Short Communication

Corticosteroids in adult respiratory distress syndrome – an inconvenient truth?

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Abstract

Objectives Recent studies have demonstrated mortality benefits from corticosteroid use in COVID-19 patients requiring respiratory support. However, clinical practice may warrant the use of corticosteroids outside the context of a clinical trial. Such data are rarely, if ever, reported. We explored the use of corticosteroids for adult respiratory distress syndrome (ARDS) indications in patients with non-COVID ARDS.

Methods We retrospectively studied patients with moderate-to-severe ARDS, admitted to our intensive care unit (ICU) between January 2018 and March 2020.

Key findings Of the 91 patients with ARDS identified, 80% were treated with a corticosteroid during their ICU admission. Of these, 73 (82%) had corticosteroids administered for reasons other than ARDS.

Conclusions Corticosteroid use for non-ARDS indications is commonplace in ARDS patients in our ICU. The use of corticosteroids outside a randomisation process in randomised clinical trials may be more common than appreciated and needs to be routinely reported.

Keywords: COVID-19; respiratory distress syndrome, adult; intensive care unit; corticosteroids

Introduction

Adult respiratory distress syndrome (ARDS) is a life-threatening condition characterised by poor oxygenation and ‘stiff’ lungs, with mortality of 32% and 45% for moderate and severe disease, respectively,[1] with a prevalence of 64.2–78.9 cases/100 000 person-years.[1] The benefit of corticosteroids in COVID-19 patients requiring respiratory support is clear in the light of recent evidence[2] and other trials are still underway.[1] Alongside other recent data supporting the use of corticosteroids in ARDS,[3] this intervention will undoubtedly be revisited in future trials. However, unlike other novel therapeutic interventions in COVID-19-like remdesivir and tocilizumab, corticosteroids are also often considered part of standard clinical care for a variety of non-ARDS indications. The aim of the work reported in this paper was to ascertain the use of corticosteroids for non-ARDS indications in patients with ARDS.

Methods

A retrospective observational single-centre case series review was conducted using data from electronic healthcare records of patients admitted to the intensive care unit (ICU) at University College London Hospital between January 2018 and March 2020 (pre-COVID-19). Our main ICU is an adult, general unit with 35 beds, in a central London teaching hospital that gets tertiary referrals for patients with haematological malignancy. As data on corticosteroid use are collected as part of the routine service at our...
institution, our Research and Development link confirmed that ethical permission was not necessary.

Our electronic health record was searched for mechanically ventilated patients with the phrase ‘ARDS’ in the notes. Their P/F ratios and hospital numbers were extracted into Microsoft Excel. The details of patients identified with moderate-to-severe ARDS, based on the Berlin definition, were manually extracted to Excel for analysis by C.M. and I.P. The radiological scans were reviewed by S.P., C.M. and A.L. Details of any corticosteroid therapy were recorded, including indication, dosing and duration. Anonymised data were used for analysis. Continuous and categorical variables are reported as median (interquartile range) and n (%), respectively.

The corticosteroid regimens were coded as per a classification previously described. Here ‘physiological’ dose is classified as ‘low’ dose at the equivalent of prednisolone 7.5 mg daily, ‘medium’ dose 7.5–30 mg, ‘high’ dose 30–100 mg and ‘very high’ >100 mg.

Results

There were 4817 admissions to our Unit (some of whom were readmissions) during the data collection period. We identified 91 patients who fulfilled the criteria for moderate-to-severe ARDS (Table 1). The median age was 53 (34–66) years, and 55% were male. Haematology/oncology patients accounted for the majority of this cohort (n = 46, 51%), while pulmonary infection accounted for the majority of ARDS aetiology (n = 64, 70%). All patients received invasive mechanical ventilation. Seventy percent of the 91 patients died in the ICU.

Seventy-three (80%) of ARDS patients received corticosteroid treatment during their ICU stay. The time from ICU admission to first dosing was 1 (0–5) day and duration was 7 (3–17) days. Corticosteroid treatment included hydrocortisone for septic shock (n = 40, 54.8%), methylprednisolone/prednisolone for ARDS (n = 13, 17.7%) and methylprednisolone/prednisolone for Pneumocystis jirovecii pneumonia (PJP) (n = 8, 11%) as well as a range of corticosteroids for miscellaneous indications (n = 12, 16.4%). A total of 131 courses were administered, including one-off doses (Table 2), with 20 patients receiving two courses, and 15 more than 2 courses. Many of the miscellaneous indications were for one-off doses of methylprednisolone or dexamethasone for haematological conditions. The regimens are described in Table 2. The doses used were mostly ‘very high’ (including pulse) or ‘high’.

Discussion

In ARDS there is an important disconnect between clinical trial patient selection and clinical practice. A majority of our patients with moderate-to-severe ARDS received corticosteroids, mostly for reasons other than ARDS, and multiple courses were common. Our study results need to be interpreted in the light of two important limitations. Firstly, our haemat-oncological subgroup is not representative or generalisable of the general ICU population. Secondly, there will be between-centre differences in prescribing practices, but the routine use of corticosteroids in patients with ARDS outside the context of a clinical trial is likely to be commonplace.

The high number of miscellaneous steroid doses observed in our study highlights the importance of documenting the indication as

| Table 1 Demographics of patients with ARDS |
|------------------------------------------|
| Demographic baseline Results (number of patients and % or median and interquartile range) |
| | Gender | Results (number of patients and %) |
| | Female | 41 (45.1%) |
| | Male | 50 (54.9%) |
| | Age | 53 [34–66] |
| | Weight (kg) | 70 [58–83] |
| | ARDS severity | Moderate 22 (24.2%) Severe 69 (75.8%) |
| | ARDS aetiology | Pulmonary infection 64 (70.3%) Non-pulmonary infection with sepsis 11 (12.1%) |
| | APACHE II score | 23 [17–27] |
| | Primary speciality | Haematology/oncology 46 (51%) Gastroenterology 9 (9.9%) Infectious diseases 9 (9.9%) Thoracic surgery 9 (9.9%) General surgery 4 (4.4%) General medicine 4 (4.4%) Respiratory 2 (2.2%) Other 8 (8.8%) Diabetes 15 (16.5%) Renal replacement therapy 42 (46.2%) Length of stay (days) 17 [9–25] ICU mortality 64 (70.3%) Patients on steroid treatment 73 (80.2%) Haematology/oncology 32 (94%) Non-haematology/oncology 27 (68%) Steroids length of treatment (days) 7 [3–17] |
| | Total | 91 |

| Table 2 Description of courses of corticosteroid treatment |
|----------------------------------------------------------|
| Steroid course/one-off doses | ARDS (N = 13) | SS (N = 40) | PCP (N = 8) | MISC (N = 70) Total (N = 131) |
| First | 7 (9.6%) | 22 (30.1%) | 5 (6.8%) | 39 (53.4%) 73 (100%) |
| Second | 4 (5.5%) | 12 (16.4%) | 3 (4.1%) | 16 (21.9%) 35 (47.9%) |
| Third | 2 (2.7%) | 3 (4.1%) | 0 | 10 (13.7%) 15 (20.5%) |
| Fourth | 0 | 3 (4.1%) | 0 | 3 (4.1%) 6 (8.2%) |
| Fifth | 0 | 0 | 1 (1.4%) | 1 (1.4%) |
| Sixth | 0 | 0 | 1 (1.4%) | 1 (1.4%) |

ARDS, adult respiratory distress syndrome; MISC, miscellaneous; N = number of courses; PJP, Pneumocystis jirovecii pneumonia; SS, septic shock.

ARDS and PCP regimen both comprise methylprednisolone and prednisolone; SS comprises hydrocortisone; MISC represents other regimens.
part of the daily dynamic of medicine reconciliation. The high doses of corticosteroid used here for non-ARDS indications may have implications if corticosteroids are studied in ARDS or COVID-19. For example, a previous analysis reported that increased corticosteroid doses were linked to worsened mortality in sepsis.[7]

Up to 25% of patients are excluded from clinical trials of ARDS because of underlying disease requiring long- or short-term concomitant corticosteroid use.[8] ARDS trials may also exclude patients with active cancer. Subsequent corticosteroid courses for other indications are often not reported.[9, 10] Similarly, some studies exploring the use of corticosteroids excluded patients who had received corticosteroids before admission[11–13] or who required corticosteroids acutely for any indication other than COVID-19[11] or were expected to need corticosteroid use.[8] ARDS trials may also exclude patients with established active cancer. Subsequent corticosteroid courses for other indications were allowed for new other indications. Indeed in the RECOVERY study,[14] 8% received corticosteroids in the usual care group.

Conclusions
In our centre, most of the moderate-to-severe ARDS patients are treated with corticosteroids for reasons other than ARDS. Clinical trials investigating the utility of corticosteroids in COVID-19 and non-COVID-19 ARDS exclude patients who are treated with other corticosteroids before[4, 8, 9, 12, 13] or during ICU admission.[4, 8, 11, 12] It is therefore difficult to extrapolate the findings of these studies to routine clinical practice, which should have implications for the design of future clinical trials.

Author Contributions
R.S. and N.A. wrote the manuscript and conceived the study. C.M. and I.P. collected data and analysed results. A.L., S.B. and S.P. verified aspects of the data. R.S. and N.A. wrote the manuscript and conceived the study. C.M. and I.P. collected data and analysed results. A.L., S.B. and S.P. verified aspects of the data.

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Conflict of Interest
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