



Fibrinolytic and Anticoagulant Therapy in COVID-19 Associated Pulmonary Embolism: A Case Report

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Abstract

Pulmonary thromboembolism is a complication that can occur in coronavirus disease-2019 (COVID-19). Efforts to prevent and therapy for thromboembolism have been a challenge to this date. The side effects of fibrinolytic, anticoagulant, and platelet anti-aggregation therapies, such as hemorrhage, are some of the causes of morbidity and mortality that must be addressed immediately. In this case, the patient received prophylaxis with the anticoagulant enoxaparin and platelet anti-aggregation agents with aspirin and clopidogrel. The COVID-19 patient presented a complication of pulmonary thromboembolism that was established using a computed tomography pulmonary angiography (CTPA) performed on his third day of care (day 14 of onset treatment) due to the patient's clinical aggravation of pulmonary manifestation. After fibrinolytic therapy had been given, the patient's clinical condition improved. However, on the 7th day after the provision of recombinant tissue plasminogen activator (r-TPA), the patient experienced a side effect of hemorrhage, and management was undertaken to address these issues by transfusions of blood components, such as cryoprecipitates, thrombocyte concentrate, fresh frozen plasma, and packed red cell. Thromboembolism occurring in COVID-19 patients is based on the Virchow triad concept, comprising endothelial injury, static blood flow, and hypercoagulation. The principle of prevention and management of thromboembolism refers to this concept. Currently, further studies are required to treat thromboembolism and the side effects of fibrinolytic and anticoagulant therapies on COVID-19 patients.

Keywords: Anticoagulant, Covid-19, Fibrinolytic, Hemorrhage, Thromboembolism

Abstrak

Tromboemboli paru merupakan komplikasi yang dapat terjadi pada penyakit coronavirus-2019 (COVID-19). Upaya pencegahan dan terapi tromboemboli masih menjadi tantangan hingga saat ini. Efek samping terapi fibrinolitik, antikoagulan, dan agen antiagregasi trombosit, seperti perdarahan, merupakan beberapa penyebab morbiditas dan mortalitas yang harus segera ditangani. Dalam kasus ini, pasien menerima profilaksis dengan antikoagulan enoxaparin serta agen antiagregasi trombosit dengan aspirin dan clopidogrel. Pasien COVID-19 mengalami komplikasi tromboemboli paru yang ditegakkan melalui *computed tomography pulmonary angiography* (CTPA) pada hari ketiga perawatan (hari ke-14 sejak onset penyakit) akibat perburukan klinis pada manifestasi paru. Setelah terapi fibrinolitik diberikan, kondisi klinis pasien mengalami perbaikan. Namun, pada hari ke-7 setelah pemberian *recombinant tissue plasminogen activator* (r-TPA), pasien mengalami efek samping berupa perdarahan, sehingga dilakukan manajemen untuk mengatasi kondisi ini dengan transfusi komponen darah, seperti kriopresipitat, konsentrat trombosit, *fresh frozen plasma*, dan *packed red cell*. Tromboemboli yang terjadi pada pasien COVID-19 berlandaskan konsep *triad Virchow*, yang terdiri dari cedera endotel, aliran darah statis, dan keadaan hiperkoagulasi. Prinsip pencegahan dan penanganan tromboemboli mengacu pada konsep ini. Saat ini, penelitian lebih lanjut diperlukan untuk menanggulangi tromboemboli serta efek samping terapi fibrinolitik dan antikoagulan pada pasien COVID-19.

Kata kunci: Antikoagulan, Covid-19, Fibrinolitik, Perdarahan, Tromboemboli

Introduction

To date, the Coronavirus disease-2019 (COVID-19) still remains a challenge for all health workers across the globe. Ever since its emergence in Wuhan, China on December 2019, COVID-19 presents an outbreak related to the increased risk of thromboembolism, including a life-threatening pulmonary embolism.¹ Coagulopathy is one of the causes of thrombosis. The process of coagulopathy occurring in COVID-19 patients plays a fairly dominant role in mortality and morbidity, has been associated with poor prognosis, and is the result of the rather complex coagulopathy mechanism pathway. The inflammation process takes place in the form of cytokine storm and lung injury caused by SARS-CoV-2 in COVID-19 patients.^{1,2}

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More and more research points out the parameters of abnormal coagulation in COVID-19 patients; a number of centers have also been using computed tomography (CT) scan, which identifies the presence of thrombus in the lungs of patients with pneumonia induced by SARS-CoV-2 infection.³ One way of assessing the instance of coagulation process in COVID-19 patients is through the D-Dimer test. An increase in the level of D-Dimer describes the activation of the coagulation and fibrinolysis process that is currently happening. In COVID-19 patients, most of whom indicate an increase in D-Dimer 2-3 times higher than normal.⁴

The provision of prophylactic therapy is vital for preventing thromboembolism.^{5,6} Studies in several countries that implement the provision of prophylactic therapy suggest satisfactory results, despite data still reporting the occurrence of venous and arterial thromboembolism in patients who have been administered with said prophylactic therapy.

Fibrinolytic and anticoagulant therapy in cases with pulmonary thromboembolism complication demonstrate their own adverse reactions, such as hemorrhages, which often poses a challenge in itself.¹ That being said, our study reported a COVID-19 case undergoing treatment at the ICU of Udayana University Hospital that develops a pulmonary thromboembolism complication who receives fibrinolytic and anticoagulant therapy, as well as the management of said adverse reaction to the therapy.

Case Report

A 75-year-old man is sent over from another hospital following a 3-day treatment with a verified diagnosis of severe COVID-19 and high blood pressure. The patient came fully conscious with a chief complaint of shortness of breath 12 days prior to his admission to the hospital. Initially, the patient had only a complaint of olfactory dysfunction, accompanied by recurrent fever, which grew more severe. This prompted him to do for a medical check-up at the nearest health facility, while also undergoing a SARS-CoV-2 rapid test, which came out reactive, resulting in his referral to the hospital. The patient has comorbidity of hypertension with the clinical conditions of the respiratory rate of 35–40 per minute, heart rate of 120 beat per minute, initial peripheral oxygen saturation of 88% with 15 lpm on non-rebreathing mask (NRM) with 125 SpO₂/FiO₂ ratio, and pneumonia in chest X-ray at the time of arrival.

The patient has a bodyweight of 75 kg, BMI of 25.3 kg/m², compos mentis with GCS of E4V5M6. Upon entering the ICU, the respiration was identified as thoracoabdominal-type, with peripheral oxygen saturation of 86% with high-flow nasal cannula at 60 lpm, 100% fraction of inspired oxygen combine with 15 lpm on NRM. The cardiovascular examination showed blood pressure of 148/92 mmHg; heart rate of 106 bpm, regular. Extremities were

warm with a capillary refill time less than 2 seconds. Supporting examination showed WBC $13.16 \times 10^3/\mu\text{L}$; neutrophil 84.1%; lymphocyte 7.7%; hemoglobin 11.7 g/dL; hematocrit 33.4 %; thrombocyte $264.00 \times 10^3 \mu\text{L}$. Coagulation profile test panel showed PT 11.1 (10.8–14.4) seconds; INR 0.97; aPTT 24.5 (24–36) seconds; D-Dimer 1,613 ng/mL; fibrinogen 554 mg/dL; ferritin 724 ng/mL; HsCRP 177.9 ng/mL; LDH 757 U/L; interleukin-6 37.65 pg/mL, procalcitonin 0.21 ng/mL. CK 110 U/L, CKMB 1.2 ng/mL, hs Troponin I 69 ng/mL. Renal function test panel showed BUN 20.8 mg/dL, creatinine serum 0.6 mg/dL, and liver function test showed SGOT 50.5 U/L, SGPT 104 U/L. Based on the blood gas analysis when the patient first entered the hospital, our study found features of type 1 respiratory failure, pH 7.43; pO_2 45 mmHg; pCO_2 34.6 mmHg; HCO_3^- 23.7 mmol/L; SO_2 85 %; Be -1 mmol/L. Chest X-ray image revealed pneumonia, cardiomegaly and, pulmonary edema.

On the first day of care, the patient was already given a prophylactic therapy for thromboembolism with low-molecular-weight heparin

(LMWH) using enoxaparin at a 0.6 mL dose every 12 hours and platelet aggregation inhibitors acetosal and clopidogrel. On the third day of care, the patient complained worsened shortness of breath and desaturation, and based on the blood gas analysis, pO_2 level decreased to 78 mmHg and pCO_2 level increased to 48.2 mmHg. A CT pulmonary angiogram suggests multiple thrombi in the right pulmonary artery branch.

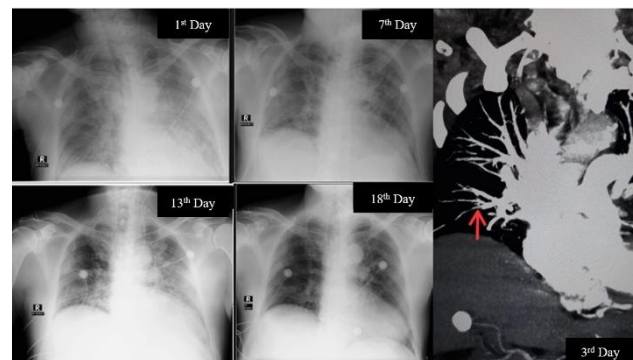


Figure 1. Thorax X-ray examination and evaluations for the 1st, 7th, 13th, and 18th day. Features of pneumonia and pulmonary edema are visible, albeit subsiding each day. The CT pulmonary angiography performed on the 3rd day of the intensive care characterizes features of multiple thrombi in the right pulmonary artery branch

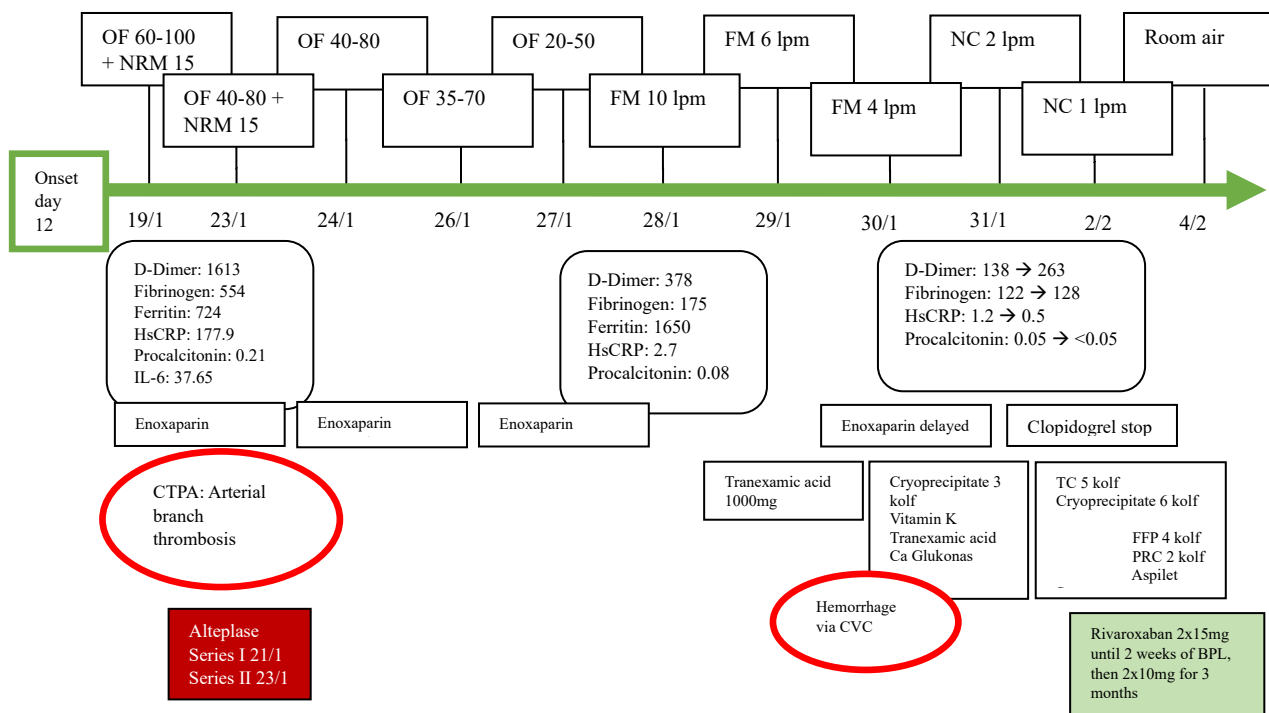


Figure 2. The disease prognosis and multimodal therapy throughout the intensive care. OF: Optiflow, NRM: nonrebreathing mask, FM: face mask, NC: nasal cannula, CTPA: computed tomography pulmonary angiogram, CVC: central venous catheter, TC: thrombocyte concentrate, FFP: fresh frozen plasma, PRC: packed red cell.

Fibrinolytic therapy was given using r-TPA alteplase at a dose of 5 mg bolus and 45 mg drip, which were completed in an hour. Enoxaparin, acetosal, and clopidogrel were continued after having been administered with alteplase. Two days after the first-series alteplase, the patient experienced yet another aggravation, which were increased shortness of breath, desaturation, indicated by the blood gas analysis test showing decreased pO₂ level at 75 mmHg and increased pCO₂ level at 44.5 mmHg. The patient was then given a second series of r-TPA alteplase therapy (48 hours after the first series). As a result, his clinical condition improved as shown by reduced coughing and shortness of breath, thereby tapering the oxygen required. On the 12th day, 7 days after the second series r-TPA alteplase therapy, there was a moderately active blood seepage through the central venous catheter wound/CVC. Therefore, the administering of enoxaparin, acetosal, and clopidogrel was postponed, and the patient was treated with an antifibrinolytic, which was tranexamic acid (complete blood supporting examination showed hemoglobin 10.6 g/dL, hematocrit 30.4%, WBC 36.33 x 10³/uL, thrombocyte 283 x 10³/μL, fibrinogen 175 mg/dL, D-dimer 378 ng/mL; coagulation profile test showed PT 10.6 seconds, INR 1.01, APTT 31.7 seconds, and procalcitonin 0.08 ng/mL).

Profuse hemorrhage took place and evaluation showed there was a decrease in hemoglobin level to 8 g/dL and prolonged coagulation physiology. The patient was treated with 9 packs of cryoprecipitate transfusion, 2 packs of PRC transfusion, and 6 packs of TC. He was also prescribed with vitamin K and calcium gluconate during the transfusion. An evaluation on the next day still showed hemorrhage, although it had reduced. He was then administered with 4 packs of FFP and 2 packs of PRC. After the active bleeding ended, the patient was prescribed with direct factor Xa inhibitor, which was rivaroxaban taken via oral

route until his discharge, and up to 3 months post-treatment.

Discussion

The patient's course of disease had entered the pulmonary hyperinflammation phase, with complaint onset 12 days after the symptoms first appeared. During that phase, cytokine storms can occur, which results in severe complication risks on COVID-19 patients, including risks of thromboembolism.^{2,6-8} The thromboembolism occurring in COVID-19 patients is built upon the Virchow triad, comprising endothelial injury, static blood flow, and hypercoagulation.^{1,5} The mechanism of endothelial injury may arise through the direct invasion mechanisms of SARS-CoV-2 into the endothelial cells or the results of inflammatory response due to proinflammatory cytokines. Patients who are treated with intensive therapy and long bed rest may lead to static blood flow.

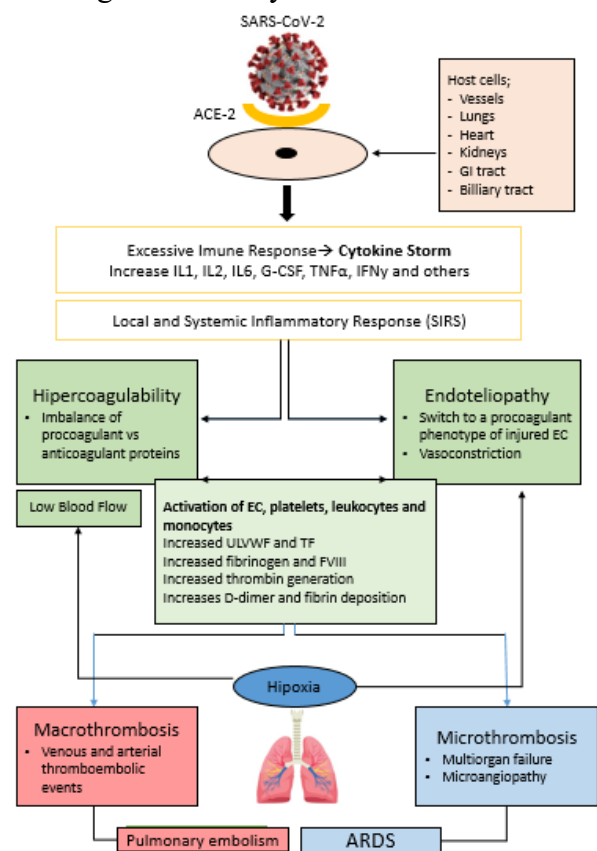


Figure 3. The pathogenesis of thrombosis and coagulopathy on COVID-19 patients. SARS-CoV-2 entered the host cells via ACE2 receptors. The cytokine storm is caused by excessive immune responses, triggering local and systemic inflammatory responses, which lead to hypercoagulation, eventually forming macro- or microthrombi.^{1,9}

The condition of hypercoagulation is exacerbated by prothrombotic factors, such as the increase in ULVWF, factor VIII, fibrinogen, NETs, and thrombotic microparticles.^{2,6} In this case, during the third day of care (day 14 of symptoms onset), the patient experienced worsening conditions with increased shortness of breath, desaturation, and blood gas analysis indicated a decrease in pO₂ level and increased pCO₂ level, thereby requiring CTPA. Results showed multiple emboli in the pulmonary arteries.

Coagulopathy in COVID-19 is described as a hypercoagulation condition, with thrombotic and hemorrhagic complications likely occurring. Even though the provision of anticoagulants as therapy and prophylaxis has been recommended, this may lead to hemorrhagic complications, even death.² Thromboelastography/TEG is currently a necessity during this pandemic.¹⁰ TEG is able to identify the main components experiencing dysfunctions, from blood clotting to the fibrinolysis phase. Moreover, TEG can recognize any thrombocyte disorders frequently manifesting in COVID-19 patients. The latest research shows different levels of hypercoagulation in COVID-19 patients based on thromboelastography studies.¹⁰ Intensively-cared COVID-19 patients require constant monitoring on their markers of coagulation, consisting of D-dimer, PT, platelets, and fibrinogen.⁶ Should any decline shows in these markers, a more aggressive critical care support is imperative. When these markers show some stability or progress, this can be a guideline for a step-down therapy if supported with clinical condition improvements. The case also underwent a coagulation profile test panel every 24 hours. Tests for D-Dimer, fibrinogen, and platelets were performed every 3 days.

In severe COVID-19 cases, there is a decrease in the fibrinolysis process caused by the release of plasminogen activator inhibitor (PAI)-1

mostly coming from infected necrotic endothelia and activated platelets.⁶ PAI-1 polymerizes fibrins in the thrombus and may inhibit tissue-type plasminogen activator (tPA)-mediated fibrinolysis.⁶ This process has the tendency to contribute to the occurrence of micro and macrovascular thrombosis. Fibrinolysis may have a critical therapeutic role in massive pulmonary thromboembolism cases of COVID-19, though the possibility of hemorrhage should be closely monitored. Aside from using heparin, thrombosis can be managed through administering fibrinolytic drugs to reduce the level of fibrin already present in the lungs. Fibrinolytic agents, such as tissue-type plasminogen activator (tPA), had been administered systemically to treat ARDS in COVID-19 cases and it has shown some degree of effectiveness in several patients. A number of studies on tPA suggest an anti-inflammatory effect in addition to its fibrinolytic effect. Its potential will assist in improving the prognosis of COVID-19 patients.^{6,11} In this case, fibrinolytic therapy was given using r-TPA alteplase, which rendered a satisfactory response. Experience of using streptokinase as a thrombolytic agent in previous cases has yet yielded optimal results.¹²

Other therapy strategies, including providing platelet aggregation inhibitors, are also no less important for preventing sepsis-induced coagulopathy in COVID-19 patients, possibly engendering disseminated intravascular coagulation.^{1,6,13} This case also involved dual antiplatelet therapy (DAPT) with aspirin and clopidogrel. Current research demonstrates that the use of clopidogrel is safe and able to inhibit the formation of thrombus.¹⁴ However, one should bear in mind the possible risks of hemorrhage from the use of DAPT, ticagrelor, and aspirin.¹⁵ Therefore, it is much advisable to use ticagrelor as a platelet anti-aggregation agent alone.¹⁶

In the event that active bleeding occurs, requiring invasive procedures, or high risks of hemorrhage in conditions with coagulopathy or DIC related to COVID-19, transfusion of blood products can be considered. Patients with active bleeding should be given thrombocyte transfusion if the thrombocyte count is $<50.000/\mu\text{L}$. In this case, the thrombocyte count was still adequate. On the basis that it wouldn't function optimally, thrombocyte transfusion was still given.^{1,13} The dose of thrombocyte transfusion is adjusted according to each individual. In general, 1 unit of apheresic platelets or an equivalent dose of platelet concentrate is given. The provision of 2 units of platelet apheresis can be considered in severe, life-threatening hemorrhage cases. The transfusion of fresh frozen plasma (a dose of 15–30 mL/kg) is given in active bleeding cases with prolonged PT or aPTT (>1.5 times than the normal value). Cryoprecipitate fibrinogen (a dose of 10 mL/kg) or fibrinogen concentrate (a dose of 30–50 mg/kg) is given to hypofibrinogenemia cases ($<1.5\text{g/L}$).¹³ In this case, active bleeding occurs, in the form of seepage in the CVC and thus the patient was given transfusions of cryoprecipitate, thrombocyte concentrate, fresh frozen plasma, and packed red cell.

The management of pulmonary thromboembolism on COVID-19 patients remains a challenge for health professionals today, both in terms of preventive measures and therapy should the thromboembolism already appears. Periodic monitoring on markers of coagulation is fundamental to the parameters of a successful therapy and the possibility of adverse reactions. The undesirable side effects of fibrinolytic therapy, anticoagulant therapy, and platelet anti-aggregation therapy must become the main concerns in its management. Further research needs to be done as a guideline for the management of thromboembolism and its management of any side effects on COVID-19 patients.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Acknowledgement

Nil.

Conflicts of Interest

There are no conflicts of interest.

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