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Clinical efficacy and drug safety of rivaroxaban in the prevention and treatment of senile thromboembolic diseases

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Abstract: As a new oral anticoagulant, rivaroxaban is equivalent to warfarin in preventing and treating thromboembolism, but it can significantly reduce the occurrence of severe bleeding and fatal organ bleeding. This article analyzes the clinical efficacy and drug safety of rivaroxaban in the prevention and treatment of senile thromboembolic disease. The results showed that after treatment, acute thrombosis disappeared in patients with acute venous thrombosis, and no new or recurrent venous thrombosis, pulmonary embolism and death occurred. In the rivaroxaban group, 3 cases of fecal occult blood were positive at 6 months and the incidence rate was 7%. During the follow-up period, there were no significant changes in laboratory blood tests for coagulation, hemoglobin, platelet and liver and kidney function during the follow-up observation of the rivaroxaban group and between the rivaroxaban group and the warfarin group ($P>0.05$). Therefore, oral rivaroxaban is an effective method for the prevention and treatment of elderly patients with thromboembolic disease. Daily 10mg rivaroxaban is a safe and effective dose for the prevention and treatment of elderly patients with thrombotic diseases. The efficacy of rivaroxaban is equivalent to that of warfarin. However, the treatment is easier with better compliance and safety.

Keywords: Rivaroxaban, venous thrombosis, thrombotic disease, treatment and prevention.

INTRODUCTION

Thrombosis and thromboembolism are the two major pathological processes of thrombotic disease and two different forms of thromboembolic disease (Esteves *et al.,* 2018). Thrombosis is a process in which blood coagulates in the heart or blood vessels, forming a solid clot, which in turn causes blood flow to stop or stagnant (Block *et al.,* 2017; Manuel *et al.,* 2018). When the blood clot falls off and blocks blood vessels in the movement of the bloodstream, affecting the blood supply of the corresponding organ, lead to thromboembolism, common such as pulmonary embolism, cerebral embolism, limb embolism, etc., severe cases can lead to catastrophic consequences or death (Guerrero *et al.,* 2018). In the process of the development of thrombotic diseases, inappropriate activation of the coagulation mechanism in the body is an important pathogenic factor (Jaimez *et al.,* 2018). As early as 1986, Virchow proposed three major elements of thrombosis, namely vessel wall damage, slower blood flow and hypercoagulability. In the elderly population, in addition to the age and activities, it has a large number of combined diseases, which greatly increases the risk of thromboembolic diseases (Chao *et al.,* 2016). Prevention and treatment of thrombotic diseases is most important for prevention, but once thrombosis is formed, appropriate anticoagulant drugs should be given in time, supplemented by non-drug treatments, such as raising limbs and intermittent pressure to improve local blood circulation (Chen *et al.,* 2015). Among the commonly used anticoagulant drugs, warfarin, unfractionated heparin, and low molecular weight heparin are most commonly used. Although the effects of these drugs for preventing and treating thrombotic diseases have been widely recognized, there are many limitations in clinical use (Sanfins *et al.,* 2018). Heparin can not be taken orally and can not be used for a long time. Especially in elderly patients, the risk of high blood pressure and high bleeding is coexisting (Marinho *et al.,* 2018). Therefore, prevention and treatment of elderly patients with thrombosis clinical treatment, there is an urgent need to explore new methods for treatment that are simpler, safer and more effective.

Rivaroxaban is highly selective and competitive with the active site of Factor Xa. This reversible combination disrupts the endogenous and exogenous pathways of the clotting cascade, inhibiting thrombin generation and thrombosis (Emir *et al.,* 2014; Francisco *et al.,* 2018). Rivaroxaban neither inhibits thrombin activity nor affects platelet aggregation caused by collagen, adenosine diphosphate, and the like. However, studies have found that rivaroxaban can effectively inhibit tissue factor-induced platelet aggregation by inhibiting the synthesis of thrombin, and this indirect inhibition is also dose-dependent (Aranda *et al.,* 2018). The effect of rivaroxaban indirectly inhibiting platelet aggregation while directly inhibiting factor Xa suggests that rivaroxaban can be used not only to prevent and treat venous thrombosis, but also to prevent and treat arterial thrombotic diseases (Fonseca

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et al., 2018). Previously in China, rivaroxaban was mainly used to prevent venous thrombosis after major orthopedic surgery. For acute or long-term treatment of deep vein thrombosis, it is recommended to use rivaroxaban daily dose of 15-20 mg. Because the subject of this experiment is elderly, and advanced age is not only a thrombotic disease but also an important risk factor for bleeding, and the glomerular filtration rate decreases with age, combined with the prolongation of the half-life of rivaroxaban in the elderly (Lopez *et al.,* 2018). This study was given rivaroxaban 10 mg/day to prevent and treat elderly patients with thrombotic diseases. The purpose of this study was to observe the efficacy and safety of rivaroxaban in the treatment of senile venous thrombosis in elderly patients and to prevent elderly patients with thrombotic diseases. Lin made a comparison. Clinical trials have found that rivaroxaban may cause adverse reactions such as nausea, tachycardia, and liver and kidney damage, in addition to increasing the risk of bleeding, but these adverse reactions should be considered rare, and the phase III clinical trials are in the surgical background.

MATERIALS AND METHODS

Data sources

During the period from 2017 September to 2018 September 2018 82 elderly patients with acute lower extremity venous thrombosis confirmed by ultrasonography in our hospital, with an average age of (81.5±5.6) years old, were regularly enrolled in our hospital after enrollment. Comprehensive examination of vascular ultrasound (upper limb arteriovenous, venous ultrasound and lower extremity arteriovenous, venous ultrasound), electrocardiogram, chest CT, brain CT, blood routine, blood biochemistry, etc., strictly enforce the efficacy and safety of the trial.

Selection and exclusion criteria

Inclusion Criteria: (1) The age is greater than or equal to 75 years; (2) Patients with acute deep vein thrombosis have been clearly diagnosed; (3) Patients with high risk of thrombosis: > 3 days in bed, combined with one of the following conditions or risk factors: respiratory failure, acute exacerbation of COPD, heart failure (New York Heart Association (NYHA) functional classification class III or IV), acute infectious disease (severe infection or infection), acute coronary syndrome, VTE (Venous thromboembolism) history, malignancy, inflammatory bowel disease, limb paralysis, palsy, chronic kidney disease, obesity (body mass index > 30) and advanced age (age > 75 years).

Exclusion criteria: (1) Cardiovascular events, severe trauma or major surgery within 6 months; (2) There is massive bleeding in the digestive tract within 6 months; (3) bnormal renal function (creatinine clearance rate is less than 30ml/min); (4) Abnormal liver function (alanine aminotransferase is 2 times higher than normal). New venous thrombosis, recurrent venous thrombosis, nonfatal pulmonary embolism, acute cerebrovascular events including ischemic stroke, hemorrhagic stroke, transient ischemic attack (TIA), etc., cardiovascular events Including acute coronary syndrome, arrhythmia, need for coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), etc., for any cause of death.

The main safety endpoint: Major bleeding or clinically significant bleeding, severe deterioration of liver and kidney function (Espinel *et al.,* 2015).

Treatment methods

82 patients with acute lower extremity venous thrombosis were randomly divided into rivaroxaban group and warfarin group, 39 patients in rivaroxaban group, 30 males and 9 females, first given low molecular weight heparin combined with rivaroxaban 10mg/ day, treatment for 3 days, after the application of rivaroxaban 10mg alone, oral, 1 / day; 43 cases of warfarin group, 34 males and 9 females, given appropriate oral warfarin combined with low molecular weight heparin treatment, When the INR(international normalized ratio) was stable at 1.6 to 2.5 (mean INR 2.04±0.42), low molecular weight heparin was discontinued, oral warfarin was continued, and INR was monitored.

Observation indicators

All patients were followed up for 12 months after receiving the corresponding treatment, and monitored for hemoglobin, platelet, coagulation function and liver and kidney function before treatment, 1 month treatment, 3 months treatment, treatment for 6 months and treatment for 12 months. The primary efficacy endpoint and safety endpoint occurred in the trial.

Ethical approval

All patients were approved by Ethics Committee of our hospital and signed on the informed consent. Ethical approval number as 17SCHD69-X.

STATISTICAL ANALYSIS

Data were statistically analyzed using SPSS 21.0 software. Data were expressed as mean ± standard deviation, and we using one-way ANOVA and Newman-Keuls method to test the accuracy of the assessment between groups; The data application percentage and composition ratio indicate that the comparison between groups is performed by the Chi square test or the exact probability test (Fisher's exact test). If the Chi square value is larger, the degree of deviation will be larger; otherwise, the deviation will be smaller.

RESULTS

Comparative analysis of general clinical data between two groups of elderly patients with acute venous thrombosis

Elderly patients with acute venous thrombosis were randomly assigned to the rivaroxaban group (rivaroxaban 10 mg/day, n=39) and the warfarin group (moderate warfarin, n=43). There were no significant differences in the age, gender composition, risk factors, previous medical history, concomitant treatment, and laboratory tests between the two groups (P>0.05). The two groups were comparable (table 1).

Comparison of the effectiveness and safety of elderly patients with acute venous thrombosis in the elderly

Acute thrombosis disappeared after treatment in patients venous thrombosis, pulmonary embolism and death occurred. The mean INRs of the warfarin group at 3 months, 6 months, and 12 months were 1.98±0.44, 2.04± 0.53, 2.03±0.49 and 2.01±0.46, respectively. During the follow-up observation period, 1 case of acute coronary syndrome occurred in the warfarin group at 6 months, the incidence rate was 2.33%; in the rivaroxaban group, 3 cases of fecal occult blood positive occurred at 6 months, the incidence rate was 7%; There were 3 cases of fecal occult blood positive in the observation group at 3 months and 6 months, the incidence rate was 13.95%. There was no significant difference in the incidence of efficacy and safety endpoint between the two groups (P>0.05). The efficacy and safety of treating venous thrombosis in elderly patients is similar (table 2, table 3). The length of hospital stay after rivaroxaban is shown in fig. 1. Figure 1 shows that warfarin and rivaroxaban can effectively alleviate venous thrombosis in elderly patients, VTE, bleeding and surgical complication will effect on the hospital stay length.

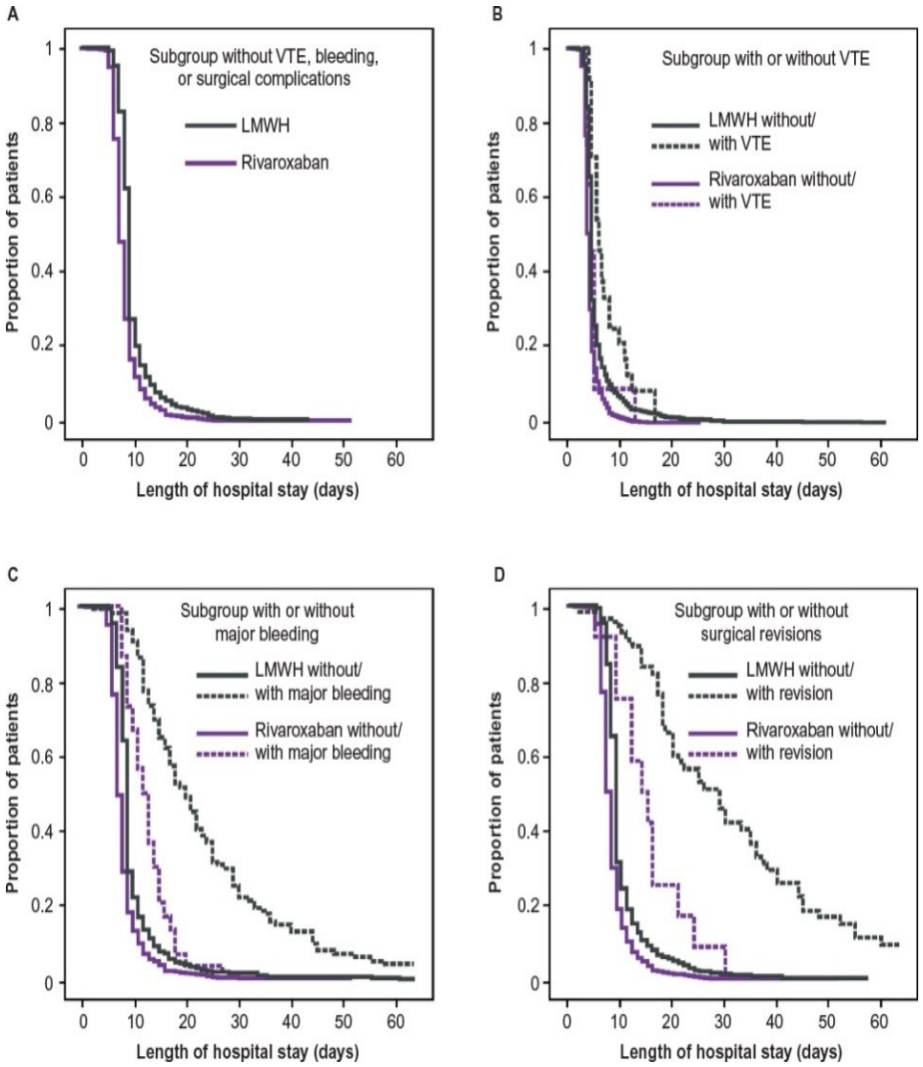

Fig. 1: Hospital stay with rivaroxaban: (A) Subgroup without VTE, bleeding, (B) Subgroup with and without VTE, (C) Subgroups with and without major bleeding, (D) Subgroups with and without surgical revisions

Table 1: Comparison of general clinical data between two groups

	Rivaroxaban group (n=39)	Warfarin group (n=43)	χ2 test	P
Age (Year)	81.4±5.6	81.5±5.8	2.981	0.015
Gender (Male/Female)	30/9	34/9		
Risk factors and past medical history				
Body mass index (kg/m2)	23.3±4.6	23.9±4.4	1.4687	0.034
Smoking	2(5.13%)	3(6.98%)		
Diabetes	11(28.21%)	11(25.58%)		
Hypertension	22(56.41%)	28(65.12%)		
Atrial fibrillation	13(33.33%)	14(32.56%)		
Heart failure (NYHA III or IV)	3(7.69%)	3(6.98%)		
Peripheral vascular disease	4(10.26%)	4(9.30%)		
Concomitant treatment				
Statins	20(51.28%)	23(53.49%)	2.854	0.002
Calcium channel blocker	13(33.33%)	17(39.53%)		
Used antiplatelet drugs	15(38.46%)	14(32.56%)		
Combined application of antiplatelet drugs	2(5.13%)	4(9.30%)		
Laboratory inspection				
Alanine transferase (u/L)	22.2±9.1	20.3±9.7	2.377	0.103
Platelets	201.3±54.6	200.9±65.9		
Hemoglobin (g/L)	120.1±18.7	120.8±18.2		
Prothrombin time (s)	14.9±2.8	14.4±2.0		
APTT (s)	38.0±4.4	38.5±4.2		

*Notes: P < 0.05 means significant difference, P < 0.01 means extremely significant difference

Table 2: Comparison of the effectiveness of two groups of elderly patients with acute venous

	Rivaroxaban group (n=39)					Warfarin group (n=43)					χ2 test
	1 month	3 months	6 months	12 months	Total	1 months	3 months	6 months	12 months	Total	
New or recurrent venous thrombosis	0	0	0	0	0	0	0	0	0	0	2.645
Pulmonary embolism	0	0	0	0	0	0	0	0	0	0	
Cardiovascular events	0	0	0	0	0	0	0	1	0	1	
Deaths	0	0	0	0	0	0	0	0	0	0	
Total	0	0	0	0	0	0	0	1	0	1	
Average INR						1.98±0.4	2.04±0.5	2.03±0.4	2.01±0.4		

Table 3: Comparison of safety between two groups of elderly patients with acute venous thrombosis

	Rivaroxaban group (n=39)					Warfarin group (n=43)					χ2 test
	1 month	3 months	6 months	12 months	Total	1 months	3 months	6 months	12 months	Total	
Major bleeding and fatal bleeding	0	0	0	0	0	0	0	0	0	0	1.792
Potential occult blood	0	0	3	0	3	0	3	3	0	6	
Hemoptysis	0	0	0	0	0	0	0	0	0	0	
Liver and kidney function deterioration	0	0	0	0	0	0	0	0	0	0	
Total	0	0	3	0	3	0	3	3	0	6	
Average INR						1.9±0.4	2.1±0.3	2.3±0.4	2.1±0.4		

Table 4: Comparison of safety between two groups of elderly patients with acute venous thrombosis (x ± s)

Observation indicators	Follow-up time	Rivaroxaban group (n=39)	Warfarin group (n=43)	χ2 test
Prothrombin time (s)	Baseline	14.88±2.78	14.40±1.97	2.372
	1 month	14.74±2.35	14.47±1.56	
	3 months	13.95±1.64	14.66±3.12	
	6 months	14.36±2.06	14.44±2.21	
	12 months	13.99±1.64	14.25±1.62	
	P Value	0.096	0.039	
Activated partial thromboplastin time (s)	Baseline	37.99±4.36	37.99±4.36	1.614
	1months	36.86±4.47	37.54±4.11	
	3months	36.83±4.47	36.67±3.65	
	6months	37.23±4.33	36.86±3.76	
	12months	36.34±4.51	35.39±5.18	
	P Value	0.061	0.021	
Hemoglobin (g/L)	Baseline	120.10±18.70	120.77±18.18	2.871
	1 month	120.13±16.96	116.84±14.19	
	3 months	117.84±15.37	116.58±15.67	
	6 months	115.37±14.33	115.94±14.67	
	12 months	114.41±16.88	117.26±16.04	
	P VALUE	0.011	0.047	
Platelets (×10g/L)	Baseline	201.31±54.64	200.88±65.93	1.975
	1months	205.79±63.73	208.65±60.80	
	3months	198.56±66.92	215.36±59.31	
	6months	209.07±57.17	204.06±62.30	
	12months	198.37±58.37	221.78±75.04	
	P Value	0.018	0.070	
Alanine aminotransferase ALT (u/L)	Baseline	22.16±9.06	20.31±9.74	2.375
	1months	21.61±10.36	23.26±9.44	
	3months	23.72±10.07	22.38±9.67	
	6months	23.49±10.69	23.04±9.97	
	12months	21.11±9.09	23.01±9.50	
	P Value	0.7016	0.008	

*Notes: P < 0.05 means significant difference, P < 0.01 means extremely significant difference

Comparative analysis of laboratory examinations in patients with acute venous thrombosis in the elderly

During the follow-up period, there were no significant changes in laboratory blood tests for coagulation, hemoglobin, platelet. Rivaroxaban does not cause significant changes in blood coagulation, hemoglobin, platelets and liver during use (table 4).

DISCUSSION

Since the discovery of heparin in 1914, anticoagulant drugs have played an extremely important role in the prevention and treatment of thromboembolic events (Fein *et al.,* 2015). On the road to anticoagulation, scientists and clinicians have been looking for a balance between anticoagulant efficacy and bleeding risk, or inconvenient, it must be monitored frequently and it is prone to anticoagulant and rivaroxaban has largely solved this problem (Golier *et al.,* 2018).

Heparin anticoagulants need to bind to antithrombin III to exert anticoagulant effects. Long-term use of heparin drugs may lead to osteoporosis and thrombocytopenia. Studies have found that the anticoagulant effect of heparin is related to its selectivity for factor Xa and it may also cause thrombin rebound and increase the risk of thromboembolism when these drugs are discontinued (Gatter *et al.,* 2015). The essential difference between rivaroxaban and heparin anticoagulants is that rivaroxaban does not need to bind to antithrombin III to directly inhibit factor Xa (Grossman *et al.,* 2015). It can be administered orally, is convenient to use, and does not cause osteoporosis (Kawamoto *et al.,* 2016). Factor Xa is located at a key site of the clotting cascade, is the junction of endogenous and exogenous coagulation pathways, and catalyzes the conversion of prothrombin to thrombin. In the coagulation cascade, the factor Xa is amplified (Hjelm *et al.,* 2016). Therefore, rivaroxaban is more effective and more efficient than direct thrombin inhibitors (eg, dabigatran) and is a safer and more effective anticoagulant (Isorni *et al.,* 2015). Thus, interference with the synthesis of vitamin K-dependent coagulation factors

inhibits blood coagulation without inhibiting the activated coagulation factors (Heer *et al.,* 2015; Norman *et al.,* 2018). Warfarin has always been the standard treatment for primary and secondary prevention of thrombotic diseases, and it is also the only oral anticoagulant drug for a long time (Hess *et al.,* 2016). However, the safety window of warfarin treatment is very narrow, and it is necessary to frequently monitor INR to adjust (Vagnarelli *et al.,* 2015). The dosage and anticoagulant effect are greatly affected by food and it is easy to interact with other drugs. It is generally believed that the probability of severe bleeding in patients with INR level greater than 3.0 is increased by 2 times, and as the INR increases, the risk of bleeding continues to increase and even life-threatening major bleeding can occur(Perl *et al.,* 2015). The rivaroxaban has a rapid onset of action, stable drug efficacy and pharmacokinetics and the drug effect is minimally affected by food. It can be used simultaneously with other commonly used drugs without monitoring, which greatly improves patient compliance (Presbitero *et al.,* 2003; Schreiber *et al.,* 2018).

The results of this study found that rivaroxaban did not cause significant changes in hemoglobin, platelets, coagulation function and liver during use. There was no need for monitoring (Sanomura *et al.,* 2014; Singh *et al.,* 2016). After treatment with rivaroxaban and warfarin, hemoglobin, There were no significant differences in platelet, coagulation function and liver, indicating that rivaroxaban is safe for elderly patients. Rivaroxaban and warfarin were used in patients with venous thrombosis without new or recurrent venous thrombosis, pulmonary embolism and death (Trzeciak *et al.,* 2016). One case of acute coronary syndrome occurred in the warfarin group at 6 months. 2.33%; in the rivaroxaban group, 3 cases of fecal occult blood positive occurred at 6 months, the incidence rate was 7.69%; 3 cases of fecal occult blood positive in the warfarin group at 3 months and 6 months. There was no significant difference in the incidence of efficacy and safety endpoints between groups.

CONCLUSION

The results of this study indicate that rivaroxaban exerts a definite therapeutic effect on the treatment of new-onset acute thrombosis in elderly patients, suggesting that rivaroxaban is feasible for the prevention and treatment of elderly patients with thromboembolic disease. Foreign countries have used 15-20mg daily for non-aged elderly patients, but this article also achieved good results for elderly patients with a daily dose of 10mg, indicating the special characteristics of the elderly.

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