The Analysis of Patients Admitted to the Emergency Department Due to Complications Related to Warfarin Treatment

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Abstract

Objective: Warfarin is the most commonly used oral anticoagulant around the world. The most important complication of warfarin is bleeding. This study was conducted to evaluate the patients who were admitted to our emergency department due to complications related to warfarin treatment.

Material and Methods: Eighty-nine patients (32 females, 57 males) were enrolled into this retrospective study. The patients were evaluated according to their age, gender, duration of therapy (year), co-administered drugs, bleeding localization, treatments, amount of blood transfusions, duration of bleeding, initial and after-treatment PT, INR, complete blood count, and aPTT.

Results: Mean duration of anticoagulant use was 3.05±2.87 years. The most common indication of warfarin was atrial fibrillation. The most frequent bleeding localization was the upper gastrointestinal tract. Thirty-four (38.2%) of the patients had major bleeding, and 55 (61.8%) had minor bleeding. Age, co-administered drugs, amount of erythrocyte suspension transfusion, presence of previous warfarin overdose history, Hb levels at admission, and duration of follow-up in the ED were different between the bleeding types.

Conclusion: In this study, we found that the bleeding complications of warfarin were associated with the aged population, presence of previous warfarin overdose history, and concomitant drug use. *(JAEM 2014; 13: 194-8)*

Key words: Oral anticoagulant treatment, warfarin, bleeding, emergency department

Introduction

Nowadays, thromboembolic diseases are among the most important causes of morbidity and mortality (1). Physicians benefit from various drugs for abnormal coagulation to minimize the adverse clinical outcomes arising from a clot. Drugs used for this purpose are divided into three groups: anticoagulants, antithrombotic agents, and thrombolytic drugs (2). An ideal anticoagulant should be rapid-acting, potent, safe, easy to administer, resistant to food-drug interactions, and affordable. In addition, a laboratory observation is not required, because the response to the drug is predictable, which is favorable for the physicians. Nowadays, there are no such coagulants that completely meet these features (3).

The most common oral anticoagulant therapy (OAT) used to prevent arterial and venous thromboembolic cases is warfarin. Warfarin acts by inhibiting the vitamin K-dependent coagulation factors. Atrial fibrillation (AF), deep vein thrombosis (DVT), valvular heart disease (VHD), pulmonary embolism (PE), and recurrent systemic emboli can be given as examples of those various clinical cases where these agents are often used for the purposes of prophylaxis and therapy (4,5). Use of oral anticoagulants in Turkey is becoming widespread due to the increase of AF prevalence (6).

The most frequent and severe complication likely to occur in patients receiving warfarin therapy is hemorrhage in organs and tissues (4, 7). In cases of warfarin therapy-dependent hemorrhage, if it is not diagnosed early and treated properly, it progresses rapidly and threatens life (8). Considering the fact that patients with such complications frequently are admitted to emergency departments, it is evident that emergency departments play a vital role in the effective and proper treatment of this patient group. This paper aims at studying the socio-demographic characteristics and clinical features of patients admitted to our emergency department due to complications related to warfarin use, as well as the results of the treatments administered to them.

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Material and Methods

This study has a retrospective design. It included patients over the age of 18 who were admitted to our emergency department due to warfarin use-related complications between May 2010 and April 2012. Cases where only the bleeding profile was found to be high in the control assessments but the patients had no complaints and patients under the age of 18 with acquired or congenital bleeding disorder whose file information was inaccessible were excluded from the study.

The data of the study were obtained from the hospital records. Researchers analyzed the case files. Researchers studied the age, sex of the patients, indications of anticoagulant therapy, drug use period, other anticoagulants used along with warfarin, way of admittance to the emergency department, existence of former warfarin overdose history, clinical findings, location of hemorrhage, type of bleeding, level of hemoglobin and hematocrit and prothrombin time (PT), activated partial thromboplastin time (APTT), levels of international normalized ratio (INR) at the moment of admittance and after the treatment period, the administered treatment, count of blood product replacement, time required to control bleeding, and length of follow-up in the emergency department. The type of bleeding was grouped as minor and major bleeding. The major bleeding group included patients with hematuria and gastrointestinal, retroperitoneal, cranial, and intra-abdominal, hemorrhage, and those patients who were hospitalized in any service or had a hemorrhage that required an invasive approach and whose hemorrhage led to 2 points in the level of hemoglobin and required more than three units of blood product transfusion. (1, 7). Patients with hemorrhage that did not fit into these criteria were included in the minor bleeding group. In addition, based on the admittance INR values of the patients, they were regrouped into three groups according to their admission INR values (0-2.9; 3-10; above 10) (1).

Statistical Analysis

We used Statistical Package for Social Sciences 15.0 (SPSS, Inc., Chicago, IL, USA) software for the assessment of the study data. We explained the socio-demographic data with mean values and percentages. We used χ^2 test to compare the factors related with the type of bleeding. We benefited from one-sample Kolmogorov-Smirnov test to assess whether the data complied with a normal distribution. We assessed those complying with a normal distribution with independent simple test and non-complying ones with Mann-Whitney U-test. We accepted a value of $p<0.05$ to be statistically significant.

Results

We assessed the records of 89 cases that met the inclusion criteria; 64% (n=57) of them were men, and 36% (n=36) was female. The average age of the patients was 67.2±13.9. Reasons to have started warfarin therapy were atrial fibrillation [27% (n=24)], coronary artery disease [19.1% (n=17)], deep vein thrombosis [11.2% (n=10)], valvular heart disease, pulmonary thromboembolism (PE), and ischemic cerebrovascular disease (with similar percentages) (Table 1).

While 22.5% (n=20) of the patients were referred from another healthcare facility, 77.5% (n=69) of them were admitted directly to our hospital without a prior visit to another healthcare facility. While the average OA use length of the patients was 3.05±2.87, 22.5%

Table 1. General descriptive findings for patients

Age (year)			67.16±13.90
Male	57	64	
Indications for Warfarin Use			
Heart Valve Disease	10	11.2	
Coronary Artery Disease	17	19.1	
Atrial Fibrillation	24	27.0	
Pulmonary Thromboembolism	10	11.2	
Deep Vein Thrombosis	10	11.2	
Ischemic Cerebrovascular Disease	10	11.2	
Peripheral Artery Disease	7	7.9	
Polycythemia Vera	2	2.2	
Type of admission to emergency department			
First time	69	77.5	
Referred from another facility	20	22.5	
Duration of Warfarin Use (year)			3.05±2.87
Complaint at the time of admission			
Cyanosis in skin	9	10.1	
Hematuria	13	14.6	
Melena-Hematochezia	15	16.9	
Nosebleed	7	7.9	
Vaginal bleeding	4	4.5	
Gingival bleeding	6	6.7	
Hemoptysis-Dyspnea	7	7.9	
Abdominal Pain	5	5.6	
Pain in Extremities	8	9.0	
History of aspirin use	35	39.3	
History of warfarin overdose	20	22.5	
Laboratory values at the time of admission			
Leukocyte (mm^3)			9.70±4.15
PT (seconds)			57.90±36.02
INR			7.60±21.17
APTT (seconds)			44.60±19.46
Hg (gr/dL)			10.81±3.47
Thrombocytes (mm^3)			229.35±81.87
INR at the time of admission			
0-2.9	28	31.5	
3-10	49	55.1	
Above 10	12	13.5	
Laboratory values after treatment			
Leukocyte (mm^3)			9.4±4.50
PT (seconds)			27.99±7.39
INR			2.40±1.15
APTT (seconds)			33.09±6.85

Table 1. General descriptive findings for patients (continued)

Hg (gr/dL)			11.09±1.82
Thrombocytes (mm^3)			217.40±71.57
Localization of hemorrhage			
Rectus Sheath Hematoma	3	3.4	
Psoas Hematoma	1	1.1	
Cruris Hematoma	5	5.6	
Pelvic Hematoma	1	1.1	
Bladder Hematoma	1	1.1	
Cervical Hematoma	1	1.1	
Administered Blood Product Transfusion			
Fresh frozen plasma suspension			1.71±1.20
Erythrocyte suspension			0.70±1.04
Follow-up time in the emergency department (hours)			9.37±11.84
Clinic for hospitalization			
Discharged from the emergency department	65	73.0	
Gastroenterology	16	18.0	
Cardiovascular surgery	1	1.1	
Urology	1	1.1	
Gynecology	2	2.2	
General surgery	1	1.1	
Otorhinolaryngology	2	2.2	
Pulmonology	1	1.1	
Exitus	-	-	

Values are expressed as n (%), mean±SD. PT: Prothrombin Time, INR: International Normalized Ratio, APTT: Activated Partial Thromboplastin Time, Hb: Hemoglobin.

(n=20) of them had previous warfarin overdose history; 39.3% (n=35) of the patients concomitantly used acetylsalicylic acid (ASA), which increased the effect of warfarin (Table 1).

According to the assessment of the complaints, 16.9% (n=15) had rectal bleeding or darkened stool, 14.6% (n=13) had hematuria, 10.1% (n=9) had cyanosis in the skin, 7.9% (n=7) had a nose bleed, 6.7% (n= 6) had gingival bleeding, 5.6% (n=5) had abdominal pain, and 4.5% had vaginal bleeding (Table 1).

Based on the clinical diagnoses, we most frequently saw gastrointestinal bleeding, with 18.0% (n=16), and with alternating frequency, rectus muscle hematoma [3.4% (n=3)], cruris muscle hematoma [5.6% (n=5)], bladder hematoma [1.1% (n=1)], pelvic hematoma [1.1% (n=1)], and iliopsoas muscle hematoma [1.1% (n=1)] (Table 1).

We assessed 38.2% (n= 34) of the cases as major bleeding and 61.8% (n=55) as minor bleeding. Compared to the average age of the minor bleeding group (64.2±13.2), the average age of the major bleeding group (71.9±13.9) was significantly higher (p=0.011). While there was no statistically significant difference in terms of sex (p=0.653) and length of OA use (p=0.563) between the groups, history of previous warfarin overdose (p=0.000), and concomitant drug use that increased the effect of warfarin (p=0.038) were statistically significant (Table 2).

Table 2. Descriptive findings for patients in terms of bleeding type

	Bleeding type		
	Major 34 (38.2)	**Minor 55 (61.8)**	**p**
Age (years)*	71.91±13.90	64.23±13.18	0.011
Male	23 (67.6)	34 (61.8)	0.653
Duration of warfarin use (years) **	2.97±2.29	3.10±3.20	0.563
History of aspirin use	16 (47.0)	8 (14.5)	0.038
History of warfarin overdose	15 (44.1)	5 (9.1)	0.000
Laboratory values at the time of admission			
Leukocyte (mm^3)	9.71±4.12	9.70±4.21	0.990
PT (seconds)	63.29±52.11	54.57±20.63	0.270
INR	11.69±33.79	5.07±3.95	0.859
APTT (seconds)	47.62±24.88	42.74±15.15	0.869
Hg (gr/dL)	8.80±2.11	12.05±3.58	0.000
Thrombocytes (mm^3)	217.71±86.15	236.98±78.97	0.266
Administered Blood Product Transfusion			
Fresh frozen plasma suspension**	1.79±1.45	1.67±1.03	0.816
Erythrocyte suspension**	1.58±1.18	0.16±0.37	0.000
Follow-up time in the emergency department (hours)**	13.08 ±16.92	7.07±6.26	0.002

*Independent Simple Test ** Mann Whitney U-Test
Values are expressed as mean±SD. PT: Prothrombin Time, INR: International Normalized Ratio, APTT: Activated Partial Thromboplastin Time, Hb: Hemoglobin

In terms of the admission INR values, 31.5% (n=28) was in the 0-2.9 group, 55.1% (n=49) was in the 3-10 group, and 13.5% (n=12) was in the above 10 group. Tables 1 and 2 provide detailed information on the laboratory values of the patients at the time of admission to the emergency department and post-treatment period.

We stopped oral anticoagulant therapy in all cases we treated. Patients with major bleeding received an average of 1.58±1.18 units of erythrocyte suspension and 1.79±1.18 units of fresh frozen plasma transfusion, while patients with minor bleeding received an average of 0.16±0.37 units of erythrocyte suspension and 1.67±1.03 units of fresh frozen plasma transfusion (p=0.000, p=0.816). The difference between the lengths of follow-up in the emergency department (time required to control bleeding) for the patients with major and minor bleeding was statistically significant (p=0.002) (Table 2).

While 73.0% of the patients were discharged from the emergency department with full recovery subsequent to bleeding control, 18.0% was transferred to the gastroenterology clinic with gastrointestinal bleeding diagnosis. Table 1 presents detailed information about the clinics where the patients were hospitalized. None of the patients included in this study died.

Discussion

Warfarin has long been used effectively and widely in patients with thromboembolic risk for the purposes of prophylaxis and treatment (9). Its usage might cause many complications, such as bleeding in organs and tissues, in particular, as it has a narrow therapeutic range (10). The decision to administer warfarin is based on the delicate balance between the reduced risk of thromboembolism and increased risk of bleeding (8). In such a case, it is highly important to analyze and identify the potential complications dependent on warfarin use.

Nowadays, physicians use warfarin therapy more frequently for the older population, in particular, and this might result in bleeding complications (11). Although no study has ever entirely enlightened the relation between age and bleeding complications, some studies have indicated that it increases in patients over the age of 80 and that it increases significantly for each decade after 40 (8, 12). Other studies with counterarguments have reported that it is not a significant determining factor for bleeding complications in patients using it (8).

The average age of the patients in this study was 67.2±13.9. This is consistent with the information that patients with advanced age are more prone to warfarin-dependent complications, which is reported by some studies in the literature (8).

Although there are only a few studies reporting the sex difference with regard to the frequency of warfarin complications, Makris et al. (13) have reported that warfarin-dependent bleeding occurred more often in women. Similarly, van der Meer et al. (12) have reported that women had more minor bleeding complications. Although both the major and minor bleeding types were more significant in men in this study, there was no statistically significant difference between the types of bleeding and sex.

Cases, such as cardiovascular diseases, ischemic stroke, coronary artery disease, deep vein thrombosis, and pulmonary thromboembolism, are among the indications of using oral anticoagulants. Among the cardiovascular diseases, mechanical prosthetic valve surgeries and atrial fibrillation, in particular, are the most frequent indications (6, 14, 15). Thromboembolic events are a substantial part of the morbidity and mortality cases related with atrial fibrillation, and the most prominent is ischemic stroke (15). The annual ischemic stroke risk for this patient group varies between 3% and 8% (16). Many randomized controlled studies have shown that oral anticoagulant therapy in AF cases significantly reduces the risk of ischemic stroke by 68% (15, 17). Similarly, patients included in this study used OA most frequently due to AF. We can attribute this fact to the increased frequency of AF due to advanced age.

Frequency of bleeding is generally related to the duration of warfarin therapy (4). Many studies have shown that as the duration of warfarin therapy increases, the major bleeding incidence also increases (1, 5, 17). In this study, we did not find any statistically significant difference between the average duration of warfarin therapy and bleeding types.

Concomitant therapy with other drugs that increase the effect of warfarin is another important factor increasing the risk of bleeding (1). Kucher et al. (17) have reported that the vast majority of the cases of bleeding is seen in patients receiving concomitant therapy with such drugs as non-steroid anti-inflammatory and anti-aggregant agents. As especially the old population uses many drugs, interactions with anticoagulant agents are frequent, and in this case, dose adjustment for anticoagulants becomes crucial (11). In this study, aspirin was the most frequent agent concomitantly used with warfarin. We identified that concomitant use of aspirin significantly increased the frequency of major bleeding.

As many studies with large patient groups have previously indicated, bleeding events caused by warfarin therapy can occur in any tissue or organ, including the brain, gastrointestinal system, or genitourinary system (1, 7, 8). Correspondingly, many studies in the literature have reported the most frequent bleeding site to be the gastrointestinal system (8, 18, 19). In this study, we observed that bleeding occurred most frequently in the gastrointestinal system in the form of upper gastrointestinal system bleeding.

Other clinical presentations of bleeding in the gastrointestinal system in patients receiving warfarin therapy can be a rectus sheath hematoma in the front abdominal wall and iliopsoas muscle hematoma (9, 11, 20). Rectus sheath hematoma occurs as a consequence of the accumulation of blood in the rectus sheath due to the rupture of the epigastric artery within the anterior rectus abdominis sheath or a tear of the rectus muscle fibers and generally causes a clinical picture similar to acute abdominal conditions by leading to irritation in the peritoneum. Physicians usually administer conservative treatment through analgesia, fluid replacement, and transfusion of blood and blood products (21). In order to avoid unnecessary surgical interventions in patients with a history of warfarin use and acute abdominal conditions, we think it is very important for doctors in the emergency department to identify this clinical picture. The main reason for admittance to the hospital was acute abdominal pain in 5.6% of the patients in this study, and none of them received surgical intervention.

Ultrasound, CT, and magnetic resonance imaging can be used to diagnose rectus sheath hematoma (21). Although ultrasound is the first option, since it is cost-effective and easily and immediately accessible and has high levels of sensitivity, CT is a much better imaging method compared to ultrasound in assessing the location and size of hematomas (11, 21). In this study, we confirmed the final diagnoses for rectus sheath hematoma and iliopsoas muscle hematoma with CT.

Various studies have investigated the relation between INR levels and the severity of bleeding in patients receiving warfarin therapy and have reached different findings. Denizbasi et al. (18) have reported that they found no significant correlations between the severity and results of bleeding and INR levels. Levine et al. (4) have similarly reported that major bleeding occurred frequently, even if prothrombin time was within the therapeutic range, and asserted that there was no clear correlation between major bleeding or bleeding rates and the anticoagulant effect. On the contrary, Palareti et al. (22) and Veeger et al. (23) have asserted that the risk of bleeding increases along with increases in INR levels. This study found no difference between the groups in terms of INR, APTT, and PT levels and bleeding severity at the time of admission.

The basic treatment approach is the replacement of blood products that the patient has lost (whole blood, erythrocyte suspension, fresh frozen plasma) and treating the defective coagulation profile. In cases where the hematoma is limited and does not reach huge dimensions, thereby causing disorder in the general medical condition, patients can be treated conservatively with appropriate supportive treatment without resorting to surgery by closely following the vital signs of the patients (11).

Comparing the groups in this study, patients with major bleeding needed significantly high amounts of both fresh frozen plasma and erythrocyte suspension. In addition, time required for controlling the bleeding in patients with major bleeding and the follow-up time in the emergency department were longer. These findings were consistent with the data of Alay et al. (1).

Study Limitations

This is a retrospective study, and we tried to include and assess patient data that were accessible in files and hospital records. As the characteristics of the patients included in the study, the predisposing factors for bleeding complications, and many other factors may differ, it is necessary to support these findings with other studies carried out with larger populations in order to reach a general assessment from these findings.

Conclusion

Nowadays, oral anticoagulants are widely used. Regular use of the drugs and close follow-up of the bleeding profile are of great importance. Therefore, it is crucial to enlighten patients and their relatives thoroughly about the adverse effects of these drugs. In this study, we found the warfarin-dependent major bleeding complications to occur more frequently in patients with advanced age and a history of previous major bleeding due to warfarin overdose and receiving other concomitant anticoagulant therapy.

Ethics Committee Approval: The study was started after ap¬proval of Trakya University School of Medicine Clinical Research Ethics Committee was obtained.

Informed Consent: Informed consent was waived due to the retrospective nature of the study.

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