Corticosteroids in critical COVID-19: Are all corticosteroids equal?

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Background. The hyperinflammation seen as part of a dysregulated immune response to SARS-CoV-2 in its most severe form leads to acute respiratory distress syndrome (ARDS), multiorgan failure and death. Corticosteroid therapy targets this hyperinflammation, otherwise known as a cytokine storm. It is the only therapeutic agent to date with a mortality benefit, with clear guidelines from national and international health authorities guiding its use.
Objectives. To compare severity-of-illness indices, survival, length of intensive care unit (ICU) stay and potential ICU complications in patients treated with different corticosteroid regimens (high-dose hydrocortisone, high-dose methylprednisolone and lower-dose dexamethasone).
Methods. In this single-centre descriptive retrospective observational study of a cohort of patients with severe COVID-19 admitted to a COVID-dedicated ICU, we compared patients treated with the three different corticosteroid regimens.
Results. In 242 cases we could not demonstrate any statistically or clinically significant difference in the outcome of patients with critical COVID-19 treated with high-dose intravenous hydrocortisone (n=88) or methylprednisolone (n=46) compared with a relatively lower dose of dexamethasone (n=108). The survival rates were 38.6%, 39.1% and 33.3%, respectively (p=0.68). Patients treated with methylprednisolone tended to have a shorter length of ICU stay (median (interquartile range) 6 (4 - 10), 4 (2 - 8) and 5 (2 - 8) days; p=0.015) and fewer episodes of nosocomial sepsis (47.7%, 32.6% and 48.1%; p=0.01).
Conclusions. Hydrocortisone or methylprednisolone can be given as an alternative to dexamethasone in the management of critical COVID-19, and this is a feasible alternative, especially in resource-constrained settings.

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SARS-CoV-2 is the third known coronavirus within the past 18 years to cause severe respiratory illness, its predecessors being severe acute respiratory syndrome (SARS) in 2002 and Middle East respiratory syndrome (MERS) in 2012.[1,2] Although the case fatality rate of SARS-CoV-2 infection is lower than those for SARS and MERS, COVID-19 has caused far greater loss of human life.[1,3]

SARS-CoV-2 enters the host predominantly via angiotensin-converting enzyme 2 receptors on pulmonary alveolar type 2 cells, causing in its most severe form widespread alveolar damage with microvascular thrombosis. If the initial innate antiviral immune response is unsuccessful in its attempts to eliminate the pathogen, a complex immune response ensues, characterised by excess proinflammatory mediators such as interleukin-2, interleukin-6 (IL-6), interleukin-7, interleukin-10, granulocyte colony-stimulating factor, interferon-gamma-induced protein 10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1A, tumour necrosis factor, and a dysregulated interferon response. This cytokine storm further inhibits adequate T-cell responses, potentially progressing to severe disease with ARDS, multiorgan dysfunction and death.[1,2,4-7]

Several therapeutic interventions are continuously being investigated, with a multitude of trials underway investigating treatment strategies based on the stage of disease progression. As per the South African (SA) National Department of Health (NDoH) rapid review summaries of 2020, only the correct use of corticosteroid therapy has been shown to have mortality benefit in the management of COVID-19.[8]

The use of corticosteroids in the treatment of COVID-19 was controversial in the early stages of the pandemic.[2] Based on earlier studies of SARS and MERS, the World Health Organization (WHO) advised against the routine use of corticosteroids owing to lack of mortality benefit, delay in viral clearance and the risk of steroid-related side-effects.[1,9] Throughout the early phase of the pandemic corticosteroid use was variable, but owing to the IL-6-driven hyperinflammation and subsequent cytokine storm evident in the critically ill, various institutions opted to include corticosteroids as part of their standard of care for severe COVID-19.[1,3,4,10]

The COVID-19 intensive care unit (ICU) at our institution opted to include high-dose corticosteroids as of April 2020. High-dose intravenous hydrocortisone was used because of its general availability and low cost, and was later replaced by high-dose methylprednisolone and ultimately lower-dose intravenous dexamethasone after the provisional data from the Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial became available.[11]

Objectives

The main objective of this study was to compare the severity of illness indices, survival, length of ICU stay and potential ICU complications in patients treated with different corticosteroid regimens (hydrocortisone, methylprednisolone and dexamethasone).

Methods

All patients with confirmed SARS-CoV-2 pneumonia admitted to the COVID-19 ICU at Tygerberg Hospital, Cape Town, SA, for respiratory support were enrolled into a prospective registry. The registry was approved by the Health Research Ethics Committee (HREC) of Stellenbosch University (ref. no. N20/04/002_COVID-19) and Tygerberg Hospital.

We extracted the data on all patients admitted from 26 March to 18 July 2020 who received at least one dose of a corticosteroid (which became standard practice as of 13 April) and excluded patients who received none. Data captured included patient demographics, comorbidities, laboratory data, indices of severity, length of ICU stay, survival, and potential complications related to corticosteroids. The indices of disease severity included the sequential organ failure assessment (SOFA) score and the arterial oxygen partial pressure to fraction of inspired oxygen ratio (PaO_2/FiO_2). Concomitant use of anticoagulants and other pharmacotherapies was documented.

High-flow nasal oxygen (HFNO) therapy was utilised as initial oxygenation for patients who were fully awake and co-operative at the time of admission, and failure of HFNO (either mechanical ventilation or sudden death) was recorded.[12] Therapeutic dose anticoagulation with enoxaparin was routinely used unless a clear contraindication was present.

We compared the data of three sequential cohorts, patients managed with: (*i*) high-dose intravenous hydrocortisone (100 - 200 mg 6-hourly); (*ii*) high-dose intravenous methylprednisolone (40 mg 12-hourly); and (*iii*) lower-dose intravenous dexamethasone (8 mg once daily). Intravenous corticosteroids were routinely given for 10 - 14 days at the time of the study. The retrospective comparison of data was also approved by the HREC of Stellenbosch University (ref. no. S20/07/003_COVID-19).

Statistical analysis

Categorical variables were expressed as frequencies and percentages and were compared using Pearson's χ^2 tests or Fisher's exact tests. Continuous variables were expressed as medians with interquartile ranges (IQRs) and were compared using the Kruskal-Wallis test.

Results

A total of 248 patients were admitted from 26 March to 18 July 2020, of whom 242 received intravenous corticosteroids. The baseline characteristics and outcome data of the three cohorts are summarised in Table 1. Of note is that all three cohorts had a mean PaO_2/FiO_2 <100. The majority of the patients had at least one comorbidity (Table 1). The hydrocortisone cohort had a higher SOFA score and mean C-reactive protein compared with the other cohorts.

The majority of the patients in all three groups received enoxaparin 1 mg/kg bd (81 of 88 patients in the hydrocortisone group, 46 of 46 in the methylprednisolone group, and 106 of 108 in the dexamethasone group). We could not demonstrate any statistically or clinically significant difference in the outcome of patients with critical COVID-19 treated with high-dose intravenous hydrocortisone or methylprednisolone compared with a relatively lower dose of dexamethasone (survival rates 38.6%, 39.1% and 33.3%, respectively; p=0.68). Patients treated with methylprednisolone tended to have a shorter length of ICU stay (median (IQR) 6 (4 - 10), 4 (2 - 8) and 5 (2 - 8) days; p=0.015) and fewer episodes of nosocomial sepsis (47.7%, 32.6% and 48.1%; p=0.01).

Discussion

In this single-centre observational study of 242 patients managed in a COVID-19-dedicated ICU we could not demonstrate any statistically or clinically significant difference in the outcome of patients with critical COVID-19 treated with high-dose intravenous hydrocortisone or methylprednisolone compared with a relatively low dose of dexamethasone. Patients treated with methylprednisolone tended to have a shorter length of ICU stay and fewer cases of nosocomial sepsis.

Prior to the landmark RECOVERY trial,[11] no pharmacological intervention had shown a clear mortality benefit in severe and critical COVID-19 disease. The investigators reported that dexamethasone reduced death by one-third in patients receiving invasive ventilation and by one-fifth in patients receiving oxygen without invasive ventilation. There was no evidence of benefit in steroid use for those not receiving respiratory support.[11] At our institution, these findings led to an immediate change in the standard of care with regard to corticosteroids.

Pre-RECOVERY, the expert opinion regarding steroid use was variable, with poor-quality data from mostly observational studies pertaining to SARS, MERS and influenza guiding current management and opinion, stating the need for more robust randomised control trials (RCTs). As per WHO recommendation, steroid use was discouraged, but studies assisting in the evaluation of its efficacy and safety were prioritised. Subsequently, the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group evaluated corticosteroid therapy and 28-day mortality in severe and critical COVID-19 disease in a meta-analysis of seven RCTs involving institutions in 12 countries with different corticosteroids at differing doses.[13-16] Their findings echoed those of RECOVERY, with the main mortality benefit shown in those who are critically ill, and showed similar mortality benefit for dexamethasone and hydrocortisone.[13-16]

In the WHO review of two meta-analyses of eight RCTs, it was estimated that the use of corticosteroids resulted in 87 fewer deaths per 1 000 critically ill patients and 67 fewer deaths per 1 000 patients in the severely ill cohort.[15] They defined critical COVID-19 by the criteria for acute respiratory distress syndrome, sepsis, septic shock or other conditions that would normally require the provision of life-sustaining therapies such as invasive or non-invasive mechanical ventilation.[15] Their findings aligned with those of the REACT group regarding adverse events, except noting a possible increase in episodes of hyperglycaemia and hypernatraemia.[15] Current WHO guidelines include corticosteroid therapy as part of the standard of care in the management of the severe and critically ill COVID-19 patient, advocating 6 mg of dexamethasone orally or intravenously daily or 50 mg of hydrocortisone intravenously 8-hourly for 7 - 10 days.[15]

The initial arbitrary daily dose of 6 mg dexamethasone in the RECOVERY trial was given on the premise that higher doses were likely to be associated with harm and delayed viral clearance.[11] The REACT meta-analysis noted that while a formal comparison

Table 1. Baseline characteristics and main outcomes of the three cohorts

	Hydrocortisone (*N*=88)	Methylprednisolone (*N*=46)	Dexamethasone (*N*=108)	*p*-value
Demographics				
Age (years), median (IQR)	54.0 (44 - 60)	52.0 (47.5 - 59.0)	54.5 (46 - 62)	0.58
Sex (male), *n* (%)	53 (60.2)	32 (69.6)	56 (51.9)	0.11
Comorbidities, *n* (%)				
Type 2 DM	52 (59.1)	24 (52.2)	47 (43.5)	0.09
Hypertension	42 (47.7)	25 (54.3)	63 (58.3)	0.33
HIV	17 (19.3)	4 (8.7)	16 (14.8)	0.02
Indices of severity, median (IQR)				
PaO_2/FiO_2 ratio	60 (51 - 87)	61.5 (49.8 - 85.3)	59.5 (44.8 - 82)	0.87
SOFA	4 (3 - 5)	4 (3 - 4)	3 (2 - 4)	<0.01
Special investigations, median (IQR)				
WCC ($\times 10^9$/L)	11.7 (9.1 - 15.7)	11.2 (9.0 - 14.8)	11.8 (8.9 - 15.5)	0.95
Neutrophil count ($\times 10^9$/L)	8.6 (6.3 - 11.5)	9.7 (7.3 - 12.0)	10.5 (7.7 - 13.0)	0.12
Lymphocyte count ($\times 10^9$/L)	1. (0.7 - 1.4)	1.0 (0.8 - 1.3)	0.8 (0.6 - 1.1)	0.01
N/L ratio	8.58 (5.50 - 13.18)	9.2 (6.4 - 14)	12.8 (8.1 - 17.8)	0.001
CRP (mg/L)	245 (142.0 - 331)	188 (121.8 - 316.8)	177 (119.3 - 279.3)	0.014
PCT (µg/L)	0.56 (0.25 - 1.65)	0.55 (0.2 - 2.4)	0.5 (0.23 - 1.0)	0.13
Ferritin (µg/L)	1 370 (799 - 2 305)	1 412 (898 - 2 890.8)	843 (458.5 - 1 284.8)	0.001
D-dimer (mg/L)	1.2 (0.4 - 9.15)	1.43 (0.4 - 13.1)	1.01 (0.63 - 3.76)	0.76
Trop T (ng/L)	11 (6 - 21)	16 (8 - 34)	15 (8.25 - 39.8)	0.26
HbA1c (%)	7.4 (6.5 - 101)	6.8 (6.1 - 8.7)	6.6 (6.1 - 10.0)	0.38
Creatinine (µmol/L)	70 (60 - 87)	73.5 (63.8 - 100.3)	65.5 (57 - 83)	0.94
eGFR (mL/min/1.73 m^2)	98 (82 - 110)	96 (76.3 - 107.3)	98.5 (82 - 107.8)	0.38
Survival, *n* (%)				
ICU	34 (38.6)	18 (39.1)	36 (33.3)	0.68
Hospital	34 (38.6)	18 (39.1)	33 (30.6)	0.23
Failed HFNO, *n* (%)				
Intubated	47 (53.4)	23 (50.0)	69 (63.9)	0.18
Sudden death	6/52 (11.5)	6/27 (22.2)	13/71 (18.3)	0.42
Overall	48/80 (60.0)	26/43 (65.1)	69/97 (71.1)	0.12
Length of stay (days), median (IQR)				
Overall	7 (4 - 10)	5 (3 - 9)	6 (3.9 - 10)	0.08
ICU	6 (4 - 10)	4 (2 - 8)	5 (2 - 8)	0.015
Complications, *n* (%)				
Nosocomial sepsis	42 (47.7)	15 (32.6)	52 (48.1)	0.01
AKI	34 (38.6)	13 (28.3)	44 (40.7)	0.76

IQR = interquartile range; DM = diabetes mellitus; PaO_2/FiO_2 = arterial oxygen partial pressure to fraction of inspired oxygen ratio; SOFA = sequential organ failure assessment; WCC = white cell count; N/L ratio = neutrophil to lymphocyte ratio; CRP = C-reactive protein; PCT = procalcitonin; HbA1c = glycated haemoglobin; eGFR = estimated glomerular filtration rate; ICU = intensive care unit; HFNO = high-flow nasal oxygen; AKI = acute kidney injury.

between a higher- and lower-dose corticosteroid and its association with mortality was not possible, a higher dose of corticosteroids was unlikely to have additional benefit.[16] In our cohorts using a higher dose hydrocortisone and methylprednisolone, there was no statistically significant mortality benefit. However, a recent review of the pharmacological principles guiding prolonged glucocorticoid treatment in ARDS suggested a potential superior response to a higher dose of corticosteroid administration by maximising glucocorticoid receptor saturation.[17] The review also favours an individualised course of corticosteroids, uniquely tailored to individual inflammatory response, as well as a gradual tapering to prevent a rebound inflammatory response. Meduri and colleagues[17,18] further stated that prolonged, higher-dose corticosteroid therapy was associated with a decrease in complications probably related to a shorter time of mechanical ventilation. Our data suggest that patients treated with a higher dose of methylprednisolone compared with the standard-dose dexamethasone had a shorter length of ICU stay and fewer episodes of nosocomial sepsis, consistent with the authors' findings.

In the SA NDoH review of potential therapies,[8] the routine use of agents such as lopinavir-ritonavir, ivermectin, remdesivir and tocilizumab has been discouraged based on present available evidence showing no mortality benefit. A review of the available evidence, as well as a review of the WHO meta-analysis pertaining to corticosteroid therapy in the management of severe and critical COVID-19, concluded that corticosteroid therapy is indicated in the treatment of hospitalised patients needing respiratory support (either invasive or non-invasive oxygen therapy).[8] COVID-19 has affected both high- and low-income countries, and it is of importance that there should be equitable access to and distribution of therapeutic agents that have proven mortality benefit. Corticosteroids are inexpensive and widely available, and therefore a feasible option for a developing region such as southern Africa to use in a widespread manner.

Study strengths and limitations

The main strength of our study is that standard therapy and disease severity of patients admitted to the ICU remained largely unchanged apart from the choice of steroid therapy. The main limitations of our study are the lack of randomisation to the type of corticosteroid used and the lack of a control group (who did not receive any corticosteroids). Furthermore, relatively few patients received methylprednisolone, which may limit the generalisability of our finding with regard to a shortened length of ICU stay and fewer episodes of nosocomial sepsis. Other limitations include the lack of Kidney Disease Improving Global Outcomes (KDIGO) acute kidney injury (AKI) staging data and subsequent need for dialysis and the use of other COVID-related illness severity scores to further assess AKI and disease severity in our cohorts.

Conclusions

Our data further support evidence that hydrocortisone or methylprednisolone can be given as an alternative to dexamethasone in the management of patients with critical COVID-19, and that this is a feasible alternative, especially in resource-constrained settings.

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