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Efficacy and Safety of Warfarin Experience in a Stroke Polyclinic in Stroke Patients

Bir İnme Ünitesinde Kardiyoembolik İnmede Warfarin Deneyimi

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ABSTRACT

Introduction: Cardioembolic stroke is associated with high morbidity and mortality, with an increased risk of recurrent stroke. Oral anticoagulation is highly effective in reducing the risk of stroke and mortality compared with placebo. Our study aimed to highlight the safety and efficacy of warfarin by analyzing the 20-year follow-up of patients on warfarin therapy.

Methods: A retrospective observational study was performed with ischemic stroke patients receiving warfarin at our stroke polyclinic between 1992 and 2012. The CHADS2 scoring system was used to assess the annual risk of stroke, and a bleeding risk score termed the HAS-BLED scoring system was calculated to estimate the risk of bleeding.

Results: In our study, 394 patients who were receiving warfarin therapy were included. The patients' median age was 66.35±13.602 years. The median follow-up period of the patients was 4.85±3.572 years. During follow-up, 79.9% of the patients revealed no complication on warfarin therapy. Thirty-seven patients had hemorrhagic complications; among these, 33 had systemic complications (including nose bleeding, hematuria, hematochezia) and 4 patients had intracerebral bleeding. The INR value related to hemorrhagic complications was >2.5 in 75.8% of 33 patients having systemic bleeding and in 75% of 4 patients having intracerebral bleeding. The HAS-BLED risk score was >3 in 72.7% of the patients experiencing systemic bleeding complications. Forty-one patients had a recurrent ischemic stroke/TIA during the follow-up. Of this patient group, the INR value at the time of recurrent ischemic stroke was <2 in 41 patients (92.7%), while the CHADS2 risk score was low in this group. Sixty-eight patients were receiving antiplatelet therapy with warfarin. In these groups, 16 patients experienced a complication during the follow-up (bleeding/ischemic), while 10 patients had bleeding complications (systemic and intracerebral).

Conclusion: The results suggest that the effectiveness and safety of warfarin depend on maintaining its dose at sufficient levels to keep the patient's INR within the therapeutic range.

Keywords: Warfarin, safety, efficacy, stroke

ÖZ

Amaç: Kardiyoembolik inme, tekrarlayan inme riski ile birlikte yüksek morbidite ve mortalite ile ilişkilidir. Oral antikoagülanlar plaseboya göre mortaliteyi ve inme riskini azaltmada oldukça etkilidirler. Çalışmamız warfarin tedavisi altında olan 20 yıl içinde takip ettiğimiz hastalarda ilacın etkinlik ve güvenirliğini ortaya koymak amacıyla planlanmıştır.

Yöntem: Retrospektif olarak planlanan çalışmamıza İnme ünitemizde 1992-2012 yılları arasında varfarin tedavisi alarak takip edilen iskemik inme tanılı hastalar dahil edildi. İnme riskini belirlemede CHADS skoru, kanama komplikasyonunun belirlemede HASBLED skoru kullanıldı.

Bulgular: Çalışmaya 394 hasta dahil edildi. Hastaların ortalama yaşı 66,35±13,60, ortalama izlem süreleri 4,85±3,57 yıldı. %79,9 hastada varfarin bağlı herhangi bir komplikasyon gözlenmedi. Otuz yedi hastada kanama komplikasyonu; 33 hastada sistemik kanama (burun kanaması, hematüri, hematokezya), dört hastada intraserebral kanama geliştiği görüldü. 33 hastanın %75,8'inde ve dört hastanın %75'inde INR değeri >2,5 idi. Sistemik kanama geçiren hastaların %72,7'sinde HAS-BLED skoru >3 idi. İzlem süresince 41 hastada tekrarlayan iskemik inme/GİA gözlendi. Bu hastaların %92,7'sinde INR değeri <2 ve CHADS skoru düşüktü. Altmış sekiz hasta varfarin ile birlikte antiplatelet tedavi almaktaydı. Bu grupta 16 hastada komplikasyon geliştiği; 10'unda sistemik/intraserebral kanama olduğu görüldü.

Sonuç: Varfarinin etkinlik ve güvenirliği hastaların INR değerlerinin terapötik aralıkta tutulması ile yakından ilişkilidir.

Anahtar kelimeler: Etkinlik, güvenirlik, varfarin, inme

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INTRODUCTION

As an anticoagulant normally used in the prevention of thrombosis and thromboembolism, warfarin inhibits the synthesis of vitamin K-dependent clotting factors (II, VII, IX, X) and the antithrombotic factors protein C and protein S. Warfarin is currently the most widely applied anticoagulant in the world, and the root cause of the increase in its use over the last decade may be traced to overwhelming evidence of its effectiveness in preventing embolic strokes in patients with atrial fibrillation (AF) (1).

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The most frequently observed side effect of warfarin appears to be hemorrhage. The risk of bleeding is augmented if the international normalized ratio (INR) is out of range. The most accurate clinical prediction rule for estimating the risk of bleeding is the HAS-BLED score (2). Despite its effectiveness, treatment with warfarin has several shortcomings. A high INR predisposes a patient to a high risk of bleeding, while INR below the therapeutic target indicates that the dose of warfarin is insufficient to offer protection against thromboembolic events. Such limitations have provided the stimulus for the development of new oral anticoagulants expected to overcome the drawbacks of anticoagulant therapy.

Our study aimed to determine the safety and efficacy of warfarin by analyzing the 20-year follow-up of patients on warfarin therapy.

METHODS

Patient Ascertainment

A retrospective observational study was performed using a convenience sample of patients receiving warfarin in our stroke polyclinic between 1992 and 2012. Inclusion criteria included patients who suffered from ischemic stroke on warfarin therapy and who were followed up monthly. The indications for management of patients with warfarin included a wide spectrum of disorders, as shown in Table 1. Data were collected from patient records at our stroke polyclinic, and chief complaints, history of present illness, past medical history, medication history, and initial and follow-up INR levels were all recorded as part of a routine neurological assessment. Bleeding complications and thromboembolic events were all retrieved from the recorded data in an attempt to determine a possible relationship between the intensity of anticoagulation and adverse outcomes.

Patient Evaluation

The C for Congestive Heart Failure, H for High Blood Pressure, A for Age, D for Diabetes (CHADS2) scoring system is a simple method used to assess the annual risk of stroke in AF. In the CHADS2 scoring system, each point increases the annual risk of stroke by a factor of 1.5.

In this study, CHADS2 was used for recurrent ischemic stroke risk classification with independent risk factors: one point was given for the presence of congestive heart failure, hypertension (systolic >160 mmHg), age greater than 75 years, and diabetes, and two points were given for prior cerebral ischemia (3).

A bleeding risk score termed HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly) was calculated to estimate the risk of bleeding for patients on warfarin therapy (4). Also, the time of the adverse events were noted from the first day of the warfarin therapy during the follow-up.

Ethics committee approval was received for this study from the ethics committee of Bakırköy Education and Training Hospital of Neurology, Neurosurgery, and Psychiatry.

Statistical Analysis

The Statistical Package for the Social Sciences statistical software package version 16 (SPSS Inc; Chicago, IL, USA) was used for data processing. Descriptive statistics were used for the demographic features of the cohort. Statistical analysis was performed by the use of the Pearson chi-square test, and a p value <0.05 was chosen for statistical significance.

Table 1. Indications for the management of patients with warfarin include a wide spectrum of disorders

Warfarin indications	n (%)
Lone AF	39.1
İsolated left ventricular akinetic/hypokinetic segment	24.1
No cardioembolic source	10.2
Transient ischemic attack	7.1
Valvular heart disease	6.6
Left ventricular akinetic/hypokinetic segment with AF	5.8
Genetic prothrombotic risk factors	3.8
Patent foramen ovale	2
Recurrent stroke on dual antiagregan therapy	0.8
Atrial septum aneurysm	0.3
Intraatrial thrombus	0.3

AF: atrial fibrillation

Table 2. Baseline clinical characteristics of patients on warfarin therapy

Baseline characteristics	Value
No. patients	394
Male sex	226 (57.4)
Age, years	66±13
Hypertension	196 (49.7)
Diabetes mellitus	76 (19.3)
Heart failure	64 (16.2)
History of stroke/TIA	64 (16.2)
Coronary artery disease	54 (13.7)
Hypercholesterolemia	51 (12.9)
Previous bleeding episode	1 (0.002)
Peripheral vascular disease	4 (0.01)
Concomitant treatment	
Antiplatelet therapy	68 (17)
ACEI/ARB	111(28.1)
Calcium antagonist	67 (17)
β-blocker	78 (19.7)
Statins	71 (18)
Digoxin	33 (0.08)
Diuretic	10 (0.02)

Data are presented as n (%) or median (interquartile range). TIA: transient ischemic attack; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker

RESULTS

In our study, 394 patients who were receiving warfarin therapy were included. The clinical characteristics of the study cohort are presented in Table 2. The patients' median age was 66.35± 13.602 years. The median follow-up period of the patients was 4.85±3.572 years.

During follow-up, 79.9 % of the patients revealed no complication on warfarin therapy. Thirty-seven patients had hemorrhagic complications;

Table 3. Risk stratification according to cardioembolic and bleeding scores

	CHADS2		HAS-BLED	
	Score	Number of % patients	Score	Number of % patients
Low risk	0	9.8	<3	27.3
Intermediate	1	34.1		
High risk	≥2	56	≥3	72.7

CHADS2: C for Congestive Heart Failure, H for High Blood Pressure, A for Age, D for Diabetes; HAS-BLED: Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly

among these, 33 had systemic complications (including nose bleeding, hematuria, hematochezia) and 4 patients had intracerebral bleeding. The INR value related to hemorrhagic complications was >2.5 in 75.8% of 33 patients having systemic bleeding and in 75% of 4 patients having intracerebral bleeding. The HAS-BLED risk score was >3 in 72.7% of the patients experiencing systemic bleeding complications (Table 3).

Forty-one patients had a recurrent ischemic stroke/TIA during the follow-up.

Of this patient group, the INR value at the time of recurrent ischemic stroke was >2 in 41 patients (92.7%), while the CHADS2 risk score was low in this group (Table 3).

Sixty-eight patients were using antiplatelet therapy with warfarin. In this group, 16 patients experienced a complication during the follow-up (bleeding/ischemic) (p=0.240). Ten patients had bleeding complications (systemic and intracerebral) (p=0.082).

DISCUSSION

Cardioembolic stroke is associated with high morbidity and mortality, with an increased risk of recurrent stroke. Oral anticoagulation (OAC) is highly effective at reducing the risk of stroke and mortality compared with placebo or control (5). In this study, our primary goal was to show the need to use OAC therapy, and its safety and efficacy by analyzing the 20-year follow-up of our patients.

There are several well-established indications for long-term oral anticoagulation, including AF, valvular heart disease, and some categories of venous thromboembolic disease. Apart from the estimated benefits and risks of long-term oral anticoagulation in an individual patient, many practical issues that interfere with the management of such treatment should also be considered thoroughly. These issues may include compliance, factors causing high INR variability, and the necessity of frequent monitoring. Involving patients in the decision and treatment management greatly improves the efficacy and safety of long-term oral anticoagulation. In our study, 394 patients were informed and monitored regularly during the follow-up, with AF being the most commonly detected reason for oral anticoagulation.

Validated schemas for assesing the risk of stroke in patients with AF include the CHADS2 score, which can determine whether specific patient characteristics or risk factors are predictive of first hospitalization (3,6,7,8). We used the CHADS2 score for predicting the risk of recurrent ischemic stroke in our study group. There are studies in the literature investigating whether these scores are associated with stroke outcome in non-AF stroke patients (9). As the components of the CHADS2 score include the same risk factors that lead up to a recurrent stroke (i.e., congestive heart failure, hypertension, age, type 2 diabetes, previous stroke/TIA), we also approved the use of this score for predicting a recurrent ischemic stroke. During follow-up, 41 patients had a recurrent ischemic stroke/TIA. The CHADS2 risk score was low in this group. This means these patients had a low risk of a recurrent ischemic stroke, whereas 92.7% of their INR levels were ineffective. Adjusted-dose warfarin with a target INR of 2 to 3 is used for certain patients with nonvalvular or valvular AF. A target INR of 2.5 to 3.5 was used for patients with a mechanical prosthetic cardiac valve. Below these levels, oral anticoagulant therapy has proven to be ineffective for a recurrent stroke. In our study group, as the CHADS2 score was low, the most estimated risk for a new stroke was the ineffective INR level. There were 3 patients with a recurrent stroke during the follow-up, while use of the INR levels were effective, 2 of them had no cardioembolic etiology for anticoagulant usage. The need to use warfarin resulted from the fact that they had ischemic stroke under dual antiagregan therapy.

Although warfarin is highly effective, it may result in bleeding. Data on the risk of bleeding are surprisingly limited, perhaps because the rates vary as a result of study design and population, definition, site of bleeding, and drug dosage. The annual incidence of bleeding in trials has been reported to be between 1.1% and 2.3% in patients treated with warfarin to achieve an INR of 2.0-3.0 (9). The European and Canadian guidelines for AF management recommend the use of the HAS-BLED bleeding risk score to assist in estimating the risk of bleeding (4,10,11). The incidence of bleeding events is higher with a higher HAS-BLED score. Annual bleeding rates are exceeded at an HAS-BLED score of >3.

During the follow-up, 37 patients presented with a hemorrhagic event; of these, 4 (1%) were intracranial hemorrhages. Thirty-three patients had systemic bleeding, 75.8% of whom had high INR levels during the incidents. Eight patients presented with systemic bleeding while their INR levels were in effective ranges: 5 of these were hypertensive, while 2 of them were under dual antiagregan therapy (warfarin+ aspirin). Four patients had intracerebral hemorrhages and 3 patients (75%) had high INR levels during the events. Only one patient's INR level was effective but he was under dual antiagregan therapy (warfarin+aspirin) for prostethic valve disease.

In a systematic review, some patient characteristics, such as advanced age, uncontrolled hypertension, history of ischemic heart disease, cerebrovascular disease, anemia, or history of bleeding, and the concomitant use of other drugs, such as antiplatelet agents, were identified as risk factors for anticoagulation-related bleeding complications (12). Although the INR levels were within expected ranges, there were additional risk factors for hemorrhagic complications, as was also the case with our patients. Correspondingly, the incidence of bleeding complications was higher with a higher HAS-BLED score (72.7% of patients' HAS-BLED scores were ≥3 for systemic bleeding, while 50% of patients' HAS-BLED scores were ≥3 for intracerebral hemorrhages). Bleeding complications resulted from not only the high INR levels, but also from high HAS-BLED scores. So, this score enabled us to make predictions on bleeding incidences in our study group.

The main challenge for clinicians is to maintain patients on warfarin once the decision is made to initiate anticoagulation. Interruptions or discontinuations in warfarin use can lead patients to experience a recurrent stroke and bleeding events. However, we saw that once warfarin therapy was continued and INR monitored regularly, complications rarely occur.

Mitigation of the risk of hemorrhage is critically important as these incidences are associated with significant morbidity and often precipitate the termination of therapy. Therefore, strategies to decrease this risk need to be aggressively sought and implemented. The control of blood pressure has been shown to significantly reduce the risk (13). The benefits achieved through the addition of aspirin to warfarin for cardiovascular disease need to be rigorously defined and justified (14,15,16). Recent guidelines advise against this combination for older patients with AF and stable coronary disease (17).

However, in our study group, patients on dual therapy (ASA+warfarin) experienced np more complications than patients on warfarin therapy alone. Also the bleeding complications were not statistically significant in the combination group (p=0.082). This means that in our study, the most reasonable factor for a new event (either ischemia or hemorrhage) was the INR level.

Variations of bleeding complications among studies in the literature could be attributed to variable INR target ranges and time spent in the therapeutic range. The incidence of intracranial hemorrhage is directly related to INR intensity, which significantly increases above an INR of 3.5 (18). Also, the first 3 months of warfarin treatment are associated with a higher risk of bleeding (19). As warfarin interacts with many medications and foods and has a long half-life, patients receiving warfarin are often at risk of over- or under-coagulation and need to be tested regularly to monitor their blood coagulation. INRs derived from prothrombin time are the strongest and most consistent predictors of bleeding complications. However, patients can be taught how to regulate their diets, medications, and monitoring of the drug by time.

In conclusion, there are many ischemic stroke patients who are being monitored and who are receiving warfarin regularly without any complications.

It seems that the effectiveness and safety of warfarin depends on maintaining its dose at sufficient levels to keep the patient's INR level within the therapeutic range.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Bakırköy Training and Education Hospital of Neurology, Neurosurgery and Psychiatry.

Informed Consent: Written informed consent was not needed to be obtained from patients who participated in this study as the study was retrospective and the names of the patients were not mentioned.

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