Emergency management of patients with Supratherapeutic INRs on Warfarin: a multidisciplinary education study

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KEYWORDS
warfarin, vitamin k, anticoagulant, reversal, guidelines, emergency management, supratherapeutic, INR

ABSTRACT

Objective
Supratherapeutic INRs exceeding 4.5 are associated with increased risk of haemorrhage. The aim of this study was to evaluate the efficacy of an educational program focused at improving emergency clinician compliance with the Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ) guidelines.

Design
A pre and post-intervention study was undertaken. Retrospective data from 1 July 2014 to 30 June 2015 and prospective data 1 January 2016 to 31 December 2016 were collected.

Setting
This study was conducted in a large tertiary care hospital in Melbourne, Victoria, Australia.

Subjects
Included were all consecutive patients in the study periods that presented to the emergency department with an initial INR result of >4.5 on warfarin only.

Interventions
Development and delivery of an educational program in accordance with the current THANZ guidelines was implemented.

Main outcome measures
To improve education regarding the correct management of emergency patients on warfarin with a supratherapeutic INR.

Results
Data on 158 patients with an INR >4.5 were collected. Data on 46 patients were excluded. Management in 31 patients did not follow recommended guidelines. There was no difference detected between groups with 17 compliant with guidelines pre-intervention and 14 post intervention; p=0.87.
Conclusion
Emergency department management of patients on warfarin with supratherapeutic INR’s requires continual quality improvement. Frequency of emergency clinician compliance with the current evidence-based guidelines was moderate and did not improve significantly with targeted education. This highlights the complexities of warfarin management and the need for multi-disciplinary engagement of patients presenting with supratherapeutic INRs.

INTRODUCTION

Warfarin, a vitamin K antagonist, is the most commonly prescribed anticoagulant for the prevention of thromboembolic disorders, despite many challenges related with its use in clinical practice. Common indications for warfarin use include atrial fibrillation, prosthetic heart valves and treatment of venous thromboembolisms (Tran et al 2013). Bleeding is the most common adverse effect. Many patient factors increase the risk of bleeding, such as age, prior bleeding history, specific comorbidities, excessive alcohol consumption and reduced renal function (Tran et al 2013).

In clinical practice, warfarin is a challenging medication to manage due to its narrow therapeutic index and potential for many significant medication and nutrient interactions. Decisions regarding warfarin dosing are guided by the International Normalised Ratio (INR) results. Strict surveillance of the INR is essential during warfarin treatment with blood testing undertaken at least every six weeks in patients with controlled therapeutic levels, and tests undertaken several times a week during initial commencement of warfarin therapy or in patients with difficulty maintaining therapeutic levels. These factors often contribute to a high incidence of over and under anticoagulation. Patients on long-term warfarin therapy incur a risk of haemorrhage of 1% to 3% per year, leading to hospitalisation or death (Tran et al 2013).

Numerous international healthcare systems have developed guidelines to improve the safe use of warfarin. Furthermore, other studies have implemented an education program targeting warfarin management in hospitalised patients with a reduction in supratherapeutic INR levels and bleeding events post education (Dharmarajan et al 2011). However, despite this, adverse events to warfarin are common.

Supratherapeutic INRs, especially those exceeding 4.5, are associated with increased risk of haemorrhage. Consensus Guidelines of the Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ) offer advice on strategies to prevent over-anticoagulation, principles for warfarin reversal and provide evidence-based management guidelines (Tran et al 2013). The aim of this study was to evaluate the efficacy of an educational program focused at improving emergency clinician compliance with the THANZ evidence-based guidelines for management of patients that presented to the Emergency Department (ED) with supratherapeutic INR levels.

METHOD

A pre and post-intervention cohort study was conducted. Retrospective data from 1 July 2014 to 30 June 2015 and prospective data from 1 Jan 2016 to 31 Dec 2016 were collected on ED patients currently anticoagulated with warfarin. Data collection included baseline demographics, medical history, INR results, bleeding risk assessment, the presence of active bleeding and administration of fresh frozen plasma, Prothrombinex and vitamin K was also collected. The ED used paper-based patient medication and blood product administration charts. Emergency clinicians used both paper-based and electronic documentation detailing the emergency management care of patients.

SETTING

The study was conducted in a large tertiary care hospital in metropolitan Melbourne, Victoria, Australia with 45 emergency beds, approximately 200 emergency nursing staff, three emergency pharmacists, 31 emergency physicians and over 60,000 adult patient presentations annually.
SUBJECTS

Subjects included all consecutive patients in the study periods that presented to the ED and had an initial INR result of >4.5.

ETHICS

Ethics approval to conduct the study was granted by The Alfred Hospital Research and Ethics Committee (Project no. 513/15).

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

STUDY DESIGN

In the pre-intervention phase, compliance of emergency clinicians with current THANZ guidelines when treating warfarinised patients who presented to the ED with a supratherapeutic INR was assessed by two independent reviewers via retrospective review of medical records. A third reviewer adjudicated disagreements in results obtained.

The intervention implemented for this study was the development and delivery of an educational program in accordance with current THANZ guidelines. Education focused on the management of patients on warfarin therapy presenting to the ED with a supratherapeutic INR with or without bleeding, stipulating the treatment required in accordance with the specific INR result. Educational programs were presented face-to-face to emergency medical and nursing staff through formal and informal sessions from 31 June 2015 to 31 December 2015. THANZ guidelines were emailed to participants and printed on lanyard cards to further consolidate this educational intervention.

In the post-intervention phase, compliance of emergency clinicians with current THANZ guidelines when treating warfarinised patients who presented to the ED with a supratherapeutic INR was assessed by two independent reviewers via retrospective review of medical records, with a final decision by a third reviewer if needed.

DATA ANALYSIS

We estimated the proportion of patients non-compliant with THANZ guidelines to be 35%. To detect a minimum clinically significant change in the proportion of patients non-compliant with guidelines to 10% with 80% power and 5% level of significance the estimated sample size for the study was 86 with 43 patients in each phase. Continuous data were reported using mean (standard deviation) with statistical significance of differences assessed using Student’s t-test. Count data were presented using proportions and statistical significance of differences assessed using the chi-squared test or if number in a cell was <5, Fisher’s exact test was used.

A p-value of <0.05 was defined to be statistically significant. All analyses were conducted using Stata v 13.0, Statacorp, College Station, Texas.

RESULTS

Data on 158 patients presenting with high INR (>4.5) were collected. Of these, data on 46 patients were excluded. Exclusion criteria and included patients are listed in figure 1.
Patient demographics, bleeding status on presentation and bleeding risk are listed in Table 1. Patients were older with an average age of 73.2 (15.4) years with no difference between the subgroups. There were more female patients in the post-intervention period \( (p=0.03) \). There were no significant differences between the two groups with regards to indication for anticoagulation, degree of bleeding on presentation, and bleeding risk.

### Table 1: Patient demographics and clinical features

<table>
<thead>
<tr>
<th>Demographics and clinical features</th>
<th>Pre-intervention (n=60)</th>
<th>Post-intervention (n=52)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72.5 (15.0)</td>
<td>74.1 (16.0)</td>
<td>0.58</td>
</tr>
<tr>
<td>Male sex</td>
<td>40 (66.7%)</td>
<td>24 (46.1%)</td>
<td>0.03</td>
</tr>
<tr>
<td>INR result</td>
<td>6.3 (1.7)</td>
<td>7.1 (3.9)</td>
<td>0.13</td>
</tr>
<tr>
<td>Anticoagulation indication:</td>
<td></td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>- Atrial Fibrillation</td>
<td>34</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>- Prosthetic Valve</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>- Pulmonary Embolism</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>- Deep Vein Thrombosis</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>- Factor V Leiden deficiency</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>- Unknown</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Bleeding Category:</td>
<td></td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>Nil</td>
<td>45</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Clinically significant</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Life threatening</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Bleeding Risk</td>
<td>13 (21.7%)</td>
<td>10 (19.2%)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Warfarin was withheld in 108 (96.4%) patients. Vitamin K was given in 42 (37.5%) patients; with a mean dose of 3.8(2.9) mg. Prothrombinex was administered to 10 (8.9%) patients and FFP to 4 (3.6%) patients. There were 17 (28.3%) patients non-compliant with guidelines pre-intervention compared to 14 (26.9%) post-intervention; \( p=0.87 \). Variables for non-compliance are listed in Table 2.
## DISCUSSION

An educational intervention to emergency medical and nursing staff did not improve adherence to current THANZ guidelines for the management of patients on warfarin with a supratherapeutic INR presenting to the ED. Despite extensive clinician experience with warfarin, management of high INR remains challenging. Reversal guidelines are regularly revised as new research and products become available making it difficult to efficiently remain current. Indeed, previous literature has highlighted the highly variable nature of clinician management (Wilson et al 2001) and poor adherence with guidelines in this area of practice (Atreja et al 2005).

Other results by Roberts and Adams (2006) demonstrated significant improvements in clinician adherence to warfarin reversal guidelines (from 48% to 75%) with the implementation of an ‘academic detailing guideline’. However, in comparison to previous reports, this study has demonstrated a relatively high rate of overall compliance with reversal guidelines (approximately 72%). This may be related to a number of factors including the availability of local electronic guidelines on the management of supratherapeutic INRs for clinicians and the presence of clinical pharmacists in the emergency department (Cohen et al 2009).

The most common reason for non-adherence identified in this study was clinician use of vitamin K when it was not indicated in patients with no or a low bleeding risk. The administration of vitamin K when not indicated was perceived as ‘benign’ practice by clinicians. This study demonstrated great clinician compliance with the management of patients who had sustained significant traumatic injury causing excessive bleeding. However this study also revealed the lack of knowledge around the potential harmful consequences of inappropriate reversal.

Management of anticoagulation in the ED also includes the care of patients using direct oral anticoagulants (DOACs) in preference to warfarin which can be challenging in the event of a traumatic bleed. However, DOACs are used in preference to warfarin due to their favourable harm profile and, significantly lower all-cause mortality. In addition, the risk of stroke and systemic embolic disease, especially haemorrhagic stroke is significantly reduced (Hanley and Kowey 2015). DOACs also have greater compliance rates when compared to warfarin (Keshishian et al 2016) particularly agents that have daily-dosing regimes, such as Rivaroxaban (Laliberte et al 2013).

Despite this, warfarin continues to be a medication seen in ED populations such as the elderly and those with renal impairment who may have contraindications to DOACS and are underrepresented in many DOAC studies (Hanley and Kowey 2015). Continued use of warfarin may also be fuelled by limited data for reversal of DOACs in the setting of life threatening bleeding and an inability to quantify anticoagulant effect, this is life threatening in the trauma patient (Cuker and Siegal 2015). Another limitation to DOAC use may be financial, however, DOACs have been shown to be cost-neutral or even cost-beneficial compared with warfarin in specific patients (Janzic and Kos 2014; Coyle et al 201).

### Table 2: Nature of non-compliance with guideline

<table>
<thead>
<tr>
<th>Reason</th>
<th>Pre-intervention (n=17)</th>
<th>Post- intervention (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K given when not indicated</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Vitamin K not given when indicated</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Vitamin K under-dosed</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vitamin K given in excessive dose</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Fresh Frozen Plasma given when not indicated</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Prothrombinex under dosed</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>No reversal of INR with clinically significant bleeding</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
A reduction in ED presentations with high INRs may become increasingly uncommon with the aid of recent advances in INR monitoring including the development of home-based and outpatient monitoring strategies utilising smartphone applications. Previous literature has established that home monitoring of anticoagulation therapy is feasible, accurate and associated with greater time in therapeutic range. However only patients who are able to successfully undertake the education required and have been deemed competent by their practitioner will be able to use home monitoring devices (Hambleton 2003). With this new technology ED management of patients who manage their INR with this technology may demonstrate a reduced incidence of inappropriate reversal, as patients will be well educated on the warfarin dosing requirements for their INR (Hambleton 2003).

Minimal Australian literature is available regarding the role of nurses in the management of anticoagulated patients. Internationally, nurses have been involved in nurse-led anticoagulation monitoring systems, hospital-based nurse practitioner-led anticoagulation services and nurse-led patient testing in general practice surgeries. Nurses often recognise medication related problems and their involvement in the management of warfarin therapy should be broadened (Bajorek et al 2006). Various healthcare systems have also developed nurse and pharmacist led anticoagulation clinics as a strategy for warfarin management. In a study undertaken by Rose et al (2017) the warfarin management of 2,000 patients via anticoagulation clinics over 39 sites was implemented. A standardised approach was used for the training and education of primary healthcare physicians, nurses and pharmacists working in these clinics. The results demonstrated a reduction in patients with critically supratherapeutic INRs and therapeutic INRs improved from 65% to 75%.

Within an emergency-nursing context anticoagulation education should focus on appropriate assessment of anticoagulated patients using scoring systems such as the HAS-BLED and awareness of potentially serious drug interactions with warfarin (Pisters et al 2010) which may lead to early escalation of patients at high risk of bleeding. However nurses need to also advocate for the patient who do not require reversal with vitamin k, as inappropriate reversal can be harmful to these patients. Increasing the involvement of emergency nurses in the assessment, management and care of warfarin patients may improve compliance with the correct emergency management of patients presenting with supratherapeutic INRs.

The growing role of clinical pharmacists within the ED has been associated with improved patient outcomes and decreased medication errors (Tong et al 2016; Patanwala et al 2012). Consequently, the ED pharmacist may also help support clinicians in the management of supratherapeutic INRs. Pharmacist-led warfarin dosing for ambulatory patients in one Australian hospital reduced the mean number of days required to reach therapeutic INR compared to standard care (Dooley et al 2011). Another Australian study demonstrated positive outcomes with 62 pharmacists successfully completing an anticoagulation education program. Future legislation is proposing that Australian pharmacists will play a larger role in the management of patients on warfarin as part of a collaborative model post discharge from hospital (Stafford et al 2010). This expansion of their scope of practice could see a future reduction of ED presentations for supratherapeutic INRs and safer ED management of these patients.

The future of anticoagulation management requires a collaborative approach. Positive clinical outcomes demonstrated in previous studies utilised a collaborative model of care involving physicians, pharmacists and nurses. Further research in this area will involve the increasing use of home testing devices and DOAC’s. Pharmacists and nurses will play an integral role with physicians in coordinating the care and education of these anticoagulation strategies. This has the potential to improve the safe ED management of these patients and, reduce the number of emergency presentations involving supratherapeutic INRs. The results of this study confirm the importance of an interdisciplinary approach to the care of patients presenting to the ED.
with supratherapeutic INRs. Further studies are required to explore the collaborative model of care and the complications that may arise from incorrect emergency management of supratherapeutic INRs, especially in patients at high risk of deep vein thrombosis (DVT) and stroke.

**LIMITATIONS OF STUDY**

As a single-centre study, these results are potentially limited in their application to other departments. As a retrospective study with convenience sampling, there is always the potential for selection bias and data extraction errors. The study was conducted in a busy, major metropolitan tertiary hospital. Junior medical staff routinely rotate every three months. It is possible that some of the clinicians in this study were not exposed to all of the intervention strategies. The study may have been more successful if the education session was relaunched in successive quarters. In addition, the development of supportive summary documents such as the indications for warfarin reversal from the THANZ guidelines along with promotional posters may have assisted with improving clinician compliance. Encouraging nursing staff to flag confirmed or potential supratherapeutic INRs to medical staff and engaging pharmacists in the management of these patients would have assisted with the implementation of the correct intervention and may have also improved medical clinician compliance. Education regarding the difficulty with titrating warfarin dosing to achieve safe INR and the adverse outcomes that can occur from over or under anticoagulation, rather than purely focusing on the THANZ guidelines may have also improved compliance in this study. Finally, a prospective study looking at complications and patient outcomes and the incidence of DVT and stroke in patients who were inappropriately reversed would further help illustrate the importance of correct reversal.

**CONCLUSION**

Emergency Department management of patients on warfarin presenting with a supratherapeutic INR requires continual quality improvement. Frequency of emergency clinician compliance with the current evidence-based guidelines was moderate and did not improve significantly with targeted education. This study also demonstrated great clinician compliance with the management of patients who had sustained significant traumatic injury causing excessive bleeding. However, this study also revealed the lack of knowledge around the potential harmful consequences of inappropriate reversal. This highlights the complexities of warfarin management and the need for multidisciplinary engagement of patients presenting with supratherapeutic INRs.

**REFERENCES**


