medicine, University Hospital Olomouc and Palacky University, I. P. Pavlova 185/6, 779 00 Olomouc, Czech Republic. [8]Department of Anaesthesiology and Intensive Care Medicine, Faculty of Medicine in Pilsen, University Hospital Plzeň and Charles University, alej Svobody 80, 304 60 Plzeň-Lochotín, Czech Republic. [9]Department of Anaesthesiology and Intensive Care Medicine, Tomáš Baťa Regional Hospital, Havlíčkovo nábřeží 600, 762 75 Zlín, Czech Republic. [10]Department of Anaesthesiology and Intensive Care, 1st Faculty of Medicine, Military University Hospital Praha and Charles University, U Vojenské nemocnice 1200, 169 02 Praha, Czech Republic. [11]Department of Pharmacology/CZECRIN, Faculty of Medicine, Masaryk University, Kamenice 5, 62500 Brno, Czech Republic. [12]Department of Paediatric Anaesthesiology and Intensive Care Medicine, Faculty of Medicine, University Hospital Brno and Masaryk University, Jihlavská 20, 625 00 Brno, Czech Republic. [13]Bloomsbury Institute of Intensive Care Medicine, Division of Medicine, University College London, Gower Street, London WC1E 6BT, UK.

Received: 4 February 2021 Accepted: 9 February 2021
Published online: 01 March 2021

Publisher's Note