SCIENCE BRIEFS

Dexamethasone in Patients Hospitalized for COVID-19

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About Us: The Ontario COVID-19 Science Advisory Table is a group of scientific experts and health system leaders who evaluate and report on emerging evidence relevant to the COVID-19 pandemic, to inform Ontario's response. Our mandate is to provide weekly summaries of relevant scientific evidence for the COVID-19 Health Command Table of the Province of Ontario, integrating information from existing scientific tables, Ontario's universities and agencies, and the best global evidence. The Science Table summarizes its findings for the Health Command Table and the public in Science Briefs.

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Key Message

A large clinical trial found that dexamethasone reduced deaths and the need for mechanical ventilation in hospitalized patients with COVID-19 who require supplemental oxygen.

Summary

Background

In some people, infection with SARS-CoV-2, the virus causing COVID-19, triggers an overreaction of the immune system that can result in severe injury to a number of organs including the lungs, heart and kidneys.

The drug dexamethasone is a corticosteroid that decreases the immune response. Therefore, it could be beneficial in people with COVID-19, but could also be harmful as it may prevent the immune system's ability to contain the viral infection.

Recently, the results of the large RECOVERY trial became available, which compared dexamethasone in addition to usual care with usual care alone.

Questions

Does dexamethasone reduce the risk of death in adults hospitalized for COVID-19?

Does dexamethasone reduce the need for mechanical ventilation?

Findings

The RECOVERY trial was a randomized controlled trial in 6,425 adults hospitalized for COVID-19: 2,104 were randomized to receive dexamethasone (6mg daily for up to 10 days), and 4,321 were randomized to receive usual care.

The effect of dexamethasone depended on the level of respiratory support that participants received at the time of enrollment into the study.

In participants who received mechanical ventilation at the time of enrollment, dexamethasone reduced the risk of death, from 41.4% in the usual care group to 29.3% in the dexamethasone group.

In participants who were not on invasive mechanical ventilation but required supplemental oxygen at the time of enrollment, dexamethasone reduced the risk of death, from 26.2% in the usual care group to 23.3% in the dexamethasone group. In these participants, dexamethasone also reduced the need for mechanical ventilation, from 10.2% in the usual care group to 7.3% in the dexamethasone group.

In participants who did not require supplemental oxygen or mechanical ventilation at the time of enrollment, dexamethasone tended to increase the risk of death at 28 days, from 14.0% in the usual care group to 17.8% in the dexamethasone group.

Interpretation

The RECOVERY trial provides conclusive evidence for the use of dexamethasone (6mg daily for up to 10 days) to reduce the risk of death in hospitalized patients with COVID-19 who require supplemental oxygen and/or mechanical ventilation.

Dexamethasone also reduces the need for future mechanical ventilation in hospitalized patients with COVID-19 who require supplemental oxygen.

In patients with COVID-19 who do not require supplemental oxygen or mechanical ventilation, dexamethasone is not effective and could even be harmful.

Background

In some people, infection with SARS-CoV-2, the virus causing COVID-19, triggers an overreaction of the immune system that can result in severe injury to a number of organs including the lungs, heart and kidneys.

Dexamethasone, a corticosteroid, decreases the immune response. This could be beneficial because it prevents an overwhelming response from the immune system but could also be harmful as it may prevent the immune system's ability to contain the viral infection.

Studies of prior outbreaks of respiratory infections have suggested potential harm of corticosteroids. For instance, in a prospective cohort study of 309 severely ill adults infected with the virus causing Middle East Respiratory Syndrome (MERS), people who received corticosteroids were less likely to clear the virus than people who did not (adjusted hazard ratio 0.35, 95% confidence interval 0.17 to 0.72), and there was no difference in the number of deaths.[1] In a meta-analysis of observational studies of people with influenza, those who received corticosteroids were more likely to die than those who did not (hazard ratio 1.75, 95% confidence interval 1.30-2.36).[2]

Conversely, in a randomized controlled trial of 277 patients with acute respiratory distress syndrome (ARDS) of different causes who received invasive mechanical ventilation at the time of randomization, the number of deaths at 60 days was reduced from 36.2% in the usual care group to 20.9% in the dexamethasone group (difference 15.3%, 95% confidence interval 4.9% to 25.9%).[3] The trial was performed before the COVID-19 pandemic and therefore did not include patients with COVID-19.

On July 17, 2020, the RECOVERY trial was published.[4] To date, this is the largest randomized trial on the effect of dexamethasone in hospitalized patients with COVID-19.

Questions

Does dexamethasone reduce the risk of death within 28 days after randomization in adults hospitalized for COVID-19?

Does dexamethasone reduce the need for invasive mechanical ventilation in adults hospitalized for COVID-19 who do not receive invasive mechanical ventilation?

Findings

The RECOVERY trial is a large randomized controlled trial conducted in the United Kingdom comparing a range of possible treatments. A total of 6,425 adults hospitalized for COVID-19 were enrolled: 2,104 participants were randomized in a

1:2 ratio to receive dexamethasone (6mg daily for up to 10 days) in addition to usual care, and 4,321 participants were randomized to receive usual care alone.

The effect of dexamethasone depended on the level of respiratory support that participants received at the time of randomization (p-value for trend <0.001).

In 1,007 participants who received invasive mechanical ventilation at the time of randomization, the risk of death at 28 days after randomization was reduced from 41.4% in the usual care group to 29.3% in the dexamethasone group (rate ratio 0.64, 95% confidence interval 0.51 to 0.81). The number-needed-to-treat to prevent 1 death was 9.

In participants who were not on invasive mechanical ventilation but required supplemental oxygen at the time of randomization, the risk of death at 28 days was reduced from 26.2% in the usual care group to 23.3% in the dexamethasone group (rate ratio 0.82, 95% confidence interval 0.72 to 0.94). The number-needed-to-treat to prevent 1 death was 35. In these participants, dexamethasone also reduced the need for mechanical ventilation, from 10.2% in the usual care group to 7.3% in the dexamethasone group (rate ratio 0.74, 95% confidence interval 0.59 to 0.92; Horby P, personal communication). The number-needed-to-treat to prevent 1 participant from receiving invasive mechanical ventilation was 35.

In 1,535 participants who did not receive supplemental oxygen at the time of randomization, dexamethasone tended to increase the risk of death at 28 days, from 14.0% in the usual care group to 17.8% in the dexamethasone group (rate ratio 1.19, 95% confidence interval 0.91 to 1.55).

Assuming that dexamethasone would be given to hospitalized patients with COVID-19 who require supplemental oxygen, but not to patients who do not require supplemental oxygen, and that the characteristics of patients with COVID-19 in hospitals in Ontario are similar to the characteristics of patients included in RECOVERY, we estimate that the appropriate implementation of dexamethasone into routine care of hospitalized patients with COVID-19 would reduce deaths in hospitalized patients in Ontario by 15% (95% confidence interval 4% to 24%) and the need for invasive mechanical ventilation by 24% (95% confidence interval 6% to 39%).

Interpretation

The large, well-performed RECOVERY trial provides strong, conclusive evidence that dexamethasone (6mg daily for up to 10 days) reduces the risk of death in hospitalized patients with COVID-19 who require supplemental oxygen and/or invasive mechanical ventilation.

Dexamethasone also reduces the need for future invasive mechanical ventilation in hospitalized patients with COVID-19 who are not on invasive mechanical ventilation but require supplemental oxygen.

In patients with COVID-19 who do not require supplemental oxygen or mechanical ventilation, dexamethasone is not effective and could even be harmful.

Although the RECOVERY trial was open to a pediatric population, the overwhelming majority of patients included in the trial were adults and results have yet to be reported for the subgroup of children. Decisions on the use of dexamethasone in children would therefore need to be made on a case-by-case basis, taking into account illness severity and using pediatric equivalent doses.

Residents of long-term care homes with COVID-19 who were not hospitalized were not included in RECOVERY. Decisions on the use of dexamethasone in residents of long-term care homes who require supplemental oxygen would therefore need to

be made on a case-by-case basis with attention to the potential for side effect, including increase in serum glucose levels (especially in patients with diabetes), fluid retention and neuropsychiatric adverse effects.

The results of RECOVERY should not be extrapolated to doses higher than 6mg of dexamethasone daily, to other corticosteroids, or to the treatment of patients without COVID-19.

Dexamethasone is widely available, inexpensive and straightforward to implement into routine care of patients with COVID-19 who require supplemental oxygen or mechanical ventilation in all hospitals in Ontario.

Methods Used for This Science Brief

We searched PubMed and Google Scholar. The search strategy used in PubMed, for example, involved the following combination of keywords: ((Dexamethasone[tiab] OR corticosteroid*[tiab]) AND covid*[tiab]). Then we searched the Cochrane COVID Review Bank, the COVID-19 Rapid Evidence Reviews, the Covid-19 TrialsTracker, the Joanna Briggs Institute's COVID-19 Special Collection, LitCovid in PubMed, the National Collaborating Centre for Indigenous Health's Updates on COVID-19, the Oxford COVID-19 Evidence Service, the World Health Organization's Global Literature on Coronavirus Disease, and other COVID-19 specific resources listed by the Guidelines International Network and the McMaster Health Forum. In addition, we retrieved reports citing relevant articles through Google Scholar and reviewed references from identified articles for additional studies. The search was last updated on July 31, 2020.

To estimate the potential impact of an appropriate implementation of dexamethasone into routine care of hospitalized patients with COVID-19 in Ontario, we assumed that dexamethasone will be given to nearly all hospitalized patients with COVID-19 who require supplemental oxygen, but not to patients who do not require supplemental oxygen, and that the characteristics of patients with COVID-19 in hospitals in Ontario are similar to the characteristics of patients included in RECOVERY. We used a fixed-effect model to combine appropriate subgroup specific log rate ratios while appropriately taking into account statistical uncertainty of estimates. Then we expressed the pooled rate ratio from the fixed-effect model as a relative reduction in deaths in hospitalized patients in Ontario and a relative reduction in the need for invasive mechanical ventilation in percent (relative reduction = (1 – rate ratio) x 100), with corresponding 95% confidence intervals. A rate ratio of 0.80, for example, would correspond to a relative reduction of 20%.

Author Contributions

PJ and AO wrote the first draft of the science brief. All authors contributed to the conception of the science brief, revised it critically for important intellectual content, and approved the final version.

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