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Effective INR Level May Be Delayed in Secondary Prevention of Stroke Due to Atrial Fibrillation with Warfarin in the Patients with Diabetes Mellitus

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ABSTRACT

Introduction: Warfarin is a drug used for anticoagulation in diseases, especially atrial fibrillation (AF). The effectiveness of warfarin is monitored by the International Normalized Ratio (INR) and should be kept between 2.0 and 3.0 in the AF clinic. This drug the significant variability in dose response and the narrow therapeutic index among individuals. However, the effective INR level may not be achieved due to some reasons, or the time to achieve the effective INR level may lengthen. Our aim in this study is to investigate whether there is a difference in terms of dose and duration in achieving the effective INR level by the warfarin treatment due to the coexistence of AF and stroke between patients with and without diabetes mellitus (DM).

Methods: A total of 70 patients whose warfarin treatment was initiated due to non-valvular AF and who were diagnosed with acute ischemic stroke were included in the study, 30 of these patients were DM patients and 40 were non-DM patients. The total dose and time values at achieving the effective INR level after the initiation of warfarin treatment according to the clinical protocol during follow-ups in hospital were statistically compared between the two groups.

Results: In the study, it was found that the total warfarin dose was significantly higher in the DM group compared to the non DM group ($p<0.05$). It was detected that the time to achieve the effective INR level was also significantly longer in the DM group than in the non-DM group ($p<0.05$).

Conclusion: In the presence of DM diagnosis, the higher dose warfarin and longer follow-up are required to achieve effective INR levels in stroke patients whose warfarin treatment was initiated due to non-valvular AF.

Keywords: Warfarin, INR, diyabetes mellitus, stroke

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INTRODUCTION

Stroke is one of the leading causes of morbidity and mortality and is a global health problem (1, 2). Approximately 80% of all strokes are ischemic type, and hypertension (HT), DM and AF are the most common risk factors. According to the Trial of Org 10172 Acute Stroke Treatment (TOAST) classification, cardioembolic stroke accounts for about 30–35% of ischemic stroke subtype and the most common etiologic cause is AF (3, 4). Due to the increase of the elderly population in communities and therefore the increase of AF rate; the cardioembolism continues to be the cause of ischemic stroke increasingly compared to the past, and this also points to several strategies. Especially in the strokes for which no cause can be identified, the idea that the cause is an embolic event is increasing. In addition, the presence of paroxysmal AF is more frequently detected with long-term monitoring of heart rhythm whose use increasingly continues in recent years (5, 6). AF prophylaxis should be done without delay in order to prevent the stroke and reduce the recurrence stroke. Oral anticoagulant which is vitamin K antagonist (warfarin), is recommended for the prophylaxis of thromboembolism caused by AF according to current guidelines (Class 1, Level of evidence A). Warfarin is the keystone of oral anticoagulant treatment for approximately sixty years and most commonly used in AF with a rate of 40–60% (7, 8).

Warfarin has the significant variability in dose response and the narrow therapeutic index among individuals. The INR value should be kept between 2.0 and 3.0 for most indications. It is targeted that the effective INR level for AF should be between 2 and 3 by decreasing or increasing the warfarin dose according to the frequent INR measurements (9).

According to our clinical observations; in patients whose warfarin treatment was initiated due to ischemic stroke caused by AF, the effective INR level can be achieved in longer duration and with higher doses of warfarin in the patients with DM compared to the patients without DM. The aim of this study is to investigate the effect of DM diagnosis in the ischemic stroke patients with non-valvular AF on the dose and duration of the warfarin treatment initiated to achieve the effective INR levels.

METHODS

The files of 2337 patients who were followed up for acute ischemic stroke by hospitalizing between January 2016 and June 2018in the Neurology Clinic of Sakarya University Training and Research Hospital, were reviewed retrospectively. Patients whose warfarin treatment was initiated according to the clinical protocol due to non-valvular AF at their hospitalization, were included in the study (Table 1).

Inclusion criteria: Patients between the ages of 18–95, patients who admitted to emergency department due to acute ischemic stroke and were

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newly diagnosed AF by 12-lead electrocardiography, patients with normal INR, patients who did not receive thrombolytic therapy, patients who were followed up in inpatient clinic until achieving the effective INR level.

Exclusion criteria: Patients with liver and kidney failure, patients with severe heart failure, patients with atrial thrombus or segmental wall motion defect detected on echocardiography, patients with antiepileptic-antibiotic-antifungal-NSAID-statin-amiodarone and antithyroid drug use, patients using oral anticoagulant therapy before hospitalization, pregnant patients, patients with cachexia or morbid obesity, patients whose warfarin treatment was discontinued due to hemorrhagic complications during hospitalization, patients using insulin prior to hospitalization, patients using oral antidiabetic drugs, patients with high fever.

Ischemic stroke patients whose warfarin treatment was initiated due to non-valvular AF were included in the study, 30 of these patients were newly diagnosed with DM and 40 were non-DM patients.

The patients were followed up for acute ischemic stroke in clinic, and warfarin treatment was initiated due to non-valvular AF was started. All of the patients were patients who were follow up in clinic until the level of INR becoming to range between 2 and 3.

The clinical protocol of warfarin dose adjustment for effective INR level in our clinic is indicated in Table 1.

The time and the total warfarin dose to achieve total effective INR level were determined, and these values were statistically compared to detect whether there was a significant difference between the groups.

Statistical Analysis

Mean, standard deviation, median lowest, median highest, frequency and ratio values were used in the descriptive statistics of the data. The distribution of the variables was measured by the Kolmogorov-Smirnov test. The Mann-whitney U test was used in the analysis of quantitative independent data. The Wilcoxon test was used in the analysis of the dependent quantitative data. Chi-square test was used to analyze qualitative independent data. SPSS 22.0 program was used in the analyzes.

RESULTS

A total of 30 DM patients (16 males) had a mean age of 72.2±11.9 years. A total of 40 patients (14 males) in the non-DM group had a mean age of 73.4±12.6 years. When the age and gender distribution of both groups were compared, no significant difference was found (p>0.05). In the group with and without DM; there was no difference between the two groups in terms of hypertension (HT), hyperlipidemia (HL) and coronary artery disease (CAD) (p: 0.935, p: 0.583, p: 0.546). Smoking rate was significantly higher in patients with DM than in patients without DM (p<0.05). In the DM patients group, total warfarin dose to achieve effective range of INR was 33.0±13.1 mg, while it was 24.4±7.5 mg in the non-DM patient group and statistically higher in the DM group (p<0.05). The time required for the INR to achieve the effective range was 4.5±1.5 days in the DM patients group, 3.6±0.9 days in the non-DM patients group and significantly longer in the DM patients group (p<0.05). The first and last INR values did not differ significantly in patients with and without DM (p>0.05) (Table 2).

The warfarin given to the effective range of INR in the HT group and the non-HT group did not show any significant difference (p>0.05). In patients with and without HL, warfarin dose did not show significant differences (p>0.05). In patients with and without CAD, warfarin dose did not show significant differences (p>0.05). In the patients between smokers and non-smokers warfarin dose did not show significant differences (p>0.05) (Table 3).

In both groups, there was a significant increase between the first measured INR value and the effective INR values (p<0.05) (Table 4).

Table 1. The dose schedule of Warfarin treatment for effective INR level

Day of treatment	INR	Dose of Warfarin
1	<1.5 1.5–1.9	5 mg
2	<1.5 1.5–1.9	Continue with the first dose
3	<1.5 1.5–1.9	Raise the dose to 1.5 times the initial dose Continue with the initial dose
4	<1.5 1.5–1.9	Raise the dose to 1.5–2 times the initial dose Raise the dose to 1.5 times the initial dose
5	<1.5 1.5–1.9	Raise the dose to 2 times the initial dose Raise the dose to 1.5 times the initial dose
6	<1.5 1.5–1.9	Raise the dose to 2 times the initial dose Raise the dose to 1.5–2 times the initial dose
7	<2	Raise the dose to 2 times the initial dose

DISCUSSION

Warfarin is an anticoagulant agent that acts on vitamin K. Vitamin K is required for the function of anticoagulant proteins C and S with coagulation factors II, VII, IX and X. Warfarin shows its effect by inhibiting the effect of vitamin K on coagulation factors and decreasing functional factor concentrations (10). Although warfarin is an important anticoagulant agent frequently used in clinical practice, the large variability associated with narrow therapeutic index and dose response may cause adverse effects such as bleeding. Therefore, in patients who have started treatment, the drug doses should be determined according to the INR levels to be measured at certain intervals and should be continued after achieving the effective INR level. The main goal should be to achieve a rapid dose of effective INR, considering that some patients may develop high doses of hemorrhage or ineffective INR may cause recurrent stroke (11). Dose response relationship change is associated with genetic, diet, comorbidities (such as acute disease, liver failure, alcohol consumption) and drug-drug interactions (12). Due to the complex multistage metabolism of warfarin, the vast majority of their interactions are mediated by CYP2C9, 1A2, 2C19 and 3A4 isoenzymes. Inhibitors or inducers of these enzymes influence the pharmacological activity of warfarin and consequently the INR values. Eventually, adverse drug reactions due to these interactions lead to events that can be severe, life-threatening, and even fatal. There is no convincing evidence that warfarin interferes with any food or food (except vitamin K) through the modulation of CYP2C9 activity (13, 14). There are many studies examining warfarin metabolism and drug-drug interactions. It is known that anti-aging drugs, antibiotic-antifungal drugs, antiepileptic drugs, antiarrhythmic drugs, statins, NSAIDs and some central nervous system drugs enter drug interaction with warfarin (15–17).

Although its mechanism has not been clearly elucidated in recent years, DM is thought to be effective on warfarin dose response. Studies have emphasized that increased risk for thromboembolic complications in patients with DM may be due to differences in the function of various endogenous proteins associated with hemostasis, including protein C and tissue factor pathway inhibitors. It is also clear from the available evidence that DM patients suffer from various vascular diseases potentially causing thromboembolic anxiety (18–23). In a study conducted by Johnson and colleagues on 911 patients with DM and warfarin, patients were divided into two groups according to HbA1 c (HbA1 c <8 and HbA1 c >8) to

Table 2. Comparison of demographic data, comorbid status, INR dose and duration in DM and non-DM patients

		DM (-)				DM (+)				p	
		Mean ± s. s. /n-%			Median	Mean ± s. s. /n-%			Median		
Age		73.4	±	12.6	76.5	72.2	±	11.9	72.5	0.605	m
Gender	Man	14		35.0%		16		53.3%		0.125	X^2
	Woman	26		65.0%		14		46.7%			
HT	(-)	9		22.5%		7		23.3%		0.935	X^2
	(+)	31		77.5%		23		76.7%			
HL	(-)	34		85.0%		24		80.0%		0.583	X^2
	(+)	6		15.0%		6		20.0%			
CAD	(-)	31		77.5%		25		83.3%		0.546	X^2
	(+)	9		22.5%		5		16.7%			
Smoking	(-)	36		90.0%		21		70.0%		0.033	X^2
	(+)	4		10.0%		9		30.0%			
Warfarin Dose		24.4	±	7.5	22.5	33.0	±	13.1	31.3	0.005	m
Effective Dose Duration		3.6	±	0.9	4.0	4.5	±	1.5	4.0	0.013	m
HgbA1C		5.8	±	0.4	5.9	7.2	±	1.3	6.9	0.000	m
Initial INR		1.1	±	0.1	1.1	1.0	±	0.1	1.0	0.069	m
Last INR		2.4	±	0.3	2.4	2.4	±	0.3	2.4	0.673	m

[m] Mann-Whitney U test/X^2 Chi-square test
DM, Diabetes mellitus; HT, hypertension; HL, hyperlipidemia; CAD, coronary artery disease; TOAST, Trial of Org 10172 in Acute Stroke Treatment; INR, international normalised ratio.

Table 3. Comparison of warfarin dose in terms of HT, HL, CAD and smoking

	Warfarin Dose			
	Min-Max	Median	Avg ± S. D	p value
HT (-) (+)	15.0–57.5 15.0–60.0	22.5 25.0	29.9±12.1 28.4±10.8	0.395 [m]
HL (-) (+)	15.0–60.0 15.0–57.5	25.0 26.3	27.2±10.2 32.1±14.1	0.237 [m]
CAD (-) (+)	15.0–60.0 17.5–57.5	25.0 25.0	27.5±10.4 30.5±13.3	0.461 [m]
Smoking status (-) (+)	15.0–60.0 15.0–57.5	25.0 30.0	27.6±10.8 30.0±12.4	0.514 [m]

[m] Mann-whitney U test, HT: Hypertension, HL: Hyperlipidemia, CAD: Coronary artery disease

Table 4. Comparison of initial and effective INR levels in both groups

INR	Min-Max	Median	Avg ± S. D	p value
First measured level	0.8–1.4	1.1	1.1±0.1	0.000w
Last measured level	2.0–3.0	2.4	2.4±0.3	

w, Wilcoxon test

investigate whether they affected the mechanism of glycemic control anticoagulation and hyperglycaemia did not lead to poor anticoagulation (24). Stage and colleagues evaluated the effect of antidiabetic drugs on patients receiving warfarin therapy, and emphasized that oral antidiabetic and insulin therapy, especially metformin, may reduce the INR level during warfarin use (15).

In our study, which was the first study to evaluate the effect of DM on achieving effective INR value in patients with acute ischemic stroke who had AF-induced ischemic stroke and who started warfarin treatment for secondary prophylaxis, patients with DM were found to have a higher dose of warfarin and a higher duration to achieve effective INR levels than non DM patients. All newly diagnosed DM patients in our study consisted of patients who started insulin only during admission for hyperglycemic control. Patients with drug use such as antiepileptic, antibiotic, antifungal, thyroid hormone, nonsteroidal anti-inflammatory drug, statin and amiodarone, which may interact with warfarin, have been excluded. According to a study by Minno et al., The exact effect of steady-state interactions may not be apparent for 2 to 3 weeks, depending on the interacting agent used. Similarly, if the inducer is interrupted, a washout period of several weeks may be required before hepatic enzymes normalize (16). For this reason, all patients in our study who were trying to prevent this effect were advised that both insulin and warfarin therapy were started at the same time as hospitalization. It is thought that the duration of excess and duration of warfarin dose required to achieve effective INR level in DM subjects compared to non DM subjects is due to the fact that DM significantly influences anticoagulation but not drug-drug interactions. For this reason, it can be predicted that patients with DM should begin with warfarin at a dose 1.5–2 times higher than the routine initial treatment to achieve effective INR levels, thus producing faster anticoagulant effects.

CONCLUSION

In conclusion, it has been found that in patients with DM who started treatment with warfarin, DM has achieved higher dose and longer duration of effective INR level because it slowed down the anticoagulation process. Therefore, if there is no significant haemorrhagic risk in these patients, warfarin dosing may be administered at a higher dose than routine administration, and the effective dosing of INR may be targeted in a shorter time. Future prospective studies should aim to explore this relationship in an independent environment and explore possible mechanisms.

Limitations: The most important deficiency in this study is that the study protocol is retrospective and the data obtained are examined according to the file records. A second shortcoming is that the number of patients is low.

Ethics Committee approval: The ethical approval was obtained from the Sakarya University Faculty of Medicine Ethics Committee for our study.

Informed Consent: The informed consent form was taken in accordance with the protocol..

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - TA; Design - TA; Supervision - BAA; Resource - YGA; Materials - SSG; Data Collection and/ or Processing - TA, YGA, BAA, SSG; Analysis and/ or Interpretation - TA, YGA; Literature Search - SSG; Writing - TA, YGA, BAA; Critical Reviews - BAA, SSG.

Conflict of Interest: There is no financial or personal conflict of interest in this study.

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