Clinical protocol for early treatment of COVID-19 in a real-world scenario: Results of a series of patients

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Abstract

Introduction: Despite the advance in vaccination, the SARS-CoV-2 infection remains a challenge for the medical community. Outpatient and hospital therapy for COVID-19 are still improving. Our study aimed to report the results of a series of patients with COVID-19 who participated in an outpatient treatment protocol since the first clinical manifestation.

Methods: A case series report of individuals aged \( \geq 18 \) years with clinical symptoms and a confirmed test for COVID-19 submitted to a treatment protocol. Patients were enrolled between May and September 2020 and followed for at least 15 days. The assessed clinical outcomes were the need for hospitalization, admission to the intensive care unit, orotracheal intubation, and death.

Results: We studied a 116 patients. The mean age was 48 ± 14 years. Females formed 53%. The main comorbidities were obesity (15.5%), systemic arterial hypertension (10.3%), type II diabetes (6%), and lung diseases (6.0%). Temperature \( \geq 37.7 \) °C (51.7%), cough (55.2%), myalgia (37.1%), headache (37.9%), and fatigue (34.5%) were the most frequent signs and symptoms. According to different disease staging, the most administered drugs were: azithromycin, ivermectin, corticosteroid, antibiotics, and anticoagulants. There was no death, and hospitalization accounted for only 8.6% of the patients (1 in ICU); none required orotracheal intubation. The mean length of hospital stay was 5.8 days.

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Frequent symptoms and signs are fever, dry cough, headache, anosmia, ageusia, sore throat, myalgia, tremors, dyspnea, and in more severe cases, pneumonia. Despite this, most patients remained asymptomatic; unfortunately, a small percentage with this highly contagious disease has a virulent course, leading to mass deaths.3–5

Regrettably, despite disease knowledge advances and how to better avoid contamination by a coronavirus, we have not had vaccines or drugs scientifically approved to treat this disease in May 2020. There were already 514,200 cases of COVID-19, and 29,314 (5.7%) individuals died due to COVID-19 in Brazil at the end of May 2020.6 At that time, feelings of frustration, hope, and sadness led to anecdotal interventions.7 Yet, it is supposed that the infection by the new coronavirus interconnects several mechanisms, i.e., inflammation, coagulation disturbances, and thrombotic phenomena.1,8–12 These processes occur in different stages of the pathophysiology of COVID-19 as they initiate with the virus invasion or early infection (stage I), followed by the pulmonary phase (stage II), and the hyperinflammation phase (stage III).13,14 As Siddiqi and his co-author demonstrated in fig. 1 of their paper, these stages are potential therapeutic targets.14 In addition, other clinical complications due to these pathological mechanisms, such as opportunistic infections and the involvement of other organs, have been observed.15,16 Therefore, studies concerning early interventions with hydroxychloroquine and azithromycin were published.17,18 However, due to low efficacy and possible cardiac complications, the administration of hydroxychloroquine was almost abandoned.19 Instead, following the approval of FDA-USA, ivermectin was used to inhibit viral replication.20–24 Shortly, we faced several randomized clinical trials (RCTs), even systematic revisions with associations between medicines, including antivirals, "immunomodulators and corticosteroids".25 Nevertheless, despite the number of studies, we are still waiting for robust and well-designed RCTs or reliable and non-biased systematic revision with meta-analysis.17,26–30

Background

COVID-19 was the name chosen for a severe acute respiratory syndrome caused by a new coronavirus (SARS-COV-2) identified in Wuhan, China, in 2019 for the first time.1 Frequent symptoms and signs are fever, dry cough, headache, anosmia, ageusia, sore throat, myalgia, tremors, dyspnea, and in more severe cases, pneumonia.2 Despite this, most patients remained asymptomatic; unfortunately, a small percentage with this highly contagious disease has a virulent course, leading to mass deaths.3–5

Inclusion criteria

Individuals aged ≥ 18 years, symptomatic (symptoms started up to 7 days before the first consultation), with a positive test for COVID-19 (RT-PCR or serology for COVID-19) between May and September 2020 and submitted to the CPET-COVID-19.

Symptomatic patients

For the present study, symptomatic patients had one or more signs or symptoms: fever, dry cough, odynophagia, anosmia, ageusia, headache, myalgia, dyspnea, delirium, and diarrehea.

Exclusion criteria

We excluded patients who disagreed with joining the study, those with a dubitable or subsequent negative test for COVID-19, and those who lost follow-up.

Place of study

The principal author and F.P. evaluated most patients in their office as an outpatient protocol. They also recruited all potential cases admitted to the Hospital da Cidade (H.C.) emergency rooms, Salvador-Brazil. Patients were admitted to this hospital when necessary.

Medical care

The first author of this study or F.P. examined and submitted every patient to the following laboratory exams and thorax imaging according to timing and symptoms of the disease process: hemogram, C-reactive protein, creatine phosphokinase, coagulation tests, liver transaminases, creatinine, urea, D-dimer, and thorax computed tomography or thorax X-ray. Based on the medical literature, we considered critical test values, for example, D-dimer 3 times the normal value; C-reactive protein > 20; substantially reduced number of lymphocytes; Substantially elevated CK and CT scan of the chest with more than 50% ground-glass involvement, as well as acute renal dysfunction.

In addition, most cases were followed up daily through remote queries by the Zoom Platform or the WhatsApp application. Furthermore, we monitored oximetry and temperature at least 3 times a day. In addition, we have strictly monitored patients with comorbidities such as diabetes, obesity, and hypertension. Clinical complications received particular support, such as investigation, suitable treatment, and evaluations at the H.C. emergency department, as necessary (Fig. 1).

Early clinical treatment protocol

CPET-COVID-19 uses the COVID-19 pathophysiology stages as therapeutic targets, as shown in Fig. 1.

Consultations

The authors obtained the opinions of G.M. (pulmonologist) regarding thorax image and A.B (neurologist) concerning neurological complaints.
Fig. 1. The algorithm of the Clinical Early Treatment Protocol for COVID-19.
Drugs

According to disease staging and patient characteristics, the principal author prescribed the following drugs: ivermectin, azithromycin, prednisolone, rivaroxaban, enoxaparin, antibiotics, and paracetamol or dipyrone.

Outcomes

The assessed clinical outcomes were the need for hospitalization, admission to the intensive care unit, orotracheal intubation, and death.

Statistical analysis

We ran Statistical Package for the Social Sciences (SPSS for Windows version 20.0) program; IBM, Armonk, NY, USA), 844052 Software: R Program, version 3.6.1 and Microsoft Excel, version 2016 (16.0.6769.2017). We used the mean and the standard deviation to describe quantitative variables with normal distribution. In addition, we expressed categorical variables in absolute numbers and percentages.

Ethics

The ethical committee for human research of Hospital Ana Nery has approved this protocol. Therefore, the author registered this study in the Brazilian Platform for Research. Furthermore, all included patients have signed the informed consent document. The drugs used were: azithromycin, ivermectin, enoxaparin, prednisolone, and symptomatic (dipyrone or paracetamol).

Results

We enrolled a 122 symptomatic patients. Six patients were negative for coronavirus, and 116 patients were eligible as a case and included in the study. Most cases are the author’s patients; others came from other physicians’ referrals or the emergency rooms of H.C. As COVID-19 is a contagious disease, some patients were relatives living in the same home. In addition, 7 patients joined the protocol with routine laboratory tests already done. The mean age observed was 48 years (SD ± 14), and females were 62 (53%). The most common comorbidities were obesity (15.5%), systemic arterial hypertension (10.3%), type II diabetes (6.0%), and lung diseases (6.0%). Temperature >37.7 °C (51.7%), cough (55.2%), myalgia (37.1%), headache (37.9%), and fatigue (34.5%) were the most frequent signs and symptoms. The following drugs and their percentage of uses were: azithromycin (100%), corticosteroids (75.9%), anticoagulants (34.5%), antibiotics (10.3%), and ivermectin (99.1%). Table 1 shows the laboratory tests concerning most inflammatory and coagulation disorders related to COVID-19 and their percentage of abnormal results. We did not mention renal function as there was no abnormal result. The significantly higher complementary test was C-reactive protein, followed by leukogram and D-dimer (see table below). One patient developed Rhabdomyolysis, and another significantly increased liver enzymes (transaminases).

| Exams                              | Patients | Abnormal results |
|------------------------------------|----------|------------------|
| **White blood cell count**         | 109      | 19%              |
| Lactate dehydrogenase (LDH)        | 88       | 11%              |
| **C-reactive protein (CRP)**       | 109      | 42%              |
| D-dimer                            | 56       | 18%              |
| Creatine phosphokinase (CPK)       | 83       | 18%              |
| Prothrombin time (P.T.)            | 80       | 18%              |

Both recovered very well in 2 weeks. Fig. 2 demonstrates the results of imaging tests (abnormal percentages of computed tomography and chest X-rays).

Hospitalization accounted for 10 (8.6%) patients, and 90% were male. Table 2 shows the characteristics of inpatients. Most non-hospitalized patients reached the status of cured up to 15 days.

Seven patients (6%) entered the study with an average white blood cell count and normal C-reactive protein results. Most white cell disorders were lymphopenia.

Discussion

Despite the advance in vaccination, SARS-CoV-2 infection remains a challenge for the medical community. Therapy for COVID-19 has advanced, but it is already on the evolution curve. Our study reported a series of 116 cases of COVID-19 submitted to CPET-COVID-19. The theoretical protocol framework follows the disease’s pathophysiological stages proposed by Siddiqi et al. According to this protocol by Siddiqi, our patients entered the study at “stage 1” of that protocol.

We developed this protocol from May to September 2020, when the medical community’s therapeutic recommendations for COVID-19, especially those of the early and outpatient phases, were under intense discussion.

During this protocol period, COVID-19 devastated populations, so time and scientific rigour were competing. Unfortunately, several reasons led to the scarcity of well-designed trials: the severity of COVID-19, different response to coronavirus infections among patients, physician concern of committing an unethical decision giving a placebo, and the use of compassionate treatment, i.e. the same has occurred with the Ebola pandemic. Consequently, most studies were case series with re purposed medicines. In addition, the FDA had approved ivermectin since in vitro, and it inhibited SARS-COV 2 replication.

The covid-19 scenario in Salvador in May 2020 was catastrophic since almost all hospitals had at least 90% of beds taken. Thus, health authorities recommended patients be isolated at home until respiratory symptoms occurred. Governments proclaimed partial lockdown and opened several new hospitals for COVID-19. The media showed a death scenario as May 2020 became the month with the highest number of deaths in Brazilian history. So, we decided to initiate this protocol; however, several observational and interventional studies, even systematic reviews, most poorly designed, had shown debatable results. After balancing the pros and cons, we decided to keep the protocol without a control group pending patients’ safety instead of scientific rigour. After all, we were testing a protocol, and we believe all drugs of this protocol are essential, even ivermectin.

Although we cannot find well-designed RCTs, 11 of the 18 RCTs had positive effects; nevertheless, the last guidelines of the European
Patients with O2 saturation between 90% and 92% were admitted to CW, whereas those below 90% to ICU. No patient required orotracheal intubation. M = male sex, Obesity I = class I obesity (BMI = 30.0–34.9 Kg/m²), Obesity II = class II obesity (BMI = 35.0–39.9 Kg/m²), BMI = Body Mass Index, AH = Arterial hypertension, DM = Diabetes Mellitus, ICU = intensive care unit, CW = COVID ward, NHF O2 = nasal high-flow O2, LOS = length of stay.

Society of Clinical Microbiology and Infectious Disease (ESCMID) do not recommend ivermectin to treat COVID-19 [39]. Yet, due to the low rate of side effects, some authors intend to repurpose ivermectin to treat COVID-19 [40]. It is worth mentioning that drugs for treating the early stage of COVID-19 are debatable [41]. Therefore, the prescription of ivermectin is still a concern [39]. In addition, several studies included azithromycin [39]; however, none found evidence to treat COVID-19 [42, 43]. Nonetheless, one study shows that a treatment kit for COVID-19 might reduce hospitalizations and deaths [44]. Overweight and obesity were our population’s most critical risk factors for COVID-19 severity, and they were responsible for 80% of hospital admission. Several reasons led to obesity increased disease severity in COVID-19, such as virus entry enhancement, the immune system being unable to provide an adequate response, increased risk for thrombus formation, and hemorrhages; the adipose tissue now considered a significant reservoir for SARS-CoV-2 and an essential source of inflammatory mediators [45, 46]. Other frequent comorbidities such as diabetes mellitus, arterial hypertension, and lung disease are well-known risk factors for bad outcomes in COVID-19 [47–49].

Moreover, we faced a patient with Rhabdomyolysis and another with elevated liver enzymes, which are not rare complications [50, 51]. Both recovered after resting and hydration. Therefore, the hospital admission rate was low for our patients. Although 8.6% of our patients developed moderate to severe viral pneumonia, none required orotracheal intubation.

We decided to share this report as we observed highly favorable clinical outcomes in patients submitted to CPET-COVID-19. We still believe our treatment has changed the natural history of COVID-19. Additionally, it seems clear to us the relationship between the chronology of pathophysiological events of COVID-19, the therapeutic rationale tied to them, and the clinical manifestations observed in these patients. Moreover, we had no clinical complications attributable to the drugs we prescribed.

Weakness of the study

The small sample size (n = 116) and the absence of a control group reduce the protocol’s potential influence on the observed clinical outcomes.

Conclusions

1. Whereas in May 2020, the case fatality rate of COVID-19 in Brazil reached 5.7%, there was no death among symptomatic patients submitted to CPET-COVID-19.

2. The study findings hypothesized that CPET-COVID-19 altered relevant clinical outcomes in patients with COVID-19; thus, randomized controlled trials should assess this hypothesis.

Consent for publication

All patients agreed to sign the informed consent form.

Availability of data and materials

Datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Author’s contribution

S.S. conceived the study idea, designed the methods, examined, and treated patients, collected data, and drafted the manuscript; F.P. collected data and cared for patients; G.M. performed the thorax imaging review end reviewed the manuscript. A.B. performed patient neurological reviews, drafted the manuscript, and executed English editing; All authors read, discussed, and approved the final manuscript.

Competitive interests

There is no conflict of interest.

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