BRIEF RESEARCH COMMUNICATION

Effect of Cyproheptadine on Ventilatory Support-free Days in Critically Ill Patients with COVID-19: An Open-label, Randomized Clinical Trial

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Abstract

Background: Serotonin is a mediator of pulmonary hypoxic vasoconstriction. Experimental studies have shown that serotonin-mediated pulmonary vasoconstriction can be inhibited by cyproheptadine. The aim of this study is to assess whether treatment with cyproheptadine compared to usual care increases ventilatory support-free days during the first 28 days in patients with coronavirus disease 2019 (COVID-19) requiring ventilatory support.

Materials and methods: This randomized, single-center, open-label clinical trial included patients who were admitted to the intensive care unit (ICU) requiring ventilatory support due to COVID-19. Patients allocated to the intervention group received cyproheptadine for 10 days. The primary outcome was ventilator-free days during the first 28 days.

Results: Nineteen patients were randomized to receive cyproheptadine and 21 to the control group. The number of ventilatory support-free days during the first 28 days was not different between the two groups (15.0; 95% CI, 0.0–24.0 days in the control group vs 7.0; 95% CI, 0.0–19.0 days in the intervention group; $p = 0.284$).

Conclusion: In patients with COVID-19 and in need of ventilatory support, the use of cyproheptadine plus usual care, compared with usual care alone, did not increase the number of ventilatory support-free days in 28 days.

Keywords: Coronavirus disease 2019, Cyproheptadine, Intensive care unit, Serotonin, Ventilatory support.

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Highlights

The number of ventilatory support-free days during the first 28 days was not different between the two groups.

Cyproheptadine does not appear to be a therapeutic option for patients with coronavirus disease 2019 (COVID-19).

Introduction

Since the discovery of the first cases of COVID-19 in December 2019 in Wuhan, China, more than 6 million people have died from the disease worldwide.[1] The pathophysiological features of the severe form of COVID-19 include a pneumonic process with diffuse alveolar damage, inflammatory infiltrate, and microvascular thrombosis.[2] According to certain research, COVID-19 patients had higher levels of platelet activation and reactivity, with an increase in platelet activation markers such as thromboxane B2, platelet factor 4, and plasma serotonin in relation to patients with acute respiratory distress syndrome (ARDS) of other etiologies.[3–6]

Serotonin is a mediator of pulmonary vascular tone and pulmonary hypoxic vasoconstriction. Experimental studies have shown that serotonin-mediated pulmonary vasoconstriction can be inhibited by cyproheptadine, a 5HT-2 receptor antagonist.[7,8] Serotonin release has also been shown to be associated with pulmonary fibrosis, with cyproheptadine attenuating this evolution by reducing transforming growth factor-β (TGF- β) release.[9]

Fluvoxamine, a selective serotonin reuptake inhibitor, has shown benefits in outpatients with COVID-19.[10,11] One potential mechanism is that fluvoxamine may reduce the storage of serotonin in platelets, thereby reducing the hyper serotoninergic state that occurs after platelet activation. The use of serotonin receptor antagonists, such as cyproheptadine, may be beneficial in the period in which serotonin release has already occurred.[12,13]

Considering this evidence and biological plausibility, the purpose of this study is to determine whether treatment with cyproheptadine, a serotonin receptor antagonist, in comparison to standard care, increases ventilatory support-free days during the first 28 days in patients with hypoxemic respiratory failure admitted to the intensive care unit (ICU) and needing ventilatory support (invasive or non-invasive).

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Materials and Methods

This is a randomized, single-center, open-label clinical trial performed in the ICUs of Hospital de Clínicas de Porto Alegre (HCPA), Brazil. The study was approved by the Research Ethics Committee of Hospital de Clínicas de Porto Alegre (CAAE 46381721.8.1001.5327; approval date: 07/12/2021). This study was conducted by the Helsinki declaration of 1975. Before randomization, each patient's or their legal representative's informed consent was obtained verbally or in writing. An impartial, external data and safety monitoring committee (DSMC) oversaw the study. The study protocol was recorded in the ClinicalTrials.gov database (NCT04979221) before initiation.

Patients at least 18 years of age who were admitted to the ICU requiring invasive or non-invasive ventilatory support due to COVID-19, confirmed by Real-time Reverse Transcription – Polymerase Chain (RT-PCR) or antigen testing, were evaluated for eligibility. Exclusion criteria were ventilatory support for more than 48 hours, tracheostomy, pregnancy or breastfeeding, refusal to consent, expected death within 24 hours of randomization, previous use of serotonin reuptake inhibitors, use of monoamine oxidase inhibitors, glaucoma, inability to use the enteral route, history of seizure, readmission to the ICU, allocation to another study, or treatment limitation.

Randomization was done through an online web-based system using computer-generated random numbers. Eligible patients were randomized in a 1:1 ratio to receive usual care plus cyproheptadine or usual care alone.

Cyproheptadine was administered to patients assigned to the intervention group at a dose of 8 mg every 8 hours for 10 days. According to the institution's clinical practice, standard care (diagnostic testing, antibiotic administration, fluid resuscitation, hemodynamic management, and ventilatory support) was used in both arms.

Demographic characteristics, SAPS 3, time of symptom onset, comorbidities, and other clinical and laboratory variables were collected. Ventilatory support [non-invasive ventilation, high-flow nasal catheter, and invasive mechanical ventilation (MV)], intravenous sedation, neuromuscular block, prone position, vasopressor, renal replacement therapy, and thromboembolic phenomena were collected daily until day 28. Patients were followed up until hospital discharge.

Outcomes

The number of days that a patient remained alive and not receiving ventilator support for at least 48 consecutive hours over the first 28 days was the primary outcome. Patients who were discharged from the hospital before 28 days were considered alive and free of ventilatory support at 28 days. Nonsurvivors on day 28 were regarded as not having any days without ventilator support. Secondary outcomes were the length of invasive MV, length of ICU and hospital stay, and ICU and hospital mortality.

Sample Size Calculation

Data from a single-center study found an average of 11.6 ± 5.0 ventilatory support-free days in 28 days.[14] Our hypothesis was that the use of cyproheptadine would increase ventilatory support-free days by 15% in 28 days. Assuming a normal distribution of the primary outcome, we calculated that 137 patients per group would provide 80% power to detect a 15% increase in the number of ventilator-free days on day 28, with an alpha error of 0.05. The number of patients included followed an adaptive strategy. Interim analyzes were planned for every 30 patients by the DSMC. Data from the interim analyzes were blinded to the executive committee. The criteria for study discontinuation in the interim analyzes were: (A) If the probability of cyproheptadine superiority was >0.986, the study would be discontinued for efficacy; (B) If the probability of superiority of usual care was >0.986, the study would be discontinued due to impairment. In the first interim analysis, the DSMC recommended the continuation of the study. The analysis was conducted using the "rstanarm" package (R 4.0.3) with neutral default priors. Subsequently, the study had to be stopped due to the progressively lower recruitment rate with the decrease in severe cases of COVID-19, in a decision shared with the DSMC.

Continuous variables were expressed as mean ± standard deviation or median and interquartile range or number of events (%). Categorical variables were presented as frequency and percentage. Differences between groups at baseline were analyzed with Student's *t*-test or Wilcoxon-Mann-Whitney test according to the criterion of normality. Fisher's exact test was applied to categorical variables.

The analysis was performed by intention-to-treat comparing the two study groups with respect to primary and secondary outcomes. A multivariate model was constructed to identify variables independently associated with the number of ventilatory support-free days in 28 days. In addition to the study group, the other variables defined a priori were variables with plausibility to be associated with the primary outcome. All analyzes were performed using IBM SPSS Statistics, version 20.0 (IBM Corp., Armonk, NY, USA). Statistical significance was set at 0.05.

Results

Between July 2021 and December 2021, 179 patients with confirmed COVID-19 infection were admitted to the ICU. Of these, 139 patients were excluded. Of the 40 patients included in the final analysis, 19 were randomized to receive cyproheptadine and 21 to the control group (Fig. 1).

The characteristics of patients at inclusion are described in Table 1. Disease severity, assessed by SAPS 3, PaO_2/FiO_2 ratio at admission, and need for MV before randomization, as well as vaccination status, were similar between the two groups. All patients received dexamethasone. No patient used remdesivir, tocilizumab, baricitinib or convalescent plasma.

The mean time to start cyproheptadine after ICU admission was 13.5 ± 9.0 hours. Only two patients discontinued the use of cyproheptadine before completing 10 days of treatment. One patient had an episode of generalized tonic-clonic seizure and discontinued use on the second day. The other patient had episodes of vomiting after ingesting cyproheptadine and discontinued the intervention on the 6th day.

The number of ventilatory support-free days during the first 28 days was not different between the two groups (15.0; 95% CI, 0.0–24.0 days in the control group vs 7.0; 95% CI, 0.0–19.0 days in the intervention group; $p = 0.284$) (Table 2). There was no significant difference in the length of stay in the ICU (14.5 ± 11.7 in the control group vs 22.5 ± 17.1 in the intervention group; $p = 0.121$) and in the hospital (19.6 ± 11.9 in the control group vs 26.9 ± 17.7 in the intervention group; $p = 0.165$), and in ICU and hospital mortality (Table 2).

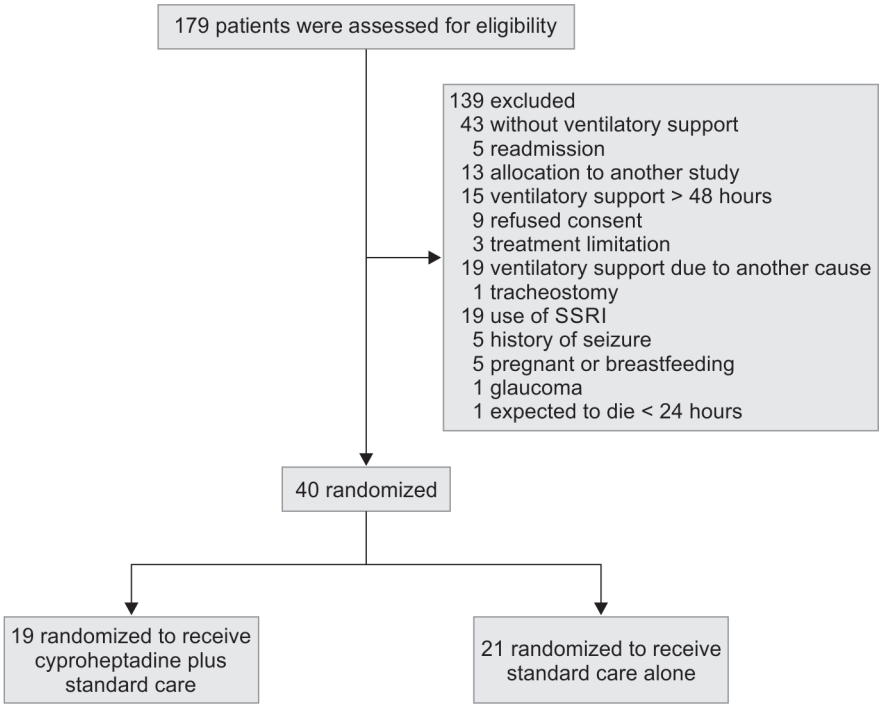

Fig. 1: Trial flowchart

In a post hoc multivariate analysis with adjustment for age, immunosuppression, C-reactive protein at admission, SAPS 3, obesity, vaccination status, PaO_2/FiO_2 ratio at admission and MV before randomization, the number of ventilatory support-free days remained without significant difference between groups (unstandardized ß-coefficient –4.32, 95% CI, 11.13–2.49).

Adverse events are described in Table 3. There was no difference in the incidence of adverse events between patients in the control group and patients who received cyproheptadine.

Discussion

In this randomized clinical trial of patients with COVID-19 in need of ventilatory support, cyproheptadine plus usual care compared to usual care alone did not increase the number of ventilatory support-free days during the first 28 days. To the best of our knowledge, this is the first clinical trial that has evaluated the use of cyproheptadine in critically ill patients with COVID-19.

According to certain research, COVID-19 patients had higher levels of platelet activation and reactivity compared to healthy controls.[3–5,15] In addition, platelet activation was shown to be associated with disease severity.[4] Zaid et al. found that platelet hyperreactivity is increased in patients with COVID-19 even in comparison with patients with ARDS of other etiologies.[6] Platelet hyperreactivity may be implicated in the high incidence of systemic and pulmonary vascular thrombosis seen in patients with COVID-19.[16,17] Platelet activation releases a series of bioactive molecules, such as serotonin. Patients with COVID-19, with or without ARDS, have significantly higher levels of serotonin than patients with ARDS of other etiologies or healthy controls.[6] Whether the elevation of serum serotonin in these patients is just a marker of platelet hyperreactivity or whether it represents a mechanism in the pathophysiology of COVID-19 remains to be explored.

Two clinical trials showed benefits in the use of fluvoxamine, a selective serotonin reuptake inhibitor, in outpatients with COVID-19.[10,11] Although one of the suggested mechanisms is the anti-inflammatory action through the activation of the sigma-1 receptor (S1R), a potential mechanism is that fluvoxamine may reduce the storage of serotonin in platelets, consequently reducing the hyper serotoninergic state that occurs after platelet activation.[13,18] This second mechanism would enhance the therapeutic potential of cyproheptadine. At an earlier stage, fluvoxamine would reduce the serotonin load on platelets, before serotonin is released by platelet activation. In a more advanced phase, such as in critically ill patients requiring ventilatory support, in which the release of serotonin has already occurred from platelet activation, it makes sense to administer a serotonin receptor antagonist, such as cyproheptadine. Unfortunately, in our study, the use of cyproheptadine at this stage of the disease showed no benefit. We even found a tendency in patients who used cyproheptadine to have longer ventilatory support, in addition to a greater need for invasive MV, with a consequent longer length of stay in the ICU and hospital. As with the other medications tested for this viral infection, the timing of cyproheptadine administration may be a determining factor for the results. An intermediate phase, neither so early as to not have a hyper serotoninergic state, nor so late as to have multiorgan dysfunction, seems to be the ideal period. The patients in our study were in an early stage of critical illness. The median time to symptom onset was less than 10 days and less than a third of patients were on MV at the time of randomization. In addition, ventilatory support for more than 48 hours was an exclusion criterion.

This study has several limitations. First, one of the key limitations of our study is the notable concern that we did not reach the anticipated number of patients as calculated by the sample size estimation. This shortfall raises concerns about the statistical power

Table 1: Baseline characteristics

Characteristics	*Control (n = 21)*	*Cyproheptadine (n = 19)*	*p*
Age, years, median (IQR)	64.0 (40.5–71.0)	56.0 (46.0–70.0)	0.957
Sex, male, *n* (%)	16 (76. 2)	14 (73. 7)	1.000
SAPS 3, mean ± SD	55.3 ± 13.3	53.6 ± 11.8	0.673
Time since symptom onset, days, mean ± SD	7.57 ± 3.78	9.32 ± 4.06	0.167
MV before randomization, *n* (%)	5 (23.8)	5 (26.3)	1.000
Comorbidities, *n* (%)			
Hypertension	9 (42.9)	9 (47.9)	1.000
Diabetes	6 (28.6)	8 (42.1)	0.510
Heart failure	1 (4.8)	1 (5.3)	1.000
Neoplasia	3 (14.3)	0	0.233
Immunosuppression	1 (4.8)	5 (26.3)	0.085
Obesity	9 (42.9)	6 (31.6)	0.527
Chronic kidney failure	1 (4.8)	1 (5.3)	1.000
Complete vaccination, *n* (%)	10/19 (52.6)	10/18 (55.6)	0.776
Origin, *n* (%)			
Emergency	13 (61.9)	11 (57.9)	0.496
Ward	3 (14.3)	1 (5.3)	
Other institution	5 (23.8)	7 (36.8)	
D-dimer on admission, median (IQR), µg/mL	0.99 (0.65–1.54)	0.77 (0.47–2.91)	0.547
PaO_2/FiO_2 ratio on admission, median (IQR)	111 (82–190)	111 (73–182)	0.418
C-reactive protein, mean ± SD, mg/L	199.6 ± 96.7	198.9 ± 112.5	0.983
Ventilatory support, *n* (%)			
HFNC	18 (85.7)	17 (89.5)	1.000
NIV	16 (76.2)	16 (84.2)	0.698
MV	12 (57.1)	15 (78.9)	0.186
Respiratory variables, mean ± SD			
Tidal volume, mL/kg of predicted body weight	6.6 ± 0.9	6.7 ± 0.8	0.728
Minute ventilation, L/min	11.2 ± 1.3	11.0 ± 1.7	0.688
Inspiratory plateau pressure, cm H_2O	27.5 ± 4.0	25.6 ± 3.4	0.234
PEEP, cm H_2O	13.3 ± 3.6	13.3 ± 3.1	0.964
Driving Pressure, cm H_2O	14.2 ± 4.6	11.9 ± 2.8	0.150
Prone position, *n* (%)	5 (23.8)	7 (36.8)	0.494
Vasopressor use, *n* (%)	10 (47.6)	14 (73.7)	0.117
Intravenous sedation, *n* (%)	14 (66.7)	17 (89.5)	0.133
Neuromuscular blockade use, *n* (%)	11 (52.4)	12 (66.7)	0.538
Tracheostomy, *n* (%)	2 (9.5)	4 (22.2)	0.398
Renal replacement therapy, *n* (%)	6 (28.6)	5 (27.8)	1.000
Thromboembolic phenomena, *n* %)	3 (14.3)	7 (36.8)	0.148

HFNC, high-flow nasal cannula; MV, mechanical ventilation; NIV, noninvasive ventilation; PEEP, positive end expiratory pressure; SAPS, simplified acute physiology score

Table 2: Study outcomes

Variables	*Control (n = 21)*	*Cyproheptadine (n = 19)*	*p*
Days alive and ventilatory support free at 28 days, median (IQR)	15.0 (0.0–24.0)	7.0 (0.0–19.0)	0.284
ICU LOS, days, mean ± SD	15.1 ± 12.3	24.2 ± 17.8	0.063
Hospital LOS, days, mean ± SD	20.4 ± 12.3	30.3 ± 22.8	0.092
ICU mortality, *n* (%)	7 (33.3)	7 (36.8)	1.000
Hospital mortality, *n* (%)	7 (33.3)	7 (36.8)	1.000

ICU, intensive care unit; LOS, length of stay

Table 3: Adverse events

Variables	*Control (n = 21)*	*Intervenção (n = 19)*	*p*
Arrhitmia, *n* (%)	3 (14.3)	3 (15.8)	1.000
Seizure, *n* (%)	0	1 (5.3)	0.475
Vomiting, *n* (%)	2 (9.5)	2 (10.5)	1.000
Constipation, *n* (%)	14 (66.7)	13 (68.4)	1.000

Cholestasis, agranulocytosis, thrombocytopenia, hepatitis and diplopia were not observed in any patients

of our findings and the ability to detect potentially meaningful effects, especially considering the nature of negative studies where smaller sample sizes can impact the ability to detect statistically significant differences or associations. Second, the study was open-label due to the costs of producing the placebo. Although this is a limitation, we believe that its impact is mitigated due to the nature of the primary outcome. Finally, the study was developed in only one center, which limits the generalizability of the results.

Conclusion

In patients with COVID-19 and need of ventilatory support, our study found that the addition of cyproheptadine to usual care did not increase the number of ventilatory support-free days in 28 days. However, it is crucial to acknowledge the limitations of our study, such as the lower-than-anticipated sample size, which may have affected the statistical power to detect potential effects.

Authors' Contributions

Márcio MB, Wagner LN, Marcos FR, Patricia S, Edino P, Miriane MSM and Thiago CL have made substantial contributions to the conception and design of the study and to acquisition of data; Márcio MB and Thiago CL performed the analysis and the interpretation of data; all authors read and approved the final manuscript.

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