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Research Article

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Effects of Cumulative Doses of Corticosteroids On the Recovery of Patients with Covid-19

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Abstract

Background: *Corticosteroids suppress the immune system and have been proposed as a treatment for the severe form of coronavirus disease 2019 (COVID-19) due to their potential ability to inhibit the COVID-19-induced cytokine storm. We aimed to evaluate the effects of cumulative doses of corticosteroids on the recovery of COVID-19 patients.*

Patients and methods: *In this descriptive cross-sectional study, we retrospectively evaluated patients with COVID-19 (confirmed by polymerase chain reaction [PCR]) receiving corticosteroids at Shahid Mohammadi Hospital, Bandar Abbas, Iran during June-October 2020. All patients had been admitted to the general wards and not the intensive care unit. COVID-19 was not severe in any of the patients. Beside corticosteroids, all patients had received similar standard COVID-19 treatment according to the National COVID-19 Committee protocols. In addition to the demographic features of the patients including age and gender, COVID-19 symptoms, respiratory rate (RR), lactate dehydrogenase (LDH) level, C-reactive protein (CRP) level, oxygen saturation (SpO_2), lymphocyte percentage and count, and lung infiltration (in chest computed tomography) on admission and at the last evaluation before discharge were extracted from the patients' medical files.*

Results: *A total of 200 patients with confirmed COVID-19 were included in this study. The mean age of the patients was 51.65 ± 9.35 years and 117 (58.5%) were male. The administered corticosteroid was dexamethasone in 55%, methylprednisolone in 32.5%, and prednisolone in 12.5%. The mean administered cumulative corticosteroid dose was equal to 82.69 ± 59.40 mg prednisolone. All COVID-19 symptoms, including fever, cough, dyspnea, headache, body ache, and anosmia/ageusia, decreased in the patients. However, there was no significant difference between patients using < 65 mg of corticosteroids and those using ≥ 65 mg of the medicine regarding the final status of symptoms. The increase in SpO_2 was significantly higher in patients using < 65 mg of corticosteroids ($P = 0.008$). Moreover, the proportion of patients with negative final CRP was significantly higher in this group ($P < 0.001$). On the contrary, hospital length of stay was significantly shorter in patients using ≥ 65 mg of corticosteroids ($P = 0.034$). The two groups had no significant differences in terms of LDH levels, lymphocyte percentage and count, RR, and the final status of lung infiltration ($P > 0.05$).*

Conclusions: *While the cumulative dose of corticosteroids equal to < 65 mg of prednisolone is associated with increased SpO_2 and decreased CRP in COVID-19 patients, it leads to prolonged hospital stay compared to the ≥ 65 mg dose of corticosteroids.*

Keywords: Covid-19, corticosteroids, clinical improvement, Shahid Mohammadi Hospital

Introduction

In December 2019, Wuhan, China witnessed the outbreak of a viral disease that soon spread not only within its borders, but also throughout the world. On February 12, 2020, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was caused by a novel coronavirus was officially called coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) [1]. COVID-19 has become globally serious due to its high prevalence, complications, and mortality [2].

Corticosteroids, such as cortisone, dexamethasone, prednisone, and prednisolone, are a group of medications that alleviate inflammation and reduce immune system activities. They resemble cortisol that is naturally secreted from adrenal glands and can

replace endogenous hormones in people with cortisol deficiency [3]. They can mitigate inflammation, hypersensitivity reactions such as asthma, and autoimmune diseases such as lupus and systemic sclerosis. Although corticosteroids are widely used to treat different diseases, they have side effects depending on their dosage and duration of use [4]. High levels of glucocorticoid cause hypercortisolism and, in some cases, Cushing's syndrome, in patients receiving corticosteroids. These medications may also increase the probability of secondary infection, in which case the patient's status will be unpredictable [4]. Corticosteroids are also severely immunosuppressive. Serious diseases, traumas, and surgeries impose great stress on the body, thereby activating the cortisol axis from the brain and elevating the cortisol level [2]. This is, of course, necessary for adapting to stress and regulating metabolism [5]. In many patients with COVID-19, the disease progresses to its critical stage and leads to an overreaction by the immune system. Severe COVID-19 infection can disrupt the cytokine and chemokine balance and the consequent cytokine storm would eventually damage the lung tissue. The level of some molecules, including interleukin 1 (IL-1), IL-2, IL-6, IL-12, tumor necrosis factor-alpha (TNF-α), chemokine (C-C motif) ligand 8 (CCL8), and C-reactive protein (CRP), elevates during this process and the infiltration of neutrophils and macrophages is greatly increased in the lungs and blood, leading to reduced T CD8+ and CD4+ cells in the peripheral blood sample [6].

Damage to the lung tissue by the host cells seems to be a major aspect of COVID-19 infection leading to the acute respiratory distress syndrome (ARDS) which, despite its devastating consequences, does not still have a suitable and definitive treatment [7]. Many physicians and researchers have, therefore, recommended corticosteroid therapy to prevent cytokine storm in patients with COVID-19. At the beginning of the COVID-19 outbreak, hospitals strictly prevented the use of corticosteroids due to their immunosuppressive properties [7]. However, extensive studies on this subject in the past months have yielded contradictory results. According to a retrospective study, corticosteroid therapy delayed the clearance of viral RNA from the respiratory system in Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV), and even influenza. It also caused complications such as mental disorders, diabetes, avascular necrosis, and increased mortality among patients with influenza [8].

The temporary guidelines provided by the WHO on May 27, do not approve of the regular use of corticosteroids for viral pneumonias due to their little benefits and probable adverse effects. The guidelines recommended the treatment only in cases of ARDS, severe asthma attacks, chronic obstructive pulmonary disease (COPD), or septic shock co-morbidities [9]. Despite the large number of patients with COVID-19, very few clinical trials have been conducted on the subject so far and limited studies have confirmed corticosteroids as appropriate solutions to treat the severe form of COVID-19 [10]. Moreover, no clinical trial has reported the net positive impact of corticosteroids in severe cases of COVID-19 [6]. While corticosteroids may become the main treatment option for patients with severe or critical COVID-19, there are extensive contradictions in the literature on their use. Considering the global challenge for finding the proper COVID-19 treatment with minimum side effects, this retrospective study was conducted to examine the effects of the cumulative doses of corticosteroids on patients with COVID-19.

Methods

The statistical population comprised all eligible patients with COVID-19 who were hospitalized in Shahid Mohammadi Hospital, Bandar Abbas, Iran during May-October 2020. Due to the declining number of inpatients at this hospital during the mentioned period, all eligible patients were included (census sampling) and sample size determination was not necessary.

Inclusion criteria: Patients with definitive COVID-19 diagnosis confirmed by polymerase chain reaction (PCR) were included.

Exclusion criteria: Patients with severe COVID-19, ICU admission, immune deficiency, end-stage renal disease, moderate renal deficiency (creatinine clearance: 30-50 mL/min), stage four severe chronic kidney disease, a need for dialysis (creatinine clearance < 30 mL/min), a history of malignancy, a history of recent myocardial infarction or unstable angina, pregnancy, systolic blood pressure > 160 mmHg, or diastolic blood pressure > 90 mmHg were excluded.

This study was approved by the Ethics Committee of Hormozgan University of Medical Sciences (IR.HUMS.REC.1399.511). After extracting the data of all eligible patients from hospital records, individuals were included if they had received corticosteroid therapy. The sum of corticosteroid doses each patient received in different wards was calculated. Each 0.75 mg dexamethasone and each 4 mg methylprednisolone were considered equal to 5 mg of prednisolone. All patients were admitted to the general ward and did not meet the criteria for the diagnosis of severe COVID-19 [11]. These criteria included tachypnea (respiratory rate > 30/min), hypoxemia (oxygen saturation ≤ 93% or PaO_2 < 300), pulmonary infiltration (> 50% lung field involvement in 24-48 hours), lactate dehydrogenase (LDH) > 245 U/I, and progressive lymphocytopenia. In addition to corticosteroids, all patients had received the standard pharmacotherapy based on the National COVID-19 Treatment Committee Protocol as follows [12]:

- Hydroxychloroquine/chloroquine phosphate: Hydroxychloroquine sulfate 200 mg or chloroquine phosphate 250 mg tablet (equivalent of 150 mg baseline dose) two tablets every 12 hours on the first day and then one tablet every 12 hours for 7-14 days; and
- One of the following medications based on the physician's decision:
  - Kaletra (lopinavir/ritonavir) 200 tablet, 50 mg every 12 hours, two tablets after a meal for 7-14 days.
  - Atazanavir/ritonavir 300 mg tablet, one tablet daily with a meal or atazanavir 400 mg daily for 7-14 days.

Patient data including age, sex, lymphocyte count, SpO_2, CRP, LDH, and length of stay in the COVID-19 ward were recorded and entered into SPSS 25 (SPSS Inc., Chicago, IL, USA). Descriptive statistics (e.g. mean and percentage) were used to describe the data. Fisher's exact and chi-square tests were per-

formed to compare the qualitative variables between the two patient groups (receiving < 65 mg or ≥ 65 mg corticosteroids). As the quantitative data of the two groups was not normally distributed (based on the Kolmogorov-Smirnov test results), nonparametric Mann-Whitney U test was adopted for their comparisons. P values less than 0.05 were considered significant.

Results

A total of 200 inpatients with COVID-19, including 117 men (58.5%) and 83 women (41.5%), were studied. Their mean age was 51.65 ± 9.35 years. The mean, standard deviation (SD), minimum, and maximum of quantitative variables at baseline are presented in Table 1.

Table 1: Mean and standard deviation (SD) of quantitative variables at baseline based on descriptive statistics

Variable	Mean	SD	Minimum	Maximum
Age (years)	51.65	9.35	27	66
Baseline respiratory rate	23.51	5.09	12	35
Baseline WBC count (µl)	6686.39	2019.67	3200	10700
Baseline LDH (U/l)	794.79	191.79	365	1263
Baseline lymphocyte percentage (%)	17.83	8.28	5.4	39
Baseline lymphocyte count (/µl)	1123.82	486.79	336	2106
Baseline SpO_2 (%)	88.36	7.53	72	100
Length of hospital stay (days)	8.84	5.55	3	26
Corticosteroid cumulative dose (mg)	82.69	59.40	25	253.33

Table 2: Effects of cumulative doses of corticosteroids on the recovery of patients with COVID-19 based on different variables

Variable		Corticosteroid dose		P-value
		≥ 65 mg	< 65 mg	
Age (Years)		53.7 ± 6.7	55.2 ± 5.4	0.712
Coughs		17	15	0.914
Dyspnea		9%	11%	0.892
Myalgia		11	10	0.921
SpO_2 variations (%)		9.99 ± 4.79	9.8 ± 8.33	0.008
Initial CRP	< 0	10	1	0.006
	+1	12	20	
	2	38	30	
	3	50	49	
Final CPR	< 0	26	44	< 0.001
	+1	34	38	
	+2	15	15	
	+3	25	3	
LDH variations		59.45	97.211	0.062
Lymphocyte variations		524.39	1000.29	0.964
Average length of stay (days)		8.61 ± 6.09	9.07 ± 4.97	-

SpO_2: Oxygen saturation; CRP: C-reactive protein; LDH: Lactate Dehydrogenase

The mean length of hospital stay was 8.84 ± 5.55 days. The mean cumulative dose of corticosteroids (in terms of prednisolone equivalent) was 82.69 ± 59.40 mg.

The elevation in oxygen saturation (SpO2) was significantly greater in the group receiving 65 mg of corticosteroids than the other group. The frequency of patients with negative CRP was increased from one to 44 and from 10 to 26 in the groups receiving < 65 mg and ≥ 65 mg of corticosteroids, respectively. The frequency of patients with CRP equal to +3 was decreased from 41 to three and from 50 to 25 following the administration of < 65 mg and ≥ 65 mg of corticosteroids, respectively. The corresponding reductions were from 30 to 15 and from 38 to 15 in case of CRP equal to +2. Based on chi-square test, the percentage of patients with a negative CRP was significantly higher in the group receiving < 65 mg of corticosteroids than in the other group. Meanwhile the percentage of patients with CRP equal to +3 was significantly lower in the group receiving < 65 mg of corticosteroids than in the other group. Based on Mann-Whitney U test, the mean length of hospital stay was significantly lower in the group taking ≥ 65 mg of corticosteroids than in the other group (P = 0.034). However, the mean reduction in the respirato-

ry rate, LDH, and COVID-19 symptom severity did not significantly differ across the two groups (P = 0.565).

According to Mann-Whitney U test, the mean SpO_2 variations were significantly higher in patients receiving < 65 mg of corticosteroids than in those receiving ≥ 65 mg of the medicine (P = 0.008).

Table 3: Effects of cumulative doses of corticosteroids on the recovery of patients with COVID-19 based on sex classification

Variable			Corticosteroid dose		P-value
			< 65 mg	≥ 65 mg	
SPO_2 variations		Male	11.14 ± 8.6	8.22 ± 6.81	0.129
		Female	8.45 ± 8.19	10.09 ± 0.50	0.003
Lymphocyte variations		Male	-7.35 ± 1.37	-7.39 ± 1.46	0.753
		Female	35.75 ± 0.98	-7.69 ± 1.46	0.774
Average length of stay		Male	7.86 ± 3.59	6.43 ± 0.194	
		Female	4.83 ± 5.8		
LDH variations		Male	186.51 ± 59.33		0.149
		Female	234.45 ± 42.91		
Male sex	Baseline CPR	0	10 (14)	1 (2)	< 0.001
		+1	10 (14)	8 (16)	
		2	8 (11)	21 (42)	
		3	40 (58)	19 (38)	
	Final CPR	0	17 (25)	20 (34)	
		+1	16 (23)	24 (48)	
		+2	11 (16)	4 (8)	
		+3	24 (35)	1 (2)	
Female sex	Baseline CPR	+1	0	12 (24)	< 0.001
		2	22 (68)	17 (34)	
		3	22 (44)	22 (44)	
	Final CPR	0	9 (28)	24 (48)	0.063
		+1	18 (56)	14 (28)	
		+2	4 (12)	11 (22)	
		+3	1 (3)	2 (4)	

SpO_2: Oxygen saturation; CRP: C-reactive protein; LDH: Lactate Dehydrogenase

Based on Mann-Whitney U test, SpO_2 elevation was significantly higher in women taking < 65 mg of corticosteroids than in those taking ≥ 65 mg of the medicine (P = 0.003), but this difference was not significant in men (P = 0.129). Comparisons between men taking < 65 mg and ≥ 65 mg of corticosteroids showed the first group to have significantly higher final negative CRP (P < 0.001). However, this difference was not significant among women (P = 0.062). The mean reduction in respiratory rate was slightly greater in men taking < 65 mg of corticosteroids than in those taking ≥ 65 mg of the medicine (P = 0.729). A similar difference was also detected among women (P = 0.350). The mean LDH reduction was higher in men and women taking ≥ 65 mg of corticosteroids than in their counterparts taking < 65 mg of the medicine. However, Mann-Whitney U test results showed no significant differences between the two groups in neither men nor women (P = 0.149 and 0.194, respectively). Based on Mann-Whitney U test, while the mean length of hospital stay was significantly lower in women taking ≥ 65 mg of corticosteroids than in those taking < 65 mg of the medicine (P < 0.001), no significant difference was observed between the two groups of men (P = 0.685). The mean elevation in lymphocyte count was higher in women who received ≥ 65 mg of corticosteroids than in those taking < 65 mg of the medicine (P = 0.751). Likewise, Mann-Whitney U test indicated no significant difference between the two groups of men (P = 0.783).

Table 4: Effects of cumulative doses of corticosteroids on the recovery of patients with COVID-19 based on age classification

Variable			Corticosteroid dose		P-value
			< 65 mg	≥ 65 mg	
SpO_2 variations	Age	< 50 years	9.96 ± 6.30	10.93 ± 8.10	0.025
		≥ 50 years	8.64 ± 8.56	8.76 ± 3.78	0.057
Lymphocyte variations	Age	< 50 years	-4.49 ± 2.36	-7.2 ± 0.66	0.046
		≥ 50 years	-6.7 ± 0.66	8.62 ± 1.05	0.070
Average length of hospital stay	Age	< 50 years	7.8 ± 6.35	8.14 ± 3.49	0.055
		≥ 50 years	6.03 ± 0.298	9.15 ± 5.19	0.401
LDH variations	Age	< 50 years	-46.34 ± 2.5	-9.75 ± 3.5	0.801
		≥ 50 years	-39.44 ± 0.7	-222.50 ± 1.5	0.26
< 50 years	Baseline CPR	0	0	0	0.42
		+1	10 (25)	10 (29)	
		2	20 (40)	20 (50)	
		3	19 (38)	10 (25)	
	Final CPR	0	20(17)	20 (34)	< 0.001
		+1	16 (23)	24 (48)	
		+2	11 (16)	4 (8)	
		+3	24 (35)	1 (2)	
≥ 50 year	Baseline CPR	+1	0	10 (16)	
		2	10 (20)	0	
		3	21 (42)	30 (50)	
	Final CPR	0	24 (48)	17 (46)	0.050
		+1	22 (44)	28 (46)	
		+2	1 (2)	3 (5)	
		+3	3 (6)	12 (20)	

SpO_2: Oxygen saturation; CRP: C-reactive protein; LDH: Lactate Dehydrogenase

The patients were divided into two age groups of < 50 years (n = 90; 45%) and ≥ 50 years (n = 110; 55%). In both age group, there was no significant difference between patients receiving < 65 and ≥ 65 mg of corticosteroids in terms of COVID-19 symptoms on the final examination. Based on Mann-Whitney U test, SpO2 elevation was significantly higher in patients < 50 years taking < 65 mg of corticosteroids than in their counterparts taking ≥ 65 mg of the medicine (P = 0.025). However, this difference was not significant in patients ≥ 50 years (P = 0.057). In both age groups, the final negative CRP was significantly higher in patients taking < 65 of corticosteroids than in those taking ≥ 65 mg of the medicine (P < 0.001 for < 50 years and P = 0.050 for ≥ 50 years). In the < 50 years group, the mean reduction in the respiratory rate was slightly greater in patients taking < 65 mg of corticosteroids than in those taking ≥ 65 mg of the medicine (P = 0.731). The opposite was true in the ≥ 50 years group (P = 0.798). The mean LDH reduction was significantly higher in patients aged ≥ 50 years who received < 65 mg of corticosteroids than patients of the same age group who took ≥ 65 mg of the medicine (P = 0.026). However, among patients who aged < 50 years, the mean LDH reduction was significantly greater in those taking ≥ 65 mg of corticosteroids than in those receiving < 65 mg of the medicine (P < 0.001). The evaluation of the ≥ 50 years group showed the mean reduction in lymphocyte percentage to be greater in patients taking < 65 mg of corticosteroids than in those taking ≥ 65 mg of the medicine, but this difference was not statistically significant (P = 0.070). In the < 50 years group, the mean reduction in lymphocyte percentage was significantly higher in patients taking ≥ 65 mg of corticosteroids than in those taking < 65 mg of the medicine (P = 0.046). In the < 50 years group, the mean elevation in lymphocyte count was significantly higher in patients taking < 65 mg of corticosteroids than in those taking ≥ 65 mg of the medicine (P = 0.036). While the opposite was true in patients who aged ≥ 50 years, the difference was not statistically significant based on Mann-Whitney U test (P = 0.067). Based on Mann-Whitney U test, in the < 50 years group, the mean length of hospital stay was significantly lower in patients taking ≥ 65 mg of corticosteroids than in those taking < 65 mg of the medicine (P = 0.005), but no significant difference was observed between the two groups of patients who aged ≥ 50 years (P = 0.401).

Discussion

Corticosteroids are immunosuppressive compounds sometimes recommended to prevent cytokine storm in the severe form of COVID-19. The current study aimed to determine the effects of cumulative doses of corticosteroids on the recovery of patients with COVID-19. A systematic review and meta-analysis con-

ducted by Yang et al. demonstrated that treatment with corticosteroids increased mortality, hospital stay, bacterial infections, and hypokalemia, but was not associated with hyperglycemia or hypocalcemia. They concluded that COVID-19 patients with a more critical status have a higher probability of needing corticosteroids, but the medicine correlated with higher mortality in patients with the pneumonia caused by the novel coronavirus [13]. Our findings confirm the mentioned results regarding a longer hospital stay. In our study, the length of hospital stay was significantly higher in patients taking < 65 mg of corticosteroids than in those taking ≥ 65 mg of the medicine, indicating that the relationship between the cumulative dose of corticosteroids and hospital stay was not linear. Similarly, in a multi-center retrospective study by Ma et al., corticosteroids were associated with higher antibiotic use and longer hospital stay [14].

There are conflicting results concerning the effects of corticosteroids on mortality. Bartoletti et al. examined adults with severe COVID-19 and reported that the effects of corticosteroid therapy in decreasing mortality were probably limited to critically-ill cases [15]. Nevertheless, Liu et al. showed that the use of corticosteroids in COVID-19-related ARDS (after adjustment of confounders) was associated with increased 28-day mortality and delayed virus RNA clearance [16]. In a study by Wu et al., corticosteroids did not reduce hospital mortality and the authors concluded that corticosteroids had no advantage in terms of hospital mortality reduction in severe cases and critically ill patients. They did not recommend the routine use of systematic corticosteroids for these patients [17]. Similarly, Liu et al. stated that treatment with corticosteroids was probably unrelated to hospital mortality in COVID-19 patients [18]. Since patient mortality was not evaluated in the current study, these results cannot be compared with our findings.

In this study, the symptoms of all the studied patients considerably improved regardless of the corticosteroid dose. These findings are in line with those of Wang et al. who reported that early, low-dose, and short-term corticosteroid prescription was associated with quicker improvement in clinical symptoms and pulmonary lesions in patients with severe COVID-19 pneumonia [19]. A systematic review by Yang et al. also reported improved clinical symptoms and oxygenation in some of the reviewed clinical observational studies [20]. In the present study, oxygen saturation was significantly increased in the group taking < 65 mg of corticosteroids than in the other group. Meanwhile, the variations in the group receiving ≥ 65 mg of corticosteroids were also positive, suggesting enhanced oxygen saturation in all patients who received corticosteroids. Overall, it seems that the majority of our findings, except for mortality (that was not examined), are consistent with the existing literature. The differences among studies in some results, e.g., the proper dose or type of corticosteroids, could be explained by the differences in the demographic characteristics of the studied populations, underlying diseases, and COVID-19 severity. Notably, the timing, potency, and duration of corticosteroid therapy must be considered when comparing the findings of various studies. To confirm our findings, more studies on larger samples are warranted.

Conclusion

Our findings suggested an association between the cumulative dose equivalent of < 65 mg prednisolone and an elevation in SpO2 and a reduction in CRP in COVID-19 patients. Moreover, the two groups did not significantly differ in terms of LDH variations, lymphocyte count and percentage and respiratory rate.

Age and sex did not affect the final status of the symptoms of the two groups. A significant rise in SpO2 in the group taking < 65 mg of corticosteroids compared to the other group was also observed in women and in patients aged < 50 years. The ratio of patients with a final negative CRP was significantly higher in the group receiving < 65 mg of corticosteroids for both age groups and in men. Age and sex did not affect the variations in respiratory rate. However, LDH reduction was significantly greater in patients aged < 50 years taking ≥ 65 mg of corticosteroids and in those aged ≥ 50 years taking < 65 mg of corticosteroids. Only age (< 50 years), but not sex, affected the variations in lymphocyte count and percentage. The length of hospital stay was significantly shorter in women and in patients aged < 50 years taking ≥ 65 mg of corticosteroids.

A similar multi-center study with a larger sample should be conducted in the entire city, province, or country to obtain more realistic results. A case-control study should also be designed to better specify the effects of the cumulative doses of corticosteroids in comparison with a control group that does not take corticosteroids. Future studies with larger samples are also required to determine the effects of cumulative doses of corticosteroids on mortality. This study was limited by the lack of a control group, due to which the results could not be compared with patients who had not taken corticosteroids.

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