ORIGINAL ARTICLE

Recanalization rate of proximal deep venous thrombosis related to therapeutic modality during six months follow-up

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ABSTRACT

Aim To evaluate the efficacy (rate of recanalization) of therapy with novel oral anticoagulants (NOAC; rivaroxaban, apixaban) compared to conventional treatment (low molecular weight heparin - LMWH and vitamin K antagonist) in the treatment of deep vein thrombosis (DVT) of the proximal segments of lower extremities.

Methods The first group consisted of patients diagnosed with DVT and treated with NOAC (n = 100), while the second group consisted of patients diagnosed with DVT, who were treated by conventional treatment (low molecular weight heparin and vitamin K antagonists) (n = 100). In the first group, NOAC was included in the initial treatment. Patients in the second group were treated with LMWH for four days, and on the fifth day vitamin K antagonist was included in therapy, international ratio (INR) was titrated to therapeutic values (2.0-3.0), and then low molecular weight heparin was excluded from the therapy.

Results There was a statistically significant difference in the estimated values of free lumen of the blood vessel between the examined groups after 30 days (p=0.0001), after 90 days (p=0.0001) and after 180 days (p=0.0001). After 180 days, the average free lumen values in the NOAC group were 85% (81-89%), which was significantly higher than the free lumen values in the second group, 73% (69-79%).

Conclusion The use of NOAC represents more efficient treatment of DVT comparing to vitamin K antagonists.

Key word: anticoagulants, therapeutics, veins

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INTRODUCTION

Deep venous thrombosis (DVT), as an essential part of venous thromboembolism (VTE), along with pulmonary embolism (PE), presents a therapeutic challenge in everyday clinical work (1). About two-thirds of VTE episodes manifest as DVT and one-third as PE with or without DVT (2). Although the problem is actual, there is an impression of very little knowledge of the same in the wider community, and the literature indicates that 28% of patients are aware of PE-related symptoms, while only 19% are aware of DVT symptoms (3).

The therapeutic modality of DVT goes in two directions. The first option is to use low molecular weight heparins (LMWH) during hospitalization (in case of contraindications the use of unfractionated heparin), and then switch to vitamin K antagonists (VKAs) or novel oral anticoagulants (NOAC), if there are no contraindications for their use (4). In addition, therapy may begin with the administration of NOAC in accordance with the pharmacological regimen of its usage (4).

Monitoring of the international ratio (INR) is still required, and understanding of potential interactions, whether pharmaceutical or dietary, might impede with their usage. The question is which therapy is a better choice for the patient himself. Recanalization following acute DVT is estimated to occur in 50% of patients, however, the effectiveness of recanalization is directly dependent on thrombus length, it is lower in proximal occlusion, and higher in women (5).

There is a strong association between PE and the presence of DVT in the lower extremities (6). Anamnestic data at the very beginning of the verification, with the analysis of laboratory parameters and the finding of colour doppler are essential. Colour doppler is the basic diagnostic method in patients with suspected DVT (7). The method is simple, non-invasive and accessible. Common femoral and/or popliteal vein incompatibility is considered a diagnostic sign of proximal DVT (7). A compression test of the iliac, femoral, or popliteal vein should be carefully reported (7). Patient monitoring is necessary in relation to the patient profile itself, as well as the existence of comorbidities.

Warfarin-based anticoagulant therapy is the oldest and most commonly prescribed pharmacological therapy used to treat DVT and to prevent stroke in patients with atrial fibrillation (8,9). However, it is a therapy that requires regular monitoring of blood coagulability associated with warfarin because warfarin therapy has a narrow therapeutic index and is associated with a risk of bleeding. With the progress of genetics and molecular biology, it is now possible to identify those patients in whom the risk of bleeding is associated with warfarin, and to respond preventively either by adjusting warfarin dose or discontinuing warfarin therapy (9). Although the risk of bleeding may be influenced by environmental factors (dietary habits) or specific disorders (e.g. liver disorders), it is now well established that warfarin sensitivity or resistance is largely genetically determined (9).

In Bosnia and Herzegovina, although NOAC are available, the use of vitamin K antagonists is still prevalent, especially due to economic reasons. The large number of patients in daily clinical work with vitamin K antagonists in therapy forced us to this research.

The aim of this study was to evaluate the efficacy (rate of recanalization) of therapy with novel oral anticoagulants (NOAC; rivaroxaban, apixaban) compared to conventional treatment (low molecular weight heparin and vitamin K antagonists) in the treatment of DVT of the proximal segments of lower extremities.

PATIENTS AND METHODS

Patients and study design

The prospective study was performed at the Department of Angiology of the Clinic for Heart, Blood Vessels and Rheumatism at the Clinical Centre University of Sarajevo between January 2019 and December 2020. There were 200 patients, of which 103 (51.50%) males. Inclusion criteria were: diagnosed DVT of the proximal segment based on anamnestic data, clinical presentation, laboratory and colour doppler findings, patients with preserved renal function (creatinine clearance > 60 mL/min), patients who had been diagnosed with DVT of the proximal segment of the lower extremities, and followed up for a period of 6 months. The exclusion criteria were: patients who had not been clearly diagnosed with DVT of the proximal segment of the lower extremities, patients with impaired renal function (cre-

atinine clearance <50 mL/min), patients who had not undergone continuous therapeutic treatment, or patients in whom initial colour doppler had not been performed at diagnosis or after 10, 30 days, and 3 and 6 months of treatment.

Patients were divided into two groups. The first group consisted of patients diagnosed with DVT of the proximal segment of the lower extremities (iliac-femoral segment) and treated with NOAC (n = 100). The second group consisted of patients diagnosed with DVT of the proximal segment of the lower extremities and were treated by the conventional treatment (low molecular weight heparin and vitamin K antagonists) (n = 100). The NOACs were included in the first group's initial treatment; patients in the second group were treated with LMWH for four days, with vitamin K antagonist added on the fifth day, international ratio (INR) titrated to therapeutic values (2.0-3.0), and then low molecular weight heparin was removed from the therapy.

During the implementation of this study, the identity and all personal data of patients were permanently protected in accordance with the regulations for the protection of identification data. After the patients signed an informed consent in which they were informed of the procedures they would undergo during the clinical study, the following measurements were performed. An ethical approval was obtained from the Ethical Committee of Clinical Centre of the University of Sarajevo.

Methods

Anamnestic data, C-reactive protein (CRP), fibrinogen, and D-dimer were done at admission, as well as colour doppler examination was done at admission, 10 and 30 days, 3 months, and 6 months. Colour doppler examination was performed at the narrowest site of occlusion, which was previously marked and documented. The same site was then observed at subsequent follow-up examinations. The examination was done with a 12L-RS Linear Probe on a VIVID S5 device (GE Healthcare, Chicago, Illinois, United States).

To analyse the activity of CRP, fibrinogen and D-dimer, samples were collected by venipuncture with a 21-gauge needle (BD Vacutainer, Plymouth, UK), and were collected in tubes (BD Vacutainer, Plymouth, Great Britain), and these samples were sent to the laboratory for analysis (Clinical Laboratory, Clinical Centre of the University of Sarajevo), without prior freezing. Fibrinogen and D-dimer activity analyses were performed on a BCS-XP Siemens Healthcare Diagnostics Products GmbH automatic coagulometer (Marburg, Germany). Analyzes of CRP activity were performed on aARCHITECT C8000 (Abbott Laboratories, Illinois, United States).

Statistical analysis

For the purpose of personal data protection, each patient was assigned an identification number that was used in statistical data processing. For continuous variables in the study, the symmetry of their distribution was first analysed using the Shaprio Wilk test. When the distribution was symmetric, the arithmetic mean and standard deviation were used to display the mean values, and to compare these variables with parametric tests (t-test). When the distribution was asymmetric, the median and interquartile range to display the mean values was used, and to compare these variables, nonparametric tests (Mann-Whitney U test) were used. Differences in repeated recanalization measurements (time intervals) were analysed using the Friedman test for repeated measurements, and Wilcoxon rank test for accurate measurements (for two time intervals). To examine the relationship and the direction of the relationship between the variables, correlation tests were used, depending on the type of variable (Spearman-rho). The value $p<0.05$ was taken as the limit of statistical significance.

RESULTS

There was no statistically significant difference in patients age between males and females (59.25±15.64 and 59.32±17.45 years, respectively; p=0.971), nor within the males/females groups themselves (p=0.203). The mean age of patients receiving NOAC therapy was 57.2±16.8 years, while the mean age of patients receiving conventional therapy was 61.3±19.9 years (p=0.075).

There were 20 (10%) patients without risk factors, 10 (5%) in the NOAC group and 10 (5%) in the conventional therapy group; 90 (45%) patients were with one risk factor, 44 (22%) in the NOAC group, 46 (23%) in the conventional therapy group; 78 (39%) patients were with two risk factors, 39 (19.5%) in the NOAC group, 39

(19.5%) in the conventional therapy group; and 12 (6%) patients were with three or more risk factors, seven (3.5%) in the NOAC group, five (2.5%) in the conventional therapy group.

Of the total number of 200 patients, 48 (24%) had previous venous thromboembolism (Table 1).

Table 1. Risk factors of 200 patients for the development of deep vein thrombosis

Risk factors	No (%) of patients
Previous venous thromboembolism	48 (24)
Cancer	24 (12)
Pregnancy	9 (4.5)
Hormonal therapy	21 (10.50)
Previous myocardial infarction	27 (13.50)
Travelling	23 (11.50)
High intensity physical activity	31 (15.50)
Immobilization	27 (13.50)
Active inflammatory process	16 (8.0)

At admission, there was no difference in the free lumen of the blood vessel between the examined groups (p=0.323). In the NOAC group, the average free lumen values were 6% (5-8%), which is almost the same as the values in the conventional treatment group 6% (4-8%). After 30 days, there was a change in the estimated values of the blood vessel's free lumen (p=0.0001) with NOAC group average free lumen values being 56.5% (50.2-60%) higher than the conventional treatment free lumen values 30 (26-36)%. The same pattern was observed after 90 and 180 days, with a change in the estimated values of the blood vessel's free lumen (p=0.0001): with the NOAC group average free lumen values of 70.5% (69-7%) after 90 days, 85% (81-89%) after 180 days were higher than the conventional treatment group free lumen values, 55% (47.2-63%) and 73% (69-79%), respectively (Figure 1, Figure 2).

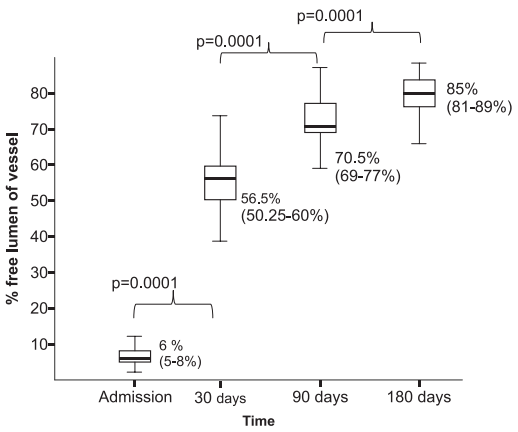

Figure 1. New oral anticoagulant (NOAC) treatment and the effect on blood vessel recanalization

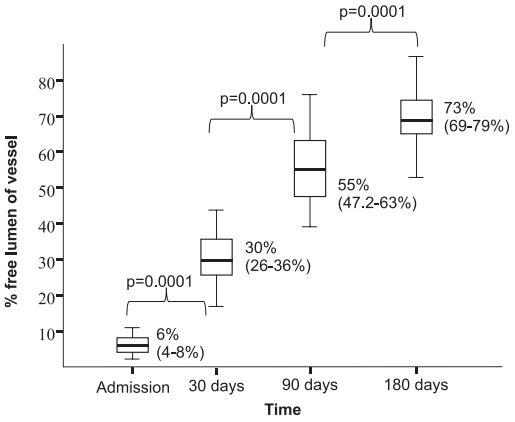

Figure 2. The effect of conventional therapy (low-molecular-weight heparin and vitamin K antagonists) on blood vessel recanalization

The Spearman's correlation test showed no difference (p>0.05) between the percentage of free blood vessel lumen at admission in either the NOAC or conventional treatment group, as well as in platelet, D dimer, fibrinogen, or CRP values.

Both the NOAC and conventional treatment group had a significant increasing trend (p=0.0001) in free blood vessel lumen between observation periods (at admission, after 30 days, after 90 days, and after 180 days) (Figure 1, Figure 2).

DISCUSSION

At the beginning of the study, there was no difference in the rate of free lumen between the two groups of patients, implying that the sample itself at the commencement of the therapy was adequate for analysis. After 30, 90 and 180 days of the therapy, the mean recanalization in the NOAC group of patients was 56.5%, 70.5%, and 85%, respectively, while in the conventional treatment group it was 30%, 55%, and 73%, respectively. The values of platelets, D dimer or CRP were not indicators of the extensiveness of the thrombotic process, and according to this research, they cannot be used as a determinant in the differentiation of symptomatology. Both therapeutic modalities are beneficial and effective, but the recanalization rate in patients with NOAC is quicker and more effective throughout the six-month follow-up at all time intervals. Current guidelines recommend that all patients who have just been diagnosed with VTE remain on anticoagulant therapy for at least 3 months, unless this therapy is strictly contraindicated (active bleeding and a very risky bleeding lesion) (9).

Piati et al. analysed 26 patients on heparin and warfarin therapy and 51 patients on rivaroxaban therapy, and had similar results to our study. After three months of warfarin therapy, recanalization was 55%, after six months 78.88%, and in patients on rivaroxaban therapy, recanalization was 83.46%, and 92.39%, respectively (8). De Athayde Soares et al. followed 88 patients with DVT for one year, where they monitored the percentage of complete recanalization, and also divided patients into two groups, those with VKAs, and those with rivaroxaban therapy. Success was higher in the rivaroxaban group, and the prevalence of postthrombotic syndrome was lower (9).

The risk of bleeding should be assessed in clinical practice, but it should not be a reason not to optimize pharmacological therapy. The NOACs include five representative drugs, of which four are a direct factor of Xa inhibitors (rivaroxaban, apixaban, edoxaban, and betriaxaban), and the fifth is a direct thrombin inhibitor (dabigatran) (12). Clinical studies that have established the use of NOACs are as effective as VKAs in stroke prevention in patients with nonvalvular atrial fibrillation and for the treatment of VTE, and present a safer therapeutic modality due to the lower rate of intracranial haemorrhage (12). The choice of the NOAC group should be based on the individual patients characteristics, as well as on the pharmacological properties of the substance itself (12). Through AMPLIFY (Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy) and AMPLIFY-EXT (Efficacy and Safety Study of Apixaban for Extended Treatment of Deep Vein Thrombosis or Pulmonary Embolism) trial apixaban was established in the VTE treatment, while the use of rivaroxaban was established through EINSTEIN-DVT (Oral rivaroxaban versus standard therapy in the initial treatment of symptomatic deep vein thrombosis and long-term prevention of recurrent venous thromboembolism) and XALIA (Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis: an international, prospective, non-interventional study) trials (13-15).

VTE treatment with dabigatran and edoxaban has not been established (16,17). Betriaxaban is still not established for use in the European Union (18). The analysis of patients in relation to the use of rivaroxaban or apixaban probably makes sense, especially because apixaban is dosed twice a day.

A limitation of the study is a small sample size. A larger sample should be used to interpret the difference in pharmacological modalities in order to confirm possible differences between them. Knowledge of the pharmacokinetic and pharmacodynamic properties of NOACs is critical, as is knowing the patient while taking into consideration his characteristics such as liver or renal condition. The distinction between provoked and unprovoked DVT, also influences the treatment, and comprehension of congenital coagulation abnormalities is something that must be reflected into daily clinical practice. All of this suggests that the usage of VKAs will continue to be a part of DVT therapy.

In conclusion, the use of NOACs should be a part of standard DVT treatment, and represents a faster and more efficient DVT treatment comp ring to vitamin K antagonists.

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TRANSPARENCY DECLARATION

Competing interests: None to declare.

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