Corticosteroid therapy for 2019-nCoV infected patients: a case series of 8 mechanically ventilated patients

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Objective

To report a series of eight cases of severe acute respiratory syndrome due to 2019-nCoV infection (Covid-19- Bilateral infiltration) who were successfully treated with high-dose short-term corticosteroid therapy.

Methods

In a single institutional, retrospective observational study at Albukairyah General Hospital, Qassim, Saudi Arabia, we report eight 2019-nCoV infected patients (3 male and 5 females) between the ages of 37-83 years with sever bilateral lung infiltration due to pneumonia.

Results

The patients required mechanical ventilation when they were administered high-dose short-term infusions of methylprednisolone for 3 days. Steroid therapy resolved the bilateral infiltration in all 8 patients, improved their O_2 saturation, abrogated their need for mechanical ventilation.

Conclusion

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

Key Clinical Message

This case series describes how dealing with patients who infected with COVID-19 and intubated and also at risk to developed acute respiratory distress syndrome. This recommendation was given a good clinical response.

Key Words

ARDS, Corticosteroids, COVID-19, MERS, Methylprednisolone, SARS, 2019-nCoV.

Introduction

Since the publication of 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]. 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 the majority of the 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, formation of the hyaline membrane, and pulmonary edema in 60% to 70% of those admitted to the intensive care unit (ICU) [4, 8]. Within a week from the onset of disease, the severely affected patients may develop dyspnea and hypoxemia, which quickly progress to ARDS and gets aggravated by the cytokine storm, thus leading to refractory respiratory failure besides multi-organ failure [9-12].

Approximately 20% of 2019-nCoV cases can develop ARDS, which counts for up to 62% mortality [13].

With the non-availability of a vaccine, social-distancing and covering the mouth with masks remain the most rigorously practiced and effective preventive measures to curtail the spread of viral infection [14], while urgent pharmacological intervention for 2019-nCoV infection-related 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 the intensive care units could only save less than 50% of patients [15]. Therefore, it is crucial to find novel ways to treat patients with ARDS caused by 2019-nCoV from progressing to achieve a better prognosis [16]. Efforts are also underway to develop 2019-nCoV-specific vaccine besides the pre-clinical and clinical assessment of the existing pharmacological agents encompassing from anti-malarial quinine /hydroxyquinoline to the existing anti-viral drugs, *i.e,* Remidesivir, Lopinavir, and antibiotics, *i.e.,* azithromycin and even stem cells [17-19]. In many cases, corticosteroid therapy has been used with encouraging results that have prompted World Health Organization (WHO) to issue special guidelines for potentially effective life-sustaining pharmacological intervention [20]. The new guidelines from WHO are based on the data obtained from two meta-analyses including 8 randomized trials and 7184 patients. Our retrospective study was designed to investigate the clinical course and treatment timeline in eight patients (3 male and 5 female) suffering from severe ARDS caused by 2019-nCoV infection. The patients were mechanically ventilated and received short-term high-dose corticosteroid therapy. The important finding of our retrospective study reveals significant benefits of high dose corticosteroids in 2019-nCoV infected patients.

Materials and methods

Between August and September 2020, eight patients (3 male and 5 female) were admitted to the ICU at Albukairyah General Hospital, Qassim, Kingdom of Saudi Arabia, with

2019-nCoV infection that was confirmed by real-time PCR based testing kit. The patients showed signs of ARDS as their levels of oxygenation started to decline steadily. 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 patients had a median age of 56.5 years and comorbidity diseases such as diabetes, dyslipidemia, and hypertension.

Results

The demographic data and baseline clinical features have been summarized in **Table-I & II.** It took an average of 10 days to progress from becoming symptomatic to intubation. Upon onset of ARDS symptoms and the worsening of patients' hemodynamic conditions, they were administered with an intravenous of methylprednisolone1000 mg once daily or in divided doses every 12 hour by infusion over four hours for three consecutive days. After this, the dose was adjusted to 0.8mg /kg once daily and then tapered to. The average duration of steroid therapy was ten days. After having received high doses, the average temperature of the patients dropped and there was a significant reduction in demand for oxygen therapy was reduced, and eventually, their intubation was removed. The average time of patients' ventilation support was four days. The patients were also kept on therapy with B- lactam+ azithromycin or respiratory quinolones to treated the secondary pneumonia that occur as one complication of COVID-19 like ARDS….etc. All patients were also subcutaneously administered low molecular weight heparin as prophylaxis for venous thromboembolism. No secondary infections were observed in the patients subsequent to steroid therapy but some of the side-effects of corticosteroid treatment were documented that included hyperglycemia, as well as high WBC counts. Figure-1 shows typical chest x-rays of a patient before and after methylprednisolone therapy.

Table-1. Baseline characteristics of COVID-19 confirmed patients:

	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**	**Case 7**	**Case 8**
Age	55 years old	56 years old	57 years old	37 years old	43 years old	83 years old	72 years old	71 years old
Gender	Male	Male	Female	Male	Female	Female	Female	Female
Weight (Kg)	70 kg	80 kg	76 kg	90 kg	68 kg	81 kg	90 kg	71 kg
Admission date	28/08/2020	12/09/2020	02/09/2020	25/08/2020	17/08/2020	03/09/2020	03/09/2020	05/09/2020
Initial symptoms	Abdominal pain, constipation, cough, SOB, febrile, dyspneic and desaturated.	Fever, vomiting, nausea, anorexia for 20 days and SOB.	Fever, cough and SOB.	SOB, cough and fever.	SOB, cough and fever.	Fever, cough, anorexia, abdominal pain for one day and body ache.	Fever for 5 days, mild cough, breathing difficulty, dizziness, body ache and her appetite was poor.	Fever, cough, SOB for 3 days.
Comorbidity	HTN	DM	HTN	HTN	DM	None	HTN	DM, HTN, Asthma, HThy & Anemia
Corticosteroid Therapy								
(Starting high dose) Dose of Methylprednisolone								
	1 gm/once/infuse	500 mg /twice /infuse	500 mg /twice /infuse	1 gm /once/infuse	500 mg /twice /infuse	500 mg /twice /infuse	1 gm/once /infuse	500 mg/once /infuse
Outcome	Improved							

Abbreviations: DM: diabetes mellitus; **HThy**: hypothyroidism; **HTN:** hypertension; **SOB:**

Table-II: Table showing recorded changes in patients' ABG in response to steroid therapy.

		ABG before Methylprednisolone					ABG after Methylprednisolone				
	Date of starting Methylprednisolone	**sPO2**	**pH**	**pCO2**	**pO2**	**HCO3**	**sPO2**	**pH**	**pCO2**	**pO2**	**HCO3**
Case 1	01/09/2020	92%	7.48	28.6	24	23.7	95%	7.47	27.3	75.3	22.6
Case 2	13/09/2020	93%	7.37	24	25	17	97%	7.37	26	65	17.4
Case 3	06/09/2020	87%	7.44	40	60.9	27.4	93%	7.44	32.9	73	25.3
Case 4	05/08/2020	97%	7.43	38.2	51	25.8	94%	7.46	37.1	54.4	26.7
Case 5	17/08/2020	77%	7.34	35	46	23	80.9%	7.47	34.5	54	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	90%	7.45	29.5	64	22.4	91%	7.42	41	69.2	26.2
Case 8	13/09/2020	87%	7.46	31.2	61	23.5	92%	7.36	35.7	83	28

Discussion

We present the data from our retrospective study involving eight mechanically ventilated patients suffering from ARDS subsequent to 2019-nCoV infection. The most significant finding of our series of eight cases is that high-dose short-term treatment methylprednisolone is effective in successfully reducing the mortality rate in 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 akin to the previous studies involving SARS-CoV and MERS-CoV patients who showed a clear relationship between elevated levels of serum pro-inflammatory cytokines, pulmonary inflammation, and extensive lung damage [21-22]. Concerning to 2019-nCoV infection, cytokine storm has been related to the severity of the disease and ARDS increases the risk of mortality in patients such that most deaths from the disease occur between one and two weeks after ICU admission [4, 13]. The aberrant release and expression of pro-inflammatory bioactive molecules and their respective receptors are primarily responsible for the disease progression to ARDS [23]. However, a recently published pro-inflammatory 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 Luminax assay [24]. Although these data call in question the prevalent notion that cytokine storm is the major 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 pro-inflammatory cytokine release [25]. Some of the risk factors that significantly influence the clinical outcome after 2019-nCoV

infection include old age, compromised immune system, organ, and coagulation dysfunction while, high-grade fever (>39℃) is associated with more likelihood of ARDS but lower probability of death [15].

In the absence of any 2019-nCoV-specific pharmacological agent, various drugs have been tried singly or as a part of a combinatorial therapeutic approach with sporadic success. Many of these drug combinations are being assessed in several of the clinical trials [26]. From amongst the established antivirals, remdesivir has already progressed to Phase III clinical trials (ClinicalTrials.gov Identifier: NCT04292730) [27]. Previously, we have proposed a combinatorial approach based on chloroquine/ hydroxychloroquine with passive immune therapy using serum from convalescent [18]. From amongst 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 non-genomic) at various steps [28]. Pharmacologically, steroids are effective in reducing 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 [29]. Nonetheless, the published data from SARS and MERS patients have shown that corticosteroids treatment has little impact on mortality; rather it delays the viral clearance due to suppression of the immune system [30-31]. 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) [32]. 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. On the same note, 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 [15]. While the administration of dexamethasone at an early stage

decreases the amount of mechanical ventilation needed and even the mortality rate in those with severe ARDS [33].

Encouraged by these reports, we hypothesized that high-dose short-term methylprednisolone therapy in mechanically ventilated SARS-CoV-2 infected patients with ARDS could rescue them from tissue damage, thereby mitigating the degree of lung injury. 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 before the progression of viral pneumonia-related ARDS. The patients were administered 1000mg given in once or divided dose of intravenous dose of methylprednisolone for three days followed by low-dose (0.8mg/kg) maintenance for ten days. The short-term high-dose "shock" therapy was favored to avoid worsening patient prognosis reported previously after corticosteroid therapy for SARS and MERS [31-32]. The initiation of high methylprednisolone dose intravenously reduced patients' fever, improved their ABG profile and led to weaning from mechanical ventilation within four days (four days) from the start of the protocol. Besides higher survival rate 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 is single-centered and patient number is small thus warranting future studies to further support our findings. Furthermore, future studies should also focus on the side-effects of steroid therapy on the patients' post-high dose steroid therapy.

Conclusion:

our series of patients shows 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.

Recommendation:

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

Author Contribution

All authors were contributed in all this study.

Conflicts of interesting

NA

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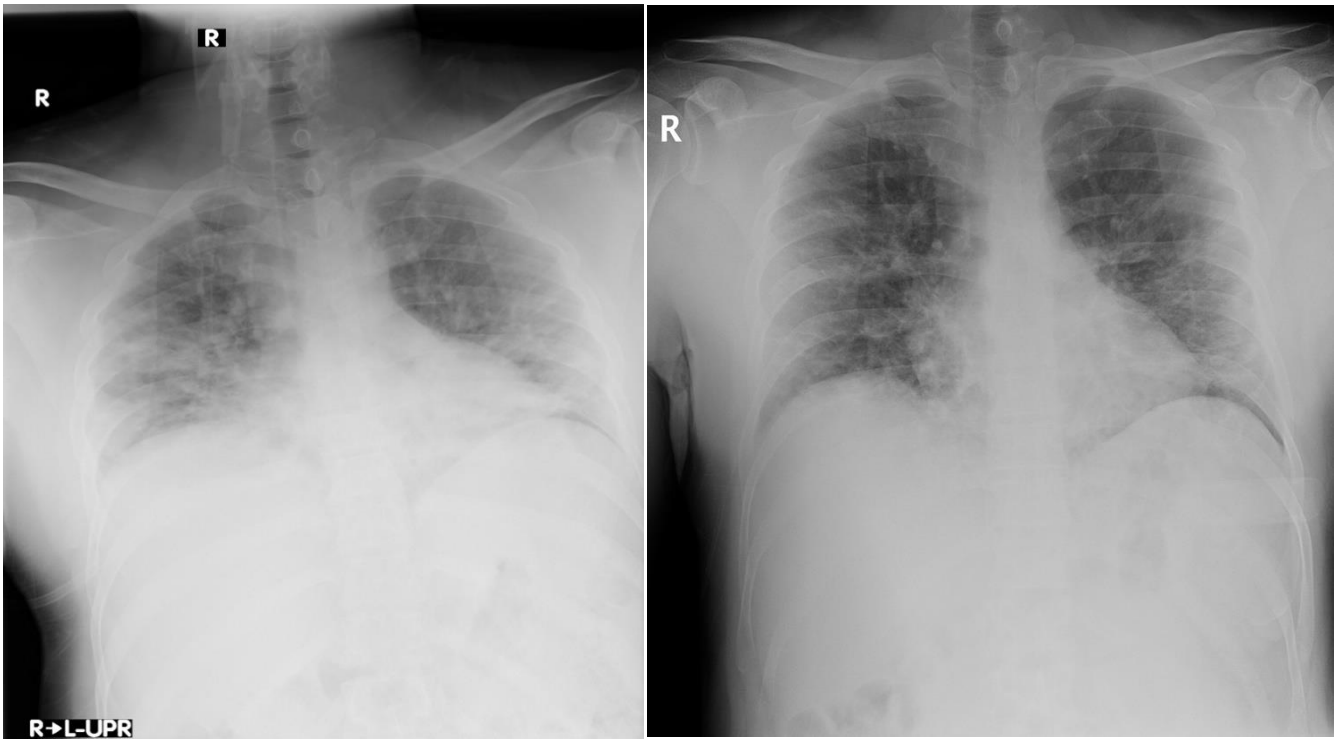
Figures 1



Before Methylprednisolone | **After Methylprednisolone**

Figure-1: A typical chest x-ray 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 short-term therapy of methylprednisolone. After three days of treatment, x-ray showed improvement in lung consolidation. PCR result commonly become negative from ± 10 days but the patients still complained from COVID-19 complication.