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Rivaroxaban use in the treatment of deep vein thrombosis: A single center experience

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ABSTRACT

Objectives: This study aims to present the clinical results of patients administered rivaroxaban for the treatment of deep vein thrombosis (DVT) in terms of efficacy and safety.

Patients and methods: A total of 78 patients (44 males, 34 females; mean age 60.9±20.6 years; range, 26 to 88 years) diagnosed with DVT had received rivaroxaban treatment at the Gülhane Education and Research Hospital's Cardiovascular Surgery Clinic between August 15, 2014 and November 3, 2017 were included in the study. Deep vein thrombosis diagnoses of the patients were confirmed by Doppler ultrasonography. The patients' epidemiological and biochemical values were evaluated. Major-minor bleeding and recurrence that occurred during rivaroxaban treatment was investigated.

Results: The mean follow-up period was 12.2±9.4 (range, 6-48) months. When anticoagulant treatments of the patients were examined, 21 patients (27%) were treated with rivaroxaban as initial treatment and 57 patients (73%) had transitioned from warfarin to rivaroxaban treatment. In patients using rivaroxaban, one patient had hypermenorrhea and two patients had epistaxis. Major bleeding was not detected. While three patients had alanine aminotransferase levels up to two times higher than the normal limit, none of the patients had clinically significant liver or kidney failure. Recurrent DVT or pulmonary embolism was not detected in the patients.

Conclusion: According to the current guidelines and literature findings novel oral anticoagulants could be used safely and efficiently as a first line drug theraphy in DVT patients due to their noninferior effectiveness to warfarin and lower side effect profile.

Keywords: Deep vein thrombosis; rivaroxaban; warfarin.

Venous thromboembolism (VTE) is the general term for all pathologic thrombosis occurring in the venous circulation, including deep vein thrombosis (DVT) and acute pulmonary embolism (PE), and is the third most common cause of death in Europe. However, only 41% of deaths due to VTE can be diagnosed, and the remaining cases are diagnosed by postmortem autopsy.[1] Risk assessment and prophylaxis are crucial in patient protection, and diagnosis and treatment are important in reducing morbidity and mortality. Warfarin, a vitamin K antagonist which acts on factor II, VII, IX, X in the coagulation cascade, is the most widely used oral anticoagulant and has been used in the treatment of systemic embolism due to atrial fibrillation (AF) or mechanical heart valve failure and VTE for many years. However, warfarin is a drug that pharmacologically interferes with a large number of foods and other drugs, requires dose adjustment followed with international normalized ratio (INR) to keep it in the narrow therapeutic range, and has bleeding complications.[2] For this reason, new oral anticoagulants that do not require dose-range monitoring, minimize drug-food interactions, have fewer bleeding complications but are as effective as warfarin, and inhibit key target molecules in the coagulation cascade, have been developed and continue to be investigated.[3] New generation drugs, also referred to as novel oral anticoagulants (NOACs), have begun to be widely used at the same level of efficacy as warfarin due to their promising properties

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and coagulation efficacy. The most important disadvantages of NOACs are the lack of readily available standard measurement methods for the level of the drug in the body and the lack of readily accessible specific antidotes in the presence of any bleeding (intracranial, gastrointestinal system [GIS] bleeding, etc.) of these drugs.[3] In addition, according to the Antithrombotic Therapy for Deep Vein Thrombosis Disease CHEST Guideline and National Treatment Guideline of Peripheric Arterial and Venous Diseases, NOACs suggested over vitamin K antagonist (VKA) therapy for treatment of the patients with DVT of lower extremity without cancer, as long-term (first 3 months) anticoagulant therapy.[4,5]

Active factor Xa is a co-molecule of the intrinsic-extrinsic coagulation cascade in thrombin formation and plays a very critical role as a rate-limiting step. Rivaroxaban is an orally administered, direct, reversible, competitive, fast and dose-dependent inhibitor of factor Xa.[6] Rivaroxaban prevents thrombin formation by both the extrinsic and intrinsic pathway by inhibiting factor Xa.[6] Three hours after oral intake, the maximum inhibitory activity is reached and the effect lasts for 8-12 hours. In addition, since factor Xa activity does not attain baseline at doses above 5 mg before 24 h, a single dose of rivaroxaban is sufficient for anticoagulation.[7]

Rivaroxaban has been reported to be a safe drug in controlled randomized reference trials involving AF, DVT, and PE.[8-10] Rivaroxaban has been used in our clinic in DVT patients with appropriate indications since 2014. This study aims to present the clinical outcomes of patients in our clinic diagnosed with DVT and treated with rivaroxaban in terms of efficacy and safety.

PATIENTS AND METHODS

A total of 78 patients (44 males, 34 females; mean age 60.9±20.6 years; range 26 to 88 years) diagnosed with DVT and administered rivaroxaban treatment at Gülhane Education and Research Hospital's Cardiovascular Surgery Clinic between August 15, 2014 and November 3, 2017 were included in the study. The retrospectively designed cross sectional study was approved by the local ethics committee. Patient data was obtained by scanning the hospital automation system and patient files. The age, sex, location of DVT, and predisposing factors of DVT were investigated. The criteria for inclusion in the study were patient age over 18 years, DVT confirmed by Doppler ultrasonography (USG), anticoagulant therapy as post-warfarin or direct rivaroxaban treatment initiation. Exclusion criteria were as follows: use of NOAC other than rivaroxaban at any time during the medical treatment of DVT diagnosis, presence of PE symptoms at diagnosis of DVT, creatinine clearance <30 mL/min, presence of clinically significant liver failure, and contraindication for anticoagulant treatment.

Anticoagulation

Patients who started rivaroxaban as an anticoagulant treatment with acute DVT diagnosis continued with 15 mg 2×1 followed by 20 mg 1×1 posology in the first three weeks. International normalized ratio was used in the follow-up of patients who had started warfarin treatment as initial anticoagulant treatment. International normalized ratio was targeted to be kept between 2-3. Warfarin was discontinued and switched to rivaroxaban 20 mg 1×1 after at least two months of warfarin use, and when at least three measurements of the last five INR values could not be kept within the 2-3 target range.

Patients who were receiving rivaroxaban treatment were followed up in terms of recurrent thromboembolism and bleeding complications. Clinically recurring venous thrombosis in the same leg, and thrombosis developing in the other leg, and development of PE while under rivaroxaban treatment was evaluated as recurrent thromboembolism. Bleeding complications were divided into clinical or laboratory significant (major-cerebrovascular, GIS, urinary system), and clinical and laboratory insignificant (minor-epistaxis, GIS, urinary system).

Urea, creatinine, aspartate transaminase, alanine transaminase, total bilirubin, and direct bilirubin values were investigated on the first, third, and sixth months after initiating rivaroxaban treatment considering potential liver and kidney cytotoxicity.

Statistical analysis

All statistical analyses were performed with PASW for Windows version 18.0 (SPSS Inc., Chicago, IL, USA) statistical programming. Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as number and percentage.

RESULTS

The mean follow-up period was 12.2±9.4 (range, 6-48) months. When anticoagulant treatment

of patients was examined, 21 patients (27%) started rivaroxaban treatment as initial anticoagulant treatment while the remaining 57 patients (73%) switched to rivaroxaban from warfarin (Table 1). When etiology of these 57 patients was examined, recurrent DVT was found in 10 patients, major surgery in seven, oral contraceptive use in four, and thrombophilia in five, while 31 patients had no predisposing factors for DVT (Table 2).

When etiology of 21 patients who began rivaroxaban as initial oral anticoagulant treatment were investigated, 14 patients had immobilization, five active cancer with history of VTE, and two had homozygote thrombophilia (Table 3). Of the 14 immobile patients, seven patients were elderly, five patients had stroke, and two patients had mental retardation. Deep vein thrombosis diagnosis was confirmed with Doppler USG and showed that 77 of the 78 patients had lower extremity proximal DVT, and one patient had upper extremity DVT.

Recurrent thromboembolism or major bleeding was not observed in the 78 patients that were followed. Clinically and laboratory insignificant minor bleeding was detected in three patients. Of the cases with minor bleeding, one patient's complaints decreased when rivaroxaban dose was reduced (15 mg 1×1). Epistaxis was found in two patients, who underwent cauterization by Department of Otorhinolaryngology, rivaroxaban 15 mg 1×1 was reinitiated, and no further epistaxis was detected. Biochemical parameters were obtained during the follow-up of the patients and in one patient, alanine aminotransferase (ALT) was elevated at least two times the baseline value and the drug was discontinued. The patient did not develop clinical kidney or liver failure.

Table 1. Demographic data of the patients

	n	%	Mean±SD
Mean age (year)			60.9±20.6
Number of patients	78	100	
Male	44	56	
Female	34	44	
Initial treatment warfarin	57		
Initial treatment rivaroxaban	21		
Mean follow-up period (months)			12.2±9.4

SD: Standard deviation.

Table 2. Etiology of patients with initial warfarin treatment

	n	%
History of major surgery	7	12
Thrombophilia	5	9
Oral contraceptive use	4	7
Recurrent deep vein thrombosis	10	18
Unprovoked	31	54
Total	57	100

Table 3. Etiology of patients with initial rivaroxaban treatment

	n	%
Immobilization	14	67
Active cancer	5	24
Homozygote thrombophilia	2	9
Total	21	100

DISCUSSION

The purpose of DVT treatment is to prevent chronic complications such as PE, pulmonary hypertension, peripheric venous disease, recurrence of VTE, and postthrombotic syndrome. Warfarin, a vitamin K antagonist, is an oral anticoagulant drug coincidentally isolated from the investigation of abnormal bleeding in cows eating sweet clover and has been used as the first choice for the treatment of thromboembolic diseases for over 60 years. It is believed that NOAC use is appropriate for patients with problems with warfarin posology, morbid obesity or low-weight, serious thrombophilic defects, or additional need for antithrombocytic drugs.[11]

Of the 21 patients in our clinic who were deemed unsuitable for warfarin treatment, NOAC treatment was started as the initial anticoagulant treatment, as for the 57 patients who had previously used warfarin, treatment was transitioned to rivaroxaban because effective INR values could not be maintained. Upon transition from warfarin treatment to NOAC, the ideal INR value is 2.5.[12] In our study, when INR was lower than the target value of 2 in the patients using warfarin, low-molecular-weight heparin was administered two hours before the next planed dose and the transition to rivaroxaban was made according to the guidelines.

Hemorrhagic complications are the most common side effects of anticoagulant therapy. Extracranial hemorrhage complications are more common than cranial hemorrhage.[13] Due to the accompaniment of comorbid diseases, patients who are prescribed anticoagulants for DVT diagnosis have more bleeding complications than patients prescribed anticoagulants for AF diagnosis.[14] In particular, advanced age and hypertension increase the likelihood of major bleeding, especially intracranial bleeding.[15,16] Although scoring systems such as the Outpatient Bleeding Risk Index (OBRI) and the ATRIA Bleeding Risk Index have

been established to calculate the likelihood of bleeding complications in patients using anticoagulants, these scoring systems are inadequate without anticipating intracranial hemorrhage.[14]

When the EISTEIN-DVT study, the DVT and PE branches of the referenced randomized controlled series known as EISTEIN, was examined, while regions of bleeding were not separated, there was no significant difference found between major and non-major bleeding rates between the warfarin group and rivaroxaban group. In the EISTEIN-PE study, there was no significant difference between the groups in non-major bleeding rates, but major bleeding was higher in the warfarin group. In particular, intracranial hemorrhage was more frequent in the warfarin group than in the rivaroxaban group.[9,10] No matter how much AF is an indication for anticoagulation, a prospective multicenter study on anticoagulant use in the Turkish population found that causes of frequent bleeding was clinically related to epistaxis, hematuria, ecchymosis and conjunctival hemorrhage, while GIS bleeding was less frequent and intracranial hemorrhage was found in only two patients. In addition, the highest bleeding rate was seen in the rivaroxaban group, and following NOAC treatment, bleeding occurred at an average of five months.[17] In our study, nonmajor hemorrhage occurred in three patients during follow-up and one patient's rivaroxaban dose was reduced due to hypermenorrhea. Epistaxis was observed in two patients and rivaroxaban treatment was reinitiated following nasal cauterization and no bleeding was detected. No intracranial or extracranial major hemorrhage was detected during our follow-up.

Warfarin has been extensively studied for many years as it is the most prescribed anticoagulant drug. Warfarin has a large number of drug interactions and at least 30 genes that affect its metabolism and activity. In particular, vitamin K epoxide reductase enzyme (VKORC1) and cytochrome P-450-2C9 enzyme (CYP2C9) gene polymorphism were responsible for 40% of warfarin dose variations.[18,19] In the EINSTEIN-PE study, the success rate of warfarin treatment at the therapeutic level (INR=2-3) was 62.7%.[10] The efficacy of warfarin varies due to many causes in patients with VTE. Studies on VTE have shown that rivaroxaban is at the same level as warfarin in terms of efficacy.[9,10] Studies on the efficacy and safety of clinical outcomes of long-term use of NOACs are carried out and the EINSTEIN Extension study on rivaroxaban reported that 20 mg/day rivaroxaban treatment after acute DVT treatment for 6-12 months was superior to placebo. In the EINSTEIN-EXT study, when rivaroxaban 20 mg/day was compared to placebo, 82% reduced risk and 6% major or clinically significant non-major bleeding was observed.[20] In a study that compared warfarin and rivaroxaban in thromboembolism treatment in Japanese patients, the results of efficacy and safety of rivaroxaban was the same as the results of the EINSTEIN study. However, this study was conducted according to the Japanese guidelines and the warfarin INR therapeutic level was maintained at 1.5-2 and rivaroxaban was administered at 15 mg daily.[21] In addition, rivaroxaban and apixaban are found that more effective than other oral anticoagulants in extended therapy in terms of preventing recurrent DVT.[22] Patients who directly started rivaroxaban in our clinic due to acute DVT initially began rivoroxaban 15 mg 2×1 for three weeks, followed by 20 mg rivaroxaban once a day. No recurrent thromboembolism was seen in patients during rivaroxaban treatment.

Although GIS side effects due to oral anticoagulants are common, dyspepsia-like symptoms (gastroesophageal reflux, gastritis, gastric and duodenal ulcer) and GIS bleeding are predominant. To explain the GIS side effects of oral anticoagulants, various mechanisms such as topical biological effect of the drug unrelated to coagulation, systemic anticoagulant effect, topical anticoagulant effect, and topical direct cytotoxic effect of the drug are brought to light.[23] Warfarin has oral bioavailability close to 100%, and is primarily absorbed by the proximal small intestine.[19] Rivaroxaban is an active drug and oral bioavailability is close to 76% when taken with meals. Rivaroxaban is absorbed from the stomach throughout the GIS.[24] Since warfarin is a prodrug and has absorption close to 100%, GIS bleeding as a side effect may be due to systemic anticoagulant effect, although dyspepsia-like symptoms may be due to direct cytotoxic effects. Rivaroxaban may cause gastric dyspepsia at a 2% rate.[24] Since rivaroxaban is an active drug aside from cytotoxic effect, gastrointestinal side effects are thought to be due to both its systemic anticoagulant effect and topical anticoagulant effect of the intraluminal non-absorbed drug. However, studies reported no statistically significant difference between rivaroxaban and warfarin in terms of treatment withdrawal rates or GIS bleeding.[9,10] In our study, neither treatment withdrawal due to gastritis-like symptoms was observed in patients undergoing rivaroxaban treatment. Furthermore, GIS bleeding was not observed in any of the patients either.

There is a high risk of thromboembolism in patients with chronic kidney failure.[25] Both prophylaxis as well as good anticoagulation-bleeding balance is crucial in this patient group. The clinical benefits of vitamin K antagonists are evident in patients with chronic kidney failure.[26] However, rivaroxaban is not recommended for patients with creatinine clearance <15 mL/min, and dose reduction is recommended in patients with rates of 15-49 mL/min since 66% of rivaroxaban is eliminated in renal pathways.[24] Our study had no patient followed up with chronic renal disease. In recent years, acute renal damage known as warfarin-associated nephropathy has become more widespread.[27] Warfarin-associated nephropathy is defined as glomerular hemorrhage in patients with INR> 3 independent of systemic hemorrhage, and renal tubular duct obstruction with erythrocytes and acute renal failure. It is stated that this condition can be seen in all patient groups whether or not they are related to chronic kidney disease.[27]

The rate of patients using warfarin in the EINSTEIN-DVT trial and in the therapeutic INR range was 66.4% at 10 months.[9] The fact that 16.2% of the patients found to have INR over 3 in a randomized controlled study of this manner may be an indication that this ratio may be higher in unregistered patients. This shows that significant portion of patients is at risk of warfarin-associated nephropathy. Furthermore, cases of rivaroxaban-associated interstitial nephritis are few but exist in the literature.[28,29] All drugs, including rivaroxaban, are followed for cytotoxicity during phase studies. Cases of rivaroxaban-associated liver damage exist. Additionally, studies carried out with a high number of patients have found that ALT values can increase by three times, and bilirubin levels can be doubled. For this reason, it is necessary to be careful for hepatotoxicity associated with rivaroxaban and to discontinue the drug in suspected cases.[30] With the widespread use of this drug, there is a greater likelihood of exposure to these cases of nephrotoxic and hepatotoxic effects. In our study, no abnormal kidney and liver function tests were observed in any patient followed by the use of rivaroxaban.

Our study had limitations. The study was retrospective and the patient number was few. Since other NOACs are seldom used in our clinic, rivaroxaban could not be compared with other anticoagulants in terms of adverse effects and efficacy.

In conclusion rivaroxaban can safely be used in DVT treatment in patients with have trouble maintaining therapeutic INR with warfarin, or INR monitorization. According to the current guidelines and literature findings NOACs could be used safely and efficiently as a first line drug therapy in DVT patients due to their noninferior effectiveness to warfarin and lower side effect profile. Therefore we believe that reimbursement of these drugs even in the acute phase of DVT would be more beneficial and safe for nearly all patients profile having DVT.

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