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ORIGINAL ARTICLE

Role of Oral Corticosteroids in Treatment of Home Isolated COVID-19 Patients

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ABSTRACT

Background: *There is a debate over the efficacy of corticosteroids (CS) in management of Coronavirus diseases 2019 (COVID-19); yet, few are declared about its role in treatment of mild conditions. Objectives: in this study, we aimed at investigating the role of corticosteroids in mild cases of COVID-19.* ***Methodology:*** *in a case control study, we included 100 patients with mild COVID-19. The incidence of improvement, disappearance of symptoms, appearance of new symptoms and deterioration were compared between cases and control group.* ***Results:*** *More than three fourths of the study participants showed improvement of symptoms, with disappearance of symptoms in 64% and 85% of group 1 and group 2, respectively. Only few numbers of patients deteriorated. Noticeably, a remarkable number of patients expressed new symptoms by the end of the study.* ***Conclusions:*** *corticosteroids has no role in clinical progression of cases with mild COVID-19. CS use should be reserved for severe symptoms of COVID-19.*

INTRODUCTION

COVID-19 outbreakis now the most common emerging infectious disease, which threatens the whole world. It was firstly reported in China, nevertheless, since March 12, 2020, COVID-19 was considered a pandemic [1]. Most of the affected patients experience an uneventful recovery; however, approximately 19% of themdevelop severe pneumonia [2]. Both clinical and epidemiological features of COVID-19 patients demonstrate that SARS-CoV-2 infection can lead to intensive care unit (ICU) admission, severe illness (16%–21%) and high mortality rate (2%–3%) [3-5].

During the initial stage of infection, the virus is eliminated through immune-mediated reaction that triggers pulmonary injury. For a while, this response maintains the infection under control. Nevertheless, there is a subsequentlung injury as a result of exaggerated immune reaction [6]. This continues in the second stage of infection with uninhibited viral replication leading to cytokine storm and successive hyperinflammatory condition [7].

DuringCOVID-19 infection, the innate immunity plays a pivotal role in progression of the disease, thus, immunosuppressive medications, such as CS, would be of value in this case. Although many studies reported positive outcomes after CS use for severe COVID-19, there are concerns about risk of concurrent viral dissemination. Examples of the augmenting bodies are the "multinational Surviving Sepsis Guidelines in COVID-19", and the Randomized Evaluation of COVid-19 thERapY (RECOVERY Trial). Both of them recommended CS use in severe COVID-19 with mechanically ventilated patients [8, 9].

Opposing scientists claim that CS use triggered unfavorable outcomes in treatment of similar viruses such as the Middle Eastern Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome Corona virus 1 (SARS-CoV-1) [10,11]. Additionally, the Centers for Disease Control and Prevention (CDC) and the Word Health Organization (WHO) discourage CS use with COVID-19 patients to induce an immunomodulatory response [12,13]. Interestingly, chronic CS consumers who had COVID-19 did not experience deterioration of their illness neither progression to severe pneumonia [14].

While most of the studies investigated the role of CS in management of severe COVID-19, minimal evidence is provided over its effectiveness in mild cases. Thus, this study aimed at evaluation of the role of CS in treatment of COVID-19 in patients with mild lung involvement where home isolation was recommended .

METHODOLOGY

After gaining approval from the Institutional Review Board, a case control study was conducted at the Isolation Department in Suez Canal University Hospital.

After seeking patients' informed consent, we included 100 patients with COVID-19 who had mild lung involvement (less than 20% abnormality) with oxygen saturation more than 95% and fit for home isolation. Patients were divided into two groups: group 1 (cases group) included 50 patients who received oral steroids in the form of prednisolone 20 mg daily plus the other lines of treatment according to the protocol of Egyptian Ministry of Health (Appendix), while group 2 (control group) included 50 patients who did not receive prednisolone. The two groups were matched for age, sex, and comorbidities.

Patients who were dependent on long-term steroid therapy due to autoimmune diseases, lung diseases, or other chronic illnesses were excluded from the study .

Enrolled patients were subjected to complete history taking (personal and medical history), clinical examination, laboratory investigations (nasal swab for COVID-19 PCR, CBC, CRP, ESR, LDH, D-Dimer, serum ferritin) and CT chest.

The CT findings were assessed on a combined score (Appendix), which was calculated from multiplication of four-point scale (to assess the nature of infiltration) by four-point scale (to assess the distribution of infiltration). The first scale ranges from one to four; one is normal attenuation, two is ground glass opacity (GGO), three is mixedGGO and consolidation, and four is consolidation. The latter scale ranges from zero to four; zero as normal, one as <25% abnormality, two as 25%–50% abnormality, three as 50%–75% abnormality, and four as 75% abnormality. Each lung zone-with a total of six lung zones in each patient-was assigned a score on the mentioned scales. Points from all zones were added for a final cumulative score, with a value ranging from zero to 96. This method of assessment was firstly described by Ooi et al in 2004 for assessment of SARS severity 15. The estimated outcomes included the incidence of improvement, disappearance of symptoms, appearance of new symptoms and deterioration. Data analysis was performed using SPSS software, version 25

RESULTS

We compared the patients' characteristics including age, sex, clinical presentation, investigations, and observed outcomes between cases and control group. We found that more than two thirds of patients were males. Around half of the cases were 35 to 44 years old, while nearly half of the control group was of younger age group. The majority of patients were of average BMI. The most common presentations were easy fatigability and fever, whilst the least common features were insomnia and dyspnea. The incidence of these presentations was nearly equal between two groups. Aside from nausea, none of the patients' characteristics showed statistically significant difference between both groups (table 1).

Table 1: Characteristics of patients

Variables	Group 1 n = 50	Group 2 n = 50	P value
Gender			
Male	33 (66)	37 (74)	0.2
Female	17 (34)	13 (26)	
Age			
18-34	17 (34)	21 (42)	
35-54	22 (44)	17 (34)	0.5
55-75	11 (22)	12 (24)	
Comorbidities			
DM	10 (20)	12 (24)	0.4
HTN	15 (30)	17 (34)	0.4
Chronic pulmonary disease	4 (80	2 (100)	0.7
Others[+]	6 (12)	5 (10)	0.3
Clinical manifestations			
Easy fatigability	37 (74)	36 (72)	0.5
Fever	35 (70)	35 (70)	0.5
Bone aches	26 (52)	23 (46)	0.3
Cough	23 (46)	31 (62)	0.08
Anosmia	18 (36)	20 (40)	0.4
Nausea	17 (34)	27 (54)	**0.03***
Headache	13 (26)	14 (28)	0.5
Abdominal pain	12 (24)	10 (20)	0.4
Loss of taste	10 (20)	20 (40)	0.2
Diarrhea	10 (20)	17 (34)	0.08
Chest tightness	10 (20)	8 (16)	0.3
Vomiting	10 (20)	4 (8)	0.07
Insomnia	8 (16)	8 (16)	0.6
Dyspnea	4 (8)	0 (0)	0.05

Presented percentage is column percentage. Others[+] include renal, hepatic, heart diseases. DM: diabetes mellitus, HTN: hyperyension.

Regarding the performed investigations, both of laboratory and CT findings showed approximately matched results between the study groups. Except WBCs, ferritin and D-Dimer, the means of all laboratory tests were within the normal range. The most common radiological finding was GGO, while crazy paving and septal thickening were the least common findings. The only statistically significant finding between the two groups was the mean of LDH level (table 2).

Table 2: Comparison of laboratory and CT findings between the study groups

Variables	Group 1	Group 2	P value
	n = 50	n = 50	
Laboratory findings			
WBCs	6.3 ± 1.6	6.2 ± 1.6	0.8
Lymphocytes	27.3 ± 9.6	28.3 ± 10.3	0.7
CRP	50.2 ± 42.9	52.9 ± 35.5	0.8
ESR	33.6 ± 20.4	27.7 ± 20.8	0.9
LDH	288.9 ± 126.6	353.4 ± 84.1	**0.02**
Ferritin	220.4 ± 413.2	166.8 ± 101.7	0.1
D. Dimer	0.370 ± 0.5	0.334 ± 0.1	0.3
CT findings			
CT score	9.08 ± 3.06	9.60 ± 3.01	
GGO n (%)	45 (90)	47 (94)	0.3
Consolidation n (%)	15 (30)	15 (30)	0.5
Crazy paving n (%)	5 (10)	5 (10)	0.6
Septal thickening n (%)	3 (6)	4 (14)	0.1

Data is presented as mean ± standard deviation, unless otherwise is indicated. Presented percentage is column percentage. WBCs: white blood cells, CRP: C reactive protein, ESR: erythrocyte sedimentation rate, LDH: lactate dehydrogenase.

By the end of the study, over three fourths of the study participants witnessed improvement of symptoms, with disappearance of symptoms in 64% and 85% of group 1 and group 2, respectively. Group 1 witnessed 1.5 times and 1.3 times increase in incidence of improvement, and disappearance of symptoms, respectively. Only few numbers of patients deteriorated. Noticeably, a remarkable number of patients expressed new symptoms. It is worthy to mention that the observed outcomes were not statistically significant different between those who received CS and those who did not (table 3).

Table 3: Comparison of outcome between the study groups

Variables	Group 1	Group 2	OR	CI	P value
	n = 50	n = 50			
Improvement of symptoms	42 (84)	39 (78)	1.5	0.5 - 4.0	0.3
Disappearance of symptoms	32 (64)	29 (58)	1.3	0.6 - 2.9	0.3
Appearance of new symptoms	12 (24)	14 (28)	0.8	0.3 - 2.0	0.4
Deterioration	6 (12)	7 (14)	0.8	0.2 - 2.7	0.5

Presented percentage is column percentage.

DISCUSSION

This study revealed that CS has no role in the course of treatment of mild cases with COVID-19. We reported no difference between those who received prednisolone and those who did not regarding symptoms improvement, appearance, disappearance, or deterioration .

Similar to our findings, multiple previous studies reported no difference in different outcomes between those who received corticosteroids and those who did not. For instance, Lu et al [16] and Gangopadhyay et al[17] found that CS did not affect the mortality rate of critically ill patients with COVID-19. Likewise, Zha et al [18] found no link between corticosteroid use and virus clearance time, hospital length of stay or duration of symptom. Also, the findings of Liang et al 19 study revealed that CS use had no effect on the hospitalization stay, viral shedding or mortality rates of critically ill patients [19].

However, other studies contrasted our findings. Most of the studies that augment CS use in COVID-19 showed positive outcomes when used among patients with ARDS or critically ill [20]. For example, Wu et al 21

reported that methylprednisolone use reduced the risk of death among patients with COVID-associated ARDS. Earlier, the Randomized Evaluation of COVid-19 thERapY (RECOVERY Trial) conducted on patients with COVID-19 showed a significantly improved outcome with dexamethasone in the treatment of severe COVID-19 requiring oxygen therapy or on mechanical ventilator [9].

On the contrary, there is also an evidence that opposes the use of CS. In a retrospective cohort study, Zhou et al[22] stated that high dose CS use was associated with higher in-hospital death.

In addition, Russell et al[23] discouraged the use of CS in cases with SARS-CoV-2 induced lung injury or shock. Ling et al[24] reported that CS caused prolongation of the duration of viral RNA detection. Therefore, based on a Chinese experts' consensus statement, specific criteria were recommended for commencement of CS in patients with COVID-19 including adults; with confirmed laboratory and imaging features; symptoms beginning within 10 days; severe hypoxia, SPO2, tachypnea, and has no oxygen supply [25].

Interestingly, timing, duration, route, and dosage of CS administration would possibly affect the outcomes. Wise choice of CS dose is recommended as dosing-up could be associated with higher mortality risk 16. Many studies reported that early and low to moderate dose of IV methylprednisolone for short term yielded rapid improvement of symptoms[26-29]. Essentially, low dose intravenous hydrocortisone was recommended by the 2017 guidelines of Society of Critical Care and the European Society of Intensive Care Medicine for treatment of septic shock [30].

The majority of the previous studies, unlike our study, assessed CS use in treatment of COVID-19 among cases with severe illness, not mild. Most importantly, those studies were retrospective, with unmatched comparison groups, and limited sample sizes .

CONCLUSION

We concluded that the affected population with COVID-19 is mostly of the old age group with multiple comorbidities. These features would oppose CS use because of their potential adverse effects.

Recommendations: Our results stand against the unnecessary use of CS in mild conditions. This would eliminate the side effects, in addition to reduction of the financial burden during treatment of COVID-19. Studying CS effect on mild disease progression is a less visited area of research that needs further investigations.

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- Each author listed in the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for it.
- This article has not been published anywhere and is not currently under consideration by another journal or a publisher.

Abbreviations:
ARDS: Acute Respiratory Distress Syndrome
COVID-19: Coronavirus diseases 2019
CS: CorticoSteroids
GGO: Ground Glass Opacity

Appendix

1. The protocol of Egyptian Ministry of Health for treatment of COVID-19
- Hydroxycholoroquine 400 mg twice daily in the first day, then 200 mg twice daily for 5 days .
- Azithromycin 500 mg once daily for 5 days.
- Paracetamol thrice daily.
- Vitamin C, Vitamin D and Zinc once daily .

2. Chest CT assessment score : = A × B × number of involved lung zones.

A. Nature of infiltration
1. Normal attenuation
2. GGO
3. GGO and consolidation
4. Consolidation

B. Distribution of infiltration
1. None
2. < 25% abnormality
3. 25%–50% abnormality
4. 50%–75% abnormality
5. 75% abnormality

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