CASE REPORT

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Corticosteroid therapy for 2019-nCoV-infected patients: A case series of eight mechanically ventilated patients

| Mabrouk AL-Rasheedi ¹ 🕩 | Yasir Alhazmi ² Nouf Almaqwashi ³ Alreshidi Mateq Ali ⁴ | ļ |
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| Abdulaziz Kardam ² Moł | ammod Sharaf ¹ Khawaja Husnain Haider ⁵ | |

¹Albukairyah General Hospital, Ministry of Health, Albukairyah, Saudi Arabia

²Clinical Pharmacy Department, King Faisal Medical City, Abha, Saudi Arabia

³Clinical Pharmacy Department College of Pharmacy, Qassim University, Buraidah, Saudi Arabia

⁴Medical Laboratory Sciences, Sulaiman AlRajhi University, Albukairyah, Saudi Arabia

⁵Department of Basic Sciences, Sulaiman AlRajhi University, Albukairiyah, Saudi Arabia

Correspondence

Mabrouk AL-Rasheedi, Albukairyah General Hospital, Ministry of Health, Albukairyah, Saudi Arabia. Email: mab6208@hotmail.com

Abstract

High-dose short-term corticosteroid therapy is effective and produces favorable clinical outcome in patients with severe 2019-nCoV infection who are candidates for mechanical ventilation with close monitor/ing for the adverse effect of corticosteroids.

KEYWORDS

2019-nCoV, ARDS, corticosteroids, COVID-19, MERS, methylprednisolone, SARS

1 | INTRODUCTION

We report an eight case series of severe acute respiratory syndrome after 2019-nCoV infection who were treated with intensive high-dose short-term corticosteroid therapy in a single institutional, retrospective, and observational study. The treatment successfully resolved bilateral infiltration in all patients, improved their O_2 saturation, and alleviated the need for mechanical ventilation.

Since the publication of the first reports about 2019-nCoV spread in Wuhan, China, in 2019, more than a million people have died due to 2019-nCoV pneumonic infection, and the ever-increasing number of infected patients has exceeded a whopping figure of 38 million in more than 190 countries, thus gaining the proportion of a pandemic.^{1,2} It spreads through respiratory droplets between close contact, defined as within 6 feet of the person and at least 15 minutes spent in

proximity. Incidentally, this is the third spread of coronavirus during the last two decades after SARS-CoV and MERS-CoV.³ Despite that, the prognosis for most infected patients has been encouraging; the effect of the virus has been devastating for others. Although much has been published regarding the transmission dynamics, disease progression, and its severity,⁴⁻⁷ the most frequent complication of 2019-nCoV is the onset of acute respiratory distress syndrome (ARDS) that is characterized by desquamation of the pneumocytes, the formation of the hyaline membrane, and pulmonary edema in 60%-70% of those admitted to the intensive care unit (ICU).^{4,8} Within a week from the onset of the disease, the severely affected patients may develop dyspnea and hypoxemia, which quickly progress to ARDS and get aggravated by the cytokine storm, thus leading to refractory respiratory failure besides multi-organ failure.⁹⁻¹² Approximately 20% of 2019-nCoV cases may develop ARDS, ~62% progressing to

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| Age | 55 y old | 56 y old | 57 y old | 37 y old | | | |
|---|---|---|------------------------|------------------------|--|--|--|
| Gender | Male | Male | Female | Male | | | |
| Weight (Kg) | 70 kg | 80 kg | 76 kg | 90 kg | | | |
| Admission date | 28/08/2020 | 12/09/2020 | 02/09/2020 | 25/08/2020 | | | |
| Initial symptoms | Abdominal pain, constipation, cough, SOB, febrile, dyspneic, and desaturated. | Fever, vomiting, nausea, anorexia for 20 d and SOB. | Fever, cough, and SOB. | SOB, cough, and fever. | | | |
| Comorbidity | HTN | DM | HTN | HTN | | | |
| Corticosteroid Therapy (Starting high dose) Dose of Methylprednisolone | | | | | | | |
| | 1 gm/once/infuse 500 mg /twice / 500 mg /twice /infuse 1 g /once/infuse infuse | | | | | | |
| Outcome | Improved | | | | | | |

TABLE 1 Baseline characteristics of COVID-19 confirmed patients

Abbreviations: DM: diabetes mellitus; HThy: hypothyroidism; HTN: hypertension; SOB: Shortness of breath.

severe symptoms and even death.¹³ There are many low prognosis indicators of ICU-admitted COVID patients, such as deep vein thrombosis and pulmonary embolism. Therefore, anticoagulant therapy is recommended for COVID patients.¹⁴

Social-distancing and the use of face masks remain the most rigorously practiced and effective preventive measures to curtail the spread of viral infection.¹⁵ Simultaneously, urgent pharmacological intervention for 2019-nCoV infectionrelated ARDS is warranted to minimize the rate of mortality. In the management of advanced cases, extracorporeal membrane oxygenation, and related forms of whole-body management in intensive care units could save less than 50% of patients.¹⁶ Therefore, it is crucial to find novel ways to treat patients with ARDS caused by 2019-nCoV for better a prognosis.¹⁷ Successful efforts have led to the development of 2019-nCoV-specific vaccine. Besides, the preclinical and clinical assessment of the existing pharmacological agents encompassing antimalarial quinine/hydroxyquinoline to the current antiviral drugs, that is, remdesivir, lopinavir, and broad-spectrum antibiotics, that is, azithromycin and even stem cells.¹⁸⁻²¹ Despite the recent availability of RNA and heat-killed virus-based vaccines, it will require Herculean effort to vaccinate every individual worldwide.

In many cases, corticosteroid therapy has been used with encouraging results that have prompted World Health Organization (WHO) to issue particular guidelines for potentially effective life-sustaining pharmacological intervention.²² The WHO's new guidelines are based on the data obtained from two meta-analyses, including eight randomized trials and 7184 patients. Our retrospective study was designed to investigate the clinical course and treatment timeline in eight patients (three males and five females) suffering from severe ARDS caused by 2019-nCoV infection. The patients were

mechanically ventilated and received short-term high-dose corticosteroid therapy. The critical finding of our retrospective study reveals significant benefits of high-dose corticosteroids in 2019-nCoV-infected patients.

2 | MATERIALS AND METHODS

Between August and September 2020, eight patients (three males and five females) were admitted to the ICU at Albukairyah General Hospital, Qassim, Kingdom of Saudi Arabia, with the 2019-nCoV infection that was confirmed by real-time PCR-based testing kit. The patients showed signs of ARDS as their oxygenation levels started to decline steadily when the average Fio2 of patients at 55% and oxygen saturation drop down to around 70%. Each patient was maintained on high-flow oxygen therapy as a supportive treatment using high-flow nasal cannulas to help improve their oxygen levels.

The median age of the patients included in the study was 56.5 years and comorbidity diseases, such as diabetes (37.5%), hypertension (62.5%) and asthma, and anemia (12.5%), respectively.

3 | RESULTS

The demographic data and baseline clinical features have been summarized in Table 1. It took an average of ten days to progress from becoming symptomatic to intubation. Upon onset of ARDS symptoms and the worsening of patients' hemodynamic conditions and all of them started on mechanical ventilation, they were administered with an intravenous

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| 43 y old | 83 y old | 72 y old | | 71 y old |
|------------------------|---|-------------------|--|-----------------------------------|
| Female | Female | Female | | Female |
| 68 kg | 81 kg | 90 kg | | 71 kg |
| 17/08/2020 | 03/09/2020 | 03/09/2020 | | 05/09/2020 |
| SOB, cough, and fever. | Fever, cough, anorexia, abdominal pain for one day and body ache. | | ough, breathing difficulty, e, and her appetite was poor. | Fever, cough, and SOB for 3 days. |
| DM | None | HTN | | DM, HTN, Asthma, HThy & Anemia |
| 500 m, | g /twice /infuse 500 | mg /twice /infuse | 1 g/once /infuse | 500 mg/ once / infuse |

of methylprednisolone 1000 mg once daily or in divided doses every 12 hours by infusion over four hours for three consecutive days. After this, the dose was adjusted to 0.8 mg/ kg once daily and then tapered down to wean off. The average duration of steroid therapy was ten days. After having received high doses, the patients' average temperature dropped, and there was a significant reduction in demand for oxygen therapy, and eventually, their intubation was removed. The average time of patients' ventilation support was 4 days. All patients getting steroid therapy showed improvement in arterial blood gases and other relevant parameters upon completion of therapy, as summarized in Table 2. The patients also received β -lactam + azithromycin or quinolones to treat secondary pneumonia that occurred as one of the complications of COVID-19-like ARDS. All patients were also subcutaneously administered low molecular weight heparin as prophylaxis for venous thromboembolism. No secondary infections were observed in the patients after steroid therapy. Still, some side-effects of corticosteroid treatment have been documented, including hyperglycemia, and high WBC counts during 10-days monitoring of the patients. Most patient X-rays showed extensive bilateral lung consolidation before starting the high-dose and short-term therapy of methylprednisolone, which showed improvement by three days after the onset of treatment (Figure 1).

4 | DISCUSSION

Our retrospective study presents the data involving eight mechanically ventilated patients suffering from ARDS after 2019-nCoV infection. The most significant finding of our series of eight cases is that high-dose short-term treatment with methylprednisolone effectively reduces the mortality rate in

TABLE 2 Table showing recorded changes in patients' ABG in response to steroid therapy

| | | ABG before the start of Methylprednisolone therapy | | | | ABG after completion of Methylprednisolone therapy | | | | | |
|--------|--|--|------|------|------|--|------|------|------|------|------|
| | Date of starting Methylprednisolone | sPO2 | pН | pCO2 | pO2 | HCO3 | sPO2 | pН | pCO2 | pO2 | нсоз |
| Case 1 | 01/09/2020 | 89% | 7.27 | 63 | 56.7 | 23.7 | 95% | 7.43 | 45 | 75.3 | 22.6 |
| Case 2 | 13/09/2020 | 87% | 7.32 | 80 | 63 | 17 | 97% | 7.37 | 37 | 78 | 17.4 |
| Case 3 | 06/09/2020 | 88% | 7.18 | 104 | 60.9 | 27.4 | 93% | 7.32 | 32.9 | 73 | 25.3 |
| Case 4 | 05/08/2020 | 85% | 7.28 | 84 | 56 | 25.8 | 94% | 7.46 | 37.1 | 77 | 26.7 |
| Case 5 | 17/08/2020 | 97% | 7.34 | 44 | 84 | 23 | 89% | 7.36 | 34.5 | 79 | 26.3 |
| Case 6 | 07/09/2020 | 95% | 7.44 | 38.6 | 65 | 26.1 | 96% | 7.38 | 39 | 79 | 24 |
| Case 7 | 07/09/2020 | 88% | 7.55 | 29.5 | 64 | 22.4 | 93% | 7.42 | 41 | 83 | 26.2 |
| Case 8 | 13/09/2020 | 87% | 7.46 | 31.2 | 61 | 23.5 | 92% | 7.36 | 35.7 | 83 | 28 |

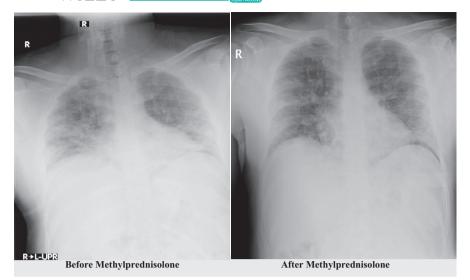


FIGURE 1 A typical chest Xray before and after initiating of methylprednisolone in 2019-nCoV-infected patient. Most of the patient X-rays showed extensive bilateral lung consolidation before starting the high-dose and shortterm therapy of methylprednisolone. After three days of treatment, X-ray showed improvement in lung consolidation. PCR result commonly become negative from ±10 d but the patients still complained from COVID-19 complication

the mechanically ventilated patients suffering from severe 2019-nCoV infection-associated ARDS.

Treatment of the patients with severe 2019-nCoV infection-associated cytokine storm culminating in ARDS remains a therapeutic challenge during the current 2019-nCoV pandemic worldwide. This situation is similar to the previous studies involving SARS-CoV and MERS-CoV patients. They showed a clear relationship between elevated levels of serum proinflammatory cytokines, pulmonary inflammation, and extensive lung damage.^{23,24} Concerning 2019-nCoV infection, cytokine storm has been related to the severity of the disease, and ARDS increases the risk of mortality in patients. Most deaths from the disease occur between one to two weeks after ICU admission.^{4,13} The aberrant release and expression of proinflammatory bioactive molecules and their respective receptors are primarily responsible for the disease progression to ARDS.²⁵ However, a recently published proinflammatory cytokine-profile comparison from 2019-nCoV-infected patients with non-2019-nCoV-infected ARDS patients showed little difference in the levels of 76 cytokines in general, and IL-1, IL-1RA, IL-6, IL-8, IL-18, and TNF- α in particular, using Luminex assay.²⁶ Although these data call into question the prevalent notion that cytokine storm is the primary cause of disease severity and fatal outcome 2019-nCoV-infected patients, further studies in larger patient cohorts are warranted to confirm these findings. This cytokine storm has been attributed to increased viral load rather than aberrant proinflammatory cytokine release.²⁷ Some of the risk factors that significantly influence the clinical outcome after 2019nCoV infection include old age, compromised immune system, organ, and coagulation dysfunction. At the same time, high-grade fever (>39°C) is associated with more likelihood of ARDS but a lower probability of death.¹⁶

In the absence of a 2019-nCoV-specific pharmacological agent, various drugs have been used either singly or combined therapeutic approaches with sporadic

success. Many of these drug combinations are being assessed in several of the clinical trials.²⁸ From among the established antivirals, remdesivir has already progressed to Phase III clinical trials (ClinicalTrials.gov Identifier: NCT04292730).²⁹ We have previously proposed a combined pharmacological approach based on chloroquine/ hydroxychloroquine with passive immune therapy using convalescent patient's serum.²⁰ From among the available armory of pharmacological agents, corticosteroids with pleiotropic effects are well-established anti-inflammatory agents via their multi-step interference of the inflammatory pathway (both genomic and nongenomic) at various steps.³⁰ Pharmacologically, steroids effectively reduce lung injury caused by inflammation in severe forms of illness due to the high levels of cytokines produced during SARS-CoV, MERS-CoV, and SARS-CoV-2 infections.³¹

Nonetheless, the published data from SARS and MERS patients have shown that corticosteroids treatment has little impact on mortality; instead, it delays the viral clearance due to suppression of the immune system.^{32,33} A recently published systemic review has compared the efficacy of corticosteroids in 8 published studies and 4051 patients (3416 SRAS, 360 MERS, and 275 SARS-CoV-2-infected patients).³⁴ Although meta-analysis showed no change in mortality in all three groups of the patients treated with corticosteroids, the study recommends their use in SARS-CoV-2-infected patients unless otherwise contraindicated. Similarly, methylprednisolone treatment lowered the risk of mortality (hazard ratio: 0.38; 95% CI: 0.20-0.72) in a retrospective cohort analysis of SARS-CoV-2-infected patients suffering from ARDS.¹⁶ In contrast, dexamethasone administration at an early stage reduces the need for mechanical ventilation with a low mortality rate in patients with severe ARDS.³⁵

Encouraged by the published reports, we hypothesized that high-dose short-term methylprednisolone therapy in

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mechanically ventilated SARS-CoV-2-infected patients with ARDS would rescue them from lung tissue damage.^{36,37} Following the methylprednisolone-based recommended protocol of the Ministry of Health, Saudi Arabia, we opted to use high-dose methylprednisolone therapy early in the process of respiratory failure at the progression of viral pneumonia-related ARDS. The patients were intravenously administered 1000-mg methylprednisolone, given in one or divided doses for three days followed by low-dose (0.8 mg/ kg) maintenance for 10 days. The short-term high-dose "shock" therapy was favored to avoid worsening patient prognosis reported previously after corticosteroid therapy for SARS and MERS.^{33,34} The initiation of high methylprednisolone dose intravenously reduced patients' fever, improved ABG profile, and weaning from mechanical ventilation within 4 days (4 days) after the start of the protocol. These results are consistent with the study wherein the weaning period was shorter in the hydrocortisone treatment group than in the control group.³⁸ Besides higher survival rates in the critically ill patients, reintubation rates were very low, followed by complete withdrawal of ventilator support in all cases within approximately one week of methylprednisolone therapy. Despite the encouraging data in terms of improved survival in the ventilated patients, our study is not without its limitations. Our data are single-centered, and the patient number is small, thus warranting future studies to further support our findings. Moreover, another limitation is the lack of a control group for comparison of the treatment outcome. Future studies should also focus on the side-effects of steroid therapy on the patients' post-high-dose steroid therapy.

5 | CONCLUSIONS

Our series of patients show that high dose of methylprednisolone for three days followed low-dose maintenance therapy in SARS-CoV-2-infected patients with ARDS may provide a good prognosis in patients with SARS-CoV-2-related complications.

6 | RECOMMENDATION

This study recommended this regimen of treatment in critical patients with COVID-19 who developed ARDS, with close monitoring for adverse effects.

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Published with written consent form of the patients.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

MR: conceived and designed the study. YH: conducted research. NM: provided research material. AK: collected data. Ma and MH: analysed and interpreted data. KH: wrote the initial and final draft of the article. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

ETHICAL APPROVAL

This study was approved from Qassim Ethical Committee, Ministry of Health, KSA

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Mabrouk AL-Rasheedi D https://orcid. org/0000-0002-4730-0575

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