Anticoagulant-related intracranial haemorrhage: time to anticoagulant reversal improving but still slower than thrombolysis for ischaemic stroke

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ABSTRACT

AIMS: This study aims to determine whether door-to-needle times (DNT) for reversal of anticoagulant-associated intracerebral haemorrhage (ICH) (1) have improved over time, (2) differ between warfarin and dabigatran and (3) are comparable to ischaemic stroke (IS) thrombolysis DNT, and (4) whether reversal is monitored.

METHODS: Retrospective review of all warfarin- and dabigatran-associated ICH presenting to Christchurch Hospital over a 15-year period. DNT data from 2013–2018 were compared between warfarin-related ICH (WRICH), dabigatran-related ICH (DRICH) and IS thrombolysis.

RESULTS: 172 WRICH were identified. Over time there were significant reductions in door-to-first-reversal-agent ($r=-0.21$, $p=0.01$), scan-to-first-reversal-agent ($r=-0.27$, $p=0.001$) and scan-to-prothrombin-complex-concentrate (PCC) ($r=-0.33$, $p=0.001$) times. In the 2013–2018 cohort, WRICH had significantly slower DNT, door-to-scan time and scan-to-needle time compared to DRICH and IS thrombolysis (all $p<0.001$). There was no statistical difference between DRICH and IS. Median DNT was 183 minutes for WRICH, 72 minutes for DRICH and 52 minutes for IS. Median time to repeat international normalised ratio was 231 minutes, and the median time to repeat thrombin clotting time was 825 minutes.

CONCLUSION: Door-to-any-reversal-agent and scan-to-PCC times have improved over time, but they remain significantly longer than IS thrombolysis times. Monitoring of reversal is inadequate, particularly for WRICH receiving PCC.

Anticoagulant-associated intracerebral haemorrhage (ICH) is a life-threatening and disabling event$^{1,2}$ with higher early mortality compared to non-anticoagulant-related ICH.$^{1,3}$ Active bleeding is longer compared with non-anticoagulant-related ICH and results in larger growth and haematoma volume.$^{4,5}$ American Stroke Association guidelines recommend correction of international normalised ratio (INR) in warfarin-related ICH (WRICH) (class 1 recommendation), but the optimal approach is uncertain.$^6$ Observational data suggest there is a mortality benefit in patients receiving combination treatment with vitamin K, prothrombin complex concentrates (PCC) and fresh frozen plasma (FFP)$^{1,7,8}$ The mortality benefit may be mediated in part by early, effective anticoagulant reversal, which is associated with smaller haematoma expansion.$^9$ PCC rapidly replenishes deficient coagulation...
factors and is more effective at early reversal of INR when compared to FFP.9 We previously reported an improved survival in WRICH with PCC use and a trend to better outcomes with earlier reversal.8,10 Ongoing revision of a local WRICH reversal protocol has shown increased and sustained use of PCC with reduced time to computed tomography (CT) imaging and reversal.8

The increasing use of dabigatran since 2011 has highlighted the need for a rapid reversal agent.11 Idarucizumab, a humanised monoclonal antibody fragment that binds to dabigatran, works within minutes and is available in Canterbury District Health Board (CDHB) with haematologist approval.12 Rivaroxaban, an alternative oral anticoagulant, has no specific reversal agent available in New Zealand. It has only been available as a fully subsidised oral anticoagulant since August 2018.13 PCC is recommended for use in these patients in event of ICH.14

Ischaemic stroke (IS) patients are prioritised for review on hospital arrival—the ‘time is brain’ mantra is well established for the public, and streamlined IS protocols have led to reduced door-to-needle times (DNT) and improvements in mortality and morbidity.15–17 This study asks whether the same priority is applied in diagnosing and treating ICH patients.

The aims of this study are to assess whether (1) DNT for receiving reversal agent(s) in WRICH has improved over time, whether these times are comparable to (2) DRICH reversal times and (3) IS thrombolysis DNT in the same centre, and whether (4) reversal is being monitored appropriately.

Methods

We performed a retrospective analysis of all WRICH, DRICH and IS patients receiving intravenous thrombolysis at Christchurch Hospital, a tertiary hospital of an approximately 550,000 catchment population.

ICH cohort

Data were derived from patient information previously published between 2004 and 2013.8,10 This was supplemented with additional data from ICH patients admitted between 2013 and 2018, who were identified through several overlapping data sources. These included:

1. the Acute Stroke Unit (ASU) register—a prospective in-house stroke database for patients treated at Christchurch Hospital
2. discharge coding data—patients with International Classification of Diseases (ICD)-10 code ICH (161 or 162.9) were identified then cross checked against the ASU register
3. a review of the New Zealand Blood Service data for PCC requests, as well as local haematologist and pharmacy records for idarucizumab use.

For each ICH identified, electronic and clinical records were reviewed to establish whether the patient was listed as having taken warfarin or dabigatran at the time of bleed. If an ICH was confirmed on imaging and the patient was taking warfarin or dabigatran at the time of the stroke, then a WRICH was defined if the INR was elevated (>1.2) on admission, and a DRICH was defined if the thrombin clotting time (TCT) was elevated on admission.

We reviewed medical records to extract basic demographics, arrival time to the emergency department (ED), time of first brain imaging, reversal agents used (including time of reversal agent administration) and coagulation tests at the time of admission and following the reversal. Time of arrival was taken as the date/time stamp recorded in the ED notes. Time of stroke onset was not reliably recorded, so therefore it could not be used. The time of imaging was taken as the time recorded on the first scan image. Time metrics were calculated, including door-to-imaging time and DNT. DNT for ICH patients was defined as the time from arrival to the documented time that the reversal agent was administered. The time of blood tests (eg, post-reversal INR check) was taken as the time when the blood test was taken. A review of the adequacy of anticoagulant monitoring analysis was limited to the 2013–2018 cohort to reflect changes to local ICH reversal protocols and the recent availability of idarucizumab.18 ICH score was calculated by reviewing the radiological imaging in combination with the recorded Glasgow Coma Scale (GCS). ICH volume was
calculated was using the standard ABC/2 formula from acute CT scans.\textsuperscript{19}

We excluded patients with ICH secondary to trauma, ruptured aneurysm, haemorrhagic transformation of cerebral infarction, tumour, arteriovenous malformation, thrombocytopenia or thrombolytic therapy. Patients who were palliated immediately after diagnostic imaging and received no reversal agents were excluded, as were patients on dabigatran before idarucizumab was available.

**IS cohort**

Data from 2013–2018 for thrombolysis DNT were derived from a prospective stroke thrombolysis registry, the details of which have been published elsewhere.\textsuperscript{20}

**Comparison**

The initial analysis for improvement over time included the full 2004–2018 cohort. We then focussed analyses on the 2013–2018 data into three comparison groups:

1. those on warfarin at time of ICH
2. those on dabigatran
3. those with IS who were thrombolysed.

For group one, scan-to-needle times were calculated separately for vitamin K, PCC and FFP. Groups two and three’s needle times were taken as time of administration of idarucizumab and thrombolytic agent, respectively. We then compared DNT, door-to-scan times and scan-to-needle times between these three groups.

Some patients had their coagulopathy reversed before imaging confirmed an ICH—this is outside the accepted protocol for ICH treatment, so these patients were excluded.\textsuperscript{13} Negative values for time from vitamin K to PCC administration (ie, PCC being given before vitamin K) were allowed (being within protocol) and fast access to PCC is to be encouraged. Scan-to-PCC time was considered the most relevant of warfarin reversal times to compare with idarucizumab times, as PCC is the most effective and rapid reversal agent.\textsuperscript{9} The adequacy of warfarin reversal was defined as an INR of less than 1.3 on repeat testing.\textsuperscript{9}

**Statistical analysis**

We used standard descriptive statistics. Stroke type according to gender was compared using the Chi-square test. Age, times to interventions and ICH volume were not normally distributed, so non-parametric tests were used. Specifically, comparisons across three or more stroke subtype groups were undertaken using the Kruskall–Wallis test, and comparisons across two groups were undertaken using the Mann–Whitney U test. Comparisons between arrival date and intervention times were undertaken by using Pearson’s correlation coefficient. Continuous data were described using mean or median interquartile ranges (IQR) or ranges. A p value of <0.05 was considered significant. All statistics were performed on SPSS version 24.

**Results**

During the 2013–2018 study period there were 63 anticoagulant-associated ICH. Eleven patients were excluded: three due to incorrect diagnosis; two were palliated from the outset; two had community scans preceding admission confirming ICH; two due to their INR results (one had an INR of 1.1 on arrival, and the other had a community INR of >20 leading to admission, which was reversed prior to their scan); and the final two were DRICH that occurred before idarucizumab was available for use.\textsuperscript{18}

Seven of the 52 eligible patients included were taking dabigatran at the time of their ICH, and the remainder were on warfarin. The 45 WRICH from the 2013–2018 cohort were added to the previously published data of 127 patients with WRICH from 2004–2013 to give a total number of 172 WRICH patients for the 2004–2018 period.

The demographic characteristics of the warfarin and dabigatran arms of our later cohort are shown in Table 1. The patient demographics from 2004 to 2013 are available in previously published data and have been shown as a combined group for comparison.\textsuperscript{8} Median IS National Institutes of Health Stroke Scale (NIHSS) was 11 (IQR 6–19.5).

PCC was not received by any patient included in our study in the years 2004–2006. Figures 1 and 2 show temporal trends for DNT and scan-to-treatment time with PCC respectively. Scan-to-needle time significantly improved over the 15-year period (r=-0.33, p=0.001). Door-to-needle (PCC) time did not reach significance (r=-0.17, p=0.10). However, both scan-to-first-reversal-agent time (r=-0.27, p=0.001) and door-to-first...
**Table 1:** Demographic variables.

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<tbody>
<tr>
<td>Median age, years (IQR)</td>
<td>79 (72–86)</td>
<td>80 (77–82)</td>
<td>79 (73–83)</td>
<td>75 (62–83)</td>
<td>&lt;0.01 (Kruskall–Wallis test)</td>
</tr>
<tr>
<td>Female sex, no. (%)</td>
<td>19 (42%)</td>
<td>4 (57%)</td>
<td>51 (40%)</td>
<td>118 (42%)</td>
<td>NS^ (Chi-square test)</td>
</tr>
<tr>
<td>Median INR on presentation (range)</td>
<td>3 (2-5)</td>
<td>N/A</td>
<td>3 (1-12)</td>
<td>N/A</td>
<td>NS Mann–Whitney U test</td>
</tr>
<tr>
<td>Deaths in hospital, number (%)</td>
<td>14 (31%)</td>
<td>2 (29%)</td>
<td>58 (46%)</td>
<td>16 (5.7%)*</td>
<td>NS (Kruskall–Wallis test; excluded ischaemic stroke)</td>
</tr>
</tbody>
</table>

^NS (Not significant).

*30-day mortality.

The IS thrombolysis cohort were younger on average compared to the other three groups listed (p<0.001). Otherwise, there was no statistically significant difference between the four groups for the variables listed in Table 1.

**Figure 1:** Door-to-needle time (ED-to-PCC time) for WRICH 2004–2018 (r=-0.17, p=0.10).
reversal-agent time \((r=-0.21, p=0.01)\) did (graphs not shown). No other times analysed showed significant change over time.

The WRICH, DRICH and IS thrombolysis cohorts over years 2013–2018 were compared by key outcome measures listed in Table 2 and in Figures 3, 4 and 5. Times were also broken down by component for WRICH: the median time from scan to vitamin K was 39 minutes, from scan to PCC was 86 minutes and scan to FFP was 126 minutes. There were also further delays (median 35 minutes) between first reversal with vitamin K and PCC infusion beginning.

Figure 3 shows WRICH is significantly slower than both DRICH (difference between two medians of 111 minutes (IQR 86–132 minutes, \(p<0.01\)) and IS thrombolysis (difference between two medians of 131 minutes (IQR 82–210 minutes, \(p<0.01\)) DNT times. There is no statistically significant difference between DRICH and IS thrombolysis DNT.

WRICH is significantly slower than both these groups for door-to-scan and scan-to-needle times. WRICH is slower than DRICH for door-to-scan time by a difference between two medians of 86 minutes (IQR 36–88 minutes, \(p<0.01\)) and scan-to-needle time by 51 minutes (range 34–66 minutes, \(p<0.01\)). WRICH is even slower compared to IS thrombolysis: for door-to-scan time by a difference between two medians of 96 minutes (IQR 32–147 minutes, \(p<0.01\), and for scan-to-needle time by 64 minutes (IQR 40–90 minutes, \(p<0.01\)). Again, there is no statistically significant difference in these variables when comparing DRICH and IS thrombolysis.

Tables 3 and 4 shows data relating to the adequacy of reversal for WRICH from the 2013–2018 cohort. The majority of WRICH patients received vitamin K as their first reversal agent. This was the only reversal agent received by four patients: for one patient the reasons for not giving further reversal agents were not documented, for two patients the reasons were a later change to palliative care and for the final patient it was due to an unclear duration of symptoms.

**Figure 2:** CT-scan- to-needle time (diagnosis-to-PCC-treatment time) for WRICH 2004–2018 \((r=-0.33, p=0.001)\).
Table 2: Key outcomes for WRICH, DRICH and IS thrombolysis cohorts (2013–2018).

<table>
<thead>
<tr>
<th>Median times, minutes (IQR)</th>
<th>Warfarin n=41</th>
<th>Dabigatran n=5</th>
<th>Ischaemic stroke n=283</th>
<th>p (Kruskall–Wallis test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Door to scan</td>
<td>123 (50–192)</td>
<td>37 (14–104)</td>
<td>27 (18–45)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Scan to first (any) reversal agent or thrombolytic</td>
<td>42 (28–78)</td>
<td>35 (21–55)</td>
<td>22 (15–31)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Door to first (any) treatment or thrombolytic</td>
<td>174 (98–248)</td>
<td>72 (34–153)</td>
<td>52 (38–75)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Door to PCC</td>
<td>183 (120–285)</td>
<td>N/A</td>
<td>N/A</td>
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</table>

Figure 3: Boxplot DNT comparison for 2013–2018 cohorts (WRICH, DRICH and IS thrombolysis).
There was large time variance from PCC administration to repeat INR testing, with a median time of almost four hours. Eight cases (18%) had no repeat INR despite reversal agents being given. However, for six of these patients, management changed to palliative care. One of the remaining two patients was initially palliated then recovered, and the other did not have documented reasons for no monitoring. Of the 16 patients whose INRs had not normalised on repeat testing, only one received further PCC dosing to achieve normal INR.

Protocol adherence for vitamin K, PCC and/or FFP dosing was followed in 29% of cases. However, in 43% of cases, vitamin K dosing was doubled from protocol 5mg to 10mg, which was unlikely to have a significant clinical impact.

Five (71%) of the DRICH cohort received idarucizumab, and one did not receive monitoring following reversal. Repeat TCT normalised in the other four cases. The median time from idarucizumab to first repeat TCT was 825 minutes (IQR 573–989 minutes).

**Table 3:** Adequacy of warfarin reversal for WRICH, 2013–2018 (N=45).

<table>
<thead>
<tr>
<th>Treatment received</th>
<th>Number of patients</th>
</tr>
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<tbody>
<tr>
<td>Reversal agents given (at any time)</td>
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<tr>
<td>Vitamin K</td>
<td>44 (98%)</td>
</tr>
<tr>
<td>Prothrombin complex concentrates (PCC)</td>
<td>36 (80%)</td>
</tr>
<tr>
<td>Fresh frozen plasma (FFP)</td>
<td>26 (58%)</td>
</tr>
<tr>
<td>First reversal agent given</td>
<td></td>
</tr>
<tr>
<td>Vitamin K</td>
<td>35 (78%)</td>
</tr>
<tr>
<td>Prothrombin complex concentrates (PCC)</td>
<td>8 (18%)</td>
</tr>
<tr>
<td>Fresh frozen plasma (FFP)</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>

**Table 4:** Adequacy of monitoring of warfarin reversal for WRICH, 2013–2018 (N=45).

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th></th>
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<tbody>
<tr>
<td>Median door-until-first-INR time, minutes* (IQR)</td>
<td>30 (16-54)</td>
</tr>
<tr>
<td>Median time from PCC (or FFP) to first repeat INR monitoring, minutes (IQR)</td>
<td>231 (102-783)</td>
</tr>
<tr>
<td>Number of patients who did not receive any monitoring following any reversal agent</td>
<td>8 (18%)</td>
</tr>
<tr>
<td>INR normal (&lt;1.3) on first testing following reversal</td>
<td>21 (57%)</td>
</tr>
</tbody>
</table>

* INR should be taken on admission, but a result is not required before giving PCC if a scan shows ICH while taking warfarin.

**Table 5:** Average ICH volume size comparison across the three cohorts.

<table>
<thead>
<tr>
<th></th>
<th>WRICH 2004–2013 (n=118)</th>
<th>WRICH 2013–2018 (n=43)</th>
<th>DRICH 2013–2018 (n=7)</th>
<th>p (Kruskal-Wallis test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ICH volume, ml (median)</td>
<td>28 (13)</td>
<td>18 (7)</td>
<td>32 (18)</td>
<td>0.041</td>
</tr>
</tbody>
</table>
Eleven patients were excluded from ICH volume calculations as they were primarily intraventricular haemorrhages (two from the WRICH 2013–2018 cohort and nine from the WRICH 2004–2013 cohort). ICH volume showed no correlation between increasing volume size and a faster door-to-needle time (p=0.156), time to CT imaging (p=0.087) or time to first repeat INR (p=0.956).

Discussion

A key finding of this study is that door-to-any-reversal-agent time in WRICH has improved over time. This supports previous studies in Christchurch Hospital that have showed improvements, particularly following protocol improvements emphasising early PCC administration. Scan-to-PCC-administration (ie, diagnosis-to-treatment) time has also improved over time. Although this is encouraging, our second key finding is more disconcerting, as it shows that these times are significantly longer (by 1–3 hours) than equivalent IS DNT in the same centre.

We treated WRICH differently to those related to dabigatran. Although the sample size is very small (and so may account for no significant difference with IS), DRICH received imaging within almost a third of the time of warfarin patients. They also received their reversal agent more rapidly, though they still had significant delays to repeat TCT testing despite idarucizumab’s rapid action. Idarucizumab, vitamin K and thrombolysis are each administered via a single injection and thus easy to give when the patient is still in the CT scanner, unlike PCC/FFP that require ordering from a blood bank and a return to the ED. ICH occurs much less commonly than IS, and the subset of ICH related to anticoagulants even less commonly. However, DRICH were treated within a much shorter time frame than WRICH, so rarity of exposure does not completely explain delays in treatment.

Another possible reason for slower treatment of ICH is the patients’ removal from the acute code stroke pathway in Christchurch Hospital once ICH is confirmed. The acute stroke team were no longer involved with ongoing management (PCC administration) via the emergency department. This has now been changed so that acute stroke nurses stay with the patient as they return to ED for PCC.

Our DNT appear to be longer compared to other published studies. One US centre developed a pharmacist-driven protocol for PCC dosing, preparation and delivery that showed improvement in median scan-to-PCC-administration time from 70 minutes (IQR 34–89 minutes) to 35 minutes (IQR 25–62 minutes). A UK centre removed the requirement of haematology pre-approval for PCC, moved PCC stock to the ED and introduced point-of-care INR testing, which showed a reduction in median
scan-to-needle time from 127 minutes (IQR 111–208 minutes) to 58 minutes (IQR 50–91 minutes).25 A real-world-based study showed times more in line with our findings: median DNT for vitamin K and PCC administration were 3.6 and 5.2 hours, respectively.26 However, even these post-protocol DNT times remain slower than our centre’s IS thrombolysis times. We believe the ‘time is brain (lost)’ mantra is valid, and therefore our anticoagulant-related ICH reversal times should be similar to thrombolysis times for IS patients.

These results raise questions such as whether ICHs are given lesser priority than IS, or whether the lack of randomised control trial (RCT) evidence of better outcomes with prompt reversal is causing a degree of therapeutic nihilism. There may be systemic as well as possible attitudinal differences in the ‘time is brain’ principle when a person presents with an ICH compared with an IS, and again when presenting with DRICH compared with WRICH. These areas require further investigation.

A strength of this study is that it is complete data from a single centre. Multiple sources were used to generate the cohorts and, as a result, are likely to have fully captured the appropriate data. Compared to other South Island centres, this centre has a highly developed stroke service with reasonable and increasing rates of thrombolysis, endovascular clot retrieval and telestroke.27 However, this is a single-centre, observational study and therefore generalisability is limited.

A limitation of this study is its retrospective nature—our data were based primarily on clinical notes. The decision to focus on the more recent cohort in regards to anticoagulant monitoring and comparison to IS thrombolysis times reduced our sample size and, consequently, the study’s statistical power. However, with significant changes including ‘code stroke’ pre-hospital notification being introduced in mid-2017, some of the data from over five years ago may not reflect contemporary practice. A separate analysis of the 2013–2018 cohort also reflects the impact of the previous study in Christchurch Hospital involving implementation of education regarding the existing ICH protocols.8 These protocols have had ongoing refinement over time and put emphasis on urgent reversal using the most effective agents (PCC and idarucizumab).

Another limitation of this study is that we reviewed adherence to Christchurch Hospital’s protocol for ICH reversal, not the clinical outcomes. However, previous studies in this centre have suggested early warfarin reversal may improve patient outcomes.8,10 Our study was limited by the small number of dabigatran patients—only nine over the four-year period, which include two prior to the availability of idarucizumab. The significantly lower intracranial haemorrhage incidence with dabigatran (compared to warfarin) in this group is supported by the RE-LY trial findings28 as well as real-world population data from New Zealand.29

A vital step for further quality improvement has been re-engaging with key stakeholders in ED, radiology and stroke service to identify any additional barriers. We have already recommended changes in our hyper-acute stroke pathway, including acute ICH reversal management remaining with the code stroke team in the initial phases. All patients with a stroke syndrome who are on oral anticoagulants will also be included as code stroke calls. Education programmes have been implemented and discussed previously.8 Due to the high number of staff in ED, it may be better to focus additional education efforts on the numerically smaller group of acute stroke nurses.

In conclusion, door-to-any-reversal-agent and scan-to-PCC times have improved in this centre over time. However, improved DNT is the target, and these times fall well short of IS DNT. Reversal monitoring was also outside of recommended guidelines. ‘Time is brain’ does not apply to IS alone. All strokes—both ischaemic and haemorrhagic—need urgent imaging and treatment.
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