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Gender Differences do not Influence the Blood Coagulopathy in Patients Undergoing Total Knee Arthroplasty: A Retrospective Thromboelastography Analysis

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Abstract

Objective: Deep vein thrombosis (DVT) is one of the severe complications after total knee arthroplasty (TKA). Gender has been considered to influence the incidence of the thrombosis formation in TKA patients. However, it remains controversial which gender would be more prone to form thrombosis. The aim of this study was to assess the effects of gender differences on coagulation status after TKA via the thromboelastography (TEG).

Methods: A total of 57 male patients who underwent primary TKA from September 2015 to January 2021 were included in this study. According to the matching principle of age, body mass index (BMI), and anticoagulation treatment, 60 female patients were selected. The conventional coagulation tests, routine blood tests, and thromboelastography were conducted before the operation, 1 day and 7 days after the operation. In addition, Doppler ultrasound was also performed 1 day before the operation and at the 7 days after the operation. The parameters of conventional coagulation tests, routine blood tests, and thromboelastography were compared between the two groups.

Results: There were no significant differences in the blood transfusion rate, the incidence of DVT during the perioperative period, D-dimer (D-D), fibrin degradation products (FDP), hemoglobin (HB), hematocrit (HCT), prothrombin time (PT), activated partial thromboplastin time (APTT), and C-reactive protein (CRP) at any corresponding time point between the male group and the female group ($P > .05$). There were no significant differences in neutrophil-to-lymphocyte ratio (NLR) preoperatively; however, there were significant differences in NLR 1 day after the surgery and 7 days after the surgery between the two groups ($P < .05$). There were significant differences in reaction time (R) and α angle 1 day after the surgery between the two groups ($P < .05$), but there were no significant differences in other TEG indexes at any corresponding time point between the two groups ($P > .05$). Binary logistic regression analysis demonstrated that gender, age**,** BMI, tourniquet application time were not independent predictors ($P > .05$).

Conclusion: Gender differences have no significant influence in TKA patients with regard to conventional coagulation tests and thromboelastography.

Keywords

gender, thromboelastography, total knee arthroplasty, deep vein thrombosis

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Introduction

Knee osteoarthritis (OA) is one of the most common forms of OA, especially in people over 50 years old, the morbidity in women is much higher than that in men.[1] For patients with end stage of OA, total knee arthroplasty (TKA) is an efficient treatment that can relieve pain and improve patients' quality of life and lower limbs function.[2]

Deep vein thrombosis (DVT) is a common complication after TKA. Without the proper prophylaxis, the incidence of DVT can reach 50% to 70%.[3] The gender difference in the incidence of OA has been reported by many studies.[4–6] However, it remains controversial which gender would be more prove to form thrombosis.[7] A meta-analysis showed that the female have a higher risk of DVT for the thicker fat layer in female patients, which makes the operation more difficult, so the vascular endothelium is more likely to be damaged during the operation.[8] However, considering the factors such as age, race, and living area, Proctor et al.[9] reported that the incidence of DVT in female is lower than that in male.

In the abovementioned studies, the difference in the incidence of DVT between male and female was mainly analyzed based on the Doppler ultrasound, but there were few studies on the change of coagulation status after TKA. The conventional coagulation tests such as prothrombin time (PT), activated partial thromboplastin time (APTT) are determined in plasma rather than the whole blood, besides, it cannot reflect the platelet function. Many studies have shown that D-dimer (D-D) has high sensitivity for diagnosing venous thromboembolism (VTE), but with low specificity, and it can only be used as an exclusion criterion for VTE.[10,11] Zhang et al.[12] reported that the rate of missed diagnosis of lower limb DVT by ultrasound amounts to 50% or so in patients without symptoms of DVT. Considering that the thrombosis may not have formed yet, but the blood coagulopathy has changed, in order to explore the changes in the blood coagulopathy, the parameters of thromboelastography (TEG) were used as the main observation indicators. Compared with the conventional coagulation tests, TEG offers an all-around analysis of a patient's coagulation status which was completely different from plasma-based tests, including the contribution of platelets, coagulation factors, fibrinogen levels, erythrocytes, and leukocytes.[13] TEG can evaluate the overall coagulation function from a single blood sample,[14] and can better distinguish the hypocoagulation and hypercoagulability state.[15–18] However, the most significant advantages of TEG are to allow measurement of global clot formation and dissolution in real time[19] and the coagulation analysis can be done at the patient's temperature.[20] Quan et al.[21] reported that the routine coagulation tests including PT, APTT, can only partially analyze a certain stage of coagulation process or a certain coagulation product. Thromboelastography which was first described in 1948 is a sensitive blood coagulation assay that can analyze the kinetics of clot formation from the initial fibrin threads to fibrinolysis. It was believed that TEG was more sensitive than routine coagulation tests.[22,23]

In this study, we aimed to assess coagulation status by TEG and conventional coagulation tests and record the incidence of DVT in TKA patients. Those data were used to determine if there was a difference in the TEG profiles between male and female in primary TKA patients and to assess whether the gender difference leads to the differences in thrombosis rate.

Materials and Methods

Patient Selection and Study Design

A retrospective, matched-controlled study was conducted in patients undergoing unilateral primary TKA from September 2015 to January 2021 after the hospital ethics committee approval. Each patient enrolled was given a written, informed consent. Patients aged more than 50 years old who were diagnosed with knee OA, but conservative treatment is ineffective were recruited in this study. Patients were excluded if they (1) had a recent history of DVT within 3 months; (2) were undergoing anticoagulant therapy within 1 month before surgery; (3) had coagulopathy; (4) had a history of lower limb fractures within 6 months; (5) had clinically significant impairment of renal function, severe liver diseases, or any other organ insufficiencies. From September 2015 to January 2021, a total of 60 male patients who underwent primary TKA were included in this study. According to the matching principle of age, body mass index (BMI), and anticoagulation treatment, 60 female patients were selected from the same time window. The enrolled patients were consecutive patients. However, three male patients were diagnosed with cancer within 6 months after TKA. One of them was diagnosed with kidney cancer and the other two were diagnosed with liver cancer. Considering the impact of malignant tumors on the coagulation function, these three male patients were also excluded from the analysis. Those patients were divided into male group and female group.

Surgical Approach and Perioperative Managements

All operations were performed through a medial parapatellar approach by the same team under general anesthesia. Patients in both groups received 15 mg/kg intravenous infusion tranexamic acid 30 min before incision and received the same dose 3 h after closing the incision. To control blood pressure, sodium nitroprusside was used as a hypotensive agent to maintain blood pressure from 100/60mm Hg to 110/70mm Hg.[24] Tourniquet was routinely used in the operation, and every 90 min, the tourniquet would be loosed for 10 to 15 min. Bone cement was used to fix the prosthesis. A drainage tube was applied and retrieved on the morning of postoperative day 2 (POD 2). After the operation, as chemical prophylaxis, 10 mg rivaroxaban was first oral administered 6 h postoperatively and then at 24-hour intervals with 10 mg dose until hospital discharge. After discharge, 10 mg/day of rivaroxaban was prescribed for 2 weeks for prophylaxis against DVT if no bleeding events occurred. After the drainage tube was removed, the patients were instructed to perform rehabilitation exercises to prevent thrombosis of the lower limbs. Color Doppler ultrasound was performed in all patients to screen for

DVT 1 day preoperatively, and 1 week postoperatively. Conventional coagulation tests, routine blood tests, and TEG were examined on preoperative day 1, postoperative day 1 (POD 1) and postoperative day 7 (POD 7).

Blood Transfusion Protocol

The use of blood transfusions was standardized according to a protocol based on the guidelines for perioperative transfusion provided by the Chinese Ministry of Health. According to this protocol, a blood transfusion was indicated if one of the following criteria was met: (1) Patients' hemoglobin (HB) concentration was <70g/L; (2) when a patient developed any anemia-related organ dysfunction, such as an alteration in mental status or palpitation (regardless of HB concentration).

Whether to give another transfusion was determined by the patients' level of HB and symptoms.

Outcome Measures

TEG and conventional coagulation tests were recorded as primary outcomes. The TEG parameters were reaction time (R, is the time elapsed until the onset of clotting, and its value increases when coagulation factor deficiency), α angle (α, is mainly affected by the rate of thrombin generation, which is essential for the conversion of fibrinogen to fibrin. The larger the α angle, the faster the formation of blood clots through this interaction), clotting time (K, reflecting the speed of thrombus formation), the coagulation index (CI, is calculated from R, K, α angle, and MA, and reflects the state of comprehensive coagulation), the maximal amplitude of the trace (MA, indicating the maximum strength of the clot), and lysis after 30 min (LY30, The percent reduction of area under the TEG tracing from MA to 30 min after MA is reached, reflecting the state of fibrinolysis).[25] Hypercoagulability was defined as followed: R < 9 min, K < 2 min, α angle > 58, or MA > 64 mm.[26] Routine blood tests and conventional coagulation tests were recorded as secondary outcomes. Tourniquet time, operation time, drainage volume, the No. of patients transfused, and the No. of transfusions per patient were recorded. The incidence of DVT was also compared between the two groups.

Table 1. Baseline Characteristics of Patients.

	Male group	Female group	*P* value
n	57	60	
Age (years)	68.8 ± 4.8	69.0 ± 5.1	.806
Body mass index (kg/m^2)	25.9 ± 3.1	26.3 ± 3.5	.458
Operation time (min)	76.4 ± 11.7	78.7 ± 11.6	.291
Tourniquet application time (min)	74.9 ± 9.9	76.6 ± 8.7	.329
Comorbidities			
Hypertension	29(50.9%)	32(53.3%)	.790
Diabetes	11(19.3%)	8(13.3%)	.382
Coronary heart disease	4(7%)	7(11.7%)	.389
Pre-operation Hct (%)	41.7 ± 3.3	40.8 ± 2.4	.077
Pre-operation Hb (g/L)	138.2 ± 11.4	135.4 ± 8.7	.139

*$P < .05$.
Abbreviations: Hb, hemoglobin, Hct, hematocrit.

Statistical Analysis

The statistical analysis was performed using SPSS 25.0 software (IBM Corp). Continuous data were presented as mean ± standard deviation. Categorical variables were described using counts and percentages. Continuous variables between male and female groups were compared with the use of the independent samples *t*-test. The Pearson's chi-squared test and the Fisher's exact test were performed to analyze the proportion of categorical variables. Binary logistic regression analysis was then performed to determine the independent predictors. $P<.05$ was considered to be statistically significant.

Results

The mean age of male patients enrolled in the study was 68.8 ± 4.8 years (range: 55-81 years) and female patients enrolled in

Table 2. Conventional Coagulation Tests, Hb, and Hct at Different Time Points.

	Time points	Male group (n = 57)	Female group (n = 60)	*P* value
D-dimer (ng/mL)	Pre-op	.7 ± 0.5	0.7 ± 0.5	.516
	POD1	4.4 ± 2.7	3.7 ± 2.4	.150
	POD7	4.5 ± 2.3	4.4 ± 2.1	.877
FDP (mg/L)	Pre-op	2.5 ± 1.2	2.7 ± 1.6	.497
	POD1	17.7 ± 18.4	13.5 ± 6.6	.096
	POD7	13.5 ± 5.3	14.2 ± 5.8	.499
PT (s)	Pre-op	11.3 ± .8	11.1 ± .5	.314
	POD1	12.3 ± 1.2	12.2 ± 1.1	.553
	POD7	11.8 ± 1.3	11.9 ± 1.0	.480
APTT (s)	Pre-op	27.7 ± 2.7	27.1 ± 2.8	.185
	POD1	30.3 ± 3.3	30.6 ± 3.8	.656
	POD7	28.6 ± 2.9	27.9 ± 2.3	.124
HB (g/L)	Pre-op	138.2 ± 11.4	135.4 ± 8.7	.139
	POD1	117.4 ± 12.5	115.5 ± 10.5	.357
	POD7	109.8 ± 13.8	108.8 ± 11.0	.670
HCT (%)	Pre-op	41.7 ± 3.3	40.8 ± 2.4	.077
	POD1	35.4 ± 3.4	34.4 ± 3.3	.121
	POD7	32.4 ± 4.1	32.3 ± 3.7	.914
CRP (mg/L)	Pre-op	6.6 ± 26.7	4.0 ± 12.8	.493
	POD1	59.2 ± 30.1	63.6 ± 25.1	.393
	POD7	85.0 ± 48.7	72.7 ± 30.8	.109
NLR	Pre-op	2.1 ± .8	1.9 ± 0.6	.095
	POD1	9.6 ± 3.7	5.9 ± 3.2	<.001*
	POD7	4.0 ± 1.6	2.9 ± 1.2	<.001*

*$P < .05$.
Abbreviations: APTT, activated partial thromboplastin time; CRP C-reactive protein; FDP, fibrin degradation products; HB, hemoglobin; HCT, hematocrit; Pre-op, pre-operation; POD1, postoperative day 1; POD7, postoperative day 7; PT, prothrombin time; TT, thrombin time; NLR, neutrophil-to-lymphocyte ratio.

the study were 69.0 ± 5.1 years (range: 60-82 years). The mean age, BMI, tourniquet time, operative time, and comorbidities were similar between the two groups (Table 1).

Conventional Laboratory Values

The routine blood tests and conventional coagulation tests of the two groups were shown in Table 2. There were significant differences in neutrophil-to-lymphocyte ratio (NLR) 1 day after surgery and 7 days after surgery between the two groups ($P < .05$). No significant differences were found with regard to conventional coagulation tests, HB, hematocrit (HCT), and C-reactive protein (CRP) between the two groups ($P > .05$) (Table 2).

Drainage Volume, the Rate of Transfusion, and Deep Vein Thrombosis

The mean drainage volume was 259.3 ± 79.6ml in male group, and 252.6 ± 99.0 mL in female group, without significant differences ($P = .688$) and the rate of transfusion, 2 of 57 males (3.5%) and 2 of 60 females (3.3%), were also comparable between the two groups. There was no statistically significant difference in the incidence of DVT between the two groups ($P = .515$).

The TEG Assessment

In terms of R and α angle 1 day after the operation, there were significant differences between the two groups, ($P < .05$) but there were no significant differences in other TEG indexes at any corresponding time point between the two groups ($P > .05$) (Table 3).

Table 3. Assessment of TEG at Different Time Points.

	Time points	Male group (n = 57)	Female group (n = 60)	*P* value
R (min)	Pre-op	5.0 ± 0.3	5.1 ± 0.9	.468
	POD1	4.6 ± 1.0	5.1 ± 1.0	.003*
	POD7	5.2 ± 1.4	5.3 ± 1.1	.661
K (min)	Pre-op	2.4 ± 0.7	2.5 ± 1.4	.450
	POD1	2.1 ± 0.9	2.4 ± 1.0	.091
	POD7	2.2 ± 1.1	2.3 ± 1.3	.676
α angle (°)	Pre-op	58.2 ± 11.7	56.9 ± 8.0	.461
	POD1	63.3 ± 8.9	60.0 ± 8.7	.044*
	POD7	64.2 ± 9.2	61.9 ± 10.5	.227
MA (mm)	Pre-op	54.0 ± 6.1	52.8 ± 6.5	.321
	POD1	56.6 ± 7.7	55.4 ± 6.2	.352
	POD7	62.3 ± 9.4	59.6 ± 8.6	.108
CI	Pre-op	−0.5 ± 2.0	−0.8 ± 2.0	.424
	POD1	0.3 ± 1.9	−0.4 ± 2.3	.085
	POD7	0.4 ± 3.0	−0.1 ± 2.7	.314
LY30 (%)	Pre-op	0.1 ± 0.2	0.3 ± 1.8	.367
	POD1	0.3 ± 0.5	0.2 ± 0.8	.605
	POD7	0.1 ± 0.2	0.1 ± 0.1	.185

*$P < .05$.

Abbreviations: CI, coagulation index; K, clotting time; LY30, lysis after 30 min; MA, maximum amplitude; Pre-op pre-operation, POD1, postoperative day 1; POD7, postoperative day 7; R, reaction time.

Independent Risk Factors for Deep Vein Thrombosis in Patients of Different Genders After Total Knee Arthroplasty

Four variables including gender, age, BMI, tourniquet application time were included in the binary logistic regression analysis. Then, binary logistic regression analysis demonstrated that gender, age, BMI, and tourniquet application time were not independent predictors (Table 4).

Discussion

DVT is an important complication of major orthopedic surgery of the lower limbs. The incidence of DVT can reach 40% if effective anticoagulation treatment is not taken.[27] Even with routine anticoagulation, a certain proportion of patients were also observed with hypercoagulable tendency. In our study, among 117 patients, despite the use of rivaroxaban for anticoagulation, DVT was observed in 8 patients (6.8%), including 3 males and 5 females. Regarding the coagulation status via the TEG, despite the significant difference in R and α angle 1 day postoperatively, no difference was observed in other TEG indexes at any corresponding time point between male and female patients.

Previous reports on the difference in the incidence of DVT between male and female after joint replacement were controversial. Yoo et al.[28] reported increased DVT incidence in females. In their series, 221 patients who underwent total hip arthroplasty before and after the surgery were performed ultrasound examinations on the lower limbs. It was found that 10 of 144 male patients (6.9%) and 13 of 77 female patients (16.9%) developed DVT after the surgery. Miyagi et al.[29] conducted a retrospective case–control study including 54 TKA patients. DVT occurred in 7 of 10 male patients (70.0%) and 5 of 44 female patients (11.4%) and they believed that men have higher risk of DVT after TKA than women.

In our study, 3 of 57 female patients (5.3%) and 5 of 60 male patients (8.3%) developed plexus venous leg muscle thrombosis. There were no significant differences in the incidence of thrombosis between the two groups ($P = .515$). Despite no

Table 4. Binary Logistic Regression Analysis to Determine Independent Risk Factors for DVT in Patients of Different Genders after TKA.

Predictors in the model	B	OR (95% CI)	*P* value
Gender	−0.419	0.564 (0.123 to 2.582)	.583
Age (years)	0.018	0.818 (0.875 to 1.184)	.818
Body mass index (kg/m^2)	0.118	1.125 (0.896 to 1.413)	.310
Tourniquet application time (min)	0.006	1.006 (0.928 to 1.091)	.884

*$P < .05$.

Abbreviations: DVT, deep vein thrombosis, TKA, total knee arthroplasty.

difference in the incidence of DVT, there may be differences in the blood coagulation status. Therefore, this study intended to find the difference between male and female through laboratory tests that reflected changes in blood coagulation status. In this study, there was no statistically significant difference between the male and female groups in factors tourniquet application time ($P > .05$). In the case of ensuring the homogeneity of the study subjects as much as possible, TEG was used as an indicator to monitor the coagulation and fibrinolysis status of patients to analyze the influence of different genders on the incidence of DVT in patients after TKA.

TEG is a quick and simple laboratory test that can broadly determine the coagulation abnormalities and is an early predictor of transfusion in trauma patients. For the detection of fibrinolysis status, TEG is more sensitive than the conventional plasma-based tests, such as APTT and thrombin time (TT).[30] Fortner et al.[31] reported that, in their prospective, controlled study, TEG was superior to the conventional coagulation tests in lowest observed effect concentration, diagnostic thresholds, and sensitivity. TEG can provide real-time point-of-care results faster than conventional coagulation tests.

There was no significant difference in the conventional coagulation tests and routine blood tests between the two groups. R of the male group was shorter than that of the female group on POD1 ($P < .05$), and the α angle was larger than that of the female group on POD1 ($P < .05$). It was indicated that, on POD1, the blood hypercoagulability state on males was more serious than that on females. However, there was no significant difference between the two groups on POD7 TEG parameters ($P > .05$)

There were several limitations in this study. First, the population of the study was relatively small, thus the possibility of type II error increased. A power analysis was performed with data, through calculation, we concluded that the probability of the type II error in this study is 23.56%, and the power of the sample size of this study is 76.44%, which is slightly less than 80%. However, these samples are all samples that we can get after rigorous screening and excluding unqualified individuals. Second, the Doppler ultrasound was only performed on 1 day preoperatively and POD7. DVT that happened later was not observed. However, the median time to diagnose DVT was 7 days after TKA.[32] So, it may be reasonable to take this follow-up interval for collecting DVT data. Third, in this study, patients who underwent TKA were given intravenous tranexamic acid to control bleeding during the perioperative period and rivaroxaban as anticoagulation therapy. Those drugs may affect the blood coagulation status. However, the hemostasis of the two groups and anticoagulant treatment measures were identical, which eliminated the impact of such drugs to a certain extent.

Conclusions

Gender differences will not significantly affect the coagulation status in TKA patients with regard to thrombelastography and conventional coagulation tests.

Authors' Contributions

Wang-yi Jin and Yong Pang contributed equally to this work. Wang-yi Jin, Xin Zheng and Kai-jin Guo designed the study and drafted the manuscript. Wang-yi Jin, Da-lin Peng, and Zi-wen Yan performed the data collection and the statistical analysis. Xing-chen Zhang and Yong Pang screened the patients. Wang-yi Jin, Sheng Pan, and Chao-ran Huang collected the information of patient samples. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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