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Original Article

Negative impacts of the administration of hydroxycloroquine and anticoagulant in patients with SARS-COV-2 infection: a randomized clinical trial

Impactos negativos da administração de hidroxicloroquina e anticoagulante em pacientes com infecção por SARS-COV-2: um ensaio clínico randomizado

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ABSTRACT: *Purpose*: To evaluate antimalarial with or without anticoagulant treatment, in patients with recent SARS-COV-2 infection. *Methods*: Clinical study carried out at Samuel Libânio Clinic Hospital, University of Vale do Sapucaí, Pouso Alegre-MG. Approved by the Ethics Committee (4.034.077) and registered in the Clinical Trials (NCT04788355). Suspected patients for COVID-19 were included in the emergency room. The groups were: C (control) with 6 patients, A (anticoagulant apixaban) with 9 patients, H (hydroxychloroquine) with 5 patients and HA (hydroxychloroquine and anticoagulant apixaban) with 8 patients. *Results*: there were no significant differences between groups. The HA group, in which there was an intervention with two drugs, presented a greater number of days with symptoms (p = 0.037) and worse results, when compared to the control: most relevant symptoms, were: cough (p = 0.001), *and* anosmia / ageusia (p = 0.011) headache (p = 0.001). *Conclusion*: The present study began when there were doubts about the use of drugs such as Hydroxychloroquine (HCQ) and apixaban (APX). The reduced "n" was defined through bureaucratic and polemic issues independent of the authors' actions. No clinical benefit was associated with HCQ and APX. There was an increase in the number of symptomatic days when HCQ and APX were administered. Despite the limitations, there was no therapeutic indication of the evaluated drugs.

Keywords: COVID-19; SARS-CoV-2; Prevention; Complications.

RESUMO: *Objetivo*: Avaliar antimalárico com ou sem tratamento anticoagulante, em pacientes com infecção recente por SARS-COV-2. *Métodos*: Estudo clínico realizado no Hospital das Clínicas Samuel Libânio da Universidade do Vale do Sapucaí, Pouso Alegre-MG. Aprovado pelo Comitê de Ética (4.034.077)

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e registrado nos Ensaios Clínicos (NCT04788355). Pacientes suspeitos de COVID-19 foram incluídos na sala de emergência. Os grupos foram: C (controle) com 6 pacientes, A (anticoagulante apixabana) com 9 pacientes, H (hidroxicloroquina) com 5 pacientes e HA (hidroxicloroquina e anticoagulante apixabana) com 8 pacientes. *Resultados*: não houve diferenças significativas entre os grupos. O grupo HA, no qual houve intervenção com dois medicamentos, apresentou maior número de dias com sintomas (p = 0,037) e piores resultados, quando comparado ao controle: os sintomas mais relevantes foram: tosse (p = 0,001), e anosmia/ageusia (p = 0,011) cefaléia (p = 0,001). *Conclusão*: O presente estudo teve início quando havia dúvidas sobre o uso de medicamentos como hidroxicloroquina (HCQ) e apixabana (APX). O "n" reduzido foi definido por meio de questões burocráticas e polêmicas independentes das ações dos autores. Nenhum benefício clínico foi associado com HCQ e APX. Houve um aumento no número de dias sintomáticos quando HCQ e APX foram administrados. Apesar das limitações, não houve indicação terapêutica dos medicamentos avaliados.

Palavras-chave: COVID-19; SARS-CoV-2; Prevenção; Complicações.

INTRODUCTION

On January 30, 2020, the World Health Organization (WHO) WHO Emergency Committee declared a global health emergency by pandemic infection with the new coronavirus SARS-CoV-2[1,2].

The treatment of respiratory infections of viral etiology consists mainly of supportive measures. Specific antiviral therapies are available for some infections, such as influenza (oseltamivir)[3]. Regarding the new coronavirus (COVID-19), there is no treatment defined as effective[4]. In early 2020, there were problems such as, unavailability of quick results for polymerase chain reaction (PCR) tests and rapid laboratory tests that caused uncertainties in the etiological diagnosis. As well as, delay in the measures of containment and treatment, beyond presentation of serious clinical developments[5]. Challenges were established, development of new therapies that would minimize symptoms, reduce the time of contagion and, mainly, reduce complications and mortality[6].

HCQ is an affordable and low-cost antimalarial[7]. Some evidence has suggested that HCQ would have an in vitro action against COVID-19[8,9,10], although the scientific literature requires better and larger studies, designed to test its effectiveness in patients infected with COVID-19[11]. A recent study demonstrated that HCQ could have a broad spectrum antiviral potential. It would block Coronavirus infection by increasing the endosomatic pH, necessary for the virus to fuse into the cell. The intervention would be in the glycosylate of severe acute respiratory syndrome coronavirus 2 (SARS-COV-2)[12] cell receptors. In 2021, a meta-analysis of 29 articles, including 3 randomized clinical trials, showed that HCQ did not reduce mortality and could even be a factor in increasing mortality in some cases[13]. In addition, HCQ had no impact on virologic cure, clinical recovery time, or improved survival in patients with COVID-19[14]. However, it is associated with some possible side effects, such as: cardiac arrhythmias, prolongation of the QT interval on the electrocardiogram and cardiac toxicity, especially when associated with other drugs, such as azithromycin[15], and the continued use or outside of research protocols, should be discouraged.

Some patients with COVID-19 may initially present with single organ insufficiency, however they may quickly progress to systemic dysfunction. One of the most common laboratory findings observed in patients with COVID-19 requiring hospitalization was the increase in D-dimmer[16]. D-dimmer results and very high fibrin degradation products are being used to guide therapy and evaluate prognosis[17]. Autopsies in individuals who died from COVID-19 showed that alveolar viral damage is followed by inflammatory reaction and multiple thrombosis in the pulmonary microvasculature. Besides the lungs, these microthrombi may involve the microvascular bed of the brain, hearts, kidneys and liver leading to organic collapse and death[18]. Thus, as recommended by the International Society of Thrombosis and Hemostasis, prophylactic use of low molecular weight heparin (LMWH) should be considered in all patients (including non-critical) who require hospitalization for COVID-19 infection in the absence of contraindications[16]. Yet, no oral anticoagulant was tested in this scenario.

Currently apixaban (APX) is approved by international and national regulation authorities widely used and safe for the prophylaxis of deep vein thrombosis reducing the risk of pulmonary and systemic embolism, in clinical scenarios described in the package insert[19]. In addition, pharmacokinetics define limited drug interactions, the fact that there is no need for laboratory monitoring and potentially better cost-effectiveness compared to other anticoagulants, hypothetically make APX a potential alternative for oral prophylaxis in patients with COVID-19[19,20,21,22].

The public urgency that Brazil and other countries in the world are currently experiencing requires resources that are active to prevent the spread of COVID-19, as well as avoid overcrowding, especially in hospitals, associated with the depletion of medical supplies and resources in the health area systems[23]. The implementation of telemedicine systems aimed at the care of symptomatic patients can reduce exposure to diseases, for example, preventing overcrowding in emergency rooms and primary care clinics[24]. Thus, the proposal of a randomized, open clinical study comparing standard treatment versus standard treatment added HCQ (400 mg daily), APX (5mg daily) or HCQ + APX (400 mg and 5 mg daily) is justified in the prevention of respiratory and systemic complications in

patients treated with suspected viral pneumonia, reported as a suspected case of COVID-19, hospitalized or in home isolation.

METHODS

Prospective, randomized, double-blind, controlled study conducted at Samuel Libânio Clinic Hospital, University of Vale do Sapucaí, Pouso Alegre-MG. Approved by the Ethics Committee (4.034.077) and registered in the Clinical Trials (NCT04788355).

The emergency department was adequately prepared to receive suspected cases of COVID-19, which after being subjected to medical screening, were notified as suspected cases, due to epidemiological, clinical, laboratory or imaging evidence.

Definition of suspicious case

According to guidelines proposed by the Ministry of Health of the Federal Government [22] suspicious cases are considered patients who present the signs and symptoms below: Flu Syndrome (FS): fever > 37.8 °C + cough or sore throat, nasal obstruction and discharge or difficulty breathing. Severe Acute Respiratory Syndrome (SARS): (FS): + dyspnea/respiratory distress or SO2 < 95% in room air or cyanosis of the lips or face. History of close or household contact with laboratory-confirmed cases for COVID-19, in the last 14 days before the onset of symptoms.

Notification of suspected case and informed consent form

The patients were notified to the municipal epidemiological surveillance and to the Internal Scientific Committee for Hospital Infection (ISCHI), and received necessary guidance and clarifications by the doctor on duty or resident in a medical clinic. Then they were invited to participate in the study. Patients were given the Informed Consent Form.

Inclusion criteria

Patients with suspected or confirmed COVID-19 older than 18 years.

Time between onset of symptoms and inclusion ≤ 14 days.

Time between hospitalization and inclusion ≤ 48 hours.

Non-inclusion criteria

Patient in hospitalization, using mechanical ventilation

History of severe ventricular cardiac arrhythmias or QTc≥480ms

Patients with severe electrolyte disorder, hypermagnesemia, or hyperpotassemia.

History of severe liver disease, defined as patient report or cirrhosis records, esophageal varicose veins, or clinical ascites on examination.

Renal dysfunction (estimated glomerular filtration rate [eGFR]<30 mL/min/1.73m2, by modification of diet in renal disease (MDRD) or method chronic kidney disease epidemiology collaboration (CKDEC).

Patients with retinopathy or macular degeneration.

Patients with pancreatitis or other serious clinical illness.

Pregnant Women.

Allergy HCQ or derivatives.

Allergy to APX or formal contraindication to use.

Previous use of another oral anticoagulant.

Blood Dyscrasia.

Major Surgery in the last 3 months.

Risk of major bleeding from any relevant clinical condition.

Exclusion criteria

Patients tested negative for COVID-19, didin't receive the intervention and were referred to clinical procedures defined by the medical team not linked to the study.

The sensitivity of PCR is not 100% accurate and it depends on: the moment of collection, form of collection. In these scenarios the clinic was contacted for evidence of COVID-19 infection. For example, in cases that the PCR is negative, but the center maintains suspicion for clinical, imaging, or epidemiological data, the patient remained receiving the medication until the suspicion is excluded. In these cases, imaging aspects (e.g., chest X-ray or CT scans) were evaluated in order to decide, together with the professional in charge of the evaluation, whether the patient should be continued as a suspect case).

In case of impossibility of swallowing for any reason, the protocol provided the use of the medications of the study via nasogastric or nasoenteric tube. After confirmation of gastric or enteral probe through an auscultatory or radiographic method, the probe was released to use by the attending physician according to the institution's protocol and the patient was kept in the study; if this release did't occur, the patient was excluded from the study.

Patients with prolonged QT interval, defined as corrected QT (QTc) for a heart rate above 450 ms in males and 470 ms in females: a next dose was suspended and the patient was withdrawn from the study.

Patients with hepatic toxicity, defined as increased TGO/TGO or bilirubin: the dose of HCQ was reduced to 100 mg daily. If liver enzymes persist after 24 hours of HCQ 1xd use, HCQ was suspended and the patient was excluded from the study.

Patients with ventricular arrhythmias were suspended from HCQ use since it reports serious adverse events and were excluded from the study.

Patients with bleeding, major hematoma, or blood dyscrasia were discontinued from the use of APX for reporting a serious adverse event and were excluded from the study.

Patients who, at any time in the process, chose to stop participating in the study and continued being treated by the hospital's medical team, according to the institution's standard protocols, also were excluded from the study.

Randomization

Observing the eligibility criteria, patients were randomized into 4 groups.

H group

HCQ + standard treatment. Patients in this group received HCQ orally - 200 mg every 12 hours for 7 days In addition, patients in this group could receive standard supportive treatment and care for COVID-19, composed of measures recommended by the literature[22].

HA group

HCQ + APX + standard treatment. Patients in this group received Hydroxiclorocchine orally - 200mg every 12 hours for 7 days + APX Oral 2.5mg every 12 hours, also for 14 days (prophylactic dose). In addition, patients in this group could receive standard supportive treatment and care for COVID-19, composed of measures recommended by the literature[22].

A group

APX + standard treatment. The group patients received APX orally - 2.5 mg every 12 hours, also for 14 days (prophylactic dose). In addition, patients in this group could receive supportive treatment and care for COVID-19, composed of those recommended by the literature[22].

Control group

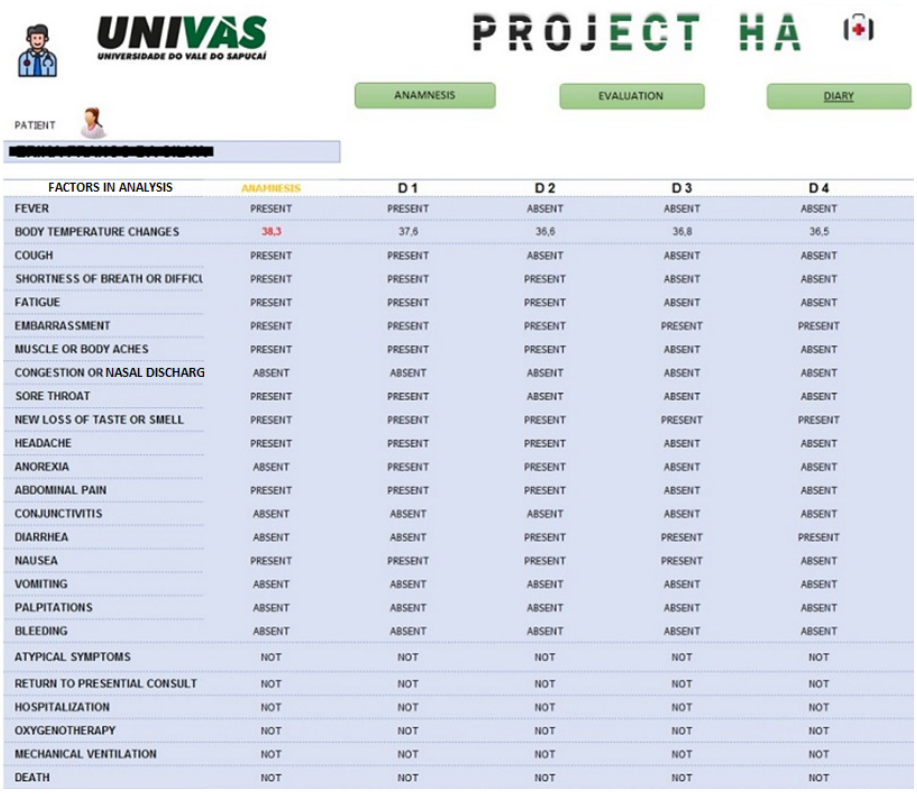
Standard treatment. The patients in this group received standard supportive treatment and care for COVID-19, composed of measures recommended in the literature[22].

Monitoring

Home isolation patients were followed up for 14 days after inclusion in the study. Were asked questions about their health conditions by telemedicine. The answers were tabulated in a spreadsheet composed of signs and symtoms, clinical evolution (Figure1).

Questions assessed

Cough, dyspnea, fatigue, malaise, myalgia, nasal discharge, odynophagia, anosmia, ageusia, headache, anorexia, abdominal pain, conjunctival congestion, diarrhea, nausea, vomiting, palpitations, bleeding. The parameters for such telemedicine evaluations were: yes or no. In cases where patients reported more serious hypotheses, they were advised to seek the hospital for face-to-face evaluation, carried out by an attending physician.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PROJECT HA

ANAMNESIS | EVALUATION | DIARY

PATIENT [redacted]

FACTORS IN ANALYSIS	ANAMNESIS	D 1	D 2	D 3	D 4
FEVER	PRESENT	PRESENT	ABSENT	ABSENT	ABSENT
BODY TEMPERATURE CHANGES	38,3	37,6	36,6	36,8	36,5
COUGH	PRESENT	PRESENT	ABSENT	ABSENT	ABSENT
SHORTNESS OF BREATH OR DIFFICL	PRESENT	PRESENT	PRESENT	ABSENT	ABSENT
FATIGUE	PRESENT	PRESENT	PRESENT	ABSENT	ABSENT
EMBARRASSMENT	PRESENT	PRESENT	PRESENT	PRESENT	PRESENT
MUSCLE OR BODY ACHES	PRESENT	PRESENT	PRESENT	ABSENT	ABSENT
CONGESTION OR NASAL DISCHARG	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT
SORE THROAT	PRESENT	PRESENT	ABSENT	ABSENT	ABSENT
NEW LOSS OF TASTE OR SMELL	PRESENT	PRESENT	PRESENT	PRESENT	PRESENT
HEADACHE	PRESENT	PRESENT	PRESENT	ABSENT	ABSENT
ANOREXIA	ABSENT	PRESENT	PRESENT	ABSENT	ABSENT
ABDOMINAL PAIN	PRESENT	PRESENT	PRESENT	ABSENT	ABSENT
CONJUNCTIVITIS	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT
DIARRHEA	ABSENT	ABSENT	PRESENT	PRESENT	PRESENT
NAUSEA	PRESENT	PRESENT	PRESENT	PRESENT	ABSENT
VOMITING	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT
PALPITATIONS	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT
BLEEDING	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT
ATYPICAL SYMPTOMS	NOT	NOT	NOT	NOT	NOT
RETURN TO PRESENTIAL CONSULT	NOT	NOT	NOT	NOT	NOT
HOSPITALIZATION	NOT	NOT	NOT	NOT	NOT
OXYGENOTHERAPY	NOT	NOT	NOT	NOT	NOT
MECHANICAL VENTILATION	NOT	NOT	NOT	NOT	NOT
DEATH	NOT	NOT	NOT	NOT	NOT

Figure 1: Worksheet that documented daily of each patient in the study (this illustration refers to the 5 -day segment)

The patients included, when admitted to the hospital, were monitored by an attending physician during the 14 days defined by the study. The following protocols were used, regardless of the group to which the patient was allocated, both for patients monitored by telemedicine at home and for those admitted to the hospital:

The exams and therapies indicated in the table below were requested or not, according to each case and at the description of the attending physician (Table 1).

Table 1: Illustrative table for laboratory, imaging and therapeutic tests

Routine Laboratory Tests
Blood count
Urea
Creatinine
Liver Enzymes
Bilirubin
C-reactive protein
D-dimmer
Electrocardiogram
Monitor the QT interval
Imaging exames
Chest radiography
Chest Computed tomography
Therapies
Antibiotics
Corticosteroids
Antivirals

The surveillance of vital parameters according to the patient's location (ward, Intensive Care Unit (ICU) or home), at least once a period, would be performed frequently in some cases, at the discretion of the attending physician, as well as measures of ventilatory support and transfer to advanced units (semi-intensive and ICU) or inpatient, according to clinical judgment and patient's need (Table 2).

If the PCR was negative, but there was suspicious of clinical, imaging or epidemiological data, the patient would continue to receive medication, until the suspicion was discarded. In such cases, aspects of the image would be assessed and the decision to keep the patient as a suspect would be decided by the investigators.

If swallowing were impossible for any reason, the protocol would provide the use of the study drugs by nasogastric or nasoenteric tube. After confirmation of gastric or enteral tube by auscultatory or radiographic method, a tube would be released for use by the attending physician, according to the institution's protocol.

Table 2: Primary and secondary outcomes

PRIMARY RESULTS
Ordinal result in 14 days
Symptomatic patient at home
Hospitalized patient without oxygen
Hospitalized patient with oxygen
Patient hospitalized in non-invasive conditions or high flow cannula
Patient on mechanical devices
Death
Hospital mortality
SECONDARY RESULTS
Ordinal result in 7 days
Need for intubation and mechanical ventilation in 7 days
Need for mechanical ventilation in the hospital
Use of rescue therapy (non-invasive ventilation or high-flow nasal cannula in 7 days)
Lenght of stay in the hospital
Occurence of tromboembolic or hemorrhagic complications
Occurence of renal dysfunction, defined as na increase in creatinine above 1,5 times the baseline value
SARS-COV-2 undetected by RT-PCR in nasopharyngeal samples with assesments every 5 days until the tenth day (Samples of nasopharyngeal smears would be discontinued after the first test was negative for SARS-Cov-2 or after the patient was discharged from the hospital, if the patient access to RT-PCR).
SECONDARY SECURITY RESULTS
Serious adverse events
ventricular arrhythmia due to increased QTc≥480ms
Severe hypoglycemia (≤ 40mg / dL)
Increase in the asymptomatic QT interval (QTc above 450 ms for men and 470 ms for women)
Acute cardiomyopathy (drop in ejection fraction below 40% in a patient with no previous history of ventricular dysfunction), as evidenced by a recent echocardiogram
Hypoacusis and loss of visual acuity
Hematological changes (anemia, leukopenia, thrombocytopenia defined by blood count)
Nausea and vomiting

Primary and secondary outcomes

Statistical methods

The Kruskal-Wallis tests were used to assess the statistical difference between the types of treatment, considering the days and symptoms. The Dunnett Multiple method compared the control group to the other groups.

RESULTS

On October 13, 2020, the study was discontinued due to political and bureaucratic issues. The sample consisted of 47 patients, of which 28 (59%) were tested positive for infection with the new coronavirus (Figure 2).

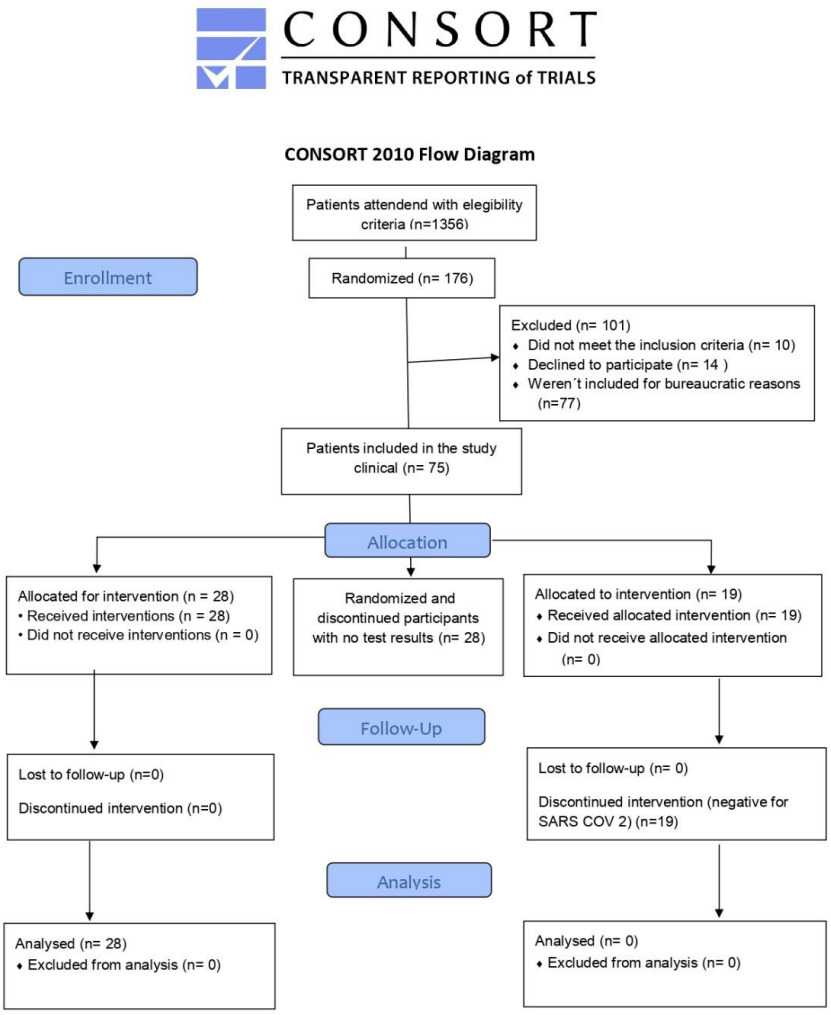

Figure 2. Consort diagram of study[25]

The basic characteristics were balanced between the control and intervention groups. The average age in the 4 groups ranged from 36 to 40 years.

Of 28 patients tested positive, 4 were obese (14.28%), 9 patients with systemic arterial hypertension (32.14%), 4 were diabetic (14.28%), 2 had asthma / Chronic Obstructive Pulmonary Disease (COPD) (7.14%) and 2 used peripheral vascular insulin (7.14%), 7 patients were considered normal (25%) (Table 3).

Primary outcome: there was no statistical difference between the groups regarding: types of treatment, considering the duration of symptoms ($p = 0.105$). By the method of Dunnett's multiple comparisons with a control, when comparing the control group with the other groups, the result of $p=0.105$, which could be observed that there was a larger difference between the groups HA and C; where: H-C showed $p=0.173$; APX-C showed $p=0.149$ and HA-C presents $p=0.037$. Therefore, the AH group that received an intervention with both drugs (HCQ and APX) had a greater number of days with symptoms: 11 days of symptom duration; while the control group the symptoms lasted 5 days ($p=0.037$).

Secondary outcome: regarding the days with symptoms: it was observed that the relevant symptoms with the greatest impact on the symptomatic days of the patients in the HA group were: cough ($p = 0.001$) and anosmia / ageusia ($p = 0.007$) and headache ($p = 0.001$).

Table 3. Characteristics of each group

	C	A	H	HA
Primary Results				
Return to the hospital	1 (16,6%)	2 (22,22%)	2 (40%)	1 (12,5%)
Hospitalization	0	0	0	0
Intensive care	0	0	0	0
Hospital mortality	0	0	0	0
Allocated Individuals				
Number	6 (21,42%)	9 (32,14%)	5 (17,85%)	8 (28,57%)
Sex	2M e 4F	3M e 6F	2M e 3F	6M e 2F
Age (average)	23 - 52 (37,5)	26 - 69 (40,6)	37–49 (41,2)	24 - 73 (41,6)
Comorbidities				
Obesity	1 (16,6%)	1 (11,11%)	0	2 (25%)
Systemic Arterial Hypertension	1 (16,6%)	4 (44,44%)	1 (20%)	3 (37,5%)
Diabetes Mellitus	1 (16,6%)	2 (22,22%)	0	1 (12,5%)
Asthma/COPD	0	0	2 (40%)	0
Vascular insufficiency	0	0	0	2 (25%)
Total	3 (50%)	7 (77,77%)	3 (60%)	8 (100%)
Adverse Effects				
Changes QT	0	0	0	0
Non-severe bleeding	0	3 (33,3%)	0	0
Severe bleeding	0	0	0	0
Severe hypoglycemia	0	0	0	0
Reduction of LVEF*	0	0	0	0
Hematological changes	0	0	0	0

Subtitle: **C (**group control), **A (**APX group), **H (**HCQ group), **HA (**HCQ and APX group). *LVEF (Left Ventricular Ejection Fraction).

DISCUSSION

The present study was designed to evaluate the use of drugs that may have a perspective of reducing complications caused by the SARS-CoV-2 virus, severe systemic inflammation and thrombotic events[26,27]. Based on the pathophysiology of the disease previously known, HCQ could determine the reduction of viremia. Preliminary studies have shown inhibition of different types of coronavirus (SARS-Cov-1, MERS-Cov, Hcov-229E and Hcov-OC43), both in vitro and in vivo (mice)[26,28]. APX, a new anticoagulant for use oral, it was evaluated according to the possibility of preventing thrombotic complications against the new Coronavirus[27].

Patients included in this study were associated with the recent generation by SARS-Cov-2 (up to 4 days after the generation of the result)[29] and with symptoms that were treated at home. A team of researchers followed the participants remotely, via telemedicine[30,31] for 15 days (period corresponding to the days of isolation determined)[32]. Using a spreadsheet (Figure 1), the researchers documented personal, epidemiological, clinical and complementary data daily through contact audio and video calls. Unfavorable clinical developments were assessed: urgency to return to immediate medical care, hospitalization, need for mechanics, intensive care or death.

In uncertain assumptions, the responsible researcher was asked to guide and organize a face-to-face consultation for the patient. 47 patients were included until the end of the study: 19 with a negative test for COVID-19 and 28 with a positive test for COVID-19. For patients with a negative result, the medication corresponding to the group was suspended immediately, while remote monitoring was maintained. The 28 patients with a positive test, provided the conditions analyzed by the study until its completion and no patient included in the study was hospitalized, according to Table 3.

The primary outcome determined the assessment of the clinical status of the patients, after the use of the proposed drugs alone or in combination, comparing them with the standard treatment, prescribed by the attending physicians at Hospital das Clínicas Samuel Libânio. The study showed an increase in the symptomatic period in patients in the intervention groups, indicating the possibility of a worsening of the healthy state of health, which, without medication, would be a brief evolution in relation to the duration of the disease, findings that corroborate with work showing that patients in the hydroxychloroquine group had longer hospital stays than those in the usual care group (16 *vs* 13 days) and were less likely to be discharged alive at 28 days (59.6% vs. 62.9%)[33].

The groups that used HCQ and APX alone, in relation to the control, had intermediate results and no statistical relevance, thus showing that there is no benefit in the use of both HCQ and anticoagulant in patients with recent infection and mild SARS-COV-2. The group with the highest average age, as well as the highest number of comorbidities among its participants, was the HA group. This situation corroborates the epidemiology of SARS-Cov-2, in which older patients with comorbidities have more unfavorable outcomes compared to younger and healthier ones[34], which is the case in group C - in which the average age was 4,1 years less than the HA group and with 50% less comorbidities among its participants. The aforementioned study[34] also determines that patients with COVID-19 disease who have comorbidities, such as hypertension or diabetes mellitus, are more likely to develop a more severe course and progression of the disease. Furthermore, older patients, especially those 65 years old and above who have comorbidities and are infected, have an increased admission rate into the intensive care unit (ICU) and mortality from the COVID-19 disease. Patients with comorbidities should take all necessary precautions to avoid getting infected with SARS CoV-2, as they usually have the worst prognosis[34].

In the present study, some patients returned to hospital care for a new medical evaluation, being prescribed only medication for anxiety. From the clinical point of view of SARS Cov-2 infection there were no complications. This situation resembles in part a study where there was a combined prevalence of depression, anxiety and sleep disorders, respectively: 45%, 47% and 34% of patients with COVID19[35].

Although the intervention groups had a longer duration of symptoms compared to the control group, these patients did not show a greater severity of the clinical condition. The increase in symptom days did not culminate in a need for emergency medical care, hospitalization, or intensive care, and did not result in death. In terms of side effects, they have not surfaced. Non-serious side effects occurred in 3 participants in Group A (mild and self-limiting nosebleeds). Clinically irrelevant side effects were observed in APX group, since oral anticoagulation, especially with new-generation drugs, is not associated with more complicated and severe epistaxis episodes, except recurrent bleeding [36].

The result of the study was partial. This factor occurred due to the discontinuation of the study. There were external interferences that determined the end of data collection, related to political conflicts and bureaucratic obstacles.

CONCLUSION

The present study began when there were doubts about the use of drugs such as HCQ and APX. The reduced "n" was defined through bureaucratic and polemic issues independent of the authors' actions. No clinical benefit was associated with HCQ and APX. There was an increase in the number of symptomatic days when HCQ and APX were administered. Despite the limitations, there was no therapeutic indication of the evaluated drugs.

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