Administration of aspirin and rivaroxaban prevents deep vein thrombosis after total knee arthroplasty

Zou Yue, Tian Shao-qi, Wang Yuan-he, Liu Jiang-jun, Sun Kang

Department of Joint Surgery, the Affiliated Hospital of Qingdao University, Qingdao 266003, Shandong Province, China

Abstract

BACKGROUND: To date, rivaroxaban has been a clinically common anticoagulant in China; however, effective prophylaxis for venous thrombosis is associated with a markedly higher incidence of perioperative hemorrhagic complications. Although it has been reported that aspirin effectively prevents deep vein thrombosis and pulmonary embolism, the use of aspirin as a routine drug for venous thrombosis after total knee arthroplasty is still controversial.

OBJECTIVE: To compare the efficacy and safety of aspirin and rivaroxaban for prevention of deep vein thrombosis after total knee arthroplasty.

METHODS: Totally 324 patients with osteoarthritis who underwent primary unilateral total knee arthroplasty were randomly divided into three groups. Twelve hours after the surgery, three groups were given aspirin, rivaroxaban and low-molecular-weight heparin respectively. All three groups were treated for 14 days, and all of the patients were followed for 4 weeks.

RESULTS AND CONCLUSION: Compared with the low-molecular-weight heparin group, the incidence of deep vein thrombosis was lower ($P < 0.05$), but hidden blood loss and wound complications were more common ($P < 0.05$) in the rivaroxaban group. There were no significant differences between the low-molecular-weight heparin group and aspirin group in the incidence of deep vein thrombosis, hidden blood loss, wound complications or incidences of lower limb swelling and subcutaneous ecchymosis ($P > 0.05$). The results confirmed that rivaroxaban has a positive anticoagulation effect but leads to increases in wound complications in patients; there are no differences in efficacy and safety between aspirin and low-molecular-weight heparin, so aspirin as part of a multimodal anticoagulation therapy after total knee arthroplasty has good clinical safety and efficacy.

Subject headings: arthroplasty, replacement, knee; factor X_a; morpholines; thiophenes; aspirin; heparin, low-molecular-weight; venous thrombosis

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Zou Yue, Studying for master's degree, Department of Joint Surgery, the Affiliated Hospital of Qingdao University, Qingdao 266003, Shandong Province, China

Corresponding author: Sun Kang, M.D., Chief physician, Doctoral supervisor, Department of Joint Surgery, the Affiliated Hospital of Qingdao University, Qingdao 266003, Shandong Province, China

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INTRODUCTION

Total knee arthroplasty (TKA) can powerfully relieve severe knee pain, deformity and limited mobility caused by rheumatoid arthritis or osteoarthritis. Venous thrombosis, including deep vein thrombosis and pulmonary embolism, is one of the most common complications after TKA. If preventive measures are not taken, the incidence of deep vein thrombosis can reach 60% within 90 days after surgery[1], while the incidence of fatal pulmonary embolism can reach 1.5%[2].

Anticoagulation guidelines often recommend anticoagulants and mechanical prophylaxis (especially the former) worldwide for prevention of post-TKA venous thrombosis. To date, rivaroxaban have been clinically common anticoagulants in China; however, effective prophylaxis for venous thrombosis is associated with a markedly higher incidence of perioperative hemorrhagic complications[3-4]. Although it has been reported that aspirin effectively prevents deep vein thrombosis and pulmonary embolism[5], the use of aspirin as a routine drug for post-TKA venous thrombosis is still controversial[6-7].

This prospective randomized controlled trial was conducted to provide guidance for clinical medication practices by comparing the efficacy and safety of aspirin and rivaroxaban for prevention of post-TKA venous thrombosis.

SUBJECTS AND METHODS

Design

A prospective, randomized, double-blind, controlled trial.

Time and setting

This study was completed in the Department of Joint Surgery, Affiliated Hospital of Qingdao University Medical School, China between July 2011 and July 2013.

Subjects

The patients who underwent TKA in the Department of Joint Surgery, Affiliated Hospital of Qingdao University Medical School and fulfilled the inclusion criteria as well as did not meet the exclusion criteria were 324 cases.

The inclusion criteria were as follows: patients who (1) met the diagnostic criteria for osteoarthritis of the knee[8]; (2) initially underwent unilateral TKA; (3) were negative for deep vein thrombosis according to the preoperative color Doppler ultrasonography on the deep veins of both lower extremities; and (4) gave informed consent for the therapeutic schedule.

The exclusion criteria were as follows: patients who (1) had a history of hemorrhagic disease or a bleeding tendency during the preoperative coagulation test; (2) had a past medical history of venous thrombosis; (3) were infused with over 2 000 mL of fluids 24 hours after surgery[9]; (4) underwent knee arthroplasty; or (5) used a combination of other drugs that might impact the findings.

A total of 324 patients were randomized into three groups using a random number table generated by a computer (Microsoft Office Excel 2010; Microsoft Corp., Redmond, USA). Rivaroxaban group comprised 102 patients (32 males and 70 females) with a mean age of 63.5 years (50 to 82 years). Low-molecular-weight heparin (LMWH) group comprised 112 patients (20 males and 92 females) with a mean age of 65.7 years (54 to 80 years). Aspirin group comprised 110 patients (28 males and 82 females) with a mean age of 62.7 years (47 to 79 years).

Related drugs were used in this experiment:

Related drugs	Source
Rivaroxaban (Xarelto), Aspirin (Bayaspirin)	Bayer, Leverkusen, Germany
LMWH sodium (Clexane)	Sanofi Corp., Paris, France

The three groups each received a different postoperative anticoagulant treatment according to the anticoagulation guidelines[10-11]: 12 hours after the operation, Rivaroxaban group was given oral rivaroxaban at a dose of 10 mg/d, the LMWH group was given subcutaneous LMWH sodium at a dose of 4 000 AxaIU (0.4 mL/d) and the aspirin group was given oral aspirin at a dose of 100 mg/d. All of the groups were treated for 14 days.

Methods

Preoperative management

The patients underwent routine examinations, including routine blood tests, routine anticoagulation measures and color Doppler ultrasonography on the deep veins of both lower extremities. The body mass index, hemoglobin, hematocrit, range of motion and the knee society score[12] were assessed in the patients before surgery.

Operation methods

All of the patients were operated on by a single surgeon using an anterior midline incision *via* a medial parapatellar approach with a tourniquet (pressure of 260 mm Hg, 1 mm Hg=0.133 kPa)[13]. All of the operations were performed under continuous epidural anesthesia with an epidural catheter in place and the use of intravenous sedation. The operations in the three groups were the same; the cemented Scorpio NRG Knee System (Stryker, Kalamazoo, USA) without patellar resurfacing was used. After surgery, a drainage tube was placed to be connected to an autologous blood transfusion device (Stryker, Kalamazoo) without clipping[14], and a pressure dressing was applied with an elastic bandage before the tourniquet was slowly released.

The rest of postoperative management

The shed blood in the autologous blood transfusion device was measured and was re-transfused through the veins within 6 hours as well as was discarded after 6 hours[15]. The drainage tubes were removed from all patients 24 hours after surgery[14]. The patients who showed clinical manifestations of hypovolemia (such as hypotension < 90 mm Hg that did not respond to crystalloid volume expansion) and tachycardia were given a blood transfusion. The patients were given antibiotics by intravenous drip for 3 days to prevent infections and oral Celecoxib capsules for analgesia after surgery. A pressure dressing was applied to the affected extremities with elastic bandages, and the affected extremities were elevated. Ankle pump exercises began 6 hours after the surgery[16]. The patients left their sickbeds and stood up with the help of physicians and began performing functional rehabilitation exercises at day 1 after surgery, including the straight-leg raise and knee flexion-extension[16]. They practiced walking with walking aids two or three times a day under the guidance of caregivers 2 days after surgery, once for 10−20 minutes.

Postoperative observation indexes

Routine blood tests were performed 3, 7 and 14 days after surgery, and the hemoglobin, hematocrit, drainage volume, and autologous and heterogeneous blood transfusion volumes were recorded during the removal of the drainage tube. In the 2nd and 4th weeks after surgery, color Doppler ultrasonography was performed on the deep veins of both lower extremities, and thromboses of the common and superficial femoral, popliteal, posterior tibial and muscular calf veins were recorded. All of the patients were followed for 4 weeks, their wound healing and wound complications (including hematoma, superficial wound infection and deep infection requiring another surgery) were observed. Any evidence of wound drainage, erythema or surrounding cellulitis identified by the medical staff was regarded as a wound complication.

The hidden blood losses of the three groups were calculated based on the gross equations[17] according to the method of Sehat[18] and Feldschuh *et al* [19].

Main outcome measures

The incidence of deep vein thrombosis, hidden blood loss,

the incidence of wound complications and the incidences of lower limb subcutaneous ecchymosis and swelling were measured.

Statistical analysis

Measurement data are reported as means and ranges, and the medians and inter-quartile ranges (IQRs) were used when the data were skewed. Enumeration data are expressed as percentage. All of the experimental data were statistically analyzed using SPSS 20.0 software (IBM Corp., Armonk, USA). To compare the data among the three groups, a one-way analysis of variance (ANOVA) test was used for normal distributions and the Kruskal-Wallis test was used for skewed distributions. For pairwise comparisons among the three groups, the Bonferroni test was used. For qualitative comparative parameters, the chi-square test was used. Significant level was set at bilateral α=0.05. Statistical power was reached to 0.8 in the comparison of continuous variables[20].

RESULTS

Quantitative analysis of subjects

All of the 324 patients were followed for 4 weeks and all of them were available for review.

Baseline analysis of subjects

No statistically significant differences were found in the preoperative data, the operation time or the dominant blood loss between the three groups ($P > 0.05$). The data of the three groups were comparable (**Table 1**).

Anticoagulant effects

There were two patients in the aspirin group (both 5 days after surgery) and one patient in the LMWH group (7 days after surgery) with symptomatic deep vein thrombosis; color Doppler ultrasonography of the lower extremities identified thromboses in the muscular calf veins. All three groups also had asymptomatic deep vein thrombosis according to regular color Doppler ultrasonography of the deep veins of the lower extremities, and there were 3, 16 and 13 patients in the rivaroxaban group, aspirin group and LMWH group respectively. The incidence of deep vein thrombosis (both symptomatic and asymptomatic) in the rivaroxaban group was lower than that in the LMWH group (2.94% *vs*. 12.50%, P=0.029) and no significant difference was found between the LMWH group and aspirin group (12.50% *vs*. 16.36%, P=0.831). None of the groups had pulmonary embolism or cardio-cerebrovascular complications.

Anticoagulant security

Both hidden blood loss and wound complications were higher in the rivaroxaban group compared with the LMWH group ($P < 0.05$), and there were no significant differences between the LMWH group and aspirin group ($P > 0.05$; **Table 2**).

Table 1 Comparison of the baseline data between the three groups

Item	Rivaroxaban group	LMWH group	Aspirin group	*P*
Patients (*n*)	102	112	110	
Males [*n* (%)]	32 (31.37◆)	20 (17.85◆)	28 (25.45◆)	0.075[b]
Age (year)※	63.5 (50 to 82)	65.7 (54 to 80)	62.7 (47 to 79)	0.750[a]
Body mass index (kg/m^2)※	27.5 (18.0 to 39.5)	27.0 (20.3 to 37.0)	27.8 (17.8 to 40.0)	0.605[a]
Prothrombin time (second)※	9.6 (7.8 to 12.5)	9.5 (7.6 to 13.0)	9.5 (7.9 to 12.7)	0.246[a]
Hematocrit (%) ※	39.41 (27.30 to 53.10)	38.76 (24.20 to 49.60)	39.12 (26.70 to 51.00)	0.147[a]
Hemoglobin (g/L) ※	131.22 (87 to 179)	128.73 (79 to 160)	129.97 (90 to 171)	0.213[a]
Knee Society Score				
Clinical (score)※	36.6 (22 to 50)	34.7 (20 to 48)	35.2 (24 to 45)	0.061[a]
Function (score)※	33.8 (25 to 45)	32.7 (25 to 50)	34.0 (20 to 50)	0.730[a]
Range of motion (°) ※	89.4 (80.0 to 105.0)	90.9 (85.0 to 115.0)	89.1 (80.0 to 110.0)	0.805[a]
Operation time (minute)△	84.9 (79 to 87)	84.4 (81 to 87)	90.6 (80 to 94)	0.841[c]
Dominant blood loss (L) ※	0.64 (0.39 to 0.90)	0.58 (0.28 to 0.79)	0.56 (0.36 to 0.84)	0.083[a]

Notes: No statistically significant differences were found in the gender, age, body mass index, prothrombin time, hematocrit, hemoglobin, Knee Society Score, range of motion, operation time and postoperative dominant blood loss ($P > 0.05$). ※: Data are expressed as mean and ranges in these lines; △: Data are expressed as the medians and inter-quartile ranges (IQRs) in this line; ◆: Data are expressed as percentage (male divide by patient). [a]*P*: a one-way analysis of variance test was used for normal distributions; [b]*P*: chi-square test was used for qualitative comparative parameters; [c]*P*: Kruskal-Wallis test was used for skewed distributions.

Table 2 Comparison of the postoperative security data between the three groups

Item	Rivaroxaban group	*P*	LMWH group	Aspirin group	*P*
Hidden blood loss (L)	1.71(1.19 to 2.97)	0.009[a]	1.18(0.77 to 2.31)	1.30(0.61 to 2.43)	0.327[a]
Lower limb swelling [*n* (%)]	38(37.3)	0.288[b]	28(25.0)	24(21.8)	0.448[b]
Lower limb subcutaneous ecchymosis [*n* (%)]	74(72.6)	0.193[b]	62(55.4)	54 (49.1)	0.427[b]
Wound complications [*n* (%)]	5(4.9)	0.027[b]	3(2.7)	2(1.8)	0.209[b]

Notes: Both hidden blood loss and wound complications were higher in the rivaroxaban group compared with LMWH group ($P < 0.05$), and there were no significant differences between the LMWH group and aspirin group ($P > 0.05$). No significant differences were found between the rivaroxaban group and LMWH group or between the LMWH group and aspirin group in the incidences of lower limb swelling and subcutaneous ecchymosis ($P > 0.05$). [a]*P*: Bonferroni test was used for pairwise comparisons, *vs*. LMWH group; [b]*P*: chi-square test was used for qualitative comparative parameters, *vs*. LMWH group. LMWH: Low-molecular-weight heparin.

No significant differences were found between the rivaroxaban group and LMWH group or between the LMWH group and aspirin group in the incidences of lower limb swelling and subcutaneous ecchymosis ($P > 0.05$; **Table 2**). No complications, such as intracranial hemorrhaging or massive hemorrhaging of the gastrointestinal tract, were found in any of the three groups.

DISCUSSION

For orthopedists, an urgent challenge is how to use anticoagulants for effective prevention of deep vein thrombosis without risking other severe complications after TKA. This needs to direct the clinical medication by evaluating the drug safety.

Rivaroxaban has a stronger anticoagulant effect on the prevention of post-TKA deep vein thrombosis. Rivaroxaban is a highly selective, oral direct factor X_a inhibitor and is characterized by a wide therapeutic window, high bioavailability, good pharmacokinetic stability and predictable efficacy[21-22]. The third phase of clinical trial show that rivaroxaban has a more significant effect on the prevention of post-TKA deep vein thrombosis than LMWH[23-24]. Our results indicate that there were 14 patients in the LMWH group with both symptomatic and asymptomatic deep vein thrombosis, but only three patients in the rivaroxaban group with asymptomatic deep vein thrombosis; the incidence of postoperative femoral superficial vein and popliteal vein stenosis in the rivaroxaban group was much lighter than that in the LMWH group, similar to those described above.

But rivaroxaban increases the postoperative hidden blood loss and postoperative wound complications in the patients. Jameson and co-workers[3] performed a multicenter, controlled study on a total of 2 762 English patients and prescribed anticoagulants following knee or hip arthroplasty; they found that rivaroxaban had a higher wound complication rate compared with LMWH. Gonez-Outes *et al* [4] also came to the same conclusion after conducting a systematic review and meta-analysis for a total of 38 747 patients. Our results indicate that rivaroxaban increases both hidden blood loss and wound complications after TKA, so we reckon that a higher hidden blood loss leads to a higher wound complication rate. Mechanism is still not clear about the hidden blood loss. Pattison *et al* [25] thought that the hidden blood loss after total joint arthroplasty was caused by hemolysis. Prasad *et al* [26] claimed that the hidden blood loss caused by massive amounts of blood swarmed into the tissue compartment and stored up the articular cavity. We reckon it is for the latter reason that leads to the increase in wound complication rate.

Our study showed that the incidence of lower limb subcutaneous ecchymosis and swelling were not significantly different between the rivaroxaban group and the LMWH group. We all know that increased hidden blood loss can aggravate the lower limb subcutaneous ecchymosis and swelling, so it should be higher in the rivaroxaban group than that in the LMWH group. We believe that this result may be related to following factors: (1) the application of pneumatic tourniquets in operation maybe leads to ischemical reperfusion injury, because we found that the affected side in most patients was severe than the contralateral side; and (2) this study included a relatively small number of patients, leading to the potential for bias in the results. A longer follow-up period is required to assess the actual consequences of these adverse outcomes, and further studies will be necessary.

Hence, clinicians using rivaroxaban for anticoagulant therapy should closely monitor the changes in the hemoglobin level and wound healing, promptly supplement blood volume and provide other symptomatic and supportive treatments.

Aspirin, when used in conjunction with other clinical care protocols, may be effective as venous thrombosis prophylaxis for certain TKA patients. Aspirin is a conventional non-steroidal anti-inflammatory drug with anticoagulation effects derived mostly from the irreversible inhibition of platelet cyclooxygenases and the selective inhibition of the synthesis of thromboxane A2[27]. Aspirin plays an effective role in preventing ischemic cardio-cerebrovascular diseases; however, there have been controversies over whether to use aspirin as a conventional drug for post-TKA venous thrombosis prophylaxis[28-29]. Brown[30] claimed that aspirin will decrease the rate of operative site bleeding without increasing thromboembolic events when aspirin is used for venous thrombosis prophylaxis after major orthopaedic surgery. Bozic and colleagues[6] analyzed clinical and administrative data from 93 840 patients who underwent primary TKA at 307 US hospitals over a 24-month period and found that after adjusting for patient- and hospital-related factors, the patients who received aspirin for venous thrombosis prophylaxis had similar odds of thromboembolism compared with LMWH patients but no significant differences in the risk of bleeding, infection or mortality. Only element lacking is that these views are retrospective studies, in which, the integrity and authenticity of the recording can affect the reliability of the results directly. So our prospective, randomized, double-blind, controlled trial further validated those described above, there were no significant differences between the aspirin group and LMWH group with regard to their efficacy for post-TKA deep vein thrombosis prophylaxis, postoperative hidden blood loss or the postoperative incidence of wound complications.

Characterized by abirritation, a mature dosage form, oral administration, low cost and no need for monitoring, aspirin can be used as a conventional, post-TKA anticoagulant drug as part of a multimodal anticoagulation therapy to reduce the doses and side effects of opioids, encouraging the patients' early mobilization[31].

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阿司匹林和利伐沙班预防全膝关节置换后下肢深静脉血栓形成

邹　玥，田少奇，王远贺，刘江俊，孙　康(青岛大学附属医院关节外科，山东省青岛市　266003)

邹玥，1987 年生，男，汉族，山东省烟台市人，青岛大学医学院在读硕士，主要从事骨关节退行性疾病及运动损伤的基础与临床研究工作。
通讯作者：孙康，博士，主任医师，博士生导师，青岛大学附属医院关节外科，山东省青岛市　266003

文章亮点：

1 临床常用抗凝药物利伐沙班在有效预防静脉血栓栓塞性疾病的同时，围手术期出血并发症发生率也明显增加。阿司匹林对深静脉血栓形成和肺栓塞具有良好预防效果，但对于是否将其作为全膝关节置换后预防静脉血栓栓塞性疾病的常规用药至今存在争议。

2 文章通过前瞻性随机双盲对照实验，对 3 种药物的深静脉血栓形成发生率、显性及隐性失血量、切口并发症率及患肢皮下瘀斑率进行比较，以期评价阿司匹林、利伐沙班和低分子肝素预防全膝关节置换后下肢深静脉血栓形成的疗效和安全性。

关键词：
植入物；人工假体；膝关节表面置换；随机双盲对照；利伐沙班；阿司匹林；低分子肝素；抗凝；静脉血栓形成；隐性失血；切口并发症
主题词：
关节成形术，置换，膝；因子 Xa；吗啉类；噻吩类；阿司匹林；肝素，低分子量；静脉血栓形成

摘要

背景：现中国临床上常用抗凝药物为利伐沙班，但有效预防静脉血栓栓塞性疾病的同时，围手术期出血性并发症发生率也明显增加。有研究表明阿司匹林对深静脉血栓形成和肺栓塞具有良好预防效果，但对于能否将其作为全膝关节置换后预防静脉血栓栓塞性疾病的常规用药至今存在争议。

目的：观察比较阿司匹林和利伐沙班预防全膝关节置换后下肢深静脉血栓形成的疗效和安全性。

方法：初次行单侧全膝关节置换的 324 例骨关节炎患者随机等分为 3 组，于置换后 12 h，分别用利伐沙班，低分子肝素，阿司匹林干预治疗 14 d。所有患者均随访 4 周。

结果与结论：与低分子肝素组相比，利伐沙班组深静脉血栓发生率降低($P < 0.05$)，隐性失血量及切口并发症率升高($P < 0.05$)。与低分子肝素相比，阿司匹林组深静脉血栓发生率、隐性失血量、切口并发症率、下肢肿胀率和皮下瘀斑率差异均无显著性意义($P > 0.05$)。结果证实，利伐沙班拥有较强抗凝效果，但并发症发生率高。阿司匹林与低分子肝素相比疗效和安全性均无差异。阿司匹林作为全膝关节置换后多模式抗凝治疗的一部分，安全有效。

作者贡献：第一作者及通讯作者完成实验设计，实验实施为通讯作者和第二、三、四作者，实验评估为第一作者及通讯作者，资料收集为第一作者，通讯作者和第二作者审核，第一作者及通讯作者对文章负责。

利益冲突：文章及内容不涉及相关利益冲突。

伦理要求：所有进入研究患者置换前本人及家属均被告知实验过程及利弊，充分了解本次治疗方案前提下均签署知情同意书，干预及治疗方案获医院伦理委员会批准。

学术术语：踝泵-即通过简单的屈伸和绕环踝关节运动，像泵一样促进整个下肢血液和淋巴回流，对预防置换后下肢深静脉血栓形成、消除置换后肢体肿胀作用巨大。跖屈时，小腿三头肌收缩变短，胫骨前肌放松伸长；背伸时，胫骨前肌收缩变短，小腿三头肌放松伸长。肌肉收缩时，血液和淋巴液受挤压回流，肌肉放松时，新鲜血液补充。

作者声明：文章为原创作品，无抄袭剽窃，无泄密及署名和专利争议，内容及数据真实，文责自负。

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