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Corticosteroid therapy for critically ill patients with COVID-19: A structured summary of a study protocol for a prospective meta-analysis of randomized trials

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Abstract

Objectives: Primary objective: To estimate the effect of corticosteroids compared with usual care or placebo on mortality up to 28 days after randomization. Secondary objectives: To examine whether the effect of corticosteroids compared with usual care or placebo on mortality up to 28 days after randomization varies between subgroups related to treatment characteristics, disease severity at the time of randomization, patient characteristics, or risk of bias. To examine the effect of corticosteroids compared with usual care or placebo on serious adverse events.

Study design: Prospective meta-analysis of randomized controlled trials. Both placebo-controlled and open-label trials are eligible.

Participants: Hospitalised, critically ill patients with suspected or confirmed COVID-19.

Intervention and comparator: Intervention groups will have received therapeutic doses of a steroid (dexamethasone, hydrocortisone or methylprednisolone) with IV or oral administration immediately after randomization.
The comparator groups will have received standard of care or usual care or placebo.

Main outcome: All-cause mortality up to 28 days after randomization.

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Search methods: Systematic searching of clinicaltrials.gov, EudraCT, the WHO ISRCTN registry, and the Chinese clinical trials registry. Additionally, research and WHO networks will be asked for relevant trials.

Risk of bias assessments: These will be based on the Cochrane RoB 2 tool, and will use structured information provided by the trial investigators on a form designed for this prospective meta-analysis.

Summary of findings: We will use GRADE to assess the certainty of the evidence.

Statistical analyses: Trial investigators will provide data on the numbers of participants who did and did not experience each outcome according to intervention group, overall and in specified subgroups. We will conduct fixed-effect (primary analysis) and random-effects (Paule-Mandel estimate of heterogeneity and Hartung-Knapp adjustment) meta-analyses. We will quantify inconsistency in effects between trials using I^2 statistics. Evidence for subgroup effects will be quantified by ratios of odds ratios comparing effects in the subgroups, and corresponding interaction p-values. Comparisons between subgroups defined by trial characteristics will be made using random-effects meta-regression. Comparisons between subgroups defined by patient characteristics will be made by estimating trial-specific ratios of odds ratios comparing intervention effects between subgroups then combining these using random-effects meta-analysis. Steroid interventions will be classified as high or low dose according to whether the dose is greater or less than or equal to 400 mg hydrocortisone per day or equivalent. We will use network meta-analysis methods to make comparisons between the effects of high and low dose steroid interventions (because one trial randomized participants to both low and high dose steroid arms).

PROSPERO registration number: CRD42020197242

Full protocol: The full protocol for this prospective meta-analysis is attached as an additional file, accessible from the Trials website (Additional file 1). To expedite dissemination of this material, the familiar formatting has been eliminated; this Letter serves as a summary of the key elements of the full protocol for the systematic review.

Keywords: COVID-19, Randomised controlled trial, Systematic Review, Corticosteroid, Dexamethasone, Hydrocortisone, Methylprednisolone, Mortality, Meta-analysis

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13063-020-04641-3.

Additional file 1.

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Authors' contributions

All authors contributed to drafting the protocol for the prospective meta-analysis. The author(s) read and approved the final manuscript.

Funding

Funding for administrative and communications support was provided by the World Health Organisation. No other specific funding for the prospective meta-analysis was received. Dr Diaz contributed to the design of the study. World Health Organisation staff contacted trial investigators to request their participation in this prospective meta-analysis and that they share outcome data.

Availability of data and materials

All data provided by the trials, including summary outcome data overall and in the specified subgroups, will be included in supplementary material of the report of the prospective meta-analysis.

Ethics approval and consent to participate

All trials received ethics approval. No ethics approval was required for this secondary data analysis.

Consent for publication

Not applicable

Competing interests

Jonathan A C Sterne is partly funded by the NIHR Bristol Biomedical Research Centre. Jesus Villar received a Research grant from MAQUET (Sörna, Sweden) to perform a clinical trial on mechanical ventilation. Srinivas Murthy is a member of the REMAP-CAP International Trial Steering Committee. Arthur Slutsky is co-PI of the Dexamethasone in COVID ARDS study and is supported by grants from the Canadian Institutes of Health Research (CIHR). Anders Perner is the sponsor-investigator of the COVID STEROID trial, which is funded by the Novo Nordisk Foundation and supported by Pfizer. Peter Jüni serves as unpaid member of steering groups or executive committees of trials funded by Abbott Vascular, Astra Zeneca, Biotronik, Biosensors, St. Jude Medical, Terumo and The Medicines Company, has received research grants to the institution from Appili Therapeutics, Astra Zeneca, Biotronik, Biosensors International, Eli Lilly, The Medicines Company, and honoraria to the institution for participation in advisory boards and/or consulting from Amgen, Ava and Fresenius, but has not received personal payments by any pharmaceutical company or device manufacturer. Derek C Angus is a member of the REMAP-CAP International Trial Steering Committee and chair of the REMAP-CAP Corticosteroid Domain-specific Working Group. Djillali Annane has been involved as an investigator and in the steering committee for CAPE-COVID that was publicly funded by a grant from the French Ministry of Health; as an investigator, chief investigator for France, and member of the Steering committee for REMAP-CAP, he received a grant from the French Ministry of health to support French sites that participated to REMAP-CAP corticosteroids domain. He has not received any personal payment from any private or public entities. Luciano C P Azevedo is the PI for the Codex trial, which received donation of dexamethasone from Aché Pharmaceuticals. Bin Du is the PI for the corticosteroids therapy in adult patients with COVID-19 and ARDS (Steroids-SARI) trial, which was funded by a grant from the Ministry of Science and Technology; and has

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