

# Incidents Related to Prothrombin Complex Concentrates n=23

# 12d

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## Definition:

Hospitals are asked to report incidents related to PCC infusion where there was delay or inappropriate transfusion. (Allergic reactions should be reported to the MHRA through the yellow card scheme, <https://yellowcard.mhra.gov.uk/>).

## Key SHOT messages

- PCC administration is an emergency treatment used for reversal of oral anticoagulants (warfarin and DOAC) which should be started within an hour of the decision being made and before the patient is transferred to other wards or departments
- Patients with suspected ICH are at high risk of death or serious sequelae and require urgent anticoagulant reversal

## Recommendations

- The ED should ensure they have a protocol with clear instructions for dose and administration of PCC. Staff should be appropriately trained in their use
- A standardised single first dose for emergency use should be adopted to reduce PCC administration delays in urgent situations
- Use of PCC should be regularly audited for timeliness and appropriateness

**Action: Medical directors, hospital transfusion teams, audit leads**

## Introduction

A total of 23 cases were reported in this category. Most PCC incidents were reported in the elderly population, median age 85 years. Only 1 patient was under 70 years of age. There were 17/23 (73.9%) reports of delayed PCC infusion. Other errors included inappropriate doses, either under or over recommended units, infusion pumps set at the wrong rate and lack of trained staff to administer the PCC.

All patients were taking anticoagulants, either warfarin or apixaban/edoxaban. Nine patients had ICH, 5/9 following falls. Six patients had GI bleeding.

## Deaths related to transfusion n=4

Four patients died (all on warfarin) possibly (n=3) or definitely (n=1) related to the delay in administration of PCC. This case has been described in Case 12d.1.

### Case 12d.1: Failure to reverse warfarin and inadequate red cell transfusion

*An elderly person was admitted with a suspected cerebrovascular accident which was not confirmed on CT. However, they were found to have a Hb of 44g/L and very high INR (confirmed on repeat testing). The patient received a single unit of red cells but no reversal of the high INR. They had*

*epistaxis earlier in the day but no other bleeding. No bleeding source was sought. The patient collapsed and died 15 hours after admission. The patient was on an acute ward which was very short staffed and usually relied on bank and agency staff.*

Of the 3 deaths with possible imputability, 1 was a patient with ICH where the long delay in receiving PCC (8 hours) was associated with expansion of the haematoma. An elderly patient fell downstairs sustaining a head injury with confirmed ICH, and the PCC administration was delayed for 5 hours. Another elderly patient on warfarin was admitted with GI bleeding where PCC was delayed by 3.5 hours due to a delay in decision-making and incorrect use of the recently implemented electronic prescribing system.



### Learning point

- The finding of a high INR should prompt urgent communication to the clinical team and appropriate actions taken especially when patients are on anticoagulants. If a decision has been made for anticoagulant reversal with PCC, this should be administered without delay

## Major morbidity n=0

There were no patients that suffered major morbidity in 2023 as a result of the PCC administration.

## Fixed dose PCC for emergencies

Delay can be reduced by using a fixed emergency dose avoiding both the need for finding the weight and use of calculations. Patients on warfarin should also receive vitamin K and follow up of the INR to ensure reversal and to determine if further PCC is required.

Continued confusion about dose and rate of infusion suggest that a fixed dose regimen might be safer. The literature demonstrates good correction of the INR in most (Bizzell, et al., 2021) including patients with ICH with a fixed dose of 2000IU (Dietrich, et al., 2021). A recent systematic review comparing fixed-versus variable-dose 4F-PCC included three randomised trials and 16 cohort studies with extracranial haemorrhage as the main indication. The authors concluded that fixed dose provides benefits in terms of dose reduction, more rapid administration, better haemostasis with reduced mortality and fewer thromboembolic events (Alwakeal, et al., 2024).

One UK centre has used a fixed dose of 1000IU for both warfarin and DOAC reversal since 2017 with clear benefit (Davies, et al., 2019). Their protocol provides for PCC removal from the refrigerator without laboratory or haematology clinical staff approval. A significant reduction in time from request to administration was demonstrated (for warfarin, mean 48 compared with 126 minutes). No significant difference was noted in mortality for standard dose (13%) and fixed dose (3%) ( $p=0.2117$ ), although the data suggest that a fixed-dose regime may reduce mortality risk. Dose reduction resulted in significant financial savings. No inappropriate use occurred.

Further evidence is presented in Chapter 6, Acknowledging Continuing Excellence in Transfusion (ACE), Case 16, where a fixed-dose regimen (1000IU) was introduced to improve management of patients with ICH and GI bleeding. Subsequent local audit results identified that 67% of patients received PCC within 1 hour of the decision being made compared with 36% pre implementation of the project. Patient survival rate has increased to 86% from 53% pre implementation. In 43% of cases, the initial dose of 1000IU of PCC was sufficient to reverse the INR without need for further PCC.

Previous publications have also supported a fixed-dose approach. Haemostatic efficiency was shown in an open-label, multicentre, randomised clinical trial. Patients with non-intracranial bleeds requiring vitamin K reversal with 4F-PCC were allocated to either a 1000IU fixed-dose of 4F-PCC or a variable dose based on weight and INR. Effective haemostasis was achieved in 87.3% ( $n=69$  of 79) in fixed and 89.9% ( $n=71$  of 79) in the variable dosing cohort. Median door-to-needle times were reduced to 109 minutes (range 16 to 796) in fixed compared with 142 (17 to 1076) for the variable dose ( $P=.027$ ). An INR < 2.0 at 60 minutes after 4F-PCC infusion was reached in 91.2% versus 91.7% ( $P=1.0$ ) (Abdoellakhan, et al., 2022). Another meta-analysis of fixed-dose versus variable-dose of PCC reviewed data from 10 studies

including 988 patients. Fixed-dose PCC was associated with reduced mortality and a shorter order-to-needle time. These authors advocated further studies focusing on clinical outcomes (Mohammadi, et al., 2022). It is not clear what the optimal fixed dose should be. Whether a fixed-dose or weight-based regimen is used, follow up of the INR for patients on warfarin (who should also receive vitamin K) is essential to ensure the dose was adequate and to determine if further PCC is required.

## Conclusion

Delayed administration is the most frequent cause for PCC incident reports (73.9%). PCC are an important treatment for immediate reversal of vitamin K antagonists and other oral anticoagulants and should be given immediately a decision is made, and certainly within an hour (NHSE, n.d.). All medical staff involved in the acute care of patients with suspected serious haemorrhage, particularly ICH, who are eligible for reversal should ensure that they know how to obtain and how to administer PCC. Delay can contribute to patient death.



## Recommended resource

### CAS Alert - Preventing transfusion delays in bleeding and critically anaemic patients

<https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103190>



## References

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