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Significance of D-dimer and soluble fibrin testing in screening of incident venous thromboembolism

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Abstract:

Background: D-dimer (DD) is useful for excluding diagnosis of venous thromboembolism (VTE) because of high sensitivity and high negative predictive value. Recently, soluble fibrin (SF) has been introduced for clinical use to examine coagulation status. However, the significance of SF in screening or diagnosis for VTE is uncertain. Thus, we examined DD and SF levels in incident VTE patients with ultrasonographic examination in their lower extremities. **Subjects and Methods:** We have conducted simultaneous measurement of DD and SF in 141 inpatients in our hospital between December 2013 and November 2014. Among them, we further selected 46 patients who were examined by lower extremity ultrasonography 1 month before or after the measurement of DD and SF. Incident VTE was diagnosed based on acute or subacute symptoms, the presence of thrombus in compression ultrasonography, and/or results from contrast-enhanced CT. **Results:** Incident VTE was found in 18 patients. SF levels were similar in VTE (+) and VTE (-) groups, while DD levels were significantly higher in VTE (+) group than those of VTE (-) group (17.7±30.4 μg/mL vs 5.1±5.2 μg/mL, $p<0.05$). When patients were classified based on surgical intervention, no significant difference in SF or DD levels was observed in peri-operative patients. However, DD levels in non-operative patients tended to be higher in VTE (+) group, compared to VTE (-) group. No such tendency was observed in SF levels. **Conclusion:** Measurement of DD but not SF may be beneficial for screening of incident VTE, especially in non-operative inpatients. Further study is necessary to determine the significance of DD and/or SF testing in VTE screening, diagnosis, and treatment in peri-operative patients.

Key words:

Venous thromboembolism, D-dimer, Soluble fibrin, Ultrasonography

1. Introduction

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE), which is a life-threatening disorder. It has been demonstrated that VTE occurs after long-term bed rest or sitting, and even watching television for more than 5 hours[1-6)]. Although accurate incidence rate is difficult to survey, it is considered to be lower in Japanese than that of Western population. However, it is reported that currently the incidence rate in Japan is remarkably increasing[7)].

Diagnosis of VTE is suggested by suspicion from nonspecific signs or symptoms and laboratory data such as elevated D-dimer (DD) level. Further, VTE is diagnosed mostly by contrast-enhanced CT, angiography, and compression ultrasonography[8)]. Since DD level is not specifically elevated by VTE, DD testing is useful for exclusion of VTE[8-11)]. However, elevation of DD level is often seen in subjects with cancer, pregnant women, aged people, and hospitalized patients. Therefore, it has been reported that DD testing is not suitable for the screening of incident VTE, especially for hospitalized patients because of highly false positive results[12)].

Soluble fibrin (SF) has been introduced for clinical use to

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Table 1. Clinical background in patients with or without VTE

	VTE (-)		VTE (+)		
	Women	Men	Women	Men	Total
All cases (N)	15	13	14	4	46
Age	67.2±19.7	71.2±15.2	70.7±16.0	69.8±15.8	69.6±16.6
Peri-operative cases (N)	4	5	6	2	17
Non-operative cases (N)	11	8	8	2	29

examine coagulation status. Recently, SF complex or SF monomer is examined in patients and reported by several researchers, and SF testing can be used for a disease marker of VTE[13-17]. However, little is known about significance of SF testing in the screening of VTE in hospitalized patients. Thus, we conducted a retrospective cross-sectional study to compare SF and DD levels in patients with and without VTE.

2. Subjects and Methods

2.1. Subjects

This retrospective cross-sectional study was performed by the collaboration of Department of Laboratory Medicine, Shimane University, and Central Clinical Laboratory and Vascular Lab, Shimane University Hospital. We included 141 patients in this study who had been simultaneously measured DD and SF from December 2013 to November 2014. Among them, we further selected 46 patients who examined ultrasonography in lower extremities 1 month before or after the measurement of DD and SF.

2.2. Ethics

The study protocol was approved by the local ethics committee of Shimane University and in accordance to the Declaration of Helsinki.

2.3. Data collection

Patient information such as age, sex, levels of DD and SF, was obtained from medical records. Incident VTE was diagnosed based on acute or subacute symptom, the presence of thrombus in compression ultrasonography, and/or results from contrast-enhanced CT and angiography.

Plasma concentration of DD and SF was measured using LIA's Auto D-dimer Neo® kit (Sysmex Co, Kobe, Japan) and Nano-pia® SF kit (Sekisui Medical Co, Tokyo, Japan), both of which were based on latex agglutination immunoassay. According to the manufacturer's information, the reference range of DD and SF were <1.0 μg/mL and <7.0 μg/mL, respectively.

2.4. Statistics

Data were expressed as mean ± standard deviation (SD). ANOVA was employed in univariate analyses of age in 4 groups classified by VTE and gender. The Student's *t*-test was employed in comparison of DD and SF levels between patients with and without VTE. All statistical analyses were performed using the SAS system statistical software (PASW Statistics 18). Statistical significance was defined as $p<0.05$.

3. Results

3.1. Background data

Clinical background of the patients is shown in **Table 1**. Incident VTE was found in 14 women and in 4 men. Mean age of all patients was 69.6±16.6 years, and no difference was found among 4 groups categorized according to the gender and presence of VTE. Surgical operation was done on 17 patients, whereas 29 patients did not receive any surgical intervention. The detail distribution of VTE (+) and VTE (-) patients with or without operation is shown in **Table 1**.

Presence or absence of VTE, comorbidity or surgery, timing of blood sampling, and DD and SF levels in patients with surgical operation were shown in **Table 2**. Among the 29 patients without operation, comorbid diseases were as follows: 10 patients with cancer (ovarian cancer n=3, uterus cancer n=3, prostate cancer n=1, colon cancer n=1, and other cancers n=2), 4 patients with cerebral infarction, 2 patients with peripheral arterial disease (PAD), 2 patients with diabetes mellitus, and 11 patients with other diseases. These findings indicate that the causative disorders of VTE frequently include 1) cancer in pelvic organ such as urology, gynecology, and rectum or sigmoid colon, 2) vascular diseases such as aortic aneurysm, dissection, heart valve disease, and PAD, 3) local or systemic inflammation, and 4) immobilization for long time due to cerebral infarction, severe illness or some other reasons.

3.2. SF and DD levels

Results of SF and DD levels in patients with or without VTE are shown (**Figure 1**). Regarding SF, no difference was observed between VTE (+) and VTE (-) groups (15.9±23.6 μg/mL vs 13.4±23.7 μg/mL, p=0.72), while DD level was significantly higher in VTE (+) group than that of VTE (-) group (17.7±30.4 μg/mL vs 5.1±5.2 μg/mL, p<0.05). When cut-off value for SF was set at 7.0 μg/mL, the sensitivity and specificity for VTE (+) were 38.9% (7/18) and 64.3% (18/28), respectively. In the case of DD, the sensitivity and specificity for VTE (+) were 94.4% (17/18) and 21.4% (6/28), respectively, when the cut-off value was set at 1.0 μg/mL. Also, the negative and positive predictive values

Table 2. Presence of VTE, comorbid disease or surgery, timing of blood sampling, and DD and SF levels in 17 peri-operative patients

	VTE	Disease/Surgery	Timing of blood sampling (Days before or after surgery)	DD (μg/mL)	SF (μg/mL)
Pre-operative group	(+)	Rectal herniation	-36	3.0	28.7
		Lung cancer	-29	3.4	7.3
		Rectal herniation	-15	2.1	0.9
		Lung cancer	-9	1.6	4.9
		Sigmoidal colon cancer	-5	8.2	4.0
	(-)	Abdominal aneurism in aorta	-35	5.0	3.5
		Rectal cancer	-29	4.6	9.6
		Ovarian cancer	-23	1.6	0.6
		Rectal cancer	-22	4.1	11.1
		Sigmoidal colon cancer	-22	2.2	7.8
		Uterus cancer	-21	2.0	51.4
		Sigmoidal colon cancer	-18	2.4	1.8
Post-operative group	(+)	Hematoma in soft tissue	1	26.9	17.8
		Kidney transplantation	13	80.4	85.2
		Kidney transplantation	27	4.6	4.8
	(-)	Spinal subdural hematoma	1	20.8	99.3
		Aortic dissection	4	4.1	5.7

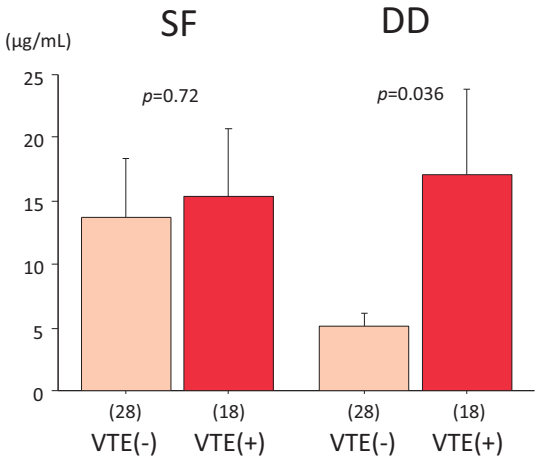

Figure 1. Comparison of DD and SF levels in all the patients with or without VTE Parenthesis indicates the number of patients.

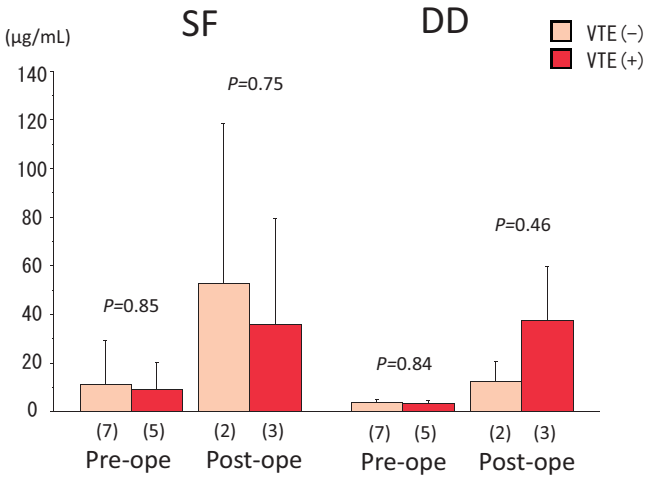

Figure 2. Comparison of DD and SF levels in peri-operative patients with or without VTE Parenthesis indicates the number of patients.

were 62.1% (18/29), 41.2% (7/17) in SF and 85.7% (6/7), 43.6% (17/39) in DD, respectively. These data suggest that as a whole, DD may be suitable as a screening marker for VTE, since DD possesses high negative predictive value and high sensitivity for VTE.

Next, we analyzed SF and DD levels in patients classified by the timing of operation and blood testing. Among 17 patients with surgical operation, 12 patients were examined by blood testing before surgery. In the pre-operative patients, no significant difference in SF or DD levels was shown between VTE (+) and VTE (-) groups (**Figure 2**). At least in 5 patients examined blood testing after surgery, there was no difference in SF or DD levels between VTE (+) and VTE (-) groups (**Figure 2**).

We further performed analysis of 29 patients without surgical operation. Although SF levels in VTE (+) and VTE (-) groups were similar (13.3±20.4 μg/mL vs 10.2±17.5 μg/mL, p=0.66), DD level in VTE (+) group was marginally higher than that of VTE (-) group (18.9±34.2 μg/mL vs 4.7±4.9 μg/mL, p=0.08) (**Figure 3**).

4. Discussion

In this cross-sectional study, measurement of DD but not SF seems to be beneficial for screening of incident VTE in hospitalized patients. However, these findings do not deny the significance of SF testing in patients with VTE. Since SF level is rapidly and tentatively elevated after VTE onset, the interval between VTE onset and blood testing remarkably affects our results. Although we tried to address this issue, it was difficult to get conclusive results regarding SF

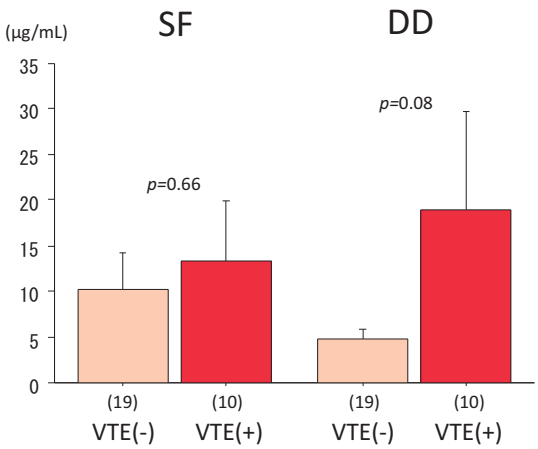

Figure 3. Comparison of DD and SF levels in non-operative patients with or without VTE Parenthesis indicates the number of patients.

testing due to retrospective study design.

We showed that DD may be beneficial for screening of incident VTE among inpatients except surgical operation. Since DD is a marker of endogenous fibrinolysis, it is suitable to detect VTE patients with a high negative predictive value[18]. Meanwhile, Righini et al. pointed out in their narrative review that DD must be integrated in comprehensive sequential diagnostic strategies including clinical probability assessment and imaging techniques, due to its poor specificity[18]. Shigemi et al. reported that DD might be useful as a pre-operative screening of VTE in gynecologic patients[19]. They classified patients into 3 groups by plasma DD level to find pre-operative VTE occurrence in 0%, 2.7%, and 23.7% in patients with ≤0.5 μg/mL, 0.6-0.9 μg/mL, and ≥1.0 μg/mL of DD, respectively. Thus, further study is necessary to determine the significance of DD measurement in pre-operative screening for VTE.

In the present study, we could not find any significant difference in SF levels of patients with or without VTE. In a previous study, however, both DD and SF increased the sensitivity and specificity for the diagnosis of VTE[20]. Another study reported that measurement of SF might be effective to early detection of incident VTE in post-operative patients with total knee arthroplasty, when combined with DD measurement[21]. This discrepancy seems to be mediated by the characteristics of SF. Because SF reflects the very early phase of a thrombotic event, the sensitivity becomes low when measured more than 3 days after the onset[22]. Indeed, in our study, an 88-years old woman, who showed 28.7 μg/mL in SF and 3.0 μg/mL in DD before surgical operation, was diagnosed acute DVT by fresh thrombus in her soleal veins in both sides after ultrasonography. Thus, simultaneous measurement of DD and SF is recommended in patients with high risk of VTE. In addition, SF is responsible for the coagulation status earlier than DD, indicating that SF is more suitable for treatment efficacy of VTE, compared with DD[21].

Taken together, we potentially found benefit of DD testing for screening of incident VTE in hospitalized patients, and of simultaneous measurement of SF in patients with high risk of VTE. However, the number of patients in this study was very small and timing of blood sampling was various because of retrospective study design, which makes the conclusion weak. There was some bias in our patients analyzed in the present study, since we found that orthopedic surgeons had not ordered SF as shown in **Table 2**. Therefore, future prospective study with protocol blood testing in a larger population is needed to clarify these issues.

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Conflicts of Interest

All authors have no conflicts of interest.

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