The BMJ

Cite this as: *BMJ* 2020;369:m2512
http://dx.doi.org/10.1136/bmj.m2512
Published: 23 June 2020

Covid-19: Demand for dexamethasone surges as RECOVERY trial publishes preprint

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Production of dexamethasone must be rapidly ramped up to meet global demand for the drug, the World Health Organization has said.[1]

The call came as the University of Oxford's RECOVERY trial published its much anticipated preprint paper[2] on the drug's effect on covid-19. The paper states that the drug cuts deaths in ventilated patients by one third and deaths in other admitted patients receiving oxygen by only one fifth.

The headline findings of the trial were reported by the investigators on 16 June and were adopted into UK practice the same day through an alert sent to doctors.[3]

WHO's director general, Tedros Adhanom Ghebreyesus, said, "The next challenge is to increase production and rapidly and equitably distribute dexamethasone worldwide, focusing on where it is needed most. Demand has already surged following the UK trial results."

Ventilation and standard care

In the preprint paper published on 22 June,[2] the study team reported that 454 of 2104 (21.6%) patients allocated to dexamethasone and 1065 of 4321 (24.6%) patients allocated to usual care died within 28 days (age adjusted rate ratio 0.83 (95% confidence interval (0.74 to 0.92); P<0.001). The randomised, controlled, and open label trial began in March 2020 and is investigating a number of potential covid-19 treatments at 176 NHS hospitals.

In the dexamethasone arm, which ended recruitment on 8 June, eligible and consenting patients were assigned in a ratio of 2:1 to a usual standard of care or to a usual standard of care plus dexamethasone 6 mg once daily (oral or intravenous) for a maximum of 10 days (or until discharge if sooner).

The preprint reported that, among the ventilated patients, 94 of the 324 patients taking dexamethasone died, compared with 278 of the 683 receiving standard care. This is a reduction of around a third, from 40.7% to 29.0% (0.65 (0.51 to 0.82); P<0.001).

Among patients receiving oxygen, 275 of the 1279 taking dexamethasone died, compared with 650 of the 2604 receiving standard care. This is a reduction in mortality from 25.0% to 21.5% (0.80 (0.70 to 0.92); P=0.002).

However, in the group of admitted patients receiving no respiratory support, 85 of the 501 taking dexamethasone died, compared with 137 of the 1034 allocated to usual care (17.0% *v* 13.2% (1.22 (0.93 to 1.61); P=0.14). The researchers concluded that the steroid did not reduce mortality in this group.

The mean age of study participants in this arm was 66.1 years, and 36% of patients were female. A history of diabetes was present in 24% of patients, heart disease in 27%, and chronic lung disease in 21%, the study found, and 56% had at least one major comorbidity.

Limitations and follow-up

John Fletcher, research editor at *The BMJ* who screened the preprint for MedRxiv, said that the trial was useful but that there were "limitations and cause for caution."

He said, "The authors have used relative reductions and chosen the subgroup with the biggest benefit to generate a headline of a one third reduction in deaths. The subgroup analysis was not specified in the trial registry and may be misleading."

Fletcher also noted that the final outcome was unknown for at least 28% of people entered in the trial, as 1807 were still in hospital at 28 days, the endpoint of the trial.

Carl Heneghan, director of the Centre for Evidence Based Medicine at the University of Oxford, said, "Given the fact this is a cheap available drug, and given the size of the effect, to me it is clear there is strong evidence to make this treatment available to the right patients admitted to intensive care units. We have seen a lot of poor quality evidence, but this is towards the spectrum of high quality evidence."

Heneghan added that he would like to see follow-up of the patient group beyond 28 days and additional analysis to see whether the drug could harm patients with mild to moderate disease.

The RECOVERY trial is funded by organisations including the National Institute for Health Research, Wellcome, the Bill and Melinda Gates Foundation, and the Department for International Development. No conflicts of interest were reported by the authors.

Correction: On 24 June 2020 we removed a duplicated sentence.

1 World Health Organization. WHO director-general's opening remarks at the media briefing on COVID-19. 22 Jun 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---22-june-2020.
2 Effect of dexamethasone in hospitalized patients with COVID-19—preliminary report. 22 Jun 2020 (preprint). https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1.full.pdf.
3 Mahase E. Covid-19: Low dose steroid cuts death in ventilated patients by one third, trial finds. *BMJ* 2020;369:m2422. doi: 10.1136/bmj.m2422 pmid: 32546467