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Evaluation of soluble fibrin and D-dimer in the diagnosis of postoperative deep vein thrombosis

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Abstract
Soluble fibrin (SF) and D-dimer are useful for making the diagnosis of deep vein thrombosis (DVT). However, the evidence for using such markers and optimal timing to diagnose postoperative DVT are unclear. We evaluate the usefulness of SF and D-dimer testing for the diagnosis of postoperative DVT. A total of 207 patients who had total hip arthroplasty or knee arthroplasty were evaluated. SF and D-dimer were tested on postoperative days 1 and 7. DVT was confirmed with ultrasonography. SF level on postoperative day 1 was the most useful, although D-dimer evaluation on postoperative days 1 and 7 was also useful. Using a SF cut-off of more than 4.00 μg ml^{-1}, the sensitivity was 90%, the specificity was 33%. Although the SF and D-dimer tests cannot be used as stand-alone tests, SF and D-dimer are valuable screening tools. We recommend two-stage screening including first with the SF or D-dimer test, followed by ultrasonography or venography.

Keywords: *D-dimer; deep vein thrombosis; postoperative condition; screening; soluble fibrin*

Introduction

Venous thromboembolism (VTE) is a common and serious complication after surgery, especially after total hip arthroplasty (THA) or total knee arthroplasty (TKA), and it is a leading cause of morbidity and mortality during the postoperative recovery period (Douketis et al. 1997, Geerts et al. 2001, Stringer et al. 1989). Without prophylaxis after THA and TKA, the overall incidence of DVT is 40–70% (Geerts et al. 2001) and 40–84% (Geerts et al. 2001, Stringer et al. 1989, Rabinov & Paulin 1972), respectively. Physical immobility and blood hypercoagulability are important factors related to the development of postoperative deep vein thrombosis (DVT). The clinical signs and symptoms of DVT are unreliable, and both venography and ultrasonography remain the 'gold standard' methods, despite their many limitations: venography is invasive, costly and not easily repeatable (Kamikura et al. 2005), while ultrasonography requires skill and manpower. As these methods are time-consuming and expensive, to perform a DVT check on all patients by venography or ultrasonography repeatedly is impossible in institutions where several thousand orthopaedic operations are performed per year. A plasma marker reflecting the presence of DVT would be a very attractive diagnostic tool that would overcome these weak points.

Coagulation and fibrinolysis occur in a complex manner in the blood, and many markers are available for detecting the products of thrombin and plasmin action in patients with thrombotic and fibrinolytic disorders (Suzuki et al. 2007). Of these markers, soluble fibrin (SF) reflects thrombin activation and the cleavage of fibrinogen in the early stage of disease, and it is used as an indicator of coagulation (Soe et al. 1996, Wada et al. 2006, Ota et al. 2005); SF detection could be a useful tool for diagnosing thrombotic diseases (Bounameaux et al. 1991). On the other hand, D-dimer is a specific

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degradation product of plasmin-cleaved, cross-linked fibrin. Therefore, it is considered to be a sensitive indicator of coagulation activation or secondary fibrinolysis, and it has been shown to be helpful in the diagnosis of DVT (Tan et al. 2009, Michiels et al. 2006, Rectenwald et al. 2005, Ota et al. 2005, Friera-Reyes et al. 2005, Ginsberg et al. 1998, Kearon et al. 2006, Kelly et al. 2002, Stein et al. 2004, Wells et al. 2001, 2003, Wijns et al. 1998, Bounameaux et al. 1994).

Several studies on D-dimer have indicated that the D-dimer assay could be used as a simple, inexpensive, screening test for VTE. Bounameaux et al. 1994. showed that the plasma D-dimer level has an overall diagnostic sensitivity of 97% and a specificity of 47% in various patient populations suspected of having DVT who were referred for venography (Bounameaux et al. 1994). However, the roles of the SF and D-dimer assays with respect to DVT screening in postoperative patients remain controversial, because the diagnostic SF and D-dimer levels are affected by many variables (primary disease, thrombus size, anticoagulant therapy and timing).

Recently, we reported the usefulness of SF and D-dimer tests after orthopaedic surgery by examination of 99 patients. In this report, we have increased the investigated number of patients (Sudo et al. 2009). The primary aim of the present study was to compare the diagnostic efficacy of the SF and D-dimer assays used as a screening test to detect postoperative DVT in patients undergoing THA and TKA. The secondary aim was to determine the optimal timing for the evaluation of SF and D-dimer levels for the diagnosis of DVT.

Materials and methods

Patients

From April 2003 to December 2007, 207 patients undergoing THA or TKA at Mie University Hospital were eligible for the study ($n = 207$: THA $n = 145$, TKA $n = 62$). In this study, we excluded patients with DVT before surgery ($n = 40$: THA $n = 24$, TKA $n = 16$). The operative diagnosis was degenerative osteoarthritis in 161 patients (THA $n = 112$, TKA $n = 49$), rheumatoid arthritis in 20 patients (THA $n = 9$, TKA $n = 11$), failure of a previous implant in 23 patients (THA $n = 21$, TKA $n = 2$) and 'other' in three patients (THA $n = 3$). None of the patients received anticoagulant therapy. The patients' sex, height, weight, body mass index (BMI, weight in kilograms divided by the square of the height in meters), operation time, blood loss during surgery and blood loss during drainage were recorded. The institutional review boards approved the study protocol, and written informed consent was obtained from all participants.

Study design

The study was designed as a prospective management trial with 7-day follow-up. All patients underwent ultrasonography, and SF and D-dimer assays before surgery. Postoperative ultrasonography was performed 4 days after surgery in consideration of the rehabilitation schedule by very skilled physicians who were blinded to the SF and D-dimer results. The popliteal and calf vein were examined in the sitting position and to perform ultrasonography in the sitting position just after the surgery was difficult. Therefore we performed ultrasonography 4 days after surgery. Postoperative SF and D-dimer measurements were performed on postoperative days 1 and 7.

Diagnosis of VTE

B-mode ultrasonography with compression and colour Doppler imaging were performed for bilateral common femoral veins, the superficial veins, the popliteal veins and the calf veins. Augmentation by calf squeezing or Valsalva's manoeuvre were included as needed. The criteria for the diagnosis of DVT were: loss of compressibility of the vein; presence of intraluminal echogenicity; and absence of venous flow using an Aplio (Toshiba Medical Systems Corp., Tokyo, Japan) sonographic scanner with a linear transducer (frequency 6 MHz).

DVT was classified as proximal if the thrombus involved the iliac, femoral or popliteal veins, and distal if the thrombus was limited to the calf veins. Patients with a proximal DVT proceeded to a pulmonary thromboembolism (PTE) survey. PTE was confirmed by helical computer tomography (CT) scan, pulmonary angiogram or ventilation–perfusion lung scan.

Laboratory studies

Citrated blood samples were taken from each patient the day before the operation and on postoperative days 1 and 7 between 06:00 a.m. and 07:30 a.m., before and after venous occlusion, in order to evaluate plasma SF and D-dimer levels. Citrated blood samples were centrifuged for 20 min at 1500***g***. The supernatants (plasma) were analysed within 4 h. Plasma SF and D-dimer levels were measured.

Measurement of plasma SF and D-dimer levels

SF was measured using the latex agglutination method (IATRO SF; Mitsubishi Kagaku Iatron Inc., Tokyo, Japan), which is based on monoclonal antibody (mAb) IF-43. mAb IF-43 recognizes a segment of the fibrin Aα chain (Aα17–78 residue segment) exposed in the E region of the fibrin monomer (FM) when the FM molecule binds

the D region of another fibrin monomer or fibrinogen. The antibody is coated for the SF assay. The normal range is <7.0 μg ml^{-1}. Plasma D-dimer levels were also measured using LPIA-ACE D-dimer (Mitsubishi Kagaku Iatron Inc.) with JIF23 mAb. The JIF23 mAb, which recognizes the plasmin-digested N-terminus of the γ-chain on the D region, was used for latex agglutination. The normal range is <1.0 μg ml^{-1}.

Statistical analysis

We compared the patients' baseline characteristics using the Mann–Whitney *U*-test and the χ^2 test. Because their distributions were skewed, the SF and D-dimer levels were log-transformed for the statistical analysis.

To determine the clinical performance of the SF and D-dimer assays, diagnostic sensitivity, specificity, best-fit value (combination of sensitivity + specificity), positive and negative predictive values, positive likelihood ratio (sensitivity / [1-specificity]) were calculated, and receiver operating characteristic (ROC) curves were constructed. The ROC curves and the area under the curve (AUC) were calculated. Analyses were performed using SAS software, version 9.1 (SAS Institute, Inc., Cary, NC, USA); $p < 0.05$ was considered statistically significant.

Results

Figure 1 shows the study flow diagram and Table 1 shows the patients' general characteristics. The series included 207 patients (32 male, 175 female). DVT tended to occur more commonly in females than in males. The patients' median age (± SD) was 64.0 ± 12.1 years. Age had a clinically relevant effect: patients with DVT were older (67.1 years) than patients without DVT (60.9 years). BMI, operation time, blood loss during surgery and blood loss during drainage did not appear to have a clinically relevant effect.

Postoperative DVT was diagnosed in 104 of 207 patients (50.2%). Of these, 92 patients (44.4%) had distal DVT and 12 patients (5.8%) had proximal DVT. Postoperative PTE was diagnosed in five of 207 patients (2.4%). We consulted cardiology with all PTE patients, and three of five patients did not need special treatment for the PTE because the PTE size was very small. None of the patients developed signs or symptoms of PTE, and there were no deaths from PTE.

Table 2 shows the SF and D-dimer results for DVT. After surgery, the SF level increased both in patients with DVT and in those without DVT, with a significant increase in the SF level on the day after surgery in the DVT group (25.7 vs 12.9 μg ml^{-1}). The SF level increased rapidly after surgery and was high 1 day after surgery. However, the SF level declined to a low level 7 days after surgery (6.6 vs 4.0 μg ml^{-1}) (Figure 1). Therefore, there was no significant difference in the SF levels 7 days after surgery between patients with and without DVT.

The D-dimer level was elevated both in patients with DVT and in those without DVT after surgery. D-dimer levels were significantly higher in patients with DVT than in patients without DVT on postoperative days 1 and 7 (day 1, 17.1 vs 10.8 μg ml^{-1}; day 7, 11.8 vs 8.9 μg ml^{-1}). No significant differences between the operative techniques were found (Table 2).

The ROC curves obtained for various cut-off values of SF on postoperative day 1 confirmed that 4.00 μg ml^{-1} is the most reasonable cut-off value for screening for DVT when using the luminescence immunoassay (LIA) assay, yielding a high sensitivity (90.4%), a fair specificity (33.0%), a positive predictive value of 57.7% and a negative predictive value of 77.3% (Figure 3). On the other hand, on postoperative day 1, for the D-dimer test using the LIA, 4.88 μg ml^{-1} is the most reasonable cut-off value for DVT screening, yielding a sensitivity of 91.4%, a specificity of 28.2%, a positive predictive value of 56.5% and a negative predictive value of 78.4%. With respect to the D-dimer test on postoperative day 7, 5.35 μg ml^{-1} is the most reasonable cut-off value for screening for DVT when using the LIA assay, yielding a sensitivity of 90.4%, a specificity of 23.3%, a positive predictive value of 54.9%, and a negative predictive value of 75.0% (Table 3).

The AUC for the SF was 0.7296 on postoperative day 1, while for D-dimer, the AUC was 0.6834 on postoperative day 1 and 0.6513 on postoperative day 7. There were no significant differences in the SF and D-dimer levels between the operative techniques. The best-fit values (sensitivity + specificity) were: 1.4002 (cut-off value, 7.61 μg ml^{-1}) for SF on postoperative day 1; 1.2654 (cut-off value, 9.78 μg ml^{-1}) for D-dimer on postoperative day 1; and 1.2842 (cut-off value, 8.26 μg ml^{-1}) for D-dimer on postoperative day 7.

Discussion

The present study demonstrates that the patients with DVT had a significantly higher SF on the postoperative day 1 and D-dimer on postoperative days 1 and 7 in Mann–Whitney *U*-tests. The incidence of VTE after THA and TKA continues to be high despite current prophylactic regimens. Fatal PTE is a catastrophic complication, with a reported incidence after THA of from 0.19% to 2.3% (Johnson et al. 1977, Khaw et al. 1993, Salzman & Davies.1980). Prevention of fatal PTE depends on appropriate use of prophylaxis and early detection and treatment of DVT. The traditional 'gold standard' test, venography, is a good test for the detection of DVT, but it is too invasive and expensive to use routinely and repeatedly

Table 1. Patient characteristics.

Characteristic	All patients ($n=207$)	Patients with DVT ($n=104$)	Patients without DVT ($n=103$)	p-Value[a]	Patients after THA ($n=145$)	Patients with DVT after THA ($n=60$)	Patients without DVT after THA ($n=85$)	p-Value[a]	Patients after TKA ($n=62$)	Patients with DVT after TKA ($n=44$)	Patients without DVT after TKA ($n=18$)	p-Value[a]
Age (years), median (range)	64.0 (12.1)	67.1 (9.5)	60.9 (13.6)	0.0005	61.0 (12.3)	64.1 (9.4)	58.9 (13.7)	0.0005	70.9 (8.1)	71.2 (8.1)	70.2 (8.2)	0.4748
Women, n (%)	175 (84.5)	98 (94.2)	77 (74.8%)	0.001	122 (84.1)	57 (95.0)	65 (76.5)	0.0026	53 (85.5)	41 (93.2)	12 (66.7)	0.0071
Body weight (kg), mean (SD)	55.7 (10.8)	55.7 (10.0)	55.8 (11.5)	0.0675	55.3 (11.1)	55.4 (10.8)	55.2 (11.3)	0.691	56.8 (10.0)	56.1 (8.9)	58.7 (12.2)	0.2414
Height (cm), mean (SD)	151.9 (8.6)	150.7 (7.2)	153.0 (9.7)	0.7815	152.8 (9.2)	151.1 (7.7)	150.0 (9.9)	0.0462	149.6 (6.7)	150.1 (6.4)	148.5 (7.2)	0.187
Body mass index (kg m^{-2}), mean (SD)	24.1 (3.8)	24.5 (3.3)	23.7 (4.2)	0.0872	23.6 (3.8)	24.1 (3.3)	23.2 (4.0)	0.0693	25.2 (3.6)	24.9 (3.2)	25.8 (4.5)	0.1514
Operation time (min), mean (SD)	112.3 (40.0)	113.8 (36.8)	110.8 (42.8)	0.1126	106.0 (41.5)	105.3 (40.3)	106.6 (42.5)	0.7480	127.0 (31.7)	125.4 (27.8)	131.1 (38.9)	0.8767
Intraoperative bleeding (g), mean (SD)	336.6 (315.0)	341.4 (368.8)	331.8 (251.0)	0.2366	350.5 (313.5)	357.3 (383.2)	345.7 (255.6)	0.3643	304.1 (40.5)	319.7 (351.4)	266.1 (222.6)	0.9197
Drain bleeding (g), mean (SD)	543.2 (324.6)	552.3 (318.0)	534.1 (332.4)	0.505	561.5 (342.2)	569.6 (359.4)	555.8 (331.5)	0.8946	500.4 (276.9)	528.6 (252.9)	431.5 (326.1)	0.1227
Total bleeding (g), mean (SD)	880.0 (504.9)	893.7 (545.5)	865.8 (462.5)	0.8573	912.0 (528.6)	926.9 (598.3)	901.5 (476.7)	0.592	804.6 (439.4)	848.3 (466.8)	697.6 (352.9)	0.2035

DVT, deep vein thrombosis; THA, total hip arthroplasty; TKA, total knee arthroplasty. [a]Mann–Whitney U-test; χ^2 test.

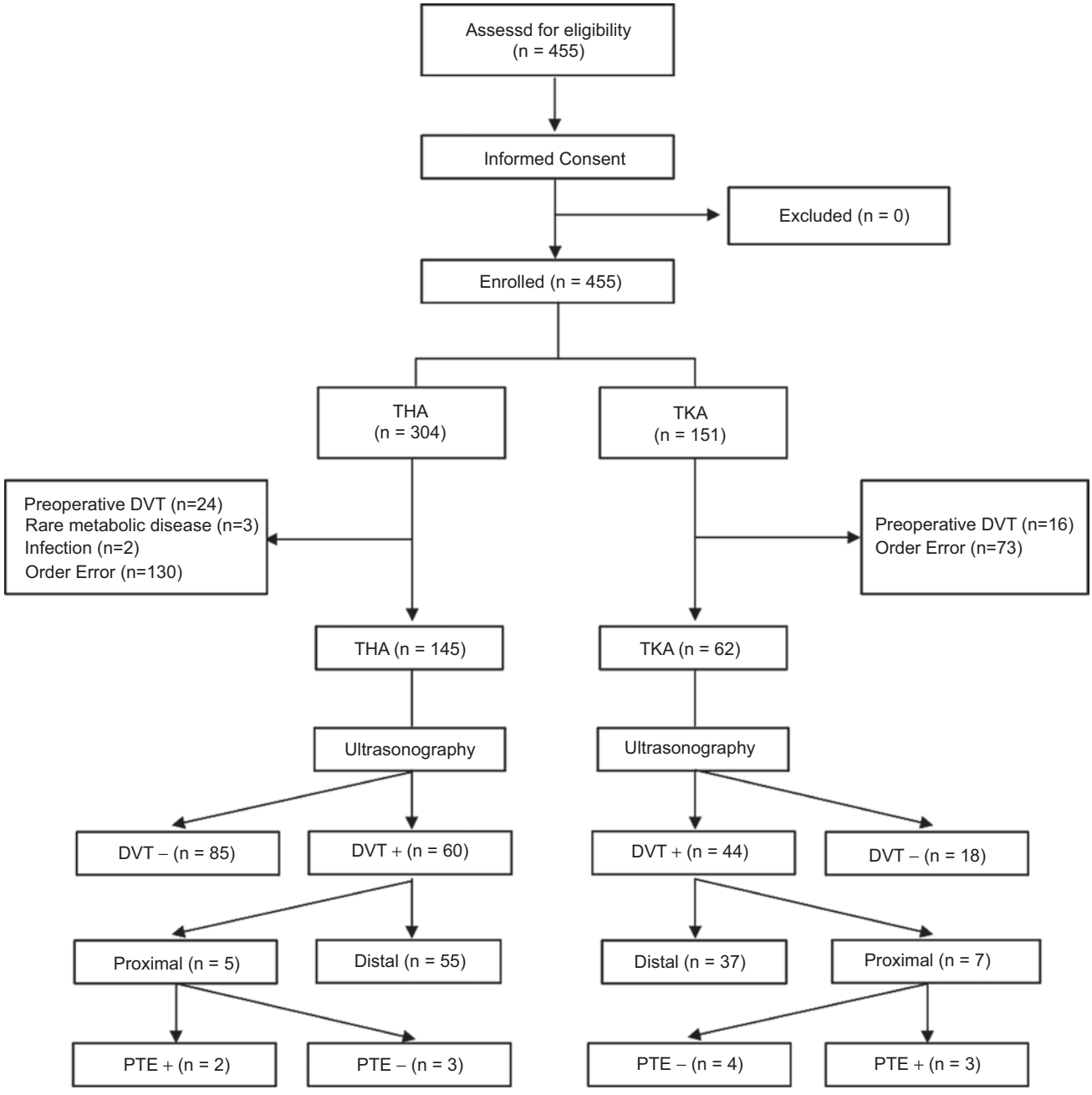

Figure 1. Study flow diagram. THA, total hip arthroplasty; TKA, total knee arthroplasty; DVT, deep vein thrombosis; PTE, thromboembolism.

for screening (Kamikura et al. 2005). Ultrasonography is also a good alternative test that is quite non-invasive compared with venography, but ultrasonography is too complicated for screening to check all operative patients repeatedly because it is too time-consuming. The use of SF and D-dimer testing has the potential to make the screening of DVT more convenient, reproducible everywhere and economical.

The pathogenesis of DVT is multifactorial and only partly understood. Several factors are thought to be involved, such as increased blood coagulability, endothelial damage and impaired fibrinolytic activity (Trotti et al. 1997). Thrombin-catalysed cleavage of fibrinogen yields several species of SF monomer (SFM) (Wada et al. 2006). When they are produced in the presence of an excess of fibrinogen, they form complexes with fibrinogen and exist as soluble monomer complexes (SMC), called SF. Under pathological conditions when blood coagulation is activated and thrombin is eventually generated, SF is known to be present in the circulating blood. Therefore, detection and quantification of SF in plasma derived from patients with thrombotic disease has been expected to provide useful information on the state and degree of intravascular

Table 2. Comparison of patients.

	SF assay (μg ml^{-1})		D-dimer assay (μg ml^{-1})	
	Postoperative day 1	Postoperative day 7	Postoperative day 1	Postoperative day 7
All patients (n = 207)				
Proximal DVT patients (n = 12, 5.3%)	39.6 (25.7)	9.3 (9.6)	12.3 (4.4)	13.0 (6.2)
Distal DVT patients (n = 93, 44.9%)	23.9 (19.3)	6.2 (10.9)	17.7 (11.5)	11.6 (5.9)
DVT absent (n = 103, 49.8%)	12.9 (17.3)	4.0 (3.1)	10.8 (8.8)	8.9 (4.8)
THA patients (n = 145, 70.0%)				
Proximal DVT patients (n = 5, 3.4%)	48.1 (29.4)	14.3 (13.5)	13.2 (3.9)	12.8 (8.8)
Distal DVT patients (n = 55, 37.9%)	25.8 (18.6)	5.6 (6.3)	17.9 (11.2)	11.6 (6.7)
DVT absent (n = 85, 58.6%)	13.3 (18.2)	4.2 (3.2)	11.1 (9.5)	8.8 (4.8)
TKA patients (n = 62, 30.0%)				
Proximal DVT patients (n = 7, 11.3%)	33.6 (23.0)	5.7 (3.3)	11.7 (4.9)	13.1 (4.4)
Distal DVT patients (n = 37, 59.7%)	21.0 (20.3)	7.1 (15.4)	17.5 (12.2)	11.6 (4.6)
DVT absent (n = 18, 29.0%)	11.1 (12.9)	2.8 (1.7)	9.4 (4.6)	9.5 (4.7)

Values are mean (SD). DVT, deep vein thrombosis; SF, souble fibrin; THA, total hip arthroplasty; TKA, total knee arthroplasty.

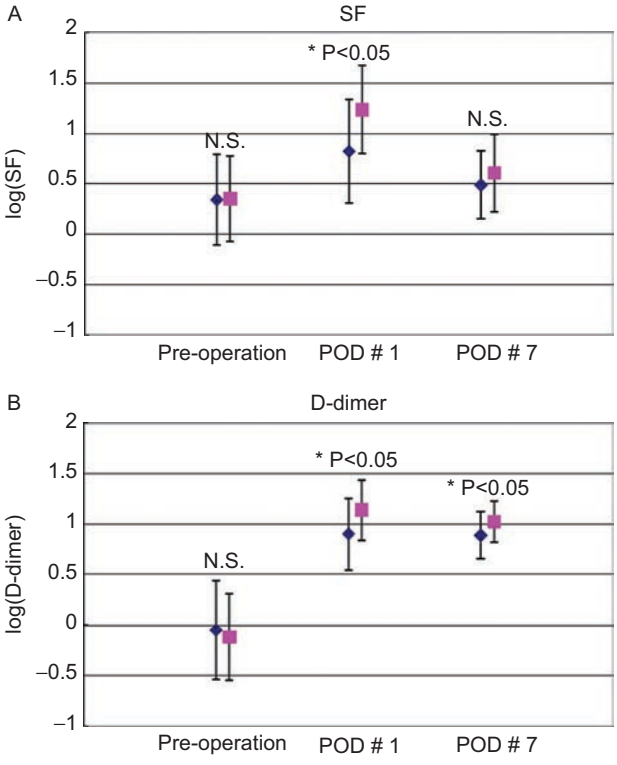

Figure 2. Plasma soluble fibrin (SF) (A) and D-dimer (B) levels. N.S., not significant; POD, postoperative day.

coagulation (Suzuki et al. 2007, Bounameaux et al. 1991, Vogel et al. 1996).

D-dimer is a fibrin-derived fragment that is released into the circulation when cross-linked fibrin is broken down by the fibrinolytic system (Stein et al. 2004, Wells et al. 2003). Elevated D-dimer levels generally can be seen with intravascular activation of the coagulation system (Tan et al. 2009, Michiels et al. 2006, Rectenwald et al. 2005, Kelly et al. 2002, Wells et al. 2001, Le Gal et al. 2006) and secondary fibrinolysis. Although both haemostasis and surgical wound bleeding may lead to fibrin formation and an increase in SF and D-dimer levels, in the present study, there were no correlations between surgical bleeding and the SF and D-dimer levels.

With regard to the difference in clinical significance between the SF and D-dimer levels, SF reflects the early phase of a thrombotic event while D-dimer reflects secondary fibrinolysis after clot formation (Bounameaux et al. 1991). Elevated levels of circulating SFM in plasma indicate that thrombin has converted fibrinogen to fibrin. SF levels elevate rapidly and diminish relatively soon after the onset (Sudo et al. 2009, Ota et al. 2005, Wada et al. 1996) In the present study, SF was elevated from 1 day after surgery. Although there have been no previous detailed reports describing longitudinal changes in SF levels after surgery, judging from the present results, SF evaluation is useful for screening for DVT in the early postoperative period. D-dimer levels have also been reported to be most useful for diagnosis of DVT within 11 days of symptom onset, and they may normalize within 15–20 days (D'Angelo et al. 1996). In other study, D-dimer levels did not normalize within 14 days in severely traumatized patients (Johna et al. 2002). In the present study, SF levels were elevated rapidly, while D-dimer levels were elevated on postoperative day 1 and remained high 7 days after surgery.

The diagnostic capability of these methods was tested using AUC analysis, and the SF assay on postoperative day 1 was the most reliable assay based on the AUC (0.72) and the best-fit values. Thus, SF evaluation for screening should be emphasized, because SF evaluation offers early detection of DVT and has an excellent best-fit value. Thus, treatment and walking exercises can be started early. D-dimer is useful when the onset of DVT is unclear in cases of idiopathic DVT because D-dimer levels remain higher for a longer period than for SF.

Our results confirmed the findings from recent studies that reported persistently elevated D-dimer levels 7

days following major orthopaedic surgery; in contrast SF levels rapidly decreased within a few days after surgery (D'Angelo et al. 1996, Johna et al. 2002, Ota et al. 2005, Sudo et al. 2009, Wada et al. 1996). As orthopaedic surgery is associated with haemostasis and surgical wound bleeding, both of which lead to fibrin formation, both SF and D-dimer may increase without any relationship to DVT. However the patients who developed DVT showed a more marked increase due to DVT. We think the longitudinal difference between SF levels and D-dimer levels is due to the difference of the coagulation system and fibrinolytic system. Our findings imply that the activation of the coagulation system induced by an operation settles within a few days; in contrast, the activation of the fibrinolytic system induced by an operation remains persistently elevated at least 7days following the operation.

Whether the cut-off value is different according to the operative procedure is not known at present. In the present study, the optimal SF and D-dimer level cut-off values for determining the DVT status of patients were examined separately after THA and TKA. The SF and D-dimer levels were similar for patients following THA and TKA. It may be necessary to study SF and D-dimer levels following other surgical procedures to determine whether the cut-off value is independent of surgery. In the present study, ROC curve analysis showed that a cut-off value of 4.00 μg ml^{-1} was the most reasonable to screen for DVT in postoperative patients. In many patients with DVT, the levels of these markers were lower than the cut-off values in the present study. This reason for this may be due to the presence of some occult thrombosis in these patients.

The sensitivity and the negative predictive values of the D-dimer test for DVT and PTE have been reported to be high (Michiels et al. 2006, Douketis et al. 1996, Friera-Reyeset al. 2005, Ginsberg et al. 1998, Kearon et al. 2006, Kelly et al. 2002, Stein et al. 2004, Wells et al. 2001, 2003, Perrier et al. 1999, van Belle et al. 2006). Pooled data from 20 studies of outpatients with clinically suspected VTE have shown a diagnostic sensitivity of 97%, with false negatives presumably explained on the basis of a small thrombus mass (sensitivity may be lower in patients with isolated, below-the-knee DVT) (Stein et al. 2004). Reber et al. showed that, in hospitalized patients, high concentrations of D-dimer due to reasons other than VTE decrease the utility of the test, and in surgical patients the situation is even more complicated, which leads to lower accuracy (Reber et al. 2000).

Vogel et al. followed 129 patients who underwent abdominal surgery. They found that evaluation of SF levels using enzyme-linked immunosorbent assay (ELISA) leads to a high sensitivity (91.7%), with a specificity of 73.2% (Vogel et al. 1996). Bongard et al. (1994) evaluated 173 patients undergoing hip surgery using the D-dimer assay (ELISA). The sensitivity and specificity for proximal DVT were 79% and 36%, respectively. Our results revealed SF and D-dimer evaluation could not be used as a stand-alone test for all postoperative patients suspected of having DVT. Our results suggest that a two-step screening process, involving an initial SF and D-dimer estimation, might significantly decrease the number of patients requiring imaging. Further studies are required to evaluate the utility of such an approach in improving clinical end points. Under postoperative condition, we put emphasis on SF evaluation for screening, because SF evaluation offers early detection of DVT, and thereby we can start early treatment and early start of walking exercises without a break. D-dimer is useful if DVT is suspected and the time of onset is unclear, because high

Table 3. Performance of the luminescence immunoassay (LIA) and pretest probability.

	Total patients (n=207)	DVT present (n=104, 50.2%)	DVT absent (n=103, 49.8%)	Sensitivity, % (n/n)	Specificity, % (n/n)	Positive predictive value % (n/n)	Negative predictive value % (n/n)	Positive likelihood ratio (95% CI)	Accuracy
SF assay result									
Postoperative day 1 (cut-off value 4.00 μg ml^{-1})									
Positive	163	94	69	90.4 (94/104)	33.0 (34/103)	57.7 (94/163)	77.3 (34/44)	1.35 (0.77–2.36)	
Negative	44	10	34						
Best fit value (cut-off value 7.61 μg ml^{-1})				0.7788	0.6214				1.4002
D-dimer assay result									
Postoperative day 1 (cut-off value 4.88 μg ml^{-1})									
Positive	170	96	74	91.4 (96/104)	28.2 (29/103)	56.5 (96/170)	78.4 (29/37)	1.28 (0.69–2.41)	
Negative	37	8	29						
Best fit value (cut-off value 9.78 μg ml^{-1})				0.6635	0.6019				1.2654
Postoperative day 7 (cut-off value 5.35 μg ml^{-1})									
Positive	173	94	79	90.4 (94/104)	23.3 (24/103)	54.9 (96/175)	75.0 (24/32)	1.18 (0.69–2.02)	
Negative	34	10	24						
Best fit value (cut-off value 8.26 μg ml^{-1})				0.7308	0.5534				1.2842

DVT, deep vein thrombosis; SF, soluble fibrin; THA, total hip arthroplasty; TKA, total knee arthroplasty; CI, confidence interval.

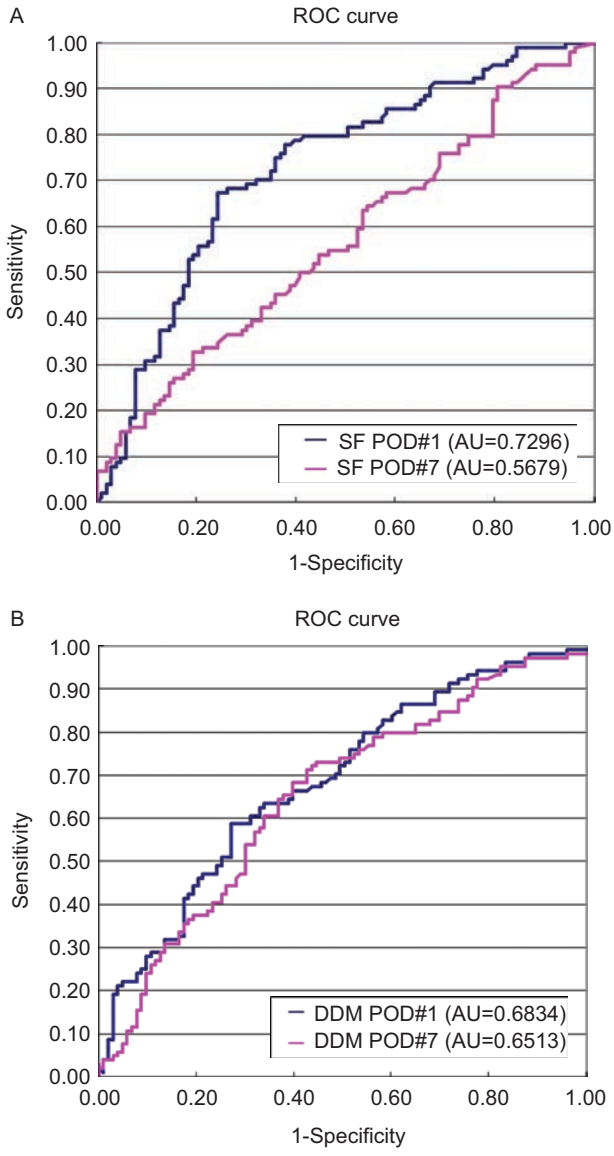

Figure 3. Receiver operating characteristics (ROC) curve for plasma soluble fibrin (SF) (A) and D-dimer (B) in the diagnosis of deep vein thrombosis. The area under the curve (AUC) of plasma SF on postoperative day 1 is 0.7296. The AUCs of plasma D-dimer on postoperative days 1 and 7 are 0.6834 and 0.6513, respectively. POD, postoperative day.

plasma levels of D-dimer are maintained for a longer period than those of SF.

This study has three main limitations. First, the number of enrolled patients was small. Second, both the sensitivity and the specificity for DVT were lower than expected. In Japan, SF and D-dimer concentrations are usually measured using LIA, while in Europe and North America, D-dimer is measured using ELISA. LIA has not been recommended instead of the ELISA method. Unfortunately, at our hospital, ELISA was not introduced, so we had to evaluate the usefulness of LIA measurement. Third, we started treatment with unfractioned heparin (UFH) or low-dose warfarin for DVT patients, which may affect SF and D-dimer levels 7 days after surgery.

In conclusion, SF evaluation on postoperative day 1 is the most useful for initial screening, with a sensitivity of 90.4% and a specificity of 33.0%. We recommend the use of SF evaluation when the time of the thrombotic event, such as an operation, is clear. This sequential approach might be useful in studies on the efficacy of antithrombotic regimens for prophylaxis of DVT in postoperative patients. SF and D-dimer assays cannot be used as a stand-alone test, and further study is needed.

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