Int J Clin Exp Med 2020;13(4):2268-2275
www.ijcem.com /ISSN:1940-5901/IJCEM0103178

Original Article

Prophylactic efficacy of two anticoagulant drugs, heparin calcium and rivaroxaban, on venous thrombosis after knee arthroplasty

Huihua Shi, Kaichuang Ye, Xinrui Yang, Xinwu Lu, Minyi Yin

Department of Vascular Surgery, Shanghai Ninth People's Hospital Affiliated to Shanghai Jiaotong University, School of Medicine, Shanghai, China

Received October 6, 2019; Accepted December 10, 2019; Epub April 15, 2020; Published April 30, 2020

Abstract: Objective: It is aimed to analyze the effect of low molecular weight heparin calcium and rivaroxaban on the prevention of venous thrombosis after knee arthroplasty. Methods: 81 gonarthrosis patients who were treated with knee arthroplasty in our hospital were selected as objects of study for retrospective analysis and divided into 2 groups according to the order of admission, including 40 patients treated with low molecular weight heparin calcium after operation in control group and 41 patients treated with rivaroxaban after operation in observation group, so as to compare the incidence of venous thrombosis, total blood loss, overt blood loss, platelet count, hemoglobin level, coagulation function and incidence of bleeding events after operation in two groups. Results: (1) After operation, the incidence of lower limb venous thrombosis was 7.32% in observation group and 25.00% in control group ($P<0.05$). (2) The total blood loss was 1125.63±245.89 ml in observation group and 1088.25±231.48 ml in control group after operation. The overt blood loss was 435.29±67.81 ml in observation group and 395.23±51.26 ml in control group after operation ($P>0.05$). (3) There was no statistical difference in Hb, PLT, PT, APTT and D-D before operation and 10 days after operation in two groups ($P>0.05$). (4) There was no statistical difference in the incidence of bleeding events 1 month after operation in two groups ($P>0.05$). (5) There was no statistical difference in the decreased levels of wound drainage, blood transfusion and hemoglobin in two groups ($P>0.05$). Conclusions: The application of low molecular weight heparin calcium and rivaroxaban to knee arthroplasty could control the bleeding and reduce the incidence of bleeding events, without any obvious influence on coagulation function. But the application of rivaroxaban could reduce the incidence of postoperative venous thrombosis more obviously, so it was more worthy of popularization and application.

Keywords: Knee arthroplasty, anticoagulants, low molecular weight heparin calcium, rivaroxaban, venous thrombosis

Introduction

The knee arthroplasty, as an effective treatment method of late-stage gonarthrosis, can alleviate the pain by means of arthroplasty and provide patients with stable joint with good function to correct joint deformity and thus obviously improve the living quality of patients [1]. However, due to the large trauma caused by knee arthroplasty, there will be various complications after operation, of which the lower limb venous thrombosis is very common [2].

Lower limb venous thrombosis refers to the abnormal coagulation of blood in venous cavity of lower limb, which leads to the obstruction of venous cavity and thus causes the venous return obstruction [3]. The lower limb venous thrombosis includes proximal venous thrombosis and distal venous thrombosis, of which the former is generally caused by the development of thrombosis in peroneal veins. In addition to the most common manifestation of lower limb edema, there will be other clinical symptoms, such as weakness, pressing pain and swelling of affected limb [4]. The onset of distal venous thrombosis is not obvious in general. Some patients may have no subjective symptom or only have the manifestation of mild pain in affected limb. With the progress of disease,

patients will have such manifestations as deep pressing pain in gastrocnemius muscle and swelling below the knee joint [5]. If the lower limb deep venous thrombosis is not discovered and treated in time, the caducous thrombi will cause pulmonary embolism and even lead to death [6].

It is found in clinical practice that the application of anticoagulants after knee arthroplasty can prevent the formation of venous thrombosis to a certain extent. In this study, the comparative analysis was conducted to compare the preventive effects of two anticoagulants, i.e. low molecular weight heparin calcium and rivaroxaban, on venous thrombosis after knee arthroplasty so as to provide more guidance for the effect and safety of knee arthroplasty.

Materials and methods

Data

The retrospective analysis was conducted to analyze the clinical data of 81 gonarthrosis patients treated with knee arthroplasty in our hospital. These patients were divided into 2 groups, including 40 patients in control group with the age of 43-72 years old, the disease course of gonarthrosis of 2-12 years, the weight of 52-71 kg and the height of 153-172 cm and 41 patients in observation group with the age of 45-75 years old, the disease course of gonarthrosis of 3-13 years, the weight of 53-73 kg and the height of 155-175 cm. (1) Inclusion criteria: this study included the patients treated with knee arthroplasty for the first time; no patients had surgical contraindications; and those whose color ultrasound examination result for deep venous thrombosis (DVT) was negative before operation. Besides, patients were enrolled regardless of gender. Informed consent form was signed by patients or their guardians. This study was approved by the Ethics Committee. (2) Exclusion criteria: this study excluded the patients complicated with active bleeding; those with bleeding tendency; those complicated with coagulation disorders; those who suffered from cerebral hemorrhage in the past 3 months; those with severe cardiopulmonary dysfunction; those who were allergic to drugs used in this study; and those who were treated with other anticoagulants in the past 3 months.

Treatment methods

Before operation, all the patients routinely received hepatic and renal function examination, coagulation function examination, blood routine examination, D-Dimer level measurement and color Doppler ultrasonography for veins of both lower limbs. The patients complicated with underlying diseases received targeted treatment actively, but they were not treated with the drugs that may affect coagulation function.

All the patients were treated with knee arthroplasty by the same team of medical workers through the same operative procedures. After the general anesthesia, the cemented prosthesis was implanted. Based on the second generation of bone cement technique, the anterior median approach of knee joint was selected for operation, with the total operative time of 2-2.5 hours. During operation, the tourniquet was used in a normative manner and then removed after pressing and dressing the wound properly. After operation, the drainage tube was indwelt, and the incision was sutured routinely.

After operation, all the patients were injected with Cefuroxim (SFDA approval number: H20080467; company name: Esseti Farmaceutici s.r.l.) through intravenous drip for infection prevention, with the dose of 0.75 g twice a day. Furthermore, Celecoxib (SFDA approval number: J20120063; manufacturing enterprise: Pfizer Pharmaceuticals LLC) combined with Tramadol Hydrochloride tablets (SFDA approval number: H20033331; manufacturing enterprise: Shenzhen Neptunus Pharmaceutical Co., Ltd.) were used for analgesia. The dose of Celecoxib was 200 mg twice a day and that of Tramadol Hydrochloride tablets was 50 mg twice a day. The patients of control group were injected with Nadroparin Calcium Injection (Fraxiparine; SFDA approval number: J20040119; manufacturing enterprise: GlaxoSmithKline (China) Investment Co., Ltd.) through subcutaneous injection 12 hours after operation, with the dose of 0.4 ml once a day. The patients of observation group were treated with Rivaroxaban tablets (SFDA approval number: H20181081; manufacturing enterprise: Bayer-AG) through oral administration 12 hours after operation, with the dose of 10 mg once a day. After operation, the patients did the same rehabilitation exercise under the guidance of the

Table 1. Comparison of general data between observation group and control group ($\bar{x}$ ± sd)/[n (%)]

Data		Observation group (n = 41)	Control group (n = 40)	t/X^2	*P*
Gender	Male	27 (65.85)	25 (62.50)	0.099	0.753
	Female	14 (34.15)	15 (37.50)		
Age (years old)		60.28±10.37	58.96±9.68	0.592	0.556
Height (cm)		162.38±8.25	165.42±8.92	1.593	0.115
Weight (kg)		60.25±5.37	61.46±4.83	1.065	0.290
Disease course (years)		6.38±3.28	6.49±3.51	0.146	0.885
Complicated diseases	Hypertension	12 (29.27)	10 (25.00)	0.187	0.666
	Diabetes	13 (31.71)	11 (27.50)	0.172	0.678

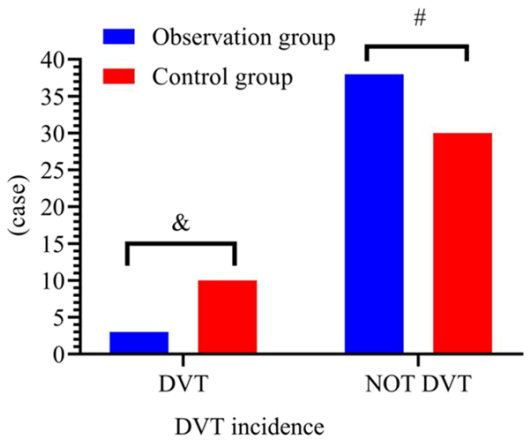

Figure 1. Comparison on the incidence of lower limb venous thrombosis between observation group and control group. The incidence of lower limb venous thrombosis was 7.32% in observation group, much lower than 25.00% in control group ($P<0.05$). &Indicates $P<0.05$ when the incidence of venous thrombosis was compared between the two groups.

same team of nursing staff for early mobilization.

Observation targets

Lower limb venous thrombosis: the incidence of lower limb venous thrombosis was compared after operation in two groups and the color ultrasound examination was conducted to determine whether there was a symptom of lower limb venous thrombosis. Diagnostic criteria [7]: few blood flow signals or no blood flow signal was detected in the veins of thrombus section. The pulse Doppler spectrum did not change with the breathing or showed no blood flow. There was no echo or hypoecho inside the lumen. The venous lumen could not be compressed.

Blood loss: the total blood loss and overt blood loss were compared in two groups. Total blood loss: the patients received blood routine examination when they ate again 2 days after operation. The blood loss was calculated through ward formula [8] and red blood cell specific volume (Hct) according to the results of preoperative examinations. Total blood loss = perfused blood volume (PBV) × 2 × (preoperative Hct-postoperative Hct)/(preoperative Hct + postoperative Hct). Overt blood loss: The overt blood loss was the sum of intraoperative blood loss, postoperative wound drainage and wound exudate after extubation. Thereinto, the wound exudate after extubation was calculated based on the principle that the exudate was 5 ml if each small gauze was saturated.

Coagulation function: the haematoglobin (Hb), platelet count (PLT), prothrombin time (PT), partially activated prothrombin time (APTT) and D-Dimer (D-D) level were measured respectively before operation and 2 days after operation in two groups.

Bleeding events: the incidences of skin ecchymosis, bleeding gums, blood in the urine, bloody stool, black stool, hemoptysis and hematemesis were compared 1 month after operation in two groups.

Drainage, blood transfusion and hemoglobin levels: compared in two groups, the wound drainage, blood transfusion, and hemoglobin levels were decreased after treatment.

Statistical analysis

The SPSS22.0 was used for statistical analysis. The measurement data was expressed as mean ± standard deviation. The independent-samples *t* test was used for data in conformity with normal distribution and the Mann-Whitney U test was used for data not in conformity with normal distribution. The paired-samples *t* test

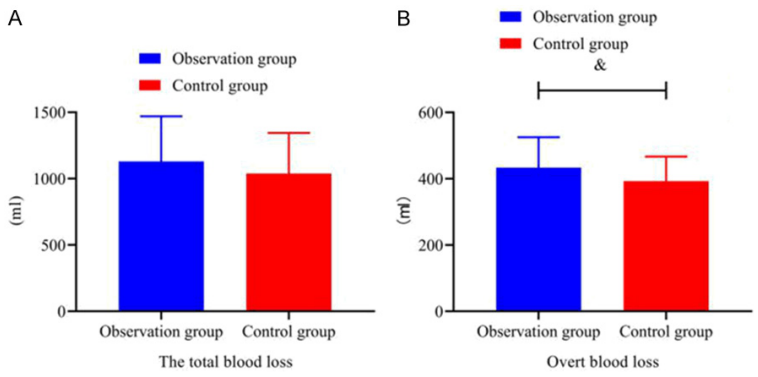

Figure 2. Comparison of blood loss between observation group and control group. The total blood loss was not statistical difference in observation group compared with that in control group (P>0.05). The overt blood loss was significantly higher in observation group compared with that in control group (P<0.05). &Indicates P<0.05 when two groups were compared.

was used for the comparison before and after operation in group. The enumeration data was represented by [n (%)]. The X^2 test was used for the comparison of enumeration data between groups. Thereinto, P<0.05 meant that the comparison had statistical significance.

Results

Comparison of general data between observation group and control group

There were no statistical differences in gender ratio, average age, average height, average weight and average disease course in two groups (P>0.05) (**Table 1**).

Comparison on the incidence of lower limb venous thrombosis between observation group and control group

After the operation, there were 3 cases of lower limb venous thrombosis in observation group and 10 cases in control group. This indicated that there was a statistical difference in the incidence of lower limb venous thrombosis in two groups (P<0.05) (**Figure 1**).

Comparison of blood loss between observation group and control group

There was no statistical difference in total blood loss between observation group and control group after operation (P>0.05). The overt blood loss has no statistical difference in observation group compared with that in control group after operation (P>0.05) (**Figure 2**).

Comparison of coagulation function between observation group and control group

In observation group, there was no obvious difference in Hb, PLT, PT and APTT before operation and 10 days after operation (P>0.05) and the D-D level reduced obviously 10 days after operation in comparison with that before operation (P<0.05). In control group, there was no obvious difference in Hb, PLT, PT, APTT and D-D before operation and 10 days after operation (P>0.05) and the D-D level reduced obviously 10 days after operation in comparison with that before operation (P<0.05). There was no statistical difference in Hb, PLT, PT, APTT and D-D before operation and 10 days after operation in two groups (P>0.05) (**Table 2** and **Figure 3**).

Comparison of bleeding events 1 month after operation between observation group and control group

The incidences of skin ecchymosis, bleeding gums, blood in the urine, bloody stool, hemoptysis, hematemesis and black stool were not statistically different in observation group 1 month after operation compared with those in control group (P>0.05) (**Figure 4**).

Comparison of wound drainage, blood transfusion and decreased hemoglobin level in two groups

After treatment, the wound drainage in observation group was 468.59±25.13 ml and that in control group was 480.13±27.81 ml. The blood transfusion in observation group was 572.16±55.34 ml and that in control group was 578.31±59.23 ml after treatment. The decreased hemoglobin level in observation group was 30.54±1.46 g/L and that in control group was 31.42±1.50 g/L after treatment (P>0.05) (**Figure 5**).

Discussion

According to the level of risk in thrombogenesis after major orthopedic operation in clinical

Table 2. Comparison of coagulation function between observation group and control group ($\bar{x} \pm sd$)

Group	Time	Hb (g/L)	PLT (× 10^9/L)	PT (s)	APTT (s)	D-D (μg/L)
Observation group (n = 41)	Before operation	100.63±10.28	204.35±50.94	11.56±0.38	27.46±3.62	768.59±80.24
	10 days after operation	112.62±12.34	212.36±62.27	11.16±0.70	31.45±2.78	325.46±60.28
Control group (n = 40)	Before operation	99.86±11.37	208.44±55.49	11.62±0.42	25.91±4.16	823.65±112.08
	10 days after operation	110.59±13.04	215.32±65.71	11.39±0.78	33.25±3.24	375.45±70.92

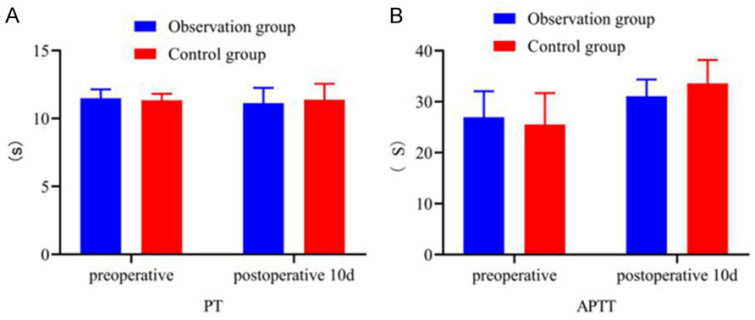

Figure 3. Comparison of PT and APTT levels between observation group and control group. There was little difference in PT and APTT levels before operation (P>0.05) and 10 days after operation (P>0.05) in two groups.

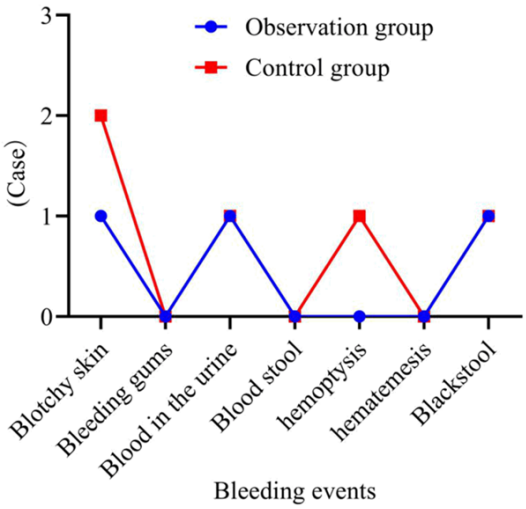

Figure 4. Comparison of bleeding events between observation group and control group. There was little difference in the incidences of skin ecchymosis, bleeding gums, blood in the urine, bloody stool, hemoptysis, hematemesis and black stool in two groups (P>0.05).

practice, the knee arthroplasty is an operation with extremely high level of risk and the risk of postoperative venous thrombosis is very high [9]. The influence factors of thrombogenesis mainly include hypercoagulable state, blood stasis and vascular damage, all of which will be affected by knee arthroplasty [10]. Hence, the knee arthroplasty plays an important role in the prevention of thrombogenesis. And the crucial method lies in the reasonable application of anticoagulants.

The low molecular weight heparin, as a common anticoagulant with definite effect and also as the first choice for anticoagulant therapy after orthopedic operation, can not only reduce the occurrence risk of bleeding complications, but also guarantee the safety of patients with no need of hematologic monitoring during medication [11]. But the route of administration is subcutaneous injection for low molecular weight heparin, so it is not convenient for patients who need to continue the therapy after hospital discharge [12]. Moreover, Yazeji T et al. [13] found that the sustained medication of low molecular weight heparin could increase the incidence of osteoporosis. It is implied that other safer and more effective and convenient anticoagulants shall be sought in clinical practice as soon as possible to achieve the prevention and treatment of venous thrombosis after orthopedic operation. The rivaroxaban used for observation group in this study is an oral anticoagulant which, with high selectivity, can directly inhibit the formation of coagulation factor Xa [14]. The coagulation factor Xa is the junction of intrinsic and extrinsic coagulation pathways, so the rivaroxaban can inhibit the coagulation of intrinsic and extrinsic pathways simultaneously and achieve a favorable anticoagulation effect [15]. In this study, there was no statistical difference in total blood loss and overt blood loss after operation in two groups (P>0.05) nor in Hb, PLT, PT, APTT and D-D before operation and 10 days after operation in two groups (P>0.05). This indicated that the application of rivaroxaban to postoperative anticoagulant therapy could achieve a similar effect to that of low molecular weight heparin, without any obvious increase in

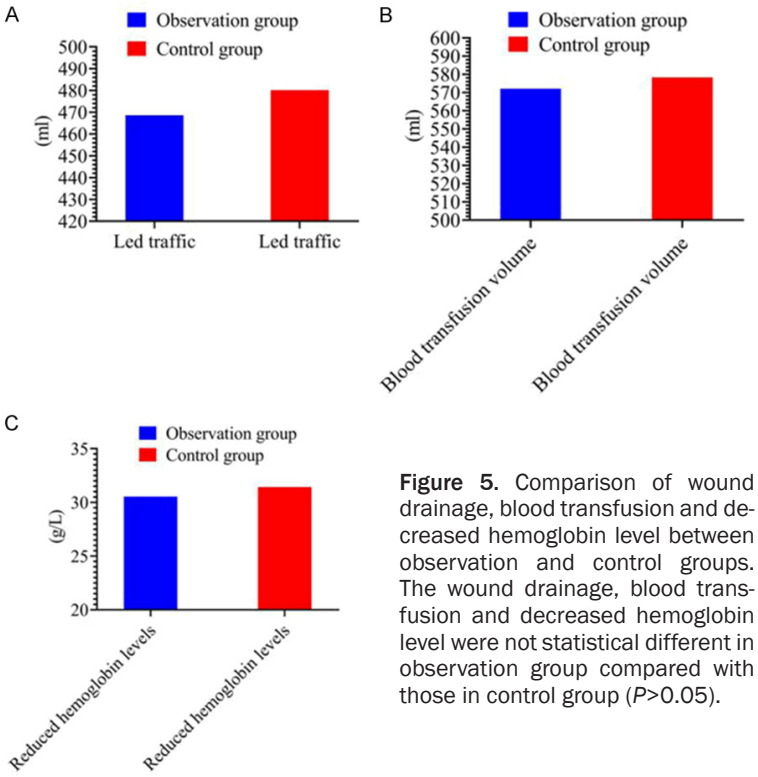

Figure 5. Comparison of wound drainage, blood transfusion and decreased hemoglobin level between observation and control groups. The wound drainage, blood transfusion and decreased hemoglobin level were not statistical different in observation group compared with those in control group ($P>0.05$).

blood loss nor any serious adverse effect on coagulation function of patients. What's more, there was no statistical difference in skin ecchymosis, bleeding gums, blood in the urine, bloody stool, hemoptysis, hematemesis and black stool 1 month after operation in two groups ($P>0.05$), and there was no statistically significant difference in wound drainage, blood transfusion and decreased hemoglobin level in two groups ($P>0.05$), which indicated that the application of rivaroxaban to postoperative anticoagulant therapy had no obvious influence on the safety of patients after operation. However, the incidence of lower limb venous thrombosis was 7.32% after operation in observation group, much lower than 25.00% in control group ($P<0.05$), which implied that the rivaroxaban, a new anticoagulant, could achieve better anticoagulation effect and obviously reduce the incidence of lower limb venous thrombosis after operation.

The patients shall be treated with rivaroxaban once a day with fixed dose through oral administration. With no need of hematologic monitoring during medication, it is convenient and safe and has become a new and important choice of anticoagulant therapy gradually. Besides, there is no obvious correlation between rivaroxaban and other drugs and foods [16, 17]. Lin Y C et al. [18] carried out a large, randomized, double-blind and prospective study and found that the rivaroxaban had better preventive effect on the formation of venous thrombosis in comparison with enoxaparin, but there was little difference in the safety of these two drugs. The systemic analysis conducted by Zou Y et al. [19] showed that the application of rivaroxaban had better preventive effect on the formation of venous thrombosis after hip and knee arthroplasty and had lower formation rate of venous thrombosis in comparison with low molecular weight heparin, which was consistent with the results of this study. Furthermore, Beyerwestendorf J et al. [20] found that there was little difference in the occurrence rate of bleeding events between patients treated with low molecular weight heparin combined with antiplatelet drugs and those treated with rivaroxaban combined with antiplatelet drugs after hip and knee arthroplasty, which verified that the rivaroxaban could achieve a similar effect to that of low molecular weight heparin. In the research conducted by Lazolangner A et al. [21], the patients were treated with rivaroxaban for anticoagulant therapy after hip and knee arthroplasty. The results showed that there was little difference in the incidences of bleeding events and lower limb venous thrombosis between patients treated with rivaroxaban and those treated with low molecular weight heparin for anticoagulant therapy, which verified that the rivaroxaban had obvious anticoagulation effect, without any increase in the risk of clinical bleeding. However, some other researches produced inconsistent results. Lindner S M et al. [22] found that the application of rivaroxaban led to some adverse reactions, such as skin rash and thrombocytosis, etc. The research carried out by Pisters R et al. [23] indicated that the application of rivaroxaban to anticoagulant therapy caused such bleeding events as blood in the urine, black stool and skin ecchymosis,

etc. As found by Jr M R et al. [24], there was little difference in the incidence of venous thrombosis between rivaroxaban group and low molecular weight heparin group, but the patients in rivaroxaban group did not suffer from symptomatic deep venous thrombosis, while those in low molecular weight heparin group suffered from symptomatic deep venous thrombosis. This implied that the rivaroxaban had better preventive effect on deep venous thrombosis.

In conclusion, the application of low molecular weight heparin calcium and rivaroxaban could control the bleeding and reduce the incidence of bleeding events, without any obvious influence on coagulation function. But these two anticoagulants had different preventive effects on venous thrombosis. The application of rivaroxaban could reduce the incidence of postoperative venous thrombosis more obviously, so it is more worthy of popularization and application. But the results of this study were not representative enough due to few objects of study, short follow-up time, nature of retrospective analysis and few study indicators. Therefore, much attention shall be paid to deeper and broader prospective studies with longer follow-up time and larger sample size in the future so as to provide more useful methods for the prevention of venous thrombosis after knee arthroplasty.

Acknowledgements

Fundamental Research Program Funding of Ninth People's Hospital Affiliated to Shanghai Jiaotong University School of Medicine (JYZZ-023).

Disclosure of conflict of interest

None.

Address correspondence to: Xinwu Lu and Minyi Yin, Department of Vascular Surgery, Shanghai Ninth People's Hospital Affiliated to Shanghai Jiaotong University, School of Medicine, No. 639 Zhizaoju Road, Shanghai 200011, China. Tel: +86-021-23271699-5591; E-mail: dpqxm9t@163.com (XWL); yinminyi9@126.com (MYY)

References

[1] Tang XB, Wang J, Dong PL and Zhou R. A meta-analysis of patellar replacement in total knee arthroplasty for patients with knee osteoarthritis. J Arthroplasty 2018; 33: 960-967.

[2] Themistoklis T, Theodosia V, Konstantinos K and Georgios DI. Perioperative blood management strategies for patients undergoing total knee replacement: where do we stand now? World J Orthop 2017; 8: 441-454.

[3] Yamagami T, Yoshimatsu R, Okubo T, Tanaka O, Miura H, Yamada K, Kitawaki J and Tsuji H. Symptomatic deep venous thrombosis of the lower extremity in a pregnant woman successfully treated with endovascular procedures. J Obstet Gynaecol Res 2013; 39: 1059-1064.

[4] Sun X, Shen L, Gu W, Shan D, Ren M, Qiu H and Gu J. Functions of inflammatory factor in non-tumor deep venous thrombosis of lower extremity. Zhonghua Yi Xue Za Zhi 2015; 95: 598-600.

[5] Paik B, Joh JH and Park HC. Anatomic and clinical risk factors for pulmonary embolism in patients with deep venous thrombosis of the lower extremity. Ann Surg Treat Res 2017; 92: 365-369.

[6] Xu J and Zhou W. The relationship between gene polymorphism of MTRR A66G and lower extremity deep venous thrombosis. Hematology 2018; 23: 828-832.

[7] Dauzat M, Laroche JP, Deklunder G, Ayoub J, Quére I, Lopez FM and Janbon C. Diagnosis of acute lower limb deep venous thrombosis with ultrasound: trends and controversies. J Clin Ultrasound 1997; 25: 343-358.

[8] Falez F, Meo A, Panegrossi G, Favetti F, La Cava F and Casella F. Blood loss reduction in cementless total hip replacement with fibrin;spray or bipolar sealer: a randomised controlled trial on ninety five patients. Int Orthop 2013; 37: 1213-1217.

[9] Kjærsgaard-Andersen P and Kehlet H. Should deep venous thrombosis prophylaxis be used in fast-track hip and knee replacement? Acta Orthop 2012; 83: 105-6.

[10] Lechner D, Wiener C, Weltermann A, Eischer L, Eichinger S and Kyrle PA. Comparison between idiopathic deep vein thrombosis of the upper and lower extremity regarding risk factors and recurrence. J Thromb Haemost 2008; 6: 1269-1274.

[11] Zee AA, van Lieshout K, van der Heide M, Janssen L and Janzing HM. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-limb immobilization. Cochrane Database Syst Rev 2017; 8: CD006681.

[12] Yan X, Yang Y, He L, Peng D and Yin D. Gambogic acid grafted low molecular weight heparin micelles for targeted treatment in a hepatocellular carcinoma model with an enhanced anti-angiogenesis effect. Int J Pharm 2017; 522: 110-118.

[13] Yazeji T, Moulari B, Beduneau A, Stein V, Dietrich D, Pellequer Y and Lamprecht A. Nanoparticle-based delivery enhances anti-inflammatory effect of low molecular weight heparin in experimental ulcerative colitis. Drug Deliv 2017; 24: 811-817.

[14] Mueck W, Lensing AW, Agnelli G, Decousus H, Prandoni P and Misselwitz F. Rivaroxaban: population pharmacokinetic analyses in patients treated for acute deep-vein thrombosis and exposure simulations in patients with atrial fibrillation treated for stroke prevention. Clin Pharmacokinet 2011; 50: 675-686.

[15] Kochar A, Hellkamp AS, Lokhnygina Y, Jones WS, Becker RC, Berkowitz SD, Breithardt G, Fox KAA, Halperin JL, Hankey GJ, Mahaffey KW, Nessel CC, Singer DE, Piccini JP and Patel MR. Efficacy and safety of rivaroxaban compared with warfarin in patients with carotid artery disease and nonvalvular atrial fibrillation: insights from the ROCKET AF trial. Clin Cardiol 2018; 41: 39-45.

[16] Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, Widimsky P, Hori M, Avezum A, Piegas LS, Branch KRH, Probstfield J, Bhatt DL, Zhu J, Liang Y, Maggioni AP, Lopez-Jaramillo P, O'Donnell M, Kakkar AK, Fox KAA, Parkhomenko AN, Ertl G, Störk S, Keltai M, Ryden L, Pogosova N, Dans AL, Lanas F, Commerford PJ, Torp-Pedersen C, Guzik TJ, Verhamme PB, Vinereanu D, Kim JH, Tonkin AM, Lewis BS, Felix C, Yusoff K, Steg PG, Metsarinne KP, Cook Bruns N, Misselwitz F, Chen E, Leong D and Yusuf S; COMPASS Investigators. Rivaroxaban with or without aspirin in stable Cardiovascular disease. N Engl J Med 2017; 377: 1319-1330.

[17] Xing J, Yin X and Chen D. Rivaroxaban versus enoxaparin for the prevention of recurrent venous thromboembolism in patients with cancer: a meta-analysis. Medicine (Baltimore) 2018; 97: e11384.

[18] Lin YC, Chien SC, Hsieh YC, Shih CM, Lin FY, Tsao NW, Chen CW, Kao YT, Chiang KH, Chen WT, Chien LN and Huang CY. Effectiveness and safety of standard- and low-dose rivaroxaban in Asians with atrial fibrillation. J Am Coll Cardiol 2018; 72: 477-485.

[19] Zou Y, Tian S, Wang Y and Sun K. Administering aspirin, rivaroxaban and low-molecular-weight heparin to prevent deep venous thrombosis after total knee arthroplasty. Blood Coagul Fibrinolysis 2014; 25: 660-664.

[20] Beyer-Westendorf J, Lützner J, Donath L, Tittl L, Knoth H, Radke OC, Kuhlisch E, Stange T, Hartmann A, Günther KP, Weiss N and Werth S. Efficacy and safety of thromboprophylaxis with low-molecular-weight heparin or rivaroxaban in hip and knee replacement surgery: findings from the ORTHO-TEP registry. Thromb Haemost 2013; 109: 154-163.

[21] Lazo-Langner A, Fleet JL, Mcarthur E and Garg AX. Rivaroxaban vs. low molecular weight heparin for the prevention of venous thromboembolism after hip or knee arthroplasty: a cohort study. J Thromb Haemost 2014; 12: 1626-1635.

[22] Lindner SM, Fordyce CB, Hellkamp AS, Lokhnygina Y, Piccini JP, Breithardt G, Mahaffey KW, Singer DE, Hacke W, Halperin JL, Hankey GJ, Berkowitz SD, Nessel CC, Becker RC, Fox KA and Patel MR; ROCKET AF Steering Committee and Investigators. Treatment consistency across levels of baseline renal function with rivaroxaban or warfarin: a ROCKET AF (rivaroxaban once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation) analysis. Circulation 2017; 135: 1001-1003.

[23] Pisters R, van Vugt SPG, Brouwer MA, Elvan A, Ten Holt WL, Zwart PAG, Kirchhof P, Crijns HJGM and Hemels MEW. Real-life use of rivaroxaban in the Netherlands: data from the xarelto for prevention of stroke in patients with atrial fibrillation (XANTUS) registry. Neth Heart J 2017; 25: 551-558.

[24] Rolando M, Amelia B, Henry M, German N, Christopher P, Paul FJP and Surgery R. Low molecular weight heparin versus rivaroxaban for thromboprophylaxis in body contouring procedures. Plast Reconstr Surg 2014; 134: 121.