A multi-centre retrospective cohort study to examine the effect of high-dose steroids in COVID-19 pneumonitis admitted to Intensive Care with acute respiratory distress syndrome.

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Introduction

Whilst the evidence for low dose early corticosteroids in COVID-19 pneumonitis is well established, the effect of larger steroid doses is yet to be investigated[1]. In this multi-centre, retrospective observational study, we examined the effect of 'pulse dose steroids' on ventilatory parameters in 94 patients with COVID-19. A recent post-hoc analysis of COVID-19 patients failed to demonstrate an improvement in the rate of survival or shorten the duration of mechanical ventilation when corticosteroid were administered in late non-resolving ARDS, however this study did not specifically examine those patients who developed lung fibrosis following the initial alveolar injury or a subsequent organising pneumonia (OP)[2]. Indeed, the decision to pharmacologically immunosuppress critically unwell COVID-19 patients with large dose steroids remains a challenge. Possible beneficial effects of reducing inflammation should be carefully weighed up against the potential deleterious impairment of anti-microbial immunity.[3]

This study was designed to evaluate the effect of short duration high-dose steroids on ventilatory parameters for patients who required prolonged mechanical ventilation with acute respiratory distress syndrome secondary to COVID-19 pneumonitis with and without radiological evidence of fibrosis or organising pneumonia. Secondary outcomes included: 14-day mortality, rate of pneumothorax / pneumomediastinum, and rate of clinically significant fungal infection.

Methodology

This was a multi-centre observational study performed at four teaching hospitals (Hammersmith Hospital, Royal Berkshire Hospital, St Mary's Hospital and Charing Cross Hospital), with the following inclusion criteria: adult patients (≥18 years) requiring invasive mechanical ventilation (with presence of all Berlin definition criteria for ARDS); confirmed PCR SARS-CoV-2 infection; and treatment with high dose steroids for treatment for COVID-ARDS.

Patients either received Methylprednisolone (500mg (n=16), or 1000mg (n=59)) or Dexamethasone (20mg (n=14), or 50mg (n=5)) for a median duration of 3 days. High dose steroids were administered at the discretion of the treating physician. All patients were managed in accordance with a lung-protective strategy, and all patients had received low dose dexamethasone in accordance with latest guidance if they were admitted following the publication of the Recovery trial[1].

Results

- Our data demonstrate a statistically significant improvement in P/F ratios over time, from baseline to day 14, in those patients who received 1g Methylprednisolone (baseline PaO2: 14.47 kPa, Day 3: 17.51 kPa, Day 7: 19.51 kPa, Day 14: 22.87 kPa , $p<0.001$) (Figure 1).
- We observed a statistically significant increase in P/F ratios for those patients who had evidence of fibrosis on CT scan, and whilst some benefit was seen in those patients who did not fibrosis on radiological imaging, this was not statistically significant (Figure 2).
- These data suggest there was a dose-response relationship between high dose steroids and mortality, however we are not able to comment on the statistical significance of this due to underpowering.
- We found no relationship between steroid administration and clinically significant adverse events such as fungal infection or pneumothoraces/pneumomediastinum (Table 1).

Table 1. Baseline patient characteristics

	20mg Dexamethasone	50mg Dexamethasone	500mg Methylprednisolone	1000mg Methylprednisolone
Age (median (IQR))	61 (48-70)	67 (47-71)	59 (50-65)	61 (52-69)
Sex: Male	64.30%	60%	68.70%	69.40%
Rate of dexamethasone 6mg use (%)	13 (93%)	5 (100%)	9 (56%)	43 (73%)
Mortality	28.6%	20.0%	37.5%	50.8%
Confirmed fibrosis/organised pneumonia (%)	7 (50%)	2 (40%)	5 (31%)	21 (35.6%)
Suspected fibrosis/organised pneumonia (%)	6 (42.9%)	3 (60%)	10 (62.5%)	26 (44.1%)
SOFA score (median (IQR))	5 (3-6)	5 (2-8)	5 (3-9)	4 (2-7)
Length of stay in ICU (days, median (IQR))	47 (34-56)	88 (40-122)	44.50 (30.50-61.75)	39 (23-59)
Duration Mechanical Ventilation (days, median (IQR))	44 (31-52)	82 (40-126)	41 (29-57)	37 (20-49)
Time from ventilation to high dose steroid (days, median (IQR))	14 (7-20)	18 (11-23)	16 (10-24)	12 (6-20)
Significant fungal infection requiring treatment	11/14 (78.57%)	1/5 (20%)	14/16 (87.50%)	34/59 (57.62%)
Pneumothoraces/pneumomediastinum	5/14 (35.71%)	5/5 (100%)	4/16 (25%)	8/59 (13.56%)

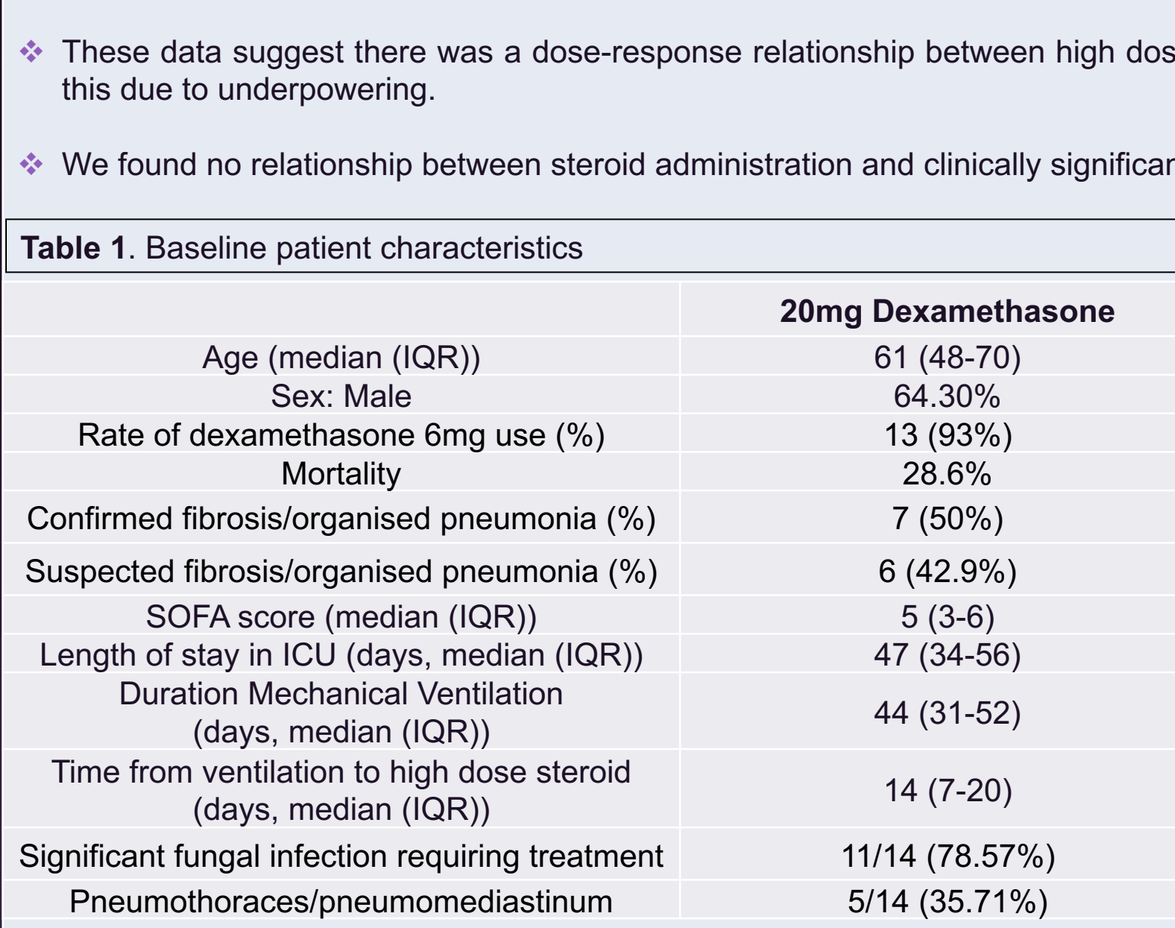

Figure 1. Change in PF ratio on day 0, and day 3, 7, 14 post steroid administration according to type and dose of steroid.
* P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.0001

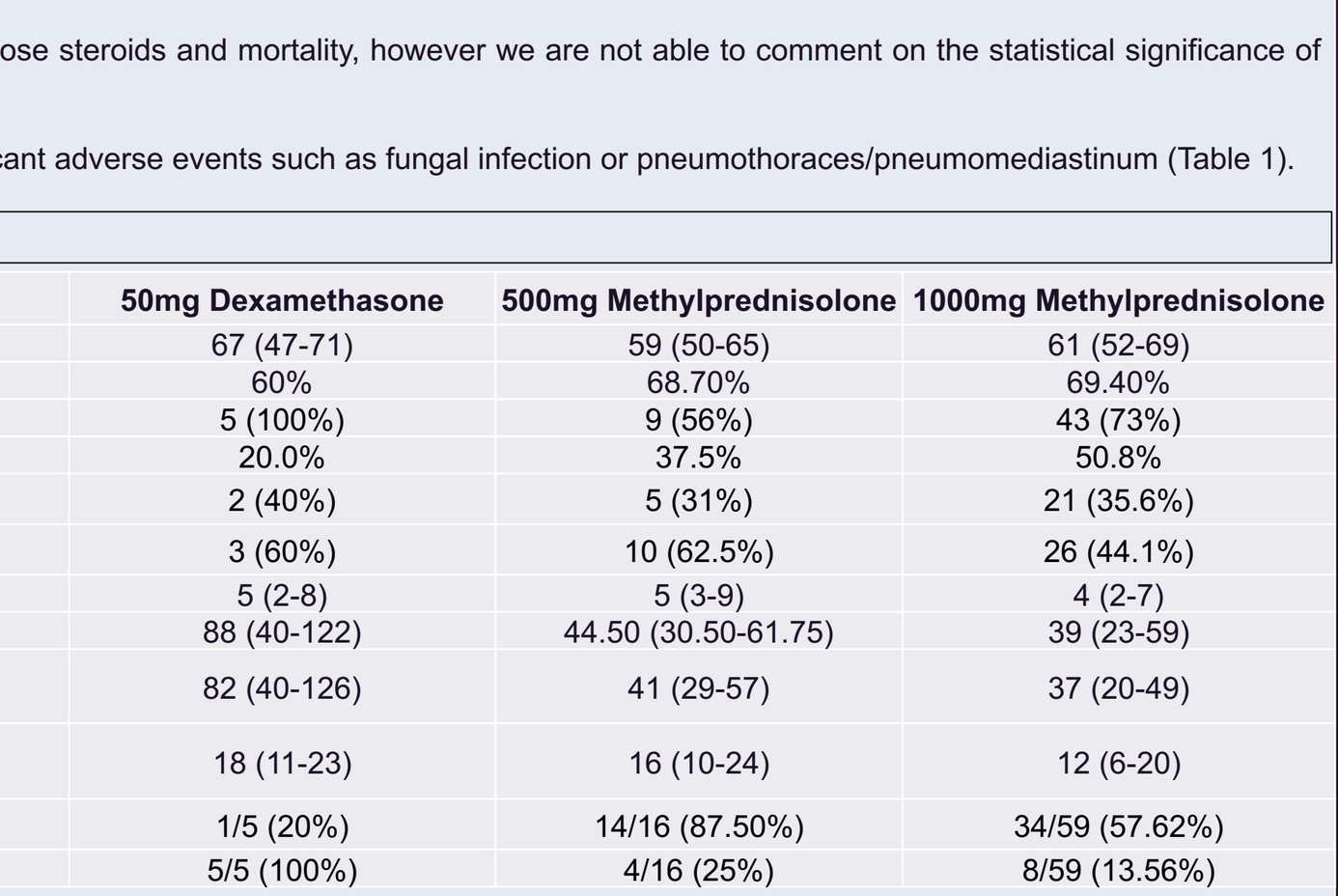

Figure 2. Change in PF ratio on day 0, and day 3, 7, 14 post steroid administration according to presence of radiologically confirmed fibrosis / organising pneumonia.
* P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.0001

Conclusions

These data suggest that high dose, short-duration steroids used in established cases of ARDS due to COVID-19 improve clinically important ventilatory parameters such as PF ratios. Of note, this improvement was greatest in those cases with radiologically confirmed organising pneumonia / fibrosis. However, we are unable to determine the effect of important confounding factors such as survivor bias due to the retrospective nature of this work.
We would recommend that future study is undertaken to determine the clinical effect of high dose steroids in patients with prolonged ARDs in addition to laboratory-based study to investigate potential mechanisms of action.

References

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These authors declare no conflicts of interest.

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