



Prognosis in Patients Who were Diagnosed as Having Stroke, Using Warfarin, and Aged Over Eighty Years: A Clinical Observation

Seksen Yaş Üstü Varfarin Kullanan İnme Tanılı Hastalarda Prognoz: Klinik Gözlem

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Abstract

Objective: Warfarin treatment is a partially preferred prophylactic treatment in patients with ischemic stroke with advanced age due to possible adverse events/drug interactions. In this study, we aimed to investigate the frequency of warfarin use, possible adverse events, and reasons for discontinuation of treatment in patients with stroke aged over 80 years.

Materials and Methods: One hundred eighty-nine of 589 patients with stroke were detected retrospectively who were over 80 years and were followed up for cardioembolic stroke between 2014 and 2018. Demographic/clinical/laboratory/radiologic data together with the reasons for discontinuation of the drug were gathered from their medical records and noted in an Excel form.

Results: One hundred eighty-nine patients (88 women) were included in the study. The mean duration of warfarin use was noted as 5.02 ± 3.4 years (minimum 6 months, maximum 11 years). Ninety-four (49.7%) were treated with new oral anticoagulants in the last 2 years due to adverse events and/or social reasons, and 90 (47.6%) were on regular follow-up with warfarin. Gastrointestinal (GIS) bleeding was noted as the most common adverse event causing drug discontinuation (41.4%), and the most important risk factor for GIS symptoms was antihyperlipidemic drug use ($p=0.001$). Irregular hypertension was the most important risk factor for adverse events due to its triggering impact on bleeding ($p<0.001$). The mean international normalized ratio (INR) level during intense bleeding was calculated as 3.8 ± 1.3 . Patients with an INR level of 2.5 or higher were more likely to experience other drug-related adverse events (peripheral edema, diarrhea, shortness of breath, headache, dizziness) compared with other INR values ($p=0.003$).

Conclusion: Especially in older stroke patients under antihyperlipidemic treatments, avoiding unnecessary drug use and making sure that the patient reaches required prophylaxis without being dependent on age is crucial.

Keywords: Elderly, stroke, warfarin, adverse effects

Öz

Amaç: İleri yaş iskemik inmeli hastalarda olası yan etkiler/ilâç etkileşimleri nedeniyle varfarin tedavisi klinik pratikte kısmen tercih edilen bir profilaksidir. Bu çalışmada seksen yaş üstü inme geçirmiş hastalarda varfarin kullanım sıklığını, olası yan etkileri ve tedavi kesilme nedenlerini araştırmayı amaçladık.

Gereç ve Yöntem: Kardiyembolik inme tanısı ile 2014-2018 yılları arasında takip edilen, varfarin kullanan 80 yaş üstü 589 hastadan düzenli takibe gelen 189'u retrospektif olarak tespit edildi. Dosyalarından demografik/klinik/laboratuvar/radyolojik bilgileri, ilacı sürdürme ve bırakma nedenleri Excel formatında kayıt edildi.

Bulgular: Seksen sekizi kadın 189 hasta dahil edildi. Varfarin kullanım süresi ortalama $5,02 \pm 3,4$ yıl (minimum 6 ay, maksimum 11 yıl) idi. Doksan dördünün varfarine bağlı (%49,7) yan etki ve/veya sosyal nedenlerle son 2 yıl içinde yeni oral antikoagülanlara tedavisi değiştirilmişken, 90'ı varfarinle düzenli takipteydi (%47,6). İlaç kesimine neden olan en sık yan etki gastrointestinal (GIS) kanama (%41,4) iken, GIS semptomları için en önemli risk faktörü antihiperlipidemik ilâçlardı ($p=0,001$). Düzensiz hipertansiyon ise kanama yan etkisini tetikleyen en önemli risk faktörü olarak izlendi ($p=0,001$). Majör kanama yan etkisi ile ilişkili ortalama uluslararası normalleştirilmiş oran (INR) düzeyi $3,8 \pm 1,3$ idi. INR düzeyi 2,5 ve üstü olan hastalarda diğer INR değerlerine göre anlamlı düzeyde daha fazla ilaca bağlı yan etkiler (periferik ödem, diyare, nefes darlığı, baş ağrısı, sersemlik hissi) görüldü ($p=0,003$).

Sonuç: İleri yaş inmeli hastalarda antihiperlipidemik tedaviler başta olmak üzere gereksiz ilâç kullanımından kaçınmak; sadece yaşa bağımlı kalmayarak hastanın ihtiyaç duyduğu profilaksiye ulaşmasını sağlamak önemlidir.

Anahtar Kelimeler: İleri yaş, inme, varfarin, yan etki

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Introduction

Stroke has high mortality and is one of the most common neurologic diseases that cause disability in society. Determining the risk factors leading to stroke is one of the most important steps in stroke prophylaxis. Although hypertension (HT), diabetes, and hyperlipidemia are among the modifiable risk factors for stroke, age is one of the major risk factors associated with stroke that cannot be modified. The older population is increasing in developed societies and older age carries greater risk for both ischemic and hemorrhagic stroke. The risk of stroke increases more than 2 times in both men and women every decade after age 55 years, and 75-89% of those who have a stroke are aged over 65 years. Of these, 50% are aged over 75 years and 25% are aged over 85 years (1,2). In addition, the profile of risk factors varies depending on age. Older individuals (especially ≥ 75 years) are at great risk for atrial fibrillation (AF) and AF-associated cardioembolic ischemic stroke (3). Stroke risk associated with AF has been reported as 1.5% between the ages of 50 and 59 years and 23.5% between 80 and 89 years (4,5,6,7,8).

Anticoagulant therapy is the gold standard in cardioembolic stroke prophylaxis. It is observed that appropriate prophylaxis cannot be performed in this age group because the use of warfarin with other medical treatments may cause serious adverse effects. A history of intracranial and/or gastrointestinal (GIS) bleeding and the presence of cognitive impairment, especially in patients aged over 80 years, significantly restrict the use of warfarin (2,9). Therefore, in order to reduce the risk of possible drug-related adverse effects, especially bleeding, a lower international normalized ratio (INR) target (1.8-2.5) is recommended in some sources, but the optimal INR value needed to prevent stroke in the elderly should be in the range of 2.0-3.0 (9,10,11).

In this context, by retrospectively determining patients who were diagnosed as having cardioembolic cerebrovascular disease (CVD), who used warfarin, were aged over 80 years, and came to regular follow-up in the neurology outpatient clinic of our hospital, we aimed to investigate adverse effects that occurred during warfarin use, patient/treatment compliance, the presence of new ischemic or hemorrhagic attacks, the possible complications of warfarin affecting systems other than the central nervous system, and the relation of those with the demographic and laboratory data of the patients.

Materials and Methods

In the first part of the study, patients aged over 80 years who were diagnosed as having cardioembolic ischemic stroke and used warfarin with regular follow-ups in the Neurology Department of Istanbul Bakirkoy District Public Hospitals Union, Health Sciences University, Bakirkoy Prof. Dr. Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital between 2014 and 2018 were retrospectively identified from the records. Demographic data, clinical follow-up, and laboratory and radiologic findings were recorded in an Excel format. Data of new attacks during warfarin use, INR values at the time of the attack, new systemic and/or nervous system related ischemic/hemorrhagic conditions, possible drug-related adverse effects, reasons for continuation or discontinuation of the drug were recorded in Excel format. According to the neuropsychometric test results, cognitive findings were grouped as mild, moderate, and severe.

Statistical Analysis

The SPSS 21 package program was used for statistical analysis. The averages of the two groups were compared using the t-test. Fisher's Exact test and the chi-square test were used to compare non-parametric data.

Ethics committee approval was received from the Ministry of Health, Istanbul Bakirkoy District Public Hospitals Union, Health Sciences University, Bakirkoy Prof. Dr. Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital (decision number: 642, date: 07.02.2017).

Results

Of 589 patients who used warfarin with a diagnosis of CVD who were aged over 80 years between 2014 and 2018, 189 patients, 88 of whom were women, who were diagnosed as having ischemic CVD (ICVD) with sufficient data in their medical records, were included in the study, retrospectively. The mean age was 85 ± 3.82 years (minimum: 80 maximum: 89); duration of disease was 9.03 ± 3.1 years (minimum: 6 months, maximum: 11 years), and the mean duration of warfarin use was 5.02 ± 3.4 years (minimum: 6 months, maximum: 11 years) (Table 1).

Although patients had multiple risk factors, 83% of patients had HT, 81% had AF, 72% had diabetes mellitus, 77.8% had coronary artery disease/congestive heart failure, and 56.6% had hyperlipidemia. In addition, patients were using one or more of the oral antidiabetic, antihyperlipidemic, antihypertensive, and antiarrhythmic treatments due to advanced age.

When the radiologic characteristics of the patients were evaluated, 79 (41.7%) patients had infarction in the territory of the middle cerebral artery, 53 (28%) of the posterior cerebral artery, 27 (14.2%) of the basilar artery and other posterior system arteries, 20 of the anterior cerebral artery, and 10 patients had multiple lacunar infarctions in territories that did not fit into a single artery's territory (detected in both anterior and posterior system arteries at the same time). No significant results were found in terms of warfarin-related adverse events (cerebral or extra-cerebral hemorrhage, peripheral edema, diarrhea, shortness of breath, headache, feeling dizzy) according to radiologic localizations ($p \geq 0.005$).

Of 189 patients, 76 (40.2%) started treatment under the age of 80 years and continued to use warfarin. Forty-two (22.2%) patients were on warfarin therapy due to CVD under new oral anticoagulant (NOAC) treatments (15-20 mg/day rivaroxaban, $n=17$; dabigatran 220 mg/day, $n=19$; apixaban 10 mg/day, $n=6$) at effective doses and with regular use.

Of the patients, 94% (49.7%) were unable to continue warfarin treatment for various reasons (e.g. adverse events, social reasons, NOAC therapy, labile INR, dementia). Of these, 90 were in regular follow-up with the diagnosis of cardioembolic ICVD (47.6%) from our hospital's outpatient clinic. Five (2.6%) patients died of neurologic and/or other causes (outside of bleeding).

When demographic data and adverse events were compared, no difference was found in terms of sex in warfarin-related adverse events ($p > 0.005$), but as the duration of disease and age increased, warfarin-related adverse events significantly increased (peripheral edema, diarrhea, shortness of breath, headache, dizziness) ($p < 0.001$) (Table 2).

When the causes of 94 patients who were unable to continue warfarin treatment were detailed (Table 2), warfarin was discontinued due to GIS bleeding (upper + lower), in 39 (41.4%) patients, due to abundant epistaxis in 10 (10.6%), and due to intra/extracranial hemorrhage in 5 (5.3%). In addition, NOAC was started in 27 (28.7%) patients due to having labile INR results and in 13 patients due to a diagnosis of dementia.

The mean INR level at the time of symptoms was 3.1 ± 2.5 in patients with GIS hemorrhage (n=39). The mean INR level of 5 patients who had to change treatment due to abundant epistaxis was 2.9 ± 1.3 .

Three of 8 patients whose medication was discontinued due to intracerebral hemorrhage under warfarin treatment had thalamic

hematoma due to hypertensive hemorrhage, but two patients who were diagnosed as having sub/epidural hemorrhage had suspected head trauma, which was noted in their medical records. The mean INR value of these patients was 3.8 ± 2.5 .

Mean INR level was 3.8 ± 1.3 in patients with major hemorrhage. Drug-related adverse events were more common (peripheral edema, diarrhea, shortness of breath, headache, dizziness) in patients with INR levels 2.5 or higher than in patients with lower INR levels (p=0.003) (Table 2).

As expected, GIS adverse effects were observed more frequently in combination therapy with warfarin as the number of drugs increased. However, the greatest and most significant difference was found in the combination therapy with antihyperlipidemic

| Patients (n=189) | | Data |
|--|---|---|
| Female/male (n) (%) | | 88/101 (46.5%/53.4%) |
| Mean age/years (min.-max.) | | 83±3.8 years (80-87) |
| Mean duration of illness/years (min.-max.) | | 8.03±2.1 (6 months-11 years) |
| Risk factors (n) (%)* | Hypertension (n) (%)* | 153 (81) |
| | Diabetes (n) (%)* | 136 (72) |
| | Hyperlipidemia (n) (%)* | 106 (56.6) |
| | Heart failure/coronary artery disease (n) (%)* | 147 (77.8) |
| | Atrial fibrillation (n) (%)* | 171 (91) |
| Mean duration of warfarin use (years) | | 5.02±3.4 years (min. 6 months, max. 11 years) |
| Education level (n) (%) | High school graduate (n) (%) | 57 (30.1) |
| | No high school graduate (Primary school graduate) (n) (%) | 132 (69.8) |

*One patient had multiple risk factors.
Min.: Minimum, Max.: Maximum

| Adverse events | INR value | Number of patients (n) |
|--------------------------------|---------------|------------------------|
| Gastrointestinal bleeding | 3.1 ± 2.5 | 39 |
| Abondant epistaxis | 2.9 ± 1.3 | 5 |
| Extra/intracerebral hemorrhage | 3.8 ± 2.5 | 10 |
| Peripheral edema | 2.6 ± 0.7 | 12 |
| Diarrhea | 2.9 ± 1.0 | 23 |
| Shortness of breath | 2.7 ± 0.2 | 16 |
| Headache | 2.5 ± 0.4 | 76 |
| Feeling of dizziness | 3.1 ± 1.6 | 82 |

Multiple adverse events were seen in one patient.
INR: International normalized ratio

| Treatments used with warfarin | GIS adverse event (n) | Total number of patients (n) | % |
|--|-----------------------|------------------------------|------|
| Antidiabetic drugs | 5 | 26 | 19.2 |
| Antihypertensive drugs | 4 | 35 | 11.4 |
| Antihyperlipidemic drugs | 3 | 21 | 14.2 |
| Antidiabetic and antihypertensive drugs | 5 | 29 | 17.2 |
| Antidiabetic and antihyperlipidemic drugs | 13 | 38 | 34.2 |
| Antihypertensive and antihyperlipidemic drugs | 9 | 25 | 36 |
| Antidiabetic and antihypertensive and antihyperlipidemic drugs | 8 | 15 | 53.3 |

GIS: Gastrointestinal

treatments. It was observed that the GIS adverse effects of warfarin were significantly more frequent in patients using oral antidiabetic and/or antihypertensive drugs with antihyperlipidemics (2- or 3-drug combinations) (n=107) than in patients who were not using antihyperlipidemic drugs (antidiabetic and/or antihypertensive drug use) (n=82) (p=0.001) (Table 3). In addition, intra/extra cerebral hemorrhage due to warfarin was more significant in patients (n=17) with irregular antihypertensive medication use in their history, as expected (p=0.001). It was observed that 41 (41/90; 45.5%) patients with mild-to-moderate cognitive impairment continued warfarin treatment and were able to come to regular follow-up for INR.

Discussion

In our study, it was observed that 94 (49.7%) out of 189 patients who were diagnosed as having cardioembolic stroke in advanced age had to stop treatment due to major complications under warfarin treatment, and 90 (47.6%) continued treatment with regular follow-up. Of the 189 patients, 76 (40.2%) were found to have started warfarin when they were aged under 80 years and were able to continue treatment afterwards. In addition, more GIS adverse effects occurred in patients using warfarin with antihyperlipidemic drugs than in patients using warfarin with other drugs. Overall, drug-related adverse events (peripheral edema, dizziness, diarrhea, shortness of breath, feeling dizzy) were found in those with an average INR value above 2.5, whereas major complications were associated with INR values of 3 or above (3.8 ± 1.3) (p=0.003).

In a study that included 553 patients with ICVD, the prevalence of ICVD in patients aged over 80 years was 33.5%, and 87.2% of patients in this age group had HT and 24.6% had AF. In the same study, lacunar infarction was detected in 41.7% of patients, cardioembolic stroke was detected in 19.7% and stroke etiology was uncertain in 31.8%. In addition, atherosclerosis-related stroke was reported in 6% of patients with ICVD aged over 80 years (5). In that study, it was emphasized that a cardioembolic etiology was a more common cause of ICVD in patients with advanced age.

HT was the first and AF was the second among risk factors in the study by Kaplan et al. (12) conducted in 2014 to investigate reasons for morbidity in patients with stroke with advanced age, and similar rates (83% HT, 81% AF) were determined in our study. In the same study, anterior and middle cerebral artery localization of infarction (64.5%; 71/110) was observed more than posterior system artery localization of infarction. Although our results did not reach statistical significance, anterior system involvement (52.3%) was higher than posterior system involvement in patients aged over 80 years. For this reason, it was emphasized that possible cardioembolic causes such as paroxysmal AF should be kept in mind in patients with ICVD with advanced age who had no significant posterior system atherosclerosis, anterior system involvement, and in whom the cause could not be determined.

When the INR results of patients with ICVD aged over 80 years (n=189) were examined, it was observed that drug-related adverse events (peripheral edema, dizziness, diarrhea, shortness of breath, dizziness) occurred more in patients with INR values above 2.5, and major complications were found to be associated with INR values of 3 or above (3.8 ± 1.3) (p=0.003). In addition, the use

of antihyperlipidemic treatments with other antihypertensive and/or antidiabetic drugs was more associated with warfarin-induced GIS adverse effects. In contrast, the GIS adverse effects in patients using warfarin with antihypertensive and antidiabetic drugs were not different than in patients using warfarin with one of the antihypertensive or antidiabetic drugs (p=0.303). In addition, it was noted that approximately half (49.7%) of patients aged over 80 years switched to NOACs, and 47.6% continued warfarin therapy. The most common adverse event that caused cessation of warfarin therapy was GIS bleeding, the second leading cause was labile INR levels.

In the literature, it has been suggested that INR values should be kept between 1.5-1.9 for the elderly patient population, but in recent studies, it has been reported that there is no difference between INR values less than 2 and INR values of 2-3 in terms of the risk of intracranial hemorrhage, which may be fatal (9,13,14). In our study, both major hemorrhage in GIS and intra/extracerebral hemorrhage were seen with mean INR values of 3 or above, whereas general adverse events were observed more frequently in INR values above 2.5. For this reason, it was determined that the values recommended in the literature should be taken into consideration in terms of overall complications in older patients using warfarin, and that this INR value was shown as above 3 in our study as shown in other studies for major mortal complications.

Forty-two (22.2%) of the patients were on warfarin therapy because they had a CVD attack under the appropriate dose and regular NOAC therapy. Although it is known that NOACs are good choices for anticoagulation in advanced age in terms of adverse events and ease of use; it has been noted that under these treatments, patients with CVDs attack have returned to warfarin, which is the gold standard anticoagulant treatment. According to studies, the mortality/morbidity risk of ischemic stroke at an advanced age is higher than the risk of anticoagulant therapy (e.g. major bleeding) (9,15). It is stated that it is not appropriate to consider "age" alone as a risk factor in the decision to start anticoagulant/antiaggregant treatment in older patients who may come to regular clinical follow-up. However, when choosing from available anticoagulant agents, physicians should consider concomitant medical conditions, medications, dependency, cost-effectiveness, and ability to participate in monitoring (9,16).

Conclusion

As a result, it is important for physicians to avoid excessive/unnecessary drug use, especially antihyperlipidemic treatments, in terms of drug adverse event control in patients with advanced age using warfarin. Also, to decide on a stroke prophylaxis that the patient needs, but not by considering the patient's age alone as a risk factor. In addition, non-discontinuation of warfarin should be encouraged in patients who have regular control and stable INR values.

Ethics

Ethics Committee Approval: Ministry of Health Istanbul Bakirkoy Region Public Hospitals Union Health Sciences University Bakirkoy Prof. Dr. Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital with the date of 07.02.2017 and 642 decision number is approved by the ethics committee.

Informed Consent: Consent form was filled out by all participants.

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Authorship Contributions

Surgical and Medical Practices: R.G.G.Ç., H.K., Concept: E.Ç., S.Ş., Design: R.G.G.Ç., H.K., Data Collection or Processing: R.G.G.Ç., H.K., E.Ç., S.Ş., Analysis or Interpretation: R.G.G.Ç., A.K., Literature Search: R.G.G.Ç., A.K., Writing: R.G.G.Ç.

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