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Oral Rivaroxaban Versus Standard Therapy in Acute Venous Thromboembolism Treatment for Vietnamese Patients

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Abstract

BACKGROUND: Direct oral anticoagulant-rivaroxaban may provide a simple, fixed-dose therapy for the management of hospital-acquired, acute venous thromboembolism (VTE) and for extended treatment, its use could skip lab observation and/or parenteral treatment.

AIM: Compare the efficacy and safety (EAS) of RIV vs. standard therapy (SDTD) in a cohort of Vietnamese patients diagnosed with symptomatic, acute VTE.

METHODS: An open-label, case-control, prospective study was conducted to check the efficacy and safety (EAS) of oral rivaroxaban (RIV) alone (15 mg 2 times/day for 3 weeks, then 20 mg 1 time/day) in a comparison to the standard therapy (STDT) (enoxaparin 1.0 mg/kg 2 times/day combining with vitamin K antagonist). Patients were treated for 6 months and followed-up for suspect reoccurring VTE and bleeding.

RESULTS: A total 187 patients were enrolled into study. 83 were provided rivaroxaban and 104 received enoxaparin overlapping with vitamin K antagonist (VKAs). Recurrent VTE occurred in 3 (3.6%) rivaroxaban-received patients compared with 5 (4.8%) standard-treatment received patients (OR: 0.74, 95% CI, 0.17 to 3.20, p > 0.05). Major bleeding events were found in 1 (1,8%) and 4 (3.9%) cases in the RIV treated and STDT cohort, respectively (OR: 0.30, 95% CI, 0.03 to 2.76, p > 0.05).

CONCLUSION: The finding of this study in Vietnamese patients with acute VTE presented comparable EAS profile with RIV versus STDT, consistent with those found in global population.

Introduction

Venous thromboembolism (VTE), (for example deep venous thromboembolism (DVT) or pulmonary embolism (PE)) is a major issue which cause annual prevalence of about 100 – 200 cases per 100,000 individual in the Western countries [1], [2]. In Asia, the prevalence of VTE has increased over recent years, however, it is often knownto be lower than that in Caucasian population [3], [4]. Anticoagulant therapy effectively minimize the rate of recurrent VTE from 25% to 3% approximately within the period from 6 to 12 months, but the risk of VTE reoccurrence was stable at around 5-10% after one year of treatment [5].

Standard guidelines on antithrombotic therapy for VTE commonly suggest the application of enoxaparin (low molecular weight heparins) plus vitamin K antagonists (VKAs). However, it still has some limitations. Enoxaparin requires uncomfortable subcutaneous injection on a daily or twice daily basis while treatment with VKAs demands lab observation and cautious dosage modification and may be complicated by interacting with food and concomitant drug. After one year, the likelihood of occuring major bleeding event with regard to the use of VKAs is approximately 1 to 2% annually [6]. As a result, the debate on balancing the advantages and the disadvantages of continuous therapy were still controversial, regardless of the high likelihood of VTE reoccurrence in a long term. An absolute method to solve several of these concerns might be introduction of new oral anticoagulant that skip the requirement for parenteral medication and routine lab observation but shows effectiveness as a single factor for acute and

continued treatment of symptomatic VTE.

Rivaroxaban (RIV), a new oral anticoagulant, acts through activedirect inhibition of activated Factor Xa and shows a quick onset of peak anticoagulant effect (within 2-4 hours after dosing) and has calculable pharmacodynamic and pharmacokinetic properties, which restrain the requirement for daily observation of anticoagulation, has a low propensity for interacting with other drugs and does not need dietary restrictation [7]. The evaluation of RIV was implemented in global clinical trial in acute symptomatic VTE patients, and showed a comparable efficacy as enoxaparin plus VKA with reduced incidence of major bleeding [8], [9].

Although there are a number of published studies on using RIV for the intervention of thrombolysis conditions in the literature, this therapy is not well documented among Asian population. Therefore, we aimed to compare the efficacy and safety (EAS) of RIV vs. standard therapy (SDTD) in a cohort of Vietnamese patients diagnosed with symptomatic, acute VTE.

Methods

Study design

This was a case-control, prospective study designed to evaluate the EAS of RIV in comparison with SDTD (enoxaparin overlapping with VKAs) in treating acute hospital-acquired VTE. The research was conducted at a teaching hospital (Cho Ray Hospital, Ho Chi Minh, Vietnam).

Subject and sampling method

Convenience sampling method is applied. All eligible patients are recommended to participate into study.

Patients were enrolled in the study if they were ≥ 18-year olds and had been diagnosed as having acute, symptomatic DVT and/or PE. Patients were not included if therapeutic dosage of parenteral anticoagulant was given to patients for over 48 hours before randomization; or if thrombectomy had been performed, a vena cava filter required for the present occasion of thrombosis; or if patients were contraindicated for using anticoagulant. Other criteria for exclusion were: having significant hepatic disease; another designation for VKAs; cerebral haemorrhage; occurrence of bleeding or an increased likelihood of occurring bleeding,; renal failure with creatinine clearance levels < 30 mL/min; a systolic blood pressure (BP) of ≥ 180 mm Hg or diastolic BP of ≥ 110 mm Hg; pregnancy or breast-feeding; or a life expectancy of ≤ 3 months.

Treatment regimens

Patients using rivaroxaban for VTE treatment were received 15 mg 2 times per day for the first 3 weeks, then 20 mg were given 1 time per day continuously. Patients distributed to STDT received injection of enoxaparin with a dosage of 1.0 mg/kg of body weight two times per day, and vitamin K antagonists (warfarin or acenocoumarol), begun during 48 hours after selection. Anticoagulation with SDTD was stopped when the INR (international normalized ratio) was recorded as 2.0 or higher for two continuous days and after the patients had been given at a minimum of 5 day. The VKAs dosing was changed to sustain an INR of 2.0-3.0. Initially, the INRs were examined frequently, and when stabile, at least one time per month.

Patients follow-up

Follow-up for discharged patients was performed for intended treatment period (6 months) and evaluated at fixed intervals that were alike for both subgroups. Any signs and symptoms of VTE recurrence, bleeding and complications were elicited using a checklist among each outpatient visit. If any of signs and symptoms of these events happened, patients were guided to inform to physician. In case of clinically suspected VTE reoccurrence, objective testing was demanded.

Outcomes

The main outcome for this study was the prevalence of reoccurring VTE consisting of symptomatic DVT or PE. The criteria for detection of recurrent PE were as follow: a new intraluminal filling deficiency on pulmonary angiography or computed tomography scan, a new cutoff of a vessel of 2.5 mm or higher in caliber on pulmonary angiography, a new non-high probability perfusion defect related to DVT as determined by ultrasonography or venography. The criteria for identification of recurrent DVT were as follow: a new non-compressible venous segment or a significant enlargement (more than 4 mm) in the caliber of the blood clots during full compression in earlier uncommon sector on venous detected by ultrasound scan or on the appearance of a filling deficiency on venography.

The outcome of safety was clinically relevant bleeding. Bleeding complications were classified as critical if it was clinically overt and required a transfusion of more than two units of packed red blood cells; was intracranial or retroperitoneal, appeared in another critical site and/or conduced to mortality. Non-critical clinical bleeding was determined as observable bleeding that did not satisfy the criteria for major bleeding complication but was related to medical intervention, infrequent use of drug or abandonment of medication, unscheduled contact with doctor, or

impairment of daily activities.

Mortality was identified as being because of PE, bleeding events or other causes happening during the time of continuous treatment. Pulmonary embolism was seen as the reason of decease if objective documentation of the disease were demonstrated, or if the reason of death was not discovered and PE could not be removed.

Statistical analysis

Desciptive statistics were conducted to analyze distribution of baseline characteristics in the two treatment arms. Qualitative variables were calculated as percentages and quantitative variables were calculated as average (± SD). Proportions and absolute differences and corresponding 95% confidence intervals (CI) were reported. Exact method was applied to calculate 95% CI. The results were recognized statistically significant if $p < 0.05$.

Results

From January 2017 to August 2018, a total of 187 VTE patients were selected into the study. Of these, 83 were given RIV and 104 received enoxaparin overlapping with VKAs. Overall, 71 patients receiving rivaroxaban (85%) had isolated DVT vs. 91 (87%) from standard treatment group; Moreover, 3.6% vs. 4.8% of patients had DVT and PE, and; 10.8% vs. 6.7% of patients had PE without DVT symptoms (Table 1). Limb swelling and leg pain were found as the most frequent signs in DVT patients while dyspnea and chest pain were mostly seen in PE patients. Their baseline and clinical characteristics appear in Table 1.

Table 1: Baseline characteristics

Characteristic	RIV (n = 83)	STDT (n = 104)	p value
Average age, (± SD)	57.08 ± 19.5	60.2 ± 16.4	0.24
Male sex, n (%)	30 (36.1)	27 (25.2)	0.13
Mean weight	55.8 ± 10.1	55.4 ± 9.0	0.84
Concomitant disease, n (%)	33 (47.1%)	58 (59.8%)	0.12
Concomitant therapy, n (%)	42 (50.6%)	49 (47.1%)	0.65
Major bleeding occurring in previous month, n (%)	1 (1.2%)	0	0.27
Creatinine clearance, n (%)			0.63
30 - < 50 mL/min	7 (8.4%)	13 (12.5%)	
50 - < 80 mL/min	28 (33.7%)	34 (32.7%)	
≥ 80 mL/min	44 (53.01%)	55 (52.9%)	
Cancer	5 (6%)	9 (8.4%)	0.74
Recent surgery	2 (2.4%)	3 (2.8%)	0.99
Immobilization (≥ 4 days)	8 (9.6%)	11 (10.6%)	0.41
Estrogen therapy	1 (1.2%)	0	0.25
Previous DVT or PE	3 (3.6%)	3 (2.9%)	0.60
Any travel > 6 hours in the past 3 weeks	0	1 (0.096%)	0.37
Puerperium	1 (1.2%)	2 (1.9%)	0.54
Known thrombophilic condition	3 (3.6%)	4 (3.8%)	0.96
Unprovoked VTE	62	71	
only DVT, n (%)	71	91	
DVT/PE	3 (3.6%)	5 (4.8%)	
Only PE	9 (10.8%)	7 (6.7%)	

Among 83 patients treated with rivaroxaban, 8.3% had been immobilized for the first 3 days of treatment. Meanwhile, there were 15 enoxaparin users who had been immobilized.

Table 2: Characteristics related to anticoagulant treatment in both subgroups

Characteristic	RIV (n = 83)	STDT (n = 104)	p value
Immobilization during the first 3 days			0.45
Complete, n (%)	1 (1.2%)	1 (0.96%)	
Relative, n (%)	7 (8.3%)	15 (14.4%)	
Mean time in INR range			
< 2.0	NA	15.3%	
2.0-3.0	NA	54.8%	
> 3.0	NA	27.9%	
Mean study treatment duration, days	167.6 ± 15.8	169.2 ± 16.4	0.61
Intended duration of treatment			
3 months	12	16	
6 months	70	88	

Note: P values were determined using Chi-square test.

Besides, in both treatment arms, only one patient was immobilized at a complete degree. In the traditional treatment group, the INR being in therapeutic range (2.0-3.0) accounted for 54.8% of the time, INR values above 3.0 and below 2.0 occupied the corresponding percentage of time of 27.9% and 15.3%, respectively (Table 2). None of participants was missing during follow-up

Table 3: Clinical outcomes

Treatment Outcomes	RIV (n = 83)	STDT (n = 104)	Risk Ratio (95% CI)	p
Recurrent VTE, n (%)	3 (3.6%)	5 (4.8%)	0.74 (0.17-3.20)	0.69
Type of VTE reoccurrence				
Fatal PE	0	0		
Nonfatal PE	1	1		
Reoccurring DVT plus PE	0	0		
Reoccurring DVT	2	3		
Death from any cause – n (%)	2 (2.4%)	4 (3.9%)	0.61 (0.11-3.43)	0.57
PE	0	0		
Bleeding	0	0		
Cardiovascular	0	0		
Other	2	4		
Bleeding event, n (%)				
Major bleeding	1 (1.8%)	4 (3.8%)	0.30 (0.03-2.76)	0.26
Clinically relevant non-major bleeding, n (%)	9 (10.8%)	11 (10.6%)	1.02 (0.40-2.59)	0.97

Note: P values were determined using Cox Proportional-Hazard Regression.

The main efficacy outcome, recurrent VTE, was confirmed in 3 cases in the novel anticoagulant subgroup and in 4 cases in the STDT subgroup. There were 6 cases of death reported in the study, 2 from treatment arm using rivaroxaban and 4 from group received enoxaparin plus VKA. However, the cause of death was not associated with VTE or bleeding complications, but other diseases such as stroke, respiratory insufficiency, and diabetes. Clinically relevant non-major bleeding events were observed in 9 cases in RIV subgroup and in 11 patients in SDTD group. Major bleeding was detected in one rivaroxaban-received patient (1.8%) and in 4 (3.8%) patients who were give enoxaparin overlapping with VKA (Table 3).

Discussion

Our analysis confirms that RIV shows comparable effectiveness to STDT in Vietnamese

patients also, with parallel safety for the intervention of symptomatic, acute VTE, and for the continuous treatment. The use of rivaroxaban presented a slight decrease in the frequency of reoccurring VTE in comparison with enoxaparin/VKA and presents acceptable likelihood of occurring bleeding event.

Our study shows that the mean age of patients receiving rivaroxaban group was 56.5 ± 20.1 years, slightly younger than those on standard therapy (61.2 ± 18.8 years). Mean age of in our study population was similar to that of EISTEIN study on Chinese patients: 58.6 ± 15.8 and vs. 59.0 ± 15.0 years, respectively [10]. Male patients accounted for 36.1% in RIV group and 25.2% in STDT group. The male proportions are lower compared to those in contemporary clinical studies [11], [12]. The risk factors that were most commonly observed in our patients were immobilization, cancer, history of thrombosis, and undergoing previous major surgery, which are consistent with population-based researches from Western countries [13], [14]. Overall, 2.4% of patients given RIV and 2.8% of those receiving STDT, underwent major surgery before, which suggested that post-operative thromboprophylaxis failed in these surgical patients. The situation of low execution of thromboprophylaxis in surgical patients has been reported in previous studies [15], [16]. On the basis of these data, the enhancement of quality should highlight the importance of conducting more appropriate prophylaxis for patients at high risk. In addition, the VTE treatment in standard therapy group was done well suggesting that the proportion of time in which the INR was in the therapeutic range (2.0-3.0) was 54.8% and for INR above 3.0 was 27.9%. Our findings were consistent with the results which was showed in other contemporary studies on VTE treatment [17], [18].

We found that rivaroxaban is non-inferior to enoxaparin in relation with efficacy and safety. The prevalence of complications occurring during 6 months of follow-up is comparable to the rate demonstrated by Wang and colleagues [10]. The frequency of reoccurring VTE in that analysis was 3.2% in both STDT and RIV groups. In our study, reoccurring VTE was identified in 3.6% of patients who received RIV versus 4.8% of patients in the STDT group. Bleeding was the most prevalent complication in this study, occurring in both treatment arms during initial therapy. Interestingly, while the rate of non-critical bleeding complications in two groups was comparable to each other groups (10.8% and 10.6%, respectively), the frequency of major bleeding was less common in rivaroxaban-given patients, 1.8% vs. 3.8% (OR: 0.26; 95% CI: 0.03-2.76). Our results seem to be slightly worse than those in the randomized clinical trials. For instance, the EINSTEIN study which compares the EAS of RIV vs. STDT (enoxaparin plus VKA) found the prevalence of major bleeding event to be 0.8% and 1.2% (OR: 0.65; 95% CI: 0.33-1.30; p = 0.21) in the RIV and STDT groups, respectively. The most likely explanation for this discrepancy could be differences in the exclusion criteria to recruit patients in both studies. Moreover, the frequency of non-critical bleeding events was identical between two arms (8.1% vs. 8.1%) [17].

Prins MH et al., implemented a comparison between oral rivaroxaban and enoxaparin combined with VKA on 8282 VTE treatment and suggested that the rate of mortality was 2.3% and 2.4% in the two subgroups. Of these, PE related mortality accounted for 0.4% of patients using rivaroxaban and 0.3% of those receiving enoxaparin combined with VKA while bleeding related to death appeared in corresponding proportion of 0.1% and 0.2% of number of patients [9]. In comparison, there were 6 patients who died during follow-up in our study, but the cause of death was non-related to VTE or bleeding.

Several restrictions of our study had been noted. Firstly, since our study was designed as open-label, there could be bias in outcomes assessment. However, endeavors were performed in order to restrict bias in investigation, consisting of the demand to apply diagnostic tests in detecting suspected reoccurring VTE, identical follow-up of all patients, and central adjudication of all outcome circumstances. Second, imbalance in patients' characteristics may lead to more hospitalization or emergency department visit recorded in one treatment arm and more "recycled" VTE codes that will be carried forward instead of being associated with a "true" recurring VTE. In order to solve this, we restrained our endpoint of "recurrent VTE" only to hospital admissions, where "VTE" was the primary code. Third, the risk of bleeding is also probably modified by characteristics that alter during the course of therapy, such as the concurrent use of other drugs, or the existence of intercurrent disease. Finally, our study was conducted in only one hospital with small sample sizes, so it was not possible to assess the true efficacy of rivaroxaban on Vietnamese subjects, therefore, it was necessary to implement more clinical trials with larger sample sizes in many different centers.

To conclude, the findings of this study confirm that the EAS of RIV are compared with those monitored in the larger clinical trials with parallel EAS and better bleeding profile compared to STDT (enoxaparin combined with VKA). The results suggest that rivaroxaban offers clinician with a new, better option in treatment of VTE for Vietnamese patients.

Ethical Approval

Research only aims to protect and improve the health of patients, not for any other purpose. This research was accepted by Ethical Review Board of Hanoi Medical University (Approval No. IRB 003121).

Informed Consent

Informed consents were collected from participating patient(s) for their anonymized information to be reported in the study.

References

1. Næss IA, et al. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost. 2007; 5(4):692-9. https://doi.org/10.1111/j.1538-7836.2007.02450.x PMid:17367492

2. Spencer FA, et al. Incidence rates, clinical profile, and outcomes of patients with venous thromboembolism. The Worcester VTE study. J Thromb Thrombolysis. 2009; 28(4):401-9. https://doi.org/10.1007/s11239-009-0378-3 PMid:19629642 PMCid:PMC3248815

3. Jang MJ, Bang SM, Oh D. Incidence of venous thromboembolism in Korea: from the Health Insurance Review and Assessment Service database. J Thromb Haemost. 2011; 9(1):85-91. https://doi.org/10.1111/j.1538-7836.2010.04108.x PMid:20942850

4. Group JJW. Guidelines for the diagnosis, treatment and prevention of pulmonary thromboembolism and deep vein thrombosis (JCS 2009). Circ J. 2011; 75(5):1258-81. https://doi.org/10.1253/circj.CJ-88-0010 PMid:21441695

5. Edwards MS, et al. A systematic review of treatment guidelines for metastatic colorectal cancer. Colorectal Dis. 2012; 14(2):e31-e47. https://doi.org/10.1111/j.1463-1318.2011.02765.x PMid:21848897 PMCid:PMC3562494

6. Sarich TC, et al. Rivaroxaban: a novel oral anticoagulant for the prevention and treatment of several thrombosis-mediated conditions. Ann N Y Acad Sci. 2013; 1291(1):42-55. https://doi.org/10.1111/nyas.12136 PMid:23701516

7. Investigators E, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010; 363(26):2499-510. https://doi.org/10.1056/NEJMoa1007903 PMid:21128814

8. Prins MH, Lensing AW. Derivation of the non-inferiority margin for the evaluation of direct oral anticoagulants in the treatment of venous thromboembolism. Thrombosis journal. 2013; 11(1):13. https://doi.org/10.1186/1477-9560-11-13 PMid:23829521 PMCid:PMC3710481

9. Authors/Task Force Members, Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, Gibbs JS, Huisman MV, Humbert M, Kucher N. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J, 2014. 35(43):3033-69.

10. Wang Y, et al. Rivaroxaban for the treatment of symptomatic deep-vein thrombosis and pulmonary embolism in Chinese patients: a subgroup analysis of the EINSTEIN DVT and PE studies. Thrombosis Journal. 2013; 11(25). https://doi.org/10.1186/1477-9560-11-25 PMid:24341332 PMCid:PMC3896794

11. Prins MH, et al. Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): a pooled subgroup analysis of two randomised controlled trials. Lancet Haematol. 2014; 1(1):e37-46. https://doi.org/10.1016/S2352-3026(14)70018-3

12. Coleman CI, et al. Effectiveness and safety of rivaroxaban versus warfarin in patients with provoked venous thromboembolism. J Thromb Thrombolysis. 2018; 46(3):339-345. https://doi.org/10.1007/s11239-018-1695-1 PMid:29881958

13. Jr, A.F., et al., A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Intern Med. 1991; 151(5):933-8. https://doi.org/10.1001/archinte.1991.00400050081016

14. Heit JA, et al. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med. 2000; 160(6):809-15. https://doi.org/10.1001/archinte.160.6.809 PMid:10737280

15. Caiafa JS, et al. Managing venous thromboembolism in Latin American patients: emerging results from the Brazilian Registry. Semin Thromb Hemost. 2002; 28(Suppl 3):47-50. https://doi.org/10.1055/s-2002-34076 PMid:12232824

16. Goldhaber SZ, Dunn K, Mac Dougall RC. New onset of venous thromboembolism among hospitalized patients at Brigham and Women's Hospital is caused more often by prophylaxis failure than by withholding treatment. Chest. 2000; 118(6):1680-4. https://doi.org/10.1378/chest.118.6.1680 PMid:11115458

17. Prins MH, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. Thromb J. 2013; 11(1):21. https://doi.org/10.1186/1477-9560-11-21 PMid:24053656 PMCid:PMC3850944

18. Büller HR, et al. Enoxaparin followed by once-weekly idrabiotaparinux versus enoxaparin plus warfarin for patients with acute symptomatic pulmonary embolism: a randomised, double-blind, double-dummy, non-inferiority trial. Lancet. 2012; 379(9811):123-9. https://doi.org/10.1016/S0140-6736(11)61505-5