Warfarin reversal: an audit of prescribing practices at Capital and Coast District Health Board

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Abstract

Aims In March 2013 the Australasian Society of Thrombosis and Haemostasis published an update of the Consensus Guidelines for Warfarin Reversal. We reviewed the prescribing practices at Capital and Coast District Health Board (CCDHB), following publication of the updated guidelines.

Methods Patients were identified through multiple sources. CCDHB Medical Records identified admissions coded as “Haemorrhagic disorder due to circulating anticoagulants” or “Anticoagulants causing adverse effects in therapeutic use”. CCDHB Haematology Laboratory identified International Normalised Ratio (INR) results ≥4.5. Wellington Hospital Pharmacy identified patients dispensed vitamin K. New Zealand Blood Service identified recipients of Prothrombinex®-VF and Fresh Frozen Plasma (FFP).

Results The management of patients with elevated INR results or bleeding on warfarin therapy was consistent with the updated guidelines in 81/149 episodes. Thirty one patients received FFP unnecessarily and 24 patients did not receive Prothrombinex®-VF when indicated. The greatest variability in management occurred in patients with bleeding complications and in patients requiring urgent warfarin reversal to allow acute surgery to proceed with only 5/31 patients and 5/21 patients having warfarin reversed as recommended. In some episodes more than one error was identified.

Conclusions The audit identified the suboptimal use of Prothrombinex®-VF and the unnecessary use of FFP in the management of warfarin reversal.

Warfarin is effectively used in a wide range of thromboembolic disorders. Patients on warfarin therapy have a 1–3% per year risk of major haemorrhage. The bleeding risk increases markedly with increasing International Normalised Ratio (INR), although most bleeding events occur within the therapeutic range. Patient factors, such as age, prior bleeding history, co-morbidities and concomitant medications also contribute to bleeding risk.

Despite the associated bleeding risk, warfarin remains the most commonly prescribed anticoagulant in New Zealand. Common indications for the use of warfarin include stroke prevention in atrial fibrillation, treatment of venous thromboembolism and prevention of thrombus formation in patients with mechanical heart valves.

New anticoagulants such as oral direct Xa inhibitors and direct thrombin inhibitors are becoming available as alternatives to warfarin, but it is likely warfarin will continue to be prescribed to those patients already stable on warfarin, with severe renal...
impairment, and for anticoagulation indications for which the new agents have not been evaluated.³

Warfarin lowers levels of factors II, VII, IX and X. Fresh Frozen Plasma (FFP) contains normal levels of all coagulation factors, whilst Prothrombinex®-VF is a three factor prothrombin complex concentrate (PCC) containing factors II, IX, X, and low levels of factor VII,⁴ both can be used to replace these factors.

Prothrombinex®-VF is the only PCC product available in New Zealand. Due to its low levels of factor VII, previous guidelines recommended the addition of FFP to reverse the warfarin effect.⁵ However, several reports have shown three factor PCCs without supplementary FFP to be effective for warfarin reversal.⁶⁻⁷

The use of FFP in the management of warfarin reversal can lead to a number of problems. The significant volume, approximately 200-250 ml per unit, can lead to transfusion associated circulatory overload. FFP is also recognised to be associated with a significant risk of allergic reactions.⁸ The patient’s ABO blood group must be known before the appropriate unit of FFP is selected and it must be thawed before it is issued from the blood bank.

Prothrombinex®-VF can be issued immediately from the blood bank. There is no requirement to check a patient’s blood group prior to issue and it can be rapidly reconstituted into a small volume for infusion. Prothrombinex®-VF has a reduced risk of transfusion associated acute lung injury, circulatory overload and allergic reactions.⁹ Prothrombinex®-VF is able to reverse an INR within 15 minutes of administration, however the infused factors have a similar half-life to endogenous factors and vitamin K should be given to sustain the reversal effect.³

In March 2013 an update of the consensus guidelines for warfarin reversal was published by the Australasian Society of Thrombosis and Haemostasis (ASTH) in the Medical Journal of Australia.³ The updated guidelines provide recommendations for warfarin reversal in different clinical settings and are consistent with other international guidelines.⁹⁻¹⁰ FFP is now only recommended in patients with life-threatening or critical organ bleeding; or in situations where PCCs are unavailable.

The New Zealand Blood Service (NZBS) as the organisation responsible for the collection of blood donations, production of blood components including FFP, and contracting the production of plasma products including Prothrombinex®-VF, has a key interest in the guideline recommendations.

The aim of this study was to review the prescribing practices for warfarin reversal at Capital & Coast District Health Board (CCDHB), in managing anticoagulated patients and warfarin-related bleeding events, following publication of the updated guidelines.

Methodology

Patients on warfarin therapy, who required intervention to reverse the warfarin effect, were identified through multiple sources. CCDHB Medical Records identified 140 admissions coded as “Haemorrhagic disorder due to circulating anticoagulants” or “Anticoagulants causing adverse effects in therapeutic use” during the 6-month audit period from the date of the publication of the updated guidelines on 4 March 2013 until 18 September 2013.
CDHB Haematology Laboratory provided a list of all INR results ≥4.5. Wellington Hospital Pharmacy provided a list of patient’s dispensed vitamin K from Pyxis MedStations®. NZBS provided a list of all recipients of Prothrombinex®-VF and FFP. Both products are routinely stored in the Blood bank in Wellington hospital and no shortages of either product occurred during the period covered by the audit.

The data sets were collated and the CCDHB electronic health record for each episode was reviewed. When multiple INRs were identified for the same patient, only those data entries used in clinical management were retained. Duplicate entries monitoring the response to an intervention were removed from the data set.

The updated guidelines provide recommendations for six patient groups, and are summarised in Table 1.

Table 1. ASTH Updated Consensus Guidelines for Warfarin Reversal

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR above therapeutic range and &lt;4.5 without bleeding</td>
<td>Lower or omit the next dose of warfarin. Resume therapy at a lower warfarin dose when the INR approaches therapeutic range.</td>
</tr>
<tr>
<td>INR ≥4.5 and &lt;10 without bleeding</td>
<td>Cease warfarin therapy, Vitamin K is usually unnecessary. If bleeding risk is high: consider vitamin K 1.0–2.0 mg orally or 0.5–1.0 mg IV</td>
</tr>
<tr>
<td>INR ≥10 without bleeding</td>
<td>Cease warfarin therapy, administer: Vitamin K 3.0–5.0 mg orally or IV; If bleeding risk is high: consider Prothrombinex®-VF, 15–30 IU/kg</td>
</tr>
<tr>
<td>INR ≥1.5 with life threatening or critical organ bleeding</td>
<td>Cease warfarin therapy and administer: Vitamin K 5.0–10.0 mg IV; and Prothrombinex®-VF 50.0 IU/kg IV; and fresh frozen plasma 150–300 mL; If Prothrombinex®-VF is unavailable, administer fresh frozen plasma 15 mL/kg</td>
</tr>
<tr>
<td>INR ≥2.0 with clinically significant bleeding</td>
<td>Cease warfarin therapy and administer: Vitamin K 5.0–10.0 mg IV; and Prothrombinex®-VF 35–50.0 IU/kg IV; If Prothrombinex®-VF is unavailable, administer fresh frozen plasma 15 mL/kg</td>
</tr>
<tr>
<td>Surgery</td>
<td>Withhold warfarin 4–5 days before surgery; Check INR day before surgery; If INR 2–3, administer vitamin K 3 mg IV; Day of surgery: If INR &gt;1.5, defer surgery or if urgent, administer Prothrombinex®-VF</td>
</tr>
</tbody>
</table>

Risk factors for bleeding are defined in the updated guidelines as a major bleed within the previous 4 weeks, surgery within the previous 2 weeks, known liver disease, a platelet count less than 50 × 10⁹/L, or concurrent anti-platelet therapy.

We adopted the International Society on Thrombosis and Haemostasis definition of major bleeding as: fatal bleeding; or symptomatic bleeding in a critical area or organ; or a fall in haemoglobin of greater than 20 g/L, or leading to transfusion of 2 or more units of whole blood or red cells.¹¹
Surgical procedures associated with high bleeding risk included cardiac, neurosurgical, abdominal vascular, cancer-related, orthopaedic or urological operations, and minor procedures like colonic polypectomy. Liver disease was defined as: evidence of cirrhosis; or bilirubin >2 × upper limit of normal; or aspartate aminotransferase/alanine aminotransferase >3 × upper limit of normal.

The updated guidelines differentiate between life threatening or critical organ bleeding, and clinically significant bleeding. Life threatening or critical organ bleeding was defined as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, or intramuscular with compartment syndrome. Clinically significant bleeding was defined as other major bleeding that was neither life threatening, nor critical organ bleeding, but caused a fall in haemoglobin of greater than 20 g/L, or led to transfusion of 2 or more units of whole blood or red cells.

This audit was conducted in accordance with the National Ethics Advisory Committee Ethical Guidelines for Observational Studies, with specific reference to audit activities.

Results

149 episodes in 136 patients required decisions on warfarin management. The management of patients with an elevated INR or bleeding on warfarin therapy was consistent with the updated guidelines in 81/149 episodes (Table 2).

In 31 episodes patients received FFP unnecessarily and in 24 episodes patients did not receive PCCs when indicated. In no instance was FFP issued by NZBS because Prothrombinex®-VF was unavailable. In 6 episodes patients received vitamin K unnecessarily and in 22 episodes patients did not receive vitamin K when indicated. In some episodes more than one error was identified.

Patients with an INR <4.5 without bleeding—Twenty-three episodes of patients with an INR <4.5 without bleeding, who had warfarin reversed, were identified. In 21/23 episodes, urgent warfarin reversal was required to allow acute surgery to proceed. Only 5/21 episodes had warfarin reversed as recommended with Prothrombinex®-VF alone. In 13/21 episodes, patients received FFP unnecessarily and in 10/21 episodes, patients did not receive Prothrombinex®-VF when indicated (Figure 1). One patient received FFP unnecessarily prior to elective surgery, and another received Prothrombinex®-VF unnecessarily after a fall.

Patients with an INR ≥4.5 and <10 without bleeding—Ninety-one episodes with an INR ≥4.5 and <10 without bleeding were identified. In 25/91 episodes patients had a high risk of bleeding. Warfarin was reversed in only 10/25 episodes. 8/25 episodes had warfarin reversed as recommended with vitamin K. One patient received FFP and another received both FFP and Prothrombinex®-VF unnecessarily. In 62/91 episodes patients were not considered a high risk of bleeding. 56/62 episodes had warfarin withheld as recommended.

In the remaining 6 episodes, patients received vitamin K unnecessarily (Figure 2). The final 4/91 episodes required warfarin reversal in preparation for elective surgery and all patients received vitamin K as recommended.
Table 2. Number of episodes requiring warfarin management decisions

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of episodes requiring warfarin management decisions</th>
<th>Number of episodes managed in concordance with the 2013 guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INR &lt;4.5 without bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute surgery</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>23</strong></td>
<td><strong>5</strong></td>
</tr>
<tr>
<td><strong>INR ≥4.5 and &lt;10 without bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk of bleeding</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>Standard risk of bleeding</td>
<td>62</td>
<td>56</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>91</strong></td>
<td><strong>68</strong></td>
</tr>
<tr>
<td><strong>INR &gt;10 without bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk of bleeding</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Standard risk of bleeding</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4</strong></td>
<td><strong>3</strong></td>
</tr>
<tr>
<td><strong>Bleeding complications of warfarin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life threatening or critical organ bleeding</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Clinically significant bleeding</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>31</strong></td>
<td><strong>5</strong></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>149</strong></td>
<td><strong>81</strong></td>
</tr>
</tbody>
</table>

Figure 1. Urgent warfarin reversal for acute surgery

Note: PTX = Prothrombinex®-VF, FFP = Fresh Frozen Plasma.
Figure 2. Warfarin reversal for INR ≥4.5 and <10 without bleeding for patients at high and standard risk of bleeding

Note: PTX = Prothrombinex®-VF, FFP = Fresh Frozen Plasma.

Patients with an INR ≥10 without bleeding—Four episodes with an INR ≥10 without bleeding were identified. In one episode, a patient had a high risk of bleeding and had warfarin reversed as recommended with vitamin K and Prothrombinex®-VF. In 3/4 episodes patients were not considered a high risk of bleeding. 2/3 episodes had warfarin reversed as recommended with vitamin K. In the third episode, the patient received Prothrombinex®-VF unnecessarily.

Bleeding complications of warfarin therapy—Thirty-one episodes of patients on warfarin therapy presenting with bleeding were identified. In 11/31 episodes patients had life threatening or critical organ bleeding and in 20/31 episodes patients had clinically significant bleeding. Only 4/11 episodes of life threatening or critical organ bleeding had warfarin reversed as recommended with Prothrombinex®-VF, FFP and vitamin K. In 3 episodes, patients did not receive Prothrombinex®-VF when indicated and in a further 3 episodes, patients did not receive FFP when indicated. Only 1/20 episodes of clinically significant bleeding had warfarin reversed as recommended with Prothrombinex®-VF and vitamin K. In 15 episodes, patients received FFP unnecessarily and in 10 episodes, patients did not receive Prothrombinex®-VF when indicated (Figure 3).
Discussion

The updated ASTH guidelines provide recommendations for warfarin reversal in different clinical settings. Adherence to the guidelines for patients with bleeding complications and patients requiring urgent warfarin reversal for acute surgery was poor.

The updated guidelines differentiate between life threatening or critical organ bleeding, and other clinically significant bleeding. Had the earlier 2004 guidelines, which did not make this distinction been applied, adherence would still be poor. Only 12/31 episodes of patients with bleeding complications and 5/21 episodes of patients requiring urgent warfarin reversal for acute surgery would have had warfarin reversed as recommended compared to 5/31 and 5/21 respectively.

This audit identified the suboptimal use of Prothrombinex®-VF and the inappropriate use of FFP. FFP remains frequently used for warfarin reversal, despite its role being reduced to supplementary therapy with Prothrombinex®-VF in life threatening or critical organ bleeding, or as an alternative if Prothrombinex®-VF is unavailable. Prothrombinex®-VF is readily available and in no instance during this audit was FFP used because of unavailability of Prothrombinex®-VF.

This audit has several limitations. While the updated guidelines were circulated at the time of publication in some Wellington Hospital departments, the awareness of a change in guidelines may not have been apparent in other departments. At the time of the audit, the CCDHB “Preferred Medicines List” still contained the previous 2004 guidelines.
It is important that institutions frequently review and maintain up to date recommendations. NZBS maintains a blood resource website for all District Health Boards which provides a link to the updated guidelines. NZBS has also developed a Reversing Warfarin App based on the updated guidelines for warfarin reversal which clinicians can download free of charge.

Patients who did not receive any blood component, plasma product or vitamin K were not identified in this audit. These patients likely had their warfarin managed as recommended by the updated guidelines by lowering or omitting the next prescribed dose of warfarin.

The updated guidelines provide new dose recommendations for Prothrombinex®-VF, FFP and vitamin K. It was not possible to audit whether prescribed doses were consistent with the new recommendations. Patient weight is often not provided with requests for blood products, or recorded in the electronic health record. Pyxis MedStations® record every medication dispensed to patients but unfortunately they record dispensing of vitamin K ampoules and not the prescribed dose. Pyxis MedStations® are not used in the CCDHB Emergency Department, where vitamin K is often prescribed.

The frequency of vitamin K prescription may be underestimated in this audit. In the future, electronic prescribing may include patient factors such as weight, which will improve the accuracy of data collection and allow audit of the adequacy of prescriptions.

In summary, this audit identified that adherence to published guidelines for warfarin reversal is poor with suboptimal use of Prothrombinex®-VF and the unnecessary use of FFP. Warfarin associated bleeding is relatively common and timely and appropriate reversal of warfarin will potentially avoid major morbidity.

Competing interests: NZBS is responsible for distribution of both Fresh Frozen Plasma and Prothrombinex®-VF to hospitals across New Zealand. NZBS contracts CSL Behring Australia to fractionate plasma collected in New Zealand to produce a range of products including Prothrombinex®-VF. NZBS received an unrestricted grant from CSL Behring Australia to develop education tools to support the implementation of the updated guidelines. The grant was used to develop the Reversing Warfarin App.

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References:


