Research Article
Open Access
CrossMark

Oral anticoagulation with rivaroxaban as thromboprophylaxis in patients recovered from COVID-19 pneumonia in Veracruz, Mexico

Abstract

Background: Patients affected by COVID-19 are at risk of various venous and arterial thrombotic events, as well as embolic risks, the risk can vary from 17% to 78% according to the different published series. Therefore, thromboprophylaxis must be imperative.

Methods: Descriptive and analytical study in patients who presented pneumonia due to COVID-19 in April and May 2020, who received LMWH during their hospital stay and at discharge with rivaroxaban 10 mg / day for 2 months. D-dimer was measured at the beginning of the study and 1 month after discharge. Thrombotic or hemorrhagic episodes are controlled after 1 and 2 months of treatment (June – July 2020).

Results: 50 patients are included, twenty women (40%) and thirty (60%) men, with a median age of 42.9 years. 32 (64%) patients had mild pneumonia and 18 (36%) patients had severe pneumonia, mean initial d-dimer 556.5 (375.2 - 1233.7) ng / ml, 56% of patients had d-dimer ≥ 500 ng / ml at the time of hospital admission. Baseline D-dimer values were significantly higher among patients with severe pneumonia. In the follow-up at one and two months after hospital discharge, we found that D-dimer values were significantly higher among patients with severe pneumonia and also, in this group of patients, the percentage of patients with D-dimer levels ≥ 500 ng / mL in the first month of follow-up, was significantly higher in the group of patients who were hospitalized for severe pneumonia. During the first month of follow-up, there was a thrombotic event and a hemorrhagic event in the group of patients with a history of severe pneumonia; by the second month of follow-up, there was a hemorrhagic event in the group of patients with mild pneumonia, but this difference in frequencies was not statistically significant.

Conclusion: In this group of patients, the incidence of thrombotic and hemorrhagic events was low, so the thromboprophylaxis scheme used in patients with recovered pneumonia due to COVID-19 is recommended. Rivaroxaban is safe to use like thromboprophylaxis.

Keywords: rivaroxaban, thromboprophylaxis, COVID-19

Volume 13 Issue 1 - 2021

Luis Del Carpio-Orantes,[1] Sergio García-Mendez,[2] Jesús Salvador Sánchez-Díaz,[3] Karla Gabriela Peniche-Moguel,[3] Elisa Estefanía Aparicio-Sánchez,[1] Orlando Israel Segura-Rodríguez,[1] Andrés Aguilar-Silva,[1] Omar García-Hernández,[1] Alejandro Escobar-Huerta,[1] Azael Ahumada-Zamudio,[1] Andrés Realino Velasco-Caicero,[1] Olga González-Segovia,[1] Ernesto Javier Pacheco-Pérez,[1] Álvaro Efrén Munguia-Sereno,[1] Edna Rosario Contreras-Sánchez,[1] Sara Nohemí Hernández-Hernández,[1] Luis Jaime Medrano-Rios,[1] Ada Lili Rosas-Lozano[4]

[1]Department of Internal Medicine, General Hospital 71, North Veracruz Delegation, Instituto Mexicano del Seguro Social, Mexico
[2]Head of Teaching and Research, Regional Hospital of High Specialty of Oaxaca, Mexico
[3]Critical Care Unit, High Specialty Medical Unit 189, North Veracruz Delegation, Instituto Mexicano del Seguro Social, Mexico
[4]Department of Hematology, High Specialty Medical Unit 189, North Veracruz Delegation, Instituto Mexicano del Seguro Social, Mexico

Correspondence: Luis Del Carpio Orantes, Department of Internal Medicine, General Hospital 71, North Veracruz Delegation, Instituto Mexicano del Seguro Social, Díaz Mirón S/N, Floresta, Veracruz, México, Tel 2292237032, Email Neurona23@hotmail.com

Received: January 18, 2021 | **Published:** February 04, 2021

Introduction

The first descriptions of pneumonia associated with Sars Cov 2 associated it with severe hypoxemic acute respiratory failure, coupled with hyperinflammation that can lead to multiple organ failure, however, with the evolution of the case study, the participation of microvascular thrombosis was observed which added comorbidity and high mortality in these pictures, currently being considered a picture of thromboinflammation.[1,2] Clinically, it is expressed as hypoxemic pneumonia and initial coagulopathy with a high expression of D-dimer and fibrinogen degradation products, with abnormal clotting times and platelets being rare. The determination of elevated D-dimer (with a cut-off of 6.494ng/ml in a Chinese study of 158 patients) is considered a risk factor for developing deep vein thrombosis associated with COVID-19 and this has been established as having a high prevalence in this virus.[3-5] An Italian study studied venous thromboembolism, which includes deep vein thrombosis and its main complication, pulmonary embolism, which appears to occur with a higher incidence in seriously ill patients who require intensive care. This study revealed the presence of asymptomatic deep vein thrombosis and independent pulmonary embolism in patients with COVID-19.[6]

A Dutch study demonstrated venous thromboembolism in patients admitted to intensive care in 27% of 184 patients, of these 81% presented pulmonary embolism; also identified arterial thrombotic events in 3.7%.[7] Other thrombotic manifestations include acute cerebrovascular disease (mainly ischemic) which was more common among 88 patients with severe COVID-19 than among those with non-severe disease (5.7% vs. 0.8%). Another study mentions that 1.5% of patients admitted to the emergency room or hospitalization present acute cerebral ischemia. A Chinese study of 1,875 cases reported 50 cases of acute cerebrovascular disease (90% ischemic and 10% hemorrhagic).[8-11] An American study in 3,556 patients diagnosed with COVID-19 reported that 0.9% had an acute stroke, of these 43.8% had a neurological deficit upon admission to the emergency room, and 56.2% developed the deficit during their hospital stay.[12]

Similarly, in patients with COVID-19, the presence of acute cardiac injury, shock and arrhythmias has been reported in 7.2%,

8.7% and 16.7% respectively, which may favor thrombotic coronary artery disease and embolism of cardiac origin.[13]

Given the above, the current concern is the management of prophylactic or therapeutic anticoagulation, there are recommendations for the use of LMWH during acute events and oral anticoagulants gaining ground in the convalescence phase, which incidentally is also considered to be of high thrombotic risk -embolic due to the long hospital stay, immobility of the patient, the presence of asymptomatic peripheral venous thrombosis and the high incidence of chronic degenerative diseases considered prothrombotic that are associated.

At the patient's discharge, it is recommended to maintain anticoagulation for at least 45 to 60 days due to post-COVID-19 thrombotic risks, preferring oral anticoagulants such as rivaroxaban, because they do not need monitoring, they can be administered in daily single doses and facilitate the discharge plan and management ambulatory.[14-16]

Material and methods

A descriptive and analytical study is carried out in patients who presented pneumonia due to COVID-19 in April and May 2020 at the General Hospital 71 of the Veracruz North delegation of the Mexican Institute of Social Security, monitoring them for two months after discharge hospitable. Confirmation of pneumonia due to COVID-19 was by RT-PCR as well as by pulmonary axial tomography; a baseline D-dimer measurement was taken in the first 5 days of hospital admission, as well as a D-dimer control in the first month of discharge, taking values greater than 500ng/mL as high thrombotic risk. All received low molecular weight heparin (enoxaparin) during their hospital stay at a dose of 1mg/kg/day, starting with rivaroxaban in a single dose of 10mg/day that was administered for 2 months.

Results

We analyzed the data of 50 patients who had a hospital stay with a confirmed diagnosis of COVID-19 pneumonia by RT-PCR, twenty women (40%) and thirty (60%) men, with a median age of 42.9 (IQR 32.7 - 61.7) years. The most frequent comorbidity was diabetes mellitus in 25 (50%) patients, followed by systemic arterial hypertension with 15 (30%) patients, 3 (6.0%) patients with peripheral vascular insufficiency and 1 (2.0%) patient with a history of arrhythmia without anticoagulant treatment.

The results of the measurement of laboratory parameters are found in Table 1, which highlights the baseline median d-dimer [556.5 (375.2 - 1,233.7) ng/mL], 56% of the patients had d-dimer ≥500 ng/mL at the time of hospital admission. Regarding the type of pneumonia, we found that 32 (64%) patients had mild pneumonia and 18 (36%) patients had severe pneumonia; with a median of 7.0 (5.0 - 15.0) days of hospital stay. At one-month follow-up, 28 (56%) patients remained with d-dimer levels ≥500 ng/mL. During the first month one patient had an ischemic stroke and one patient had upper gastrointestinal bleeding. For the second month of follow-up, there was one patient who presented self-limited epistaxis. Measurement of demographic and clinical variables of patients with a confirmed diagnosis of COVID-19 stratified by type of pneumonia.

Table 1 Results of the measurement of demographic and clinical variables of patients with COVID-19 who were discharged with anticoagulant treatment*

Variable	Result n = 50
Demographic variables	
Gender	
Woman	20 (40.0)
Man	30 (60.0)
Age; years, median (IQR)	42.0 (32.7 – 61.7)
Previous comorbidities	
Diabetes mellitus	25 (50.0)
Systemic hypertension	15 (30.0)
Vascular insufficiency	3 (6.0)
Arrhythmia	1 (2.0)
Variables associated with COVID-19	
Leukocytes; cells / mm^3, median (IQR)	9,800.0 (7097.5 – 11,850.0)
Neutrophils; cells / mm^3, median (IQR)	7,850.0 (5,275.0 – 10,527.5)
Lymphocytes; cells / mm^3, median (IQR)	1,105.0 (865.0 – 1,527.5)
Platelets; cells / mm^3, median (IQR)	198,000.0 (167,750.0 – 327,000.0)
Basal D-dimer; ng / mL, median (IQR)	556.5 (375.2 – 1,233.7)
Baseline D-dimer ≥500 ng / mL	28 (56.0)
Type of pneumonia	
Mild pneumonia	32 (64.0)
Severe pneumonia	18 (36.0)
Days of hospital stay; median (IQR)	7.0 (5.0 – 15.0)

Citation: Carpio-Orantes LD, García-Mendez S, Sánchez-Díaz JS, et al. Oral anticoagulation with rivaroxaban as thromboprophylaxis in patients recovered from COVID-19 pneumonia in Veracruz, Mexico. *J Anesth Crit Care Open Access.* 2021;13(1):12–15. DOI: 10.15406/jaccoa.2021.13.00463

Table Continued...

Variable	Result n = 50
Measurement of d-dimer at the first month of follow-up, and of thrombotic and hemorrhagic events at one and two months of follow-up.	
D-dimer at the first month; ng/mL, median (IQR)	454.0 (377.2 – 705.0)
D-dimer ≥500 ng / mL at first month	28 (56.0)
Thrombotic events during the first month	1 (2.0)
Bleeding events during the first month	1 (2.0)
Thrombotic events during the second month	0 (0.0)
Bleeding events during the second month	1 (2.0)

*Results expressed with n and %, except when otherwise indicated

We performed a comparative analysis of the demographic and clinical variables stratified by the type of pneumonia that they presented during the hospital stay (Table 2); we found that in terms of gender there were no differences regarding the frequency of presentation of mild or severe pneumonia. However, the median age was lower in the group of patients with mild pneumonia compared to the median age of patients with severe pneumonia [35.5 (32.0 - 48.7) VS 56.6 (41.7 - 73.5) years, respectively) and that this difference was statistically significant (p = 0.001). Regarding comorbidities, we found that only diabetes mellitus was significantly more frequent among patients with severe pneumonia (72.2 VS 37.5%; p = 0.038). With regard to systemic arterial hypertension, vascular insufficiency, and a history of arrhythmia, there was a tendency to be more frequent in the group of patients with severe pneumonia, but it was not statistically significant.

Table 2 Results of the measurement of demographic and clinical variables of patients with a confirmed diagnosis of COVID-19 who were discharged with anticoagulant treatment stratified by type of pneumonia*

Variable	Mild pneumonía n = 32	Severe pneumonía n = 18	p
Demographic variables			
Gender			
Woman	13 (40.6)	7 (38.9)	1.000§
Man	19 (59.4)	11 (61.1)	1.000§
Age; years, median (IQR)	35.5 (32.0 – 48.7)	56.6 (41.7 – 73.5)	0.001ɣ
Previous comorbidities			
Diabetes mellitus	12 (37.5)	13 (72.2)	0.038§
Systemic hypertension	7 (21.9)	8 (44.4)	0.117§
Vascular insufficiency	1 (3.1)	2 (11.1)	0.291§
Arrhythmia	0 (0.0)	1 (5.6)	0.360§
Variables associated with COVID-19			
Leukocytes; cells / mm^3, median (IQR)	9,800.0 (7,275.0 – 11,225.0)	9,400.0 (6,667.5 – 12,600.0)	0.531ɣ
Neutrophils; cells / mm^3, median (IQR)	7,505.0 (5,225.0 – 8,740.0)	7,990.0 (5,250.0 – 11,000.0)	0.342ɣ
Lymphocytes; cells / mm^3, median (IQR)	1,225.0 (1,020.7 – 1,617.5)	925.0 (645.0 – 1,210.0)	0.005ɣ
Platelets; cells / mm^3, median (IQR)	203,000.0 (169,750.0 – 345,750.0)	181,000.0 (166,000.0 – 268,500.0)	0.322ɣ
Basal D-dimer; ng / mL, median (IQR)	410.0 (341.7 – 556.7)	1,880.0 (1,175.0 – 3,187.0)	0.001ɣ
Baseline D-dimer ≥500 ng / mL	11 (34.4)	17 (94.4)	0.001§
Days of hospital stay; median (IQR)	7.0 (5.0 – 7.0)	17.0 (14.0 – 20.2)	0.001ɣ
Measurement of d-dimer at the first month of follow-up, and of thrombotic and hemorrhagic events at 1 and 2 months of follow-up.			
D-dimer at the first month; ng/mL, median (IQR)	390.0 (349.2 – 463.2)	835.0 (655.0 – 1,125.0)	0.001ɣ
D-dimer ≥500 ng / mL at first month	2 (6.3)	16 (88.9)	0.001§
Thrombotic events during the first month	0 (1.0)	1 (5.6)	0.360§
Bleeding events during the first month	0 (0.0)	1 (5.6)	0.360§
Thrombotic events during the second month	0 (0.0)	0 (0.0)	1.000§
Bleeding events during the second month	1 (3.1)	0 (0.0)	1.000§

*Results expressed with n and %, except when otherwise specified. §Chi square. ɣU of Mann-Whitney

Citation: Carpio-Orantes LD, García-Mendez S, Sánchez-Díaz JS, et al. Oral anticoagulation with rivaroxaban as thromboprophylaxis in patients recovered from COVID-19 pneumonia in Veracruz, Mexico. *J Anesth Crit Care Open Access.* 2021;13(1):12–15. DOI: 10.15406/jaccoa.2021.13.00463

Regarding the variables associated with COVID-19, we found the values of lymphocytes [925.0 (645.0 1,210.0) VS 1,225.0 (1,020.7 - 1,617.5) lymphocytes; p = 0.005] were significantly lower in the group of patients with severe pneumonia. The white blood cell and platelet values tended to be lower in the group of patients with severe pneumonia, but this difference was not statistically significant. Baseline dimer values were significantly higher among patients with severe pneumonia [1,880.0 (1,175.0 - 3,187.0) VS 410.0 (341.7 - 556.7) ng/mL; p = 0.001]; in addition, the percentage of patients with baseline d-dimer ≥500 ng/mL with severe pneumonia (94.4 VS 34.4%; p = 0.001) and hospital stay [17.0 (14.0 - 20.2) VS 7.0 (5.0 - 7.0); p = 0.001], were also significantly higher among patients with severe pneumonia.

In the follow-up at one and two months after hospital discharge, we found that D-dimer values were significantly higher among patients who had severe pneumonia [835.0 (655.0 - 1,125.0) VS 390.0 (349.2 - 463.2); p = 0.001]; Additionally, in this group of patients, the percentage of patients with d-dimer levels ≥500 ng/mL at the first month of follow-up was significantly higher in the group of patients who were hospitalized with severe pneumonia (88.9 vs. 6.3%; p = 0.001). During the first month of follow-up, there was a thrombotic event and a hemorrhagic event in the group of patients with a history of severe pneumonia; for the second month of follow-up, there was a hemorrhagic event in the group of patients who had mild pneumonia, but this difference in frequencies was not statistically significant.

Conclusion

In this group of patients, the incidence of thrombotic events associated with COVID-19 is low compared to that reported in the world literature, probably favored by the anticoagulation strategy applied with LMWH in the acute stage and rivaroxaban in the convalescent stage, and In the presence of overt prothrombotic (diabetes, hypertension) and thrombotic risk factors (pneumonia and elevated baseline D-dimer and persistently elevated in the convalescent phase), the incidence of bleeding events is low and with self-limited events. More studies based on this regimen are needed to give further weight to the recommendation.

Conflicts of interest

The authors declare there are no conflicts of interest.

References

1. Del Carpio–Orantes L. Del 2019–nCoV al COVID–19, caracterizando la enfermedad. *Med Int Méx.* 2020;36(3):414–417.
2. Gris JC, Perez–Martin A, Quéré I, Sotto A. COVID–19 associated coagulopathy: The crowning glory of thrombo–inflammation concept. *Anaesth Crit Care Pain Med.* 2020;39(3):381–382.
3. Connors JM, Levy JH. COVID–19 and its implications for thrombosis and anticoagulation. *Blood.* 2020;135(23):2033–2040.
4. Koleilat I, Galen B, Choinski K, et al. Clinical characteristics of acute lower extremity deep venous thrombosis diagnosed by duplex in patients hospitalized for coronavirus disease 2019 [published online ahead of print, 2020 Jun 25]. *J Vasc Surg Venous Lymphat Disord.* 2020;S2213–333X(20)30348–6.
5. Cho ES, McClelland PH, Cheng O, et al. Utility of D–dimer for diagnosis of deep vein thrombosis in COVID–19 infection [published online ahead of print, 2020 Jul 29]. *J Vasc Surg Venous Lymphat Disord.* 2020;S2213–333X(20)30420–0.
6. Cattaneo M, Bertinato EM, Birocchi S, et al. Pulmonary Embolism or Pulmonary Thrombosis in COVID–19? Is the Recommendation to Use High–Dose Heparin for Thromboprophylaxis Justified?. *Thromb Haemost.* 2020;120(8):1230–1232.
7. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID–19. *Thromb Res.* 2020;191:145–147.
8. Zhang L, Feng X, Zhang D, et al. Deep Vein Thrombosis in Hospitalized Patients with COVID–19 in Wuhan, China: Prevalence, Risk Factors, and Outcome [published correction appears in Circulation. *Circulation.* 2020;142(2):114–128.
9. Mao L, Jin H, Wang M, et al. Manifestaciones neurológicas de pacientes hospitalizados con enfermedad por coronavirus 2019 en Wuhan, China. *JAMA Neurol.* 2020.
10. Merkler AE, Parikh NS, Mir S, et al. Risk of Ischemic Stroke in Patients with Covid–19 versus Patients with Influenza. Preprint. *medRxiv*. 2020;2020.05.18.20105494.
11. Qin C, Zhou L, Hu Z, et al. Características clínicas y resultados de los pacientes con COVID–19 con antecedentes de accidente cerebrovascular en Wuhan, China. *Carrera.* 2020;51.
12. Yaghi S, Ishida K, Torres J, et al. SARS2–CoV–2 y accidente cerebrovascular en un sistema de salud de Nueva York. *Carrera.* 2020; 51.
13. Wang D, Hu B, Hu C, et al. Características clínicas de 138 pacientes hospitalizados con neumonía infectada por el nuevo coronavirus de 2019 en wuhan, China. *JAMA.* 2020.
14. Paranjpe I, Fuster V, Lala A, et al. Association of treatment dose anticoagulation with in–hospital survival among hospitalized patients with COVID–19. *J Am College Cardiol.* 2020.
15. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID–19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow–up. *J Am Coll Cardiol.* 2020.
16. Del Carpio–Orantes L, González–Segovia O, Mojica–Ríos F, et al. Neumonía grave por COVID–19 curada con prono consciente y tocilizumab. Comunicación de un caso y revisión de la evidencia terapéutica farmacológica. *Med Int Méx.* 2020;36(4):585–595.