J Orthop Sci (2010) 15:57–63
DOI 10.1007/s00776-009-1410-3

JOURNAL OF
ORTHOPAEDIC SCIENCE

Original article

Rheumatoid arthritis: a risk factor for deep venous thrombosis after total knee arthroplasty? Comparative study with osteoarthritis

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Abstract

Background. Recent advances in the understanding of blood coagulation processes favor an inflammatory basis for thrombotic events. In this study, thrombotic risk after total knee arthroplasty (TKA) was assessed and compared between patients with rheumatoid arthritis (RA) and those with osteoarthritis (OA).

Methods. Subjects comprised 199 patients (238 knees) with RA and 156 patients (169 knees) with OA. Serum D-dimer levels were measured before and after the operation. Low-dose unfractionated heparin was given for 7 days when patients had a history of previous venous thromboembolism or had a D-dimer level or ≥10 μg/ml of D-dimer on postoperative day 1. Doppler ultrasonography (DUS) was routinely performed preoperatively and on postoperative day (POD) 7 for diagnosing a deep venous thrombosis (DVT).

Results. D-dimer levels on PODs 0, 1, and 7 were, respectively, 4.6, 37.2, and 11.2 μg/ml for RA and 1.8, 42.3, and 13.6 μg/ml for OA. The incidence of DUS-confirmed DVT was 20.6% in the RA group and 43.2% in the OA group, indicating a much higher incidence of postoperative DVT in OA patients ($P < 0.001$). Interestingly, when patients taking nonsteroidal antiinflammatory drugs (NSAIDs) or those >65 years of age were excluded, the incidence of DVT was comparable in the RA and OA groups. Symptomatic pulmonary embolism and DVT occurred in two and one OA patients and in one and two RA patients, respectively, with one post-discharge DVT included in each group.

Conclusions. The present study revealed that the incidence of DVT following TKA was significantly lower in RA patients than in those with OA. However, when the patients were matched for age and NSAID use, the incidence of DVT was equivalent in the two groups. These findings may allow us to reconsider a prophylactic regimen for venous thromboembolism in patients with RA.

Offprint requests to: Y. Niki
Received: January 5, 2009 / Accepted: September 3, 2009

Introduction

Venous thromboembolism (VTE) is a potentially life-threatening complication in patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA). VTE clinically incorporates signs and symptoms of two interrelated but distinct clinical conditions: deep vein thrombosis (DVT) and pulmonary embolism (PE). The seventh American College of Chest Physicians (ACCP) guidelines for VTE,[1] which are widely accepted evidence-based guidelines concerning the use of VTE prophylaxis, define THA and TKA as having the highest risk of postoperative VTE. The incidence of VTE has so far been considered lower in Japan than in Europe or North America, and VTE has been underdiagnosed and undertreated over the past three decades. However, the incidence is currently increasing and has reached 22.6% for THA and 48.6% for TKA,[2] resulting in increased awareness of the need for VTE prophylaxis in Asian countries.

To date, various risk factors predisposing to VTE have been identified and can be applied to the screening of patients for increased VTE risk prior to surgery.[3] These proven factors comprise heart failure, obesity, age >75 years, history of VTE, varicose veins in the lower extremities, and estrogen therapy; they also include certain inflammatory states, such as certain neoplasms,[4,5] inflammatory bowel disease,[6,7] and septicemia.[8,9]

At present, joint arthroplasty is a promising surgical intervention applicable to patients with several inflammatory arthritides, such as rheumatoid arthritis (RA), ankylosing spondylitis, and psoriatic arthritis. Indeed, these inflammatory arthritides account for a substantial proportion of the primary reasons for performing joint arthroplasty. However, whether inflammatory arthritis is a potential candidate predisposing patients to postoperative VTE remains controversial.

In fact, contradictory results on the association between RA and VTE have been reported in the litera-

ture. The main scenarios supporting accelerated thrombosis in RA patients show that active RA exhibits hypercoagulability with reduced fibrinolysis[10] and elevated levels of autoantibodies such as anti-cardiolipin antibodies and anti-phospholipid antibodies.[11–13] Conversely, reports advocating a lower thrombotic risk in RA patients have noted that frequent administration of nonsteroidal antiinflammatory drugs (NSAIDs), younger age distribution, and lower body mass index (BMI) in RA patients may decrease the incidence of VTE.[14–16] The present study assessed and compared thrombotic risk after TKA between patients with RA and those with noninflammatory arthritis, osteoarthritis (OA), to clarify whether RA represents a predisposing factor to VTE following joint arthroplasty.

Materials and methods

Patient characteristics

A consecutive series of 425 knees from 373 patients who underwent primary TKA between October 2003 and June 2007 were enrolled. Among them, 18 knees from 18 patients were excluded from the study for the following reasons: Anticoagulation prophylaxis was contraindicated in eight patients owing to the presence of high bleeding risk or renal impairment; three refused routine anticoagulation therapy; and seven refused postoperative laboratory testing on a routine basis as required by the study protocol. As a result, the RA group comprised 238 knees from 199 patients, and the OA group comprised 169 knees from 156 patients.

Patient demographic characteristics in the two groups are shown in Table 1. The mean age at the time of TKA was 59.9 years (range 25–84 years) in the RA group and 74.2 years (range 40–88 years) in the OA group. The risk of VTE in each patient was individually assessed based on the presence of proven risk factors, as follows: heart failure; obesity (BMI ≥ 30); age >75 years; history of VTE; varicose veins in the lower extremities; use of estrogen therapy; use of warfarin; specific disease conditions including diabetes mellitus, neoplasm, and inflammatory bowel disease. The mean number of risk factors per patient was 1.06 for the RA group and 1.79 for the OA group, indicating a significantly higher VTE risk in the OA group than in the RA group.

As blood rheological properties are closely related to venous circulation and potentially affect susceptibility to VTE, preoperative levels of hemoglobin and hematocrit were measured. The mean values of hemoglobin and hematocrit were, respectively, 12.3 g/dl and 35.3% in the OA group and 11.3 g/dl and 32.5% in the RA group. There was no statistically difference between the two groups (Table 1).

Regarding preoperative oral administration of NSAIDs, in the RA group, 131 patients used NSAIDs daily, 24 patients used them on demand, and 44 patients did not use NSAIDs. In contrast, in the OA group, 9 patients used NSAIDs daily, 44 patients used them on demand, and 103 patients did not use NSAIDs. Anti-tumor necrosis factor (TNF) inhibitors were administered to 16 patients in the RA group (etanercept, $n = 4$; infliximab, $n = 12$) and no patients in the OA group.

As patient age, BMI, frequency of NSAID use, and number of risk factors at the time of TKA differed significantly between the RA and OA groups (Table 1), patients taking NSAIDs and those ≤65 years of age were excluded from each group, and statistical analyses were performed again. These exclusions were made because the use of NSAIDs and patient age reportedly affect the incidence of VTE.[16] Demographic data for the two groups after these adjustments were made are shown in Table 2.

The study was approved by the institutional human subjective research committee, and informed consent was obtained from all patients participating in the study.

Antithrombotic protocol

Serum D-dimer levels were measured on postoperative days (PODs) 0, 1, and 7. When patients displayed a D-dimer level of ≥10 μg/ml on POD 1, low-dose unfractionated heparin (LDUH) (5000 units) was given subcutaneously three times a day from POD 2 to POD 8. An equivalent dose of LDUH was given to high-risk patients with either a history of previous VTE or three or more risk factors.

Doppler ultrasonography (DUS) was routinely performed in all patients preoperatively and on POD 7 for diagnosing DVT. Warfarin was administered orally to patients with DUS-confirmed DVT, starting on POD 7 and continuing for 3 months. Patients were followed for symptomatic VTE until ≥3 months after TKA.

Bleeding complications were recorded as described previously.[17] They were classified as "major" if clinically overt (clinically apparent bleeding or signs and/or symptoms suggestive of bleeding with confirmatory imaging studies such as ultrasonography or computed tomography) and meeting one or more of the following criteria: involvement of a critical site (intracranial, retroperitoneal, intraspinal, intraarticular, gastrointestinal, pericardial); bleeding index ≥2.0 (calculated as the baseline hemoglobin level, in grams/liter, minus the hemoglobin level at the end of treatment plus the number of units of packed red blood cells or whole blood transfused); need for medical or surgical intervention; fatal bleeding.

Table 1. Demographic characteristics of patients with RA and OA

Characteristic	RA	OA
No. of knees	238	169
No. of patients	199	156
Age (years) (range)*	59.9 (25–84)	74.2 (40–88)
Sex (no. of patients/knees)		
Male	20/17	17/16
Female	218/182	152/140
BMI (range)*	21.8 (14.0–33.9)	25.0 (16.2–33.3)
No. of knees, by no. of risk factors		
0	114	35
1	57	44
2	18	44
3	38	24
4	9	12
5	2	10
Mean*	1.06	1.79
Medications (no. of knees/patients)		
NSAIDs		
None*	47/44	112/103
On demand	32/24	48/44
Daily*	159/131	9/9
Oral steroid*	82/70	0/0
Anti-TNF inhibitor*	18/16	0/0
Preoperative levels of blood rheological parameters[a]		
Hemoglobin (g/dl)	11.3 ± 1.8	12.3 ± 1.5
Hematocrit (%)	32.5 ± 4.6	35.3 ± 3.4
CRP level (mg/dl)[a]		
Preoperative*	1.27 ± 1.87	0.34 ± 0.88
Postoperative day 1	4.83 ± 2.73	4.54 ± 2.84

RA, rheumatoid arthritis; OA, osteoarthritis; BMI, body mass index; NSAIDs, nonsteroidal antiinflammatory drugs; TNF, tumor necrosis factor

* $P < 0.05$, RA vs. OA

[a] Values are expressed as the mean ± SD

Table 2. Demographic characteristics of patients matched for age and NSAIDs non-use

Characteristic	RA	OA
No. of knees	42	102
No. of patients	39	95
Age (years), mean (range)	75.0 (65–84)	75.7 (65–88)
Sex (no. of knees/patients)		
Male	5/4	12/12
Female	37/35	90/83
BMI (range)	23.4 (18.8–29.4)	24.8 (16.8–33.3)
No. of knees, by no. of risk factors		
0	7	14
1	15	30
2	4	35
3	15	13
4	1	7
5	0	4
Mean	1.71	1.82
Medications (no. of knees/patients)		
Oral steroid*	8/6	0/0
Anti-TNF inhibitor	2/2	0/0
CRP level (mg/dl)[a]		
Preoperative	0.39 ± 0.74	0.28 ± 0.45
Postoperative day 1	4.99 ± 2.78	4.78 ± 1.83

* $P < 0.05$, RA vs. OA

[a] Values are expressed as the mean ± SD

Statistical analysis

The RA and OA groups with and without adjustment for age and NSAID use were compared for the following: age; BMI; rate of NSAID use; incidence of DUS-confirmed asymptomatic DVT; incidence of symptomatic DVT or PE; incidence of bleeding complications; rate of LDUH use; and serum D-dimer levels on PODs 0, 1, and 7. Statistical analyses were performed using Student's *t*-test for continuous variables and a χ^2 contingency table for dichotomous values. $P < 0.05$ was considered statistically significant.

Results

Time course of changes in serum D-dimer levels

Serum levels of D-dimer on PODs 0, 1, and 7 were, respectively, 4.6 ± 0.51, 37.2 ± 2.6, and 11.2 ± 0.46 μg/ml for RA and 1.8 ± 0.41, 42.3 ± 5.5, and 13.6 ± 1.2 μg/ml for OA (Fig. 1). Serum D-dimer levels were thus significantly higher in the RA group than in the OA group preoperatively ($P < 0.05$), whereas similar time courses of D-dimer levels were seen for the two groups postoperatively, although tending to be slightly higher in the OA group than in the RA group.

Incidence of VTE

Preoperatively, DUS-confirmed DVT was found in 21 patients (8.8%) in the RA group and 19 patients (11.2%) in the OA group, with no significant difference between groups (Table 3). On POD 7, the incidence of DUS-confirmed DVT was 20.6% in the RA group and 43.2% in the OA group, indicating more frequent DVT in the presence of OA than in RA ($P < 0.001$). Proximal DVT was identified in eight RA patients (3.3%) and seven OA patients (4.1%), showing no significant difference. All patients were available for follow-up for ≥3 months after TKA and were checked for development of symptomatic VTE. During the first 3 months after TKA, symptomatic PE was found in two patients in the OA group and one patient in the RA group, and symptomatic DVT was found in two patients in the RA group and one patient in the OA group, including one case of postdischarge DVT in each group.

According to the existing literature dealing with comparative analysis of DVT risk between RA and OA, the incidence of DVT has been considered low for RA patients potentially because of the frequent administration of NSAIDs and younger age distribution among patients with RA.[16] Patients using NSAIDs or who were

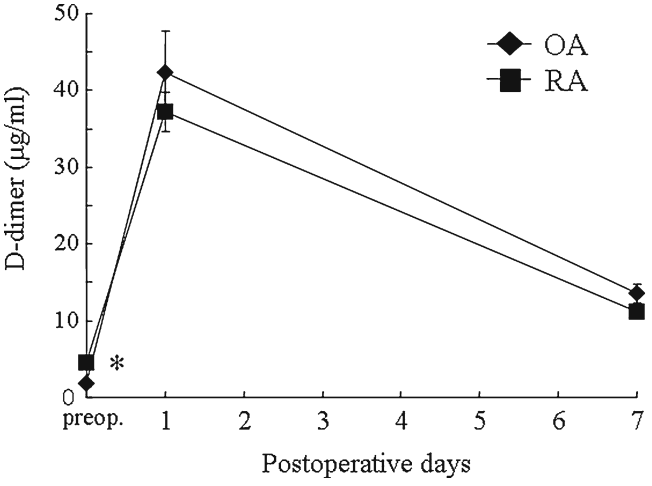

Fig. 1. Time course of plasma D-dimer levels after total knee arthroplasty. Data are given as the mean ± standard deviation. *Preop*., preoperative. *$P < 0.05$, rheumatoid arthritis (*RA*) vs. osteoarthritis (*OA*)

Table 3. Incidence of VTE and bleeding complications within first 3 months after TKA

Parameter	All patients		Patients matched for age and NSAIDs non-use	
	RA ($n = 238$)	OA ($n = 169$)	RA ($n = 42$)	OA ($n = 102$)
Asymptomatic DVT (no. of knees)				
Preoperative	21 (8.8%)	19 (11.7%)	4 (9.5%)	10 (9.8%)
Postoperative day 7	49 (20.6%)*	73 (43.2%)	16 (38.1%)	43 (42.2%)
Proximal DVT	8 (3.3%)	7 (4.1%)	2 (4.8%)	4 (3.9%)
Symptomatic DVT (no. of knees)				
In-hospital	1	0	0	0
After discharge	1	1	1	1
Symptomatic PE (no. of knees)	1	2	0	1
LDUH use (%)	67.7	72.5	78.6	72.5
Major bleeding (no. of knees)	1	2	0	1

VTE, venous thromboembolism; TKA, total knee arthroplasty; DVT, deep vein thrombosis; PE, pulmonary embolism; LDUH, low-dose unfractionated heparin

* $P < 0.001$, RA vs. OA

≤65 years of age were therefore excluded from each group to adjust the patient demographics between groups and elucidate the precise effects of the chronic inflammation of RA on the development of VTE. After this adjustment, no significant differences were identified between the RA and OA groups regarding age, sex, BMI, or number of preexisting risk factors for VTE (Table 2).

Interestingly, the incidence of DVT was 38.1% for RA and 42.2% for OA after the adjustments, suggesting that the incidence of DVT was quite similar in the two groups; thus, RA itself does not appear to represent a predisposing factor for DVT. In addition, regarding symptomatic VTE, the incidences of PE and DVT were not significantly different (Table 3).

Approximately 70% of patients in our TKA series received LDUH during the postoperative course according to our screening protocol of anticoagulation therapy (Table 3). Major bleeding complications during LDUH administration were seen in two patients with OA (gastrointestinal bleeding, $n = 1$; surgical site bleeding, $n = 1$) and one patient with RA (gastrointestinal bleeding).

Discussion

As total joint arthroplasties, such as TKA and THA, are becoming promising surgical interventions for treating joint destruction associated with RA and related inflammatory arthropathies, important issues facing the patients undergoing total joint arthroplasty are increasingly highlighted, including postoperative VTE. TKA and THA have been defined as carrying the highest thromboembolic risks according to accumulated evidence, such as the finding that the incidence of DVT after joint arthroplasty can reach 50%, and fatal PE occurs in 1%–6% without thromboprophylaxis.[18] These data have been derived predominantly from patients with OA, however, and the precise thromboembolic risk in patients with RA remains poorly understood.

To date, certain studies dealing with postoperative VTE risk in patients with RA have documented that the incidence of DVT is 3–10 times lower in patients with RA than in patients with OA.[14,15] Another retrospective study of the incidence of postdischarge VTE after joint arthroplasty reported that only 1 of 103 patients with RA developed symptomatic DVT during a 1-year follow-up.[16] These studies reached the identical conclusion that the decreased incidence of symptomatic VTE in patients with RA was attributable to frequent use of NSAIDs with the resulting antiplatelet activity. However, those studies appear to include the following drawbacks: (1) the studies were not prospective investigations; (2) the studies focused only on symptomatic VTE and did not include asymptomatic VTE; and (3) the precise effects of the chronic inflammation in RA on developing VTE were not clarified, as most RA patients used NSAIDs preoperatively. The present study therefore prospectively investigated the incidence of both symptomatic and asymptomatic DVT in patients with RA undergoing TKA, with particular emphasis on comparison between patients with RA and OA, none of whom were using NSAIDs.

According to the results from all patients enrolled, patients with RA displayed significantly higher D-dimer levels preoperatively, reflecting accelerated fibrin formation and fibrinolysis in the preoperative phase due to constitutive inflammation. Conversely, postoperative D-dimer levels were not significantly different between patients with RA and OA. As expected, the incidence of DUS-confirmed DVT on POD 7 in patients with OA was double that in patients with RA, potentially because in our RA series approximately 78% of patients were orally administered NSAIDs both pre- to postoperatively. Interestingly, when patients taking NSAIDs or ≤65-years-old were excluded, the incidence of DUS-confirmed DVT was comparable between the RA and OA groups. Whether chronic inflammatory diseases such as RA are associated with the development of VTE after joint arthroplasty thus remains controversial.

Historically, inflammation has had little to do with the coagulation response; and a traditional view was that the blood coagulation pathway is simply triggered when tissue factor derived from the cell surface of leukocytes, particularly monocytes, comes in contact with factor VII/VIIa in the blood.[19,20] During the 1990s, however, the picture changed in light of new observations that inflammatory mediators such as endotoxin, tumor necrosis factor-α (TNF-α), and CD40 ligand play crucial roles in the activation of tissue factor.[21–23] Recent studies support an inflammatory basis for the blood coagulation process,[24] and chronic inflammatory conditions may shift the hemostatic balance to favor the activation of coagulation, as has been documented clinically in inflammatory bowel diseases including ulcerative colitis and Crohn's disease.[6,7] Although the best known scenario of inflammation-induced hypercoagulation is the induction of tissue factor, other possible mechanisms can be considered, including impairment of the protein C anticoagulant pathway by down-regulating the expression of thrombomodulin and endothelial cell protein C receptor on endothelial cells,[25,26] and up-regulating levels of plasminogen activator inhibitor (PAI)-1 and subsequent impaired ability to remove thrombus (i.e., fibrinolysis).[27] Mounting evidence has proven elevated levels of TNF-α and PAI-1 in patients with RA,[28,29] and these patients are prone to thrombotic complications after joint arthroplasty. However, according to the

present study, the incidence of VTE after TKA is basically equivalent between RA and OA patients despite the standardization of risk factors for VTE in the two groups. At present, we believe that these unexpected results can be explained by the fact that (1) the inflammation of RA can be tightly controlled using anti-TNF inhibitors and (2) the pre- and postoperative C-reactive protein (CRP) levels of the RA patients were regulated to levels similar to those in OA patients (Tables 1, 2).

As hemoglobin and hematocrit levels tend to be low in patients with RA, blood rheology should not be overlooked in regard to DVT pathogenesis when considering DVT risk in RA patients. However, whether blood rheology affects a patient's susceptibility to postoperative DVT remains unclear despite the close relation between blood rheological properties and venous circulation. Hemoglobin and hematocrit levels do not appear to have been defined as risk factors for DVT in previous studies.[30,31] The present study, however, could not disregard the influence of these two parameters, as values tended to be lower in RA patients than in OA patients and could not be matched during comparisons of RA and OA. Whether blood rheology represents an alternative etiology for DVT is a potential subject for future studies.

In our TKA series, the overall incidence of DUS-confirmed DVT was 20.6% in the RA group and 43.2% in the OA group, indicating a much lower incidence of postoperative DVT in RA patients. A recent study showed that the incidence of symptomatic VTE in patients with RA undergoing joint arthroplasty was low owing to daily administration of NSAIDs,[16] supporting the present findings. Even though lower DVT risk in RA was attributable to younger age and higher frequency of NSAID usage at the time of TKA — rather than to the disease itself — surgeons should pay close attention to the prophylactic use of anticoagulant therapies for thromboembolic events after TKA in patients with RA.

Finally, our findings must take into consideration three major limitations of this study. First, a multiple regression analysis should have been used to analyze the effects of all independent variables as potential risk factors for VTE. However, in our cohort, LDUH was administered only to the patients with increased risk of VTE based on assessments of their preoperative risk score or their D-dimer level, which created a bias regarding the indication for anticoagulant therapy after TKA in our cohort. As use of anticoagulant therapy is considered to be the most critical factor influencing the incidence of VTE, it is worthless to analyze risk factors of VTE in this cohort. In fact, when a stepwise multiple linear regression analysis was performed in this cohort, use of LDUH was paradoxically defined as a significant risk factor of VTE with the largest odds ratio because LDUH was used in the patients with a high VTE score.

Second, the precise effects of NSAIDs on the incidence of VTE following TKA remain unclear as the present study did not directly confirm whether the reduced incidence of VTE in RA patients was attributed to frequent administration of NSAIDs or the disease itself. The patients should be randomized to use of NSAIDs preoperatively in both RA and OA cohorts, which is a potential subject for future study.

Third, because one investigative group reported that oral steroid use is one of the risk factors for postoperative VTE,[32] we should have elucidated whether steroid use affected the incidence of VTE in our cohort. However, the type, dosage, and duration of steroid use varied considerably from case to case; and the net steroid usage could not be explained by daily steroid dosage at the time of examination. Further studies, including a randomized controlled trial, on the use of NSAIDs or steroid in larger cohorts of RA patients are needed so we can better understand the true magnitude of VTE risk following TKA in patients with RA.

The authors did not receive and will not receive any benefits or funding from any commercial party related directly or indirectly to the subject of this article.

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