

Prediction of Venous Thromboembolism after Total Knee Arthroplasty Using Blood Coagulation-Fibrinolysis Markers: A Systematic Review

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leukocyte elastase released from activated leukocytes, e-XDP, was significantly elevated in patients with venous thromboembolism and noted that the sensitivity and specificity, both 75%, might be clinically important for a cutoff value of 8.2U/mL.

CONCLUSION: D-dimer and e-XDP levels are significantly elevated in patients with venous thromboembolism after total knee arthroplasty. However, their clinical importance remains low.

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Key words: Venous thromboembolism; Knee arthroplasty, total; Blood coagulation-fibrinolysis marker; Multidetector computed tomography

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ABSTRACT

AIM: To account for changes in blood coagulation-fibrinolysis using blood markers after total knee arthroplasty with and without venous thromboembolism, and to determine the etiology of postoperative venous thromboembolism after total knee arthroplasty.

MATERIALS AND METHODS: A systematic literature search was conducted during November and December 2014. The electronic databases searched were PubMed, MEDLINE®, and Cochrane Library. English only and no data restriction were used. The search keywords were total knee arthroplasty AND venous thromboembolism, deep vein thrombosis, pulmonary embolism AND D-dimer, SFMC, PAI-1 appearing in the title, abstract, or keyword fields. Eight articles were identified, and the full texts of these articles were read and analyzed for validity in blood coagulation-fibrinolysis markers with vs. without venous thromboembolism after total knee arthroplasty.

RESULTS: Only D-dimer level has been a useful blood coagulation-fibrinolysis marker in the detection of venous thromboembolism after total knee arthroplasty since the 1990s. However, the D-dimer cutoff value varies from 3 to 10µg/mL and sensitivity and specificity vary from 68% to 54.5% and from 94.4% to 90%, respectively. A recent study reported that the level of fibrin degradation products of

INTRODUCTION

Venous thromboembolism (VTE) is a common complication after total knee arthroplasty (TKA). It is important to identify postoperative VTE, particularly fatal pulmonary embolism (PE) and symptomatic PE, which can threaten the lives of patients. Antithrombotic drugs are administered to reduce the postoperative risk of VTE, but the incidences of fatal and symptomatic PE have remained at 0.15% and 0.41%^[1,2], respectively. In fact, some reports have found no difference in the incidences of fatal and symptomatic PE since the 1990s^[1,2].

It is not known how postoperative blood coagulation-fibrinolysis, a cause of VTE, can be changed, and only a few reports are concerned with changes after surgery, particularly orthopedic surgery. Here we review and account for changes in blood coagulation-fibrinolysis using blood markers after TKA with and without VTE and attempt to determine the reasons for development of VTE after TKA.

METHODS

We applied the patient, intervention, comparison, outcome (PICO) process to develop our study topic before conducting a systematic review. Patients were those who had undergone TKA and developed VTE, intervention was TKA, comparison was patients with and without VTE after TKA, and outcome was change in blood coagulation-fibrinolysis markers [D-dimer, soluble fibrin monomer complex (SFMC), and plasminogen activator inhibitor type 1 (PAI-1)]. A systematic literature search was conducted during November and December 2014. The electronic databases searched were PubMed, MEDLINE®, and the Cochrane Library. English only and no data restriction were used. The search terms were TKA AND VTE, deep vein thrombosis (DVT), PE AND D-dimer, SFMC, PAI-1 appearing in the title, abstract, or keyword fields. The search identified 132 articles. Two reviewers selected the articles. Removal of duplicates left 59 articles, of which eight remained after removal of unrelated articles. The full texts of these articles were available and were analyzed for validity of blood coagulation-fibrinolysis markers in patients with VTE vs. without VTE after TKA.

RESULTS

Study data, including author; country and year in which study was conducted; number, disorder(s) (OA, osteoarthritis, and RA, rheumatoid arthritis), and mean age of participants; and administration of prophylactic antithrombotic therapy, are presented in Table 1.

Post-TKA blood coagulation-fibrinolysis sample data are presented in Table 2. Patients were assessed for DVT (deep vein thrombosis) or VTE (venous thromboembolism) using ascending venography or MDCT (multidetector-row computed tomography) and the level of blood-coagulation-fibrinolysis markers D-dimer, fibrin monomer, and fibrin degradation products of leukocyte elastase released from activated leukocytes, e-XDP.

VTE after TKA was assessed by the presence of DVT using ascending venography in the 1990s and early 2000s. The high sensitivity and specificity of multidetector-row computed tomography (MDCT) in the detection of both DVT and PE make it valuable in the assessment of VTE after TKA¹³⁻⁵¹. Furthermore, various blood coagulation-fibrinolysis markers were investigated in the 2000s. D-dimer level has been a useful blood coagulation-fibrinolysis marker in the detection of VTE after TKA since the 1990s; however, the cutoff value for D-dimer level varies from 3 to 10 µg/mL, and sensitivity (68–54%) and specificity (94.4–90%) are also widely variable. It was recently reported that the level of fibrin degradation products of leukocyte elastase released from activated leukocytes (e-XDP) was significantly elevated in patients with VTE and that the sensitivity (75%) and specificity (75%) might be clinically important for a cutoff of 8.2U/mL.

DISCUSSION

Blood Coagulation-Fibrinolysis Markers Predicting VTE after TKA: 1994–2008

Thrombus, which contains fibrin, is formed by thrombin. Thrombin should be measured if the thrombus has formed, but thrombin cannot be measured to be degraded promptly. Therefore, the blood coagulation marker, SFMC, can be measured instead of thrombin. Similarly, plasmin is needed to degrade fibrin, but plasmin also cannot be measured to be degraded promptly. A marker of blood fibrinolysis, D-dimer, is measured instead of plasmin.

In clinical practice, contrast-enhanced computed tomography (CT) would be performed in a patient with VTE symptoms, such as dyspnea or lower-extremity edema. In clinical study of postoperative TKA, CT has been performed in a patient without VTE symptoms. When CT reveals a thrombus in deep vein or pulmonary artery and blood coagulation markers are elevated, VTE, or active thrombus, can be diagnosed. However, when CT reveals a thrombus in deep

Table 1 Study Data for Blood Coagulation-Fibrinolysis after Total Knee Arthroplasty.

Author	Country	Year	Number of Participants	Disorder	Mean Age (Years)	Prophylactic Antithrombotic Therapy
Dunn et al.	United Kingdom	1994	90 [†]	Not described	Not described	None
Bounameaux et al.	Switzerland	1998	130	Not described	Not described	Administered
Reber et al.	Switzerland	2000	130	Not described	Not described	Administered
Shiota et al.	Japan	2002	28	OA and RA	68.1	None
Chen et al.	Taiwan	2008	78	Not described	67	None
Yoshitaka et al.	Japan	2008	100	OA and RA	71	None
Kim et al.	Korea	2011	297	OA	68	Not described
Watanabe et al.	Japan	2011	68	OA and mild RA	71	None

[†] Includes total hip arthroplasty.

Table 2 Sample Data for Blood Coagulation-Fibrinolysis after Total Knee Arthroplasty.

Authors	Venous Thromboembolism		Postoperative Day of Assessment	Blood Coagulation Marker				
	Assessment	Apparatus		Sample	Postoperative Day of Sampling	Cutoff value	Sensitivity (%)	Specificity (%)
Dunn et al.	DVT	Ascending venography	5–7	D-dimer	1 3 6	Not found	Not found	Not found
Bounameaux et al.	DVT	Ascending venography	8–12	D-dimer	3	3 µg/mL	73.5	58.8
Reber et al.	DVT	Ascending venography	8–12	Fibrin monomer	3 6	Not found	Not found	Not found
Shiota et al.	DVT	Ascending venography	10–18	D-dimer	7	10 µg/mL	94.4	90
Chen et al.	DVT	Ascending venography	7–10	D-dimer	7	> 2 µg/mL	68	55
Yoshitaka et al.	VTE	MDCT	> 15 µg/mL on day 5	D-dimer	3	4.55 µg/mL 7.25 µg/mL	85.7 83.3	54.5 55.6
Kim et al.	DVT	Doppler sonography		D-dimer	6	Not found	Not found	Not found
Watanabe et al.	VTE	MDCT	6	D-dimer	4	7.5 µg/mL	75	63
			4	e-XDP	1	8.2 U/mL	75	59

vein or pulmonary artery and no blood coagulation markers are elevated, VTE cannot be diagnosed, as it may still be undeveloped^[6]. This is known as inactive thrombus. In clinical practice, it is therefore difficult to distinguish between active and inactive thrombus with CT only; blood coagulation-fibrinolysis markers must be measured for diagnosis. However, these markers can also become elevated by surgery itself, making differentiation between active and inactive thrombus the most difficult at that time. This is the reason that prediction of VTE, particularly after surgery, has been investigated by only a few authors.

The first study identifying blood coagulation-fibrinolysis markers predicting postoperative VTE after TKA was published in 1994 by Dunn *et al*^[7], who found that D-dimer level is significantly elevated on days 1, 3, 6 in patients with DVT, but cutoff value and sensitivity and specificity were not investigated. In 1998, Bounameaux *et al*^[8] found that D-dimer level was significantly elevated in patients with DVT on day 3 after TKA. Thereafter, other studies were published by Reber *et al*^[9] in 2000, Shiota *et al*^[10] in 2002, and Chen *et al*^[11] in 2008. The timing of elevations and cutoff values of markers, along with sensitivities and specificities, are shown in table 2. Shiota *et al*^[10] found that D-dimer level was significantly elevated in patients with DVT on day 7 after TKA, but the cutoff value varied and not clinically important. Reber *et al*^[9] reported that the SFMC level was significantly elevated in patients with DVT on days 3 and 6 after TKA, but there was no clinically important cutoff value. In the past, there were no blood coagulation-fibrinolysis markers for predicting postoperative VTE after TKA using ascending venography.

Present State of Blood Coagulation-Fibrinolysis Markers Predicting VTE after TKA

In 2008, Yoshitaka *et al*^[12] were the first to investigate VTE after TKA using MDCT. Their findings are presented in table 2. However, they investigated only patients in whom the D-dimer level was more than 15µg/mL on day 5 after TKA. Kim *et al*^[13] were the first to investigate DVT using Doppler sonography, but they did not investigate PE. Watanabe *et al*^[14] reported that e-XDP level on day 1 and D-dimer level on day 4 after TKA were significantly elevated in patients with VTE and noted that the sensitivities and specificities for e-XDP^[9] and D-dimer levels might be clinically important (Table 2). e-XDP is the fibrin degradation product of leukocyte elastase released from activated leukocytes. We believe it may be possible to predict postoperative VTE after TKA using both e-XDP and D-dimer levels, and we consider leukocytes to be associated with the development of VTE early after TKA. However, thus far e-XDP level has not been investigated; multicenter studies will be required to determine whether e-XDP level is useful as an early predictor of VTE.

Future use of blood coagulation-fibrinolysis markers after TKA

In 2014, Watanabe *et al*^[15] reported that PAI-1^[16] level 90 s after release of the pneumatic tourniquet during TKA was significantly elevated in patients with VTE. PAI-1 inhibits plasminogen activator and leads to production of fibrin or thrombus. We believe inactivated fibrinolysis due to PAI-1 may lead to VTE after TKA. In fact, early after TKA, the fibrinolysis is inactivated by PAI-1 and thrombus is formed. And thrombus degraded by leukocyte elastase released from activated leukocytes, which we believe this leukocyte elastase released from activated leukocytes may lead to the development of fatal and symptomatic PE. In the future, we hope to be able to predict the development of VTE and to understand the mechanism of development of symptomatic and fatal PE through changes in blood coagulation-fibrinolysis.

CONCLUSIONS

D-dimer and e-XDP levels are significantly elevated in patients with VTE after TKA. However, their clinical importance considered low. Fibrinolysis should be further investigated.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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