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Safe and effective early start of oral anticoagulant therapy in ambulatory patients with COVID-19

Seguridad y efectividad de la terapia de anticoagulación temprana en pacientes ambulatorios con COVID-19

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COVID-19, oral anticoagulation, outpatient treatment.

Palabras clave:
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ABSTRACT

The current pathophysiological knowledge of COVID-19 patients includes inflammation and micro-thrombus, so hospitalized patients receive low-molecular weight and unfractionated heparin, but not all patients can access these drugs. Our objective is to inform our experience with oral anticoagulants in different doses in ambulatory COVID-19 patients. **Material and methods:** This study presents a retrospective case series of COVID-19 patients, with confirmed PCR diagnosis. According to the disease burden criteria, every patient received supportive treatment plus rivaroxaban or apixaban on different doses and oxygen if needed. The team evaluated the clinical course of the disease, laboratory markers, imaging studies and the presence of complications. The statistical analysis was done with SPSS 21. **Results:** This study included forty-one patients with moderate to severe disease, from a universe of 300 patients with confirmed COVID-19 infection; the patients were allocated into one of three groups based on the severity degree and received intense anticoagulation, usual anticoagulation and usual anticoagulation plus platelet blockade. The median age was 50 years (30-75), 64% male. The D-dimer and ferritin were above normal levels in all patients. The group under intense anticoagulation had higher D-dimmer and ferritin, as well as lower lymphocyte count. This group had a shorter recovery time. **Conclusions:** In COVID-19 patients, the early initiation of oral anticoagulation at home was safe and effective, without the need for hospitalization. We found ferritin as the most important serum marker to define the patient's stage.

RESUMEN

*Los conocimientos fisiopatológicos actuales de los pacientes de COVID-19 incluyen la inflamación y la microtrombosis, por lo que los pacientes hospitalizados reciben heparina de bajo peso molecular y no fraccionada, pero no todos pueden acceder a estos medicamentos. Nuestro objetivo es informar nuestra experiencia con anticoagulantes orales en diferentes dosis en pacientes ambulatorios con COVID-19. **Material y métodos:** Este estudio presenta una serie de casos retrospectivos de pacientes de COVID-19, con diagnóstico confirmado. Cada paciente recibió un tratamiento de apoyo, además de rivaroxabán o apixabán en diferentes dosis y oxígeno si era necesario, según los criterios de carga de la enfermedad. El equipo evaluó el curso clínico de la enfermedad, los marcadores de laboratorio, los estudios de imagenología y la presencia de complicaciones. El análisis estadístico se hizo con SPSS 21. **Resultados:** Nuestra experiencia incluyó 41 pacientes con enfermedad moderada a grave, de un universo de 300 pacientes con infección por COVID-19 confirmada; los pacientes fueron asignados a uno de los tres grupos, de acuerdo con el grado de gravedad, y recibieron anticoagulación intensa, anticoagulación habitual y anticoagulación habitual más bloqueo plaquetario. La edad media fue de 50 años (30-75), 64% de hombres. El dímero D y la ferritina estaban por encima de los niveles normales superiores en todos los pacientes. El grupo bajo anticoagulación intensa tenía mayor dímero D y ferritina, así como menor cantidad de linfocitos. Este grupo tuvo un tiempo de recuperación más corto. **Conclusiones:** En los pacientes con COVID-19 la iniciación temprana de la anticoagulación oral en el hogar fue segura y eficaz, sin necesidad de hospitalización. Encontramos que la ferritina es el marcador sérico más importante para definir la etapa del paciente.*

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INTRODUCTION

The several clinical complications of COVID-19 are due to thrombosis and generalized inflammatory events.[1-3] The rapid progress of the COVID-19 pandemic has limited the ability to regulate the treatment in early stages of the disease, and most research directs towards seriously ill patients.[4,5] The RECOVERY trial[6] documented a significant decrease in 28-day mortality in critically ill patients, who received dexamethasone management.

Regarding thrombotic complications, the evidence is not clear yet. Forty percent of the infected patients develop mild symptoms with fever, cough, myalgia, arthralgia, onychophagia, fatigue, dyspnea, diarrhea, and headaches; 40% developed moderate symptoms with radiological evidence of pneumonia; 15% had severe pneumonia that requires supplemental oxygen; and 5% developed severe complications such as acute distress syndrome, thromboembolism, coagulation disorders and multiorgan failure.[7,8] The guidelines and recommendations for early outpatient management of COVID-19 patients establish only palliative measures such as: control of fever, rest and hydration without more effective prevention towards critical complications.[9]

There are significant restrictions to early stage anticoagulation therapy in the official outpatient management guidelines for COVID-19, including the National Institute of Health (NIH)[9] and the guidelines of the Secretary of Health of Mexico.[10] The WHO *(World Health Organization)* declared COVID-19 as a pandemic, on March 11, 2020, and 8 months after, one in every five infected patients progresses towards severe stages and need hospitalization.[11]

Many patients with moderate or even severe symptoms seek for outpatient care, due to lack of conclusive evidence, infodemics, hospital saturation, high costs and possible exposition to infection.[12,13]

Luca Carsana et al., in northern Italy, published their histopathological findings in lung SARS-CoV-2 specimens from 38 dead patients, with capillary congestion, interstitial edema, dilated alveolar ducts, hyaline membranes composed of fibrin and serum proteins, loss of pneumocytes, hyperplasia and atrophy of type II pneumocytes, proliferation of myofibroblasts, alveolar granulation tissue, obliterative fibrosis, and significant thrombosis of small blood vessels (diameter less than 1mm) in 33 autopsies.[12]

The critical COVID-19 patients develop pulmonary and systemic thrombosis in small

Table 1: Description the signs and symptoms clinic, laboratory and cabinet features.

Positive test PCR for SARS-CoV-2	Obtained by nasal swab • Mild sickness: focal areas with increased opacity, with a reticular pattern, ground glass with diffuse distribution
Lesions on radiographic film and/or simple chest tomography consisting of	• Moderate illness: consolidation patches associated with a reticular pattern, ground glass with subpleural distribution, associated with thickening of sedept. Interlobular and intralobular • Severe illness: frank airspace consolidations large areas of ground glass, with thickening interlobular sedept and cobblestone appearance, paving lesions and/or crazy paving
Clinical manifestations	Anosmia, respiratory distress, pharyngeal burning, decrease in capillary saturation values, dry cough, hyperthermia, myalgia, arthralgias, headache, abdominal pain or bloating, sickness, diarrhea
Laboratory	D dimer values, ferritin, DHL • Moderate increase in dimer D. Values from 500 to 800 mg/mL • Severe increase in D-dimer values. Values above 800 mg/mL • Ferritin > 300 mg/dL • Lymphocyte count

Table 2: Criteria for ambulatory anticoagulation.

Group	Findings	Management
7 Full anticoagulation	Present 2 or more of the following • Patients with 2 or more comorbidities • Basal saturation less than 90% • Markers of thrombosis or inflammation with severe increase • Severe injuries in radiology	Rivaroxaban 30 mg/day (15 mg every 12 hours) for 10 days (+)
6 Formal Antico-agulation more anti-aggregation	Presence of any of those previous • Comorbidities: 2 or more • Previous management with anticoagulation or anti-aggregation • Markers of thrombosis or inflammation with a moderate increase • Moderate injuries in radiology	Rivaroxaban 15 to 20 mg/day (+) or apixaban 10 mg/day for 15 days (+) more clopidogrel 75 mg or ASA 100 mg/day
5 Formal anticoagulation	Presence of 1 or more of those previous • Comorbidities: 1 or more • Markers of thrombosis or inflammation with a moderate increase • Previous anticoagulation and/or anti-aggregation management • Moderate injuries in radiology	Rivaroxaban 15 to 20 mg/day or apixaban 10 mg/day for 15 days (+)
4 Prophylactic anticoagulation and anti-aggregation	Presence of 2 or more of those previous • Comorbidities 1 or more • Previous separate management of prophylactic anticoagulation and/or anti-aggregation • Mild injuries in radiology	Rivaroxaban 5 to 10 mg/day or apixaban 2.5 mg every 12 hours more clopidogrel 75 mg/day or ASA 100 mg/day for 15 days (+)
3 Prophylactic anticoagulation	Presence of anyone • Comorbidities 2 or more • Minor injuries in radiology	Rivaroxaban 5 to 10 mg/day or apixaban 2.5 mg every 12 hours for 30 days
2 Anti-aggregation	Presence of • Comorbidities 1 or more	Clopidogrel 75 mg/day or ASA 100 mg/day for 30 days
1 Without drug	• Absence of comorbidities • Laboratories and radiology in normal ranges • Basal saturation greater than 90%	Without antithrombotic pharmacological management
Criteria for initial referral to other healthcare centers	• Patients with tachypnea, hemodynamic instability, intolerance to the oral route • Stroke in the past year • Known presence of vascular malformations • History of gastric ulcer, polyps, epistaxis, hypermenorrhea, or history of bleeding or hemorrhage in the last six months • History of seizures or psychiatric illness • Uncontrolled hypertension (SAT > 150 mmHg or TAD > 90 mmHg) • Previous management with vitamin K inhibitors • History of liver or kidney failure	
Criteria for suspending outpatient oral anticoagulant management	• Hemorrhage: major bleeding or presence of minor bleeding on 2 or more occasions • Hypertensive crisis: all patients were asked to have a digital manometer at home and to administer each dose of anticoagulant only if the previous pressure measurement was within normal ranges. In the case of high values, management with oral amlodipine 5 mg was indicated. If the pressure was controlled within the 1st hour, the anticoagulant intake was allowed to continue. Otherwise, the continuity of the study will be evaluated • Neurological or alertness disorders • Decision to transfer to the hospital due to clinical deterioration or request of the patient • Lack of attachment to driving • Loss to follow up • Express the patient's desire to discontinue the anticoagulant	

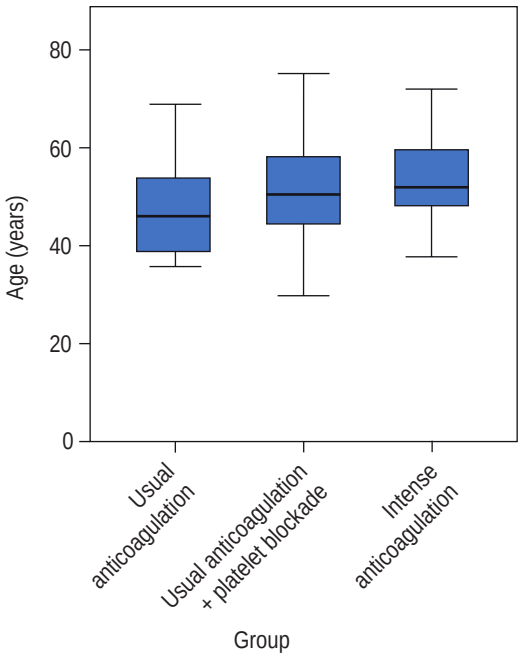

Figure 1: Age distribution between in groups.

vessels,[14,15] possibly related to the typical ground glass tomographic images,[16,17] that may lead to further complications or even death. These findings favour the decision to administer anticoagulants.[11]

The Massachusetts General Hospital[18] suggested measuring the D-dimmer in every in-hospital COVID-19 patient, with the recomendation for parenteral anticoagulation, when confirmed high levels. There are current indications for using oral anticoagulants, either that directly inhibit Factor Xa (rivaroxaban, apixaban), or thrombin (dabigatran).[5,13]

The EINSTEIN[19] and AMPLIFY[3] trials showed the safety and efficacy in the management of high doses of Factor Xa inhibitors in patients with acute pulmonary thromboembolism. The European Society of Cardiology (ESC) 2014[13] guidelines for the management of pulmonary thromboembolism, recommend therapies for up to 3 weeks with these oral anticoagulants, when hospitalization or parenteral drugs are not possible.[3,19]

Tang et al.,[20] documented a decrease in mortality of critical COVID-19 patients with previous coagulopathy, high D-Dimer and prophylactic anticoagulants?[21,22] Nonetheless, the treatment with drugs with supposed antiviral action over SARS-CoV-2, such as lopinavir, ritonavir, favipiravir, chloroquine and hydroxychloroquine, predominate, despite negative evidence of benefit.[23,24]

To date, there are no publications confirming the benefit of oral anticoagulants at different doses in patients with COVID-19. Treatment with enoxaparin is limited in our environment, due to high cost, parenteral application and high demand,[5,25,26] these problems make oral anticoagulants an alternative.

We inform our experience regarding oral anticoagulants, in different doses, in ambulatory COVID-19 patients, under the authors' criteria, based on the previous evidence for small vessels thrombosis and compassionate approach.

MATERIAL AND METHODS

The authors retrospectively analyzed ambulatory patients' clinical records with SARS-CoV-2, treated with rivaroxaban and apixaban at different doses, from May to September 2020.

Table 1 states the diagnostic criteria to confirm SARS-CoV-2, based on clinical, laboratory and cabinet information, subsequently followed through office consultation or by telephone,

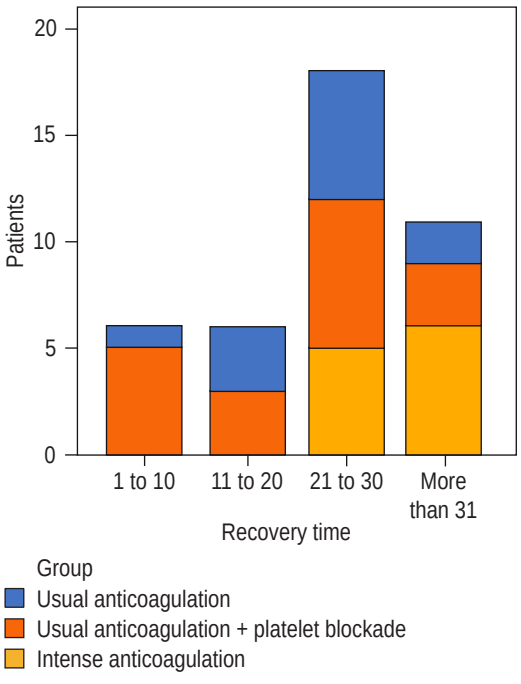

Figure 2: Recovery time in the groups.

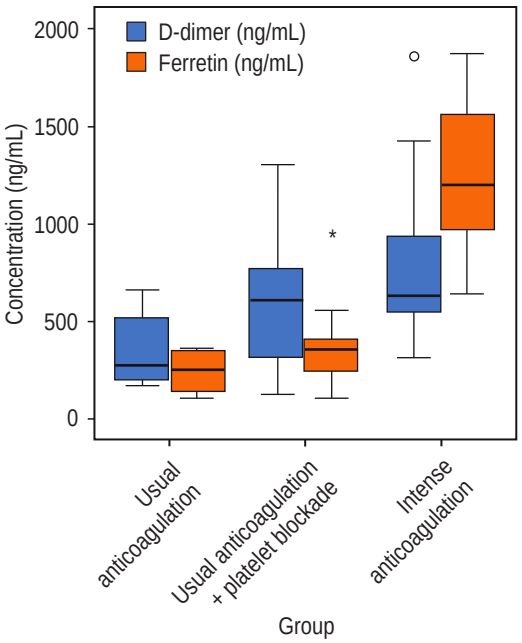

Figure 3: D-dimer and ferritin concentration in plasma in the groups.

emphasis the clinical progress, adherence to treatment, complications and adverse events.

The statistical analysis was done using SPSS 21 software and expressed in median ± standard deviation, frequency and percentages according to bivariate analysis with U Mann Whitney and χ^2.

According to the comorbidities and risk factors detected, as well as the results obtained in baseline and follow-up studies, management groups according to the original criteria, as discussed in *Table 2* classified the patients.

RESULTS

The analysis included 41 patients, from a group of 300 with a recent diagnosis of SARS-CoV-2 infection. The *Table 2* summarizes three different allocation groups: The group with intense anticoagulation consisted of 12 patients, the usual anticoagulation plus platelet blockade group with 18 patients, and in the usual anticoagulation group, with 11 patients; 92.6% of the patients received rivaroxaban and the rest apixaban.

All the patients received supplemental oxygen if needed, azithromycin 500 mg every 24 h for five days and intramuscular prolonged release dexamethasone 21-isonicotinate 8mg/day for five to seven days.

The median age was 50 years old (from 30 to 75) *(Figure 1)*, 64% men, middle socioeconomic status and most of them living in Mexico City.

The comorbidities were: overweight or obesity 21%, systemic arterial hypertension 12%, diabetes mellitus 5%, obstructive pulmonary disease 10%, history of venous thrombosis 5%, hypothyroidism 2.5%, dyslipidemia 5%, kidney disease 5%.

The *Figure 2* shows the recovery time in the different groups. All the patients received ambulatory treatment; all with moderate to severe disease, tolerated the oral anticoagulation and showed faster recovery; only one patient presented mild sub-conjunctival hemorrhage.

The laboratory disclosed elevated D-Dimer and Ferritin, but higher in the intense anticoagulation group *(Figure 3)*.

The lymphocyte count was normal in the usual anticoagulation and anticoagulation plus platelet blockade groups; below 1,100 mm^3 in the intense anticoagulation group *(Figure 4)*.

The 114 patients presented a mild or moderate form of COVID-19 and received

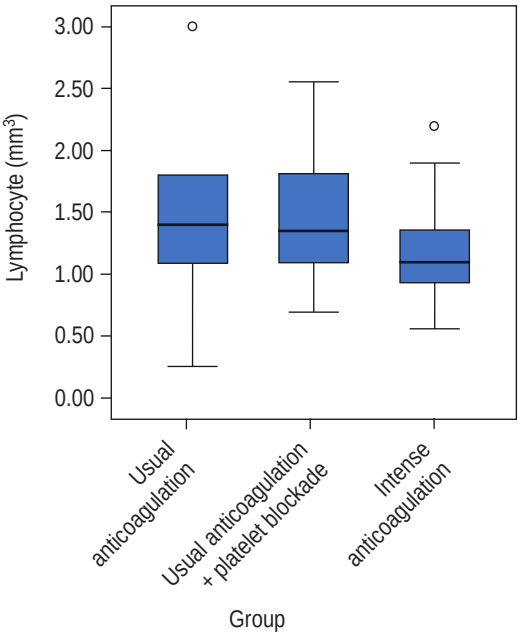

Figure 4: Level of lymphocyte in the groups.

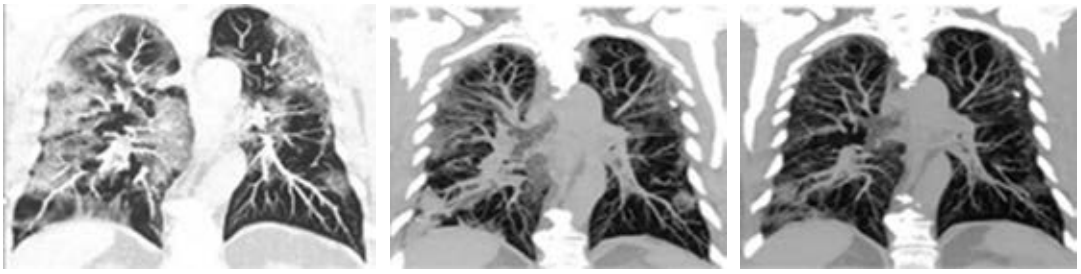

Figure 5: Tomographic course of a patient treated with maximum dose from left to right, the first picture documents pneumonia severe with what was needed in the initial consultation the following are days seven and 14 of the beginning of the outpatient treatment established in the protocol.

prophylactic anticoagulation plus platelet blockade. They had a positive PCR test for COVID-19 and mild or negative radiological imaging, especially ground glass and a mild reticular pattern *(Figure 5)*. The most frequent comorbidity was overweight and hypertension. All these patients continued ambulatory treatment without complications.

All the patients received an additional pharmacological scheme based on vitamin supplements (vitamins C and D), antioxidants (Quercetin and N-Acetyl cysteine) in addition to zinc.

DISCUSSION

The systemic inflammatory response and generalized microthrombosis result from COVID-19[11,12] infection. The current guidelines focused on the treatment of the inflammatory phase suggest concomitant management with enoxaparin in a hospital setting.

It is justified the extrapolation of the Factor Xa inhibitors, as described for the patients with acute pulmonary thromboembolism, on the European Society of Cardiology[13] treatment guide, to treat moderate to severe COVID-19 patients, in order to reduce the risk of thrombosis. The treatment was proven safe and effective, none of the treated patients required hospitalization, not even the patients with lymphopenia. Ferritin had a higher correlation than D-Dimer to clinical deterioration and severity of the radiological lesions. Therefore Ferritin can be used to determine if anticoagulation therapy should be indicated.

Our experience proved that oral anticoagulation therapy is safe and effective for ambulatory COVID-19 patients, even in severe cases.[21,25] The patient has to be educated to identify early sings of worsening, such as oxygen saturation and vital signs, and the need to report them to the physician to establish the need for a further clinical test to ensure the treatment's safety.

CONCLUSIONS

This study showed that oral ambulatory anticoagulation is safe and effective in COVID-19 patients, especially with thrombotic risk factors. Our results showed that both the elevation of ferritin levels and the decrease in the lymphocyte count correlate with the severity of the disease and may suggest the initiation of oral anticoagulation at high doses without increasing the risk of bleeding.

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