Research Paper Medical Science

The Use of Protrombin Complex Concentrate (Cofact) in the Treatment of Gastrointestinal Hemorrhaging Induced by Warfarin (Case Report)

Nedim ÇEKMEN Assoc. Proff Güven Hospital Department of Anesthesiology and Intensive Care

Emine KURUCA Nurse Güven Hospital Department of Anesthesiology and Intensive Care

ABSTRACT

Prothrombin complex concentrate (PCC) is recommended for emergency reversal of oral warfarin anticoagulation. A 78-year-old female was diagnosed with pulmonary embolism and observed with warfarin treatment was admitted to intensive care unit (ICU) with the sudden development of hypotension, abdominal pain, vomiting and melana. With endoscopy, gastrointestinal hemorrhaging was diagnosed. Laboratory analyses showed INR 18 with other laboratory values as normal. With a conservative approach in the treatment, warfarin use was ceased and volume replacement, fresh blood, fresh frozen plasma (FFP) and 10 mg of vitamin K was administered. Despite conservative approach in the treatment, INR 13 with continued melana, the patient was administered with a total of 2000 IU PCC iv infusion. After PCC, dropped to INR 1.6 and it was observed that the patient's melana gradually decreased. The patient was discharged from ICU. PCC treatment serves as an effective rapid hemorrhage control resource in the emergency anticoagulant reversal setting.

KEYWORDS Anticoagulation reversal, critical care, gastrointestinal hemorrhage, prothrombin complex concentrates

Introduction

Warfarin is the most frequently used oral anticoagulant therapy (OAT) in clinically practiced treatments and for the purpose of prophylaxis and blocks vitamin K dependent coagulation factors (II, VII, IX, X) and inhibitors (protein C and S).[1-3] Major bleeding is a common problem in people taking OAT, occurring at a rate of 2.4–8.1 % per patient-year.[3] Intracranial hemorrhage (ICH) (17–30 %) and gastrointestinal (GI) hemorrhaging (30–60 %) is perhaps serious complication of OAT; Current therapeutic options for reversal of OAT in patients with major hemorrhage are FFP, PCC (Cofact®) (PCC; which includes the vitamin-K dependent coagulation factors II, VII, IX and X) and recombinant factor VIIa, administered in combination with vitamin K.[2-6] Although FFP is still often used, PCC offers substantial benefits over FFP and is the 'gold standard' therapy.[4-6] Whereas PCC can be rapidly prepared and corrects vitamin K antagonist-induced impairment of hemostasis within 30 minutes of administration, FFP must be thawed and large volumes infused, leading to delayed and often inadequate correction of anticoagulation.2,[4-6] In our case, we have introduced PCC in the development and treatment of GI hemorrhaging induced with the use of warfarin.

Case

A 78-year-old female presented to the emergency department with a 1-week history of abdominal pain and vomiting. She was diagnosed with pulmonary embolism and observed with warfarin treatment (8 days) was admitted to ICU with the sudden development of hypotension, abdominal pain, vomiting and melana. She had no history of systemic problems. She was confused and his Glasgow coma score was 13. Her Acute Physiology and Chronic Health Evaluation II score (APCHE II) was 18, and his Multiple Organ Dysfunction Score was 4. On examination, the patient's vital signs were: blood pressure, 68/42 mmHg; heart rate, 128 beats/min (irregular); respiratory rate, 29 breaths/min; temperature, 36.4 ºC; and oxygen saturation, 85 % (on air). The patient's chest was clear, with normal breath sounds. Arterial blood gas analysis showed metabolic acidosis due to hypoxemia. With endoscopy, GI hemorrhaging was diagnosed. Laboratory analyses showed hemoglobin 8.3 g/dL, Hematocrit **(**Htc) 24 %, thrombocyte 166.000/µL, PT 148, aPTT 133, INR 18 with other laboratory values as normal. Electrocardiogram and echocardiography revealed normal ventricular function and no signs of ischemia. With a conservative approach in the treatment, Warfarin use was ceased and volume replacement, 2 units of fresh blood, 6 units of FFP and 10 mg of vitamin K was administered. Despite providing blood, FFP and vitamin K, with hemoglobin at 10.8 g/dL, Htc 31%, thrombocyte 202 000/µL, PT 56, aPTT 88 and INR 13 with continued melana, the patient was administered with a total of 2000 IU PCC iv infusion. After PCC, PT dropped to 15, aPTT to 37 and INR to 1.6 and it was observed that the patient's melana gradually decreased. Three days after being admitted to ICU, the patient was transferred to service with the hemorrhaging having ceased, the general situation improved and the vital signs having stabilized. Two days following treatment in service the patient was discharged.

Discussion

Bleeding complications are the most common side effect of OAT, notably if risk factors such as high INR levels, long term use of oral anticoagulants and age over 70 years are present (1-4). When patients experience major or life-threatening bleeding, it is essential to administer exogenous factors II, VII, IX and X. The method chosen to increase these levels depends on the urgency for reversal, which is determined by primarily the INR and the severity of the bleeding.[4-6]

For patients with very minor bleeding, withholding the warfarin intake alone is sometimes sufficient, but the coagulopathy will not be corrected for 3-5 days.[2-4] This can be done with either FFP or PCC. The main advantage of FFP is its wide availability, but its use in warfarin reversal is limited by the large volume which is normally required to be given quickly. Because of these limitations with FFP, most clinical guidelines recommend the use of PCC for the rapid reversal of warfarin anticoagulation.[4-6] PCC produce more rapid correction of the INR compared to FFP and are associated with better clinical outcome.[7-11]

The optimum dose of PCC for OAT reversal has not been established. Approximate dosing of PCC can be calculated based on patient bodyweight, the INR before treatment, and the target INR. In line with current guidelines, the protocol in our hospital is to use PCC to achieve this and stop bleeding in patients taking OAT. A uniform standard dose of 30 IU/kg conco-

mitant with 5 mg iv vitamin K has been advocated for use in OAT patients with major hemorrhage.[7-10]

Holster et al.[7] reported that the (endoscopic) management, when facing a suspected OAT-associated GI hemorrhage. Holster et al[7] reported that OAT should be stopped and also correcting coagulopathy with administration of PCC, recombinant factor VIIa and even hemodialysis should be considered, whereas FFP and vitamin K have no place. We observed that the target range was achieved as early as 18 min and PCC provided effective clinical hemorrhage control.

Yasaka et al.[8] reported that the effect of PCC on the INR and blood coagulation system in two emergent patients treated with warfarin. An 80-year-old woman developed massive subcutaneous hemorrhage and had an INR above 10. An 83-year-old man had pleural effusion with an INR value of 6.69 and pleural puncture was immediately required. They were administered 500 IU of PCC to the two patients (17.2 IU/kg and 12.5 IU/kg) with 10 mg of vitamin K. The INR decreased to 1.12 and 1.85, respectively) In our case, we showed INR 18. With a conservative approach in the treatment, warfarin use was ceased and volume replacement, fresh blood, FFP and 10 mg of vitamin K was administered. Despite conservative approach in the treatment, INR 13 with continued melana, the patient was administered with a total of 2000 IU PCC iv infusion. After PCC, dropped to INR 1.6.

Wong[9] reported that a 71-year-old male on warfarin (to reduce stroke risk) presented with headache. The patient appeared lucid and well. However, INR was 4.1. Head computed tomography (CT) indicated a large right-sided subdural hematoma. PCC; with vitamin K the INR within minutes of administration. The patient underwent neurosurgery without complications, and was discharged after 5 days, with no residual neurological symptoms. In our case, we showed INR 18. Despite conservative approach in the treatment, INR 13 with continued melana. After PCC, dropped to INR 1.6.The patient was discharged after 5 days.

Numerous studies of PCC in OAT reversal have shown target INR to be reached within 10–15 min.[7-9] Lorenz et al.[10] have shown that PCC infusion was successful in rapidly returning INR to 1.4 or below in all patients. Furthermore, PCC provided effective clinical hemorrhage control in 98 % of patients. Hickey et al.[11] reported that PCC for urgent reversal of warfarin resulted in faster reversal and lower red cell transfusion requirement with fewer adverse events than FFP. We showed that, the target range was achieved as early as 18 min and PCC provided effective clinical hemorrhage control. Thrombotic complications are the most feared adverse events when using PCC..[4-8] We observed that no thrombotic complications after PCC in the patient.

In conclusion, PCC can safely be used for the rapid reversal of anticoagulation needed in urgent situations such as emergency surgeries or severe bleedings as the reversal was documented 15 minutes following PCC administration. In this type of hemorrhaging, despite administering blood, FFP and vitamin K, the use of PCC for treatment of patients who's INR does not decrease is an alternative that should certainly be borne in mind. Further comparator studies with other reversal agents are needed.

Declaration of conflicting interest
The authors declare that there are no conflicts of interest.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not for-profit sectors.

Authors' Contributions
All authors contributed to the medical management of the patient and preparation of the manuscript. All authors have read and approved the content of the manuscript.

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