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Chapter 7

Coagulation and Fibrinolysis Markers and Their Use for the Prediction of High Risk Patients with Venous Thromboembolism Following Total Hip Arthroplasty

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Additional information is available at the end of the chapter

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1. Introduction

Patients undergoing elective total joint arthroplasty of the lower extremities are at particularly high risk for venous thromboembolism (VTE). Randomized clinical trials have demonstrated the rates of deep vein thrombosis (DVT) following total hip or knee arthroplasty in patients not given thromboprophylaxis to be 42-57 % and 41-85%, respectively [1]. Therefore, perioperative thromboprophylaxis has been a crucial part of the management of these patients for more than 20 years. The administration of anticoagulant drugs, such as vitamin K antagonists, unfractionated heparins, low-molecular weight heparins and a pentasaccharide, is the most effective method of reducing the risk of VTE after major orthopedic surgical procedures. In contrast, although the appropriate uses of these agents are assumed to only minimally increase the bleeding tendency, higher prophylactic efficacy is naturally associated with a higher risk of bleeding complications. The American College of Chest Physicians (ACCP) Guidelines recently downgraded the strength of most pharmaco-prophylactic recommendations in order to achieve a more balanced trade-off between the reduction of thrombotic events and the increase in bleeding events. [2] However, a strong recommendation for routine use of anticoagulants after surgery was included in the previous edition. The American Academy of Orthopaedic Surgeons (AAOS) Guidelines also recommend that orthopedic surgeons evaluate patients' risks for pulmonary embolism (PE) and serious bleeding complications and individualize pharmacologic prophylaxis based on a risk-benefit ratio [3,4]. However, the best way to manage patients depending on their risk for VTE remains controversial because several forms of thromboprophylaxis following surgery are now available.

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Approaches to assessing individual risks of hospitalized patients for VTE can be applied to determine whether anticoagulant drugs are indicated for thromboprophylaxis [5-7]. These assessments, however, are usually complex and difficult to use in everyday practice [8]. Also, alternative indications limited to patients undergoing surgery are lacking, and the associations between postoperative VTE and reported risk factors such as obesity, age or varicose veins have not yet been adequately investigated. Only one risk factor, previous history of VTE, has sufficient evidence indicating that some of these patients may be at even higher risk [9, 10].

Measurements of blood coagulation parameters, such as prothrombin time (PT), activated partial thromboplastin time (aPTT), plasma levels of D-dimer, and so on, are frequently used to assess clotting function and the coagulation state in patients. Although previous considerations of these global screening tests did not facilitate the diagnosis of thrombotic events [11, 12], recent biochemical studies of the coagulation and fibrinolysis systems have expanded the availability of specific and sensitive tests which can detect coagulation state abnormalities. Several different markers have been found to be elevated in clinical disorders, in which the coagulation and fibrinolysis states are out of balance (e.g. disseminated intravascular coagulation, acute myocardial infarction, cerebral infarction, and VTE).

Some of these coagulation markers are sensitive to coagulation state changes in patients undergoing invasive procedures. We previously examined changes in the profiles of some coagulation markers in patients undergoing primary total hip arthroplasty (THA). According to our results, the plasma levels of soluble fibrin (SF) and plasminogen-activator inhibitor-1 (PAI-1) sensitively represented hypercoagulable states which might be associated with postoperative VTE, and we suggested a screening method for evaluating VTE risk in patients undergoing THA using these two markers [13]. Although further investigation is needed, this screening test may be useful for grouping postoperative patients into risk categories. This chapter first provides general information about coagulation markers, which we investigated for diagnosing VTE, and then gives a brief overview of our suggestions pertaining to the screening test for evaluating individual postoperative VTE risk.

2. Coagulation markers associated with thrombosis

2.1. D-dimer

D-dimer is a specific fragment of a cross-linked fibrin clot that is released into the blood when a clot is lysed by plasmin. The utility of measuring D-dimer for the diagnosis of VTE has been extensively studied. D-dimer is detectable at levels greater than 500 ng/mL of fibrinogen equivalent units in nearly all patients with VTE. In general, it is a sensitive test but lacks specificity for the diagnosis of DVT and is, therefore, only useful when negative [14, 15] because plasma levels of D-dimer are increased in a variety of inflammatory and prothrombotic conditions associated with activation of coagulation, such as surgery, trauma, and infection.

2.2. Thrombin-antithrombin Complex (TAT)

The activation of coagulation leads to thrombin products in plasma, but this is regulated in part through interactions with protease inhibitors, such as antithrombin III (AT III). TAT complexes are formed following the neutralization of thrombin by ATIII. TAT is a sensitive marker for thrombin formation, and its elevation in plasma is suggested to alter hemostatic activation. However, TAT formation represents only an indirect measurement of an activated coagulation system [16], and is frequently influenced by peripheral blood sampling techniques under venous occlusion. Thus, measurement of TAT has a low diagnostic accuracy for thrombotic events [17], though marked and persistent TAT level increases may deserve further investigation.

2.3. Soluble Fibrin (SF)

Activated thrombin produces fibrinogen, forming a fibrin monomer that rapidly polymerizes to form a clot. Small amounts can dissolve and circulate in plasma as "soluble fibrin". SF molecules have a strong tendency to polymerize and thus have a short half-life and are present physiologically only at very low concentrations. This is why SF is regarded as a very sensitive marker showing a hypercoagulable state when significantly elevated in plasma. The hypercoagulable state is often caused by various invasive procedures, such as surgery, and plasma levels of SF are recognized to rise rapidly during and after surgery [18, 19].

2.4. Plasminogen-activator inhibitor-1 (PAI-1)

PAI-1 is an important component of the coagulation system that down-regulates fibrinolysis in the circulation. PAI-1 is synthesized by the endothelium and smooth muscle cells in arteries. Elevated plasma PAI-1 in non-surgical patients has been documented in subjects who subsequently developed vascular ischemic events [20-22]. Also, plasma levels of PAI-1 are associated with surgical invasion, and the resultant increase in levels of the fibrinolytic inhibitor is regarded as being a major contributor to fibrinolytic shut-down [18, 23].

2.5. Preoperative VTE risk assessment

There are numerous risk factors for VTE in surgical patients, including the type and extent of surgery or trauma, duration of hospitalization, a history of previous VTE or malignancy, and inherited hypercoagulable states [24-27]. To prevent the development of postoperative VTE, surgical patients should be assessed for risk factors and given thromboprophylaxis as indicated. According to the ACCP Guidelines, surgical patients, excluding those undergoing orthopedic surgical procedures, can be divided into 4 risk groups (very low, low, moderate, or high) depending on the operations being performed. Patients undergoing major orthopedic surgery, such as THA, total knee arthroplasty or hip fracture surgery, are always regarded as being at high risk, and the ACCP Guidelines recommend postoperative anticoagulation (Grade 1B) or portable intermittent pneumatic compression (IPC) (Grade 1C) for thromboprophylaxis.

2.6. Postoperative VTE risk assessment according to SF and PAI-1

According to preoperative risk assessment, most patients undergoing major orthopedic surgery will be in the "high risk" group. However, the state of hypercoagulation following surgery may vary depending on many factors (e.g. patient responsiveness to invasive procedures, types of surgery, duration of surgery, and anesthetic technique). To assess how severe the hypercoagulable state is in patients, acute and sensitive coagulation markers are needed. As mentioned above, we investigated coagulation markers to evaluate their utilities for VTE risk screening following primary THA.

We investigated 170 consecutive patients who were scheduled to undergo primary THA. Patients were excluded if they had any of the following conditions: (a) body weight <40kg; (b) cerebral or gastrointestinal bleeding within the previous 6 months; (c) preoperative intake of anticoagulant or antiplatelet agents; (d) severe renal insufficiency (estimated glomerular filtration rate (eGFR) <30 mL/min-1/1.73 m-^{2})[28]; (e) hepatic failure; (f) allergic to contrast agents; or (g) coagulation or fibrinolysis disorder. All patients were operated on under general anesthesia, and THA was performed through a minimally-invasive anterolateral approach with the patient in the lateral decubitus position. Postoperative mobilization followed a set protocol supervised by experienced physiotherapists. Early walking with a tolerable weight load with crutches or a walker was performed from the day after surgery.

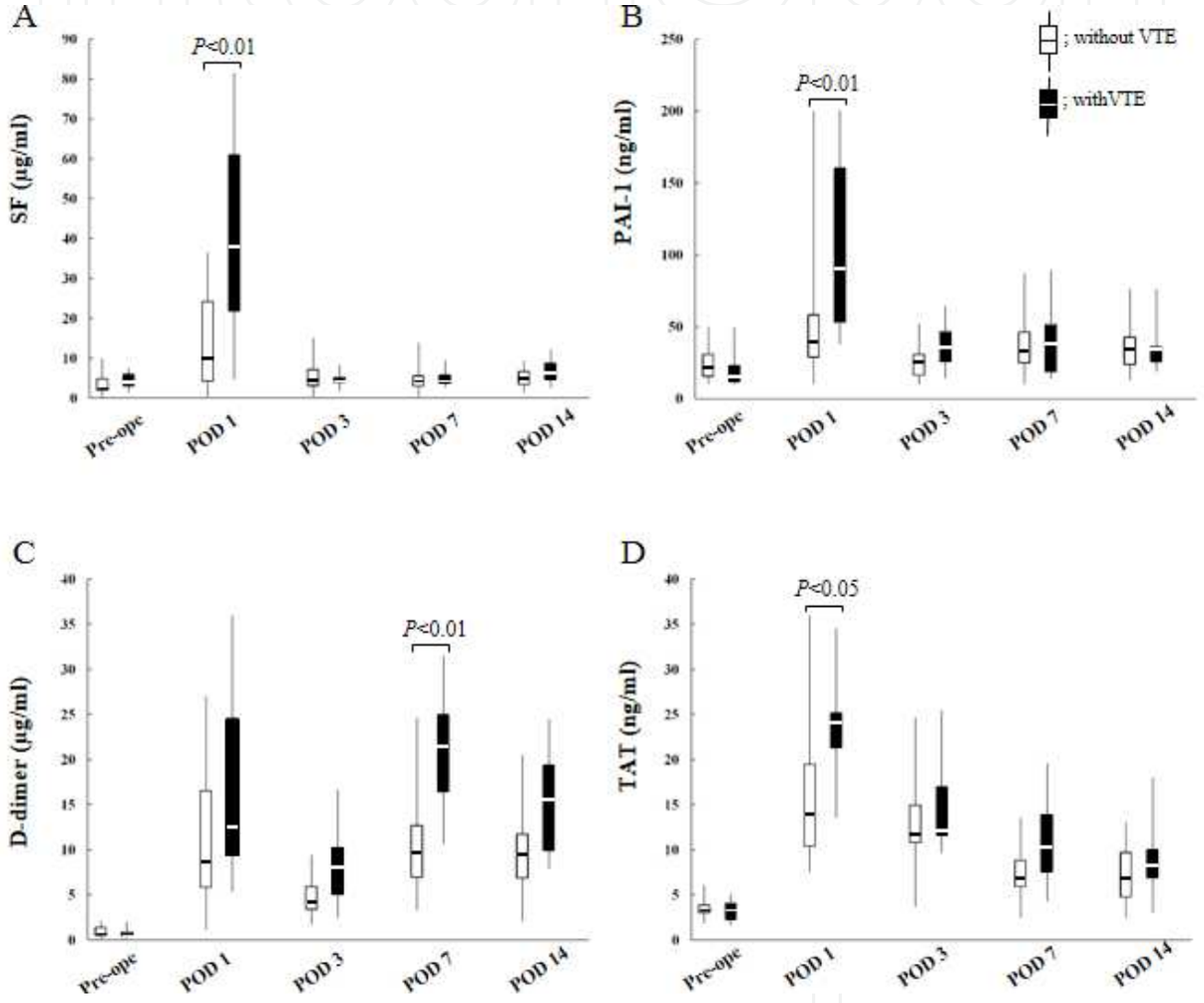
Blood samples were obtained from peripheral veins preoperatively, after a brief fast, and on postoperative days 1, 3, 7, and 14. Plasma SF levels were measured with a latex photometric immunoassay (IATRO SF II; Mitsubishi Chemical Medience Corporation, Tokyo, Japan) using IF-43 monoclonal antibody raised against a urea-solubilized fibrin monomer. PAI-1 was measured using a latex photometric immunoassay (LPIA-tPAI Test; Mitsubishi Chemical Medience Corporation, Tokyo, Japan). Plasma D-dimer levels were also assayed employing a latex photometric immunoassay (LPIA-ACE D-dimer; Mitsubishi Chemical Medience Corporation, Tokyo, Japan). The normal limit was <0.7 μg/mL. TAT was measured by enzyme-linked immunosorbent assay (ELISA) with a reference range of 0.1–5.0 ng/mL (Enzygnost TATmicro; Siemens Healthcare Diagnostics Inc., Tokyo, Japan).

There were two patient groups: IPC group (67 patients) and fondaparinux (FPX) group (103 patients). During surgery, IPC was concurrently performed on all patients in both groups under general anesthesia, and the patients were intravenously administered unfractionated heparin (UFH) in a single dose of 20 IU/kg of body weight. IPC was postoperatively maintained until the day patients started walking, usually 1-2 days after surgery, and this was the only thromboprophylaxis for the IPC group. In addition to IPC, the patients in the FPX group were also subcutaneously administered 2.5 mg of FPX daily for 14 days starting on postoperative day 1. For the detection of postoperative VTE including PE and DVT, angiography of the pulmonary artery and deep vein of the pelvis and the lower limbs was performed for all patients on postoperative day 7 by 64-slice multidetector row computed tomography using a nonionic contrast agent.

Postoperative VTE was detected in 17 (25%) of the IPC patients, and 8 (7%) of the FPX patients. The difference in the frequency of VTE occurrence between the IPC and FPX groups was statistically significant ($p < 0.01$). All DVT presented in calf veins, and there were no cases with symptomatic DVT or PE.

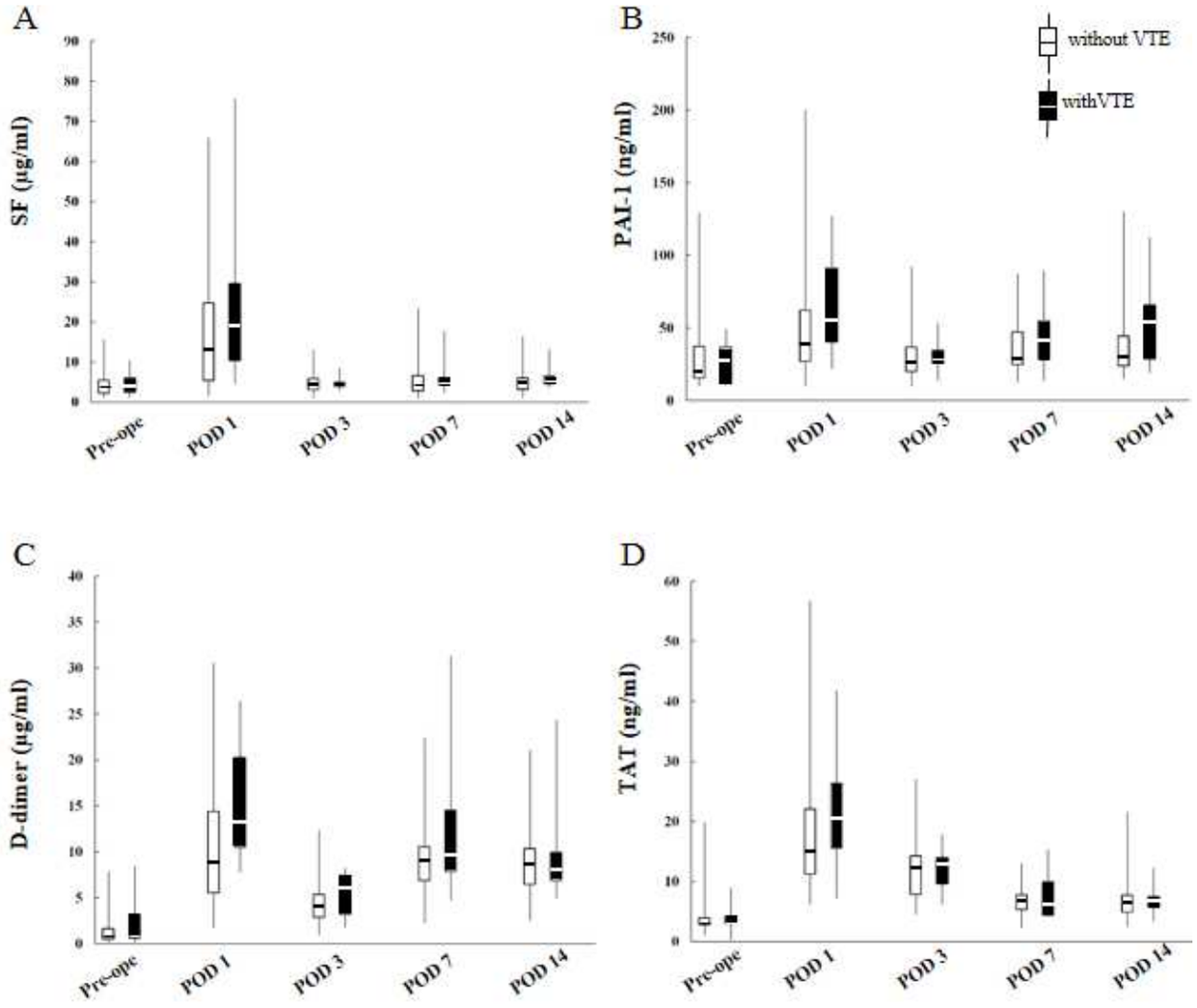
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In the IPC group, plasma levels of SF on postoperative day 1 were significantly higher in patients with VTE than in those without VTE (Figure 1, p< 0.01). Similar to SF, plasma levels of PAI-1 on day 1 were also significantly higher in the patients with VTE in the IPC group (Figure 1, p< 0.01). On the other hand, SF and PAI-1 levels showed similar tendencies in patients with and without VTE in the FPX group (Figure 2). In both the IPC and the FPX group, plasma D-dimer levels showed bimodal peaks that were evident on postoperative days 1 and 7. In the IPC group, significant differences were found on postoperative day 7 (p< 0.01, Figures 1 and 2). IPC patients with VTE also had higher TAT levels on postoperative day 1 (p< 0.05).



Plasma levels of soluble fibrin (SF) (A), plasminogen activator inhibitor type 1 (PAI-1) (B), D-dimer (C), and thrombin-antithrombin complex (TAT) (D) in patients who received only intermittent pneumatic compression were measured preoperatively (pre-op) and on postoperative days 1 (POD1), 3 (POD3), 7 (POD7), and 14 (POD14). The boxes represent the interquartile ranges. The perpendicular lines (whiskers) represent the 5th and 95th percentiles and the horizontal bars in the boxes indicate the median values. On the day after surgery, the plasma levels of SF, PAI-1, and TAT were found to be significantly increased in the venous thromboembolism (VTE) group as compared with the non-VTE group ($p < 0.01$, $p < 0.01$, $p < 0.05$, respectively). The changes in D-dimer levels showed bimodal peaks on postoperative days 1 and 7 in both groups. Significant differences were observed in the D-dimer levels measured on postoperative day 7 ($p < 0.01$).

Figure 1. Changes in coagulation and fibrinolysis markers in patients who received only intermittent pneumatic compression after total hip arthroplasty

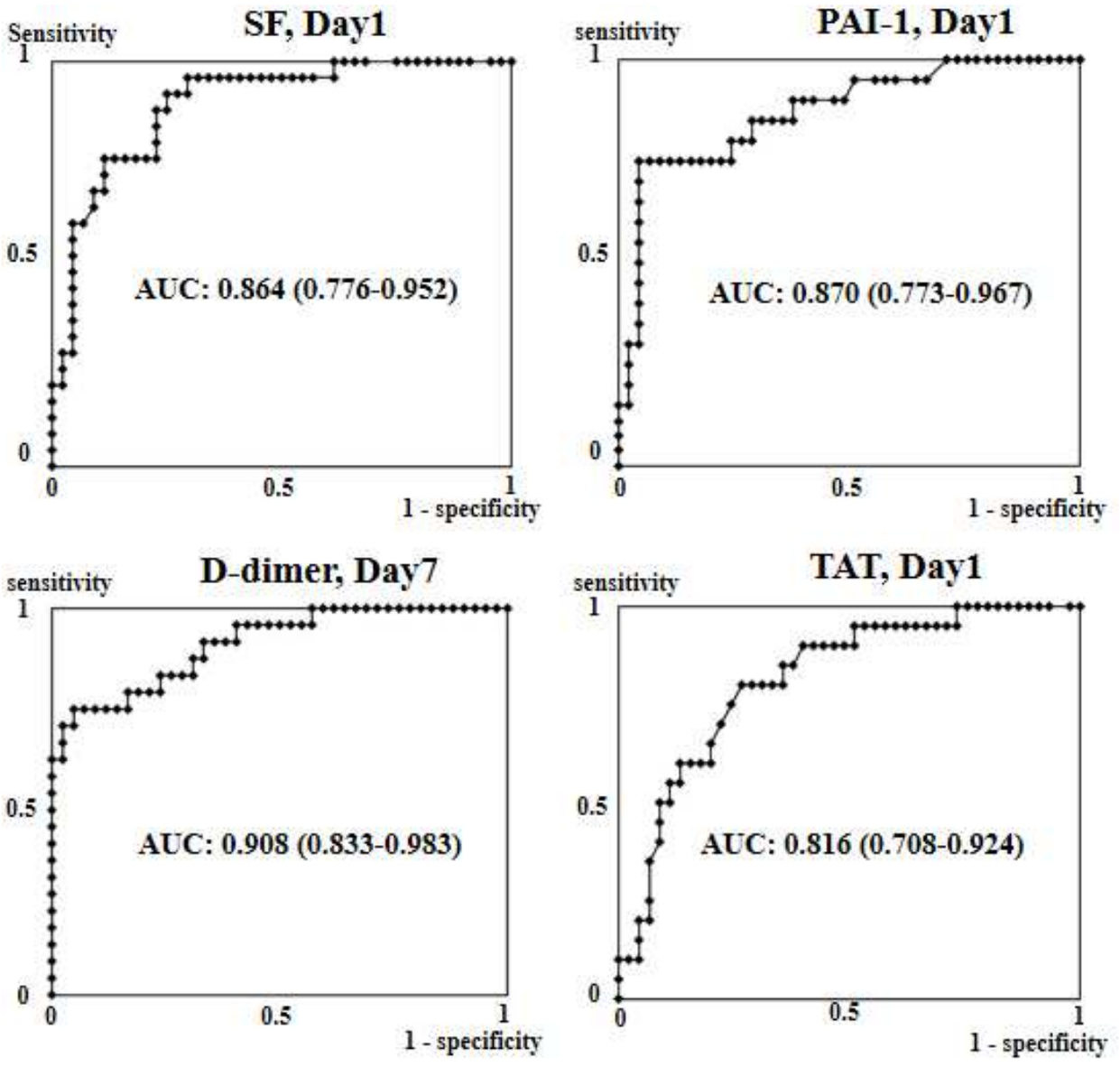


Plasma levels of soluble fibrin (SF) (A), plasminogen activator inhibitor type 1 (PAI-1) (B), D-dimer (C), and thrombin-antithrombin complex (TAT) (D) in patients who received subcutaneous injections of fondaparinux sodium were measured preoperatively (pre-op) and on postoperative days 1 (POD1), 3 (POD3), 7 (POD7), and 14 (POD14). The boxes represent the interquartile ranges. The perpendicular lines represent the 5th and 95th percentiles and the horizontal bars in the boxes indicate the median values. There were no statistically significant differences in the levels of SF, PAI-1, D-dimer, and TAT between the patients with and without VTE in the fondaparinux group.

Figure 2. Changes in coagulation and fibrinolysis markers in patients who received subcutaneous injections of fondaparinux sodium after total hip arthroplasty

Figure 3 shows the receiver operating characteristic (ROC) curve for each marker on postoperative day 1 (for SF, PAI-1, and TAT) and day 7 (for D-dimer). The ROC curves provided the cut-off levels for these markers, and the SF cut-off level was determined to be 19.8 μg/mL with a sensitivity of 88% and a specificity of 62%. The cut-off level of PAI-1 was 53.5 ng/mL with a sensitivity of 78% and a specificity of 72%, and that of TAT was determined to be 18.1 ng/mL with a sensitivity of 85% and a specificity of 66%. Of these markers, multivariate logistic regression analysis revealed SF and PAI-1 to have the strongest associations, statistically, with a thrombotic tendency.

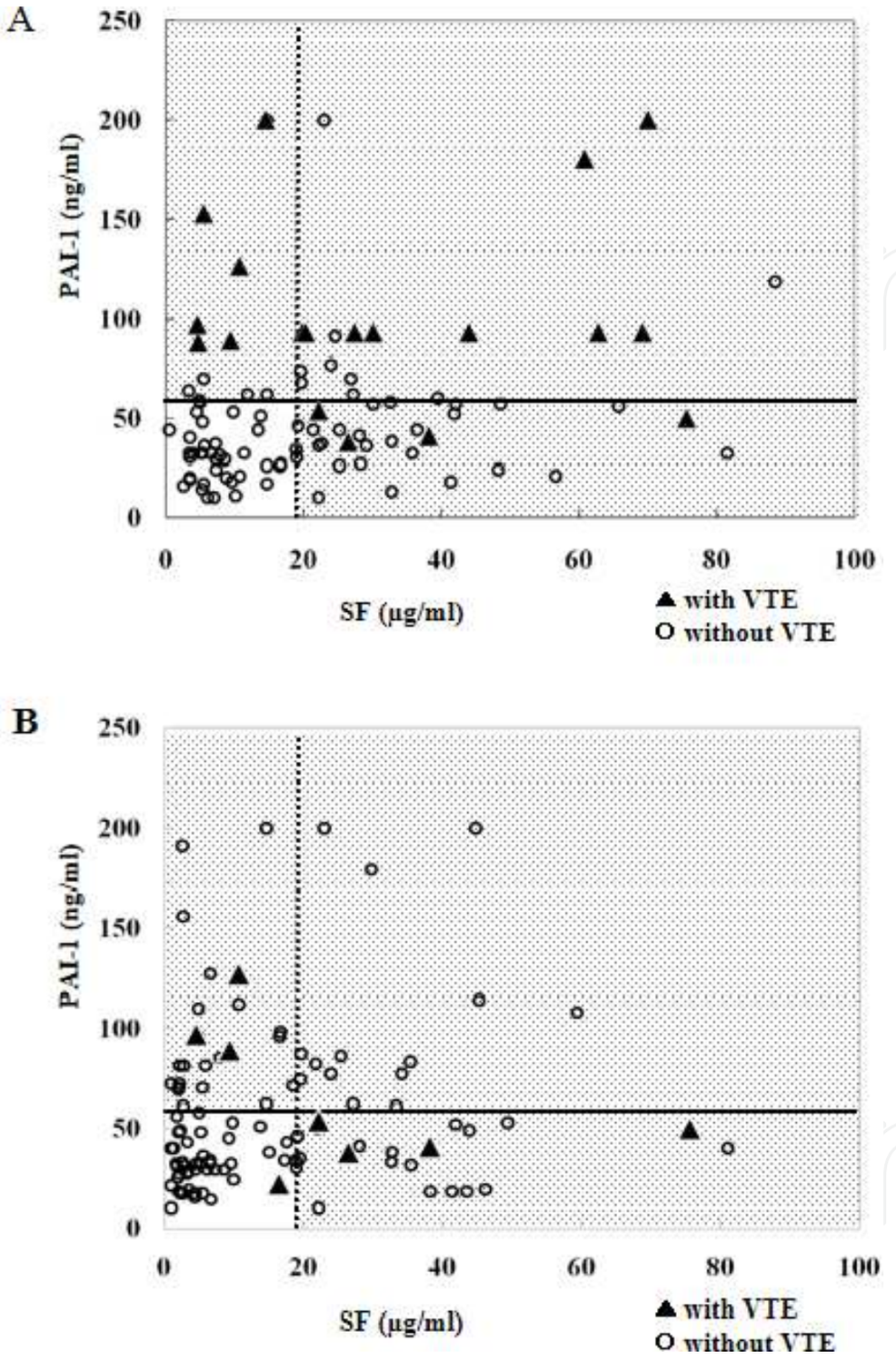
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In each diagram, the area under the ROC curve is shown, as well as the 95% confidence interval in parentheses.

Figure 3. Receiver operating characteristic curve analyses of the accuracies of quantitative soluble fibrin (SF), plasminogen activator inhibitor type 1 (PAI-1), and thrombin-antithrombin complex (TAT) levels on postoperative day 1 and D-dimer levels on day 7

Figure 4 shows the scatter graph of SF and PAI-1 levels, with 2 lines at each cut-off level. These lines divide patients into 2 groups, with higher and lower levels, and these divisions provided a sensitivity of 100%, a specificity of 67%, and a positive predictive value of 50% for postoperative VTE. In addition, when this criterion was applied to patients of the FPX group, 7 of the 8 with VTE met the criterion, yielding a negative agreement rate of 98.0% (48/49).



Increases in either SF or PAI-1 on postoperative day 1 above their cut-off levels provided 100% sensitivity and 67% specificity for predicting VTE when patients were not administered fondaparinux sodium postoperatively (A). In addition, when this criterion was applied to patients who received subcutaneous injections of fondaparinux following surgery, 7 of 8 patients with VTE met the criterion, yielding a 98.0% (48/49) negative agreement rate (B).

Figure 4. Discriminating postoperative venous thromboembolism (VTE) using levels of soluble fibrin (SF) and plasminogen activator inhibitor type 1 (PAI-1)

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As shown in the scatter graphs, pharmaco-prophylaxis reduced the incidence of VTE especially in the high-risk group. In addition, the incidence of VTE in the low-risk group was not different from those obtained with other methods of thromboprophylaxis. The blood analysis on the day after surgery indicated almost half of patients to be in the low-risk group. It was suggested that patients with low plasma levels of SF and PAI-1 might not need pharmaco-prophylaxis following surgery. The blood analysis, which we have suggested as a means of risk assessment, was very simple to use and would likely be acceptable to many institutions. However, further investigation is necessary due to the small sample size in this study.

Highly invasive surgery has been shown to commonly result in a hypercoagulable state [16, 29], resulting in elevated plasma SF. SF reflects acute intravascular fibrin formation as well because SF is one of the circulating materials contributing to fibrin clots [30]. PAI-1 is also produced at the site of inflammation following tissue injury [18, 23]. It was suggested that plasma levels of SF and PAI-1 in the early phase after surgery reflect an imbalance between coagulation and fibrinolysis which contributes to excessive fibrin deposition in the vascular wall [31]. We believe that the combined measurement of SF and PAI-1 on postoperative day 1 is a useful screening method for patients at high risk for postoperative VTE and for determining whether pharmaco-prophylaxis after THA is indicated.

Because the results of SF and PAI-1 assays can be obtained within several hours on the day after surgery, whether pharmaco-prophylaxis is indicated can be determined on postoperative day 1. However, the optimal timing for the initiation of pharmaco-prophylaxis is one of the issues raised by thromboprophylaxis, and the administration of anticoagulant agents following this screening test might be regarded as being relatively late. There has been debate in the literature regarding the issue of how to maximize efficacy while minimizing bleeding risk [32] because the peak efficacy of anticoagulant agents depends on the timing of the first injection [33, 34]. According to a systematic review [33], the incidence of DVT was 19% in patients to whom low-molecular-weight heparin (LMWH) was administered 12 hours before surgery, 12% in patients given LMWH during surgery, and 14% in those treated postoperatively. In our study, low-dose UFH was administered once during surgery and postoperative anticoagulation was performed 24 hours after surgery. According to our results, the initiation of anticoagulation, as performed in this study, appears to be both reasonable and appropriate.

The present study has limitations. First, VTE could be initiated during the operation [35, 36], in the postoperative period without mobilization [37], or 1-2 months after surgery [38, 39]. Thus, evaluations of VTE occurrence may vary depending on the timing of imaging tests, duration of follow-up, or the duration of postoperative thromboprophylaxis. Second, our study was limited to a single center, and the sample size was too small to draw conclusions about the efficacy of our alternative prophylaxis regimen.

3. Summary

Individual risk assessment is becoming a widespread method for determining whether prophylaxis, especially in patients undergoing major orthopedic surgery, is indicated. VTE

developing after surgery might be induced by a hypercoagulable or regulated fibrinolytic state during the early postoperative phase. Thus, the proposed screening test using SF and PAI-1 on the day after surgery may be of value in providing information about whether the coagulation state is unbalanced, and in predicting VTE following THA. We anticipate that selective pharmacological thromboprophylaxis, based on the plasma levels of SF and PAI-1 on the first postoperative day, will be achieved with an alternative thromboprophylaxis regimen.

Characteristics	IPC group		p value	FPX group		p value
	Patients with VTE N = 17	Patients without VTE N = 50		Patients with VTE N = 6	Patients without VTE N = 97	
Age, years	68 (8)	62 (12)	N.S.	58 (8)	61 (12)	N.S.
Gender: Male/Female, no.	3/14	17/33	N.S.	6/0	21/76	N.S.
Weight, kg	58 (14)	58 (13)	N.S.	59 (14)	58 (13)	N.S.
Body mass index	24 (6)	23 (5)	N.S.	24 (5)	24 (5)	N.S.
Primary hip disease, no.			N.S.			N.S.
OA	15	36		4	79	
RA	0	3		0	7	
ANFH	2	6		2	11	
PVS	0	1		0	0	
Preoperative plasma levels of:						
Triglycerides, mg/dL	92 (35)	108 (40)	N.S.	99 (32)	98 (41)	N.S.
Total cholesterol, mg/dL	228 (44)	199 (31)	N.S.	202 (26)	222 (36)	N.S.

Values are presented as means (SD). IPC, intermittent pneumatic compression; FPX, fondaparinux sodium; VTE, venous thromboembolism; OA, osteoarthritis; RA, rheumatoid arthritis; ANFH, avascular necrosis of femoral head; PVS, pigmented villonodular synovitis; N.S., not significant.

Table 1. Patient characteristics

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