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Original research article

Upper gastrointestinal bleeding in the setting of excessive warfarin anticoagulation: Risk factors, and clinical outcome

Leili Pourakari [a,b,c], *Samad Ghaffari* [b], *Niloofar Zamani* [a], *Kourosh Masnadi-Shirazi* [b], *Nasrin Khaki* [b], *Arezou Tajlil* [b], *Ata Hassani Afshar* [c], *Nader D. Nader* [c,*]

[a] *Department of Medicine, Tabriz Branch, Islamic Azad University Tabriz, Iran*
[b] *Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz 51666, Iran*
[c] *Department of Anesthesiology, State University of New York at Buffalo, Buffalo, NY 14214, United States*

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ABSTRACT

Aim: Gastrointestinal tract is the most common source of severe bleeding following excessive warfarin anticoagulation (EWA). We aimed to describe the risk factors and outcome associated with upper gastrointestinal bleeding (UGIB) in patients admitted with EWA.
Methods: Demographics, clinical, laboratory and endoscopic findings of patients admitted with EWA from 2003 to 2015 were reviewed. Hospital mortality, blood product utilization and hospital length of stay were recorded. Regression analyses were performed for prediction of GI bleeding and mortality in patients with EWA.
Results: Medical records of 157 women and 121 men were reviewed. From 41 patients presented with UGIB, 31 (75.6%) underwent esophagogastroduodenoscopy. Preexisting peptic ulceration (32.2%) was the most common source of bleeding in these patients. Hospital mortality was 9.8% in patients with UGIB which was similar to those without. In average, patients with UGIB required 2 units more packed red blood cells and fresh frozen plasma. Older age ($P = 0.045$) and previous history of peptic ulcer disease ($P < 0.001$) were the predictors of UGIB in patients with EWA.
Conclusion: Presence of past or current peptic disorders was the strongest predictor of UGIB in patients with EWA. Despite comparable hospital mortality, these patients required more transfusion of blood products.
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Introduction

The indications for long-term warfarin therapy for the prevention of arterial/venous thromboembolism are expanding [1]. As the elderly population expands in the society, the number of the patients treated with warfarin has markedly increased in the recent years [2]. Because of warfarin's narrow therapeutic window and remarkable interaction with various food or medications, treatment with warfarin requires

* *Corresponding author at*: University at Buffalo, 252 Farber Hall, Buffalo, NY 14214, United States. Tel.: +1 716347909.
E-mail address: nnader@buffalo.edu (N.D. Nader).
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frequent monitoring of international normalized ratio (INR) and dose adjustments [3]. Bleeding is the most serious and dreaded complication of long-term treatment with warfarin which increases with the intensity of anticoagulation; and spontaneous bleeding occurs in nearly 10% of patients annually [4]. For most indications an INR below 3.5 is targeted [5] and higher INR values are associated with an increase in the risk of bleeding [6]. Non-steroidal anti-inflammatory drugs are commonly co-prescribed for patients using warfarin and through several mechanisms contribute to the multiple-fold increased risk of upper gastrointestinal (GI) bleeding (UGIB) [7,8]. Corticosteroids are among commonly prescribed medications and also have interaction with warfarin and on the other hand increase the risk of UGIB [9].

The number of patients presenting with UGIB while on warfarin treatment is growing [10] and they account for around 10% of non-variceal GI bleedings [11]. GI tract is the most common site of bleeding in warfarin users who experience life-threatening hemorrhages [12]. Overall mortality remains around 10% for UGIB, which is mostly reflective of the severity of comorbidities [13,14]. We aimed to study the factors associated with UGIB, the endoscopic findings and the outcomes in a cohort of patients admitted with INR level higher than 3.5. We hypothesized that probability of UGIB could be predicted based on the preexisting risk factors such as advanced age or history of peptic ulcer disease.

Methods

In a cross-sectional retrospective study we evaluated the medical records of patients admitted with the final diagnosis of excessive warfarin anticoagulation (EWA) from July 2003 to July 2015 to the heart center affiliated with Tabriz University of Medical Sciences. Study protocol was reviewed and approved by the Institutional Research Committee on Ethics and was exempted from informed consent process due to its retrospective nature. Identifiable health information was handled cautiously to ensure patient privacy act.

Inclusion and exclusion criteria

EWA was defined as INR level above 3.5 on admission. Only patients receiving warfarin prescribed for their medical condition were identified. Patients with intentional or accidental overdose were excluded. Patients with high INR levels attributable to other medical conditions such as liver disease or coagulopathies were excluded. Moreover those with incomplete medical records were not enrolled.

Independent variables

An excel sheet was developed and demographic data including age, gender, living place (urban/rural), level of education were recorded. Indications for anticoagulation were also recorded with options that included atrial fibrillation, mechanical heart valve implantation, and deep venous thromboembolism. Upper gastrointestinal bleeding was characterized by hematemesis and/or melena. Warfarin dosage in milligram and duration of treatment in months along with medication history were recorded. Polypharmacy was defined as concomitant use of more than 5 different medications at the time of admission. Comorbidities including diabetes mellitus, congestive heart failure, hypertension, cerebrovascular accident, chronic kidney disease (defined as estimated glomerular filtration rate less than 60 mL/min), history of past or current peptic ulcer disease (PUD), chronic obstructive pulmonary disease, cerebrovascular accident and neoplastic disease were recorded. Laboratory findings including hemoglobin (Hb), prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), platelet count, mean corpuscular volume (MCV), blood urea nitrogen (BUN), creatinine (Cr), white blood cell (WBC) on admission and on subsequent days were also collected. The number of transfused units of packed red blood cell (PRBC) and fresh frozen plasma (FFP) was recorded. Findings on esophagogastroduodenoscopy (EGD) including peptic ulceration, superficial erosions, mucosal hematoma or malignancies were also recorded.

Statistical analysis

The primary endpoint was the occurrence of UGIB in patients admitted with EWA and the secondary endpoints were units of FFP and PRBC transfusion, and hospital length of stay. For statistical analysis collected data were exported from Excel worksheet to SPSS ver. 22.0 (Chicago, IL, USA). All categorical variables were analyzed using chi-square test and expressed as frequencies and percentages. All continuous variables were analyzed by *t*-tests and were expressed as mean $\pm$ standard deviation. Risk factors for UGIB were examined by univariate and multivariate regression analysis. Multivariate regression analysis for factors with historical association with UGIB or those with a $P < 0.15$ in univariate analyses, was performed. Null hypotheses were rejected when the Alpha errors were less 0.05.

Results

From 308 patients who were admitted with a supratherapeutic INR, 278 met the inclusion criteria. Among 278 patients, 218 were symptomatic with overt source of bleeding on admission and 60 were identified purely based on their supratherapeutic INR level. Forty-one patients (14.7%) were either admitted with or experienced UGIB during hospitalization. A total of 31 patients (75.6%) underwent EGD during index hospitalization. Preexisting peptic ulceration was the most common findings in endoscopy. Table 1 summarizes the endoscopic findings of the patients who underwent EGD for UGIB.

Demographics and associated comorbidities

Table 2 demonstrates the demographics and the frequency of associated co-morbidities of patients according to the occurrence of UGIB. In univariate analysis, there was no difference in terms of gender, level of education and living place (urban vs. rural), yet patients who experienced UGIB were significantly older ($P = 0.045$). Among those who had UGIB, 20 patients (48.8%) had hypertension, 9 patients (21.9%) had diabetes mellitus, 5 patients (12.2%) had ischemic heart disease and 14 patients (34.1%) had congestive heart failure. The frequencies of these

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