



Non-Major Bleed in a Non-Hospitalized Patient with COVID-19 on Direct-Acting Oral Anticoagulant Apixaban - A Case Report

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Abstract

Coronavirus Disease (COVID-19) has presented significant challenges and burden to healthcare. Majority of patients have mild-moderate disease and are managed in a non-hospitalized home care setting by family physicians. COVID has pathological mechanisms that include endothelial injury and hypercoagulability due inflammatory mediators. COVID has shown to increase the risk of thromboembolism in hospitalized patients with severe disease and especially those in intensive care, and therefore D-dimer testing on admission and initiation of anticoagulant medication form an important part of hospital-based treatment. However, there is still little evidence suggesting an increased risk of thrombosis in mild-moderate non-hospitalized COVID patients who are not immobilized. Ordering a multitude of investigations including D-dimer in home isolated patients may sometimes affect clinical decisions, as D-dimer may be raised non-specifically due to inflammation. Currently routine D-dimer screening and anticoagulation is not recommended in non-hospitalized patients. In immobilized homecare COVID patients with multiple risk factors for thrombosis, a D-dimer may be done and an appropriate decision to start a direct-acting oral anticoagulant like apixaban may be taken. Apixaban can cause bleeding mostly non-major and rarely major. Patient should be well advised to be alert and timely report the same.

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Introduction

Coronavirus disease (COVID-19 caused by SARS-CoV-2) has presented with diverse signs and symptoms, clinical decision challenges, and a significant burden on healthcare workers and infrastructure. It is known that >90% have mild symptoms and maintained oxygen saturation, therefore can be managed effectively with isolation and care at home or COVID basic repurposed isolation and care centers [1]. For such majority of patients, the Family Physicians (FPs) are the foundation of the community healthcare system to tackle the pandemic. Evolution of digital healthcare has further empowered patients and FPs towards meticulous monitoring and management of COVID.

COVID though initially regarded as primarily a viral respiratory disease affecting the airway and lungs, during the course of the pandemic further research suggested endothelial injury and systemic inflammation as part of its pathology [2]. The well-known Virchow's triad implicates endothelial injury, and a hypercoagulable state (due to inflammatory mediators stimulating the coagulation cascade), and immobilization (as seen in hospitalized patients) contributing to stasis, as the factors leading to thrombosis. D-dimer levels in blood is a known marker for thrombosis in the presence of such risk factors, and this test is recommended to predict risk of thrombosis, poor patient outcomes and mortality in hospitalized and Intensive Care Unit



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(ICU) patients [3,4]. Anticoagulation therapy is also recommended in hospitalized COVID patients as a significant component of treatment. However, thrombosis risk in non-hospitalized, mild COVID cases in homecare who are not immobilized, has not been ascertained, and there is no confirmed recommendation or established use of assessing D-dimer in these patients or giving Direct-Acting Oral Anticoagulants (DOACs) [5,6].

Case presentation

A 75-year-old male patient sought a digital consultation with family physician for symptoms of fever of 101 °F for past 1-day, sore throat, weakness, and decreased smell and taste. An RT-PCR was immediately recommended along with 4 hourly monitoring of temperature and oxygen saturation (by pulse oximetry). The RT-PCR was positive for COVID, with a Cycle Time (Ct) of 24. Oxygen saturation was maintained $\geq 95\%$, therefore the patient was treated in home isolation and care. Patient had history of hypertension controlled on telmisartan 40 mg once daily. Patient had no other comorbidities. A baseline blood test (done on day 3) with Complete Blood Counts (CBC), C-Reactive Protein (CRP) and blood sugar was within normal limits, and patient was advised to repeat the same on day 8.

Patient was asked to continue telmisartan and vitamin supplements that he was already taking, and was also started on paracetamol 6 hourly, povidone-iodine gargling twice daily, and Ivermectin once daily for 5 days (in accordance with national protocol) [7]. Daily sharing with family physician of 4 hourly oxygen saturation and temperature charts was instructed, along with advice given for twice daily conscious proning with intermittent deep breathing, and once daily 6-minute walk test to exclude subclinical hypoxia. The patient was to immediately report oxygen saturation drop $< 95\%$. He was also advised on diet, physical activity, rest and hygiene.

The patient decided to also take an opinion from his cardiologist, who recommended additional blood tests of serum creatinine, lipid profile, and inflammatory markers including D-dimer. This was performed on day 5 and D-dimer was seen to be 1000 mcg/L with serum creatinine and lipid profile within normal limits. The patient was started on apixaban 2.5 mg twice daily. On day 8 (2nd week of illness), patient was symptomatically improved with fever < 100 °F and oxygen saturation maintained $\geq 95\%$ at all times. Blood tests were repeated that showed a Neutrophil-Lymphocyte Ratio (NLR) of 4, D-dimer of 1050 mcg/L, and CRP of 22 mg/L. Blood sugar and platelet counts were normal. Patient was advised by FP for no further medication, to continue oxygen saturation monitoring, and complete the 2-week isolation period. However, the cardiologist advised to continue apixaban for a total of 4 weeks.

Patient repeated RT-PCR on his own on day 14, which was negative. At 3 weeks, the patient presented with a dark red patch at the upper back of his neck. The patch was macular (flat) with irregular borders and there were no accompanying symptoms like itching, pain, burning sensation, irritation or ulceration. There was also no history of trauma. The patch was discovered incidentally by his care giver while starting to give him a hair trim (Figure 1). Clinical examination was suggestive of a subcutaneous bleed. Patient had been on apixaban for almost 3 weeks at this time. Patient was investigated with CBC, CRP, D-dimer and prothrombin time (INR). CBC parameters including platelet count were in normal range. CRP was 9 mg/L, D-dimer was 700 mcg/L, and PT-INR was 1.2. Apixaban was withdrawn, and patient put on observation. The patch lightened in a week

and resolved completely within 10 days without any treatment or intervention. Patient was asked to follow up for any post-COVID symptoms for 3 months and advised to take first dose of COVID vaccination there after.



Figure 1: Subcutaneous bleed noticed in-patient taking apixaban for 3 weeks.

Discussion

The incidence of thrombosis in COVID patients in the hospitalized setting has seen to be as follows: Venous Thromboembolism (VTE) 28% and 10% in ICU and non-ICU patients respectively; Arterial Thromboembolism (ATE) 3-5% and 2% in ICU and non-ICU patients respectively [8]. Overall deep vein thrombosis rate was 20-28% and pulmonary embolism rate was 13-19% (both higher in ICU vs non-ICU patients). Mortality rate in hospitalized COVID patients was 23% (in those with thromboembolism) and 13% (without thrombosis) suggesting more than 70% higher mortality rate if thrombosis develops [9]. A 4-fold rise in D-dimer on admission (> 2000 $\mu\text{g/L}$) could effectively predict in-hospital mortality [3]. Therefore D-dimer tests on hospital admission and during treatment monitoring, and starting prophylactic anticoagulants in hospital setting is recommended.

However, the risk of thrombosis in non-hospitalized COVID patients is not known [10]. There have been isolated case reports of patients presenting with episodes of pulmonary embolism, stroke and myocardial infarction weeks to months post homecare and recovery from COVID [11]. However a retrospective study in 220588 patients suggested that 30 day post-COVID VTE incidence outside of the hospital is not significantly increased with SARS-CoV-2 infection and therefore suggesting an absence of need for routine use of outpatient thromboprophylaxis outside of clinical trials [12].

D-dimer can be elevated non-specifically in infections and inflammation as would be seen in several COVID patients [13]. Also age corrected D-dimer in elderly (10 $\mu\text{g/L} \times \text{age}$) should be taken as cut off which in this case would be 750 $\mu\text{g/L}$ [14]. Therefore, doing D-dimer in homecare patients with mild-moderate COVID who are not immobile may cause anxiety, affect clinical decisions, and lead to many more patients receiving DOACs than required. D-dimer testing and initiating anticoagulation may be justified in homecare COVID patients with significant risk factors like past history of thrombotic events, immobility, multiple CVD risk factors or past intervention/procedures, cancer, and kidney, liver or heart failure.

Apixaban shows a rate of non-major bleeds of 5-6/100 patient years and major bleeding rate of 1.5-2 (0.5 for intracranial hemorrhage)/100 patient years [15]. Non major bleeds include subcutaneous bleeds, epistaxis, hematuria, hemoptysis and gastro-intestinal bleeding. Most of these non-major bleeds show spontaneous resolution on drug cessation. The patient should be counselled and explained about timely reporting these adverse drug events.

Conclusion

COVID patients with mild-moderate symptoms who are physically mobile and managed in home care are at low risk for thrombosis that is similar to the general population. D-dimer test may show elevated levels in COVID patients as a non-specific marker of inflammation. D-dimer testing routinely or starting direct-acting oral anticoagulants are not required in home care COVID patients unless significant multiple risk factors, past history of thrombosis, or immobilization is present. Apixaban is one of the effective DOACs with an established safety profile, but is still best initiated by a specialist. Apixaban rarely causes serious bleeding, however non-major bleeds are not uncommon but mostly resolve. The patient should be explained about the signs of such bleeding episodes and report them timely to the treating physician.

References

- Gomez T, Anaya YB, Shih KJ, Tarn DM. A Qualitative Study of Primary Care Physicians' Experiences with Telemedicine During COVID-19. *J Am Board Fam Med.* 2021; 34: S61-S70.
- Levy JH, Iba T, Gardiner EE. Endothelial Injury in COVID-19 and Acute Infections: Putting the Pieces of the Puzzle Together. *Arterioscler Thromb Vasc Biol.* 2021; 41: 1774-1776.
- Zhang L, Yan X, Fan Q, Liu H, Liu X, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *J Thromb Haemost.* 2020; 18: 1324-1329.
- Poudel A, Poudel Y, Adhikari A, Aryal BB, Dangol D, et al. D-dimer as a biomarker for assessment of COVID-19 prognosis: D-dimer levels on admission and its role in predicting disease outcome in hospitalized patients with COVID-19. *PLoS One.* 2021; 16: e0256744.
- National Institute of Health - nih.gov: COVID-19 Treatment Guidelines-Antithrombotic Therapy in COVID-19. 2021.
- Chandra A, Chakraborty U, Ghosh S, Dasgupta S. Anticoagulation in COVID-19: current concepts and controversies. *Postgrad Med J.* 2021; 139923.
- Indian Council of Medical Research - icmr.gov.in: Clinical Guidance for Management of Adult COVID-19 patients. 2021.
- Boonyawat K, Chantrathammachart P, Numthavaj P, Nanthatanti N, Phusanti S, et al. Incidence of thromboembolism in patients with COVID-19: a systematic review and meta-analysis. *Thrombosis J.* 2020; 18: 34.
- Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, et al. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. *EClinicalMedicine.* 2020; 29: 100639.
- Ozsu S, Gunay E, Konstantinides SV. A review of venous thromboembolism in COVID-19: A clinical perspective. *Clin Respir J.* 2021; 15: 506-512.
- Uppuluri EM, Shapiro NL. Development of pulmonary embolism in a nonhospitalized patient with COVID-19 who did not receive venous thromboembolism prophylaxis. *Am J Health Syst Pharm.* 2020; 77: 1957-1960.
- Roubinian NH, Dusendang JR, Mark DG, Vinson DR, Liu VX, et al. Incidence of 30-Day Venous Thromboembolism in Adults Tested for SARS-CoV-2 Infection in an Integrated Health Care System in Northern California. *JAMA Intern Med.* 2021; 181: 997-1000.
- Yao Y, Cao J, Wang Q. et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. *J Intensive Care.* 2020; 8: 49.
- Urban K, Kirley K, Stevermer JJ. PURLs: It's time to use an age-based approach to D-dimer. *J Fam Pract.* 2014; 63: 155-158.
- Ole-Christian W Rutherford, Christian Jonasson, Waleed Ghanima, Fabian Söderdahl, Sigrun Halvorsen. Comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in atrial fibrillation: a nationwide cohort study, *European Heart Journal - Cardiovascular Pharmacotherapy.* 2020; 6: 75-85.