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LIMB-THREATENING DEEP VENOUS THROMBOSIS COMPLICATING WARFARIN REVERSAL WITH THREE-FACTOR PROTHROMBIN COMPLEX CONCENTRATE: A CASE REPORT

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☐ **Abstract—Background: Three- and four-factor prothrombin complex concentrates (PCC) are gaining popularity for acute reversal of vitamin K antagonist-associated bleeding. Although acute thrombosis after PCC administration has been described, it seems to be rare. Case Report: An 83-year-old woman on warfarin for history of deep venous thrombosis (DVT) presented to the Emergency Department with life-threatening gastrointestinal bleeding, requiring urgent PCC administration. After stabilization, she subsequently developed a new limb-threatening upper-extremity DVT. Why Should an Emergency Physician Be Aware of This?: As PCC therapy gains popularity for reversal of anticoagulant-induced bleeding in urgent bleeding scenarios, the emergency physician must be aware of the complications of PCC administration, including new limb-threatening DVT.** © 2016 Elsevier Inc.

☐ **Keywords—prothrombin complex concentrate; three-factor; limb-threatening; deep venous thrombosis; warfarin reversal**

INTRODUCTION

Prothrombin complex concentrate (PCC) is a concentrated plasma product that, depending on the particular brand, contains various amounts of vitamin K-dependent clotting factors. PCC is made in three-factor (Factors II, IX, and X) and four-factor (II, VII, IX, and X) formulations. It is gaining popularity as an alternative to fresh frozen plasma (FFP) for the reversal of vitamin K antagonist-associated bleeding. The American College of Chest Physicians recently recommended four-factor PCC as a first-line agent for acute vitamin K antagonist-associated major bleeding (1).

As compared to FFP, PCC more rapidly corrects international normalized ratio (INR; 41 min vs. 115 min) and more consistently achieves complete INR reversal (2,3). Much smaller volumes (1–2 mL/kg vs. 15 mL/kg) of PCC are required for administration, which is not only advantageous in patients sensitive to fluid overload, such as those with congestive heart failure, but also requires less time to administer (4). Unlike FFP, PCC can be prepared for administration quickly, whereas FFP requires ABO typing and must first be thawed and then warmed before it can be administered, delaying administration by over 1 h (5). The risk for transfusion-related acute lung injury (TRALI) with FFP administration is not present with PCC, as the antibodies responsible for TRALI are removed during the manufacturing process (5).

Alternatively, there are known risks and complications of PCC. The primary safety concern is its association with thrombogenic events such as stroke, myocardial

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infarction, pulmonary embolism, disseminated intravascular coagulation, and deep venous thrombosis (DVT) (6). PCC is also significantly more expensive than FFP. It costs approximately $5080 per dose, compared to approximately $300–600 for the equivalent dose of FFP (7).

CASE REPORT

An 83-year-old woman on warfarin therapy due to a history of lower DVT presented to the Emergency Department (ED) with the acute onset of lower gastrointestinal bleeding. Although her initial ED vital signs (temperature 36.6°C, heart rate 77 beats/min, blood pressure 139/72 mm Hg, respiratory rate 20 breaths/min, and SpO_2 95% on room air) did not suggest hemodynamic compromise, she experienced several large bloody bowel movements shortly after initial assessment. The patient then became unresponsive, bradycardic, and hypotensive, with continued active bleeding. Although her laboratory results, including INR and hemoglobin, were still pending, we initiated both emergent red blood cell transfusion and warfarin reversal with PCC. At the time of treatment, the only PCC available from our hospital pharmacy was a three-factor PCC (brand name Profilnine®; BDI Pharma, Columbia, SC) and 4570 units (50 units/kg × 1 dose) were administered into an 18-gauge peripheral intravenous line (i.v.) in the left arm. The patient's vital signs subsequently stabilized and her mental status recovered to baseline. Her initial INR drawn prior to PCC administration later returned at 1.9, with a hemoglobin level of 11.6 g/dL. Inpatient colonoscopy was unsuccessful, as multiple recent attempts to traverse the left side of her colon were limited by angulation and fixation due to advanced diverticular disease. Although unverified, the Gastroenterology team suspected a diverticular source as the cause of the patient's bleeding.

Approximately 2 h after the administration of PCC, the patient reported severe pain in her right hand and wrist, the contralateral side from PCC administration. A 16-gauge i.v. in the right forearm was promptly removed. The emergency physician noted that the patient's right hand and wrist were significantly more swollen, tender and cool than the left (Figure 1). Despite normal capillary refill and a normal radial pulse, rapidly progressive discoloration and pain with passive movement of the right upper extremity raised concern for an extending DVT. Venous duplex ultrasound revealed an occlusive DVT involving the right axillary, brachial, and basilic veins. The vascular surgery service emergently evaluated the patient and recommended initiation of a heparin drip for treatment of what was considered limb-threatening venous occlusion. After consultation with both vascular surgery and the Gastroenterology service, we felt that the risk of re-bleeding was outweighed by the risk of loss of limb, and a heparin drip was initiated. Within 30 min, the patient was able to move her right hand with significantly less pain and had improved range of motion (Figure 2). The patient eventually recovered from both acute life- and limb-threatening events.

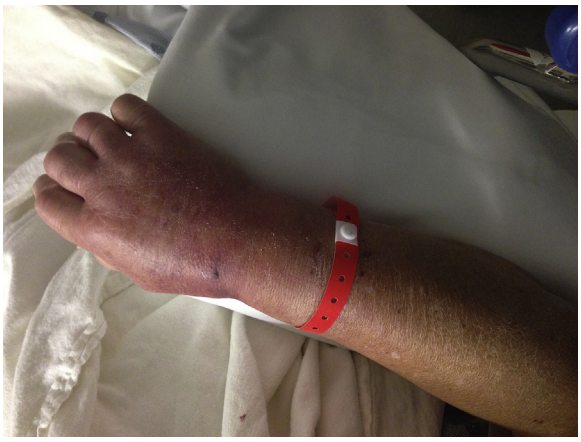

Figure 1. Right hand upon initial complaint of pain. Noted is moderate swelling and dark reddish-purple discoloration. Distal to the allergy bracelet, the extremity was extremely tender to touch.

DISCUSSION

We report a case of acute, rapidly progressive upper-extremity DVT that resulted in limb-threatening tissue ischemia as a complication of three-factor PCC administration. Although the risk for thrombogenesis after PCC administration is not precisely known, a meta-analysis of 27 studies suggests it is <3% (8). A more recent randomized controlled study comparing FFP with four-factor PCC reversal found the risk of thromboembolic

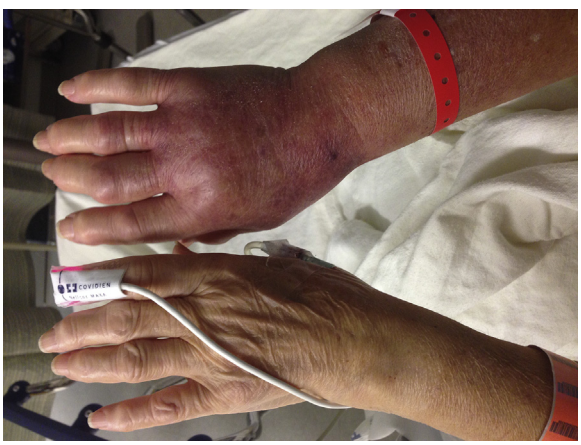

Figure 2. Right hand and wrist 30 min after initiation of intravenous heparin. Right upper extremity (affected with deep venous thrombosis) as compared to left (unaffected, normal extremity). At this point in time, the patient began to feel some relief of pain.