

Incidents Related to Prothrombin Complex Concentrate (PCC) n=18

11d

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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)

Key SHOT messages

- PCC administration is an emergency treatment used for reversal of oral anticoagulants (warfarin and DOAC) and should be started within an hour of the decision being made before the patient is transferred to other wards or departments
- PCC does not affect heparin treatment and should not be used for its reversal. Use protamine sulphate for heparins with advice from a haematologist
- The ED should ensure they have clear instructions for PCC administration and have 24-hour access to it
- The use of fixed dose PCC simplifies management and can reduce the time to treatment
- Medical and nursing staff working in the ED should be trained in the prescription, reconstitution, and administration of PCC

Recommendation

- All ED must have a protocol for use of PCC with clear instructions for dose, reconstitution, and administration. Staff should be appropriately trained in using PCC
- Use of PCC should be regularly audited for timeliness and appropriateness

Action: Medical directors of acute Trusts/Health Boards

- The haemostasis task force of the BSH should consider guidance on the use of a fixed dose of PCC for emergency treatment

Action: Haemostasis task force of the BSH

Introduction

PCC incidents mainly occurred in an elderly population aged 70 years or more, median age 82 years. There were 3 younger patients, 1 a teenager. There were 11 reports of delayed infusion, and 1 inappropriate treatment for a patient receiving heparin. Other issues were inappropriate infusion rates and confusion over the dose.

All patients (except 1) were taking anticoagulants, either warfarin or apixaban/edoxaban; 1 patient was on low molecular weight heparin and was prescribed PCC when the instruction from the haematologist was to give protamine sulphate. This patient in his 80s had COVID-19 pneumonitis and severe epistaxis. Six patients had intracranial haemorrhage and 1 was admitted with head injury.

The SHOT CAS alert released in 2022 also addresses preventable PCC delays. One of the recommended actions was for all healthcare organisations to ensure their transfusion policies and procedures include agreed criteria where rapid release of PCC is acceptable without the initial approval of a haematologist.

Deaths related to transfusion n=0

There were no deaths reported that were related to the PCC incidents.

Major morbidity n=2

Case 11d.1: PCC delay because of need to weigh the patient

A woman in her 80s on apixaban for AF, with upper GI bleeding was in the ED and received red cells. Confusion was caused by the requirement for her weight, and she was not well enough to get off the trolley. This hospital had a fixed dose policy but shared on call haematology staff with another NHS organisation who use a weight-based dose. It was not clear if she received the dose but was put on an end-of-life pathway and died unrelated to the PCC issues.

She was described as having major morbidity and was very unwell.

Case 11d.2: Difficulties in accessing PCC resulting in delayed administration and extension of ICH

An elderly patient on apixaban presented to the ED following trauma with a head injury at 17:31. The report of a head CT at 22:25 showed ICH. PCC was requested. On this site the transfusion laboratory was shut after midnight, so PCC was kept in the emergency drugs cupboard with access restricted to the site manager and pharmacists. The PCC could not be found in the emergency drugs cupboard. The on-call pharmacist was contacted who recommended discussion with the transfusion laboratory at the main site. The main site BMS offered to transport the PCC but to prevent further delay the clinician chose to transfer the patient to the main site where PCC was issued (06:42). A repeat CT scan the next day showed extension of ICH.

This demonstrates the potential impact of delay in administration of PCC in ICH and the importance of replenishing emergency stock to ensure 24/7 availability of these emergency products.

Delays n=11

Delays were caused by poor communication, transfer of patients between departments or setting inappropriately long infusion times. Patients with intracranial bleeding experienced delays of 4, 6 and 8 hours.

Case 11d.3: Off licence use of PCC

A teenager was very unwell and admitted to the intensive care unit with an initial diagnosis of APML. The patient had coagulation disturbances and was prescribed PCC 3000IU but received 1000IU. FFP, platelets and cryoprecipitate were also given which were appropriate for AML with coagulopathy, however there is no literature to suggest PCC is indicated or appropriate in this setting.

The two commercial preparations of PCC available are currently only licensed for reversal of vitamin K antagonists. There is published evidence for benefit in haemorrhage in patients on DOAC (Hitchcock et al. 2021, Milioglou et al. 2021, Milling et al. 2021, Nederpelt et al. 2021), however there are specific reversal agents for DOAC (Cuker et al. 2019, Gomez-Outes et al. 2021) demonstrated to be of benefit in ICH (Vestal et al. 2022). PCC carry a risk of thrombosis and are relatively contraindicated in the setting of disseminated intravascular coagulation.

PCC (two different products available) have been used off label in a variety of other settings (Tanaka et al. 2021), particularly cardiac surgery (Katz et al. 2022, Santana and Brovman 2022).

Case 11d.4: Long delay in treatment for ICH with staffing and communication issues

A patient on warfarin presented with frontal ICH. CT confirmed this diagnosis 21 hours after admission. After rapid discussion with the haematologist at 17:00, PCC was requested and issued at 17:40. This plan was not communicated to the ward staff until 21:00. The ward was very busy and short-staffed with many sick patients. The need for additional staff was escalated without success. The patient was difficult to cannulate, and the PCC was given at 01:50 the next morning (about 8 hours from the decision) and with a slow rate as 1500IU took over 1 hour and 50 minutes to administer.

Additional factors included unfamiliarity of staff with PCC prescription and administration.

Learning points

- Medical and nursing staff working in emergency departments and medical/surgical admissions units should be trained in the use of PCC so that it can be administered without delay for specific anticoagulant reversal in the face of major haemorrhage
- The staff should be aware of the indications and also have clear information about how to administer it
- PCC should be rapidly accessible, and consideration given to keeping a stock in the ED (note that this blood product must be fully traceable)
- Immediate reversal of anticoagulant should take place (and certainly within an hour) especially in cases of suspected ICH



Commentary

Fixed dose PCC

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). More recently haemostatic efficiency was shown. In an open-label, multicentre, randomised clinical trial, patients with non-intracranial bleeds requiring VKA 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. 2021). 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.

Use of PCC for DOAC reversal

PCC may also be used for DOAC (Sweidan et al. 2020). Canadian authors recommend the specific antidote idarucizumab 5g for a patient on dabigatran. For a patient on a Xa inhibitor (apixaban, rivaroxaban), PCC 2000IU is recommended; if significant bleeding persists after 1 hour, a second dose of 2000IU of PCC should be considered. While not approved in Canada, a specific antidote to Xa inhibitors, andexanet alfa, has also been used in these situations as a continuous infusion (Callum et al. 2021).

Reversal of oral anticoagulation in patients with ICH has been reviewed noting the importance of rapid treatment (Kuramatsu et al. 2019). A meta-analysis of reversal agents (PCC, idarucizumab and andexanet) for bleeding related to DOAC evaluated 60 studies with 4735 patients. Mortality of those with ICH was 20%; effective haemostasis was achieved in 75-81% and was similar for all agents and a particularly high thromboembolism rate was noted for andexanet (Gomez-Outes et al. 2021). New agents are in development including ciraparentag, a small molecule that works against several anticoagulant agents (Ansell et al. 2022).

Near miss cases n=1

An elderly woman had her weight incorrectly recorded resulting in an inappropriately high dose of PCC. Fortunately, this was recognised, and the prescription revised down to the correct dose.

Conclusion

PCC is an important treatment for immediate reversal of vitamin K antagonists and other oral anticoagulants and should be given immediately once a decision is made to reverse anticoagulant effect. All clinical 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, reconstitute, and administer PCC. Delays can contribute to patient death.



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