Improving the use and timeliness of anticoagulation reversal for warfarin related intracranial haemorrhage

Carl Hanger, John Geddes, Tim Wilkinson, Michele Lee, Scott Pearson, Andrew Butler, Krishna Badami

ABSTRACT

BACKGROUND: Warfarin-related intracranial haemorrhage (WRICH) is a life-threatening complication of warfarin use. Rapid and complete reversal of the coagulopathy is required. Reversal protocols which include prothrombin complex concentrates (PCC) are now recommended. We report on a quality improvement project to implement and refine such a protocol.

METHODS: Retrospective and then prospective audits of all WRICH patients presenting to a single centre. The protocol development and subsequent refinements are described. Outcomes included times to scanning, treatment and overall door-needle times, as well as use of PCC.

RESULTS: Across the three cohorts, use of PCC increased over time from 15% to 100% of eligible patients (p<0.001). There were significant improvements in median time to scanning (1.9 to 1.5 to 1.3 hours, p=0.03) and median door-needle times (4.5 to 2.9 to 1.9 hours, p=0.018). Key steps in the change process included (1) identifying need for change, (2) utilising senior clinical opinion leaders, (3) using “Plan-do-study-act” cycles, (4) involvement of all relevant stakeholders, (5) having a broad implementation and education plan, (6) a “change friendly” environment and (7) collaborating across departments.

CONCLUSION: The introduction (and revisions) of an anticoagulation reversal strategy for WRICH has led to increased PCC use and reduced times to both diagnosis and treatment. Further work is required to improve door-needle times and monitoring.

Warfarin is commonly used to prevent thromboembolism in conditions such as atrial fibrillation. Haemorrhages are potential complications of warfarin therapy and warfarin related intracranial haemorrhage (WRICH) is one of the most devastating of these. WRICH constitute between 10–15% of all intracerebral haemorrhage (ICH). The 40–68% early mortality in WRICH is higher than primary ICH and there is severe disability in many survivors. Prolonged bleeding due to the coagulopathy leads to haemorrhagic expansion (HE) and increased final volume of the ICH. Both HE and volume of bleed are independent predictors of poor outcomes.

While guidelines recommend urgent reversal of anticoagulation in WRICH, there are still a range of strategies suggested, possibly reflecting the paucity of randomised controlled data available. The main therapeutic options include vitamin K, fresh frozen plasma (FFP), recombinant factor VIIa and prothrombin complex concentrates (PCC) or combinations of these. Historically, FFP together with Vitamin K has been the mainstay of reversal in the US, whereas treatment that includes PCC has become more commonly used elsewhere. Reversal with FFP is readily available, but takes time to prepare and administer, and requires larger plasma volumes for adequate reversal. Reversal of the coagulopathy is often incomplete in the first few hours after FFP. In comparison, PCCs are quick to administer, correct the international
normalised ratio (INR) rapidly and are lower volume infusions. The use of PCC is recommended in many haematological reversal guidelines but has been less consistent in stroke literature until recently.

We recently showed an improved survival in WRICH with PCC use, and a trend to better outcomes with earlier reversal. While the time window for reversal is uncertain, it is assumed to be as soon as possible to minimise HE. In the stroke thrombolysis literature, door-to-needle times are closely monitored and minimised. Despite the mantra of “time is brain” equally applying to WRICH treatments, there has been less emphasis placed on the urgency of reversal of bleeding. Many studies report door-to-treatment times of many hours, which seem too slow for a life threatening situation. Thus both timing and completeness of reversal with treatment should be focused on.

An initial audit of anticoagulation reversal in WRICH at our institution (1996–2006) revealed very poor use of reversal strategies, with little standardisation of practice. Doses of vitamin K and FFP varied markedly and PCC was not used at all. Because of the inadequacy of our anticoagulation reversal, we developed a local protocol to emphasise the importance of both adequacy and urgency of reversal. There was a specific intent of increasing the use of PCC. A variety of strategies were employed over time to introduce this protocol and then refine it. A repeat audit showed that while there was a successful uptake of the PCC based protocol, with improved patient outcomes, there remained significant delays (median 2.7 hours from CT to PCC). In response to these audit findings, further refinements in both protocol and service delivery have been made.

We wish to share this process of change in order to help others also implement change. The aims of this quality improvement project are to (1) describe the protocol changes made, (2) describe the strategies used to change clinical behaviour and (3) to assess the effectiveness of strategies in reversing anticoagulation in WRICH, using key outcome measures.

**Methods**

**Context**

Christchurch, New Zealand is a city with one acute hospital and two rehabilitation hospitals (population catchment of 520,000), to which all ICH patients are admitted. The acute site has all the acute services expected in a tertiary referral hospital, including a neurosurgical unit and an acute stroke unit (ASU) established in 2004. WRICH is a relatively uncommon but serious condition presenting to an Emergency Department (ED) with annual attendances of 90,000.

![Figure 1: Timeline.](image-url)
Study timeline

This paper reports on a series of retrospective and then prospective audits of the adequacy of coagulopathy reversal in all patients presenting with WRICH to Christchurch (Figure 1). An initial audit from 1996 to 2006 inclusive (data not shown) showed inadequate reversal and no PCC use. As a result of that audit, a protocol for WRICH reversal was developed and the results re-audited (2nd audit) and published. Further refinements of the protocol were required and a prospective 3rd audit of all WRICH was completed for July 2010–Oct 2013.

The results presented here are a combination of the previously published data for 2004–2011 and subsequent data (until Oct 31, 2013) with an emphasis on treatment protocols in place at the time (no protocol [< 1/2/09], after first protocol [1/2/09–31/12 inclusive] or post Emergency Department (ED) protocol [1/2/12–31/10/13]), with a view to documenting and explaining any changed practice over time.

Case finding

ICH patients were identified from discharge coding data, using international classification of diseases (ICD-10) coding of ICH (I61 or I62.9). These data were cross-checked with the prospective stroke register in ASU. The electronic and laboratory records for each person with an ICH were then reviewed to identify those with a WRICH. A WRICH was defined if there was (1) an ICH confirmed on imaging or post-mortem studies (includes those with intraventricular haemorrhage alone) and (2) an elevated INR >1.2 on admission and (3) patient taking warfarin at the time of stroke. The clinical notes of each of these WRICH patients were reviewed to collect data on treatments given.

Exclusions were: ICH secondary to trauma or thrombocytopenia, thrombolysis or heparin-related ICH, haemorrhagic transformation of an infarct, subdural and subarachnoid bleeding, asymptomatic micro-bleeds and patients presenting to hospital late (>24 h of onset). Some patients were clearly dying from the outset and were given palliative cares only. Patients whose clinical notes stated palliative intent at outset were not included in the analyses of treatments or timeliness.

Outcome measures

‘ED arrival-scan’ times measure time to obtain a diagnosis, whereas ‘scan-treatment’ times reflect the urgency of reversal. The combined ED arrival-treatment times reflect the overall efficiency of both diagnosis and treatment, equivalent to “door-to-needle time” for thrombolysis.

The volume of ICH was calculated using standard ABC/2 formula from acute CT scans.

Times of presentation to ED, scanning and blood tests were taken from ED clinical records and from times recorded on the images or blood test results. For each reversal agent given, the administration time as recorded by the administering nurse was used, rather than when it was prescribed.

The local ethics committee considered these studies as audits and did not require formal ethics committee review (URB/10/EXP/016).

Statistics

Between group comparisons for continuous variables were undertaken with ANOVA and for categorical variables were undertaken with the Chi-square test.

Results

Stages of protocol development

Development of first protocol

Immediately following the initial audit (unpublished) which showed inadequate reversal of the coagulopathy in WRICH patients, a group involving haematologists, general and stroke physicians was convened to develop the first WRICH reversal protocol (Appendix). This was based on general haemostasis guidelines and emphasised the urgent use of PCC and reduced the role of FFP. This advice differed from some ICH specific guidelines at the time, which did not specify which agents should be used. This protocol was widely disseminated through resident medical officer (RMO) teaching sessions, discussion with General Medicine senior medical officers (SMO) and inclusion in local handbooks (both paper and electronic versions). There was a grand round presentation to a broad audience of physicians, RMOs and other clinical staff within the hospital.
During the implementation phases of the first protocol the group identified several potential issues which might contribute to delays. These included: (1) clinicians attitudes (“nothing will alter outcome”), (2) procedural (delays in access to CT scanning, a requirement to contact on call haematologist or blood transfusion specialist and to have INR result before being able to access PCC) and (3) educational (staff unsure how to access or give PCC, or how fast to give it).

**Development of ED protocol**

In response to the results of an audit of the first protocol, a different approach, with wider clinical representation, was deemed appropriate. A presentation to all ED physicians and discussion with the blood transfusion service resulted in the convening of a group focused on urgent reversal within ED. There was representation from stroke physicians, ED and the blood transfusion service. Similarities to the thrombolysis pathway for ischaemic stroke, where minimising delays is crucial, were made. Initial thoughts were to develop a “reversal kit” to accompany the patient to CT scanning, similar to the thrombolysis kit.

At that time, perceived critical barriers causing delays included: (1) the location where reversal occurs (ED or ASU) and who delivers it, (2) need for INR result before PCC released by New Zealand Blood Service (NZBS), (3) perception of less urgency for scanning by ED staff for some patients (eg less unwell with higher Glasgow coma scale (GCS)), (4) need to telephone on call haematology or NZBS specialist for permission to use PCC, (5) delivery of PCC to ED from NZBS and (6) practical issues with administering PCC to patient. It was apparent that these predominantly ED-based issues were different from those addressed in our first protocol when the focus was on ASU staff.

The revised protocol took several iterations to get to its final form (Appendix). Steps which were important in the protocol development included the following.

- An urgent CT scan should be considered for any patient who presents with a stroke syndrome and is taking warfarin.
- If ICH is seen on this urgent CT, the ED transit nurse with the patient immediately activates the “urgent reversal” pathway by faxing a blood bank request form (with “URGENT warfarin reversal haemorrhage” sticker attached to it) to NZBS and phoning ED to prepare for the reversal. For practical reasons, it was not deemed feasible to start the infusion in the scanning room and the consensus was for patient to immediately return to ED for this. Thus, the urgent reversal “kit” became a flow chart with the appropriate fax and phone numbers included and a blood bank request form (marked “URGENT warfarin reversal haemorrhage”).
- Because WRICH is life threatening, it was unanimously agreed that urgency was paramount and systemic barriers such as the requirements for a raised INR result and a phone call to the blood specialist were removed. On return to ED, nurses give PCC, then Vitamin K, before starting FFP infusion (FFP needs time to thaw). There were some concerns about the duration of PCC infusion, with some existing protocols stating maximum infusion rate of 3ml/minute. After deliberation, the ED protocol allows for an initial slow push, followed by an increased rate of infusion up to 10ml/minute. This enabled the entire PCC dose to be delivered in 10–15 minutes via syringe pump.
- To minimise time spent in ED, the ASU would prepare a bed during the PCC infusion and then “pull” the patient from ED as soon as possible after this. This might occur before FFP was given.

**Practical implementation of ED protocol**

Our initial discussions for the ED protocol did not involve the radiologists, and the first few patients presenting with a stroke syndrome and on warfarin exposed this oversight. However, it was quickly rectified.
### Table 1: Demographic variables of the three cohorts.

<table>
<thead>
<tr>
<th></th>
<th>No protocol</th>
<th>First protocol</th>
<th>ED protocol</th>
<th>Between group comparisons (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=59)</td>
<td>(n=53)</td>
<td>(n=25)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (mean, years) (IQR)</strong></td>
<td>77.9 (75–84)</td>
<td>77.8 (73–83)</td>
<td>75.3 (69–84)</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Gender (% female)</strong></td>
<td>49%</td>
<td>38%</td>
<td>28%</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Indication for warfarin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>47 (80%)</td>
<td>42 (79%)</td>
<td>15 (60%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Prosthetic heart valve</td>
<td>3 (5%)</td>
<td>6 (11%)</td>
<td>2 (8%)</td>
<td></td>
</tr>
<tr>
<td>Venous thrombo-emboli</td>
<td>4 (7%)</td>
<td>3 (6%)</td>
<td>4 (16%)</td>
<td></td>
</tr>
<tr>
<td>Systemic emboli</td>
<td>2 (3%)</td>
<td>0</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (5%)</td>
<td>2 (4%)</td>
<td>3 (12%)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean INR on presentation (range)</strong></td>
<td>2.8 (1.6–8.8)</td>
<td>2.8 (1.6–6.1)</td>
<td>3.4 (1.3–11.9)</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>ICH volume -mean (ml)</strong></td>
<td>24.1 (11.1)</td>
<td>29.4 (10.1)</td>
<td>37.5 (32.0)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>ICH volume</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small (&lt;5ml)</td>
<td>15 (25%)</td>
<td>12 (23%)</td>
<td>4 (16%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Medium (5–30ml)</td>
<td>24 (41%)</td>
<td>21 (40%)</td>
<td>7 (28%)</td>
<td></td>
</tr>
<tr>
<td>Large(&gt;30ml)</td>
<td>15 (25%)</td>
<td>18 (34%)</td>
<td>12 (48%)</td>
<td></td>
</tr>
<tr>
<td><strong>Location of ICH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brainstem</td>
<td>0</td>
<td>2 (4%)</td>
<td>0</td>
<td>0.30</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>11 (19%)</td>
<td>4 (7%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Deep</td>
<td>22 (37%)</td>
<td>24 (45%)</td>
<td>11 (44%)</td>
<td></td>
</tr>
<tr>
<td>Lobar</td>
<td>21 (36%)</td>
<td>21 (40%)</td>
<td>11 (44%)</td>
<td></td>
</tr>
<tr>
<td>IVH alone</td>
<td>5 (8%)</td>
<td>2 (4%)</td>
<td>2 (8%)</td>
<td></td>
</tr>
<tr>
<td><strong>ICH score mean (median)</strong></td>
<td>2.0 (2)</td>
<td>1.8 (2)</td>
<td>2.0 (2)</td>
<td>0.80</td>
</tr>
<tr>
<td><strong>Initial GCS mean (median)</strong></td>
<td>11.8 (14)</td>
<td>12.0 (14)</td>
<td>12.0 (14)</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>Palliated from onset in ED</strong></td>
<td>13 (22%)</td>
<td>18 (34%)</td>
<td>2 (8%)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Patients with intraventricular</strong></td>
<td>30 (51%)</td>
<td>29 (55%)</td>
<td>14 (56%)</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Acute hospital length of stay</strong></td>
<td>7.3 (5.8)</td>
<td>6.4 (6.4)</td>
<td></td>
<td>0.64</td>
</tr>
<tr>
<td><strong>Total hospital length of stay</strong></td>
<td>22.2 (19.4)</td>
<td>19.5 (19.5)</td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Admitted from</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community</td>
<td>56 (95%)</td>
<td>47 (89%)</td>
<td>25 (100%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Residential care</td>
<td>3 (5%)</td>
<td>6 (11%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Deaths in hospital</td>
<td>30 (51%)</td>
<td>23 (43%)</td>
<td>11 (44%)</td>
<td>0.70</td>
</tr>
</tbody>
</table>
through direct discussions between ED and radiology specialists. There was added value for the radiologists, as the protocol ensured a rapid “pull” of the patient from the scanner back to ED, thus reducing delays in the scanner.

Education about the revised protocol was achieved in several different ways. There were teaching sessions for the following groups: ED nurses, ASU staff (medical and nursing) and general physicians. It has been incorporated into local acute medicine, ED and stroke guidelines. There has been a further grand round presentation. ED nurses developed a one-page practical guide for PCC administration, which includes preparation and infusion rates. Discussions between clinicians about cases where there had been delays raised awareness of the protocol, highlighted the urgency of treatment and contributed to the success of the protocol.

Table 2: Key outcomes for the three cohorts.

<table>
<thead>
<tr>
<th>Treatments given</th>
<th>No protocol</th>
<th>First protocol</th>
<th>ED protocol</th>
<th>Difference between cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K</td>
<td>43 (93%)</td>
<td>34 (97%)</td>
<td>21 (91%)</td>
<td>P=0.62</td>
</tr>
<tr>
<td>Prothrombin Complex Concentrates (PCC)</td>
<td>7 (15%)</td>
<td>30 (86%)</td>
<td>23 (100%)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Fresh Frozen Plasma (FFP)</td>
<td>30 (65%)</td>
<td>18 (51%)</td>
<td>16 (70%)</td>
<td>P=0.30</td>
</tr>
<tr>
<td>Median number of units FFP given (IQR)</td>
<td>2 (2–4)</td>
<td>1 (1.0–1.8)</td>
<td>1 (1.0–2.0)</td>
<td>P=0.001</td>
</tr>
<tr>
<td>Median number of treatment agents given (IQR)</td>
<td>2 (1–2)</td>
<td>2 (1–3)</td>
<td>3 (2–3)</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median time in hours (IQR)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ED arrival to scan</td>
<td>1.9 (1.3–4.0)</td>
<td>1.5 (0.9–2.6)</td>
<td>1.3 (0.8–1.9)</td>
<td>P=0.03</td>
</tr>
<tr>
<td>Scan to Vitamin K</td>
<td>1.4 (0.8–3.3)</td>
<td>1.3 (0.6–1.8)</td>
<td>0.8 (0.4–1.3)</td>
<td>P=0.08</td>
</tr>
<tr>
<td>Scan to FFP</td>
<td>2.4 (1.9–3.7)</td>
<td>2.4 (1.1–3.6)</td>
<td>2.8 (1.7–4.5)</td>
<td>P=0.89</td>
</tr>
<tr>
<td>Scan to PCC</td>
<td>3.0 (2.2–4.2)</td>
<td>2.4 (1.6–3.1)</td>
<td>1.5 (0.9–2.4)</td>
<td>P=0.14</td>
</tr>
<tr>
<td>Scan to first (any) treatment</td>
<td>1.3 (0.7–3.1)</td>
<td>1.2 (0.6–1.7)</td>
<td>0.7 (0.5–1.1)</td>
<td>P=0.03</td>
</tr>
<tr>
<td>ED arrival to first (any) treatment</td>
<td>4.5 (2.2–7.2)</td>
<td>2.9 (1.7–4.9)</td>
<td>1.9 (1.5–2.4)</td>
<td>P=0.018</td>
</tr>
<tr>
<td>ED arrival to PCC</td>
<td>5.6 (3.9–7.0)</td>
<td>4.4 (2.5–9.2)</td>
<td>2.8 (1.8–4.2)</td>
<td>P=0.08</td>
</tr>
<tr>
<td>Median time (hours) from PCC (or FFP) to first INR monitoring</td>
<td>9.8 (3.7–17.8)</td>
<td>6.1 (2.5–12.2)</td>
<td>3.3 (1.4–5.1)</td>
<td>P=0.001</td>
</tr>
<tr>
<td>INR checked at some time</td>
<td>32 (70%)</td>
<td>27 (77%)</td>
<td>16 (80%)</td>
<td>P=0.60</td>
</tr>
<tr>
<td>INR normal (&lt;1.3) on first testing</td>
<td>16 (50%)</td>
<td>23 (85%)</td>
<td>14 (88%)</td>
<td>P=0.003</td>
</tr>
</tbody>
</table>
Outcomes

There were no demographic differences between the three cohorts (Table 1), except that in the ED cohort, fewer were treated as palliative from outset.

The number of patients given PCC increased following the first protocol and again following the ED protocol (p<0.001) (Table 2). Compliance with protocol dosing of PCC (all given 25–50 IU/kg, most given 50 IU/kg) was complete in all patients (latter two cohorts). The only exceptions were in patients in whom active treatment was changed to palliation.

FFP dosing was higher in the no-protocol cohort (expected as PCC generally not used), whereas subsequent FFP use was 1–2 units, in accordance with protocol (one patient given three units due to difficulty accessing PCC), (p<0.001).

The development of the first and then ED protocols not only improved the use of PCC, but also reduced variation in time to treatment. ED to scan times were significantly faster over time (p=0.03) with greater consistency.

Time from diagnosis (scan) to treatment with individual agents showed non-significant trends toward faster treatments with Vitamin K and PCC, whereas FFP was given at similar times throughout. The time from scan to first treatment (any agent, but usually PCC or Vitamin K) was significantly faster with marked reduction in variability.

The combined time (door-needle) was faster, with significant improvements in ‘ED to first reversal (any agent)’ and a trend for ‘ED to PCC reversal’ times.

The number of patients who had some monitoring of the adequacy of reversal did not significantly alter. However, both the timeliness and the completeness of reversal (INR <1.3) did improve significantly.

Discussion

Our implementation and then refinement of a WRICH anticoagulation reversal strategy was successful in changing several components of clinical practice for this emergency condition. The most obvious success was in the increased and sustained use of PCC for anticoagulation reversal. Timeliness of scanning (diagnosis) and time to reversal also improved significantly, with much less variation in response times. Both the use of PCC and the speed of reversal have been shown to be associated with better outcomes after WRICH.12

The improvements in overall ‘ED arrival to treatment’ times reflect more efficient diagnosis and treatment, equivalent to the ‘door-needle time’ for thrombolysis.17 These improvements fit with the ‘time is brain (lost)’ concept and while the times have improved and are better than some reports,21,13 there is no room for complacency. Earlier and complete reversal is likely to be better14 and ongoing quality improvements to reduce door-needle times are needed. Systemic barriers to sourcing PCC from the blood bank have been reduced, similar to other studies.20,21 To minimise any delays and to keep it simple, our protocol deliberately did not depend on determining the INR, in contrast to a recent guideline.22 Point of care INR testing in the ED is an alternative approach to minimise delays21 but was not used here. The protocol also encouraged that PCC reversal should be given as soon as possible in ED, rather than deferred until the patient is in the ASU. ED delivery may be associated with better patient outcomes.23

Not only did reversal with PCC increase, but prescribing of Vitamin K and FFP was maintained with better compliance with dosing. It is important that PCC is not used in isolation from other agents, as it is the combination of PCC, Vitamin K and small doses of FFP that reverses most rapidly, completely and with lasting effect.11 Combined treatment options may be associated with lower mortality,24 although value of low dose FFP in addition to PCC is debated.25 Some recommend the use of combination of a 4-factor PCC (contains factors II, VII, IX and X) and Vitamin K without FFP.26 In the development of the ED protocol, this was discussed. We chose to keep low dose FFP in the protocol because of (1) the PCC available was a 3-factor PCC and does not have reliable amounts of factor VII and (2) the need for complete, rapid and sustained reversal and (3) the extreme mortality and morbidity of WRICH. Removal of FFP from the protocol would certainly simplify the protocol and is a future consideration.
Checking the INR after reversal did not improve and may reflect a failure of the protocol or failure in the transfer of information between clinical areas. Others have noted similar delays. These post-reversal checks were indicated when the patients reached the ASU, rather than while still in the ED. This suggests that while the protocol is effective within the ED, its reach into ASU was less effective. The educational efforts for the ED protocol were primarily directed to ED staff, but need to include ASU. Point of care INR testing might also assist with more timely checking of reversal.

The protocol wording about monitoring reversal may be ambiguous and has been revised (Appendix). It is reassuring that despite a lack of increase in INR checks, those that were checked were done earlier and were more likely to have normalised, reflecting improved reversal strategies.

While warfarin use may change with the introduction of direct-acting oral anticoagulants (DOACs), many patients will still require warfarin, such as those with prosthetic heart valves or renal impairment and those already stabilised on warfarin. Thus there is a continued need both for protocols such as this, as well as for the urgent reversal of DOACs.

Translating guidelines into routine clinical practice is often a slow process and was the focus of this study. The introduction of our protocols reflects many aspects of a successful change process. We suggest some key elements of success were: (1) identifying a need for change, (2) utilising senior clinical opinion leaders, (3) using “Plan-do-study-act (PDSA)” cycles, (4) involvement of all relevant stakeholders, (5) having a broad implementation and education plan, (6) working within a “change friendly” environment and (7) collaborating across departments with common goal of improving patient and systems outcomes. These are each explored below.

The initial poor audit results provoked strong discussions, stimulated key senior clinicians to take action and created a desire for change. This desire for change overcomes the inertia encountered in an “unfreeze-transition-refreeze” sequence. Guidelines alone are poor effectors of change, but when guidelines are combined with key clinical opinion leaders who see a need to change because of local data showing poor performance, it is more likely changes will occur. Following the first protocol implementation, PCC use improved, yet delays in reversal were common. When ED physicians saw these delays, they then became the key drivers in promoting further changes, which resulted in the development of the ED protocol.

Use of the PDSA audit cycle provides the ability to progressively enhance systems and provides a method of feedback to stakeholders. Identification of a need for change then initiates development of new standards (first protocol). However, completion of the full audit cycle with ongoing data collection, analysis and refining the processes is essential to achieve persisting change. Repeated audit cycles have kept this relatively uncommon, but serious, condition in clinicians’ minds and allowed both consolidation and then further changes of the protocols. At the time of writing, we are just completing a fourth audit (data not shown) and further refinement of the protocol (Appendix).

We were able to resolve conflicting advice from different guidelines (stroke specific versus haematology) through involving stakeholders from a range of professions. Involvement of all stakeholders is a key aspect of achieving practice change. There needed to be a consultation phase before implementation. The lack of initial involvement of one critical group (radiologists) was promptly corrected with discussions between key players. The initial protocol failed to deliver the impact we had hoped for, largely because it missed the ED physicians. ED physicians identified further barriers to change and were critical in championing the ED protocol.

Implementation and education was achieved through a variety of means. These included teaching grand rounds, local paper and online versions of the protocol in different locations (The Bluebook, Stroke and ED guidelines). Translating guidelines into practice may be most effective using multifaceted strategies including audit, opinion leaders and reminder systems. While we did not have reminders, our use of multiple methods and ensuring our guideline was easily accessible via local intranet may have helped embed our
change. Senior nurses and nurse educators helped disseminate the protocol to all ED staff. ED staff could see added value of the protocol for other patient groups with life threatening bleeding such as GI bleeds while on warfarin. A particularly important and ongoing method of embedding the protocol has been rapid critical incident feedback and discussion between relevant senior clinicians when a protocol violation has occurred. This helps to reinforce both the presence and importance of the protocol and identifies further barriers.

While our protocol introduction appears to have been successful, there may be alternative explanations for our results. The introduction of guidelines alone may have worked, irrespective of the advocacy, implementation and education. However, this is unlikely based on slow or poor uptake of guidelines alone. A government mandated ‘six-hour rule’ for ED discharges may have increased urgency regardless of our protocol. While this six-hour rule creates a sense of urgency, it nearly thwarted our ED protocol. There was initial hesitancy to bring the patient back from scanning to ED because of this rule. However the ED clinicians advocated for this using a “best for patient-best for system” argument. Collaboration between departments ensured ASU “pulled” the patient from ED as soon as the PCC infusion finished. As with any new agent, knowledge of PCC may have been incidentally learnt, leading to improved uptake. However, it is more likely that the introduction of a dedicated protocol containing PCC increased awareness. One aspect of change strategy that we did not employ, but is promoted in many models, is employing a dedicated change agent. A change agent may have achieved successful implementation of the protocols sooner. Our use of local opinion leaders may have been slower, but their longer tenure promotes sustained change beyond the temporary employment of a change agent.

We have outlined the successful introduction of an improved WRICH anticoagulation reversal strategy, which over time has led to improved clinical urgency, but there is still room for improvement of door-needle times.

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Author information:
Carl Hanger, Older Persons Health Specialist Service, Burwood Hospital, Stroke Service, Christchurch Hospital, Department of Medicine, University of Otago, Christchurch; John Geddes, Older Persons Health Specialist Service, Burwood Hospital, Department of Medicine, University of Otago, Christchurch; Tim Wilkinson, Older Persons Health Specialist Service, Burwood Hospital, Department of Medicine, University of Otago, Christchurch; Michele Lee, Older Persons Health Specialist Service, Burwood Hospital, Department of General Medicine, Christchurch Hospital, Christchurch; Scott Pearson, Emergency Department, Christchurch Hospital, Christchurch; Andrew Butler, Haematology Department, Christchurch Hospital, Department of Medicine, University of Otago, Christchurch; Krishna Badami, New Zealand Blood Service, Christchurch.

Corresponding author:
Dr H Carl Hanger, Geriatrician, Older Persons Health Specialist Service, Burwood Hospital, Christchurch 8140.
carl.hanger@cdhb.health.nz

URL:
REFERENCES:


Appendix

First reversal guidelines for warfarin-related intracerebral haemorrhage

All patients with a warfarin-related ICH and an elevated INR (>1.2) should have rapid reversal of the coagulopathy. Do ALL of the following:

- Cease warfarin.
- Give 5–10mg Vitamin K intravenously.
- Prothrombin complex concentrate (Prothrombinex-HT is available in New Zealand) 25–50IU/kg intravenously.
- Fresh frozen plasma (150–300ml) IV.

Notes:

- Vitamin K takes 6–24 hours to be effective.
- Fresh frozen plasma contains all the relevant clotting factors but requires large volumes (two or more litres) to adequately replace clotting factors.
- Prothrombin complex concentrate acts rapidly (within 15 minutes) and is accessed through contacting New Zealand Blood Service doctor on call.
- Prothrombinex™-HT used in New Zealand may not contain sufficient factor VII, hence concurrent use of a small amount of FFP as well.
- Monitoring:
  - INR alone is not useful for monitoring the effectiveness of clotting factor replacement. It is only useful for monitoring warfarin use in steady state situations.
  - Monitoring should be done immediately after treatment using a coagulation screen (INR, APTT, thrombin time and fibrinogen). If still abnormal, more coagulation factors should be given immediately.
  - If normal recheck in 4–6 hours (reflecting shortest half life of factor VII and Vitamin K onset of action).
  - If normal again, then recheck at 24 hours or sooner if patient clinically unstable.
- The risk of thrombotic events during this short-term reversal appears very low, even in patients with prosthetic heart valves.


Revised (ed protocol) guidelines for intracerebral haemorrhage while on warfarin: reversal of the warfarin-related coagulopathy 2012

Background

- ICH while taking warfarin is life threatening medical emergency with a mortality of between 43–70% at 30 days.
- Initial ICH volume and further haemorrhagic expansion are both independent predictors of mortality.
- ICH volume is not maximal at the outset but can continue to increase for several hours or up to 24–48 hours if taking warfarin.
- Most warfarin-related ICHs occur with the INR within the “therapeutic” range.
- Warfarin causes functional deficiencies of several different clotting factors which need immediate replacement in the setting of ICH while taking warfarin.

Reversal guidelines

- Any patient with both (1) an acute intracerebral haemorrhage and (2) taking warfarin should have immediate intravenous reversal of the coagulopathy. This includes:
  - Stop warfarin.
  - Give Vitamin K 5–10mg intravenously immediately.
• Give Prothrombin complex concentrate (PCC) 50 units/kg intravenously immediately.

• Give Fresh Frozen Plasma (150–300ml) (1–2 units).

Notes:

• Vitamin K takes 6–24 hours to be effective.

• Prothrombin complex concentrate (PCC) rapidly reverses the coagulopathy within 15 minutes. It is accessed by either
  • Following “life-threatening bleed on warfarin” protocol in Emergency Department (warfarin reversal pack to accompany patient to CT scanner from ED) or
  • contacting New Zealand Blood Service Doctor on call.

• If PCC is NOT available, Vitamin K (as above) and larger doses of Fresh Frozen Plasma (FFP) can be given (at a dose of 15–30ml/kg) but produces suboptimal anticoagulation reversal.

• Monitoring:
  • INR is not useful for monitoring the effectiveness of clotting factor replacement. It is only useful for monitoring warfarin use in steady state situations.
  • Monitoring should be done immediately after treatment using a coagulation screen (INR, APPT, Thrombin time and fibrinogen). If still abnormal, more coagulation factors should be given immediately.
  • If normal recheck in 4–6 hours (reflecting shortest half life of factor VII and vitamin K onset of action).
  • If normal again, then recheck at 24 hours or sooner if patient clinically unstable.

• The risk of thrombotic events during this short-term reversal appears very low, even in patients with prosthetic heart valves.

• Oral thrombin inhibitors (Dabigatran) related ICH
  Like warfarin related ICH, these patients need urgent reversal of the coagulopathy. See notes in * section for dabigatran reversal Blue Book Section 14.8.5 (Haematology).

• Longer-term management
  This requires an individual assessment of the risks and benefits of restarting warfarin or not. Most should not restart warfarin, but it is dependent on indications for anticoagulation, location and severity of bleed, comorbidities, age and concurrent medications.

Intracranial haemorrhage on warfarin
This pathway covers reversal of warfarin-related coagulopathy in patients with intracranial haemorrhage while on warfarin.

There is a different process for patients with:
- Oral thrombin inhibitors (dabigatran) related intracranial haemorrhage
- Patients with oral thrombin inhibitors (dabigatran) related intracranial haemorrhage
- Other life-threatening bleeds while on warfarin
  - Reversal of warfarin coagulopathy for other life threatening bleeds eg, upper gastrointestinal bleeds or trauma, might have specific clinical criteria for reversal eg, endoscopic findings or clinical manifestations of shock. Seek advice from relevant senior medical staff.
  - The process of reversal using prothrombinex, FFP and Vitamin K is the same as this pathway describes and can be used for any life-threatening bleeds where reversal is deemed appropriate.

About intracranial haemorrhage in patients on warfarin
About intracranial haemorrhage in patients on warfarin
medical emergency urgently

Assessment
1. **Arrange Urgent CT Head.**
   - Fax a CT request to 81504, and
   - Page the Radiology Registrar on 8911, or
   - Use E-request when this becomes available, but phone to make sure an urgent CT is being organised.

2. **To prevent any delays in administering intravenous reversal of coagulopathy:**
   - Do not wait for the results of an INR. Reversal is required even if INR is in the sub-therapeutic range (INR 1.5 or above).
   - Before CT Head, arrange Prothrombinex VF and Fresh Frozen Plasma (FFP).

Prothrombinex VF and Fresh Frozen Plasma (FFP)
Obtain Prothrombinex and Fresh Frozen Plasma for patients on warfarin with life-threatening bleeding (including intracranial bleeding):
1. Complete the Blood Components Form (QMR022B) and clearly write “Life-threatening bleed in patient on warfarin”.
2. Include required dose of Prothrombinex, based on the patient's estimated weight (50 units/kg).
3. Request 1 unit (approximately 300mL) Fresh Frozen Plasma (FFP). On the form, write “on telephone confirmation of bleed”.
4. Send in the Lamson tube, or arrange sample delivery, to the Blood Bank and inform them via phone.
5. When reconstituting prothrombinex do not shake the vials. For full reconstitution instructions see the blood resource folder G.

Nursing guidance Note: Prosthetic heart valves are not a contraindication to reversal in this situation as the risk of thrombotic events during this short term reversal appears very low.

3. **Reversal should not be given until CT confirmation of intracranial bleed. In the rare circumstances that a CT cannot be done and reversal is deemed appropriate and urgent, discuss with the consultant.**
Management

1. As soon as intracranial haemorrhage is confirmed by CT Head, call the ED, ward or ICU staff and ask them to:
   - Reconstitute the required dose of Prothrombinex VF, which should have arrived by now, in preparation for administration. If the CT is normal, the Prothrombinex can be returned unused.
   - Tell the Blood Bank to prepare and send the FFP.
   - Draw up 5mg of Vitamin K for IV administration.

2. Immediately return with the patient to Emergency Department, ward or ICU.

3. Administer reversal as quickly as possible:
   - Stop warfarin.
   - Give Prothrombinex VF 50 units/kg IV, immediately on its arrival from the Blood Bank.

   Prothrombinex Give FFP 1 unit (approximately 300 mL) on its arrival from the Blood Bank.
   - Give 5mg Vitamin K IV immediately. Vitamin K takes 6–24 hours to be effective.

4. **Monitor reversal.**

Monitoring

- Monitoring after reversal is essential and should include blood testing 15–30 minutes after administering Prothrombinex + FFP, then at 4–6 hours, and at 24 hours at least.
- Send a coagulation screen (INR, APTT, thrombin time and fibrinogen) immediately after treatment.
- If still abnormal, contact the Transfusion Medicine Specialist via the Blood Bank or seek acute haematology advice.
- If normal, recheck in 4–6 hours (reflecting shortest half-life of factor VII and Vitamin K onset of action).
- If normal again, recheck at 24 hours or sooner if the patient is clinically unstable.

5. **Longer-term management:**

   - Requires an individual assessment of the risks and benefits of restarting warfarin or not.
   - Most should not restart warfarin. However, it is dependent on indications for anticoagulation, location and severity of bleed, comorbidities, age and concurrent medications.