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Case-controlled Study

Coronavirus 2019 disease: Are corticosteroids the key treatment? A retrospective case-control study in Brazil

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ABSTRACT

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is the putative cause of coronavirus disease 2019 (COVID-19), a serious disease that has severely impacted the world. Although vaccines have been developed, it will take time to inoculate the global population. Current guidelines have focused on the treatment of severe cases in hospital settings; however, a void has been created regarding appropriate measures for those in the initial stage of COVID-19 and those experiencing moderate disease severity progressing to desaturation. We assessed clinical outcomes in patients with COVID-19 with pneumonia at initial presentation treated with corticosteroids.

Methods: Data of 177 consecutive high-risk patients with COVID-19, monitored by telemedicine, were collected and analyzed. Of those, 68 patients were in the initial inflammatory phase of the disease without desaturation and received corticosteroids. The outcomes were evaluated after a follow up of 14 days. Four patients were immediately referred to the hospital because they had explicit desaturation at presentation.

Results: After 14 days, all patients in the inflammatory phase at presentation who were treated with corticosteroids before desaturation were alive and without complications. However, of the four patients with desaturation, one died at the hospital.

Conclusion: In this study, the use of corticosteroids during the initial pulmonary phase of COVID-19 before desaturation, in addition to daily monitoring of patients, prevented disease progression, decreased the risk of complications and incidence of hospitalization and death. However, additional studies with larger number of patients are needed to confirm these findings.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is the putative cause of coronavirus disease 2019 (COVID-19), a complex disease that affects the entire body and has demonstrated remarkably high global mortality [1,2]. The survival rate of patients with COVID-19 requiring intensive care is approximately 50% [1]. Although vaccines are currently available, it will take time for the world to return to normal life [3]. The scientific and medical community are focused on academic and clinical research to reduce COVID-19 mortality rates in response to this global emergency [4]. To date, according to the guidelines recommended in the literature, the first-line treatment involves the use of the corticosteroid dexamethasone; however, it is indicated only for critically ill hospitalized patients [5].

Studies have shown that when early intervention is inadequate or ignored, patient with Covid-19 disease can inexorably progress to the need for hospital care if not assisted and even death [6]. Therefore, early intervention is important because initial ambulatory disease is very different from the later extreme disease requiring hospitalization and more complex treatment(s) [7]. This study aimed to investigate whether the use of corticosteroids during the pulmonary inflammatory phase of COVID-19 changes the prognosis of the disease. Moreover, the clinical and demographic characteristics, treatment orientations, and outcomes of patients during the pulmonary phase of COVID-19 disease are presented in this study.

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2. Patients and methods

This study was registered at Plataforma Brasil (The Brazilian Government Ethical Committee Research site; number 62741922.8.0000.0029) (https://plataformabrasil.saude.gov.br/visao/pesquisador/gerirPesquisa/gerirPesquisaAgrupador.jsf), and also at Research Registry site; registration unique identifying number (UIN) researchregistry8318, https://www.researchregistry.com/browse-the-registry#home/. This manuscript was described according to the STROCSS criteria [8].

This was a retrospective case-control study including 177 consecutive high-risk patients aged above 18 years and diagnosed with COVID-19, lucid and oriented, and belonged to a community in Brazil attended via telemedicine between April 19, 2020 and April 20, 2021. Diagnosis of COVID-19 was confirmed using RT-PCR of a nasopharyngeal swab specimen or serology in 86% of patients and through epidemiological link with a household member confirmed to be COVID-19 positive or exhibiting very specific symptoms, such as anosmia and ageusia, in 14% of patients. Patients under 18 years of age or those with cognitive alterations were excluded. All patients provided informed consent for publication of the study.

The demographic and clinical characteristics, symptoms, laboratory and chest computed tomography (CT) findings, and medical treatment were obtained from the medical records. The onset of the disease was defined as the first day of observation of symptoms. The patients were dichotomized in viral, inflammatory or pulmonary, and severe phase according to Lin [9]. A total of 177 consecutive patients with COVID-19 diagnose were enrolled in this study.

Among the patients examined, at first contact, 125 were in the viral phase of the disease (first five days of being symptomatic); of those, 20 progressed to the inflammatory phase. At the time of enrolment, 48 patients were in the initial inflammatory phase of the disease with persistent fever, asthenia, cough, and respiratory distress but still had adequate oxygen saturation. Four patients were in the critical phase of the disease, severely ill, with oxygen saturation <92%, and were immediately referred to the hospital (Table 1).

A complete evaluation was performed for all patients; the main symptoms are summarized in Table 2.

Patients were counseled to monitor symptoms daily, including oxygen saturation, heart rate, and temperature, and immediately report any changes to the medical team. Treatment was primarily based on clinical criteria, of which oxygen saturation was the most important. Patients who experienced changes in oxygen saturation were asked to verify, and if saturation started to drop, were alerted to treatment (Figs. 1 and 2).

Due to the socioeconomic status of our country, only critical tests, such as complete blood count, D-dimer, and high-sensitivity CRP, were requested. Chest CT was requested on day 7 of the disease or before the patient became highly symptomatic for those who could afford it, and 8% among them exhibited mild pulmonary alterations with <25% involvement (Fig. 3).

Two patients were completely asymptomatic and were not treated because the levels of infection markers in their blood were normal.

The patients were asked to record details of disease progression every day. In case of persistent fever and cough, severe asthenia, chest pain, respiratory distress, drop in oxygen saturation (never to < 94%), CT revealing pneumonia, or high levels of blood infection markers, such as C-reactive protein (CRP), corticosteroids were prescribed. After rigorous evaluation of patients, the treatment was initiated. In most cases, oral prednisolone was prescribed at a loading dose of 1 mg/kg body weight for one day and 0.5 mg/kg body weight for an additional 4–5 days. A total of 68 patients were prescribed corticosteroids at home during the initial inflammatory phase of the disease, and four critically ill patients were prescribed corticosteroids at the hospital by assistant doctor (Table 3).

Table 1
Phase of the disease at patient's presentation.

Phase of the disease	Number of patients (Total 177)	% of patients
Viral phase	125	70.62
Initial inflammatory phase	48	27.11
Desaturation phase (critically ill)	4	2.25

Table 2
Main clinical symptoms in enrolled patients with COVID-19.

Symptoms	% of patients
Cough	33.33
Fever	39.54
Dyspnea	6.77
Chest pain	9.6
Precordialgia	2.25
Muscle pain	12.42
Palpitation	2.82
Asthenia	54.23
Anosmia	23.16
Ageusia	24.29
Sore throat	18.64
Headache	28.66
Nasal Symptoms: Runny nose (13), nasal burning (4)	9.6
Gastrointestinal symptoms: abdominal pain (5), diarrhea (22), nausea (6), vomiting (7)	22.59
Dizziness	6.21
Panic attacks	4.51
Cutaneous Exanthema	2.25
Burning eye	4
Articular pain	2.82

Fig. 1. Representative images of patient number 11, a diabetic, obese male patient, at first contact exhibited an oxygen saturation of 97% and was feeling well.

Fig. 2. Image of the same patient number 11 on day 9. His oxygen saturation level decreased to 94%. He was alerted to undergo treatment after confirmation of drop in oxygen saturation level.

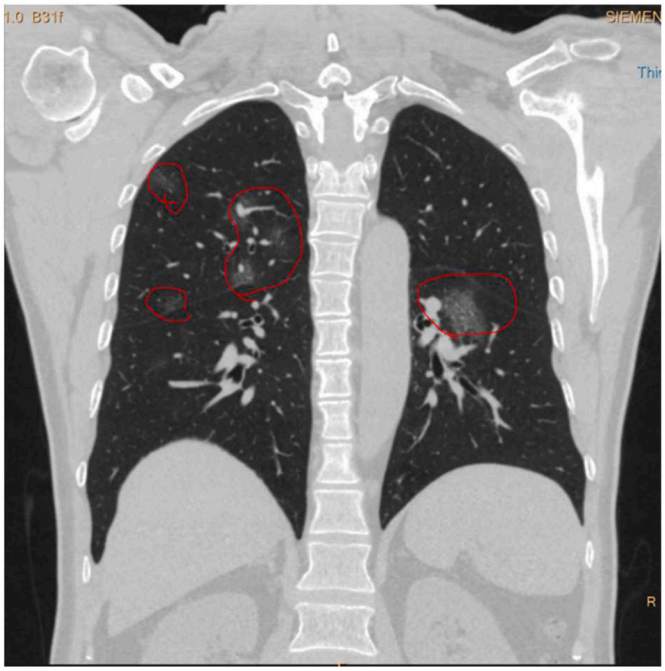

Fig. 3. Covid-19 pulmonary lesion: Discrete ground-glass opacities are highlighted. Patient number 27, a male patient presented with persistent fever on day 7, underwent chest CT that revealed mild impairment.

Table 3
Clinical characteristics of patients receiving corticosteroids.

Phase of the disease	Number of patients (Total 72)	% of patients
During inflammatory phase of the disease (at home)	68	94.44
Critically ill patients (at the hospital)	4 (all male)	5.55

Oral prednisolone or prednisone was prescribed to 62 patients, whereas six patients received dexamethasone and four patients with oxygen desaturation received methylprednisolone pulse therapy at the hospital. Adjuvant inhaled budesonide was also prescribed for patients with persistent cough or respiratory discomfort, as shown in Table 4.

Anticoagulation with subcutaneous enoxaparin 40 mg/day was prescribed in the absence of contraindications, such as thrombocytopenia, renal disease, or active bleeding, to 20 patients during the inflammatory phase of the disease who were at high risk of thrombosis. However, in some patients who could not afford enoxaparin, this prescription was stopped, and those at high risk were prescribed aspirin 100 mg/day for 30 days with good results.

The patients were also instructed to maintain vigorous hydration, do moderate exercise, such as walking, and healthy nutrition along with breathing exercise. All patients were followed for 14 days or if any complaint(s) persisted.

Four critically ill patients that reached us with explicit oxygen desaturation and severe adinamia were referred to the hospital. Their condition deteriorated between days 9 and 12 of disease onset.

3. Results

Based on demographic characteristics, 53% were female and 47% male, with a mean age of 44 years. Four women were pregnant and two were lactating. Most patients exhibited comorbidities (Table 5).

Among critically ill patients, all were male aged 30–74 years. One of them exhibited 75% pulmonary ground-glass opacity and all had high CRP levels. Three of them were discharged after six days in the hospital; one with chronic obstructive pulmonary disease with small lung capacity died after a long stay at the hospital.

After 14 days, all 68 patients who were in the inflammatory phase at presentation and treated with corticosteroids before desaturation were alive and without complications. However, among the four who were critically ill with explicit desaturation at presentation and immediately referred to the hospital, one patient died.

4. Discussion

Corticosteroids were abandoned at the beginning of the pandemic owing to the risk of possible immunosuppression and interference with viral elimination [10]. However, the RECOVERY study broke the main paradigm of science and illustrated whether corticosteroids would be safe during the progression of COVID-19. This study recommends dexamethasone at low doses only in hospitalized and critically ill patients [5]. Although dexamethasone was recommended during the later phase of the disease as they did not find good results in patients who did

Table 4
Types of corticosteroids used.

Main types of corticosteroids used	Number of patients (Total 68)	% of patients
Oral prednisolone or prednisone	62	91.18
Dexamethasone	6	8.82
Inhaled budesonide (prescribed as an adjuvant therapy with other oral corticosteroids for highly symptomatic patients)	20	

Table 5
Major comorbidities presented by patients.

Comorbidity/previous Pathological condition	% of patients
Hypertension	25,42
Diabetes	10.73
Obesity	10.73
Overweight	13.55
Cardiopathy	3.38
Asthma	5.64
Tuberculosis	1.33
Psychiatric illness: depression (12), anxiety (7), bipolar disorder (2), borderline (1)	12.42
Hepatitis	0.56
Meningitis	0.56
Prostate cancer	0.56
Breast cancer	1.12
Uterus cancer	0.56
Thyroid neoplasia	2.25
Hypothyroidism	4
Thalassemia minor	0.56
Hemochromatosis	0.56
Hodgkin lymphoma	0.56
Chronic pulmonary obstructive disease	0.56
Psoriatic arthritis	0.56
Intestinal adenoma with bleeding	0.56
Gout	0.56

not need oxygen support [5], it was contrary to these findings as corticosteroids were prescribed to avoid oxygen desaturation. It was hypothesized that they used the corticosteroid dexamethasone at very low doses instead of moderate doses of prednisolone. Studies have shown that methylprednisolone has greater penetration into the lung, the target organ affected during COVID-19 [11], and treatment at the right time at the right dosage in patients with moderate to severe pneumonia caused by COVID-19 may benefit from moderate doses of corticosteroids [12]. Moreover, recent studies have shown good results in patients prescribed corticosteroids at home at the beginning of the inflammatory phase or from day 6 of observation of symptoms [13].

According to Ye et al., early use of corticosteroids can inhibit immune defense mechanisms and increase the viral load, which may worsen the condition [14]. However, the patients were not expected to experience desaturation to start corticosteroid therapy because of associated risks, and the condition could become progressively worse, making complete recovery difficult. The right time and dosage of corticosteroids are extremely important for patient recovery [14].

In this study, day 8 of observation of symptoms appeared to be a "milestone" and was termed the "D Day" of the disease because it was either the day of resolution or continued progression. Notably, majority of patients who were likely to progress to the inflammatory phase of the disease as well as asymptomatic patients started corticosteroid therapy on day 8 of symptoms. Therefore, the medical team was particularly attentive between days 7 and 9. Therefore, most patients who progressed to the inflammatory phase of the disease began to use corticosteroids on day 8 of the disease. Although attempts were made to avoid using corticosteroids too early to escape the viral phase, this usually occurred between days 7 and 9 of the illness. However, if the patient's oxygen saturation dropped to <94%, corticosteroids were started even on day 7 or before because there could have been an error in counting the correct day or a more aggressive strain was involved.

According to Ye, glucocorticoids are mainly indicated for use in patients who experience cytokine storm. The inhibition of excess initial inflammation through the use of corticosteroids during the early stage of the cytokine storm effectively prevented the occurrence of ARDS and provided protection against organ damage [14]. It has been established that corticosteroids should be used to control cytokine storms because they reduce the risk of intubation and death [15].

Studies have shown that corticosteroid pulse therapy resulted in increase in survival rate in decompensated patients with desaturation and high inflammatory response [16]. Lopez suggested that high-dose corticosteroid pulse therapy increases the survival rate of critically ill patients with COVID-19 based on the fact that these patients are likely to be intubated, which is akin to a "death sentence" postponed for some days [16].

The patient was also prescribed adjuvant inhaled budesonide. The STOIC study showed that patients with COVID-19 who received inhaled budesonide had a considerably faster resolution than those who did not. Moreover, it reduced clinical deterioration in 90% of patients with COVID-19 [17]. Later, other studies showed the pivotal role of corticosteroid use in the treatment of patients with COVID-19 [12]. Corticosteroids are affordable drugs with only moderate side effects in short-term use [18].

In addition to corticosteroids, prophylactic enoxaparin was prescribed for some patients despite anticoagulation prescription being controversial in patient with COVID-19. Although COVID-19 is a thromboembolic disease, there is no consensus on the use of anticoagulants, therapeutic or prophylactic, the right time of their use, or even whether they should be used. Studies have found that the use of prophylactic anticoagulation reduced mortality in patients with COVID-19 when admitted to the hospital [19]. Contrarily, other studies have found that the therapeutic use of enoxaparin in patients with COVID-19 led to a 2.3-fold increase in mortality; therefore, anticoagulation may not be effective in this disease. Moreover, some authors agree that most patients die of hypoxia secondary to acute renal failure, shock, or multiple organ failure. Although thrombosis may have contributed to mortality, it did not appear to be specifically related [20].

Azithromycin or clarithromycin was prescribed only to patients who presented with persistent fever during the inflammatory phase [21].

Compared to other studies, these patients experienced good outcomes with the use of corticosteroids during the inflammatory phase in addition to daily monitoring. Previous studies have shown that mild illness with mild pneumonia occurred in 81% of cases, and severe disease with dyspnea, blood oxygen saturation ≤93%, high respiratory rate (≥30 breaths/min), or pulmonary infiltrates >50% in 24–48 h occurred in 14% of cases. Critical illness involving septic shock, multiple organ dysfunction, or respiratory failure has been reported in 5% of cases [22]. In this study, among the 173 cases that were monitored since the viral phase and the beginning of the inflammatory phase, there was neither hospitalization or death nor desaturation <93%, and all patients experienced complete recovery with in-home intervention.

In case of patient's saturation dropped below 94%, it was difficult to recover without hospitalization and intensive care. Therefore, compared with previous reports, this study population experienced no critical or severe disease progression, which could be because they were promptly treated with corticosteroids at the beginning of the inflammatory phase of the disease. However, four patients showed severe illness, and one among the four patients with desaturation died at the hospital.

Treatment of COVID-19 is largely targeted at hospitalized patients with advanced stage of the disease. Early intervention has been questioned because no robust studies have addressed the monitoring and treatment of patients with mild and moderate COVID-19. However, when early approach is ignored, COVID-19 patients often progress to hospitalization and death. Corticosteroids and telemedicine should be used as a part of a broad therapeutic approach [6].

Moreover, medical field has invested considerable effort and resources in disease prevention through awareness and vaccination campaigns [23]. When prevention fails, we should focus on patients receiving early diagnosis and intervention to increase the probability of successful treatment [24]. Although we have focused on physical distancing, alcohol-based disinfectant gels, and mask use to prevent COVID-19 [25], it is advised that the patient only sees the doctor when they experience oxygen desaturation and exhibit symptoms of hypoxemia [26]. This leads to a vacuum in the initial stage of the infection and runs the risk of no longer having control over the disease, which can lead to intubation and worse prognosis [27]. When the disease progresses to

the inflammatory phase, corticosteroids are the main and most important drugs used in these patients. The use of these drugs at the right time and dosage was associated with a dramatic and rapid improvement in the course of the disease and reduction in blood inflammatory markers and clinical symptoms. Finally, in this study, corticosteroids were breakthrough in the treatment of patients with COVID-19.

Strengths and limitations of this study. To the best of our knowledge, this is one of the first study that used corticosteroids for the treatment of patients with COVID-19 in early inflammatory phase. However, small number of patients did not allow us to draw definitive conclusions, requiring additional studies with a greater number of patients.

5. Conclusions

In this retrospective observational study, the use of corticosteroids during the initial pulmonary phase of COVID-19 before desaturation, in addition to daily monitoring of patients, decreased the risk of complications and incidence of hospitalization and death. Without intervention, disease may progress to a critical stage with a lower chance of survival. With increasing numbers of deaths from COVID-19, combining the use of early corticosteroids at the ideal stage of disease progression is an economically feasible approach with little risk compared with the complications of COVID-19. However, additional studies with larger number of patients are needed to confirm these findings.

Abbreviations

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CRP, C-reactive protein; CT, computed tomography.

Ethical approval

All the patients gave their performed consent.

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Authors' contributions

SSR designed, executed, collected data, and performed literature review; CNR, ACRC, and JRC collected data and EAJ critically reviewed the data. All the authors have read and approved the manuscript.

Registration of research studies

Name of the registry: This study was registered at Plataforma Brasil and also at Research Registry site;

Unique Identifying number or registration ID: The Brazilian Government Ethical Committee Research site; number 62741922.8.0000.0029) and Registration Unique identifying number UIN 8318.

Hyperlink to your specific registration (must be publicly accessible and will be checked)

Guarantor

Salete da Silva Rios is the Garantor

Provenance and peer review

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Informed consent

All patients provided informed consent to participate in the study.

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Declaration of competing interest

The authors have no conflicts of interest.

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