Chlorpheniramine Intranasal Spray to Accelerate COVID-19 Clinical Recovery in an Outpatient Setting: The ACCROS Trials

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Abstract

Purpose: Our group demonstrated the safety, efficacy, and antiviral effect of intranasally administered Chlorpheniramine Maleate (CPM) for treating coronavirus disease 2019 (COVID-19). Since the nasal cavity is the portal of entry for COVID pathogens, sensory and upper respiratory symptoms (URS) (e.g., cough, ageusia, anosmia, nasal congestion, etc.) are significant symptoms in the course of the disease. Intranasal therapies could alleviate the disease-induced URS faster. This study evaluated the effectiveness and safety of intranasal CPM for treating mild to moderate COVID-19-induced URS in the outpatient setting.

Methods: The two-part **A**ccelerating **C**OVID-19 **C**linical **R**ecovery in an **O**utpatient **S**etting (ACCROS) research study was conducted to collect evidence from a randomized, double-blinded placebo-controlled trial (ACCROS-I). Both parts enrolled patients with mild to moderate COVID-19 confirmed by reverse transcription-polymerase chain reaction. The primary endpoint in ACCROS-I was time to clinical recovery, defined as the change from baseline to day 7 in COVID-19 symptoms reported as the percent change (Δ%) in the daily symptoms score (DSS) and the severity of the disease symptoms using a visual analog scale (VAS), on a scale of 1-10 (10=worst symptoms). COVID-19 patients (n = 101) were recruited and assigned to either a 10-day CPM treatment (n=61) or placebo (PLB) (n=40) in addition to standard of care (SoC). Secondary endpoints included the incidence of hospitalization and the proportion of patients with URS on day 7. ACCROS-II data were collected from medical records of COVID-positive subjects using a standardized form. Cohorts of patients treated with CPM and SoC (CPM+Soc) were compared for the duration of general symptoms and URS. Patient information was collected as part of routine visits and telehealth consultations.

Results *ACCROS-I:* There was a statistically significant difference in the rate of clinical recovery ($P<0.05$) in Δ%DSS (M -18.8±SEM 7.9%) and Δ%VAS (-8.6±5.1%), such that the CPM group reported fewer symptoms than PLB. The proportion of patients who reported sensory deficits and URS at day 7 was significantly lower ($P<0.05$) in CPM vs. PLB for ageusia (1.7% vs. 15.0%), cough (16.4% vs. 35.0%) and nasal congestion (8.1%vs.20%). None of the patients required hospitalization.

ACCROS-II: There was a statistically significant reduction ($P<0.05$) in total days reporting URS for general symptoms of COVID-19 in CPM+SoC (5.1 ± 0.1) compared to SoC (11.0 ± 0.2). CPM+SoC users also showed fewer days with cough, anosmia, and ageusia. Persistent anosmia (over 29 days) was found in 3% of the patients on SoC, whereas no persistent anosmia was reported in the CPM+SoC cohort ($X^2 = 10.18$; $P<0.001$).

Conclusion: The result of this two-part study supports the conclusion that intranasal CPM is an antiviral agent that can be administered intranasally to treat COVID-19-induced symptoms effectively. Intranasal CPM accelerates clinical recovery and reduces URS in patients with mild to moderate COVID-19. This study's important implications include individuals returning to daily life faster, reducing community and individual economic burden, and decreasing healthcare utilization.

Trial registration: ClinicalTrials.gov.; ID: NCT05449405 ACCROS-I retrospectively registered on 7/13/2022, NCT05520944 ACCROS-R retrospectively registered on 08/27/2022.

Introduction

It has been over three years since the initial case of coronavirus disease 2019 was reported as a severe and life-threatening illness that can result in pneumonia, respiratory failure, multi-organ failure, and death. Despite extended vaccination campaigns and acceptance of early multidrug treatments (EMT), it is well-known that COVID-19 is still a worldwide public health concern [1]. COVID-19 is a clinical syndrome characterized by a viremic phase followed by a mast cell-mediated hypersensitivity-like immune response and acute respiratory distress syndrome [2–5]. Based on COVID-19 pathophysiology, various EMT options have been proposed and were shown effective in decreasing hospitalizations and death [6–8]. For instance, antiviral therapies, monoclonal antibody treatments, and steroids have been accepted as standards of care for COVID-19. Evidence suggests that EMT of symptomatic high-risk COVID-19 patients, with both oral and intranasal antihistamines, reduces fatality rate and hospitalizations [9–12]. A recent study showed that EMT in nursing homes could dramatically reduce hospitalization rates and improve survival [6]. Our clinical group has documented a decreased morbidity and mortality in patients receiving early treatment protocol and utilizing repurposed, easily accessible medications for the early management of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [7, 8].

Despite the success in reducing hospitalization and mortality, the impact of COVID-19 is still strongly felt. Few studies have considered that COVID-19 is generally regarded as one of the leading causes of absenteeism among first responders, healthcare personnel, workers, and those involved in the education [13]. It is worth noting that some CDC estimations suggest that approximately 30% of patients develop persistent or chronic COVID-19 symptoms (long COVID) [14, 15]. However, therapies are lacking to accelerate clinical recovery and alleviate disease-induced sensory and upper respiratory symptoms (URS) (e.g., cough, ageusia, anosmia, nasal congestion, etc.) that could lead to chronic manifestations of the disease.

Chlorphenamine Maleate (CPM) is a first-generation antihistamine that relieves symptoms associated with allergies, hay fever, common cold, cough, and nasal congestion, probably owing to the anti-inflammatory and immunomodulatory properties of the drug [16, 17]. Various studies have documented the antiviral properties of CPM against SARS-Cov-2 [11, 18–20]. Previously, our group reported the safety and efficacy of intranasally administered CPM to treat COVID-19 [11] and allergic rhinitis [21]. Since the nasal cavity is the portal of entry of the disease and many early manifestations are in the upper respiratory tract [22], it is plausible that an intranasal-administered therapy could decrease clinical symptomatology and accelerate clinical recovery. Such therapeutic strategies by allowing individuals to return to their daily life quicker, may have tremendous economic and public health implications.

Accordingly, the main goal of the present study was to examine the effectiveness of CPM intranasal spray as part of the early treatment of mild to moderate COVID-19. To this end, a two-part research study

was conducted to collect evidence from a randomized, double-blinded, placebo-controlled trial and a retrospective cohort study in patients with PCR-proven or antigen COVID-19 infection. It was hypothesized that intranasal CPM would accelerate clinical recovery, particularly the alleviation of sensory and URS, in patients with COVID-19.

Methods

Part 1: Accelerating COVID-19 Clinical Recovery in an Outpatient Setting (ACCROS-I)

A randomized, double-blind, placebo-controlled study was conducted for 28-days. Randomization and matching were performed by someone not associated with the care or assessment of the patients using a computer-generated random number table (with a 20% random element) using an allocation ratio of 1:1 as previously described [23]. Evaluation for each subject was conducted during and after administration of the treatment to assess any local or systemic adverse reactions (anticholinergic effects) such as drowsiness, dry mouth, nose and throat, nausea, vomiting, loss of appetite, constipation, headache, increased chest congestion, and nasal irritation.

Subjects

After informed consent was obtained, subjects were randomized to either CPM or PLB in addition to standard of care (SoC). The placebo nasal spray was formulated identically to the CPM formulation minus the active ingredient. The study was approved following the statutes of the Declaration of Helsinki by the Institutional Ethics Committee and Investigation of the Department of Education and Research Masters in Zoonotic and Infectious Diseases of the Universidad Nacional Autonoma de Honduras and the IRB of the Hospital CEMESA. The trial was registered on ClinicalTrials.gov: NCT05449405.

The inclusion criteria were adults aged 18 to 65 years of either sex, positive polymerase chain reaction or antigen confirmed for SARS-CoV-2 infection by nasopharyngeal swab, with either mild symptoms (minimal or asymptomatic respiratory symptoms in addition to a positive test), or light symptoms including respiratory symptoms such as cough, fever, no oxygen desaturation (Room air SpO2 < 92%). Patients were randomized within 48 of initiation of the symptoms. The exclusion criteria included: patients with more than seven days of symptoms and more than five days since COVID-19 positive with a nasopharyngeal PCR test, hypoxemia (Room air SpO2 < 92% plus severe polypnea, hospitalized patients, subjects with known hypersensitivity to CPM and any of the inactive ingredients, subjects receiving therapy with monoamine oxidase inhibitors (MAOIs; rasagiline, selegiline, isocarbonboxasid, phenelzine, tranylcypromine), and those with issues with narrow-angle glaucoma, urinary retention, severe hypertension or severe coronary heart disease. Participants had to be able to provide informed consent, able to self-administer the nasal spray, and record clinical signs of COVID-19 symptoms as defined by FDA COVID-19 Guidance Document [24]. All patients were treated using EMT standard of care protocol utilizing medications for the early management of SARS-CoV-2 as previously described [8].

Intervention

Both treatments (CPM vs. PLB) were administered as two spray doses in each nostril (100 µL of the solution per nostril) three times a day using a 1.0% CPM solution (for the active drug group). The total daily dose from the CPM was 12 mg per day, approximately half (1/2) of the daily maximum oral recommended amount (24 mg). A commercially available open angle swirling effect atomizer (GentleMist®; Dr. Ferrer BioPharma, Hallandale Beach, FL, USA) was utilized to administer the treatment. The atomizer was designed to generate a swirling effect by opening a spray cone from a tapered nozzle bottle to ensure the most efficient and enhanced drug delivery and aid in patient compliance. Subjects were instructed to use the atomizer following a 12–15º angle to augment the medication deposition in the nasopharynx, the focal point of viral infection, as previously described [11, 25, 26].

Study Outcomes

The main outcome variable was clinical recovery, defined as the change from baseline to end of the treatment period in COVID-19 symptoms (baseline to day 7) as measured by the co-primary endpoints' percent change (Δ%) in symptom resolution in daily symptoms score (DSS) and symptoms of the severity of the disease using a (VAS) on a scale of 1–10 (no signs to worst symptoms). Briefly, the DSS is a well-established instrument comprised of a four-point severity rating scale ranging from 0 to 3: 0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; and 3 = severe symptoms [27]. The DSS consists of six individual symptom scores: four nasal symptoms (runny nose, blocked nose, sneezing, and itchy nose) and two ocular symptoms (gritty feeling or red or itchy eyes, and watery eyes). Each day, the patient rates the severity of each symptom using this scale. Results were entered in an electronic diary. The main symptom sum score was calculated for each patient with a maximum of 18. The VAS is a general simple quantitative method that may be used for the evaluation of the severity of symptoms, a 10 cm line to grade the severity of symptoms from "no symptoms" (0 cm) to "the highest level of symptoms" (10 cm) is utilized [28]. Secondary outcomes included the proportion of patients reporting sensory and URS of cough, ageusia, anosmia, and nasal congestion on day 7. Hospitalization rates were also monitored during the 28-day study. Close safety monitoring of all the patients was conducted before and after administering the intranasal spray. The study schema is summarized in Table 1.

Statistical analyses

Statistical analyses were performed using SPSS Version 26.0 (IBM Corp., Armonk, NY, USA) to calculate descriptive and inferential statistics. Independent samples t-test and Chi-Square (X^2) tests were used to compare the groups (CPM vs. PLB) in continuous variables and categorical variables, respectively (baseline and day 7, 14, and 28).

Part 2: Accelerating COVID-19 Clinical Recovery in an Outpatient Setting: Retrospective Analysis (ACCROS-II)

A retrospective cohort study (ACCROS-II) was conducted in countries where the CPM intranasal spray is commercially available (Cuba, Dominican Republic, Panama). Data from June 2021 to July 2022 were

collected from all COVID-positive subjects from electronic and hard copy medical records using a standardized form. Patient information was collected as part of routine visits and telehealth consultations. Two cohort groups compared patients that received CPM nasal spray and standard of care (CPM + SoC) vs. SoC alone.

Subjects

Subjects were divided into two groups based on prescription CPM nasal spray and standard of care CPM + SoC and SoC alone. They were evaluated by the total number of days with COVID-19 symptoms, including cough, nasal congestion, ageusia, and anosmia. The rate of hospitalization among the cohorts was also evaluated. The study was approved by the following the statutes of the Declaration of Helsinki by the Institutional Ethics Committee and the investigation department of Clinica Universitaria Unión Médica, Santiago de Los Caballeros, DR. The trial was registered on ClinicalTrials.gov: NCT05520944.

The inclusion criteria were patients > 18 of either sex, positive polymerase chain reaction or antigen confirmed for SARS-CoV-2 infection by nasopharyngeal or oropharyngeal swabs, regardless of COVID-19 vaccination status. The exclusion criteria comprised a history of immunodeficiency or receiving immunosuppressive therapy, a significant disease, hospitalized patients with COVID-19, or a drug that precluded the subject's CPM use.

Data collection

From electronic medical records, data collected included demographics, underlying diseases, medical history, comorbidities (hypertension, rhinitis, diabetes, asthma, chronic sinusitis, etc.), symptoms (cough, general COVID-19 symptoms, ageusia, and anosmia), concomitant medications, the rate of hospitalization). If the patient used CPM nasal spray, then data collected also included the number of days the patient used CPM nasal spray. Patients were matched for the period of treatment and outbreak of COVID-19.

Study Outcomes

The main outcome variable was clinical recovery, collected as the total number of days with manifestation and symptoms from the beginning of treatment. Secondary outcomes included the rate of hospitalization.

Statistical analyses

Descriptive statistics were used to describe the demographic means of the two treatment groups, standard deviations or medians as appropriate for continuous variables and numbers, and percentages for binary and categorical variables. A priori alpha level of 0.0125 was considered statistically significant to account for multiple comparisons via Bonferroni adjustment. Mean days with symptoms were compared between the cohorts vias person *T-test* for normally distributed data. The association between categorical variables, including the proportion of hospitalized patients among the group, was captured using Pearson's Chi-square test/Fisher's exact test.

Results

ACCROS-I

A total of 101 patients met inclusion and were recruited in this study, CPM (n = 61) and PLB (n = 40). The subjects' characteristics are summarized in Table 2. All patients but one were vaccinated for SARS-CoV-2, and there was no difference in the subjects' characteristics between the groups. When compared with PLB, there was a statistically significant ($P < 0.05$) difference in clinical recovery. The CPM group showed faster Δ% recovery as revealed by the difference in symptom scores in both DSS (-18.8 ± 9.3%) and VAS (-8.6 ± 5.1%) compared to PLB after 7 days of treatment (Fig. 1: A and B).

There were no differences in sensory or URS between the groups on day one (Fig. 4). However, the proportion of patients reporting symptoms was lower in the CPM group for ageusia ($X^2 = 6.69$; $P = 0.01$), cough ($X^2 = 4.62$; $P = 0.03$), and nasal congestion ($X^2 = 4.64$; $P = 0.02$) on Day 7 (See Table 3). Although not statistically significant ($X^2 = 3.03$; $P = 0.08$), the proportion of patients reporting anosmia on day 7 was higher in the PLB (15%) than in the CPM (4.9%) group (Fig. 2).

The study subjects did not require hospitalization nor the use of corticosteroids after day 7. Overall, patients were compliant as reported using the spray for 10 days in both the CPM (10.5 ± 0.5 days) and PLB (10.6 ± 0.5) groups. Besides some mild discomfort felt by subjects immediately after applying the spray, the participants reported neither adverse reactions nor side effects. Symptom resolution on day 14 was not different between the groups.

ACCROS-II

In this retrospective study, medical records of 1119 were screened, from which a total of 660 patients with COVID-19 were included in the study (Fig. 3). The subjects' characteristics are summarized in Table 4. Of the 660 patients, 330 received CPM + SoC as treatment and 330 received SoC alone. The mean age of patients with COVID-19 was 46, with 310 (47%) male. 596 (90.2%) patients were vaccinated against COVID-19. 5% received one dose, 66% received two, and 8.3% received three doses. The most common comorbidity was hypertension which included 185 (28.2%) patients (Table 4 shows subject characteristics).

Figure 4 shows a statistically significant difference ($P < 0.001$) between receiving CPM + SoC vs SoC in a clinical course. It can also be noted that each individual symptom (anosmia, cough, and ageusia) was on average less lasting (3–5) in the CPM + SoC cohort compared to the SoC alone.

Discussion

This work examined the effectiveness of CPM intranasal spray as part of early treatment for COVID-19 in an outpatient setting. Current findings support early intervention with intranasal CPM as an emerging strategy to accelerate recovery with enormous public health implications. In ACCROS I, the main finding is

that adding CPM intranasal spray as part of EMT accelerates clinical recovery and URS alleviation to 7 days in patients with COVID-19. In ACCROS II, the main finding was CPM nasal spray as part of the standard of care for COVID-19, accelerates clinical recovery and decreases sensory and upper respiratory symptoms in an outpatient setting. Early intervention to treat COVID-19 has been recognized as a strategy for reducing hospitalization and mortality [7, 8]. CPM is an effective intranasal agent to address SARS-CoV-2 infection early in the course of the disease (viremic phase) when symptoms are usually mild [6, 7, 9–11]. Faster recovery will allow individuals to return to daily life quicker, reducing economic stress, healthcare overutilization, and medical centers overflow during outbreaks.

Mounting evidence suggests that CPM has both antiviral and anti-inflammatory actions that could be beneficial in treating COVID-19 [11, 18–20, 29]. Furthermore, molecular modeling and preliminary clinical data analyzed the antiviral activity of CPM, comparing the chemical structure of different over-the-counter drugs. CPM was structurally like drugs, known to have an anti-inflammatory and antiviral effect in drug-receptor interactions [18, 30]. *In vitro* studies have supported the anti-SARS-CoV-2 properties of CPM, which have also been seen in clinical studies [10, 11, 18–20]. Preliminary data from our group found that CPM can affect the three predefined compartments at comparable levels indicating its multitarget effect during the virus replication cycle by affecting viral adsorption, replication, and direct virucidal effect with a potential broad-spectrum antiviral application reducing the probability of antiviral resistance significantly [31]. If taken together, these data suggest intranasal CPM substantially decreases the recovery time, reducing the most bothersome symptoms present in long COVID-19 syndromes, such as anosmia, ageusia, and cough.

Besides the antiviral effects of CPM, other therapeutic properties of the drug could also be implicated in the rapid amelioration of both sensory and URS in this patient population. First, CPM, a potent bitter taste receptor (T2R) agonist, may stimulate sinonasal innate immunity triggering host defense mechanisms while blocking Ig-E-mediated mast cell activation and cytokine expression [32–34]. Moreover, drugs with T2R stimulation have been proposed and proven effective in early clinical trials in COVID-19 [12, 35]. Second, CPM displays anticholinergic, bronchodilatory, and decongestant activity [36–39]. In the present study, the proportion of patients reporting sensory (anosmia and ageusia) and URS of nasal congestion and cough were remarkably lower than those in the PLB group. Although the underlying mechanisms to explain these effects were not investigated, we speculate that direct viral inhibition and the T2R, anticholinergic, and anti-inflammatory properties of CPM facilitated the recovery in these patients.

The associated limitations come with a relatively small clinical sample size as some of the findings cannot be generalized to other populations. This study be replicated in double-blind clinical trials among large and diverse groups and possibly evaluate several COVID-19 variants, yielding the most clinically relevant data. A limitation of both studies is the inability to evaluate if any other household members were infected with COVID-19. ACCROS-I was undertaken in multiple countries with a different SoC, though this effect should be minimized by randomization. ACCROS-II was a retrospective chart review study that may suffer from typical issues affecting these trials, including selection bias, incomplete records, subjective descriptions, and interpretations.

Conclusion

CPM nasal spray as part of EMT for COVID-19 accelerates clinical recovery and decreases sensory deficiencies and URS in an outpatient setting. Given the well-known safety profile of CPM, additional studies to expand the use of CPM to various subpopulations, and evaluation of nasal CPM to decrease transmission of the virus within households, healthcare settings, and other community groups are urgently needed.

Declarations

Author Contributions All the authors, FVP, EJPM, MLT, JG, CLF, GBE, MB, MFVP, SAAR, AC, ZC, SGF, JPT, NG, JDW, FR have contributed to the study conception, design, data collection, statistical analysis, and drafting of the manuscript.

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Conflict of interest All the authors report no conflict of interest.

Ethical approval the study was approved by the following the statutes of the Declaration of Helsinki by the Institutional Ethics Committee, and the investigation department of Clínica Universitaria Unión Médica.

Consent to Participate Written and verbal informed consent were obtained from the patients where applicable.

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Tables

Tables 1 to 4 are available in the Supplementary Files section.

Figures

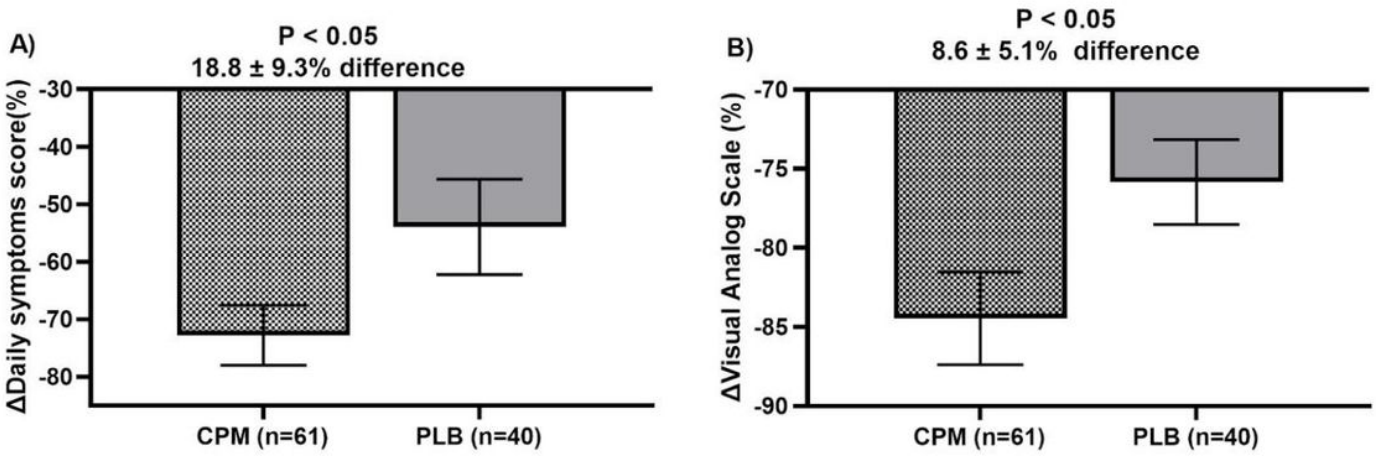

Figure 1

A:B Changes in Visual Analogue Scale and Daily Symptoms Scores (for COVID-19 symptoms) in response to 7 days of treatment.

Data are Mean ± SEM. Student T-tests were used for statistical comparisons. CPM: Chlorpheniramine Maleate; Placebo: PLB.

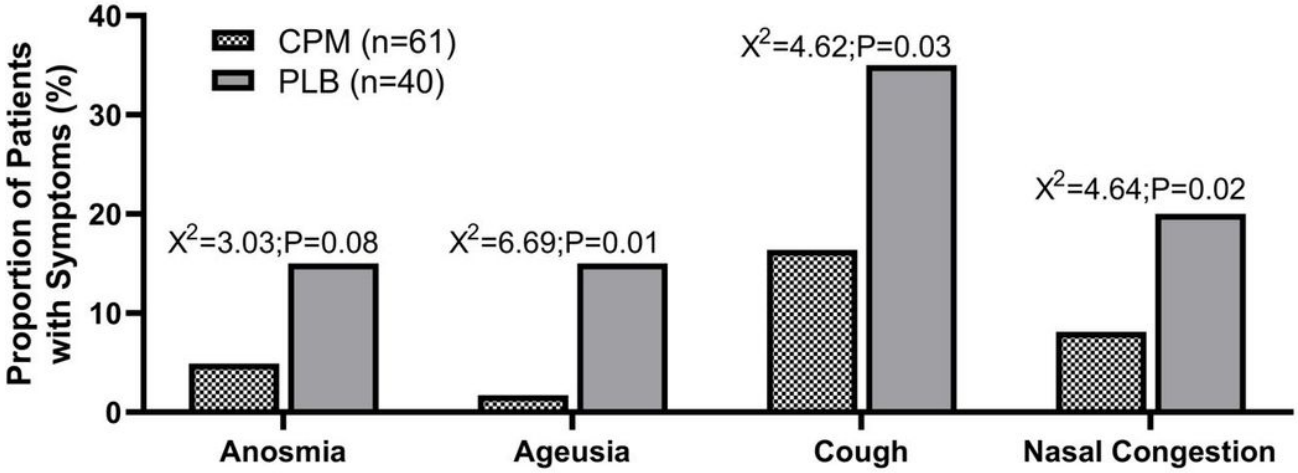

Figure 2

COVID-19-related sensory and upper respiratory symptoms in response to 7 days of treatment

Chi-squared tests (X^2) were used for statistical comparisons. CPM: Chlorpheniramine Maleate; PLB: Placebo.

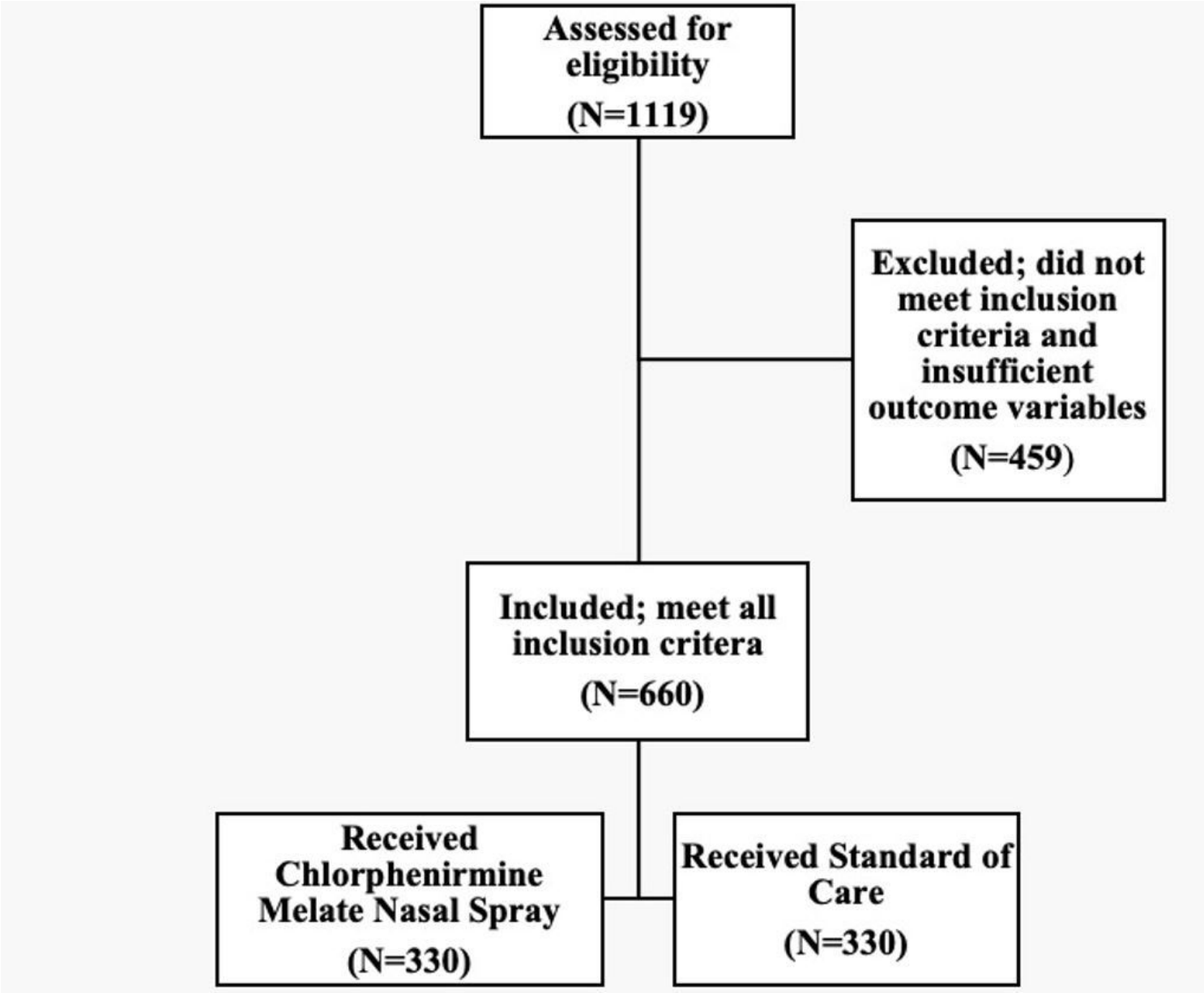

Figure 3

ACCROS- 2 Eligibility Screen

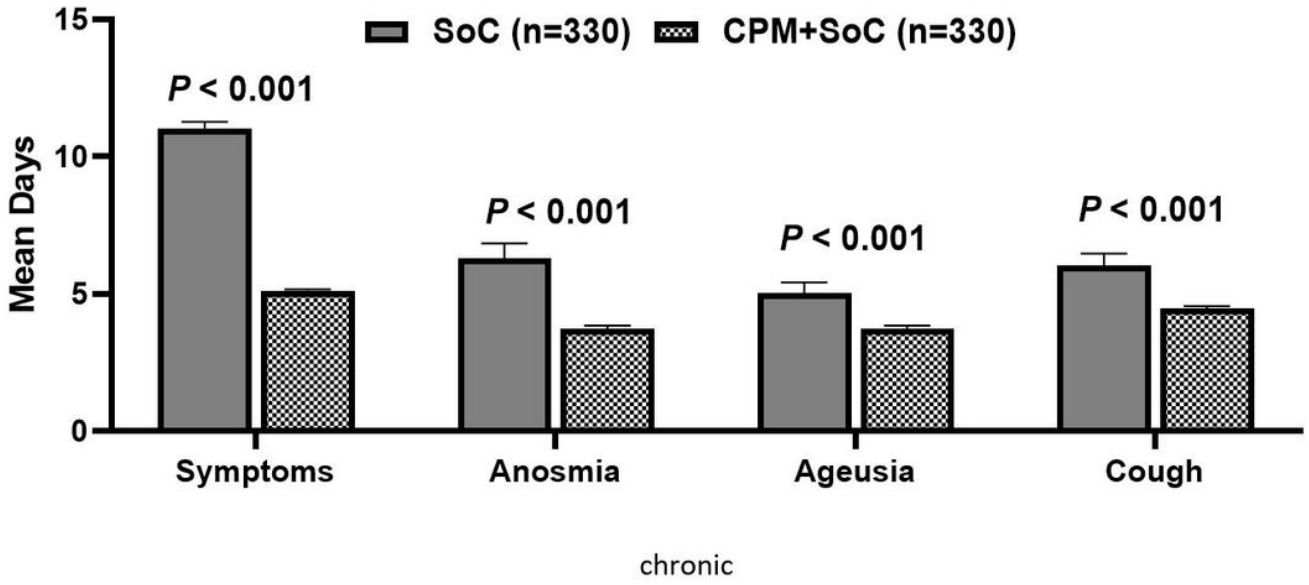

Figure 4

COVID-19-related sensory and upper respiratory symptoms in response to intranasal CPM treatment

Data are Mean ± SEM. Student T-tests were used for statistical comparisons. CPM: Chlorpheniramine Maleate; Placebo: PLB.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.docx