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Research Article

The Effect of Steroid Therapy in the Outcome of Severe Cases of COVID Pneumonia and Comparison between Hydrocortisone and Methylprednisolone in Treatment of Severe Cases

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Abstract

Introduction: Recommendation of steroid use in COVID-19 infected patients are still inconsistent. While it is recommended by Surviving Sepsis Campaign for patients with severe disease who are intubated and have ARDS, On the other hand, Infectious disease society of America restricted its use to only randomized controlled trials. This raises the question of whether steroids are beneficial or harmful in treating COVID 19 infected patient, and when is the optimal time of initiation of therapy.

Aim and Objectives: To evaluate the outcome of patients with severe COVID 19 pneumonia who received steroids (Hydrocortisone and Methylprednisolone) from clinical, laboratory and radiological point of view.

Materials and Methods: This is a retrospective observational study at Latifa Women and children hospital, Dubai, within the period of March 2020 - May 2020. Patients diagnosed with severe COVID-19 infection and received steroid treatment were included in the study.

Results: The mean age of all patients was 49 years, and ranging between 40 and 58 years, while the mean body mass index of the study cases was 27.77, ranging between 23 and 32.49. Of the 41 patients, 85.4% of cases were males. Diabetes mellitus, hypertension, hypothyroidism and hyperlipidemia were present in 47.5%, 35%, 4.9 and 2.4% respectively.

Conclusion: Our study showed that there was no significant difference between hydrocortisone and methylprednisolone in the management of cases with severe COVID 19 pneumonia regarding the need of oxygen or mechanical ventilation, length of stay and death.

Keywords: *COVID-19; Coronavirus; SARS-CoV-2; Pneumonia; Steroids; Hydrocortisone; Methylprednisolone*

Introduction

In March 2020, the WHO officially announced Coronavirus outbreak as Pandemic, to date it has effected more than 4.5 Million people worldwide and has a death toll of around 300000, it has led to worldwide crisis in all sectors. There is so much uncertainty and unknown about the virus in addition to significant variability in the course of the disease.

Recommendation of steroid use in COVID-19 infected patients are still inconsistent. While it is recommended by Surviving Sepsis Campaign for patients with severe disease who are intubated and have ARDS, On the other hand, Infectious disease society of America restricted its use to only randomized controlled trials, this recommendation is based on data of steroid use in the treatment of influenza and MERS suggesting that steroid therapy might not be appropriate in the treatment of SARS-CoV-2 infection.

It is observed that infection with COVID 19 has different phases. The first phase is caused by viral replication leading to appearance of mild symptoms, followed by the stimulated immunity phase causing progression of the severity of the disease. Steroid's effect is noted to vary depending upon the timing of starting therapy in comparison to disease phase. If administered in the early stage it can increase the viral replication, might delay adaptive immunity development, hence is expected to be harmful.

During the pulmonary phase, administration of steroids is anticipated to blunt the inflammation severity and subsequently prevent the hyper-inflammation phase. For patients who develop the Cytokines storm which is a severe hyper-inflammation phase, low dose of steroid might be insufficient requiring either higher doses of steroids or specific IL6 targeted immunosuppressive therapy (e.g. tocilizumab). The window for optimal benefit of steroid therapy can be missed if steroid administration was delayed due to fear of side effects.

This raises the question of whether steroids are beneficial of harmful in treating COVID 19 infected patient, and when is the optimal time of initiation of therapy.

Materials and Methods

Study design

This was a retrospective cohort study of adult patients admitted at Latifa Women and Children's Hospital (LWCH), Dubai, UAE, between March and May 2020 during the COVID-19 pandemic who were diagnosed with severe COVID-19 pneumonia.

Patient selection

All patients admitted to Latifa Women and Children's Hospital, Dubai, UAE, during the study period who were diagnosed with severe COVID-19 infection and received steroid treatment were included in the study. Patients were labeled as severe COVID-19 pneumonia if they had one major or three (or more) minor criteria as shown in table 1.

- **Minor criteria:**
  - Patients with respiratory rate > 30 breaths/min
  - Multilobar infiltrates in the chest X ray
  - Confusion/disorientation
  - Uremia (blood urea nitrogen level ≥ 20 mg/dl)
  - Leukopenia (White blood cells < 4000 cells/uL)
  - Thrombocytopenia (platelet count < 100000/uL)
  - Hypothermia (core temperature < 36°C)
  - Hypotension requiring aggressive fluid resuscitation
  - Severe respiratory distress
  - SpO_2 ≤ 93% on room air
- **Major criteria:**
  - Septic shock with need for vasopressors
  - Respiratory failure requiring mechanical ventilation

Table 1: *Shows minor and major criteria to diagnose severe Covid 19 pneumonia.*

Inclusion criteria

- Patients 13 years or older.
- Severe COVID 19 pneumonia.
- Received Steroid therapy as part of management.

Exclusion criteria

- Pregnant women.
- Children less than 13 years old.

Data collection

The data was collected from the computerized registry database. To begin with, there were 41 patients diagnosed as severe COVID-19. Patients were categorized into two groups; the first group (Hydrocortisone group) included 29 patients who treated with hydrocortisone while the second group (Methylprednisolone group) included 13 patients who received the Methylprednisolone.

Demographic data were collected for all study participants, including age, weight, sex, nationality and blood groups. Comorbidities including diabetes mellitus, hypertension, cardiac disease, chronic pulmonary diseases, chronic kidney disease, in addition to risk factors such as smoking and alcohol consumption were included as well.

Other data collected

- Inflammatory markers [CRP, procalcitonin, WBCs count (< 4 x 10^3/uL), lymphopenia (< 1 x 10^3/uL) and thrombocytopenia (< 100 x 10^3/uL)].
- Lactate dehydrogenase (LDH) and ferritin.
- Renal function tests (RFT).
- Liver function tests (LFT).

These data were collected at the time of admission and discharge to evaluate time taken to improve compared with clinical improvement.

Statistical analysis

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS 20). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

Descriptive statistics

1. Mean, Standard deviation (± SD) and range for parametric numerical data, while Median and Interquartile range (IQR) for non-parametric numerical data.
2. Frequency and percentage of non-numerical data.

Analytical statistics

1. Student T Test was used to assess the statistical significance of the difference between two study group means.
2. Mann Whitney Test (U test) was used to assess the statistical significance of the difference of a non-parametric variable between two study groups.
3. Chi-Square test was used to examine the relationship between two qualitative variables.
4. Fisher's exact test: was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells.

Outcome of the study

The primary objective was to compare the effect of the two drugs on the outcome including the morbidity and mortality.

The secondary objective was to observe the clinical outcome by measuring various variables including the duration of hospital stay, the need and duration of ICU admission, the need and duration of oxygen supply, requiring mechanical ventilation and the development of side effects such as hypertension and gastrointestinal complications.

Results

During the study period, 41 patients were labeled to have severe COVID-19 pneumonia out of which 29 patients were included in the first group (Hydrocortisone group) and 13 patients were included in the second group (methylprednisolone group). The mean age of all patients was 49 years, and ranging between 40 and 58 years, while the mean body mass index of study cases was 27.77, ranging between 23 and 32.49. Of the 41 patients, 85.4% of cases were males. Diabetes mellitus, hypertension, hypothyroidism and hyperlipidemia was present in 47.5%, 35%, 4.9 and 2.4% respectively (Table 2).

Cortisone		N	Mean ± SD	%
Age (ys)		41	49.00 ± 9.2	
BMI (%)		40	27.77 ± 4.72	
Gender	Male	35		85.4%
	Female	6		14.6%
Ethnicity	Asian	40		97.6%
	African	1		2.4%
DM	No	21		52.5%
	Yes	19		47.5%
HTN	No	26		65.0%
	Yes	14		35.0%
Hypothyroidism	No	39		95.1%
	Yes	2		4.9%
Hyperlipidemia	No	40		97.6%
	Yes	1		2.4%
Fever	No	2		4.9%
	Yes	39		95.1%
Cough	No	12		29.3%
	Yes	29		70.7%
O_2 requirement	No	0		0.0%
	Yes	41		100.0%
Need of Mechanical ventilation	No	27		65.9%
	Yes	14		34.1%
Multilobular involvement	No	0		0.0%
	Yes	41		100.0%
Leucopenia	No	38		92.7%
	Yes	3		7.3%
Lymphopenia	No	12		29.3%
	Yes	29		70.7%
Abnormal LFT	No	6		14.6%
	Yes	35		85.4%
Abnormal RFT	No	26		63.4%
	Yes	15		36.6%

Thrombocytopenia	No	30		73.2%
	Yes	11		26.8%
Abnormal Ferritin	No	3		7.3%
	Yes	38		92.7%
Abnormal LDH	No	3		7.3%
	Yes	38		92.7%
Death	No	39		95.1%
	Yes	2		4.9%
			Median (IQR)	
Onset of $ prior to admission (days)		39	5 (3 - 7)	
Duration of O_2		39	15 (9 - 26)	
CXR improvement (days)		33	10 (7 - 17)	
Improving Ferritin		24	16.5 (7.5 - 26)	
Improving LDH (days)		21	14 (5 - 27)	
Length of hospital stay (days)		36	19 (15 - 24.5)	
Duration of MV			15.5 (10 - 19)	
Steroid treatment duration			8.0 (5 - 11)	

Table 2: *Description of personal and medical characteristics among all cases.*

There was no significant difference between both study groups regards to personal, medical characteristics and clinical presentation (Table 3).

		Methylprednisolone		**Hydrocortisone**		**t test**	
		N	**Mean ± SD**	**N**	**Mean ± SD**	**p value**	**sig.**
Age (ys)		13	51.00 ± 8.30	12	48.00 ± 9.58	0.337	NS
BMI (%)		28	26.59 ± 4.99	28	28.27 ± 4.61	0.308	NS
		N	**%**	**N**	**%**	**Fisher exact test**	
						p value	**sig.**
Gender	Male	12	92.3%	23	82.1%	0.645	NS
	Female	1	7.7%	5	17.9%		
Ethnicity (Nationality)	Asian	12	92.3%	28	100.0%		
	African	1	7.7%	0	0.0%		
DM	No	4	30.8%	17	63.0%	0.056	NS
	Yes	9	69.2%	10	37.0%		
HTN	No	7	53.8%	19	70.4%	0.480	NS
	Yes	6	46.2%	8	29.6%		
Hypothyroidism	No	13	100.0%	26	92.9%	1.000	NS
	Yes	0	0.0%	2	7.1%		
Hyperlipidemia	No	12	92.3%	28	100.0%	0.317	NS
	Yes	1	7.7%	0	0.0%		

Fever	No	1	7.7%	1	3.6%	0.539	NS
	Yes	12	92.3%	27	96.4%		
Cough	No	5	38.5%	7	25.0%	0.469	NS
	Yes	8	61.5%	21	75.0%		
O_2 requirement	Yes	13	100.0%	28	100.0%		
Need of Mechanical ventilation	No	8	61.5%	19	67.9%	0.734	NS
	Yes	5	38.5%	9	32.1%		
Multilobular involvement	Yes	13	100.0%	28	100.0%		
Leucopenia	No	11	84.6%	27	96.4%	0.232	NS
	Yes	2	15.4%	1	3.6%		
Lymphopenia	No	2	15.4%	10	35.7%	0.276	NS
	Yes	11	84.6%	18	64.3%		
Abnormal LFT	No	1	7.7%	5	17.9%	0.645	NS
	Yes	12	92.3%	23	82.1%		
Abnormal RFT	No	7	53.8%	19	67.9%	0.492	NS
	Yes	6	46.2%	9	32.1%		
Thrombocytopenia	No	7	53.8%	23	82.1%	0.073	NS
	Yes	6	46.2%	5	17.9%		
Abnormal Ferritin	No	0	0.0%	3	10.7%	0.539	NS
	Yes	13	100.0%	25	89.3%		
Abnormal LDH	No	1	7.7%	2	7.1%	1.000	NS
	Yes	12	92.3%	26	92.9%		
Death	No	12	92.3%	27	96.4%	0.539	NS
	Yes	1	7.7%	1	3.6%		
Complication of steroids (HTN)	No	9	75.0%	20	74.1%	1.000	NS
	Yes	3	25.0%	7	25.9%		
Complications of steroids (GIT)	No	11	84.6%	25	89.3%	0.645	NS
	Yes	2	15.4%	3	10.7%		

Table 3: *Description and comparison between the two groups regarding the clinical presentation and laboratory findings.*

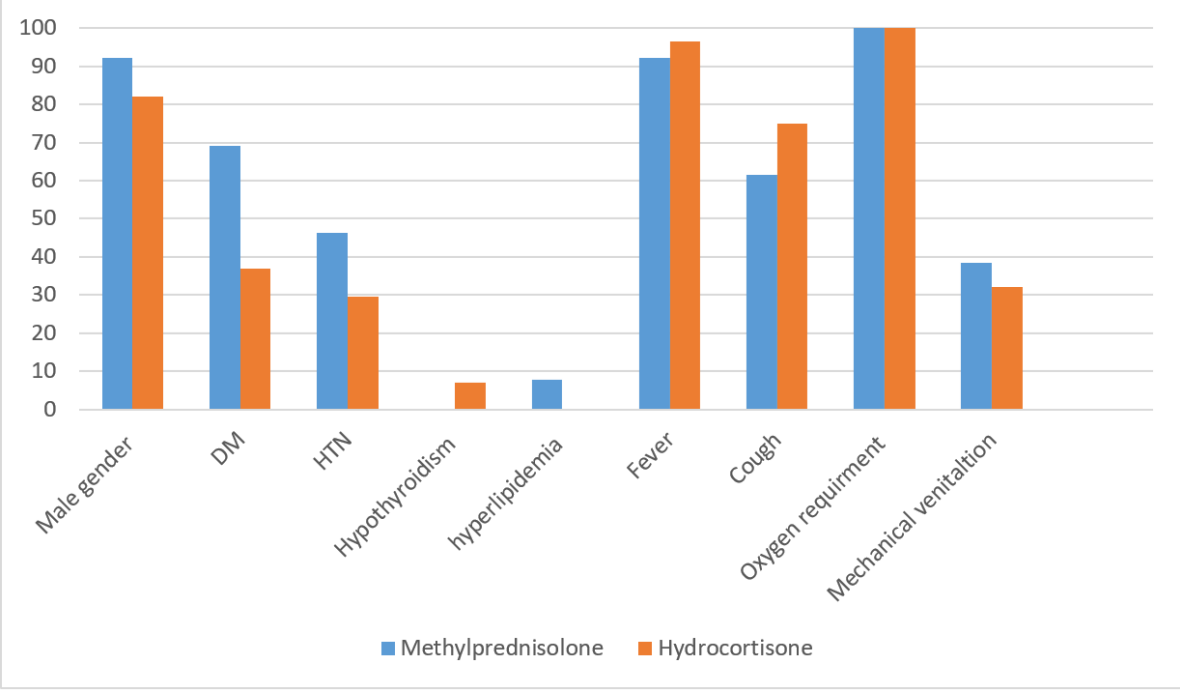
Table 4 shows the comparison between the two study groups regarding the outcome.

Discussion

Our study compared the effect of two forms of steroids hydrocortisone and methylprednisolone that were administered in patients with severe COVID-19 infection and we compared the clinical outcome, as well as improvement of laboratory parameters in both groups. Data was collected retrospectively from the patients' electronic medical records after obtaining approval from our ethical committee for the study.

	Methylprednisolone		Hydrocortisone		Mann Whitney test	
	N	Median (IQR)	N	Median (IQR)	p value	sig.
Onset of $ prior to admission (days)	12	3 (1.5 - 6.5)	27	5 (3 - 7)	0.061	NS
Duration of O_2	13	18 (11 - 26)	26	13 (8 - 22)	0.157	NS
Duration of MV	5	12 (10 - 15)	5	19 (16 - 23)	0.175	NS
CXR improvement (days)	10	10 (7 - 24)	23	11 (7 - 17)	0.922	NS
Improving Ferritin	6	6 (3 - 27)	18	19 (13 - 25)	0.271	NS
Improving LDH (days)	5	14 (13 - 37)	16	13 (4.5 - 26)	0.535	NS
Length of hospital stay (days)	11	19 (16 - 27)	25	19 (15 - 22)	0.481	NS
Steroid treatment duration	13	9 (7 - 12)	28	8 (5 - 10.5)	0.324	NS

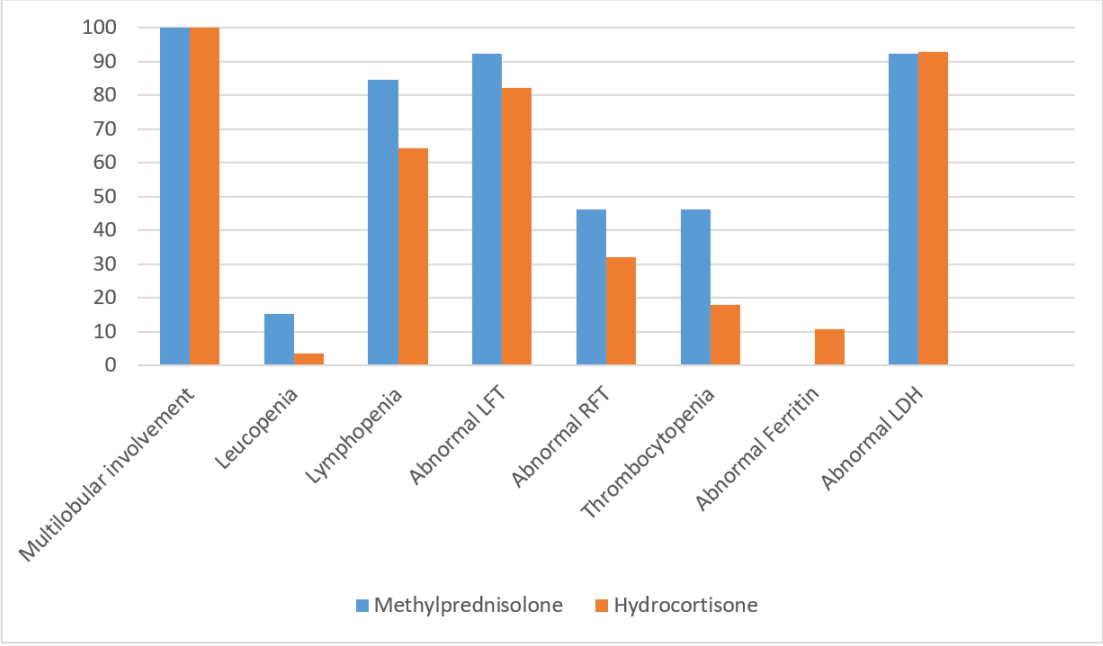
Table 4: *Comparison between the two groups regarding the outcome.*



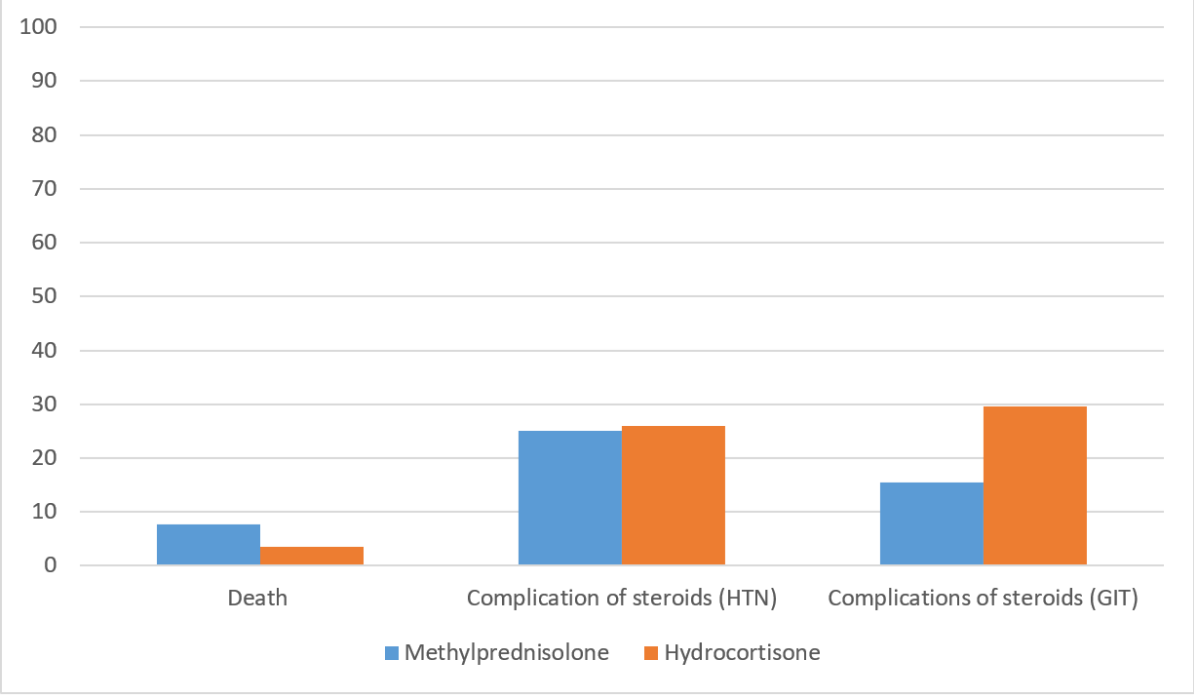
Graph 1: *Description and comparison between the two groups regarding the clinical presentation.*

Our study showed that the mean age for affected patients was 49 years and the mean BMI was 27.77. Males were more commonly affected than females.

The most common presenting symptom in all patients was fever presented in 96.4% of all patients and the median onset of symptoms was 5 days (3 - 7 days). In the full blood count our study showed that leucopenia presented in 7.3%, lymphopenia 70.7% while thrombo-



Graph 2: *Comparison between the two groups regarding radiology and laboratory findings*



Graph 3: *Description and comparison between the two groups regarding morbidity and mortality.*

cytopenia 26.8% of all patients. Other laboratory investigations renal function tests (RFT), liver function tests (LFT), abnormal ferritin and abnormal lactate dehydrogenase (LDH) presented in 36.6%, 85.4%, 92.7% and 92.7% respectively. In the chest X-ray, multilobular involvement was a constant finding in all patients.

All patients needed ICU admission and oxygen support but only 34.1% were in need for mechanical ventilation. In addition, the median oxygen therapy duration was 15 days (9 - 26 days) while the median for mechanical ventilation was 15.5 days (10 - 19 days). Improvement of inflammatory markers LDH and Ferritin took 14 days (5 - 27 days) and 16.5 days (7.5 - 27 days) respectively. The duration of improvement of chest X-ray findings was 10 days (7 - 17 days) and the corticosteroid therapy for all patients was 8 days (5 - 11 days).

Out of 41 patients with severe disease only 2 patients died represented 4.9% and 39 patients discharged home represented 95.1%.

There was no difference between the two groups (hydrocortisone and methylprednisolone) regarding the demographic data, ethnicity and the comorbidities including diabetes mellitus, hypertension, hypothyroidism and hyperlipidemia.

Both groups were comparable regarding the onset of symptoms, presenting symptoms, laboratory and chest X ray findings, need for oxygen support, mechanical ventilation and the duration of corticosteroid therapy used.

Both drugs were observed to be safe, there was no reported complications from both drugs including either hypertension or gastrointestinal complications.

In this study, both study groups showed no significant difference regarding mortality (P value 0.539).

Because COVID-19 is an emerging infectious disease, the optimal treatment for affected individuals has not yet been established. An early study 2016 in china by Long Y., *et al*. which included 5,327 patients. Severe disease was defined as PaO_2 < 70 mm, O_2 saturation < 93% and tachypnea > 30 breaths/minute. Patients with severe disease who received steroid had improved survival, while in patients without severe disease the use of steroid was not beneficial. Moreover, Methylprednisolone when given in doses of > 160 mg/day equally correlated with increased risk of death [1].

Fang X., *et al*. 2020 studied 78 patients admitted with COVID-19 out of which 23 had severe disease and 55 had mild disease, patients were given Methylprednisolone 40 mg/day. It concluded that steroid use had no impact on viral clearance timing (PCR of nasopharyngeal samples) [2]. Furthermore, Wu C., *et al*. 2019 conducted a retrospective study of 201 patients with COVID pneumonia to study the risk factors associated with death in Wuhan, China. It showed that 42% of patients progressed to ARDS, leading to death in around half of them. Steroid was given to severe patients so if reflects worse outcome but among subgroup of patients with ARDS, steroid use has shown decrease in mortality rate. Therefore, it is remarked that steroid use is connected to an overall better outcomes despite its use in most severe patients [3].

In a study done by Shya., *et al*. they concluded that glucocorticoid therapy was found to reduce the duration of fever, but not mortality, duration of hospitalization or lung inflammation absorption. Long-term use of high-dose glucocorticoids increased the risk of adverse reactions such as coinfections, so routine use of systemic glucocorticoids for patients with COVID-19 cannot be recommend [4].

The RECOVERY Collaborative Group reported that dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support [6].

A meta-analysis conducted by Zhenwei Yang., *et al*. concluded that patients with severe conditions of COVID 19 infection are more likely to require corticosteroids. Corticosteroid use is associated with increased mortality in patients with coronavirus pneumonia.

In Summary of the above, it is yet premature to have a definite conclusion. Viral titers might increase if steroids are administered early during the disease course (first five days. On the other hand if given late in the disease course, it doesn't seem to affect viral titer. Although it was mainly administered to sickest patients, steroid therapy was found to improve patient outcomes. This advocates that steroid may be of benefit or at least unlikely that it causes harm.

Our results showed that there is no difference between the two-glucocorticoid drugs hydrocortisone and methylprednisolone regarding the outcome including hospital stay, need and duration of oxygen, mechanical ventilation need and duration, chest X ray improvement and death.

However, this study has several limitations. The small sample size and the short duration as we included patients' data for only 2 months from March to May 2020. The study did not show the follow up of the patients and if they developed any long-term morbidities after discharge. In addition, it did not prove that the use of steroids in the management of severe COVID 19 patients if beneficial or not.

To the best of our knowledge, this is the first study published to compare the hydrocortisone and methylprednisolone drugs in the management of COVID-19 patients.

Conclusion

In conclusion, our study showed that there was no significant difference between hydrocortisone and methylprednisolone in the management of cases with severe COVID 19 pneumonia regarding the need of oxygen or mechanical ventilation, length of stay and death.

Acknowledgement

This work is dedicated to the spirits of all the martyrs of doctors around the world.

Statement of Ethics

All data were collected and analyzed retrospectively in this study. The study was approved by the Dubai Scientific Research Ethics Committee (DSREC) of the Dubai Health Authority (DHA) with reference No. DSREC-05/2020_21.

Disclosure Statement

The authors have no potential conflicts of interest to disclose.

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Author Contributions

E.T.: Analysis, conception, manuscript drafting, critical analysis, and final approval.

E.A.: Design, conception, data acquisition, manuscript drafting, critical analysis, and final approval.

N.A.: Data collection, manuscript drafting, critical analysis, and final approval.

D.H.: Conception, data analysis, manuscript drafting, critical analysis, and final approval.

E.E.: Conception, analysis, manuscript drafting, critical analysis, and final approval.

A.M.: Data collection, manuscript drafting, critical analysis, and final approval.

M.Z.: Data collection, manuscript drafting, critical analysis, and final approval.

A.S.: Data collection, manuscript drafting, critical analysis, and final approval.

M.S.: Data collection, manuscript drafting, critical analysis, and final approval.

M.H.: Data collection, manuscript drafting, and final approval.

H.A.: Data collection, manuscript drafting, and final approval.

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