

Prothrombin complex concentrate for warfarin-induced bleeding in a patient with a mechanical aortic valve

Rahul Kar^a, Erik Abel^b, Pamela Burcham^b and Michael S. Firstenberg^{c,*}

^a The Ohio State University College of Medicine, OH, USA

^b Department of Pharmacy, The Ohio State University Wexner Medical Center, Columbus, OH, USA

^c Department of Surgery, The Summa Health Care System, Akron, OH, USA

* Corresponding author. Department of Surgery, The Summa Health System, 75 Arch Street, Suite 407, Akron, OH 44309, USA.
Tel: +1-330-3849001; fax: +1-330-3849002; e-mail: firstenbergm@summahealth.org (M.S. Firstenberg).

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Abstract

Reversal of anticoagulation-induced bleeding in the perioperative period can be challenging, particularly with an unstable patient with a mechanical valve. We present a case of life-threatening bleeding successfully managed with a prothrombin complex concentrate as an alternative to fresh frozen plasma.

Keywords: Bleeding • Blood • Coagulation/anticoagulation

INTRODUCTION

Mechanical cardiac valves have the advantage of increased structural durability compared with bioprosthetic valves, but they mandate continuous anticoagulation to minimize thromboembolic complications. Long-term anticoagulation with warfarin comes with risks of catastrophic bleeding complications and requires routine monitoring. The risk of warfarin-induced bleeding complications is well known and is typically managed with vitamin K (phytonadione) and/or fresh-frozen plasma. Prothrombin complex concentrates (PCCs) have been used successfully in patients with warfarin-associated coagulopathy and traumatic intracranial haemorrhage [1]. However, despite their increasing use and the recommendations for use in these situations [2], the safety of these agents in patients with mechanical cardiac valves is poorly described and controversial. We describe the successful use of PCC in a postoperative patient with a mechanical aortic valve, who experienced a life-threatening haemorrhagic complication while on therapeutic anticoagulation with warfarin.

REPORT

Our patient is a 58-year old female with a St Jude mechanical aortic valve implanted in 1990, who underwent elective repair of a symptomatic and enlarging ascending aortic aneurysm. Her procedure was performed using femoral vein-to-artery bypass with replacement of her ascending aorta to the proximal arch. The proximal and distal anastomosis was performed using a circumferential strip of felt. Her postoperative course was uneventful, and she was restarted on her routine dose of warfarin (2 mg per oral daily (QD)). On her insistence, based on previous experiences and contrary to our medical advice and current standard of care and

guidelines, she was discharged home on postoperative day (POD) 5 with self-administered enoxaparin (60 mg every 12 hours) pending therapeutic levels of warfarin. At discharge, her international normalized ratio (INR) was 1.4, haemoglobin (Hgb) was 10.3 g/dl and renal function was normal.

She returned to the emergency department 3 days later (POD #8) complaining about acute onset of shortness of breath, diaphoresis and dizziness. She was tachycardic (heart rate = 116 bpm), tachypnic (24 breaths/min) and hypotensive (80/46 mmHg). Her INR was 2.6 and haemoglobin was 6.6 g/dl. Her last dose of enoxaparin was >12 h prior, having missed her evening dose due to her symptoms. A chest X-ray, which had been clear at discharge, showed a moderate left-sided pleural effusion. Computed tomography (CT) scanning was performed to evaluate a potential source of bleeding and while the source was unclear, imaging did show a large left haemothorax. Transthoracic echocardiography showed no evidence of tamponade or effusion with normal valvular and biventricular function. As she was becoming more symptomatic (blood pressure: 69/31 mmHg), 2 l of normal saline and 2 total units of packed red blood cells with consideration for fresh-frozen plasma (FFP) vs prothrombin complex concentrate (PCC) consistent with current guideline recommendations for management of severe warfarin-induced bleeding [2], and for expeditious correction, 1090 units (25 units/kg) of Profilnine SD (Grifols Biologicals, Inc., Los Angeles, CA, USA) were administered. A chest tube was placed and drained 1600 ml of dark red blood. These interventions controlled her bleeding and her symptoms improved. Repeat INR was 1.7 and Hgb was 10.2. She received a total of 6 units of blood, but no other blood products were administered, and there was minimal additional drainage from the chest tube. Multiple imaging studies failed to show an obvious source of bleeding or aortic pseudoaneurysm, and by hospital day 7 her anticoagulation was resumed with a target INR of 1.7–2.2 and she was discharged home. This range was arbitrarily chosen based on our clinical

experience with managing patients with warfarin-related bleeding complications and cardiac devices that require continuous anticoagulation such as ventricular assist devices. This target INR was maintained for 30 days, at which time she resumed her usual dosing regimen of warfarin with a goal INR of 2.0–3.0. Ten months post-operatively, she is doing well and has not experienced any bleeding or thromboembolic complications, and repeat CT imaging of her aortic valve has not demonstrated any pathological abnormalities.

DISCUSSION

The PCC used in our patient, Profilnine, is one of several commercially available PCCs. It contains lyophilized human plasma-derived factors IX, II, X and VII and is indicated for prevention and control of bleeding in patients with haemophilia B-associated factor IX deficiency. Currently used PCCs differ in which factors are contained relative factor concentrations, viral inactivation methods and the inclusion of additives such as heparin, protein C and antithrombin [3]. In general, PCCs have ~25× greater concentration of clotting factors than FFP. A study of 42 patients with an INR of >2 who required emergent normalization prior to an invasive procedure or to control active bleeding who were treated with a PCC and vitamin K demonstrated a 98% clinical efficacy. In this study, 6 patients had serious adverse events with 3 deaths. In all patients, baseline comorbidities precluded a definitive causation between PCC administration and the adverse event [4].

Currently, guidelines for the management of warfarin-induced bleeding advocates FFP, PCC and vitamin K [2] administration with doses of each based on the extent of bleeding, degree of haemodynamic stability and overall clinical picture. PCCs have theoretical advantages over FFP for the correction of warfarin-induced bleeding, despite minimal evidence supporting use in patients with mechanical valves [3]. First, since PCCs are lyophilized and stored either refrigerated or at room temperature, they can be rapidly reconstituted and administered immediately in cases of acute life-threatening bleeding. In addition, since the volume administered (10 ml for our patient) is typically far less than that of FFP, it can be administered quicker and safer as these patients are susceptible to symptomatic acute volume overload. Unlike FFP, which has a half-life of 1.5–2 h, PCCs have a half-life of $\sim 25 \pm 8$ h, which is pharmacodynamically more appropriate to counteract the effects of warfarin, which has a half-life of 40 h. Since both FFP and PCCs help resupply the vitamin K-dependent factors, neither agent is sufficient as vitamin K supplementation is still required to make new functional coagulation factors. Furthermore, due to different mechanisms of action along the complex clotting pathways, PCCs have little benefit, and hence are not indicated, in the setting of unfractionated or low-molecular weight heparin-induced bleeding [3, 4]. While FFP carries risks of blood-borne

infections and a significant risk of transfusion-related lung injury, PCCs have not demonstrated these risks to date [3].

The use of PCC is not without danger. The mortality rate in studies investigating the safety and efficacy of PCC for warfarin reversal ranged from 7 to 46% [4, 5]. Complications include deep vein thrombosis, myocardial infarction, renal infarctions, stroke and limb ischaemia, but ongoing modification of preparation techniques, increased understanding of dosing risk/benefit ratios and potential impact of patient comorbidities all have reduced the risk of thrombotic events [5]. While these studies have included patients with mechanical valves, none has specified a temporal relationship from the time of placement of the valve. This would help discern the relative risk of bleeding and post-PCC thrombotic complications including massive intracardiac thrombosis and tamponade from extensive pericardial thrombus [5]. The long-term follow-up of patients receiving PCC is also lacking.

Conclusions

Our case demonstrates the effectiveness of prothrombin complex in reversing the effects of warfarin in a perioperative patient with a mechanical aortic valve presenting with severe haemorrhage. With more patients being treated with anticoagulants, bleeding complications are also going to be more frequent and potentially more severe, and therefore it is of critical importance to having agents to rapidly and safely reverse their effects.

Conflict of interest: none declared.

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