Maine Medical Center
Department of Emergency Medicine
Journal Club Summary Template

Date: 11/19/20	**Presenter Name:** Ben Pare

Article Citation: Dexamethasone in Hospitalized Patients with Covid 19 – Preliminary Report

Peter Horby, et al

Country(ies): United Kingdom**,** 176 Hospitals. Part of the RECOVERY Trial, designed to evaluate potential treatments for patients hospitalized with covid 19

Funding Source(s): Medical Research Council and National Institute for Health Research

☐ None Stated

Purpose

Research Question(s): Does the use of dexamethasone in hospitalized patients with Covid-19 reduce the rate of 28 day mortality compared to those treated with "usual care" alone?

☐ None Stated

Hypotheses: Glucocorticoids may modulate inflammation-mediated lung injury and thereby reduce progression of covid positive patients to respiratory failure and death

☐ None Stated

Study Purpose: To complete a randomized, control trial to study the effectiveness of glucocorticoids on reducing mortality in covid-19 patients

Methods

Study Design: prospective, randomized control trial including data from 176 UK hospitals from the dates March 19, 2020 through June 8, 2020

Outcome(s) ***[or Dependent Variable]:***
Primary Outcome: all-cause mortality within 28 days from administration (or not) of dexamethasone
Secondary Outcomes: time until discharge from the hospital
Time until receipt of Invasive mechanical Ventilation or ECMO (for those who came into the hospital not requiring those interventions)
Receipt of renal hemodialysis
Major cardiac arrhythmia

Receipt and duration of mechanical ventilation

Intervention *[or Independent Variable]:* Dexamethasone vs. no dexamethasone for hospitalized, covid 19 patients

Ethics Review: ☐ IRB Review ☐ IACUC Review ☐ Other: ☐ None Stated

Research Setting: 176 hospitals in the UK

Study Subjects: hospitalized patients that had clinically suspected OR laboratory confirmed Covid-19 infection and no medical history that would put patients at risk if they participated in the trial. Initially, recruited only those at least 18 years of age, but the age limit was removed on May 9, 2020. Pregnant or breastfeeding women were eligible.

Randomized using a web based system, participants were randomized to a 2:1 ratio to receive either the usual standard of care or the usual standard of care plus IV or oral dexamethasone (6 mg once daily for up to 10 days, or until hospital discharge if sooner)

Inclusion Criteria:
Suspected or confirmed Covid-19 infection
Hospitalized
Consented

Exclusion Criteria:

11,303 patients recruited, 1948 excluded right off the bat

Of those 1948:
For 357 patients, dexamethasone was unavailable at the hospital at the time of enrollment. These patients were excluded from entry in the randomized comparison between dexamethasone and usual care and hence were not included in this report.
For the remaining 1707, not considered suitable for dexamethasone due to either having another reason that dexamethasone was indicated, or dexamethasone was contraindicated

Of remaining 9355, 2930 were assigned to receive other active treatments

That left 6425 participants in this study

Study Interventions:

Study Groups:

Instruments/Measures Used: A single online follow up form was to be completed when the patients were discharged, had died, or at 28 days after randomization, whichever occurred first.

Data Collection:

Data Analysis:

***A priori* sample size calculation?** ☐ Yes ☐ No ☐ Not Described ☐ N/A

Yes; if 28-day mortality was 20%, then the enrollment of at least 2000 patients in the dexamethasone group and 4000 in the usual care group would provide a power of at least 90% at a two-sided P value of 0.01 to detect a clinically relevant proportional reduction of 20% (an absolute difference of 4 percentage points) between the two groups

Statistical analyses used:
Hazard ratio from Cox regression was used to estimate mortality rate ratio

Adjustment for potential confounders? ☐ Yes ☐ No ☐ Not Described ☐ N/A
If yes, list:

Yes; mean age in the dexamethasone group as 1.1 years older than the usual care group; estimates of mortality rate ratios were adjusted for age in three categories, <70, 70-79, and >80

Results

Study participants:

89% of patient had confirmed Covid 19 infection, mean age 66.1 years with a standad deviation of 15.7 years, diabetes 24%, heart disease 27%, chronic lung disease 21%, and 56% had at least one major coexisting illness

Median duration of treatment in dexamethasone group was 7 days

8% of usual care group received dexamethasone

Use of azithromycin was similar in dexamethasone group and usual care group (24% and 25%, respectively), and 0 to 3% of patients received hydroxychloroquine, lopinavir–ritonavir, or interleukin-6 antagonists during

follow-up. After remdesivir became available in the United Kingdom on May 26, 2020, the drug was administered to 3 patients in the dexamethasone group and 2 patients in the usual care group.

Brief answers to research questions *[key findings]:*

Mortality at 28 days was significantly lower in the dexamethasone group than in the usual care group, with deaths reported in 482 of 2104 patients (22.9%) and in 1110 of 4321 patients (25.7%), respectively (mortality rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P

Perhaps most notable finding was in patient's requiring mechanical ventilation; In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81)

In those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94)

However, there was no clear effect of dexamethasone among patients who were not receiving any respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55)

The receipt of dexamethasone was associated with a reduction in 28 day mortality among those with symptoms for more than 7 days, but not among those with a more recent symptom onset.

Additional findings:

Patients in the dexamethasone group had a shorter duration of hospitalization than those in the usual care group (median, 12 days vs. 13 days) and a greater probability of discharge alive within 28 days

The greatest effect regarding discharge within 28 days was seen among patients who were receiving invasive mechanical ventilation at randomization

The risk of progression to invasive mechanical ventilation was lower in the dexamethasone group than in the usual care group (risk ratio of 0.92)

The greater mortality benefit of dexamethasone in patients with Covid-19 who are receiving respiratory support and among those recruited after the first week of their illness suggests that at that stage the disease may be dominated by immunopathological elements, with active viral replication playing a secondary role.

Limitations:

Only 89% of the patients involved in this study actually tested positive for covid

The article never defined “usual care” for covid patients

8% of the usual care group patients did receive dexamethasone

Only studied in UK, can we externally validate this study to US?

Clinical Implications

Applicable?

Yes; this study illustrates that we should not send home the walking well that we believe (or may be confirmed) Covid patients with dexamethasone

In patients we suspect have covid, or have tested positive for covid that we are admitting to the hospital, AND are requiring supplemental O2 or are intubated due to covid related issues, may be worth talking with admitting team about giving a dose of dexamethasone while in ED.

Feasible?

I believe this article presents entirely feasible patterns that we can implement in our daily practice (i.e. not sending home suspected covid patients on steroids)

Clinically relevant?

Absolutely relevant especially as we try to find relevant treatments for covid 19

Comments:

Level of evidence generated from this study

☐ Ia: evidence obtained from meta-analysis of randomized controlled trials
☐ Ib: evidence obtained from at least one randomized controlled trial
☐ IIa: evidence obtained from at least one well-designed, controlled study without randomization

☐ IIb: evidence obtained from at least one other type of well-designed quasi-experimental study
☐ III: evidence obtained from a well-designed, non-experimental study
☐ IV: expert committee reports; expert opinion; case study; case report

This study is level 1B.

Additional Comments/Discussion/Notes

Interesting to note that there was a greater mortality benefit of dexamethasone in patients with Covid-19 who are receiving respiratory support and among those **recruited after the first week of their illness** suggests that at that stage the disease may be dominated by immunopathological elements, with active viral replication playing a secondary role.