RHEUMATOLOGY RESEARCH JOURNAL

Vol. 5, No. 4, Oct 2020,
Webpage: http://rheumres.org
Email: editor@rheumres.org
ISSN:2476-5856
doi: 10.22631/rr.2020.69997.1104

Original Article Open Access

Glucocorticoids could be safe in COVID-19; a case series

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel virus which has led to a pandemic. There is no approved treatment for coronavirus disease 2019 (COVID-19). Over time, physicians came to understand that in some severe patients, glucocorticoids could be considered as a second line treatment option. As there are a limited number of reports addressing the use of glucocorticoids (GCs) in patients with moderately severe COVID-19, this article presents the results in patients who referred to our national team and received glucocorticoids as part of their medication.

This descriptive and prospective study iincludes 35 clinically-diagnosed moderate to severe COVID-19 cases in outpatient and inpatient settings. Patients received intravenous dexamethasone, oral prednisolone, and pulsed methylprednisolone. Demographic data, clinical signs and symptoms, laboratory and chest CT findings of patients were recorded.on average Men comprised 60% of this group of patients.on admission Lymphocyte counts were depleted in a majority of patients (54.3%). Shortness of breath, O2 sat, and respiratory rate improved 48 to 72 hours after administration of glucocorticoids. Almost all patients had favorable clinical courses were improved during treatment with glucocorticoids, except one who had superimposed bacterial and candida infection. CT scan findings showed bilateral peripheral patchy infiltrations with ground glass opacities as the dominant pattern of lung involvement (60%). One patient was admitted to the intensive care unit. The results of our study showed that the administration of glucocorticoids in the early stages of COVID-19 disease is not only effective, but is also safe and prevents the progression of the disease.

Keywords: COVID-19, Glucocorticoids, Safety

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel virus has led to a pandemic within a few months (1). Symptoms can vary drastically; some carriers may be asymptomatic, whereas others can experience acute respiratory distress syndrome (ARDS) and death. There is no approved treatment for coronavirus disease 2019 (COVID-19); supportive management is recommended according to each patient's history. Various antiviral treatment options were mentioned in guidelines such as remdesevir, lopinavir/ritonavir, interferon, ribavirin, and arbidol (2).

Apart from immune-booster agents (i.e. antivirals), the role of immunomodulation is a matter of dispute among practitioners involved in managing patients with COVID-19. Yufang et al. proposed a two-phase model pathophysiology of the novel coronavirus invasion, highlighting the role of inflammation. Trials have been undertaken and have shown the beneficial role of glucocorticoids in faster improvement and relief of symptoms (3). At first, the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) recommended that corticosteroids should not be used routinely in patients with COVID-19 for treatment of viral pneumonia or acute respiratory distress syndrome (ARDS) unless indicated for other conditions, such as asthma, chronic obstructive pulmonary disease exacerbation, or septic shock. Some authors

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Received: 12 June 2020; **Accepted:** 27 September 2020

believed that no clinical data indicated that net benefit is derived from corticosteroids in the treatment of respiratory infection due to RSV, influenza, SARS-CoV, or MERS-CoV (4,5). Over time, physicians suggested that that in some severe patients, glucocorticoids could be consid-ered as a second line treatment option. As the number of reports addressing the use of glucocorticoids in patients with moderately severe COVID-19 is limited, we decided to publish our results in patients who referred to our national team and received glucocorticoids as part of their medication.

Materials and Methods

Study population, setting, and data gathering

This descriptive and prospective study included 35 clinically-diagnosed moderate to severe COVID-19 cases who referred to *Baghaeipour Clinic, Shahid Sadoughi Hospital*, Yazd, Iran, from March 25th to April 20th , 2020 in either outpatient or inpatient settings. Diagnosis was made according to national guidelines, based on clinical symptoms, chest computed tomography (CT), and a positive reversed-transcriptase polymerase chain reaction (RT-PCR) from a nasopharyngeal sampling. Molecular tests were requested for all patients, yet cases considered as COVID-19 did not necessarily show positive results on RT-PCR assay. All patients were monitored for proper renal and liver function with no evidence of failure.

Data from each physician was gathered through a predefined form (created with Google Forms). including clinical signs and symptoms, comorbidities, and paraclinical data, including laboratory and chest CT findings, were collected at baseline, at weeks 2 and 4, or at discharge. In addition, information was attained on the use of antivirals and/or antibiotics as well as the regimen used in glucocorticoid therapy at the discretion of the treating physician. All patients received supplementary oral calcium carbonate and were monitored for clinical course and possible adverse drug reactions including hypert-ension, hyperglycemia, and oral/genital candidiasis.

Informed consent was obtained from all patients in regards to the additional off-label glucocorticoid therapy. Patients were also informed about sharing data about their medical records.

Exclusion and inclusion criteria

Patients were included in the study if they met the following criteria: A) Aged 18 to 70 years; B) Indication of glucocorticoid administration; C) No corticosteroid usage due to other diseases; D) Lack of uncontrolled diabetes, uncontrolled blood pressure, cardiovascular disease, and osteoporosis; E) No kidney or liver impairment; F) Lack of confirmed history of allergic reactions following admin-istration of glucocorticoids; G) Lack of systemic fungal infections; H) Lack of pregnancy and lactation.

Intervention

Glucocorticoid regimen

Three main regimens of glucocorticoids were utilized in patients by our team; dexamethasone, oral prednisolone, or pulsed methylprednisolone. Eight patients received intrav-enous dexamethasone 4 mg, twice daily for 4 to 7 days. Twenty patients received an oral prednisolone regimen based on 25 mg every other day for five doses (10 days) followed by 12.5 mg every other day for an additional two weeks; this group comprised the majority (twenty) of pati-ents. Seven patients received pulsed methylprednisolone (500 mg, 1 to 3 times) during their hospitalization course. Details of the different types of glucocorticoids admini-stered in outpatients and inpatients are shown in Figure 1.

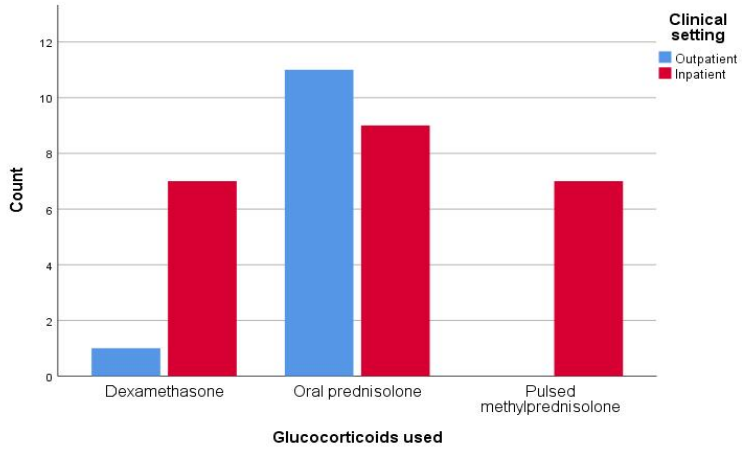

Figure 1. Various glucocorticoid regimens administered to patients with COVID-19, categorized by clinical setting, either outpatient (blue bars) or hospitalized (red bars)

Antiviral/ antibiotic regimen

Hydroxychloroquine, an antimalarial drug with poten-tial antiviral effects, was prescribed for 29 (82.9%) pat-ients. Lopinavir/ritonavir (Kaletra) accounted for 20 (57.14 %) patient prescriptions (16 of them were hospitalized). Oseltamivir was used mainly in patients who referred to our outpatient clinics (4 out of 6 patients). Nine antibiotics given rece-ived no antiviral treatment (3 of them were

hospitalized). Among the variety of antibiotics used, azithromycin was the most common agent, accounting for 30.6% of patients. One patient received a combination of meropenem, line-zolid, cefuroxime, and doxycycline as a consequence of elevated pro-calcitonin levels. Four patients were treated with tetracycline alone (along with an antiviral agent). Overall, nine patients did not receive any antibiotic treatment (four of them were hospitalized).

Ethical approval

This study was initiated after obtaining the Ethics ID (IR.SSU.MEDICINE.REC.1399.322692) from the Ethics Committee of Biomedical Research, School of Medicine, Shahid Sadoughi University of Medical Science, Yazd, Iran.

Statistical Analysis

Data summarization was done utilizing descriptive statistics. Continuous data was reported as means ± standard deviations, or medians and interquartile ranges, where applicable. Statistical analysis was performed using IBM SPSS version 23.0 (Windows).

Results

Patient characteristics and clinical features

In this study, 35 patients with COVID-19 who received different types of glucocorticoids were evaluated (Table 1). Patients were studied in both outpatient (37.1%) and inpatient (62.9%) settings. One patient was admitted to the intensive care unit (ICU). Men comprised (60%) 21 of this group of patients, the mean age of which was 50.7 (±15.1) years. Dyspnea and fever were the most common symptoms. The median number of days it took the patients to seek medical care was 7 (interquartile range: 4 – 10). Hyposmia or dysgeusia appeared in four patients concomitantly with cough and/or hemoptysis. Sixteen (45.7%) patients had a comorbidity,with diabetes being the most commonly observed condition.

Table 1. On-admission clinical characteristics and demographic data

Characteristic	Patients (n = 35)
Setting – n (%)	
Outpatient	13 (37.1)
Inpatient	22 (62.9)
Mean age ± SD (range)	50.7 ± 15.1 (70)
Sex – n (%)	
Male	21 (60.0)
Female	14 (40)
Symptoms on presentation – n (%)	
Dyspnea	25 (75.8)
Fever	24 (72.7)
Cough/ Hemoptysis	11 (33.3)
Myalgia	11 (33.3)
Hyposmia/ Dysgeusia	4 (12.1)
Gastrointestinal symptoms	4 (12.1)
Sore throat	1 (3.0)
Fatigue	1 (3.0)
Duration of symptoms prior to admission – median of days (interquartile range)	7 (4, 10)
Comorbidities – n (%)	16 (45.7)
Diabetes mellitus	6 (17.1)
Rheumatic diseases	4 (11.5)
Asthma	3 (8.6)
Prostatic cancer	1 (2.9)
Hypertension	1 (2.9)
Coronary artery disease	1 (2.9)
Ventricular septal defect	1 (2.9)
Obesity	1 (2.9)
Arrythmia	1 (2.9)
Major depressive disorder	1 (2.9)

Characteristic	Patients (n = 35)
End-stage renal disease	1 (2.9)
Mean O2 sat percent ± SD (range)	88.7 ± 6.9 (29)
Lymphopenia – n (%)	19 (54.3)
PCR for nCoV-2019	
Positive	12 (34.3)
Negative	4 (11.4)
Not available	19 (54.3)
Chest CT involvement pattern – n (%)	
Bilateral	21 (60.0)
Non-significant	9 (25.7)
Unilateral	5 (14.3)

SD; Standard deviation, CT; Computed tomography, PCR; Polymerase chain reaction

Paraclinical findings

Lymphocyte counts were depleted on admission in a majority of patients (54.3%). Nucleotide amplification assay for nCoV-2019 was available to only for 45.7% of patients; 34.3% of patients revealed positive results. Qualitative troponin tests and electrocardiographic studies showed nothing of clinical significance in any of the patients. CT scan of the chest was requested for all patients with pulmonary symptoms. The results showed bilateral peripheral patchy infiltrations with ground glass opacities as the dominant pattern of lung involvement (60%). Also noteworthy is that nine (25.7%) patients showed non-significant lung involvement.

Follow-up

Patients were followed for two weeks, the details of which are given in Table 2. The safety of glucocorticoids was assessed using criteria such as the presence or absence of fungal infections, hyperglycemia or hypertension, exacerbation of the disease and the occurrence of secondary bacterial infections. Patient improvement was defined and assessed based on the absence of fever, improvement of respiratory symptoms including cough, shortness of breath, O2, sat, and respiratory rate.patients' symptoms? improved on average 48 to 72 hours after the administration of glucocorticoids. Almost all patients had favorable clinical courses during treatment with glucocorticoids, except one who received dexamethasone in a critical setting with superimposed bacterial and candida infection. More details on clinical outcomes are illustrated in Table 3, 4, 5, and Figure 2.

Table 2. Improvement status in patients diagnosed with COVID19

Variable		Frequency	Percent
Improvement status	Considerable improvement	34	97.1
	Re-hospitalized (ICU admission)	1	2.9

Table 3. Comparison of O2 sat on days 3, 7, and 14 compared to the baseline day in inpatients and outpatients

Variable		Days	Min-Max	Mean±SD	*p value*[*]
O2 sat (%)	Outpatients	Baseline	(89-96)	95.25±2.00	-
		Day 3	(94-98)	96.58±0.99	0.002
		Day 7	(95-98)	96.66±0.88	0.006
		Day 14	(95-98)	96.66±0.88	0.006
	Inpatients	Baseline	(79-94)	88.77±4.08	-
		Day 3	(84-95)	89.77±4.2	0.373
		Day 7	(78-96)	91.33±7.1	0.373

Variable	Days	Min-Max	Mean±SD	*p value*[*]
	Day 14	(90-96)	93.88±2.26	0.012

[*] The Wilcoxon test was used to find any statistical differences.

Table 4. Comparison of cough on days 3, 7, and 14 of compared to the baseline day in inpatients and outpatients

Day			Base line	Day 3	Day 7	Day 14
Variable			percent	percent	percent	percent
Cough	Outpatients	Zero[*]	0	0	41.7	75
		1	25	66.7	50	16.7
		2	58.3	33.3	8.3	8.3
		3	8.3	0	0	0
		4	8.3	0	0	0
	Inpatients	Zero[*]	0	0	0	33.3
		1	11.1	33.3	77.8	44.4
		2	55.6	44.4	11.1	22.2
		3	33.3	22.2	11.1	0
		4	0	0	0	0

[*]Cough was scored as: zero: no, 1: mild, 2: moderate, 3: severe and 4; very severe cough

Table 5. Comparison of lymphocyte count on days 3, 7, and 14 of compared to the baseline day in inpatients and

Day		Base line	Day 3	Day 7	Day 14
Variable		Lymphopenia (percent)	Lymphopenia (percent)	Lymphopenia (percent)	Lymphopenia (percent)
lymphocyte count	Outpatients	67	18	5	0
	Inpatients	72	10	3	0

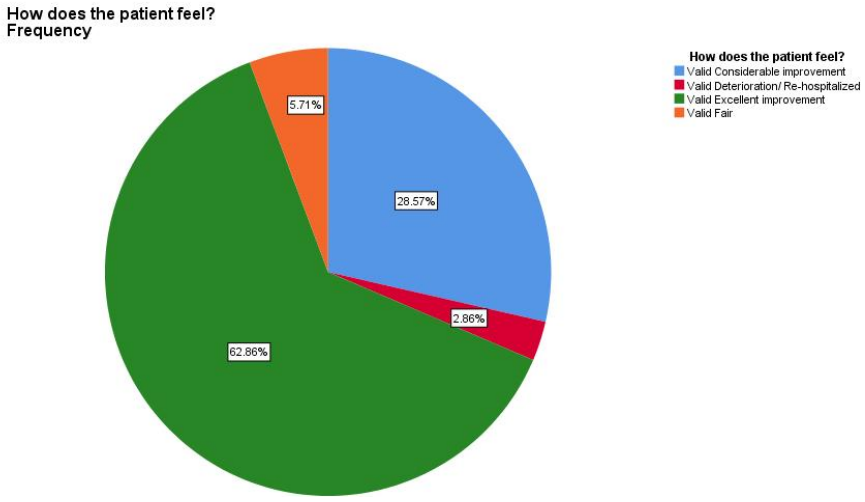

Figure 2. Overall patient satisfaction after four weeks of follow-up

Discussion

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel virus which led to a pandemic within a few months of its outbreak. There is no approved treatment for coronavirus disease 2019 (COVID-19); supportive management is recommended according to each patient's history. Apart from immune-booster agents (i.e. antivirals), the role of immunomodulation is a matter of dispute among practitioners involved in managing patients with COVID-19. This study comprises of 35 patients with moderate to severe cases of COVID-19 who received glucocorticoids with different protocols by a team comprising a pulmonologist, infectious disease specialist, general internist, and rheumatologists involved in caring for COVID-19 patients. The sample size was rather good in comparison to other studies (7, 8). Twenty patients received the author's unique protocol of 25 mg oral prednisolone as an alternate-day (every other day, EOD) regimen to minimize potential susceptibility to secondary infection (6). Out of 35 patients, two cases of anosmia were isolated who were in close contact with known COVID-19 patients and were resistant to local anosmia. Diagnosis for these two patients were based on PCR test. All other patients had typical pulmonary involvement of COVID-19 based on CT scan findings. The most common presenting features were fever, cough, and dyspnea in the majority of patients. In contrast to other studies, a considerable number of patients had no remarkable medical history or comorbidity, followed by patients who were suffering from allergic or rheumatology disorders. Only one patient required intensive care. A unique feature of this study was the judicious early intervention with glucocorticoids, given not too late after overwhelming organ failure and, of course, not too early. This was based on the hypothesis that preventing irreversible organ damage (primary prevention) is key and all attempts should be made to halt the pathologic process before progressive and irreversible cardiovascular collapse; this counteracts the earlier theory of starting the GC regimen in critical and severe cases of the disease. If the use of glucocorticoids is associated with risk and harm, this risk may be greater in critically ill patients and those with advanced disease. On the other hand, if glucoc-orticoids can be beneficial for patients with COVID-19, and if they are meant to be life-saving, they can be prescribed in the earlier stages so that the patient does not develop irreversible organs damage and shock (before entering into the critical phase—a secondary prevention). Our results are excellent regarding the hospital course. Only one patient deteriorated and needed rehospitalization and mechanical ventilation; this patient was non-responsive to critical care, developed overwhelming sep-sis, and eventually died of circulatory collapse. All other pati-ents had favorable outcomes, even during their hospital stay. The mean length of hospital stay for our patients was around 6 days, which is comparable to other studies (9). An interesting finding of the current study is the consid-erable number of patients (25%) who did not receive any antibiotic in the setting of glucocorticoid use. This result can only be compared to 5% as in the study by Zhou et al. (10).

Hallmarks of the current study were pointing out the discrimination of different glucocorticoid regimens in COVID-19. The authors believe that the most critical points in the outcome of patients receiving glucocorticoids are the type, dose, duration, intervals, and of route of administration of glucocorticoids that may have a great impact on the safety profile of glucocorticoid use. The current study shows that glucocorticoids are not only effective, but also safe, the most important reason for which is the every-other-day (EOD) prescription protocol. Mortality in 1 out of 35 patients (less than 3%) with moderate to severe COVID-19 is an excellent result compared to other series. While the overall mortality rate of patients with COVID-19 is around 3-5%,in hospitalized patients this number rises to around 8% and far more than 30% in patients admitted to intensive care settings (11). The major limitation of the current study is the rather heterogeneous group of patients with mixed severity, comprising 2 cases of isolated anosmia without pulmonary

involvement, which may make the current results somewhat heterogeneous. Other limitations were the partially missing data of hospital courses regarding general and ICU care as well as the non-balanced number of patients in each arm of GC use. Nevertheless, the clear message of the current study is that GCs may be helpful enough to be used safely in selected COVID-19 patients in early phases of vital organ involvement with good clinical outcome.

Conclusion

This study showed that judicious administration of glucocorticoids in the early stages of COVID-19 disease could be not only effective, but also reliably safe and could halt the pathophysiologic process of disease.

Acknowledgments

The authors cordially express their gratitude to all the clinicians who collaborated in providing their useful data:, Mansouri Sedigheh MD, Morteza Ramezani MD, Bita Baghaei MD, Parandoosh Hashemizadeh MD, Hamideh Mazidi MD, and Romina Delangiz MD.

Conflict of interest

None.

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