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The Effectiveness of New Oral Anticoagulants in the Treatment of Lower Extremity Venous Thrombosis: A Retrospective Clinical Study

ABSTRACT

Objective: This clinical study included a retrospective evaluation of 138 patients using new oral anticoagulants (rivaroxaban, dabigatran, apixaban, edoxaban) for lower extremity deep vein thrombosis.

Methods: 138 patients using new oral anticoagulant drugs were included in the retrospective study. Demographic characteristics, diagnosis and treatment charts, radiological images, epicrisis notes of the patients were recorded. Records of each patient were reviewed during their 12 months of follow-up. New oral anticoagulant efficacy; It was evaluated by measuring thigh and calf diameters before and after treatment, whether there was recanalization in Doppler USG (recanalization > 75%), recanalization time, bleeding side effects and recovery times with treatment, and recurrence rates. The data were analyzed statistically using a statistics program.

Results: A significant difference was found when the mean thigh diameter measurements measured at the beginning of the treatment (Mean $\pm$ SD: 75,41) and the mean thigh diameter measured after the treatment (Mean $\pm$ SD: 54,63) were compared ($p < 0.05$). A significant difference was found when the mean calf diameter measurements (Mean $\pm$ SD: 43.99) measured at the beginning of the treatment and the mean calf diameter measured after the treatment were compared ($p < 0.05$). Post-treatment Doppler USG showed complete recanalization rate in 54% (75 patients) at 3 months and 25% (35 patients) at 6 months. At the end of the 6th month, the total recanalization rate occurred in 80% (110) patients.

Conclusions: New oral anticoagulants (rivaroxaban, dabigatran, apixaban, edoxaban) are very effective in the treatment of lower extremity deep venous thrombosis, both in providing recanalization and in terms of clinical improvement in early and midterm.

Keywords: New Oral Anticoagulants, Deep Vein Thrombosis, Thrombophilia.

Alt Ekstremitte Venöz Tromboz Tedavisinde Yeni Oral Antikoagulanların Etkinliği: Retrospektif Klinik Çalışma

ÖZET

Amaç: Bu klinik çalışma alt ekstremitte derin ven trombozu nedeniyle yeni oral antikoagulan ilaç (rivaroksaban, dabigatran, apiksaban, edoksaban) kullanan 138 hastanın retrospektif olarak incelenmesini içermektedir.

Gereç ve Yöntem: Retrospektif çalışmaya yeni oral antikoagulan ilaç kullanan 138 hasta dahil edildi. Hastaların demografik özellikleri, tanı ve tedavi şemaları, radyolojik görüntüleri, epikriz notları kaydedildi. Her bir hastanın kayıtları takip edildikleri 12 ay boyunca incelendi. Yeni oral antikoagulan etkinliği; tedavi öncesi ve sonrası uyluk ve baldır çaplarının ölçülmesi, doppler USG’de rekanalizasyon olup olmadığı (rekanalizasyon > %75), rekanalizasyon süresi, kanama yan etkileri ve tedavi ile iyileşme süreleri, rekürrens oranları ölçülerek değerlendirildi. Veriler istatistik programı kullanılarak istatistiksel olarak incelendi.

Bulgular: Tedavi başlangıcında ölçülen uyluk çap ölçümleri ortalaması (Ort $\pm$ SS:75,41) ile tedavi sonrası ölçülen uyluk çap ortalaması (Ort $\pm$ SS:54,63) karşılaştırıldığında anlamlı fark bulundu ($p < 0.05$). Tedavi başlangıcında ölçülen baldır çap ölçümleri ortalamaları (Ort $\pm$ SS:43,99) ile tedavi sonrası ölçülen baldır çap ortalaması karşılaştırıldığında anlamlı fark bulundu. ($p < 0.05$). Hastalarda tedavi sonrası doppler USG de tam rekanalizasyon oranı 3.ayda %54 (75 hasta) ,6 ayda %25 (35 hasta) da görüldü.6.ay sonunda toplam rekanalizasyon oranı %80 (110) hastada gerçekleşmiştir.

Sonuç: Yeni oral antikoagulanlar (rivaroksaban, dabigatran, apiksaban, edoksaban) alt ekstremitte derin venöz tromboz tedavisinde, erken ve orta dönemde hem rekanalizasyonun sağlanmasında hem klinik düzelme anlamında oldukça etkilidir.

Anahtar Kelimeler: Yeni Antikoagulan Ajanlar, Derin Ven Trombozu, Trombofili.

INTRODUCTION

New oral anticoagulants (NOACs) with a wider therapeutic range and less food exposure are also very current in the treatment of venous thrombosis and prophylaxis. In recent years, new oral anticoagulant agents have been preferred in the treatment of serious diseases with high thrombosis risk (such as deep venous thrombosis, pulmonary embolism, atrial fibrillation), since they have less potential for side effects and do not require routine blood tests (1). Warfarin, a vitamin K antagonist, has been replaced by new oral anticoagulants in the standard treatment of deep venous thrombosis. Studies have shown that NOACs keep the risk of major bleeding in a more reliable range (2). Similarly, significant reductions were seen in the risk of stroke and systemic embolism (3). We retrospectively present the clinical results of NOACs that we use in the treatment of the Lower Extremity deep venous thrombosis (DVT) over 138 patients.

MATERIAL AND METHODS

138 patients who were diagnosed with DVT for the first time in the cardiovascular surgery outpatient clinic between January 2015 and June 2018 were included in the study. After obtaining the approval of the ethics committee (Ankara Education and Research Hospital; Decision Number:368/2020, Date: September 17,2020) the patient records were examined retrospectively and the data were obtained. There were 242 patients diagnosed with DVT who were using oral anticoagulant drugs. Patients who received vitamin K antagonist (warfarin) treatment, who were heparinized with a diagnosis of acute and subacute DVT and who received endovascular therapy (venous stent, vena cava inferior filter, pharmacomechanical thrombectomy) were excluded from the study. Thus, a homogeneous patient population (138 patients) receiving only oral anticoagulant (rivaroxaban, dabigatran, apixaban, edoxaban) was created and more specific results were tried to be achieved. New oral anticoagulant efficacy; It was evaluated by measuring the thigh and calf diameters before and after the treatment, whether there was recanalization (recanalization > 75%) in the doppler USG taken at the 3rd and 6th months, recanalization time, bleeding side effects and recovery times with treatment, and recurrence rates.

Data analysis: Minitab 16 version (Minitab Inc. State College, Pennsylvania, USA) statistical program was used for analysis of patient data. The

Pearson correlation coefficient was calculated for the investigation of the relationship between the parametric data, and the Spearman correlation coefficient for the investigation of the relationship between the nominal data. Student's t test was used for parametric data, and Mann-Whitney U-Wilcoxon Rank Sum W test was used for nominal data to investigate the difference between groups, and $p < 0.05$ was considered significant. The X2 test was used to investigate whether there was a difference between the groups in terms of the individual distribution of the causative diseases.

RESULTS

Data of 138 patients using NOACs (rivaroxaban, dabigatran, apixaban, edoxaban) for the treatment of deep venous thrombosis were evaluated. 46% (64) of the patients were male and 54% (74) were female. The mean age of the patients was found as Mean $\pm$ SD: 56.72. Of the patients who received NOACs treatment with a diagnosis of DVT, 28% (38 patients) used apixaban, 26% (36 patients) rivaroxaban, 26% (36 patients) dabigatran, 20% (28 patients) edoxaban. When the duration of treatment was examined, it was understood that 15% (21 patients) were treated for 3 months, 49% (36 patients) received 6 months of treatment, 49% (68 patients) received 12 treatments.

A significant difference was found when the mean thigh diameter measurements (Mean $\pm$ SD: 75,41) measured at the beginning of the treatment and the mean thigh diameter measured after the treatment (Mean $\pm$ SD: 54,63) were compared ($p < 0.05$). Similarly, a significant difference was found when the mean calf diameter measurements (Mean $\pm$ SD: 43.99) measured at the beginning of the treatment and the mean calf diameter measured after the treatment were compared ($p < 0.05$).

Post-treatment Doppler USG showed complete recanalization rate in 54% (75 patients) at 3 months and 25% (35 patients) at 6 months. At the end of the 6th month, the total recanalization rate occurred in 80% (110) patients. Postthrombotic syndrome occurred in only 5% (7 patients) of the treated patients. The recurrence rate was 5% (7 patients) in all patients using NOACs. There was no significant difference between recurrent DVT due to etiological reasons. During the 12-month follow-up of 138 patients, the major bleeding rate was observed in 2% (3 patients), and the minor bleeding rate was observed in 4% (6) patients (Table 1).

Table 1. Patient demographic characteristics

Number of patients (138)	Number	Percent
Age		
Average age	Mean±SD: 56.72	
Age range (years)	(22-88)	
Sex		
Male	64	46
Female	74	54
Use of NOACs		
Apixsaban	38	28
Rivoksaban	36	26
Dabigatran	36	26
Endoksaban	28	20
Full recanalization time		
3 Months	75	54
6 Months	35	25
12 Months	21	15
Average thigh diameters (cm)		
Before	Mean±SD: 75.41	
After	Mean±SD: 54.63	
Average calf diameters (cm)		
Before	Mean±SD: 43.99	
After	Mean±SD: 41.13	
Postrombotic syndrome	7	5
Recurrence	7	5
Major bleeding	3	2
Minör bleeding	6	4

When the etiology of deep venous thrombosis was examined, it was seen that genetic factors played a role in 17% (24 patients) of 138 patients using NOACs. The most common cause in patients was immobilization with 30% (41 patients). Post-surgical DVT was seen in 15% to 21 patients. Cancer was observed in 12 to 16 patients in the etiology of patients using NOACs (Table 2).

Table 2. DVT etiology of patients

DVT causes	Number (n)	Percent (%)
Genetic factors	24	17
Factor V Leiden mutation 13 (54 %)		
Protrombin mutation 6 (25%)		
Antithrombin III deficiency 3 (13%)		
Hyperhomocysteinemia 2 (8 %)		
Cerrahi operasyon sonrası	21	15
Immobilization (Hemiplegia, Paraplegia, long travel)	41	30
Traumatic (vascular injury)	6	4
Oral contraceptives	8	6
Obesity	6	4
Cancer	16	12
Other	16	12

The most common localization of DVT was femoro-popliteal involvement with 30% (42 patients). This was followed by common femoral vein involvement in 28% (39 patients) and popliteal vein involvement in 17% (23 patients) (Table 3).

Table 3. DVT site

DVT localization	Number (n)	Percent (%)
Common femoral vein	39 left:22	28
External illac vein	13 left:8	9
Popliteal vein	23 left:14	17
Popliteal –femoral vein	42 left:26	30
Femoral and illiac ven	21 left:15	15

In the statistical analysis, no significant relationship was found between the causes of the disease and recurrence rates, postthrombotic syndrome (PTS) development rates, recanalization rates and diameter measurements, and treatment durations.

DISCUSSION

Venous thromboembolism (VTE) is a multifactorial disease and patients may have more than one risk factor at the same time. The more risk factors the patient has, the higher the risk of developing venous thromboembolism (4).

Three main pathological mechanisms that facilitate the development of VTE were described by the famous pathologist Rudolf Virchow in the early 19th century. Stasis, vascular wall damage and hypercoagulability in the blood are the three main criteria and the presence of at least one criterion in the patient is sufficient to increase the risk. DVT is a disease that should be started as soon as the diagnosis is made due to its high prevalence and potentially fatal outcomes (5).

In the untreated follow-up of deep vein thrombosis, pulmonary embolism (PE), post-thrombophlebitic syndrome (PTS) with extremely high long-term morbidity and pulmonary hypertension may occur. Therefore, treatment should be started as soon as the diagnosis is made. The aim of the treatment is to prevent these three complications, as well as the prevention of relapses. Therefore, it is recommended to continue long-term treatment when necessary. Acute DVT treatment; It has two phases: initial treatment and long-term treatment after the onset. In the treatment, it is aimed to prevent new attacks in the long term by treating the acute attack and preventing the clot from spreading and embolization to the lungs (6,7,8).

Most cases of DVT are hidden and usually resolve spontaneously without complications. When symptomatic DVT is diagnosed, 40% of patients have silent PE. According to an epidemiological model, more than 370 000 deaths were caused by VTE in six European countries with a total population of 454.4 million people in 2004. 34 percent of these patients died unexpectedly or within hours of the acute incident, before treatment could begin or take effect. In 59 percent of the other patients, death was caused by acute PE, which was diagnosed after death. (9,10,11)

Symptomatic PE develops in approximately 4% of patients treated with DVT. PE develops in about 1% of postoperative patients. The long-term morbidity of DVT is the postthrombotic syndrome that develops in approximately one quarter of symptomatic proximal DVT cases. Most cases develop within 2 years afterwards. PE and DVT may progress in 13% of the patients, although they have received full treatment (9,10).

Anticoagulant therapy is recommended for 3-12 months, depending on the site of thrombosis and the presence of ongoing risk factors. Lifetime anticoagulation therapy can be recommended for

recurrent episodes of dvt, chronic clotting problem, or life-threatening PE. This treatment protocol has less than 12% cumulative risk of bleeding complications. To continue long-term anticoagulant therapy, the benefit-risk ratio should be evaluated at regular intervals (11).

The purpose of long-term treatment in DVT is to prevent recurrent VTE attacks that are not directly related to the acute event. In patients with DVT that develops secondary to a transient risk factor, anticoagulation for 3 months is included in all guidelines as a very strong recommendation. Similarly, 3-month anticoagulant therapy is considered to be sufficient in patients with first distal DVT that are not triggered. The main problem is how long the treatment will continue in the first proximal DVT cases that are triggered. Long-term anticoagulant therapy is particularly beneficial in male patients, patients with moderate-to-advanced post-thrombotic syndrome and high d-dimer levels one month later. Therefore, long-term treatment is recommended if the risk of bleeding is low and effective anticoagulant follow-up can be performed in patients who have had their first attack. In the second DVT attack that is not triggered, long-term secondary protection is appropriate. Low Molecular Weight Heparin (LMWH) is recommended in the first 3-6 months of long-term anticoagulant administration in DVT and cancer patients. Then anticoagulation should be given with LMWH or warfarin until the cancer is cured or for a long time. Each patient undergoing long-term anticoagulation should be explained in detail the risk-benefit ratio of the treatment and the patient's preferences should be considered. It is recommended to evaluate the benefit-risk ratios at regular intervals for patients whose treatment period is extended (12, 13,14). In our study, which we examined retrospectively, patients using NOACs received early response in distal thrombosis within the first 3 months. Sufficient response was obtained in the first 3 months, especially in women using oral contraceptives and patients with genetic etiology at a young age.

Warfarin is the first anticoagulant drug used in the treatment of venous thromboembolism. Due to the narrow therapeutic range, routine International normalized ratio (INR) monitoring, high drug-food interaction and potential for bleeding, it has offered an alternative to the constant search for new anticoagulants. Alternative NOACs are used instead of warfarin in the treatment of deep venous thrombosis due to its wide therapeutic range, less drug-food interaction, no need for INR follow-up and less bleeding potential.

The pharmacological properties and guideline recommendations of NOACs have been defined in large studies (Table 4).

Table 4. Pharmacological properties and recommendations of new oral anticoagulants

	Rivaroksaban	Dabigatran	Apiksaban	Endoksaban
Action	Factor xa inhibitor	Factor IIa	Factor xa inhibitor	Factor xa inhibitor
Bioavailability	80-100 %	3-7 %	50-66 %	62 %
Renal elimination	33 %	80 %	27 %	50 %
Antidote	Andexanet alfa	Idaricuzimab	Andexanet alfa	Andexanet alfa
Half life (hours)	7-13	12-17	8-15	8-10
Interaction	p-glycoprotein transporter inhibitors + CYP3A4 inhibitors	p-glycoprotein transporter inhibitors	p-glycoprotein transporter inhibitors + CYP3A4 inhibitors	p-glycoprotein transporter inhibitors + CYP3A4 inhibitors
Non-bleeding side effects	Peripheral edema 5 %	Dyspepsia 35 %	Rare	Rare
Conditions and Recommendations	In the initial and continuation treatment of DVT and PE	Treatment of DVT and PE Recurrence DVT,PE	Treatment of DVT, PE to prevent recurrence,	Treatment of DVT, PE to prevent recurrence,
	Prophylaxis after total knee and hip replacement	Prophylaxis after total knee and hip replacement	Prophylaxis after total knee and hip replacement	Prophylaxis after total knee and hip replacement (in Japan) *

* The table was created as a result of meta-analysis and clinical studies. (Ref: 8,17,18)

There are many multi-population prospective, double-blind, randomized studies on NOACs. The data of 27,023 patients in all phase 3 studies comparing rivaroxaban, apixaban, edoxaban, and dabigatran with vitamin K antagonists were examined in a meta-analysis and according to the following results, VTE recurrence was found to be similar in the NOACs and warfarin groups (2.0%; 2.2%, respectively.). Major bleeding was found 39% lower in NOACs users compared to Vitamin K antagonists (VKA) users (p = 0.02). In

the subgroup analysis, NOACs resulted in less VTE recurrence in patients 75 years of age and older and in cancer patients than in patients using warfarin. (p = 0.003 for 75 years old and p = 0.02 for cancer subgroup) As a result, studies have shown that direct thrombin and Factor Xa inhibitors are at least as successful as standard treatments in the treatment of acute VTE (15,20).

Standard doses have been established for the use of new oral anticoagulants (Table 5).

Table 5. Standard doses of new oral anticoagulants in the treatment of DVT

New oral anticoagulant	Initial treatment	During the treatment	Long-term treatment
Dabigatran	LMWH or unfractionated heparin*	Dabigatran 150 mg 2x1	Dabigatran 150 mg 2x1
Rivaroksaban	15 mg 2x1	20 mg 1x1	20 mg 1x1
Apiksaban	10 mg 2x1	5 mg 2x1	2.5 mg 2x1
Edoksaban	LMWH or unfractionated heparin *	Edoksaban 60 mg 1x1	Edoksaban 60 mg 1x1

Dabigatran and edoxaban initially need a heparin bridge. Standard treatment doses should be applied by calculating patient-based benefit / risk. (Ref:8,17,18)

However, the recommendation of clinicians is to adjust the treatment doses on patient basis by calculating benefit / risk. Dose adjustment is recommended for elderly patients, cancer patients, and patients with renal insufficiency. Clinical applications of two NOACs (dabigatran and

apixaban) initially require a heparin bridge. Some antimalarial (quinidine), anti-fungal (ketoconazole), anti-tuberculosis (rifampicin), and antibiotic drugs (clarithromycin) may increase NOACs-drug interactions through P-gp or CYP3A4 pathways. LMWH treatment is recommended for VTE

patients with active cancer (16,17,18). One of the important conclusions we have drawn from the study is that age, cancer, immobilization stand out as etiological reasons (more than half of the patients) and have features in terms of treatment. One of the controversial points is which treatment option will be more appropriate in the elderly and cancer patients. With the introduction of two antidotes (idaricuzimab for dabigatran and andexanet alfa for factor Xa inhibitors), the potential for use of NOACs in patients with high bleeding risk is expected to increase. Especially in elderly patients over 75 years of age, the risk of developing DVT is higher and the risk of bleeding is much higher. Therefore, new oral anticoagulants are preferred. Because, as mentioned above, the bleeding potential is lower in patients using NOACs. Because LMWHs are preferred by clinicians due to their antitumoral effects in patients of this age, larger studies are needed on this subject. It is recommended not to use these agents in patients with creatinine clearance ≤ 15 ml / min, prefer low doses of factor Xa inhibitors rather than dabigatran in patients with 15-30 ml / min, and dose selection according to the risk of bleeding in patients with 30-50 ml / min. Similarly, low dose preference is recommended for patients over 80

years of age and patients with body weight less than 60 kg. Benefit / risk calculation should be considered especially in the elderly and cancer patients (19,21).

However, there are still some controversial points in terms of NOACs. Studies on the use of new NOACs in patients such as antiphospholipid syndrome (APS) have not been terminated. Since there are no clinical studies completed with these drugs in patients with APS, the available information on the drugs in question is still limited. Disadvantage of NOACs treatment; It is not used in children, advanced liver and kidney patients, mechanical heart valve patients and it is more costly.

CONCLUSION

As a result, as can be understood from the data of the patients included in the study, the measurements of the leg diameters of the patients and the thrombus recanalization were achieved in the ideal measurements in the 3rd and 6th months. New oral anticoagulant drugs (rivaroxaban, dabigatran, apixaban, edoxaban), which have been used for more than ten years, provide sufficient efficacy in the treatment of deep venous thrombosis due to their more advantages and clinical improvement in patients

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