

Analysis of Risk Factors for Lower-limb Deep Venous Thrombosis in Old Patients after Knee Arthroplasty

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Abstract

Background: Deep venous thrombosis (DVT) is a common complication of arthroplasty in old patients. We analyzed risk factors for lower-limb DVT after arthroplasty in patients aged over 70 years to determine controllable risk factors.

Methods: This was a retrospective study of 1,025 patients aged >70 years treated with knee arthroplasty at our hospital between January 2009 and December 2013. Of 1,025 patients, 175 had postoperative lower-limb DVT. We compared medical history, body mass index (BMI), ambulatory blood pressure, preoperative and postoperative fasting blood glucose (FBG), preoperative blood total cholesterol, triglyceride, high- and low-density lipoprotein cholesterol, and preoperative homocysteine (Hcy) between thrombus and non-thrombus groups. B-mode ultrasonography was used to detect lower-limb DVT before the operation and 7 days after the operation in all patients. Logistic regression analysis was used to determine risk factors for DVT.

Results: Incidence of diabetes ($P=0.014$), BMI ($P=0.003$), preoperative FBG ($P=0.004$), postoperative FBG ($P=0.012$), and preoperative Hcy ($P<0.001$) were significantly higher in the thrombus group. A significantly greater proportion of patients in the non-thrombus group had early postoperative activity ($P<0.001$) and used a foot pump ($P<0.001$). Operative duration was significantly longer in the thrombus group ($P=0.012$). Within the thrombus group, significantly more patients had bilateral than unilateral knee arthroplasty ($P<0.01$). Multivariate logistic analysis revealed BMI, preoperative Hcy, postoperative FBG, long operative duration, bilateral knee arthroplasty, and time to the activity after the operation to be predictive factors of DVT. At 6-month follow-up of the thrombus group, 4.7% of patients had pulmonary embolism and 18.8% had recurrent DVT; there were no deaths.

Conclusions: Obesity, inactivity after operation, elevated preoperative Hcy and postoperative FBG, long operative duration, and bilateral knee arthroplasty were risk factors for DVT in patients aged over 70 years.

Key words: Arthroplasty; Deep Venous Thrombosis; Elderly

INTRODUCTION

The prevalence of knee osteoarthritis is high; 37% of the population aged over 60 years and 40% of the population aged 70–74 years have clinically defined knee osteoarthritis.^[1] Total knee arthroplasty is an effective treatment for severe knee osteoarthritis; however, arthroplasty can cause extensive damage of tissue and vascular endothelium and lead to platelet activation and initiation of the coagulation cascade. Postoperatively, severely limited patient activity, slow blood flow, and blood in a hypercoagulable state greatly increase the possibility of deep venous thrombosis (DVT). The prevalence of DVT after arthroplasty is 40–60%, and 90% of pulmonary embolisms originate in a lower-limb vein. When thrombosis

involves the femoral vein, iliac vein, or inferior vena cava, the possibility of pulmonary embolism is 50%.^[2,3] Pulmonary embolism can endanger the lives of patients,^[4] but in recent years, with the use of anticoagulant drugs for the prevention of DVT, the incidence of DVT has decreased to about 6–12%.^[5] Prevention of DVT through timely detection and treatment of thrombus can help prevent the occurrence of pulmonary embolism. More arthroplasty procedures are performed at our hospital than at most in the Asian region. Because thousands of cases of arthroplasties are performed here each year, doctors in our orthopedics department are aware of the problem of thrombosis resulting from arthroplasty and anesthesia.

This was a retrospective study of patients hospitalized for knee joint replacement at our institution. The study protocol was approved by the Ethics Committee of our institution. Routinely collected patient data, such as demographics,

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biochemical index, body mass index (BMI), surgical methods, postoperative management, and comorbidities were available to us as electronic medical records and enabled us to analyze risk factors for DVT in old patients after arthroplasty.

METHODS

Patients

Of 1,025 patients aged >70 years (376 were male, 649 were female; mean age 76.8 ± 11.4 years) with unilateral or bilateral knee osteoarthritis treated with arthroplasty at our institution from January 2009 to December 2013, 175 (17.1%; 39 were male) experienced postoperative DVT. All operations were performed with patients under general anesthesia, and all prostheses were fixed with bone cement. Estimated blood loss was <400 ml in each operation. Postoperatively compressive stockings, a foot pump (in some patients), and low-molecular-weight heparin were used to prevent lower-limb DVT. Patients' blood pressure was maintained within the normal range with the use of antihypertensive drugs perioperatively. Fasting blood glucose (FBG) was maintained at a normal level with insulin preoperatively in patients with diabetes mellitus, except those with liver or kidney dysfunction, atrial fibrillation, blood dyscrasia, lower-extremity varicose veins, poor glycemic control preoperatively, malignant tumors, or diseases of the immune system. Each patient's height (m) and weight (kg) were measured, and BMI calculated (kg/m^2).

Blood pressure measurement

We determined each patient's mean systolic blood pressure (mmHg) and mean diastolic blood pressure (mmHg) preoperatively using ambulatory blood pressure.

Blood collection and laboratory methods

All patients underwent a fasting blood test on the morning of the day of surgery and the morning of the 1st day postoperatively. Plasma was separated, and we used an automatic biochemistry instrument (Hitachi 7600, Hitachi Ltd., Japan) to detect pre- and post-operative FBG (FBG, mmol/L) and preoperative total cholesterol (TC, mmol/L), triglyceride (TG, mmol/L), high-density lipoprotein cholesterol (HDL-C, mmol/L), low-density lipoprotein cholesterol (LDL-C, mmol/L), and serum homocysteine (Hcy, $\mu\text{mol}/\text{L}$).

Lower-limb ultrasonography

Doctors experienced in the use of B-mode ultrasound examined patients' lower limbs for thrombus before the operation and 7 days after the operation in all patients. Patients lay in the supine position, and the scan was conducted from cranial to caudal. Patients were divided into two groups by the presence or absence of venous thrombosis in a lower limb. In the thrombus group, repeat ultrasonography of the deep veins of the lower limb was performed 2 weeks postoperatively. Six months follow-up for all patients was conducted by telephone interview.

Statistical analysis

SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for data analysis. Categorical data were compared using the Chi-square test and Fisher's exact test. For normally distributed continuous data, mean \pm standard deviation (SD) was calculated, and the independent Student's *t*-test was used for comparison. Skewness was described using median and interquartile range and tested using the Kruskal-Wallis test. Multivariate logistic regression was used to determine independent predictors of DVT. Odds ratio (OR) and 95% confidence interval (CI) were calculated using logistic regression. Differences with $P < 0.05$ were considered statistically significant.

RESULTS

Baseline characteristics

Table 1 presents baseline characteristics by groups. Patients in the thrombus group had a significantly higher incidence of diabetes mellitus ($P = 0.014$) and a significantly higher BMI ($P = 0.003$) than in the non-thrombus group. Sex; age; histories of dyslipidemia, coronary heart disease (CHD), and cerebral infarction; presence of renal disease, presence of respiratory disease; duration of hypertension; and mean systolic and diastolic blood pressures did not differ significantly between groups [Table 1].

Biochemical indexes

Biochemical indices for the two groups are presented in Table 2. Preoperative FBG ($P = 0.004$), postoperative FBG ($P = 0.012$), and preoperative Hcy level ($P < 0.001$) were significantly higher in the thrombus group than in the

Table 1: Baseline characteristics of patients in the two groups

Items	Thrombus group (<i>n</i> = 175)	Non-thrombus group (<i>n</i> = 850)	<i>P</i>
Number of patients (<i>n</i> (%))	175 (17.1)	850 (82.9)	<0.001
Man (<i>n</i> (%))	39 (38.4)	337 (39.6)	0.637
Mean age (years)	77.2 ± 13.4	76.1 ± 11.5	0.823
Past medical history (%)			
History of diabetes	34.6	23.5	0.014
History of dyslipidemia	22.4	23.8	0.138
History of CHD	66.4	63.8	0.086
History of cerebral infarction	56.3	58.2	0.214
Renal disease (%)	2.8	3.1	0.669
Respiratory disease (%)	19.3	20.1	0.924
BMI (kg/m^2)	31.2 ± 5.2	26.4 ± 3.2	0.003
Average SBP (mmHg)	135.1 ± 23.9	141.2 ± 22.8	0.684
Average DBP (mmHg)	92.3 ± 11.7	94.2 ± 13.7	0.738
Stage 1 hypertension (%)	54.5	57.8	0.383
Stage 2 hypertension (%)	24.4	27.6	0.193
Stage 3 hypertension (%)	21.5	19.6	0.071
Duration of hypertension (years)	22.6 ± 7.1	21.6 ± 7.2	0.469

BMI: Body mass index; CHD: Coronary heart disease; DBP: Diastolic blood pressure; SBP: Systolic blood pressure.

non-thrombus group. Preoperative TC, preoperative TG, preoperative HDL-C, and preoperative LDL-C did not differ significantly between groups [Table 2].

Surgical methods and postoperative management

Table 3 presents a comparison of unilateral versus bilateral knee joint replacement, operative duration, and postoperative management by groups. Within the thrombus group, the incidence of lower-limb DVT was significantly higher in patients with bilateral knee arthroplasty than in those with unilateral knee arthroplasty ($P < 0.01$). Patients in the thrombus group had significantly longer operations ($P = 0.012$), and significantly fewer patients in the thrombus group than in the non-thrombus group began ambulating within 5 days postoperatively ($P < 0.001$) and used a foot pump ($P < 0.001$) [Table 3].

Logistic regression analysis of independent predictors for deep venous thrombosis

Table 4 presents the results of logistic regression used to evaluate the association between DVT and the incidence of diabetes mellitus, BMI, preoperative FBG, postoperative FBG, preoperative Hcy, bilateral knee arthroplasty, operative duration, and early postoperative ambulation. Results revealed BMI, preoperative Hcy, postoperative FBG, long operative duration, bilateral knee arthroplasty, and ambulation within 5 days postoperatively to be independent predictors of DVT [Table 4].

Follow-up

Six months after discharge from the hospital, patients were interviewed by telephone by trained interviewers. For patients unable to be interviewed, outcomes were elicited from a family member or a primary caregiver. Of the 850 patients in non-thrombus group, 130 (15.3%) declined to be interviewed, and 177 (20.8%) were lost to follow-up. Functional outcome data were thus available for 543 patients (63.9%), of the 543 patients, 77 (14.2%) had lower-limb edema; Lower-limb DVT was ruled out by ultrasound examination. Organized thrombus was detected in the 175 patients in thrombus group by B-mode ultrasonography 2 weeks postoperatively. Each of these patients underwent placement of a vena cava filter and was discharged 2 weeks after filter placement and continued on anticoagulation therapy with oral rivaroxaban or warfarin. Six months after discharge from hospital, 14 of the 175 patients (8.0%) with filters declined to be interviewed, and 12 (6.9%) were lost to follow-up. Of the remaining 149 patients, 28 (18.8%) had recurrent DVT related to the discontinuation of anticoagulation therapy and 7 (4.7%) had pulmonary embolism. There were no deaths.

DISCUSSION

The incidence of DVT after arthroplasty in patients aged older than 70 years has rarely been reported. To reduce the incidence of DVT after knee arthroplasty in these older patients, we examined the clinical and follow-up data of patients aged older than 70 years who had undergone knee

Table 2: Biochemical indexes by group

Items	Thrombus group (n = 175)	Non-thrombus group (n = 850)	P
Preoperative TC (mmol/L)	4.31 ± 1.23	4.51 ± 2.11	0.759
Preoperative TG (mmol/L)	2.51 ± 0.23	2.14 ± 0.33	0.082
Preoperative HDL-C (mmol/L)	1.57 ± 0.35	1.62 ± 0.13	0.754
Preoperative LDL-C (mmol/L)	2.43 ± 0.15	2.761 ± 0.27	0.576
Preoperative FBG (mmol/L)	7.31 ± 0.71	6.36 ± 0.31	0.004
Postoperative FBG (mmol/L)	8.45 ± 0.22	6.14 ± 0.67	0.012
Preoperative Hcy levels (μmol/L)	25.42 ± 8.13	18.43 ± 2.31	<0.001

FBG: Fasting blood glucose; TG: Triglyceride; Hcy: Homocysteine; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TC: Total cholesterol.

Table 3: Surgical methods and postoperative management by group

Items	Thrombus group (n = 175)	Non-thrombus group (n = 850)	P
Unilateral knee joint replacement (n = 712), n (%)	68 (9.6)*	644 (90.4)	<0.001
Bilateral knee joint replacement (n = 313), n (%)	48 (15.4)	265 (84.6)	<0.001
Operative time (h)	3.12 ± 0.22	2.52 ± 0.18	0.012
The proportion of patients began ambulating within 5 days postoperatively (%)	49.7	75.3	<0.001
Use of the foot pump after operation, n (%)	34 (19.3)	298 (35.1)	<0.001

*Compared with bilateral knee joint replacement, $P < 0.01$.

Table 4: Multivariate analysis of predictive factors of DVT

Variables	Multivariate analysis		
	OR	95% CI	P
History of diabetes	1.47	0.87–3.98	0.135
BMI (kg/m ²)	1.08	1.05–1.11	0.001
Preoperative FBG	1.41	0.94–2.11	0.095
Postoperative FBG	2.47	1.48–4.31	0.004
Preoperative Hcy levels	3.41	1.31–6.73	0.006
Bilateral knee arthroplasty	2.01	1.62–7.38	0.002
Operation time	1.69	1.06–2.67	0.024
Ambulation beginning within 5 days postoperatively	3.92	2.38–6.05	0.012
Use of the foot pump	0.91	0.84–1.01	0.090

DVT: Deep venous thrombosis; BMI: Body mass index; FBG: Fasting blood glucose; Hcy: Homocysteine; OR: Odds ratio; CI: Confidence interval.

arthroplasty. DVT and pulmonary embolism can seriously affect a patient's quality of life and prognosis and is associated with high rates of mortality and disability.^[6,7] Sasaki *et al.*^[8] used Doppler ultrasound to measure blood flow pre- and post-operatively in patients with lower limb arthroplasty. They found that lower-limb venous blood flow was significantly lower 3 days postoperatively

and 1-week postoperatively than preoperatively, a difference that disappeared within 2 weeks. In addition, Sasaki *et al.* found that venous blood flow had decreased more after knee arthroplasty than after hip arthroplasty 3 days after surgery, demonstrating relevance between changes in venous hemodynamics and DVT. Older age is often associated with vascular sclerosis, poor venous valve function, and high blood viscosity. These factors, combined with reduced activity postoperatively, can lead to lower limb DVT. A new study has shown that the incidence of lower-limb DVT in older patients is twice that of other age groups.^[9]

Of all hypertensive patients in China, 75% also have hyperhomocysteinemia.^[10] Hcy is the intermediate product of methionine metabolism and can participate in the formation of thrombus. Hyperhomocysteinemia may damage the vascular endothelial cells, promote the proliferation of smooth-muscle cells, and change blood coagulability and platelet function.^[11] A key enzyme in the metabolic pathway of Hcy is 5,10 methylenetetrahydrofolate reductase (MTHFR), and the 677th C-T gene mutation of MTHFR (C677T) may lead to changes in Hcy levels. Yin *et al.*^[12] reported that the frequency distribution of the TT genotype of MTHFR in the venous thrombosis group was higher than in the control group and the TT genotype of MTHFR C677T may be a genetic risk factor for DVT. Hyperhomocysteinemia is considered an independent risk factor for venous thrombotic disease.^[13] Our study shows that Hcy levels were higher in thrombus group than in the non-thrombus group and confirmed that an elevated Hcy level may be involved in the formation of lower-limb DVT.

Thrombus tends to form more often in the veins of the lower limbs than in other sites. The primary risk factors for DVT are advanced age and BMI exceeding the normal range.^[14] As Table 1 shows, BMI was higher in the thrombus group than in the non-thrombus group. In the social with an aging population, many knee arthroplasties are performed in patients with advanced age and obesity.^[15,16] Obese patients can have more obesity-related surgical complications (e.g., diabetes mellitus, cardiovascular disease, peripheral vascular disease, and stroke) and lower activity levels,^[17] and have been reported to have slow venous blood flow. Their poor venous valve function can be conducive to the formation of venous thrombus in the lower-limb. Our study also confirms that BMI was higher in the thrombus group than in the non-thrombus group.

Hyperglycemia can damage vascular endothelium, induce the release of various inflammatory mediators *in vivo*, and further activate the coagulation system. It can also cause the formation of venous thrombus.^[18] Hyperglycemia can delay wound healing^[19] and postoperative ambulation. Early ambulation after knee arthroplasty is important not only for recovering activity and knee joint function, but also for preventing DVT.^[20] Old patients in poor physical condition may be willing to perform activities in bed, but

it has been reported that activity performed in bed did not reduce the risk of thrombosis in the lower limbs.^[21] Our study showed that early ambulation after knee arthroplasty was significantly associated with reduced incidence of DVT.

Operative duration of bilateral knee arthroplasty is relatively longer and the amount of blood loss greater. Postoperatively, because patients remain inactive in bed and take more time to become ambulatory,^[22] they are at increased risk of venous thrombosis in the lower-limb. In a retrospective comparison of 153,259 patients with bilateral total knee arthroplasty and 3,672,247 patients with unilateral total knee arthroplasty, Memtsoudis *et al.*^[23] found significantly more complications of bilateral total knee arthroplasty (12.2%) than of unilateral total knee arthroplasty (8.2%) in the perioperative period. In another retrospective analysis, Meehan *et al.*^[24] compared 11,445 patients with bilateral total knee arthroplasty and 23,715 patients with unilateral total knee arthroplasty and found the incidence of pulmonary embolism in bilateral total knee arthroplasty to be relatively greater than in unilateral total knee arthroplasty. In the present study, the incidence of lower-limb DVT was higher in patients with bilateral than with unilateral knee arthroplasty. To reduce the postoperative risk of venous thrombosis in old patients with many comorbidities, only unilateral joint arthroplasty should be performed, and operative duration should be reduced. The use of a foot pump postoperatively is effective in increasing lower-limb blood circulation and should be implemented if conditions permit.

It is common for old patients with osteoarthritis to have comorbidities of hypertension, diabetes mellitus, and CHD. Postoperative pain can lead to sympathetic excitation, which can aggravate hypertension and CHD.^[25,26] Pain, stress reaction, and emotions after surgery lead to endocrine abnormalities that accelerate the secretion of epinephrine, endothelin, and 5-hydroxytryptamine, all of which can lead to an increased hypercoagulable state in arthroplasty patients and easily induce DVT and pulmonary embolism.^[27] Therefore, not only should we pay attention to the risk of thrombosis caused by surgery and anesthesia *per se*, we should also actively take measures to facilitate anticoagulation postoperatively, such as ensuring adequate fluid intake, early postoperative activity, and control of blood glucose. Patients contraindicated for a bilateral procedure should undergo only unilateral knee arthroplasty.

We recognized two limitations in the present study. First, this is a retrospective study; we could not completely eliminate the effect of other factors for DVT. Second, the number of patients in this study had insufficient, thus further prospective studies with larger sample size are needed to confirm risk factors of DVT.

Despite various measures to prevent lower limb DVT, it may still develop in some old patients. Further exploration of the pathogeny and preventive measures of lower-limb DVT should be conducted.

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