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COMPARISON OF RISK FACTORS FOR WARFARIN-ASSOCIATED BLEEDING

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Abstract

Objectives: Warfarin is the most commonly used oral agent for long-term anticoagulation. Nevertheless, bleeding is the most frequent side effect of warfarin, increasing mortality and morbidity and thereby restricting its use. Risk factors for bleeding include age, comorbid diseases, use of drugs that may interact with warfarin, and previous history of stroke or gastrointestinal bleeding. Using a questionnaire-based method, this study aimed to compare the risk of bleeding in two groups of warfarin users with and without a history of warfarin-related bleeding.

Materials and Methods: A total of 201 patients, including 100 who had bleeding during warfarin use in our outpatient clinic and 101 patients who were followed up with the international normalization rate, were included in the study. Risk factors in warfarin-related bleeding were evaluated by the researcher with a questionnaire created as a result of the literature review. Data were statistically analyzed.

Results: The prevalence of bleeding was 2.8 times higher in patients aged 65 years and older (confidence interval: 1.40-5.56) and 5.6 times higher in patients with comorbid diseases (confidence interval: 1.376-22.770). A history of stroke increased major bleeding 3.2 fold (confidence interval: 1.08-9.61). We also observed that lack of education might be a risk factor for warfarin-related bleeding.

Conclusion: We believe that older patients under warfarin treatment should be informed according to their education status, and their medications and comorbid diseases should be monitored regularly by the same centers.

Keywords: Warfarin, oral anticoagulation, bleeding, risk.

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Introduction

Thrombotic diseases are the leading cause of death today. In the United States (USA), six million people are affected by thrombotic events, and two million die annually.[1] It is clear how substantial the prevention and treatment of thrombotic events are. The use of rational methods of anticoagulant therapy is vital in life. Until recently, only one agent was used for long-term or life-long oral anticoagulation. In recent times, direct anticoagulant drugs have entered our lives.

Warfarin is used by millions of patients each year for chronic or paroxysmal atrial fibrillation, hypercoagulation conditions, prosthetic heart valves, recurrent deep vein thrombosis, and vascular diseases. Warfarin is a vitamin K antagonist required for synthesizing clotting factors II, VII, IX, and X, the endogenous anticoagulant proteins C and S.[2,3] The efficacy of warfarin, a drug with a narrow therapeutic range, is indicated by the international normalization ratio (INR). INR can be affected by drug interactions, diet, alcohol consumption, acute illnesses, liver disease, and changes in unknown factors. Therefore, warfarin dose adjustments should be made at regular intervals.[4] The most important complication of warfarin is bleeding. Bleeding rates during anticoagulation therapy range from 12 to 40%.[5,6] In five studies with warfarin atrial fibrillation (AF), the annual major bleeding rate was 1.3%, and the intracranial bleeding rate was 0.3%.[7] Monitoring regimens based on patient characteristics, intensity and duration of anticoagulant therapy, and simple prediction rules can reduce the risk of warfarin-induced bleeding.[8] Therefore, we wanted to investigate the risk factors that cause bleeding in cases of warfarin-induced bleeding in the region. The aim of this study, designed as a prospective study, was to investigate the factors that can trigger bleeding in warfarin use.

Materials and Methods

This study was carried out between November 2007 and September 2010 in a Research Hospital, Department of Internal Medicine, Division of Hematology, in Edirne, Turkey. A hundred patients admitted to Emergency Service with bleeding and hospitalized were included in the study. As the control group, 101 patients without bleeding who were followed in the outpatient clinics were taken.

Inclusion criteria for the study were; the use of warfarin, being 18 years of age or older, being a volunteer to participate in the study, and having a history of no other known hemostatic disorders leading to bleeding. While patients admitted to the hospital with warfarin-related bleeding were assigned to the patient group, patients without a history of warfarin-related bleeding were assigned to the control group.

An informed consent form was obtained from the patient and control groups. A questionnaire was prepared to determine the risk of warfarin users with and without bleeding. In this form, clinical and laboratory data were

determined in the case and control groups. Also, an in-group evaluation for specific data was carried out in the patient group. Study groups were examined according to the risk scoring system obtained from the study by Landefeld et al.[5]

Statistical Analysis

Statistical analyses were made using the statistical program STATISTICA AXA 7.1 with serial number AXA507C775506FAN3. Mann-Whitney U test was used to compare normal distributions of measurable data between groups, as the single sample Kolmogorov Smirnov test showed no normal distribution. Pearson $\chi 2$ and Fisher's exact $\chi 2$ tests were used for qualitative data. Spearman's Rho correlation analysis was used to evaluate the relationship between variables. Variables below $p<0.20$ were assessed by stepwise logistic regression to determine risk factors for warfarin-induced hemorrhage. Median (Min-Max) values and arithmetic mean ± Standard deviation was given as descriptive statistics. The significance limit for all statistics was selected as $p <0.05$.

Results

The study group consisted of 201 patients, 100 (49.75%) in the patient group and 101 (50.25%) in the control group. The mean age of the participants was 66.97±9.94 years in the patient group and 64.29±13.24 years in the control group. Half of the sample group were male participants. Most of the patients (n=121, 60.20%) were at 65 years or above 65 years. When the patient group was classified in terms of age, the difference found was statistically significant (p=0.001). When patients aged 65 years and over were compared with patients aged under 65 years, no significant difference was found between gender and bleeding (p=0.230), but the difference in educational level was statistically significant (p<0.001) (Table 1).

The INR value above 3.01 was higher in the patient group, whereas 3.0 and below was higher in the control group (Figure 1). When the distribution of INR levels was analyzed, it was found as 8.75±6.45 in the patient group and 2.25±1.77 in the control group (Figure 2). When the patient group was compared with the control group in terms of INR levels, the difference found was statistically significant (p<0.001) (Table 2).

When the INR follow-up rates of the patients were examined, it was observed that 64% of the patient group and 98% of the control group had INR follow-ups at a single center. Regarding the regularity of INR follow-up, 60% (n=60) of the patient group and 96% (n=97) of the control group had regular INR controls. The difference was statistically significant for follow-up at a single center (p=0.005) and regularity of follow-up (p<0.001) (Table 2).

Table 1. Demographic features

Characteristics		Patient Group n=100		Control Group n=101		Total		P*
Age (Years)		**Mean ± Sd**		**Mean ± Sd**		range		0.111
		66.97±9.94		64.29±13.24		18-69		
		n	**%**	**n**	**%**	**n**	**%**	p[a]
Age category	<65	33	33	47	46.53	80	39.80	**0.05**
	≥65	67	67	54	53.47	121	60.20	
Sex	Female	44	44	56	55.45	100	49.75	0.105
	Male	56	56	45	44.55	101	50.25	
Educational Status	Illiterate	21	21	11	10.89	32	15.92	0.027
	Literate	14	14	9	8.91	23	11.44	
	Primary or Secondary School	58	58	65	64.36	123	61.19	
	High School	3	3	13	12.87	16	7.96	
	High Education	4	4	3	2.97	7	3.48	

* Mann-Whitney U Test; [a]: Pearson Chi-Square Test; Sd: Standard deviation.

When the frequency of follow-up was analyzed, it was found that 40% (n=40) of the patient group and 77.2% (n=78) of the control group had a follow-up frequency of every 1-2 months. In terms of the frequency of INR follow-up, the difference was statistically significant (p<0.001) (Table 2).

The most common site of bleeding in the patient group was the upper gastrointestinal tract in 39% (n=39). The frequency of hematuria was 14% (n=14), and the rate of double or more focal bleeding was 22% (n=22). The difference in terms of the bleeding site was statistically significant (p<0.001) (Table 3).

Regarding the presence of a history of stroke, 23% of the objects in the patient group and 55.4% of the objects in the control group had a history of stroke. A statistically significant difference was found between the groups (p<0.001). When the patient group was compared in terms of stroke history, the difference was statistically significant (p<0.001) (Table 2).

As a result of binary comparisons, gender, age group (<65, ≥65), comorbid disease, and stroke were included in logistic regression analysis, and age and comorbid diseases were found to affect bleeding. Hemorrhage was 2.8 (confidence interval:1.409-5.563) times over 65 years of age and 5.597 (confidence interval:1.376-22.770) times more in patients with the comorbid disease.

In the paired comparisons, when the parameters which are less than p <0.20 were evaluated by logistic regression analysis, it was found that the history of stroke was increased by 3.224 (confidence interval: 1.081-9.61) fold in major bleeding (2 or more units require erythrocyte suspension).

Table 2. Possible risk factors for bleeding

Characteristics		Patient Group (n=100)		Control Group (n=101)		Total		p[a]
		n	**%**	**n**	**%**	**n**	**%**	
INR levels	<2.00	5	5	48	47.52	53	26.37	**<0.001**
	2.00-3.00	5	5	40	39.60	45	22.39	
	3.01-5.00	15	15	11	10.89	26	12.94	
	5.01-10.00	32	32	1	0.99	33	16.42	
	>10.00	43	43	1	0.99	44	21.89	
Follow-up status in a fixed center	Yes	64	39	99	98.02	163	81.09	**<0.001**
	No	36	95	2	1.98	38	18.91	
Regular follow-up rates	Yes	60	60	97	96.04	157	78.11	**<0.001**
	No	40	40	4	3.96	44	21.89	
Follow-up frequency	<1 month	20	57	15	14.85	35	17.41	**<0.001**
	1-2 month	40	34	78	77.23	118	58.71	
	2-6 month	10	59	7	6.93	17	8.46	
	>6 month	4	80	1	0.99	5	2.49	
	Unfollowed	26	26	0	0.00	26	12.94	
Drug use	No	29	29	65	64.36	94	46.77	**<0.05**
	Yes	71	71	36	35.64	107	53.23	
Drugs interacting with warfarin	NSAID	21	21	4	3.96	25	12.44	**<0.001**
	ASA	27	27	16	15.84	43	21.39	>0.05
	Amiodarone	10	10	2	1.98	12	5.97	**<0.05**
Presence of Comorbid Diseases	Available	97	98.1	87	86.14	184	91.54	**0.006**
	Unavailable	3	1.9	14	13.86	17	8.46	
Comorbid diseases	Diabetes Mellitus	13	8.1	22	21.78	35	17.41	**0.002**
	Hypertension	63	39.1	64	63.37	127	63.18	
	Heart disease	58	36	58	57.43	116	57.71	
	Chronic kidney failure	6	3.7	2	1.98	8	3.98	
	Chronic liver disease	2	1.2	1	0.99	3	1.49	
	Malignancy	10	6.2	0	0.00	16	7.96	
	COPD	6	3.7	3	2.97	9	4.48	
Stroke History	Available	23	23	56	55.45	79	39.30	**<0.001**
	Unavailable	77	77	45	44.55	122	60.70	

[a]: Pearson Chi-Square Test; NSAID: Nonsteroidal anti-inflammatory drug; ASA: Acetylsalicylic acid, COPD: Chronic obstructive pulmonary disease.

Table 3. Distribution of the bleeding site of the patient group (n=100)

The bleeding site	**n (%)**	
Upper gastrointestinal bleeding	39 (39)	**p<0.001**
Hematuria	14 (14)	
Lower gastrointestinal bleeding	3 (3)	
Nose bleeding	4 (4)	
Mucosal bleeding	4 (4)	
Subcutaneous hematoma, ecchymosis	6 (6)	
Intramuscular or intra-abdominal hematoma	3 (3)	
Hemoptysis	2 (2)	
Intracranial bleeding	3 (3)	
Other multiple, double, or triple bleedings	22 (22)	
Total	100 (100)	

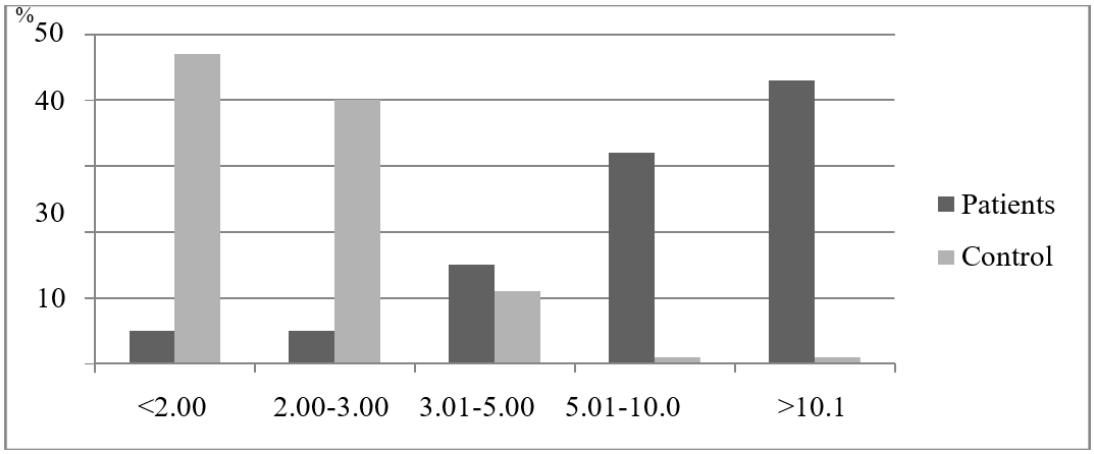

Figure 1. International normalization ratio distribution rate of patients and control group

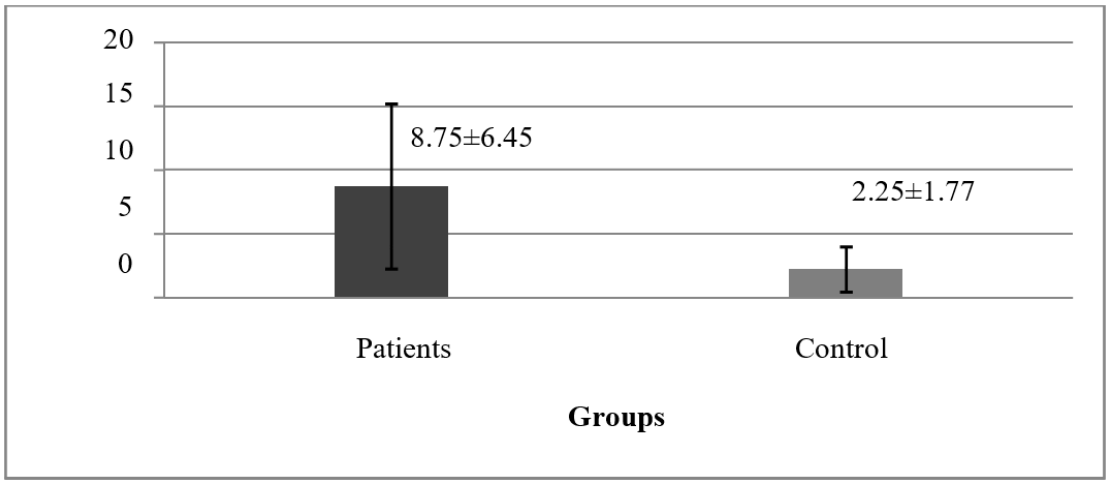

Figure 2. Mean international normalization ratio of patients and control groups values

Discussion

As known, the most substantial complication limiting the use of warfarin is bleeding. Physicians prescribe medicine for both short and long-term anticoagulation indications, but because of fear of bleeding and predictions of insufficient monitoring, patients cannot use it. We thought that our study would have an important place in daily medical practice besides its academic importance. At the end of this study, we determined the risk factors for bleeding and tried to create a risk classification system and compare it with the recent ones. For this purpose, we focused on age, sex, occupation, education, comorbid diseases, drug, stroke history, and patient follow-up.

Being 65 years old or older is a known risk factor that aggravates bleeding risk due to warfarin. In a study of 565 patients by Landefeld, it was found that elderly patients had a 3.2 times greater risk of major bleeding.[6] In the study of Beyth et al., it was found that being 65 years and older has a 2.7-fold risk of bleeding.[9] In the study of Shireman et al., it was determined that patients with AF aged 70 and over were at high risk, and it was found that being 70 years and older had a 1.63 times higher risk of bleeding.[10] In the study of Fihn et al., it was found that the risk of bleeding increased 1.10 times over the age of 80 years.[11] In the study of Wallvik et al., the risk of bleeding was 2.9 times increased in patients aged 60-69, 4.8 times in patients aged 70-79, and 6.6 times increased in patients aged 80 and over.[12] We conducted this study inspired by the study of Landefeld, who took 65 years and over as the risk group in terms of age. Older age was identified as a risk factor in Cox regression analysis, and over 65 years of age increased the risk of bleeding by 2.8 times. So our data also support the literature. For this reason, we believe that physicians who are considering prescribing warfarin should consider this situation and provide follow-up and information to the elderly group.

Gender is very substantial in the pharmacokinetic and pharmacodynamic effects of drugs. The incidence of side effects of some drugs varies according to gender. The decrease in oxidation by cytochrome p450 enzymes occurs more in men than in women. It is often claimed that women are more sensitive to certain medicines.[13] The role of gender in the bleeding complications of warfarin is controversial. In this study, we have not detected the effect of gender on bleeding. Studies emphasizing the existence of male or female superiority or that gender does not matter, [14–16] some studies have argued that the female gender increases the risk of bleeding[10,17,18] while some studies have reported that the male gender increases the risk of bleeding.[19,20]

It was emphasized that warfarin use, follow-up, and education level were important in the occurrence of bleeding complications.

Illiteracy, which was not statistically significant, was higher in the patients' group. Although there was a statistically significant difference between the groups, the level of education was not found as a risk factor in

the Cox regression analysis. Using a drug that is affected by many conditions of metabolism, such as warfarin, requires a certain intellectual level. Therefore, it is clear that illiteracy or a low academic level will increase the risk of bleeding. The reason that we have not been able to define this variable as a risk factor can be related to the low number of cases. We think that literacy, which is a parameter that cannot be considered in the patient group using warfarin, is a point to be considered with these data.

This study's results emphasize a situation. Approximately half of the participants in the control group had an INR value of less than 2, which might be suggested that they do not take warfarin. The same situation is observed in the whole world. Even though the INR controls were well monitored in multicentric randomized trials, in real life, this rate did not exceed 77% even in Sweden, where the best follow-up program is existing[21] In a study by Kalra et al., the rate of patients with INR <2.00 was 25%, the rate of patients with 2.0-3.0 was 66%, the rate of patients with INR >3.00 was > 9%.[22] In daily practice, the rate of patients with INR <2.0 is 26%, the rate of patients with 2.0-3.0 was 61%, and the rate of patients with INR >3.0 was 13%. As can be understood from these rates, reaching the target INR value is an unsolvable problem in the world.

The levels in the control group were found to be compatible with the average world levels. Reaching the target INR level in a warfarin-prescribed patient is never close to 100%. Below the therapeutic range, these patients are at risk of thromboembolic events even though they are on medication; there is a need for appropriate responsive drugs at fixed doses.

There was a significant difference between the patient and the control group in whether the follow-up was performed at a single center. In a study performed by Matchar DB et al., a comparison was made between the self-INR follow-up of a group of patients and INR follow-up in the clinic.[23] No difference was found between the two approaches in terms of reduced stroke risk, death, and major bleeding rates. Only minor bleeding rates increased. Based on these results, we believe that a warfarin-prescribed patient must be in follow-up for INR at a single center to reduce the patient's risk of bleeding. The adherence of patients to follow-up may be increased through self-monitoring.

Another important factor for holding the INR levels in the therapeutic ranges is regular INR monitoring. Frequent and regular follow-ups will prevent bleeding complications. The national guide recommends monitoring every 3-4 weeks.[24] The rate of regular follow-up was 96% in our non-bleeding control group and 60% in the patient group. This result is parallel with the hypothesis that the regularity of INR monitoring reduces the risk of bleeding.

In the analysis of the follow-up interval comparison of the patient and control groups, we found a result against the patient group, especially between the 1-2-month follow-up interval and non-follow-up. This situation leads

us to the opinion that not exceeding the follow-up period of 4-8 weeks may be a precaution to prevent possible bleeding.

Warfarin users are generally elderly patients, and since comorbidities are common in this group, they use multiple drugs. Therefore, we investigated the rate of drug consumption interacting with warfarin (Acetylsalicylic acid (ASA), Nonsteroidal anti-inflammatory drug (NSAID), amiodarone, e.g.). We found that this type of drug use was higher in the patient group. In the study of Zhang, in the concomitant use of warfarin and cephalosporins, an increased prevalence of bleeding was determined in comparison with the single use of warfarin.[25] However, a similar association was not detected in the association with NSAID/cyclooxygenase-2 inhibitors, amiodarone, and fenofibrate. In our study, the rate of NSAID and amiodarone usage in the patients' group was higher than in the control group. Especially randomly used ASA and NSAID drugs are commonly prescribed drugs that increase the risk of warfarin-associated bleeding. We recommend avoidance of usage of these drugs as much as possible, and if the administration is obligatory, the frequency of INR follow-up should be increased, and the patient must be informed about it.

The most common bleeding site was the upper gastrointestinal system. It should be noted that the most common bleeding site in warfarin users is GIS, and daily fecal control should be recommended for melena-hematochezia.

When the ratio of comorbid diseases was compared in the patients and control groups, comorbid disease rates were higher in the patient group. In this study, we found that the presence of comorbid disease increased the risk of 5.6-fold bleeding. The most common comorbidities in the study of Shireman et al. were hypertension and heart disease.[10] The most common comorbidities in this study were hypertension, heart disease, and diabetes. The reason why the group of patients with the comorbid disease is riskier for bleeding might be the use of multiple drugs and drug interactions, so these patients should be adequately informed and monitored at regular intervals.

When the stroke history was compared between the groups, we found that the stroke rate was higher in the control group. In our study, we found that the presence of a stroke history increased the risk of major bleeding 3.2-fold. Landefeld et al. Also found that stroke history increased the risk of major bleeding.[5] Patients with a history of stroke should be considered risky in terms of major bleeding.

As a result, it should be noted that the group of patients with long-term anticoagulation indications will face some problems. In addition to changing the standard of living of the patient and the habit of going to the physician, physicians need to give enough time to this patient group and inform the patients. The most important limitations of warfarin are metabolism and frequent laboratory monitoring. Anticoagulant drugs, which are effective in long-term anticoagulation and do not require laboratory monitoring and do not have

drug-nutrient interaction, have revolutionized this field. In fact, oral direct thrombin inhibitors and factor Xa inhibitors have been used in this field, and oral direct antithrombin inhibitor has been indicated for use in AF and ischemic stroke prophylaxis. In these circumstances, the throne of the warfarin was shaken. However, in indications such as prosthesis heart valve and childhood thrombosis, warfarin remains a gold standard treatment option.

The limitation of the study was that the sample group was smaller than other similar studies.

Ethical Considerations: The University Medical Faculty Ethics Board approved the study. (Number: 2008/101).

Conflict of Interest: The authors declare no conflict of interest.

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