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Morning Brief : Scientific Review

24 June 2020

The purpose of the Morning Brief is to **summarize** and present key information, research articles and other relevant publications pertaining to critical care and COVID-19. We aim to prioritise information, articles and publications released in the preceding 24-48hours.

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Content of the brief

- **Topic: Recovery trial**

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Articles of Interest

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Pragmatic
Inclusion – hospitalised with confirmed or suspected Covid-19
Pregnant and breast-feeding women eligible
Protocol published when the trial started
Simple randomisation with allocation concealment
Treating clinician could decide if dexamethasone was contra-indicated or definitely indicated – these patients were excluded from analysis
Not blinded
Intervention 6mg dexamethasone oral or IV for 10 days
Primary outcome all-cause mortality at 28 days
4.8% not followed for 28 days
Pre-specified sub-group analysis
Intention-to-treat analysis
Decision to stop enrolment in this arm was based on sample size calculations by the blinded trial steering committee – once they could observe 28 day mortality was about 20%, they considered a 4% difference in groups to be clinically relevant (a proportional reduction of one fifth) and estimated that 2000 patients would be needed in the dexamethasone arm

Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report

Peter Horby, Wei Shen Lim, Jonathan Emberson, Marion Mafham, Jennifer Bell, Louise Linsell, Natalie Staplin, Christopher Brightling, Andrew Ustianowski, Einas Elmahi, Benjamin Prudon, Christopher Green, Timothy Felton, David Chadwick, Kanchan Rege, Christopher Fegan, Lucy C Chappell, Saul N Faust, Thomas Jaki, Katie Jeffery, Alan Montgomery, Kathryn Rowan, Edmund Juszczak, J Kenneth Baillie, Richard Haynes, Martin J Landray,
RECOVERY Collaborative Group

doi: https://doi.org/10.1101/2020.06.22.20137273

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Results

Results reported 98 days after protocol was drafted and adopted into practice later the same day

About 15% of hospitalised patients in UK enrolled in trial

2104 dexamethasone

4321 usual care

Mean age 66 yrs, 36% female

24% diabetes, 27% heart disease, 21% chronic lung disease, 56% at least one major comorbidity

82% PCR confirmed Covid-19

At randomisation 16% were already receiving invasive mechanical ventilation or ECMO

60% on O2 only

In dexamethasone arm, median number of days of Rx was 6 days

7% of the usual care group received dexamethasone

Around 24% of patients in both groups received azithromycin and very few received hydroxychloroquine, lopinavir-ritonavir, IL6 antagonists, none remdesivir

Table 1: Baseline characteristics by randomized allocation and level of respiratory support received

	Treatment allocation		Respiratory support received at randomization		
	Dexamethasone (n=2104)	Usual care (n=4321)	No oxygen received (n=1535)	Oxygen only (n=3883)	Invasive mechanical ventilation (n=1007)
Age, years	66.9 (15.4)	65.8 (15.8)	69.3 (17.6)	66.7 (15.3)	59.0 (11.5)
<70	1142 (54%)	2506 (58%)	660 (43%)	2149 (55%)	839 (83%)
≥70 to <80	467 (22%)	860 (20%)	338 (22%)	837 (22%)	152 (15%)
≥80	495 (24%)	955 (22%)	537 (35%)	897 (23%)	16 (2%)
Sex					
Male	1338 (64%)	2750 (64%)	892 (58%)	2462 (63%)	734 (73%)
Female*	766 (36%)	1571 (36%)	643 (42%)	1421 (37%)	273 (27%)
Number of days since symptom onset	8 (5-13)	9 (5-13)	6 (3-10)	9 (5-12)	13 (8-18)
Respiratory support received					
No oxygen received	501 (24%)	1034 (24%)	1535 (100%)	0 (0%)	0 (0%)
Oxygen only	1279 (61%)	2604 (60%)	0 (0%)	3883 (100%)	0 (0%)
Invasive mechanical ventilation	324 (15%)	683 (16%)	0 (0%)	0 (0%)	1007 (100%)
Previous diseases					
Diabetes	521 (25%)	1025 (24%)	342 (22%)	950 (24%)	254 (25%)
Heart disease	586 (28%)	1171 (27%)	519 (34%)	1074 (28%)	164 (16%)
Chronic lung disease	415 (20%)	931 (22%)	351 (23%)	883 (23%)	112 (11%)
Tuberculosis	6 (<0.5%)	19 (<0.5%)	8 (1%)	11 (<0.5%)	6 (1%)
HIV	12 (1%)	20 (<0.5%)	5 (<0.5%)	21 (1%)	6 (1%)
Severe liver disease	37 (2%)	82 (2%)	32 (2%)	72 (2%)	15 (1%)
Severe kidney impairment	167 (8%)	358 (8%)	120 (8%)	253 (7%)	152 (15%)
Any of the above	1174 (56%)	2417 (56%)	911 (59%)	2175 (56%)	505 (50%)
SARS-Cov-2 test result					
Positive	1702 (81%)	3553 (82%)	1198 (78%)	3144 (81%)	913 (91%)
Negative	213 (10%)	397 (9%)	182 (12%)	398 (10%)	30 (3%)
Test result not yet known†	189 (9%)	371 (9%)	155 (10%)	341 (9%)	64 (6%)

Results are count (%), mean ± standard deviation, or median (inter-quartile range). * Includes 6 pregnant women. † SARS-Cov-2 test results are captured on the follow-up form, so are currently unknown for some. There was a significant (2p=0.008) difference in mean age between those allocated dexamethasone and those allocated usual care, but no significant differences between these groups in any other baseline characteristic. The 'oxygen only' group includes non-invasive ventilation.

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454/2104 (21.6%) in dex arm died by 28 days
1065/4321 (24.6%) in std care arm died
0.83; 95% CI 0.74 to 0.92; P<0.001
In mechanically ventilated patients:
rate ratio 0.65 [95% CI 0.51 to 0.82]; p<0.001)
= 35% reduction in 28 day mortality
O2 non-invasively:
rate ratio 0.80 [95% CI 0.70 to 0.92]; p=0.002
No respiratory support:
Rate ratio 1.22 [95% CI 0.93 to 1.61]; p=0.14
Number needed to treat to prevent 1 death among mechanically ventilated patients = 8

Patients on invasive mechanical ventilation at randomisation were on average 10 years younger than those not receiving any support and had symptoms prior to randomisation for 7 days longer
This also meant that there was greater benefit of dexamethasone in patients with symptom duration longer than 7 days

Table 2: Effect of allocation to dexamethasone on main study outcomes

	Treatment allocation			
	Dexamethasone (n=2104)	Usual care (n=4321)	RR (95% CI)	p-value
Primary outcome:				
28-day mortality	454 (21.6%)	1065 (24.6%)	0.83 (0.74-0.92)	<0.001
Secondary outcomes:				
Discharged from hospital within 28 days	1360 (64.6%)	2639 (61.1%)	1.11 (1.04-1.19)	0.002
Receipt of invasive mechanical ventilation or death*	425/1780 (23.9%)	939/3638 (25.8%)	0.91 (0.82-1.00)	0.049
Invasive mechanical ventilation	92/1780 (5.2%)	258/3638 (7.1%)	0.76 (0.61-0.96)	0.021
Death	360/1780 (20.2%)	787/3638 (21.6%)	0.91 (0.82-1.01)	0.07

RR=Rate Ratio for the outcomes of 28-day mortality and hospital discharge, and risk ratio for the outcome of receipt of invasive mechanical ventilation or death (and its subcomponents). Estimates of the RR and its 95% confidence interval are adjusted for age in three categories (<70 years , 70-79 years, and 80 years or older). * Analyses exclude those on invasive mechanical ventilation at randomization.

Secondary outcomes:
Duration of hospitalisation median 12d vs 13 d
Probability of discharge rate ratio 1.11 (95% CI 1.04 – 1.19)
Among those not on mechanical ventilation at baseline:
Rate ratio for progression to invasive mech vent or death was 0.91 (95% CI 0.82 – 1.00, p = 0.049)
Progression to invasive mech vent risk ratio 0.76 [95% CI 0.61 to 0.96]; p=0.021
More detailed analyses of cause-specific mortality, need for renal dialysis or hemofiltration, and duration of ventilation are in preparation.

Discussion

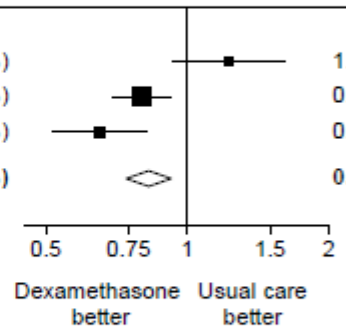
“It is likely that the beneficial effect of corticosteroids in severe viral respiratory infections is dependent on using the right dose, at the right time, in the right patient.”

“The greater mortality benefit of dexamethasone in patients with COVID-19 who required respiratory support, and among those recruited after the first week of their illness, suggests that at this stage the disease is dominated by immunopathology, with active virus replication playing a secondary role.”

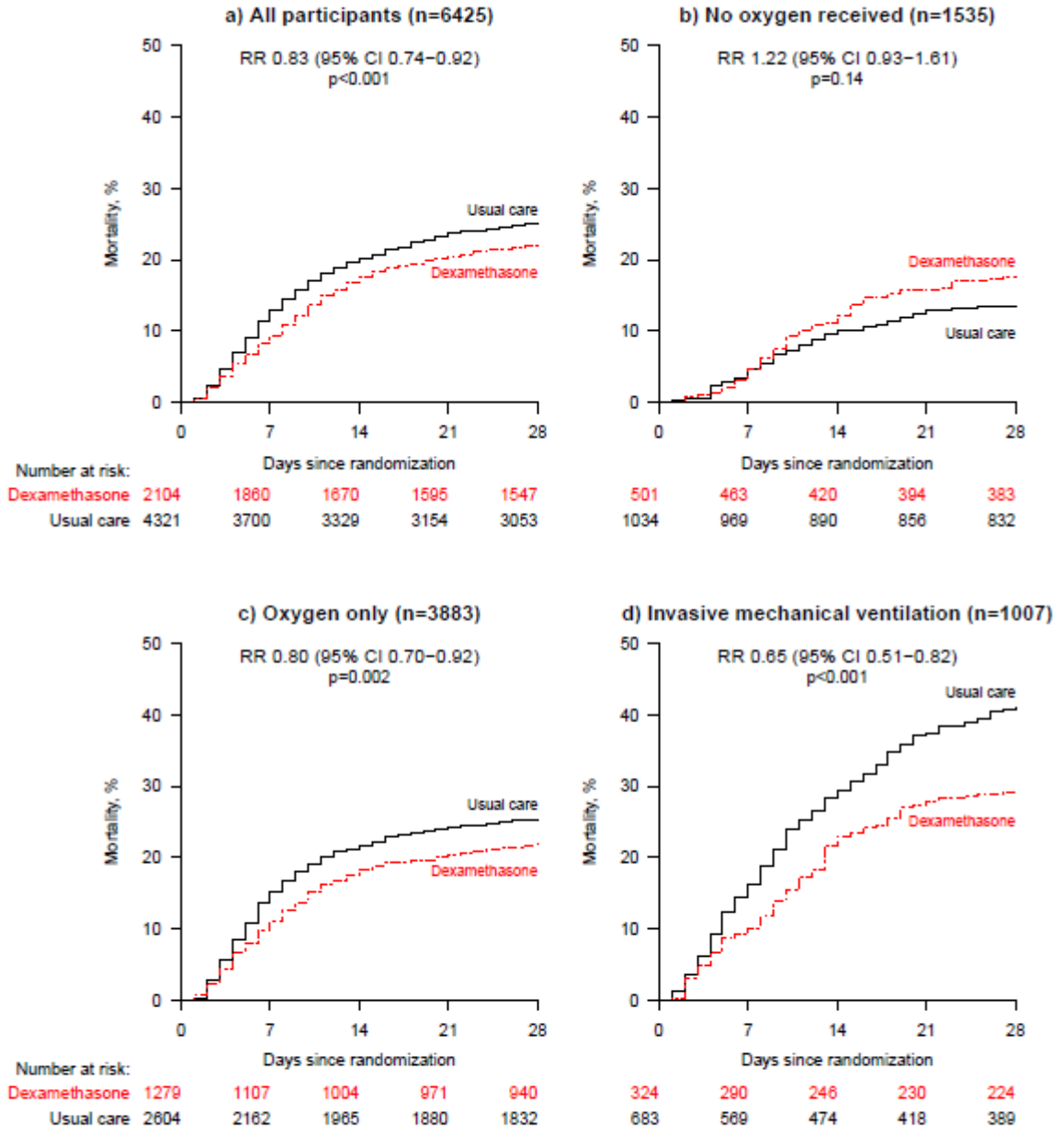
Figure 2: Effect of allocation to dexamethasone on 28-day mortality by level of respiratory support received at randomization

Respiratory support at randomization	Dexamethasone	Usual care	RR (95% CI)
No oxygen received	85/501 (17.0%)	137/1034 (13.2%)	1.22 (0.93–1.61)
Oxygen only	275/1279 (21.5%)	650/2604 (25.0%)	0.80 (0.70–0.92)
Invasive mechanical ventilation	94/324 (29.0%)	278/683 (40.7%)	0.65 (0.51–0.82)
All participants	**454/2104 (21.6%)**	**1065/4321 (24.6%)**	**0.83 (0.74–0.92) p<0.001**

Trend across three categories: χ^2_1=11.49; p<0.001



RR=age-adjusted rate ratio. CI=confidence interval. Subgroup-specific RR estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to the 95% confidence intervals. The 'oxygen only' group includes non-invasive ventilation. Note: in the RECOVERY trial press release of 16 June 2020, effects in subgroups of level of respiratory support received were shown with 99% CIs, not 95% CIs as inadvertently stated. The age-adjusted rate ratio and 99% confidence intervals remain unchanged in this analysis: no oxygen required, RR 1.22 (99% CI 0.86–1.75); oxygen only, RR 0.80 (99% CI 0.67–0.96); invasive mechanical ventilation, RR 0.65 (99% CI 0.48–0.88).



RR=age-adjusted rate ratio. CI=confidence interval. The 'oxygen only' group includes non-invasive ventilation. Note: in the RECOVER trial press release of 16 June 2020, effects in subgroups of level of respiratory support received were shown with 99% CIs, not 95% CI inadvertently stated. The age-adjusted rate ratio and 99% confidence intervals remain unchanged in this analysis: no oxygen required RR 1.22 (99% CI 0.86–1.75); oxygen only, RR 0.80 (99% CI 0.67–0.96); invasive mechanical ventilation, RR 0.65 (99% CI 0.48–0.88).

This summary was prepared by Dr E Maasdorp as part of the daily brief to the TBH ICU team.