Reducing delays to administration of prothrombin complex concentrate in patients with vitamin K antagonist-related intracerebral haemorrhage

Abstract

Background/Aims Four-factor prothrombin complex concentrate is the first-line treatment in vitamin K antagonist-related intracerebral haemorrhage. Early administration is associated with improved patient outcomes. A quality improvement project investigated delays in prothrombin complex concentrate administration in vitamin K antagonist-related intracerebral haemorrhage in order to reduce the time from computed tomography scan confirming intracerebral haemorrhage to prothrombin complex concentrate administration (scan-to-needle time).

Method Twenty patients were identified by retrospective audit over a 3-year period. The median scan-to-needle time for prothrombin complex concentrate was 156 minutes. Several points of delay were identified, including contacting both haematology and transfusion departments for prothrombin complex concentrate dosing and dispensing.

Following this audit, interventions were brought in which included the introduction of a protocol with a prothrombin complex concentrate dosing algorithm, negating the need to contact haematology before administration. A dedicated supply of prothrombin complex concentrate was given to the stroke unit avoiding the need to contact the transfusion service.

Results A re-audit showed a 68% reduction in median scan-to-needle time from 156 minutes to 49 minutes. Prospective data collection is ongoing.

Key words: Intracerebral haemorrhage; Prothrombin complex concentrate; Stroke; Vitamin K antagonist; Warfarin

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Introduction

Vitamin K antagonist-related intracerebral haemorrhage accounts for around 10–20% of all cases of intracerebral haemorrhage (Parry-Jones et al, 2015) and carries a worse prognosis than intracerebral haemorrhage unrelated to vitamin K antagonist because of a doubled risk of haematoma expansion (Brouwers et al, 2014). Haematoma expansion in intracerebral haemorrhage is an important indicator of neurological deterioration and a poor prognostic factor (Davis et al, 2006). Vitamin K antagonist-related intracerebral haemorrhage has a high case fatality. In patients with international normalised ratio between 2 and 3 at the time of intracerebral haemorrhage, the 3-month mortality rate is 52% (Meretoja et al, 2012).

Four-factor prothrombin complex concentrate is currently recommended in the National Clinical Guideline for Stroke as first-line treatment in cases of vitamin K antagonist-related intracerebral haemorrhage (Royal College of Physicians, 2016) as it is the most effective agent to achieve timely reversal of vitamin K antagonist and reduction of international normalised ratio (Steiner et al, 2016). The speed of administration of prothrombin complex concentrate is important because the faster the reduction in international normalised ratio, the lower the risk of haematoma expansion (Kuramatsu et al, 2015). The need for rapid treatment of acute ischaemic stroke is now well established, with protocols for administration of key therapies including intravenous thrombolysis and thrombectomy. However, there is less recognition of the potential importance of rapid treatment in patients with intracerebral haemorrhage.

Reducing door-to-needle times for administration of prothrombin complex concentrate has become a focus for improving outcomes for patients with intracerebral haemorrhage.

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A quality improvement initiative achieved a 50% reduction in door-to-needle times for prothrombin complex concentrate administration and a significant reduction in 30-day case fatality in patients with intracerebral haemorrhage by implementing three main changes within the stroke service: point-of-care international normalised ratio testing, immediate supply of prothrombin complex concentrate in the emergency department, and a vitamin K antagonist-related intracerebral haemorrhage protocol that negated the need for discussion with haematologists (Parry-Jones, 2015; Paroutoglou and Parry-Jones, 2018).

Many of these implemented changes are potentially translatable to other centres. The authors therefore developed a quality improvement initiative to improve the management of vitamin K antagonist-related intracerebral haemorrhage by reducing prothrombin complex concentrate door-to-needle times at the University College London Hospital hyper-acute stroke unit. The authors built on the existing strategy by also implementing simulation training for treatment of vitamin K antagonist-related intracerebral haemorrhage.

The audit

Methods

The authors identified 30 patients between October 2012 and October 2015 who had radiological evidence of intracerebral haemorrhage on computed tomography, who were taking vitamin K antagonist and who had received same-day prothrombin complex concentrate treatment. Clinical notes, radiology and laboratory results were reviewed and data collected on demographics, time of admission, time of computed tomography of the head, point-of-care international normalised ratio result, laboratory international normalised ratio result, time of vitamin K administration, time of prothrombin complex concentrate administration, and details of any relevant delays.

Results

Full clinical records were available for 20 of the 30 patients. The mean age at presentation was 77 years with 11 (55%) male and nine (45%) female patients. A point of care international normalised ratio was documented in nine cases (45%) with a mean value of 2.8. Laboratory international normalised ratio on admission was available in 16 cases (80%) with a mean value of 3.0. Admission international normalised ratio was not available for two patients because the sample haemolysed, for one patient the sample was under-filled and one patient did not have an international normalised ratio sent on admission. Point-of-care international normalised ratio was documented in nine cases with a mean value of 2.8 (1dp) (range 2–4).

The median time from arrival in the emergency department to computed tomography scan was 32 minutes (range 11–222 minutes). The median time from computed tomography scan confirming haemorrhage to vitamin K administration was 64 minutes (range 18–420 minutes); the median time from scan confirming haemorrhage to prothrombin complex concentrate administration was 156 minutes (range 63–540 minutes). In three cases prothrombin complex concentrate was given after transfer to the surgical intensive care unit at the National Hospital for Neurology and Neurosurgery, as transfer to a critical care unit was considered higher priority than reversal. Nine patients died as a result of intracerebral haemorrhage.

The intervention

The primary aim was to reduce delays in the reversal of vitamin K antagonist in patients presenting with an intracerebral haemorrhage. Based on the results of the audit three key interventions were identified.

First, a new protocol for managing anticoagulant-associated intracerebral haemorrhage was introduced. Importantly this protocol included a clear prothrombin complex concentrate dosing algorithm, and stated that vitamin K antagonist reversal should take place before any transfer to neurosurgical intensive care at National Hospital for Neurology and Neurosurgery (Figure 1).

Second, the authors sought to eliminate delays in administration of prothrombin complex concentrate and vitamin K. After discussion with the haematology department a dedicated hyper-acute stroke unit supply of prothrombin complex concentrate was organised, rather

University College London Hospital HASU protocol for anticoagulant-associated ICH

1. Anticoagulation-associated ICH is an *emergency*

- **Rapid recognition** – always ask about anticoagulants with acute stroke symptoms *regardless of onset time*
- **Urgent scanning** – go straight to CT if safe to do so
- **ICH on scan** – initiate immediate treatment
- **Treatment must be given *before* any critical transfer to National Hospital for Neurology and Neurosurgery.** Infusion can be continued during transfer

Anticoagulants

Vitamin K antagonists: Warfarin, Sinthrome
Direct oral anticoagulants: Apixaban, rivoraxaban, edoxaban
Dabigatran: antidote available – see below

2. Give vitamin K and Octaplex for ICH with warfarin or Sinthrome

- **Check point-of-care INR** using Roche Coaguchek device (plus lab INR for audit only)
- **Give vitamin K** at 10 mg IV stat (in thrombolysis nurse bag)
- **Dose Octaplex** based on patient weight and point-of-care INR (see table below)
- **Prescribe Octaplex** on A&E prescription chart
- **Collect Octaplex** from HASU fridge
- **Draw up Octaplex** and administer over 15 minutes (regardless of dose) in a driver

	<60 kg	60–80 kg	>80 kg
INR 1.3–3.9	1000u	1500u	2000u
INR 4.0–6.0	1500u	2000u	2500u
INR >6	3000u	3000u	3000u
Clinically unstable requiring anaesthetist support and INR >1.2	3000u	3000u	3000u

3. Thrombolysis call Nurse to record and re-order HASU stock of Octaplex

- Fill out the tracing forms in all used boxes with patient detail label, date/time, and batch label from vial
- Place tracing forms in the blood product tracing boxes in A&E or HASU
- Return any unused boxes to HASU fridge
- Phone blood transfusion to inform them of use of HASU Octaplex
- Transfusion will send courier with new stock, who will also take unused stock back
- Record details and times as per thrombolysis for door to needle audit

Blood Transfusion:
Extn: 78522/78523
Bleep: 7060

4. Thrombolysis call SpR to inform haematology and recheck INR after treatment

- Ensure Haematology SpR informed of case after Octaplex given – on call SpR (bleep 7050); via switch out-of-hours
- Repeat INR 30 minutes and 6 hours after end of infusion of Octaplex (laboratory INR, not point-of-care)
- If repeat INR >1.2, seek Haematology advice on further management
- Consider future anticoagulation requirements in high risk cases

5. ICH on direct oral anticoagulants (apixaban, dabigatran, rivaroxaban, edoxaban)

- Contact Haematology on call registrar (bleep 7050); via switch out-of-hours; for dabigatran antidote and advice for all other direct oral anticoagulants
- Send urgent coagulation screen, thrombin time (dabigatran only) and anti-Xa assay (apixaban, rivaroxaban, edoxaban)

Figure 1. Protocol for anticoagulant-associated intracerebral haemorrhage. CT = computed tomography; HASU = hyper-acute stroke unit; ICH = intracranial haemorrhage; INR = international normalised ratio; Octaplex = prothrombin complex concentrate.

than needing to contact the transfusion service to dispense the drug. Vitamin K was also added to the thrombolysis bag that is brought to each thrombolysis call.

Third, simulation training on management of vitamin K antagonist-related intracerebral haemorrhage was introduced to fully embed this protocol among staff and to increase awareness of the urgency of vitamin K antagonist reversal in intracerebral haemorrhage. This training was given to doctors and nurses in the hyper-acute stroke unit. There was further training for thrombolysis nurses including demonstration vials of prothrombin complex concentrate to familiarise nurses with drug preparation.

The re-audit

Methods

For the re-audit, data collection was prospective over an 11-month period (from July 2016 to May 2017) on the hyper-acute stroke unit at University College London Hospital. All patients who received prothrombin complex concentrate were included in the study.

As previously, the following information was obtained from patient notes and the electronic results system: demographics, time of admission, time of computed tomography of the head, point-of-care international normalised ratio result, laboratory international normalised ratio result, time of vitamin K administration, time of prothrombin complex concentrate administration, and details of any relevant delays.

Results

Following the introduction of these interventions, prospective data were collected over an 11-month period (July 2016 to May 2017). Twelve patients presented with vitamin K antagonist-related intracerebral haemorrhage during this period.

The median scan to needle time for prothrombin complex concentrate fell from 156 minutes (pre-intervention) to 49 minutes (a 68% reduction). In cases where transfer to a neurosurgical centre was required, all patients received prothrombin complex concentrate at University College London Hospital before transfer to the National Hospital for Neurology and Neurosurgery. The median scan to vitamin K administration time was 53 minutes post-intervention (64 minutes pre-intervention) (Figure 2).

Discussion

The results of the initial audit were striking in that no patients received prothrombin complex concentrate less than 60 minutes after identification of intracerebral haemorrhage. The authors believe that the main factors contributing to this delay were:

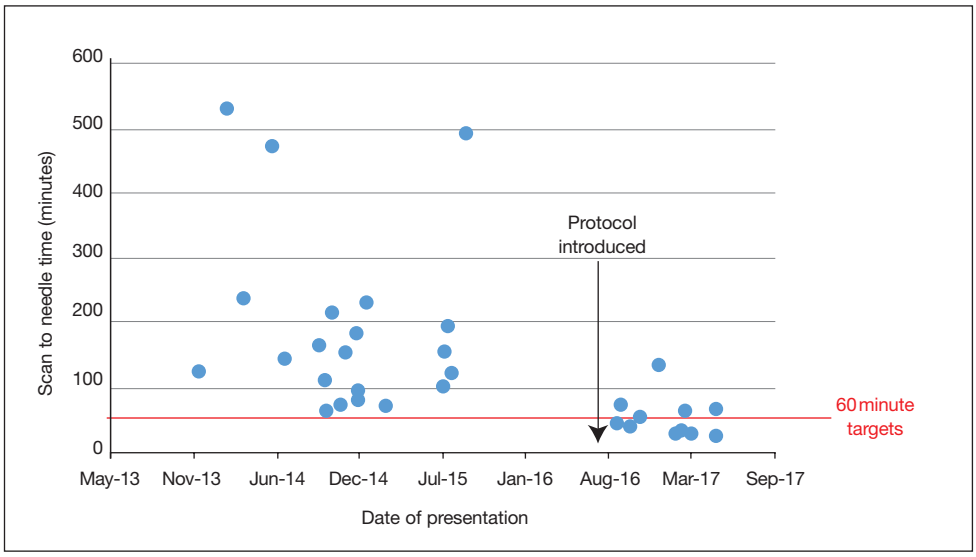

Figure 2. Running chart showing scan to needle time for prothrombin complex concentrate administration in patients with vitamin K antagonist-related intracerebral haemorrhage.

1. Limited knowledge of the urgency of vitamin K antagonist reversal in vitamin K antagonist-related intracerebral haemorrhage despite rapid diagnosis by computed tomography scan
2. The requirement for case-by-case discussions with the haematology department for advice on prothrombin complex concentrate dosing and for authorisation of prothrombin complex concentrate use
3. A lack of familiarity among nursing staff in preparing and administering prothrombin complex concentrate because of the infrequency of vitamin K antagonist-related intracerebral haemorrhage (around one case per month).

Furthermore, in three cases, the delay was because the patient needed to be transferred to a critical care unit, which was considered higher priority than reversal of vitamin K antagonist.

Several interventions were introduced with the aim of reducing delays in administration of prothrombin complex concentrate in cases of intracerebral haemorrhage. In line with those used in the successful Salford Royal quality improvement initiative (Parry-Jones, 2015) a vitamin K antagonist-related intracerebral haemorrhage protocol was introduced that negated the need for discussion with haematologists, and an immediate supply of prothrombin complex concentrate within the hyper-acute stroke unit was organised. This removed the need for prothrombin complex concentrate to be couriered from the transfusion lab which is off site. In addition, the authors increased awareness of the importance of rapid vitamin K antagonist reversal in patients with vitamin K antagonist-related intracerebral haemorrhage and introduced a vitamin K antagonist-related intracerebral haemorrhage scenario into simulation training attended by both current and new members of staff. Vitamin K antagonist-related intracerebral haemorrhage simulation training has been repeated several times throughout the year and has formed part of the induction for new staff joining the department.

This project has shown that improvement in time to prothrombin complex concentrate administration in patients with vitamin K antagonist-related intracerebral haemorrhage can be achieved in a central London hyper-acute stroke unit. The vitamin K antagonist-related intracerebral haemorrhage protocol has undergone subsequent review and has been adapted to include guidance on managing intracerebral haemorrhage in patients receiving direct oral anticoagulants. The pragmatic steps of securing a dedicated supply of prothrombin complex concentrate and a hyper-acute stroke unit-specific protocol can reduce scan-to-needle times, and the authors anticipate that this will be applicable to cases of intracerebral haemorrhage in patients taking direct oral anticoagulants. As the number of patients with atrial fibrillation on anticoagulation rises, improving the management of intracerebral haemorrhage in this setting is essential (Lane et al, 2017).

Prospective data collection is ongoing to monitor whether the positive changes seen in the period studied are sustained in the longer term. It is hoped that by continued education through regular simulation sessions staff will be equipped to manage these cases efficiently and safely.

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Conflicts of interest

The authors declare no conflicts of interest.

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Key points

- Vitamin K antagonist-related intracerebral haemorrhage has a high case fatality rate. Reducing the rate of haematoma expansion by prompt administration of prothrombin complex concentrate is associated with improved outcomes.
- The authors identified multiple factors contributing to delays in the administration of prothrombin complex concentrate in patients with vitamin K antagonist-related intracerebral haemorrhage at a tertiary UK hyper-acute stroke unit.
- Introducing a protocol including guidance on dosing negated the need to consult haematology before administering prothrombin complex concentrate, while providing a dedicated stroke unit supply of prothrombin complex concentrate avoided the need to consult the transfusion laboratory in the acute setting. Staff also attended simulation training to fully embed the protocol in the department.
- A 68% median reduction in scan-to-needle time was achieved (from 156 to 49 minutes) for prothrombin complex concentrate administration in patients with vitamin K antagonist-related intracerebral haemorrhage. Prospective data collection is ongoing to ensure that this positive change is sustained.

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