11d Incidents Related to Prothrombin Complex Concentrate (PCC) n=21

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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

- Failure to administer PCC in a timely manner contributes to patient deaths
- Lack of clear understanding of the processes involved in ordering, procuring, and administering PCC has been identified as a common factor in the delays reported
- PCC dosing errors continue to be reported

Recommendations

- PCC are used mainly for oral anticoagulant reversal in an elderly vulnerable population. The ED should ensure they have a protocol for their use with clear instructions for dose and administration, and ensure that staff are appropriately trained in their use
- Use of PCC should be regularly audited for timeliness and appropriateness

Action: Medical directors of acute NHS Trusts/Health Boards

Introduction

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 ICH are at high risk of death or serious sequelae and require urgent anticoagulant reversal.

PCC incidents were reported mainly in an elderly population, median age 71 years. There were 4 patients under 60 years of age. There were 12/21 reports of delayed PCC infusion. Other errors included administration of either under or over recommended doses.

All patients were taking anticoagulants, either warfarin or apixaban/edoxaban. Ten patients had ICH (8 delayed infusions and 2 received less than the recommended dosage).

Deaths related to transfusion n=2

There were 2 deaths possibly related (imputability 1) to failure to administer PCC in patients with ICH, both aged >80 years.

Case 11d.1: Failure to administer PCC to an elderly man with ICH

A request was made from the ED to the transfusion laboratory to issue PCC 1000IU to reverse warfarin for a patient with an acute subdural haematoma resulting from a fall. PCC was issued at

00:58 but never collected. At 12:25 the PCC was returned to stock by the transfusion laboratory. A verbal handover in the ED stated that the patient had received the PCC and was also documented wrongly in the patient notes. Failure to give PCC was considered contributory to his death.

Case 11d.2: Failure to give PCC for ICH due to misunderstanding of a new IT system

An elderly man on edoxaban for AF presented to the ED with a history of a fall at home. He sustained another fall in a cubicle in the ED hitting his head. A CT scan of his brain demonstrated ICH. PCC was prescribed on the new electronic patient record system (which had only been in use for a month) at 17:56 however the request was not automatically received in the laboratory. PCC was not issued until nearly 4 hours later at 21:39 when the laboratory was contacted by telephone. This delay was considered contributory to the patient's death.

The staff considered that training for the new system had been rolled out too rapidly and was inadequate.

Major morbidity n=2

Case 11d.3: Life-threatening delay in administration of PCC for GI haemorrhage

A woman in her 50s on warfarin (metallic heart valves) presented to the ED with melaena and a Hb of 48g/L. PCC was authorised by the on-call haematologist at 06:30 but not requested until much later, at 17:55. The patient was topped up with red cells but failed to receive PCC as the INR result was delayed (coagulation analyser recorded INR as >10 but was recorded on LIMS as 'unable to analyse' in error). She developed haemodynamic instability requiring transfer to ICU for inotropic support. Endoscopy was eventually done at 02:00.

A review identified the following concerns:

- Lack of understanding by both admitting and ward teams of the importance of immediate reversal of warfarin in the context of life-threatening bleeding
- Failure to appreciate that the risk of bleeding far outweighs the risk of thrombosis so the advice from cardiology consultant to the ward team that the INR should not be less than 2 was poor
- Delayed reporting of INR result
- Poor communication between the haematology consultant and the night team about administration of PCC and vitamin K

Case 11d.4: Incomplete dose of PCC given without prescription for a patient with ICH

A dose of 3000IU PCC was advised by the consultant haematologist for a patient with ICH; this correct dose was issued from the transfusion laboratory. At 21:58 the nursing notes documented that 3000IU had been given, but only 2000IU was given and not correctly recorded by an agency nurse working in a busy ED. The patient was admitted to ICU and made a full recovery. A vial of 1000IU PCC was returned to laboratory from ED 12 days after issue.

Delays n=12

Delays were caused by poor communication, transfer of patients between departments or setting inappropriately long infusion times. Patients with ICH experienced delays up to 12 hours.

Case 11d.5: Delayed PCC administration for ICH

A man in his 70s on anticoagulants for AF and with left sided weakness arrived in the ED at 02:01. At 07:15 it was noted that the patient had a long wait in ED. A CT scan showed ICH. At 10:40 the haematology registrar advised PCC which was issued, but not administered until 2 hours later, 11 hours after admission. There were delays in the prescribing, ordering, collection, and administration of the drug due to lack of knowledge (new nurse and agency nurse looking after the patient).

Case 11d.6: Delay in adequate reversal of anticoagulation following pelvic fracture

An elderly lady fell sustaining a fracture of her pelvis. She was on warfarin for AF and was admitted at 05:55. Scanning suggested active bleeding and at 08:21 the MHP was activated; a haematology registrar advised an inappropriately low dose of PCC (15IU/kg). A corrected dose of 50IU/kg was given 3 hours later. Death was not thought related to the suboptimal first PCC dose.

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

Additional cases can be found in the supplementary information on the SHOT website (https://www.shotuk.org/report-summary-and-supplement-2022/).

Learning points

- Medical and nursing staff working in the ED and medical/surgical admissions units should be trained in the use of PCC so that it can be administered without delay for anticoagulant reversal in the face of major haemorrhage
- 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?

The two PCC are currently only licensed for reversal of vitamin K antagonists. There is published evidence for benefit in haemorrhage in patients on DOAC (see references in Annual Report for 2021). There are specific reversal agents for DOAC demonstrated to be of benefit in ICH (Vestal et al. 2022).

Continued confusion about dose and rate of infusion suggest that a fixed dose regimen might be safer. The literature was reviewed in the Annual SHOT Report for 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. 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).

Ciraparantag is a new reversal agent in trial, a small synthetic molecule. In two randomised placebo-controlled, dose-ranging trials in normal adults, treated with either apixaban or rivaroxaban, haemostasis was assessed by whole blood clotting time. This agent resulted in dose-dependent reversal of both agents with minimal side effects. (Ansell et al. 2022).

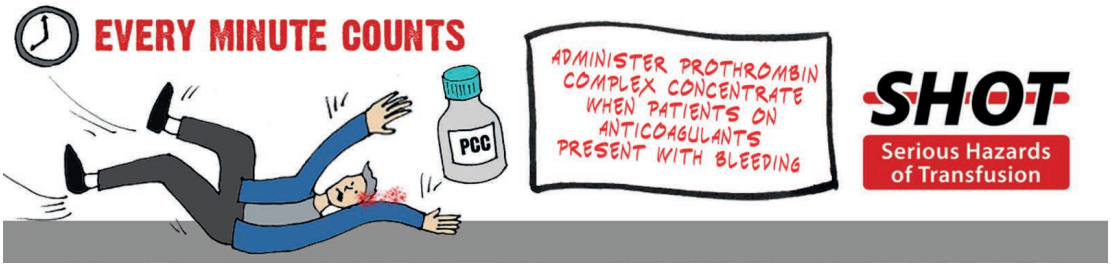
Near miss cases n=1

Two vials of PCC had transposed compatibility labels after a printer had been jammed; the labels were re-printed and applied to the wrong vials. The error was discovered at the pre-administration checks and the vials returned to the laboratory for re-labelling.

Conclusion

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. 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 and how to administer PCC. Delay can contribute to death.

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.



References

Ansell J, Bakhru S, Laulicht BE, et al. Ciraparantag reverses the anticoagulant activity of apixaban and rivaroxaban in healthy elderly subjects. *Eur. Heart J.* 2022;**43**:985-992 doi: 10.1093/eurheartj/ehab637

Gomez-Outes A, Alcubilla P, Calvo-Rojas G, et al. Meta-Analysis of Reversal Agents for Severe Bleeding Associated With Direct Oral Anticoagulants. *J. Am. Coll. Cardiol*. 2021;**77**(24): 2987-3001.

SHOT. Preventing transfusion delays in bleeding and critically anaemic patients SHOT/2022/001 (2022) https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103190 [accessed 28 April 2023].

Vestal ML, Hodulik KJ, Mando-Vandrick ML, et al. Andexanet alfa and four-factor prothrombin complex concentrate for reversal of apixaban and rivaroxaban in patients diagnosed with intracranial hemorrhage. *J. Thromb. Thrombolysis.* 2022;**53**(1):167-175.