Prothrombin complex concentrate and fatal thrombotic adverse events: A complication to keep in mind

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1. Introduction

Oral anticoagulants are routinely prescribed for the prevention or treatment of thromboembolic events, with millions of prescriptions being issued for anticoagulation in the United States every year (1). On the other side, the risk of major hemorrhage increases dramatically with the use of anticoagulation reaching 1.7% to 3.4% in patients on vitamin K antagonists (VKA), for example (2). Prothrombin Complex Concentrate (PCC) has been approved for the reversal of VKA-associated major bleeding, but it is also often used off-label to reverse coagulopathy in patients receiving non-VKA anticoagulants or in patients with liver disease (3,4). Although PCC infusion can quickly reverse the anti-coagulation effect of VKA and save lives in certain critical situations, it is associated with increased risk of thromboembolic events such as pulmonary embolism, deep vein thrombosis, and cerebrovascular accident. Here, we present the first case of ST-segment elevation myocardial infarction with cardiogenic shock and passed away. This is the first reported case of acute myocardial infarction that occurs in a patient without hemophilia and after the first prothrombin complex concentrate infusion.

2. Case Report

A 70 year-old man presented to our emergency department because of worsening generalized weakness over the last three days. The patient is previously known to have cholangiocarcinoma diagnosed six months ago when he developed diffuse jaundice and lower extremities edema. Back then, he was found to have multiple liver lesions with a CA 19-9 level of 10,616 u/mL. The liver biopsy demonstrated diffuse intra-hepatic cholangiocarcinoma, and he was started on regular cycles of chemotherapy with gemcitabine and oxaliplatin. At the same time, he was diagnosed with lower extremities deep vein thrombosis and was treated with rivaroxaban. Other medical history is relevant for hypothyroidism for which he was maintained

Summary

Thromboembolic events such as deep vein thrombosis and pulmonary embolism are well-known complications that can occur after prothrombin complex concentrate therapy. However, acute myocardial infarction is a very rare but potentially life-threatening complication that was exclusively described in patients with bleeding disorders who received chronic and recurrent concentrate infusions. We report the case of a 70 year-old male patient with cholangiocarcinoma who was admitted to our hospital with worsening fatigue and weakness. His stay was complicated by uncontrolled bleeding secondary to rivaroxaban use and advanced liver disease. By the end of the prothrombin complex concentrate infusion used to reverse his coagulopathy, patient developed ST-segment elevation myocardial infarction with cardiogenic shock and passed away. This is the first reported case of acute myocardial infarction that occurs in a patient without hemophilia and after the first prothrombin complex concentrate infusion.

Keywords: Prothrombin complex concentrate, thromboembolic adverse event, ST-segment elevation myocardial infarction, liver disease

Released online in J-STAGE as advance publication April 23, 2018.

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on replacement therapy, and chronic kidney disease (Baseline estimated glomerular filtration rate around 57 mL/min). Among his home medications, he was also taking furosemide and spironolactone to control his ascites. He never smoked cigarettes, did not consume alcohol or used illicit drugs. At baseline, patient was fully oriented and ambulatory with a walker. At this time, he presented one week after his last chemotherapy cycle because of weakness and confusion. Family provided the history and said that for the last few days he was getting weaker, unable to ambulate on his own, and was getting confused from time to time. Upon evaluation, patient was afebrile, had a heart rate of 96 beats per minute, with a blood pressure of 83/57 mmHg. On physical examination, he was lethargic, confused, but arousable to painful stimuli. He was moving all his extremities and recognized his family members, but was not oriented to place or time. He was diffusely jaundiced and had bilateral lower field crackles on lungs examination. His abdomen was distended and dull to percussion, and he had bilateral lower extremities 3+ pitting edema. Blood work showed slightly decreased white blood cells count, with anemia (Hemoglobin of 10 g/dL) and thrombocytopenia (Platelets of 50,000/μL). He also had acute kidney injury with a creatinine level of 2.3 mg/dL (Baseline of 1.6 mg/dL), and prolonged international normalized ratio (INR) and partial thromboplastin time (4.9 and 46.4 s respectively). Total bilirubin level was 6.3 mg/dL and aspartate and alanine aminotransferases were around two-times the normal level. Baseline electrocardiogram (ECG) showed right bundle branch block (Figure 1), and 2-D echocardiography was within normal range.

Patient was admitted to the intensive care unit for a presumed diagnosis of sepsis. He received broad spectrum antibiotics, resuscitated with fluids and maintained on low dose norepinephrine keeping his mean arterial blood pressure around 65 mmHg. Pancultures were drawn, Rivaroxaban was held, and abdominal paracentesis was performed urgently ruling out spontaneous bacterial peritonitis. Few hours later, patient started bleeding around his intravenous lines and from the site of paracentesis, and developed epistaxis. Emergent peripheral blood smear showed only low platelets count and macrocytic anemia without any schistocytes ruling out disseminated intravascular coagulation. The patient's coagulopathic state was attributed to both the use of rivaroxaban and worsening liver failure with prolonged INR secondary to the progression of his cholangiocarcinoma. Since rivaroxaban has no antidote commercially available on the market (Andexanet Alfa being still studied), the decision was taken to administer prothrombin complex concentrate (PCC) to try to control the bleeding. For a pre-treatment INR of 4.9, we administered PCC at a dose of 35 u/kg and at a rate of 0.12 mL/kg/minute. By the end of the infusion, the medical team noted some changes on the heart monitor. An ECG performed at that time showed evolving antero-septo-lateral ST-segment elevation myocardial infarction (Figure 2). Troponin level rose acutely from 0.02 to 3.95 μg/L. No cardiovascular intervention was possible at that time in the settings of anemia, thrombocytopenia, prolonged INR and active bleeding. Shortly after, patient went into cardiac arrest. All the efforts to resuscitate him were unsuccessful, and the patient expired.

3. Discussion

Adverse events following PCC infusion are common and can range from minor incidents such as headache, nausea or vomiting, to more severe and lethal

Figure 1. Baseline ECG. Initial ECG showing sinus rhythm with right bundle branch block.
complications suchlike a fatal thromboembolic event. Venous thromboembolism including deep vein thrombosis and pulmonary embolism are more common than arterial events such as cerebrovascular accident (5). Myocardial infarctions are actually quite unusual, but have been reported in few patients who suffered from hemophilia, after receiving large cumulative doses of PCC infusions (6). Our article describes the first case of STEMI that occurred in a PCC-naïve patient with no genetic bleeding disorder.

Myocardial infarction associated with the use of PCC is a well-described, but rare, clinical event. There have been around 16 such cases reported in the literature exclusively in patients with hemophilia who were exposed to recurrent infusions of PCC (6). Although some factors are known to increase the risk of venous thromboembolism complications of PCC therapy such as liver diseases and crush injuries, they do not appear to play a major role in the pathogenesis of myocardial infarctions related to the use of these concentrates (6). The management of such complication should it happens is debatable mainly because its pathogenesis remains poorly understood. Most previously reported cases were managed conservatively with opiate analgesia, nitrates, diuretics, anti-arrhythmics and inotropes (6). Anticoagulants, anti-platelets, thrombolytic therapy or even percutaneous interventions are not a plausible or wise choice owing the high risk of bleeding complications in this population. Matter of fact, most of these patients who underwent post-mortem autopsy were surprisingly found to have myocardial hemorrhage without any evidence of coronary atherosclerosis or thrombosis (6). This might actually refute the assumption that myocardial infarction was caused by arterial thrombosis due to a hypercoagulable state produced by the infusion of PCC.

In the literature, no consensus is currently available for the treatment of PCC-induced myocardial infarction. We would suggest immediate stopping of the infusion, stabilizing the patient with symptoms control (analgesia/nitrate) and hemodynamic support if needed. In any case, our patient was too sick to even consider any kind of revascularization approach or anti-thrombotic therapy in view of his active bleeding.

Keep in mind that prevention of complications is way better than treating them. For the time being and until new randomized controlled trials come up with a definitive answer, we advise against the routine use of PCC for coagulopathy reversal in patients with liver disease. However, PCC might be an option for prudently selected patients with excessive, life-threatening bleeding, after weighing risks and benefits of such therapy.

In conclusion, PCC is not a completely benign therapy and subsequent fatal complications can occur. Awareness of these adverse events and familiarity with the predisposing factors is crucial for avoiding and treating such complications should they arise. Finally, decision on PCC usage must be tailored on a case by case manner.

References

1. Barnes G, Lucas E, Alexander G, Goldberger Z. National trends in ambulatory oral anticoagulant use. Am J Med. 2015; 128:1300-1305.

2. Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition)
3. Huang W, Cang W, Derry K, Lane J, Drygalski A. Four-factor prothrombin complex concentrate for coagulopathy reversal in patients with liver disease. Clin Appl Thromb Hemost. 2017; 23:1028-1035.

4. Lesmana C, Cahyadinata L, Pakasi L, Lesmana L. Efficacy of prothrombin complex concentrate treatment in patients with liver coagulopathy who underwent various invasive hepatobiliary and gastrointestinal procedures. Case Rep Gastroenterol. 2016; 10:315-322.

5. Sarode R, Milling T, Refaai M, Mangione A, Schneider A, Durn B, Goldstein J. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients with vitamin K antagonists presenting with major bleeding. Circulation. 2013; 128:1234-1243.

6. Hough R, Hampton K, Preston F, Channer K, West J, Makris M. Recombinant VIIa concentrate in the management of bleeding following prothrombin complex concentrate-related myocardial infarction in patients with haemophilia and inhibitors. Br J Hematol. 2000; 111:974-979.

(Received March 5, 2018; Revised April 1, 2018; Accepted April 14, 2018)