Oral Anticoagulant Therapy May Prevent Mortality in Peripheral Vascular Surgery

Oral Antikoagülan Tedavi Periferik Damar Cerrahisinde Ölümü Engelleyebilir

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ABSTRACT Objective: Atherosclerotic peripheral arterial disease is associated with an increased risk of myocardial infarction, stroke, and death from cardiovascular causes. Antiplatelet drugs protect from major cardiovascular events, but the role of oral anticoagulant agents is unclear in the prevention of cardiovascular complications in patients with peripheral arterial disease. **Material and Methods:** We assigned patients with peripheral arterial disease treated surgically. According to the medical treatment in postoperative and follow-up periods, the patients were divided into two groups: Anticoagulant therapy [patients receiving oral anticoagulant agents with a target international normalized ratio (INR)=2.0-3.0, n=78] and the patients not receiving oral anticoagulant agents (n=56). In both groups, medical treatment was combined with antiplatelet therapy in some patients. The primary outcome was death and secondary outcome was limb amputation. **Results:** A total of 134 patients were treated surgically. The mean follow-up period was 30 months. Revision due to bleeding, occlusion of the graft, embolism of non-treated arteries, myocardial infarction and stroke occurred in 6 patients receiving anticoagulant therapy (7.69%) and in 5 patients not receiving anticoagulant therapy (8.92%, p=0.48). Death and limb amputation occurred only in patients not receiving anticoagulant therapy (12.5%, p=0.02 and 5.4%, p=0.071). **Conclusion:** In patients with peripheral arterial disease treated surgically, the oral anticoagulant therapy may be effective for preventing death.

Key Words: Peripheral vascular surgery; anticoagulant treatment; mortality

ÖZET Amaç: Aterosklerotik periferik arter hastalığı miyokard enfarktüsü, inme ve kardiyovasküler nedenlere bağlı olarak gelişen ölüm ile riski ile ilişkilidir. Antiplatelet ilaçlar majör kardiyovasküler olaylardan korur, ancak periferik arter hastalığı olan hastalarda kardiyovasküler komplikasyonların önlenmesinde oral antikoagülan ajanların rolü belirsizdir. **Gereç ve Yöntemler:** Çalışmaya cerrahi olarak tedavi edilen periferik arter hastalığı olan hastaları seçtik. Postoperatif dönemde ve takip sırasında uygulanan tıbbi tedaviye göre hastalar iki gruba ayrıldı: Antikoagülan tedavi alan [oral antikoagülan ajan alan hastalar, hedef uluslararası normalize oranı (INR)=2,0-3,0, n=78] ve oral antikoagülan ajan almayan hastalar, (n=56). Her iki grupta, bazı hastalarda tıbbi tedavi antiplatelet tedavi ile kombine edildi. Birincil sonuç ölüm ve ikincil sonuç ekstremite amputasyonu oldu. **Bulgular:** Yüz otuz dört hasta cerrahi olarak tedavi edildi. Ortalama takip süresi 30 ay oldu. Kanama nedenli revizyon, greft tıkanması, tedavi edilmemiş arterlerin embolisi, miyokard enfarktüsü ve inme, antikoagülan tedavi alan 6 (%7,69) hastada, antikoagülan tedavi almayan 5 (%8,92) hastada meydana gelmiştir (p=0,48). Ölüm ve ekstremite kaybı sadece antikoagülan tedavi almayan hastalarda görüldü (%12,5, p=0,02 ve %5,4, p=0,071). **Sonuç:** Cerrahi olarak tedavi periferik arter hastalığı olan hastalarda, oral antikoagülan tedavi ölümü önlemede etkili olabilir.

Anahtar Kelimeler: Periferik damar cerrahisi; antikoagülan tedavi; mortalite

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Peripheral arterial disease (PAD) is most frequently caused by atherosclerosis that may result in myocardial infarction (MI), stroke or death in patients with peripheral arterial disease.[1,2] The American

College of Cardiology and the American Heart Association recommend that antiplatelet therapy is indicated to reduce the risk of MI, stroke, and vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia.[3-6] It is also reported in the same guideline that, in the absence of any other proven indication for warfarin, adding antiplatelet therapy to reduce the risk of adverse cardiovascular ischemic events in individuals with atherosclerotic lower extremity PAD is of no benefit and is potentially harmful due to increased risk of major bleeding.[3,7] Information regarding the efficacy and safety of oral anticoagulation, with or without antiplatelet therapy, in patients with peripheral arterial disease is limited.[8] Therefore, we reviewed a retrospective analysis to determine whether oral anticoagulation [target international normalized ratio (INR) 2.0 to 3.0] therapy has salvaged from mortality and limb amputation in patients with PAD.

MATERIAL AND METHODS

The data were reviewed retrospectively in Cardiovascular Clinics at Konya Training and Research Hospital between June 2008 and September April 2013. Atherosclerotic peripheral arterial disease as atherosclerosis of the arteries of the lower extremities was eligible for enrollment in the study. Atherosclerosis of the lower extremities was defined as intermittent claudication with objective evidence of peripheral arterial disease, ischemic pain at rest, non-healing ulcers or focal gangrene, previous amputation, or arterial revascularization. All patients had symptoms including both intermittent claudication and critical limb ischemia. Aneurysmatic disease and embolectomy were excluded from the data. Peripheral vascular surgery included mainly aorto-bifemoral and femoropopliteal bypass. Distal bypass of lower extremity and extra-anatomic bypass were also included in the review.

General anesthesia and spinal/epidural anesthesia were used to perform the surgery according to the primary pathology of the patients. Grafts of dacron, polytetrafluoroethylene with or without ring, saphenous vein and biological grafts were chosen to bypass while performing surgery.

Patients were divided into two groups according to the whether they have anticoagulant therapy or not. Patients who treated surgically randomly received oral anticoagulant therapy in the postoperative period. Antiplatelet agents including clopidogrel and aspirin (recommended dose, 81 to 325 mg per day) were also added to the medical therapy in suitable patients. After the operation, INR values were measured every month or more frequently. Patients were followed for a minimum of 2.5 years or a maximum of 4.5 years.

Doppler ultrasound and magnetic resonance imaging were the tools to determine the patency of the grafts. Ejection fraction of left ventricle was measured by the methods of transthoracic echocardiography and myocardial scintigraphy.

The primary outcome was death from all causes and the secondary outcome was limb amputation occurring in the postoperative and follow-up periods. Causes of death were as follows: aspiration pneumonia, myocardial infarction, acute renal insufficiency and sepsis.

STATISTICAL ANALYSIS

Convenience of quantitative data on normal distribution was examined with Kolmogorov Smirnov test. If data were not normally distributed, the analyses were performed with Mann Whitney U test in the groups. Descriptive statistics were shown as medians (25-75 percentiles). Qualitative data were analyzed with Chi-square test, and the descriptive statistics were demonstrated as frequencies (percentage). $p<0.05$ was considered statistically significant.

RESULTS

The baseline characteristics of the patients participating in the study are shown in Table 1. The mean age was 60 years in patients receiving anticoagulant therapy and 7.7% of them were females. The mean age was 68 years in patients not

receiving anticoagulant therapy and 10.7% of them were females (p=0.001). 37.2% of the patients receiving anticoagulant therapy and 16% of the patients not receiving anticoagulant therapy had some form of antiplatelet therapy including clopidogrel and acetylsalicylic acid (p=0.039 and p=0.398, respectively). There were no significant differences in the use of other medications between the two patient populations.

During follow-up, Doppler ultrasound and magnetic resonance imaging were performed postoperatively in symptomatic patients (Table 2). The graft was occluded in 3 patients under the vision of Doppler ultrasound and in 2 patients under the screening of magnetic resonance. Polytetrafluoroethylene with ring (n=1), polytetrafluoroethylene (n=1) and saphenous vein graft (n=1) were identified to be occluded with Doppler ultrasound. Saphenous vein graft (n=2) was identified occluded with magnetic resonance imaging. There were no statistically significant differences in the use of these grafts with these radiological tools between the two patients population (p=0.522 and p=0.991 respectively).

The first primary outcome (all causes of mortality) occurred in 7 of the 56 patients not receiving anticoagulant therapy, as compared with 0 of the 78 patients receiving anticoagulant therapy (0%) (p=0.002). The second outcome (limb amputation) occurred in 3 patients not receiving anticoagulant therapy, as compared with 0 of the 78 patients receiving anticoagulant therapy (0%) (0%) (p=0.071).

TABLE 1: Baseline characteristics of the patients.

	Anticoagulant therapy	Non-anticoagulant therapy	p value
Age	60.50(54.75-66)	68(61-71)	0.001
Female	7.7 (%)	10.7 (%)	0.766
Diabetes mellitus	16.7 (%)	14.3 (%)	0.894
Hypertension	14.1 (%)	32.1 (%)	0.022
Chronic obstructive pulmonary disease	7.7 (%)	5.4(%)	0.734
Chronic ishemic heart disease	26.9 (%)	25 (%)	0.96
Ejection fraction	60(42.75-65)	60(45-60)	0.587
Claudication	80.8 (%)	66.1 (%)	0.084
Critical limb ischemia	10.3 (%)	7.1 (%)	0.752
Wound	9.0 (%)	3.6 (%)	0.303
Reoperation	14.1 (%)	7.1 (%)	0.326

TABLE 2: Follow-up of the patients.

	Anticoagulant therapy	Non-anticoagulant therapy	p value
Postoperative complications	7.7 (%)	8.9 (%)	1
Medical treatment after surgery			
Clopidogrel	21.8 (%)	7.1 (%)	0.039
Acetylsalicylic acid	15.4 (%)	8.9 (%)	0.398
Follow-up			
Graft patency			
Doppler ultrasound	14.1 (%)	8.9 (%)	0.522
Magnetic resonance imaging	14.1 (%)	12.5 (%)	0.991
Limb amputation	0 (%)	5.4 (%)	0.071
Mortality	0 (%)	12.5 (%)	0.002

DISCUSSION

Adding an anticoagulant (such as warfarin) to antiplatelet therapy would increase the benefit of antiplatelet agents by reducing the incidence of major cardiovascular events in patients with peripheral arterial disease.[4,5] This idea was the result of the favorable effects of the combination of moderate-intensity oral anticoagulant and antiplatelet therapies in patients with coronary artery disease.[9-12] Some randomized trials reflected this hypothesis, but they had variable clinical practices.[8,13]

In the WAVE trial and the Department of Veterans Affairs Cooperative Study, the authors investigated the efficacy and safety of combination antithrombotic therapy with an antiplatelet agent and an oral anticoagulant (target INR, 2.0 to 3.0) over the efficacy and safety of antiplatelet therapy alone in patients with peripheral arterial disease. Both trials found that combination therapy was not more effective than antiplatelet therapy alone in preventing major cardiovascular complications.

HEMORRHAGIC EVENTS

The patients of these two trials had suffered from serious bleeding and hemorrhagic stroke. The rates of serious bleeding and hemorrhagic stroke among patients receiving a combination of oral anticoagulant and antiplatelet therapy were high in the WAVE trial (5.5 of 100 and 0.51 of 100 patient-years, respectively). These results are similar to the Department of Veterans Affairs Cooperative Study; among patients receiving oral anticoagulant therapy and aspirin were 4.1 of 100 and 0.61 of 100 patient-years, respectively.[14] Therefore, it appears that patients with peripheral arterial disease treated with oral anticoagulation may be more likely to have bleeding complications, including hemorrhagic stroke, compared to patients with coronary artery disease.[15] In our study, we did not observe any serious bleeding or hemorrhagic stroke in our patient population, this is because of close monitoring of INR values in every two weeks, or the most likely explanation for this finding is, chance.

MORTALITY AND MORBIDITY

Mortality rate associated with the oral anticoagulation therapy in patients with peripheral vascular disease was unexpected. The anticipated secondary benefit of oral anticoagulation therapy is to reduce the risk of mortality from heart disease or cerebral vascular disease. In a prospective randomized study, the authors found that death (2.8%) rate from heart disease and stroke was similar in the warfarin+Aspirin group (target INR, 1.3 to 1.8) as compared to the aspirin group (100 mg; 3.0%).[13] These observations were found to be consistent with the results of the Thrombosis Prevention Trial (TPT).[16] Likewise, nonfatal myocardial infarction occurred at the same frequency (3.7%) in each group, as did nonfatal stroke (1.3%). In our study, the death was seen only in non-anticoagulant therapy group (12.5%), this explanation was supported by the advanced age compared to the other group (p=0.001).

Critical limb ischemia is the most advanced form of peripheral arterial disease and it is associated with a high risk of cardiovascular events, including major limb loss. Observed probability of 1-year amputation-free survival and the associated hazard ratios for death or major amputation at 1 year, stratified by the PREVENT III (PIII) critical limb ischemia risk score were as follows; 86.4% at low risk (≤3), 74.1% at medium risk (4-7) and 56.1% at high risk (≥8).[17] In our study, only 7.1% of the patients had critical limb ischemia and 5.4% of the patients had limb amputation in non-anticoagulant therapy group (p=0.071). This result was surprising, however, it did not reach a statistical significance.

There are several limitations of this study. First, both groups have small number of patients to reach statistically significant results. Second, the reasons of mortality are unclear because of the missing data. Finally, limited data makes difficult to comment the results.

CONCLUSION

We compared the effects of anticoagulant therapy on mortality and limb amputation in patients with peripheral vascular surgery. We concluded that anticoagulant therapy may be effective for preventing mortality.

Conflict of Interest

Authors declared no conflict of interest or financial support.

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