Type and Timing of Reversal Agents in Patients Receiving Warfarin Who are Hospitalized for Major Bleeding

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Abstract

Background
In patients with warfarin-induced major bleeding, prompt administration of reversal agents increases coagulation factors and may allow early surgical correction of bleeding. However even with reversal agents, mortality is high. In this analysis the type and timing of reversal agents were evaluated

Methods
Review of warfarin treated non-trauma patients admitted to a University Hospital with ISTH defined major bleeding between October 2009 and January 2013.

Results
84 patients met entry criteria with a mean age 67.8 ± 14.3 years including 46 % females. The mean INR on admission was 3.6 ± 2.4. The site of major bleeding was central nervous system in 33 (39%), abdomen in 28 (33%), chest in 6 (7%) and other in 15 (18 %). Reversal agents including vitamin K, fresh frozen plasma (FFP), or prothrombin complex concentrate (PCC) were given to 83 patients. Forty patients required either major surgery (25 patients) or a therapeutic procedure (14 patients) to stop bleeding. Death occurred in 15 patients (18%) but the admission INR was not predictive of mortality (p=0.52, Kruskal–Wallis test). The INR was never completely corrected (INR<1.1) in 31 (37%) patients, 9 of whom died.

Conclusions
Patients with warfarin-induced major bleeding receive ineffective anticoagulation reversal, have delayed times to therapeutic procedures, and have a high mortality rate. Whether earlier administration of these agents or administration of newer agents would reduce hospital mortality requires further study.
Introduction

Major bleeding associated with warfarin has a high mortality rate [1]. Reversal agents including vitamin K, fresh frozen plasma (FFP) and, more recently, prothrombin complex concentrate (PCC), are recommended to rapidly correct the coagulopathy [2] and to allow early surgical treatment of the bleeding source. However, despite the use of reversal agents, mortality still remains high [3]. The reason for this lack of improvement is uncertain. One hypothesis is that delay in the administration of reversal agents or even administration of less effective reversal agents may contribute to the high mortality in warfarin treated patients who have major bleeding. This manuscript analyzes the type and timing of reversal agents used in these patients.

Methods

From October 2009 until January 1, 2013, 539 non-trauma patients who were admitted to a University Hospital with an ICD-9 code of hemorrhage, major bleeding, or coagulopathy were identified. Only those patients known to be receiving warfarin at the time of admission and those meeting ISTH criteria for major bleeding [4] were included in this analysis. Summary statistics were calculated and the Wilcoxon Rank Sum test was used to examine associations between mortality and age as well as admission INR, hemoglobin, and estimated glomerular filtration rate.

Results

A total of 84 patients met entry criteria. The mean age was 67.8 ± 14.3 years and 46% were female. The mean INR on admission was 3.6 ± 2.4. The site of bleeding was central nervous system (33 patients), abdominal (28 patients), chest (6 patients) and other site (15 cases). The mean hemoglobin on admission was 10.6 ± 2.8 gm/dl. The most common reversal agent used was a combination of vitamin K and fresh frozen plasma (Table 1).

Discussion

A disadvantage of novel oral anticoagulant agents is the lack of a reversal agent. However, this study demonstrates a high mortality rate in patients with a modestly elevated INR, the majority of whom received a reversal agent for major bleeding. We report substantial delays in the administration of these agents and substantial delays in the time to surgical procedures required to stop bleeding. In addition, the use of PCC, which provides factors II, IX, and X (three factor) or II, VII, IX, X (four factor) and which now is the preferred reversal agent, was used infrequently in this study. The infrequent use of PCC for major bleeding in patients receiving anticoagulation has also been reported in a recent clinical trial [5]. Whether or not more timely administration of reversal agents or the use of more effective reversal agents will reduce mortality in warfarin treated patients with major bleeding should be the subject of future studies.

<table>
<thead>
<tr>
<th>Reversal agent(s)</th>
<th>Admission INR</th>
<th>Time to Reversal Therapy (hours)</th>
<th>Time to Procedure to Correct Bleed (hours)</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K n=49</td>
<td>4.4 ± 2.8</td>
<td>4.9 ± 6.7</td>
<td>11.7 ± 8.3</td>
<td>18.4 %</td>
</tr>
<tr>
<td>Fresh Frozen Plasma(FFP) n=78</td>
<td>3.6 ± 2.4</td>
<td>5.3 ± 7.6</td>
<td>11.1 ± 10.0</td>
<td>17.9 %</td>
</tr>
<tr>
<td>Prothrombin Complex n=2</td>
<td>5.9 ± 4.5</td>
<td>0.6 ± 0.5</td>
<td>5.5</td>
<td>0 %</td>
</tr>
<tr>
<td>Vitamin K and FFP n=45</td>
<td>4.4 ± 2.8</td>
<td>4.2 ± 4.7</td>
<td>11.7 ± 8.3</td>
<td>17.8 %</td>
</tr>
</tbody>
</table>

Table 1
References


