Elevated international normalized ratio in the ED: clinical course and physician adherence to the published recommendations

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Abstract

Objective: Describe the course of patients with an elevated international normalized ratio (INR) in the emergency department (ED) and determine physicians’ adherence with treatment recommendations.

Methods: One-year retrospective review of all ED patients with an INR >5.0.

Results: Ninety-four patients met the entry criteria. Bleeding was present in 28.7% patients. Two thirds of the major bleeding episodes were of gastrointestinal origin. Physicians’ adherence decreased as bleeding and INR increased. At the lowest risk, adherence was 66.6%, whereas at the highest risk, it was 36.3%. Two thirds of patients were admitted to the hospital, one fourth were discharged, and 7.4% were observed in an observation unit. Average length of stay was 3.8 days.

Conclusion: Adherence to the recommendations regarding managing elevated INR was suboptimal. There is a need for formal endorsement of recommendations by emergency medicine organizations and development of disposition criteria based on bleeding status and site of bleeding.

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1. Introduction

Excessively elevated or supratherapeutic international normalized ratio (INR) due to warfarin therapy is a common presentation in the emergency department (ED). Annual incidence rates of fatal, major, and minor bleeding during warfarin therapy have been reported as 0.6%, 3.0%, and 9.6%, respectively, which are 5 times the expected rates in those without warfarin therapy [1]. Higher rates of bleeding complications due to supratherapeutic INR have been reported in several studies [2-6]. Current recommendations from the American College of Chest Physicians (ACCP), the British Society for Hematology, and the Australasian Society of Thrombosis and Hemostasis recommend treat-
ment of patients with an elevated INR based on their bleeding status and the numerical value of the INR elevation [7]. However, there is widespread variability in current clinical practice [8]. Some physicians hold the coumadin dose of asymptomatic patients with a modest INR elevation and follow them expectantly, whereas others treat the coagulopathy with vitamin K, fresh frozen plasma (FFP), or both. Furthermore, currently, there are no recommendations for disposition of patients with an elevated INR, and disposition is left to the individual judgment of the ED physician. The purpose of this study was to determine the clinical course and resulting outcomes of patients presenting to the ED with supratherapeutic INR secondary to warfarin therapy, as well as assess physician adherence with the current therapeutic approaches recommended by the ACCP (Table 1).

2. Methods

We performed a retrospective chart review of all patients presenting to the Cleveland Clinic Foundation ED with an INR >5.0 between January 1, 2001, and December 31, 2001. Eligible patients were identified by a search of the ED computerized laboratory database and International Classification of Diseases, Ninth Revision codes (790.92 and E934.2) ascribed to them by the hospital billing records. Patients were excluded if the INR elevation was not related to warfarin or if the medical record was unavailable. Patient records were abstracted from the hospital electronic database (Lastword: IDX Systems Corporation, Burlington, Vt) and verified by a manual chart review. The data recorded included demographic and clinical variables, laboratory results, treatment in the ED, disposition (discharge or admission to the clinical decision unit or the hospital), length of stay, and outcome. All the patients in the study were seen and evaluated by emergency medicine staff attending physicians. Once the patient was admitted to the hospital, care and final disposition were delegated to inpatient attending physicians. Physician adherence to the recommendations was measured by the appropriate administration of vitamin K or FFP based on INR level and presence of major bleeding, as outlined by the Sixth ACCP Consensus Conference (Table 1). The route of vitamin K administration was not used as a criterion to assess adherence, as there is lack of clear consensus among the different recommendations [7,9,10]. Excessively elevated INR value was defined as N 5.0 and was used as the cut point for entry into the study.

3. Data analysis

Bleeding complications were divided into major and minor episodes based on the classification proposed by Makris and Watson [11] (Table 2). Statistical analyses were performed using the SPSS 9/PC+ program (SPSS Inc, Chicago, Ill). Descriptive statistics were computed for demographic data and study variables. Differences in outcome variables were determined by the \( \chi^2 \) test for independence and multivariate analysis of variance. Linear regression models with dummy variables were used to determine the relationships among ED treatment, patient

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**Table 1** Sixth ACCP recommendations on managing patients with high INR values and physician adherence

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Recommendations</th>
<th>Number of patients</th>
<th>Number (%) of patients given Vitamin K</th>
<th>FFP</th>
<th>PRBC</th>
<th>Physician adherence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR &gt;5.0 but &lt;9.0; no major bleeding</td>
<td>Omit next dose or two or give vitamin K (1-2.5 mg PO) (^a)</td>
<td>53</td>
<td>10 (18.9)</td>
<td>9 (17.0)</td>
<td>4 (7.5)</td>
<td>66.6</td>
</tr>
<tr>
<td>INR &gt;9.0; no major bleeding</td>
<td>Omit warfarin and give vitamin K (3-5 mg PO) (^a)</td>
<td>30</td>
<td>23 (76.7)</td>
<td>5 (16.7)</td>
<td>2 (6.7)</td>
<td>57.1</td>
</tr>
<tr>
<td>INR &gt;20; major/serious bleeding</td>
<td>Omit warfarin and give vitamin K (10 mg slow IV), supplemented with FFP/prothrombin complex if required (^a)</td>
<td>11</td>
<td>6 (54.5)</td>
<td>8 (72.7)</td>
<td>6 (54.5)</td>
<td>36.3</td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>Omit warfarin and give FFP/prothrombin complex with vitamin K (10 mg slow IV) (^b)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

Adapted with permission from *Chest*. 2001;119(1 Suppl):22S-38S.

NA indicates not applicable.

\(^a\) The vitamin K dose may be repeated, if necessary.

\(^b\) The vitamin K and FFP/prothrombin complex may be repeated, if necessary.

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**Table 2** Criteria for major bleeding

1. Any bleeding resulting in death as determined clinically, radiologically, or at autopsy
2. Intracranial, retroperitoneal, or intraocular (excluding conjunctival)
3. Muscle hematomas causing compartment syndrome
4. Bleeding from any orifice and any of the following:
   (a) Systolic blood pressure <90 mm Hg
   (b) >2 g drop in hemoglobin
   (c) Oliguria
5. Any invasive procedure required to stop bleeding (including nasal packing by otolaryngology)
6. Hemoptysis accompanied by \( \text{O}_2 \) saturation <90%.
characteristics, and their outcomes. The study was approved by the Institutional Review Board at the Cleveland Clinic.

4. Results

A total of 96 patients with INR $\geq$ 5.0 were identified. Two patients were excluded because their increased INR values were unrelated to warfarin. Thus, 94 patients were included in the study. The average age ($\pm$ SD) was $63.3 \pm 15.9$ years (range, 16–93 years), with 44 men (46.8%) and 50 women (53.2%). Bleeding was present in 27 patients (28.7%) at the time of initial ED presentation, 11 (11.7%) of whom were classified as having major bleeding episodes. Sixty patients had INR values ranging from 5.0 to 8.9, whereas 34 patients had INR values $\geq$ 9.0. Vitamin K, FFP, and packed red blood cells (PRBC) were given to 39 (41.2%), 18 (19%), and 12 (12.8%) patients, respectively. Atrial fibrillation, deep venous thrombosis, and valve replacement surgery were the major clinical indications for warfarin therapy and accounted for 83% of cases (Fig. 1).

Gastrointestinal source of bleeding accounted for 40% of bleeding episodes and as much as 64% of all major bleeding episodes (Fig. 2). Vaginal bleeding was more likely to be major, whereas most of the urinary and other mucocutaneous bleeding were minor. One patient with epistaxis required posterior nasal packing and was classified as having a major bleeding. One patient with intracranial bleeding has a known history of central nervous system hemangioblastoma, and another patient with documented coronary artery disease developed a non-ST segment elevation myocardial infarction associated with a hemoglobin drop of 2.6 g. There were no fatal episodes.

Patients were divided into 4 groups according to the presence of bleeding and their INR values, as per the current ACCP recommendations [7] (Table 1). There was no significant difference in major bleeding between INR classes (43.7% if INR 5–8.99; 36.3% if INR $\geq$ 9.0, $P = .70$). Patients with INR $\geq$ 9.0 were more likely to receive vitamin K ($P < .01$). Those with major bleeding were also more likely to get FFP and PRBC ($P < .01$). However, patients with major bleeding were not more likely to get vitamin K ($P > .05$), and only 54.5% of patients with major bleeding received any dose of vitamin K. Overall physicians’ adherence to the recommendations was 51.9%. Adherence was 66.6% in patients with INR values ranging from 5 to 8.99 and decreased to 57.1% in patients with INR values $\geq$ 9.0. Patients with major bleeding rates were treated according to the recommendations in only 36.3% of cases. Lack of adherence in patients with major bleeding was mostly because of failure to administer vitamin K (73.9% of cases).

The subcutaneous route of administration was used in 51.6% of the patients who received vitamin K. Among those with major bleeding who received vitamin K, the intravenous route (the recommended route in such conditions) was used only in 50% of patients.
The time for the INR to return to therapeutic range averaged 43.2 hours (range, 6-110 hours). Vitamin K therapy significantly shortened time to normalization of INR. The route of vitamin K administration also affected the time to INR normalization (Table 3). The intravenous route was associated with the fastest decline in INR, followed by subcutaneous and oral routes, respectively (after excluding patients who received concomitant FFP or RBC transfusions along with the vitamin K).

Sixty-two patients (66.0%) were admitted to the hospital, but many were admitted secondary to other comorbid problems. Among the 47 patients who presented primarily because of bleeding, elevated INR, or both showed that 14 (29.8%) were discharged directly from ED, 6 (12.7%) were kept in the clinical decision unit, and 27 (57.4%) were admitted to the inpatient unit. Five of the 6 (83%) patients admitted to the clinical decision unit were discharged within 24 hours, whereas 1 was admitted to the hospital for observation. The mean length of stay was 3.8 days (n = 37; range, 1-24 days).

The length of stay for patients with major bleeding was 7.5 days compared with 2.8 days in those with minor or no bleeding (P = .04). Asymptomatic patients admitted to the clinical decision unit with excessively elevated INR did not develop any bleeding complications. This was true for any coagulopathy level, including patients with INR > 9.0.

Patients presenting with bleeding were more likely to be admitted compared with patients with asymptomatic INR elevation (80.8% vs 28.6%, P < .001). The likelihood of admission correlated with several clinical and treatment variables including age, INR, bleeding, bleeding source, PTT, treatment with FFP, and PRBC transfusion (r² = .80). However, there was no single variable that played a dominant role in disposition decision.

5. Discussion

The Sixth ACCP Consensus Conference on Antithrombotic Therapy proposed recommendations for managing patients with supratherapeutic INR levels. In our study, overall physicians’ adherence to the recommendations was 51.9%, although it varied with the level of INR and the presence of bleeding. Studies have shown that FFP has a variable content of vitamin K–dependent clotting factors and does not always lead to a sustained INR decrease when used alone [12]. Hence, all major consensus statements recommend using vitamin K in addition to FFP or clotting factor concentrate in patients presenting with major bleeding. However, in our study, only 54.5% of patients with major bleeding were treated with vitamin K. This could be because of lack of awareness of ACCP recommendations, partly because there are no formalized recommendations on managing elevated INR from emergency medicine organizations such as the American College of Emergency Physicians, the Society for Academic Emergency Medicine, and the American Academy of Emergency Medicine. It could also be because of failure to implement ACCP recommendations correctly. Further studies are needed to determine how physicians’ practice behaviors could be effectively changed and its impact on adverse clinical outcomes.

Current ACCP recommendations do not advocate subcutaneous vitamin K administration. More than half of the patients who received vitamin K in our study received it through the subcutaneous route. A recently published survey of anticoagulation clinics also suggested substantial underutilization of oral vitamin K [13]. However, data on route of vitamin K and its effect on patients’ clinical course are less certain. Studies have shown that response to subcutaneous vitamin K may be unpredictable and sometimes delayed [14].

Current consensus statements recommend close follow-up for patients with coagulopathy but fall short of recommending admission or discharge criteria. We found higher incidence of major bleeding complications when bleeding originated from the gastrointestinal tract, vagina, muscle, or brain, and these episodes occurred even at slightly elevated INR levels. None of the asymptomatic (nonbleeding) patients who were admitted to the clinical decision unit develop any complication(s) during their hospital stay. Based on our data, we postulate that the absence of bleeding at ED admission may be a better predictor of discharge safety than the INR value. Glover and Morrill [15] have shown that conservative management of nonbleeding patients with supratherapeutic INR levels is a safe strategy. This is important because it may obviate or decrease the need for hospitalization of nonbleeding patients and result in significant cost saving. Larger prospective studies, however, are needed to confirm this hypothesis.

Our study is limited by its retrospective design. The timing for the INR levels to normalize is based on serial laboratory tests. It is conceivable that the actual time for INR to normalize may have been earlier than found in the study. This study generates hypothesis, and the findings require validation in larger prospective trials.
6. Conclusions

The presence of bleeding and its origin may be better predictors of adverse outcome than the absolute value of elevated INR. This may be an important consideration in deciding the disposition status of patients. Although ACCP recommendations exist for the management of elevated INR, there is a need for formal endorsement by emergency medicine organizations. Adherence to current ACCP recommendations was limited especially with respect to the use of vitamin K in patients with major bleeding.

References