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

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SOUHRN

Cíl: Gastrointestinální trakt (GIT) je nejčastějším zdrojem závažného krvácení při nadměrné antikoagulaci warfarinem (excessive warfarin anticoagulation, EWA). Naším cílem bylo určit rizikové faktory a výsledný stav spojené s krvácením do horní části GIT (upper gastrointestinal bleeding, UGIB) u pacientů přijatých s EWA.
Metody: Zkoumali jsme demografické charakteristiky, klinické, laboratorní i endoskopické nálezy u pacientů hospitalizovaných s EWA mezi roky 2003 až 2015. Dále jsme zaznamenávali nemocniční mortalitu, použití krevních derivátů i délku hospitalizace. Pomocí regresních analýz jsme se pokusili vypracovat způsob predikce krvácení do GIT a mortality u pacientů s EWA.
Výsledky: Prohlédli jsme nemocniční záznamy 157 žen a 121 mužů. Ze 41 hospitalizovaných pacientů s UGIB jich u 31 (75,6 %) bylo provedeno ezofagogastroduodenoskopické vyšetření. U těchto pacientů byly nejčastějším zdrojem krvácení (32,2 %) již přítomné peptické vředy. Nemocniční mortalita pacientů s UGIB činila 9,8 %, což byla podobná hodnota jako u nemocných bez UGIB. Pacientům s UGIB bylo v průměru nutno podat dvě jednotky erytrocytárního koncentrátu a čerstvě zmrazené plazmy. U pacientů s EWA byly prediktory UGIB vyšší věk (p = 0,045) a vředová choroba v anamnéze (p < 0,001).
Závěr: U pacientů s EWA byla nejsilnějším prediktorem vzniku UGIB přítomnost peptického vředu, ať již v anamnéze, nebo v současnosti. Přes srovnatelnou nemocniční mortalitu bylo u těchto pacientů nutno častěji provádět transfuzi krevních derivátů.

Keywords:
Esophagogastroduodenoscopy
Upper gastrointestinal bleeding
Warfarin

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 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/1,73 m^3), 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 ± 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 comorbidities were comparable in patients with and those without UGIB. Sixty-one percent of the patients with UGIB had a positive history of PUD, while this condition was reported only in 5.9% of 237 patients without UGIB ($p < 0.001$). Chronic kidney disease showed a trend to be more common in patients who experienced UGIB ($p = 0.064$). Additionally, both groups were similar in terms of ABO blood group, indication for anticoagulation, warfarin dosage and the duration of treatment.

Polypharmacy and medications

Polypharmacy was reported in 17 out of 41 patients with UGIB and 105 out of 237 patients without UGIB (41.5% vs.

Table 1 – Esophagogastroduodenoscopic findings of patients with upper gastrointestinal bleeding.

Location	Erosion	Ulcer	Tumor	Others[a]	Total location
Esophagus	2	3	0	2	9
Stomach	5	6	1	0	12
Duodenum	3	1	0	0	4
Total lesion	10	10	1	2	23

There was no identifiable lesion in 11 patients who underwent esophagogastroduodenoscopy (EGD).
[a] Others category included one case of sliding hiatal hernia and one case of Zenker's diverticulum. Two patients (one esophageal ulcer and one gastric ulcer) received interventional sclerotherapy to control bleeding.

Table 2 – Demographic and associated co-morbidities of GI bleeding in patients with supratherapeutic warfarin anticoagulation.

	No GI bleeding (N = 237)	GI bleeding (N = 41)	Odds ratio (95% CI)	*p*-values
Gender				
Male (N = 121)	104 (86.0%)	17 (14.0%)	1.10 (0.56–2.16)	0.865
Female (N = 157)	133 (84.7%)	24 (15.3%)		
Age (years)	63.8 ± 16.8	68.6 ± 13.1	1.02 (1.00–1.04)	0.042*
Living place				
Urban (N = 203)	64 (85.3%)	11 (14.7%)	1.01 (0.48–2.13)	1.000
Rural (N = 75)	173 (85.2%)	30 (14.8%)		
Education status				
< High school (N =162)	137 (84.6%)	25 (15.4%)	0.88 (0.45–1.73)	0.735
> High school (N = 75)	100 (86.2%)	16 (13.8%)		
Diabetes mellitus	32 (13.5%)	9 (22.0%)	1.80 (0.79–4.12)	0.159
Hypertension	95 (40.1%)	20 (48.8%)	1.42 (0.73–2.77)	0.308
Ischemic heart disease	32 (13.5%)	5 (12.2%)	0.89 (0.33–2.44)	1.000
Congestive heart failure	73 (30.8%)	14 (34.1%)	1.17 (0.58–2.35)	0.716
Atrial fibrillation	127 (53.6%)	24 (58.5%)	1.22 (0.63–2.39)	0.613
Mechanical valve implant	77 (32.5%)	8 (19.5%)	0.50 (0.22–1.14)	0.066
Chronic obstructive pulmonary disease	27 (11.4%)	2 (4.9%)	0.40 (0.10–1.75)	0.275
Active smoking	25 (10.7%)	6 (14.6%)	1.43 (0.55–3.73)	0.431
Cerebrovascular accident	29 (12.2%)	7 (17.1%)	1.48 (0.60–3.64)	0.448
Chronic kidney disease (eGFR < 60 mL/min/1.73 m^3)	112 (47.3%)	26 (63.4%)	1.94 (0.98–3.84)	0.064
History of peptic ulcer	14 (5.9%)	25 (61%)	24.9 (10.9–57.0)	<0.001*
Concomitant use of acetyl salicylic acid	69 (29.1%)	11 (26.8%)	0.89 (0.42–1.88)	0.853
Polypharmacy < 5 drugs	105 (44.3%)	17 (42.5%)	0.93 (0.47–1.83)	0.865
Duration of warfarin treatment (months)	37.2 ± 62.0	31.8 ± 51.2	1.00 (0.99–1.01)	0.626
Dose of warfarin (mg)	4.1 ± 2.3	4.0 ± 1.6	0.96 (0.81–1.13)	0.625

* Statistically significant difference.

44.3%, respectively), which was similar between the two groups. Aspirin was used in 11 patients (26.8%) in the UGIB group and clopidogrel was used in 1 patient (2.43%) at the time of admission. A similar ratio of patients with no UGIB were receiving aspirin and clopidogrel upon admission. Anti-inflammatory medications (non-steroidal anti-inflammatory drugs [NSAIDs] and/or corticosteroids) were used by 12 patients, 29.3% of with UGIB, which was similar to 75 cases (31.6%) among patients without this complication.

Laboratory findings

Mean hemoglobin level was 9.2 ± 3.2 gm/dL in those presenting with UGIB and was significantly lower than the rest of the cohort ($p = 0.003$). Moreover, BUN, WBC count and MCV were significantly higher in these patients ($p = 0.015$, <0.001 and 0.041; respectively). Nevertheless platelet count, PT and INR were similar between both groups. Laboratory findings on admission in patients with and without UGIB are shown in Table 3.

Clinical outcomes and transfusion requirement

Overall, 25 patients (9.0%) did not survive hospitalization among which 8 patients (32.0%) had UGIB. Among 8 patients with UGIB, 4 had other concomitant major bleeding including 2 with intracranial hemorrhage and 2 with massive hemoptysis that were accountable for mortality therefore leaving only 4 patients who expired merely due to UGIB. Four out 41 patients (9.8%) died in patients with UGIB, which was similar to 8.0% hospital mortality in patients manifested with bleedings from sources other than GI tract. A trend was observed in terms of longer length of hospital stay in patients with UGIB (5.9 ± 5.4 days) compared to those without this complication (4.7 ± 3.5 days) ($p = 0.069$).

Patients with UGIB required transfusion of 2.5 ± 2.5 units while those with other forms of bleeding required significantly less PRBC (0.5 ± 1.2 units, $p < 0.001$). Similarly, the requirement for FFP was significantly higher in patients who manifested with UGIB (4.5 ± 4.4 units vs. 2.6 ± 2.6 units; $p = 0.011$). Fig. 1 shows the number of the transfused units of PRBC and FFP in both groups. Overall, 47.0% of the transfused PRBC units and 22.6% of the transfused FFP units were used for patients with UGIB. In contrast, those with UGIB on average received 0.2 ± 1.6 mg vitamin K, which was significantly lower than the amount of vitamin K used for patients without UGIB (1.8 ± 4.7 mg; $p < 0.001$).

Multivariate regression model was constructed in order to identify the independent variables associated with the occurrence of UGIB. Multivariate binary logistic regression model for prediction of UGIB is shown in Table 4. History of PUD was identified as an independent predictor of UGIB with almost 100 folds increase in the risk of bleeding (95% CI: 26.6–465.6; $p = 0.034$).

Discussion

Our study population consisted of consecutive patients admitted with EWA during 12 years in the main referral

Table 3 – Laboratory findings on admission in patients with supratherapeutic warfarin anticoagulation.

	No GI bleeding (N = 237)	GI bleeding (N = 41)	*p*-values
Prothrombin time (s)	37.6 ± 4.1	37.2 ± 5.3	0.584
Partial thromboplastin time (s)	79 ± 35	96 ± 52	0.054
International normalized ratio	8.40 ± 2.04	8.12 ± 1.86	0.421
Platelets (× 1000/μL^{-1})	238 ± 90	238 ± 96	0.997
Hemoglobin (g/dL)	11.6 ± 2.5	9.2 ± 3.2	<0.001*
Mean corpuscular volume (fL/RBC)	82.9 ± 8.9	86.2 ± 5.4	0.041*
White blood cell count (× 1000/μL^{-1})	9.4 ± 4.6	12.1 ± 5.0	<0.001*
Blood urea nitrogen (mg/dL)	23.9 ± 16.1	35.1 ± 25.9	0.015*
Serum creatinine (mg/dL)	1.27 ± 0.85	2.37 ± 4.70	0.059
Estimated glomerular filtration rate (mL/min)	65.8 ± 29.4	53.1 ± 33.5	0.015*

* Statistically significant difference.

Table 4 – Multivariate binary logistic regression model for prediction of upper GI bleeding.

	Coefficient	SE	Wald	*p*-value	HR	95% CI for HR	
						Lower	Upper
Age (years)	0.032	0.024	1.78	0.183	1.032	0.985	1.081
Mechanical valve implant	0.678	0.779	0.76	0.384	1.971	0.428	9.070
Chronic kidney disease	–0.613	0.678	0.82	0.366	0.542	0.143	2.047
History of peptic ulcer	4.711	0.731	41.58	<0.001	111.19	26.56	465.56
White blood cell (× 1000/μL^{-1})	0.098	0.046	4.54	0.033	1.103	1.008	1.208
Partial thromboplastin time (s)	0.023	0.007	11.08	0.001	1.023	1.009	1.037
Mean corpuscular volume (fL/RBC)	0.065	0.046	2.04	0.153	1.067	0.976	1.167
Constant	–13.825	4.351	10.10	0.001	0.000		

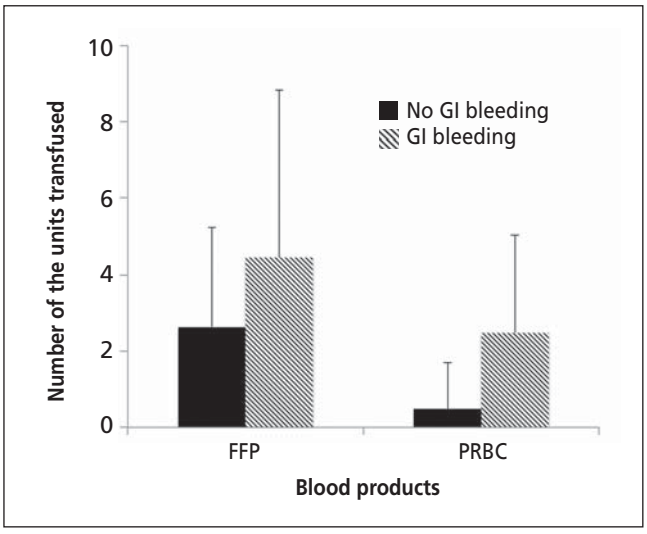

Fig. 1 – The average units of transfused fresh frozen plasma and packed red blood cells for patients with and without upper GI bleeding is shown. GI – gastrointestinal.

heart hospital in the northwest of Iran where warfarin is the only available oral anticoagulant. In this cohort nearly one fifth of patients presenting with some type of bleeding, had UGIB. The mortality in the setting of UGIB as the sole presentation of EWA was remarkable and UGIB was the cause of death in 4 out of 25 patients who did not survive hospitalization.

We observed a correlation between the older age and occurrence of UGIB, also a trend of association between chronic kidney disease and the frequency of UGIB. Other investigators have also shown the association between chronic kidney disease and bleeding of any type after initiating warfarin particularly in older patients [15]. Previous history of PUD was a major predictor of UGIB, which emphasized the need for a closer follow-up of anticoagulation with more frequent INR testing in these patients.

NSAIDs and corticosteroids have been shown to contribute to the development of erosive gastritis and GI bleeding through several mechanisms [7,16,17]. Surprisingly, the prevalence of NSAIDs (including acetyl salicylic acid), as well as corticosteroids, was similar regardless of UGIB in our series. Since NSAIDs and aspirin (with inhibitory effects on platelet function) were not routinely administered in patients on warfarin anticoagulation, the use of these medications was not associated with a higher risk of UGIB. Likewise, patients who were susceptible to UGIB were treated with proton pump inhibitors; which might have led to the lack of difference in the frequency of UGIB in the setting of EWA.

Duodenal ulcers were the most common endoscopic findings in a study on patients experiencing UGIB while using warfarin [7]. These investigators were unable to identify the source of bleeding in 12.0% of cases in EGD. Thomopoulos et al. reported on the endoscopic findings of the patients who were on long-term anticoagulation [10]. Similar to this current work, these investigators found that preexisting ulcers were the most common source of UGIB. They were also unable to identify the source of bleeding in one third of the patients. None of the previous studies focused on patients with excessive anticoagulation. Priority in correcting of coagulation status and hemodynamic resuscitation of UGIB patients with transfusion of blood products have led to delays in performing EGD in these patients. Some small and superficial mucosal abrasions could have healed by the time EGD was performed and therefore, the probability of negative EGD exams was higher in these patients. Spontaneous esophageal intramural hematomas have been rarely reported in patients without concomitant coagulopathies, mostly being reported in the setting of warfarin anticoagulation or thrombolysis [18–20]. Interestingly; there were two patients in our cohort who manifested intramural hematoma of the esophagus.

In another study of non-coagulopathic patients with UGIB from the region similar to ours, PUD was the most common cause of UGIB followed by gastric/duodenal erosions while 9.0–13.3% of EGDs were normal [21]. We believe that the cause of UGIB is generally independent of the state of anticoagulation EWA. Despite the similarity in the pattern and location of UGIB between the patients with normal coagulation and those consuming oral anticoagulants, certain pathologies such as esophageal hematoma are probably associated with excessive anticoagulation.

Berger et al. have shown that only about one half to two thirds of patients with an indication for anticoagulation actually receive warfarin [22]. The risk-benefit ratio for oral anticoagulation is carefully weighed in for the fragile patients especially in cases where follow-up is not feasible. EWA is an uncommon diagnosis and accounts for 0.23% of all final diagnoses in our center during the study time-period yet carried a significant mortality.

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 compared to patients without GI bleeding. We conclude that identifying patients at risk of developing UGIB in the setting of EWA will assist the clinicians in decision-making for the choice of available treatments. Early correction of EWA may decrease the extent of bleeding thereby, improving its associated mortality. Due to its retrospective design, this study suffers from the absence of follow-up data and lack of information regarding continuation of warfarin and recurrence of bleeding episodes.

Conflict of interest
None declared.

Funding body
None.

Ethical statement
The authors state that the research was conducted according to Declaration of Helsinki.

Informed consent
The authors state that the informed consent requirements do not apply to this study.

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