CASE REPORT

An Important Dilemma: Fibrinolytic Treatment in Bleeding Diathesis

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Keywords: fibrinolytic treatment; fresh frozen plasma; pulmonary embolism; ultrasonography

Abbreviations:
aPTT: activated partial thromboplastin time
BE: base excess
BP: blood pressure
DIC: disseminated intravascular coagulopathy
ECG: electrocardiogram
FFP: fresh frozen plasma
HCO3: bicarbonate
IHTS: International Society on Thrombosis and Haemostasis
INR: international normalized ratio
JAAM: Japanese Association for Acute Medicine
O2: oxygen
PaO2: partial pressure of oxygen
PESI: pulmonary embolism severity index
PT: prothrombin time
SIC: sepsis-induced coagulopathy
SOFA: Sequential Organ Failure Assessment
SpO2: oxygen saturation

Abstract

Pulmonary embolism is a clinical condition with high mortality rates in all age groups. The treatment includes anticoagulation and fibrinolytic therapy, and clinical management is challenging in cases of bleeding diathesis. Sepsis-induced coagulopathy (SIC), which has been recently defined to cause disruption of coagulation cascade accompanied by organ dysfunctions, is regarded as a major cause of mortality. It is noteworthy that there is no decrease in fibrinogen levels, unlike disseminated intravascular coagulopathy (DIC). This study aimed to present the management of a 70-year-old female patient who was admitted to emergency department with atypical complaints and diagnosed with pulmonary embolism due to deep vein thrombosis and septic shock. The clinical success of fibrinolytic therapy following the administration of fresh frozen plasma (FFP), although the patient had elevated international normalized ratio (INR), is presented in this case report. Since elevated INR and thrombocytopenia, which are observed in SIC, are caused by the inhibition of fibrinolysis, fibrinolytic therapy can be a rational treatment choice considering the profit/loss rate.

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Introduction

Pulmonary embolism is a life-threatening clinical condition. Its 30-day mortality is 3.9% and one-year mortality is 12.9% in all age groups.[1] Patients with pulmonary embolism may present to the emergency department with complaints such as difficulty in breathing, chest pain, swelling on legs, syncope, or cardiac arrest. Hypotension, tachycardia, tachypnea, or hypoxia may also be detected in these patients.[2] Different modalities are used in the treatment of low-medium-risk and high-risk pulmonary embolism, but fibrinolytic therapy is the milestone of high-risk pulmonary embolism.[3] Absolute contraindications of fibrinolytic therapy include intracranial mass, recent stroke, active bleeding, and bleeding diathesis.[3]

Bleeding diathesis involves an inherited or acquired disorder affecting primary or secondary hemostasis.[4] The main causes of bleeding diathesis are drug use and diseases that cause thrombocytopenia.

Sepsis-induced coagulopathy (SIC) is particularly recognized as a precursor to disseminated intravascular coagulopathy (DIC).[5] It is a clinical condition characterized by prolonged international normalized ratio (INR) and thrombocytopenia and increases short-term mortality.[6] Recent studies have shown that DIC may occur due to other reasons and that the initial designation of SIC is the correct procedure.[4,5,7,8] In addition, it is known that severe sepsis or septic shock increases the likelihood of DIC.[9]

This case report presents the clinical success of half-dose fibrinolytic therapy following the administration of fresh frozen plasma (FFP) in a patient with bleeding diathesis and high-risk pulmonary embolism.

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	04:10	05:05	09:00[a]	16:30
pH	6.949	7.002	7.195	7.283
pO2 *(mmHg)*	55.1	59.3	66.7	69.3
pCO2 *(mmHg)*	33.0	28.0	25.4	28.1
HCO3 *(mmol/L)*	6.1	6.6	9.5	15.4
BE *(mmol/L)*	−23.4	−22.3	−17.1	−13.4
Lactate *(mmol/L)*	9.5	9.5	7.4	2.1

Table 1. Blood Gas Analyses of the Patient
Abbreviations: BE, base excess; HCO3, bicarbonate; pCO2, partial carbon dioxide pressure; pO2, partial oxygen pressure.
[a]The arterial blood gas after the alteplase treatment. The alteplase treatment started at 06:00.

Report

A 70-year-old female patient was admitted to the emergency department with complaints of nausea, vomiting, and diarrhea. She had no chest pain or difficulty in breathing. Her medical history revealed that she had been diagnosed with myelodysplastic syndrome, diabetes mellitus, and hypertension and that her treatment with lenalidomide was discontinued two weeks prior; she was also diagnosed with popliteal deep vein thrombosis and was recommended to wear compression socks, and low-molecular-weight heparin was initiated one week prior. The drugs used by the patient were moxifloxacin, fluconazole, valacyclovir, tolterodine, insulin aspart, benidipine, nebivolol, and enoxaparin. The emergency department vital parameters were as follows: blood pressure (BP), 70/40mmHg; pulse, 95 beats/min; respiratory rate, 26 breaths/min; oxygen saturation (SpO2), 80%; and body temperature, 38.4°C (101.1°F). The physical examination findings were as follows: drowsiness; GKS: E3,V4,M6(13); limited orientation and cooperation; variegated appearance on skin; decreased turgor and tonus; rough breathing sounds; tachypneic breathing; and 1cm-diameter difference in the right leg. The electrocardiogram (ECG) findings were as follows: sharp T waves and significantly enlarged QRS wave. The Rapid Ultrasound in SHock (RUSH) in the evaluation of critically ill patients protocol was performed to explicate hypotension; it revealed enlarged right ventricle and D sign. There was no pericardial effusion. The size of the inferior vena cava was 1.9cm and had a collapse of >50%. There was no response to compression in the right popliteal vein. She showed signs of dehydration and was given 500ml saline. The case was considered to be septic shock due to three positive findings of systemic inflammatory response syndrome along with a BP of 75/50mmHg and the lack of reaching the targeted mean arterial pressure, and norepinephrine infusion and broad-spectrum antibiotic therapy were commenced. The laboratory parameters were as follows: pH, 6.949; partial pressure of oxygen (PaO2), 55.1mmHg; partial pressure of carbon dioxide (PaCO2), 33.0mmHg; bicarbonate (HCO3), 6.1mmol/L; base excess (BE), -23.4mmol/L; lactate, 9.5mmol/L; K, 8.06mEq/L; Cr, 3.63mg/dL; blood urea nitrogen (BUN), 88.3mg/dL; hemoglobin (Hb), 9g/dL; platelet (PLT), 210,000; prothrombin time (PT), 32.7%; INR, 2.79; activated partial thromboplastin time (aPTT), 69.7s; alanine transaminase (ALT), 792IU/L; aspartate aminotransferase (AST), 885IU/L; total bilirubin, 0.83mg/dL; albumin, 37g/L; fibrinogen, 220mg/dL; and D-Dimer, 6,000ng/mL. Urinalysis revealed 1,360 leukocytes. Compared with the tests conducted two weeks prior, test results revealed impaired renal and hepatic functions. Based on ECG findings and signs of hyperkalemia, she was treated with calcium gluconate, salbutamol, and insulin. The patient was hypotensive and had impaired renal function. The ratio PaO2/fraction of inspired oxygen (FiO2) was 260. The Sequential Organ Failure Assessment (SOFA) score was nine and revealed impairment in three organ systems. The quick SOFA score was three; the National Early Warning Score was fifteen. She had a SIC score of four and an International Society on Thrombosis and Haemostasis (IHTS; Carrboro, North Carolina USA) overt-DIC score of five and was considered to have coagulopathy secondary to sepsis.

Considering pre-diagnosis of pulmonary thromboembolism, thorax CT-angiography was performed, which revealed filling defects compatible with thrombus in the left and right pulmonary arteries. She had elevated INR and did not receive vitamin K antagonist therapy. She had a pulmonary embolism severity index (PESI) score of 210 and was considered Class 5. Although the patient was considered to need fibrinolytic therapy, she was contraindicated to it due to the elevated INR levels; 10ml/kg FFP was administered to the patient. As she had significant metabolic acidosis and the urine output rate was 0.5ml/kg/h despite sufficient fluid resuscitation at the emergency department, ultrasound-guided dialysis catheter insertion was performed through the femoral region. As the mean arterial pressure continued to decrease with inotropic support, half-dose alteplase treatment was performed after obtaining the consent of patient's relatives. Blood gas parameters before and after fibrinolytic therapy are shown in Table 1. No hemorrhagic complication developed during or after fibrinolytic therapy. The vital parameters following fibrinolytic therapy were as follows: BP, 110/70mmHg; pulse, 80 beats/min; respiratory rate, 22 breaths/min; and SpO2, 95% under two liters of O2. The patient underwent dialysis in the emergency department and was admitted to the intensive care unit.

There was no deterioration in the vital signs within the first few days at the intensive care unit. She had gingival bleeding at the day of admittance and was treated in accordance with the dialysis schedule, and the need for O2 was ended. The patient became septic again and died at day 48 following fibrinolytic therapy despite the treatment provided.

Discussion

Pulmonary embolism is a life-threatening clinical condition.[3] Near-term mortality in patients with high PESI scores reaches 24%.[10] Therefore, it is essential to rapidly recognize pulmonary embolism in the emergency department and commence appropriate treatment. Heparin and fibrinolytic therapy used in the treatment of pulmonary embolism causes increased life expectancy.[3,11] In this case, the patient's PESI score was high, and the vital signs were stabilized with the treatment given to the patient.

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Both PT and aPTT are prolonged in patients with acquired vitamin K deficiency. However, patients with vitamin K deficiency are admitted to hospitals with major bleeding.[12] There was not a clear conclusion about vitamin K deficiency in this patient since the factor levels could not be evaluated in the emergency department. However, the emergency department treatment was sufficient since there is no other agent used in the treatment of vitamin K deficiency.

Sepsis-induced coagulopathy is a clinical condition, which is observed in patients with sepsis and recognized as a precursor to DIC.[8] The 28-day mortality rates have been reported to be between 27% and 56%.[6] It is characterized by patients with low platelet counts, prolonged PT, and a SOFA score of at least four.[5] Similarly, the diagnosis of DIC is made based on the IHTS and Japanese Association for Acute Medicine (JAAM; Tokyo, Japan) scores.[4,13] Although the JAAM and IHTS criteria involve fibrinogen and fibrin degradation products, it has been reported that coagulopathy developed with no hypofibrinogenemia in DIC secondary to sepsis.[14] Sepsis-induced coagulopathy is characterized by endothelial dysfunction and anticoagulation disorder. The vascular endothelial surface is coated by membrane-binding proteoglycans and glycosaminoglycan side-chains, which provide critical antithrombotic effects.[15] Endothelial cells produce tissue-type plasminogen activator and plasminogen activator inhibitor-1 and balances fibrinolysis to inhibit fibrin generation and deposition.[8] This may explain why patients benefit from fibrinolytic therapy and why no complications develop in patients despite expected hemorrhagic complications. In this patient, the SIC, IHTS DIC, and JAAM DIC scores were four, five, and five, respectively. The patient had SIC or DIC; however, since both treatment modalities are similar, she was administered vitamin K and 10ml/kg FFP. A Multiple Organ Dysfunction Syndrome score of nine accompanied by pulmonary embolism suggested that the patient's mortality was cumulatively higher.

The use of fibrinolytic drugs such as alteplase is contraindicated since they exert their effects by interfering with coagulation cascade. The initiation of fibrinolytic therapy after reduction of INR level to normal values may be life-saving. Despite treatment without waiting for INR level after FFP due to the clinical deterioration of this patient, both dialysis catheter insertion and fibrinolytic treatment could have been performed. Fibrinolytic treatment was performed at half-dose in accordance with the recommendations of guidelines, and the patient's vital parameters reached normal levels. It has been considered that the vital parameters were normalized due to the treatment given for the patient's septic condition. It was considered that the mortality rate would be very high if the treatment was not administered to the patient with massive pulmonary embolism accompanied by sepsis. The targeted therapy in the early period had increased the patient's chance to survive.

Conclusion

Administering FFP is useful in patients diagnosed with SIC or DIC and thrombotic complications. This patient survived due to alteplase treatment given following the correction of bleeding diathesis. However, there is a need for in vitro studies to clarify this issue further.

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