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CASE REPORT

Management of two major postoperative bleeding complications after mandible reconstruction with fibula free flap in a patient under chronic warfarin treatment

Abelardo Medina[a] and Ignacio Velasco Martinez[b]

[a]Division of Plastic Surgery, Department of Surgery, School of Medicine, University of Mississippi Medical Center, Jackson, MS, USA; [b]Department of Oral Maxillofacial Surgery and Pathology, School of Dentistry, University of Mississippi Medical Center, Jackson, MS, USA

ABSTRACT

We present a case of two separated life-threatening postoperative bleeding complications after mandible cancer resection and microsurgical fibula flap in a patient under permanent warfarin treatment. We used fresh frozen plasma, prothrombin complex concentrate to control bleedings. We consider to maintain similar patients in heparin/enoxaparin bridging for 1–2 weeks.

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Perioperative bleeding; warfarin; fibula free flap

Introduction

Patients treated with lifelong anticoagulation can develop significant complications, either thromboembolic (TE) or bleeding events, during the perioperative period [1]. Vitamin K antagonists (VKA) are one of the most common therapeutic approaches to prevent TE by interfering the production of vitamin K-dependent clotting factors [2]. Unfortunately, due to its mechanism of action, VKA agents such as warfarin predispose patients to late onset of postoperative bleedings due to the lack of stable secondary clots [1]. In order to prevent these complications, bridging therapies with unfractionated heparin (UFH) and low molecular weight heparin (LMWH) have been recommended. However, in high TE-risk patients, the preoperative therapeutic anticoagulation regimen has to be resumed soon after surgery, when the bleeding concerns have clinically decreased [3]. Patients bearing mechanical heart valves (MHV) are in this category and require a multidisciplinary management to appropriately balance these risks [4–6]. This management is especially challenging during free flap procedures that intrinsically have high risk of postoperative bleeding and flap thrombosis. This case report describes a patient with MHV that developed two separated episodes of significant bleeding during the first month after a large mandible reconstruction with microsurgical procedure.

Case report

A 60-year-old male that was diagnosed with pT4aN0 clear cell odontogenic carcinoma of the left mandible. He was planned for tracheostomy, segmental mandible resection, left selective neck dissection, and reconstruction with left osteoseptocutaneous fibula free flap (FFF). His past-medical history was relevant for mechanical bi-leaflet mitral valve replacement (MVR) 4 years prior for which he was on warfarin (6 mg PO daily). The patient went through an extensive preoperative assessment that included multidisciplinary tumor board review and surgical recommendation, assessment by different specialties (anesthesia, cardiology, oral maxillofacial, plastic surgery, dentist, etc.) and multidisciplinary session of virtual surgical planning (VSP). In addition, EKG and bloodwork (type and screen, electrolytes, INR, PTT, BUN, creatinine, eGFR, glucose, CBC and differential) were requested. The INR was checked prior to the surgery to ensure its value was $\leq$1.5 (patient's value was 1.06). The patient was evaluated by his cardiologist preoperatively and instructed to stop warfarin 4 days prior to surgery and

CONTACT Abelardo Medina amedina@umc.edu Assistant Professor of Surgery, Division of Plastic Surgery – Department of Surgery, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS, 39216, USA

switch to therapeutic enoxaparin injections (30 mg SC BID). The cardiologist also suggested to re-start enoxaparin (80 mg BID) and warfarin (5 mg daily) when postoperative bleeding has been controlled. The enoxaparin could be stopped when INR $\geq$2 (with goal of INR 2–3).

The surgical procedure was uneventful, and patient did not have any unusual intraoperative bleeding (Figure 1). The in-hospital cardiology team was consulted postoperatively for anticoagulation management. They recommended starting a heparin infusion (1000 units/h) on postoperative day 1 and bridging to warfarin at his previous dose when possible. This therapeutic approach was in concordance with suggestions of the patient's cardiologist. Our institution has in place both aPTT and anti-factor Xa assays to monitor unfractionated heparin. In our patient, the anticoagulation monitoring approach was done with aPTT. Since our patient did not experience any significant intra- and early post-operative bleeding and following the routine management for similar cases, on day 2 (POD#2), the surgical ICU team began bridging the patient to warfarin. The following day, patient started progressive bleeding in the donor site of the FFF (through the skin graft and through the adjacent drain) that became bloody and with an output of ~100 mL/h (Figure 2). Warfarin was discontinued, and conservative therapies were attempted such as applying compressive dressings and immobilization with AFO boot to his leg. However, the patient required transfusion of several units of packed red blood cells (PRBCs) due to hemoglobin drop. The decision was made to stop the heparin infusion for 4 h and reverse his INR to baseline by using fresh frozen plasma (FFP).

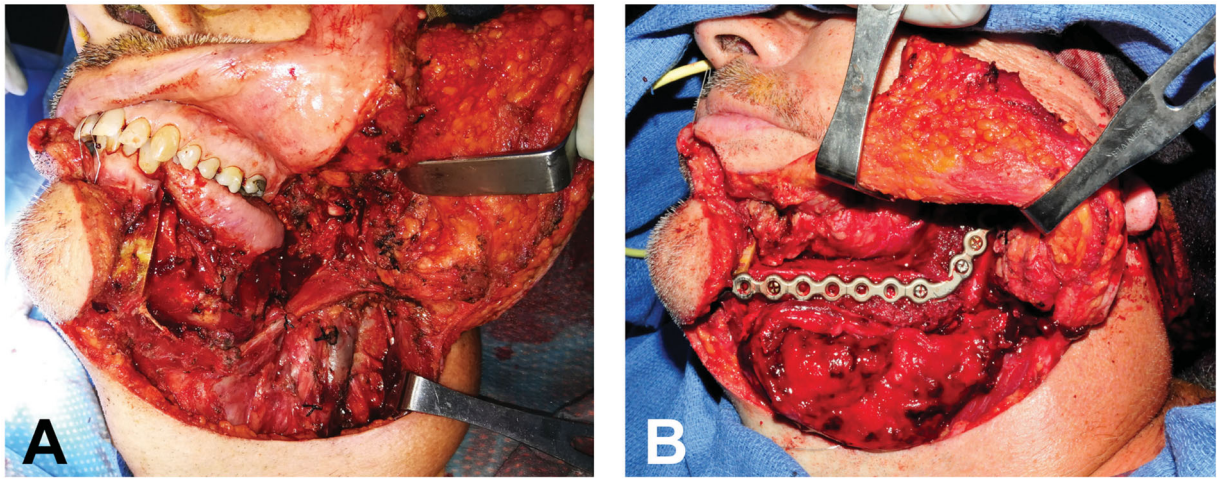

Figure 1. Patient underwent tracheostomy, segmental mandible resection, left selective neck dissection, and reconstruction with left fibula free flap (FFF). His past-medical history was relevant for mechanical bi-leaflet mitral valve replacement 4 years prior for which he was on warfarin (6 mg PO daily). (A) Intraoperative resection. (B) Mandible reconstruction with two segments FFF and reconstruction plate.

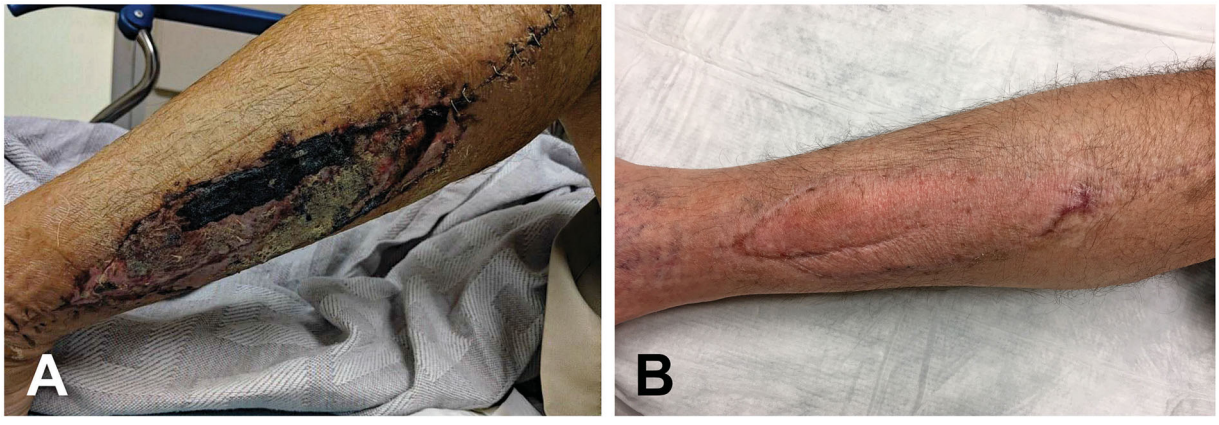

Figure 2. (A) Postoperative day 3, patient started progressive bleeding in the FFF donor site reaching an output of ~100 mL/h of blood. (B) Six months after discharge. Donor site of FFF is fully healed.

Vitamin K was not administrated during this hemorrhagic episode. After receiving blood products (8 units PRBCs and 2 units FFP), the local bleeding dramatically decreased and once again the fluid collected in the drain became serosanguinous in nature. Following a discussion with the surgical ICU team, the heparin infusion was restarted at a flat rate of 500 units/h. During this bleeding event, the patient's hemoglobin value was in average 7.01 (ref. range 13–17 g/dL) with standard deviation of 0.63 and median of 7.2. The hemoglobin values showed significant fluctuations over short intervals due to the need of blood transfusion. The patient had no further bleeding episodes while in the hospital. He was discharged (POD#17) with an order of bridging from enoxaparin (1 mg/kg SC BID) to his previous dose of warfarin until his INR reached therapeutic range for 2 consecutive days. Patient was followed closely in our outpatient clinic until an appropriate healing on his FFF donor site was achieved (Figure 2).

Thirty days after his operation, the patient noticed progressive left-sided facial edema. He initially went to an outside hospital where they aspirated the area with a needle to drain fluid presumably from salivary gland origin. No fluid was obtained, and the patient returned home with a compressive dressing. The swelling continued to worsen so he consulted our emergency room complaining of difficulty swallowing (Figure 3). His INR on presentation was 2.49. A CT scan of the neck with IV contrast was performed which showed a 9.1 cm hematoma lateral to the left mandible with an internal focus of hyperdensity concerning for active hemorrhage. He was admitted to the surgical ICU for airway monitoring and reversal of his anticoagulation. A repeated CT scan showed larger hematoma and extensive edema of airway mucosa (Figure 3). The patient underwent nasal intubation for airway protection and was subsequently taken to interventional radiology for evaluation. The angiogram demonstrated no evidence of active bleeding or suggestions of any potential bleeding site (Figure 3). INR value was corrected with FFP, vitamin K and human prothrombin complex concentrate (PCC). In this bleeding event, the hemoglobin value was in average 8.57 g/dL (SD 1.24; median 8.5) with important variations again due to blood transfusion. Once his hemoglobin was stabilized with PRBCs, he was resumed on a flat heparin infusion at 500 units/h and monitored with aPTT protocol. The skin on his neck and face remained tight several days after admission so he was taken to the operating room for hematoma drainage. The tracheostomy was reopened at the same time for ongoing airway edema.

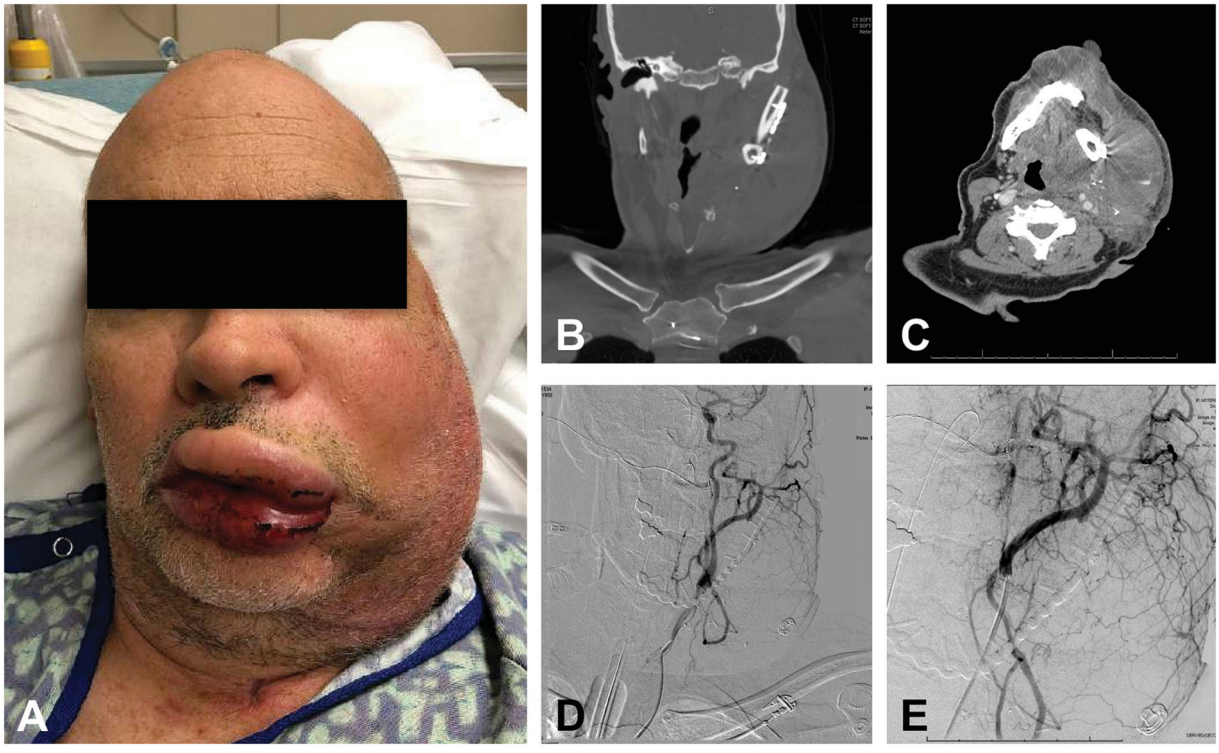

Figure 3. (A) Thirty days after his operation, patient consulted our emergency room complaining of progressive facial edema and difficulty swallowing. His INR on presentation was 2.49. (B–C) A CT scan of the neck with IV contrast was performed which showed a 9.1 cm hematoma lateral to the left mandible with an internal focus of hyperdensity concerning for active hemorrhage. (D–E) The angiogram demonstrated no evidence of active bleeding or suggestions of any potential bleeding site.

Post-operatively, he was restarted on a titratable, full anticoagulation heparin infusion, but again patient developed increasing facial swelling. He was placed back on the flat heparin infusion which he tolerated well. Once the swelling in his face and neck improved, he was slowly transitioned back to warfarin and was discharged home 14 days after his admission. After these two life-threatening bleeding events, the patient returned to his baseline condition and completed his radiation treatment following the tumor board's recommendation (Figures 2 and 4). He has follow-up in our clinic every 3 months. He has no experienced additional bleeding episode and his primary care physician has no initiated any additional assessment for coagulation disorders.

Discussion

Vitamin K antagonists (VKA) are used in different clinical conditions with underlying high risk of TE events. VKA agents as warfarin interfere the production of vitamin K-dependent clotting factors by inhibiting vitamin K epoxide reductase [2]. As platelet aggregation and vasoconstriction required for primary hemostasis

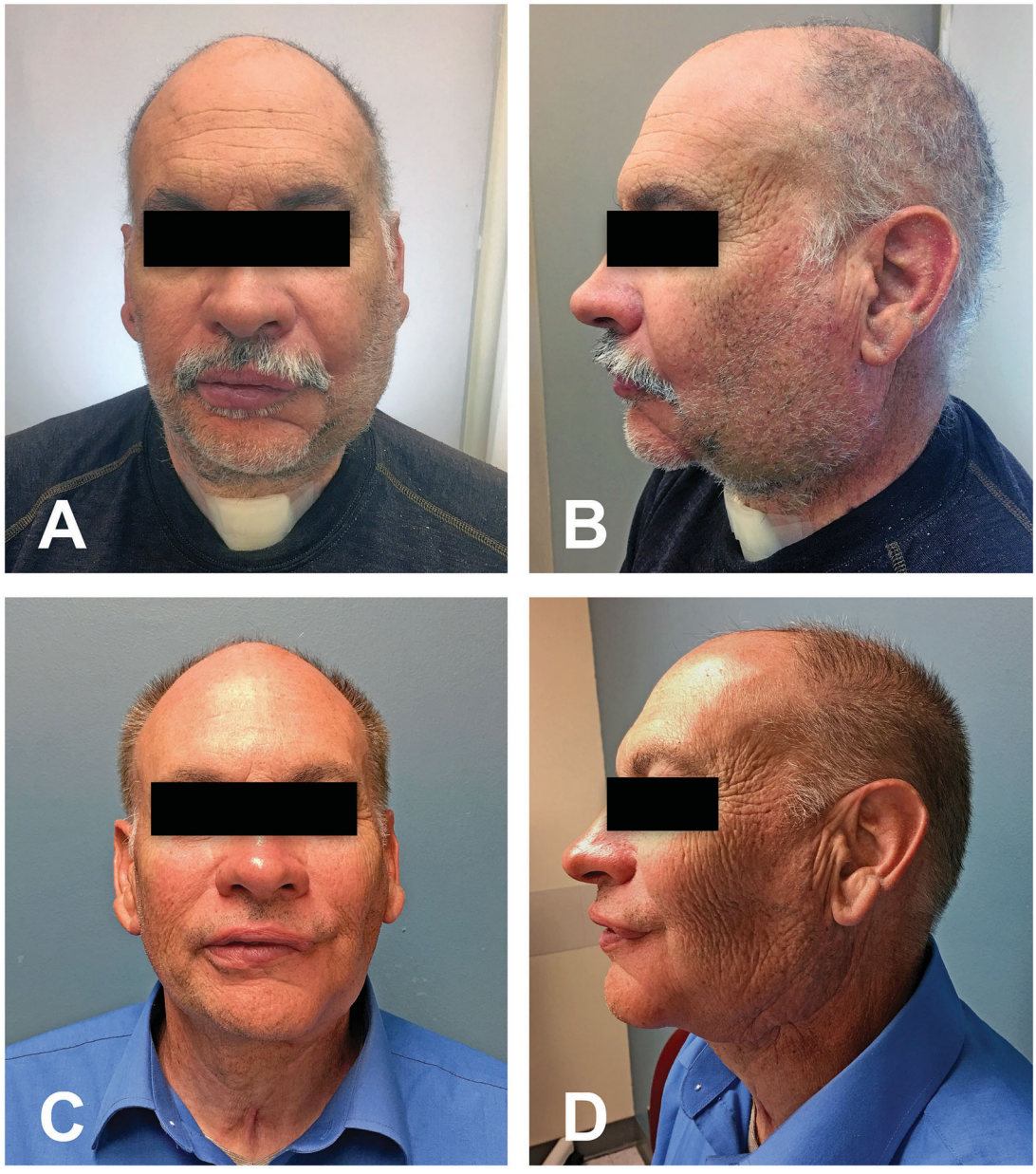

Figure 4. (A–B) Follow-up in outpatient clinic 30 days after the second bleeding event. Patient has minimal facial edema, no local pain and normal mouth opening. Tracheostomy cannula was removed, and the opening is healing satisfactorily. (C–D) Six months after last surgery. The patient fully recovered from these two bleeding events, completed his radiation therapy and returned to his normal activities.

are not affected, patients under VKA treatment may develop a late onset of postoperative bleeding due to the lack of stable secondary clots [1]. However, there is no clear consensus whether VKAs should be temporarily stopped, adjusted or maintained during the perioperative period. Furthermore, warfarin has unpredictable pharmacokinetics that make it challenging to reach the patient-specific therapeutic INR range in clinical practice [7]. In fact, extended periods of inadequate anticoagulation expose patients to higher risk of TE events [8]. In addition, there are contradictory reports about the correlation between maintaining warfarin and the incidence of severe perioperative bleedings during skin cancer surgeries [9–18]. By contrast, the interruption of warfarin in these settings may significantly increase the risk of serious vascular complications such as stroke, myocardial infarction, prosthetic valve thrombosis and pulmonary embolism [19]. Therefore, bridging with short-acting anticoagulant such as UFH or LMWH is recommended to manage the patient during the perioperative period [3,20–22]. In clinical cases with high-bleeding rates (i.e. mitral MHV, history of bleedings, active malignancy, thrombocytopenia, poor renal function), authors have proposed the use of prophylactic rather than therapeutic doses of bridging strategies [4–6]. Additionally, since the incidence of TE events is very low, postprocedural anticoagulation should be indicated in high TE-risk patients and resumed only after the hemostasis at the surgical site has been secured [3].

In practical terms, the benefit of anticoagulation and blood transfusion as needed largely outweigh the risk of suboptimal or no anticoagulation approaches [23–25]. Even though there is no specific validated data for patients bearing MHV, the AHA/ACC task force recommends VKA interruption based on patient age, valve location and number, type of MHV and the presence of concomitant TE risk factors such as atrial fibrillation, cardiomyopathy and previous stroke [3,26].

Using general risk factors for TE, the transitory interruption of lifelong VKA therapy in MHV patients may produce not only perioperative TE events, but also gradual asymptomatic non-obstructive MHV thrombosis for several weeks or months before causing a serious clinical problem [27]. In contrast, anticoagulant bridging in left-sided MHV patients with either UFH or LMWH is associated with considerable risks of bleeding [22]. In this regard, Schulman et al. reported that the onset of hemorrhagic complications and their severity is mainly correlated to the complexity of the surgical procedure [5]. Accordingly, there are no reports that clearly establish how to control a life-threatening perioperative bleeding event in a patient with MHV who underwent an extensive mandibular cancer excision with neck dissection and FFF reconstruction. Since the risk of important bleeding with this therapy during major surgeries may reach up to 20% of the cases [28], our team managed this MHV patient's postoperative course in ICU environment.

As suggested in literature, we stopped the warfarin 4 days prior to surgery to allow the restoration of the clotting factor activity [29]. We indicated enoxaparin as bridging therapy because of its easy subcutaneous administration, quick transition to therapeutic range, weight-based dosing without the need of multiple coagulation tests and lower incidence of thrombocytopenia [5,20,22,27,29]. We stopped the enoxaparin 12 h before the surgery [26]. The heparin infusion was started 12 h after the operation and the warfarin resumed on the POD#2 with frequent monitoring of INR [26,30]. Unfortunately, at POD#3, our patient developed significant bleeding from the donor site of the FFF. As recommended, we reversed the anticoagulation deleterious effect by stopping the heparin infusion for several hours and using and FFP intravenously [31]. The heparin infusion was restarted at a flat rate of 500 units/h. During his second bleeding complication (POD#30), the INR was corrected up to its baseline value with FFP, vitamin K and human prothrombin complex concentrate [31]. Once his hemoglobin stabilized with PRBCs, the patient required a flat heparin infusion at 500 units/h to control local bleeding and edema. This heparin rate is the lowest acceptable dose to prevent TE events in MHV patients in a cardiovascular ICU setting. At this point, considering the special clinical condition of this patient, the cardiology team favored the addition of aspirin low dose (81 mg oral daily) and the discontinuation of therapeutic dose of heparin/enoxaparin once the INR was over 2. The final goal was to slowly reach an INR of 2.5–3 with the lowest possible dose of warfarin (5 mg PO daily).

Although our institution has implemented anti-factor Xa assay, the aPTT protocol was used in our patient to titrate the unfractionated heparin (UFH) dose. Even though recent publications are still reporting similar administrated UFH dose with both approaches in critically ill patients [32], there is increasing consensus that anti-factor Xa assay is a more accurate tool than aPTT for heparin activity monitoring and should be requested in selective cases despite the higher cost [33]. The anti-factor Xa assay uses nonbiologically derived reagents to measure the inhibition of factor Xa, and therefore, it is not affected

by coagulation factors (i.e. factor XII or V), warfarin administration or sampling factors [34,35].

FFP is the traditional and widely validated therapy that is still used alone or in combination with prothrombin complex concentrate (PCC) to reverse anticoagulation. Currently, multimodal hemostatic therapeutic approach is used in 60% of patients that experience perioperative bleeding [36]. Along with potential risks of pathogen transmission, the FFP use may cause fluid overload and subsequent acute lung injury. In addition, the FFP administration is inevitably delayed due to the need of crossmatch and product thaw. The PCC manufacturing process includes purification and viral inactivation to reduce the risks of pathogen transmission. The advantages of PCC compared to FFP are: more rapid to prepare (VKA reversal in less than 30 min) and less volumes required (no more than 200 mL). However, similar rates of late bleeding events and no significant differences in in-hospital mortality have been reported in these two therapeutic approaches [37]. Furthermore, the available systematic review of randomized controlled trials could not find significant differences between the use of PCC and FFP [38].

Conclusion

The management of warfarin and other anticoagulation medications require a multidisciplinary approach to find the right balance between TE and hemorrhagic events. Both types of events can cause devastating morbidity and mortality. The need for VKA discontinuation and the implementation of bridging therapies during the perioperative period will depend on the clinical assessment and risk factors of each patient. In future similar cases, it is very likely that we will delay the re-establishment of the oral anticoagulation beyond the time that post-operative bleeding seems to be under control. It is reasonable to consider to maintain the heparin/enoxaparin bridging for 1 or 2 weeks before the transition into VKA.

Disclosure statement

No potential conflict of interest was reported by the authors.

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