CASE REPORT

Reversal of anticoagulation with four-factor prothrombin complex concentrate without concurrent vitamin K (phytonadione) for urgent surgery in a patient at moderate-to-high risk for thromboembolism

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SUMMARY

Successful vitamin K antagonist (eg, warfarin) reversal with 4-factor prothrombin complex concentrate (4F-PCC) without vitamin K (phytonadione) for emergent surgery in a patient at moderate-to-high risk for thromboembolism is reported. This approach may decrease the risk for development of thrombus, as it limits the amount of time the patient's anticoagulation is subtherapeutic. It also may increase the risk of bleeding, so patient selection is essential if this strategy is employed. Caution must be exercised to complete the procedure or surgery in the window of peak 4F-PCC effect (~1–6 hours postinfusion).

BACKGROUND

Any reversal of anticoagulation inherently increases the risk of thromboembolism as the patient's underlying risk is unmasked by the removal of the anticoagulant. Thus, the need for emergent surgery in patients who are anticoagulated due to a moderate-to-high thromboembolism risk requires judicious consideration of the risks of anticoagulation reversal and the benefit and timing of surgery. Similarly, once the need for emergent reversal is clear, treatment options must be thoughtfully evaluated. The treatment most often recommended for major bleeding or urgent surgery is four-factor prothrombin complex concentrate (4F-PCC or PCC) in combination with vitamin K (phytonadione).[1] 4F-PCC is recommended in preference to fresh-frozen plasma (FFP) for major bleeding and urgent reversal for life-saving surgery due to its faster onset of action and easier dose delivery. When 4F-PCC is given, simultaneous administration of intravenous vitamin K (phytonadione) is recommended.[2 3] 4F-PCC has primarily been evaluated in clinical trials in comparison with FFP, with both arms receiving vitamin K.[4 5] 4F-PCC and vitamin K complement each other in terms of onset and duration, with 4F-PCC providing rapid reversal and vitamin K resulting in slow synthesis of the vitamin K-dependent factors resulting in a normalisation of the INR in ~12–36 hours (figure 1).[6] However, vitamin K is a fat-soluble vitamin and, as such, can be stored in the body (especially with larger doses) and may present a significant oppositional force when the reinitiation of anticoagulation is desired (the so-called 'depot' effect).[6]

Four-factor PCC contains vitamin K-dependent factors II, VII, IX and X, as well as proteins C and S, and is indicated in adult patients requiring urgent reversal of vitamin K antagonists (VKA) in the event of acute major bleeding or urgent surgery. 4F-PCC is an expensive agent; the average wholesale price (AWP) in the USA is $6625–13 250 (€5890–11 780) for 2500–5000 units ($2.65/unit, dosing range of 25–50 units/kg for 100 kg individual). There has been a previous publication of successful reversal of VKA anticoagulation with three-factor PCC (3F-PCC) without vitamin K.[7] To the best of our knowledge, no case reports or clinical trials have highlighted the use of 4F-PCC without vitamin K.

CASE PRESENTATION

A man aged 79 years weighing 100 kg presented to the emergency department with difficulty in walking and pain after sustaining a crush injury when a motor vehicle rolled over his right lower leg. On admission, X-rays reveal proximal fibular fracture. Compartment syndrome was diagnosed, requiring emergent surgery. Medical history included atrial fibrillation, diabetes mellitus type 2, hyperlipidaemia, hypothyroidism, coronary artery disease, sleep apnoea, osteoarthritis, peripheral neuropathy and myocardial infarction. His

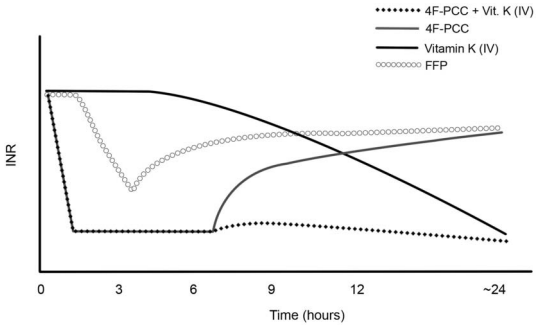

Figure 1 Onset and duration of vitamin K antagonist reversal treatments.[6] (Adapted, used with permission.) 4F-PCC, four-factor prothrombin complex concentrate; Vit. K, vitamin K (phytonadione); FFP, fresh-frozen plasma. INR, international normalised ratio.

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medications included warfarin therapy for stroke prevention (atrial fibrillation) and his INR was found to be slightly elevated to 3.2 (target 2.0–3.0). His CHA2DS2-VASc score was calculated at 4, putting the patient at moderate-to-high risk for a thromboembolic event (with risk increased with recent trauma). He also reported an allergy to vitamin K (unknown reaction). Emergent reversal of INR was deemed necessary.

TREATMENT

Four-factor PCC (Kcentra) was given at a dose of 25 U/kg (2500 units) infused over 10 min without the concurrent use of vitamin K.

OUTCOME AND FOLLOW-UP

The INR was re-evaluated 30 min after conclusion of the infusion and found to be 1.8. The patient proceeded to surgery; a four-compartment fasciotomy was completed with minimal bleeding and no complication. When the INR was measured the following day, the patient was found to be at therapeutic level of 2.4. The patient's haemoglobin and haematocrit were stable in the postoperative period and no bleeding was noted.

DISCUSSION

This case demonstrates the successful use of an alternative VKA reversal strategy. To the best of our knowledge, the use of non-activated 4F-PCC alone for urgent surgery without vitamin K has not been published elsewhere. Others, however, have previously suggested that an individualised approach based on risk could include the possible use of 4F-PCC without vitamin K.[8] Our patient required rapid reversal in order to have urgent surgery but also had a moderate-to-high risk of thrombosis due to his age, medical history and chief symptom. The use of 4F-PCC alone may represent the best treatment option for select patients because of its short half-life of effect. This non-traditional approach was initially considered because our patient had a reported vitamin K allergy; however, there may be merit in considering this approach more broadly after further evaluation. It should be noted that this approach exposes the patient to greater risk of bleeding and is not in line with current anticoagulation guidelines, which suggest that 4F-PCC should be given with vitamin K.[1] This approach is also costly and may not be an option in all areas. Even so, the patient who is given 4F-PCC alone is rapidly reversed and likely able to undergo major surgery if the surgery can be completed in the window of peak 4F-PCC activity and with low-to-moderate risk of bleeding. The peak 4F-PCC activity occurs 1–6 hours postinfusion (as measured by factor plasma concentrations) after which all factor concentrations, particularly factor VII, are reduced (factor VII mean residence time is 6.1 hours).[9] Those given 4F-PCC alone are then able to reattain a therapeutic INR in an expeditious manner, in this case, the next day without any additional VKA (rebound effect). This approach likely decreases the risk for development of a life-threatening thrombus when compared with 4F-PCC plus vitamin K as it limits the amount of time the patient is subtherapeutic. This approach should be weighed against the standard of care, which is full, longer lasting reversal with 4F-PCC and vitamin K with possible bridging with heparinoids. For many patients, the standard approach is likely preferable at this point. However, there may be select patients for whom the provider wishes to tip the balance towards more rapid thromboembolic protection (at the cost of increased risk of bleeding) and avoid the need/duration of postoperative bridging or subtherapeutic anticoagulation. A potential pitfall of reversal without vitamin K could be the possibility of the majority of 4F-PCC supplied coagulation factors being consumed during a lengthy surgery without newly synthesised factors present to contribute to haemostasis (since no vitamin K is given). This complication could be remedied by repeat dosing of 4F-PCC or FFP if excessive bleeding or elevated INR occurs intraoperatively or postprocedurally. It should be noted that repeat dosing with any blood factors (4F-PCC, FFP, etc) is currently a more expensive therapeutic option than giving vitamin K when blood factors are initially given. It is unclear how often the need for more blood factors would occur. The safety, efficacy or cost-effectiveness of redosing 4F-PCC or supplementing it with FFP is unclear at this point.

In terms of resumption of VKA, if the INR remains subtherapeutic postoperatively, resumption of VKA and heparin anticoagulant bridging should be performed as per current guidelines and local practice standards for postoperative anticoagulation.

This case suggests that 4F-PCC without vitamin K may be a reasonable treatment consideration in emergent reversals for certain surgeries that will take place in the near future (6 hours) in select patients at moderate-to-high risk of thromboembolic events. Future research investigating efficacy and safety in using 4F-PCC without vitamin K for anticoagulation reversal and subsequent emergent surgery is warranted in order to provide more substantial evidence of the merits and risks of this approach.

Learning points

- Four-factor prothrombin complex concentrate (4F-PCC) without vitamin K may be a reasonable treatment consideration in emergent vitamin K antagonist reversal for certain surgeries that will take place in the near future.
- Peak 4F-PCC activity occurs 1–6 hours postinfusion after which all factors, particularly factor VII concentrations, are reduced.
- A potential benefit of this approach is more rapid reattainment target INR, with less time subtherapeutic.
- A potential pitfall of this approach is coagulation factor consumption during a lengthy surgery increasing risk of bleeding.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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