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Correlation Between D-Dimer Level and Deep Venous Thrombosis in Patients With Acute Spinal Cord Injuries

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Objective: Venous thromboembolism is a serious life-threatening complication of S SCI. Measurement of D-dimer levels is used as a screening test for deep vein thrombosis. However, trauma, surgery, and motor weakness are known as factors that affect D-dimer levels. Thus, the aim of this study was to examine the correlation between D-dimer levels and deep vein thrombosis in relation to the comorbidities in acute spinal cord injury.
Design: A retrospective observational study was conducted at a hospital's rehabilitation department. Forty-five patients without pharmacologic thromboembolic thromboprophylaxis 5–90 days after the onset of injury were enrolled.
Results: Fourteen patients (31%) were diagnosed with deep vein thrombosis using duplex ultrasonography. The mean ± SD D-dimer levels were 2.15 ± 2.74 and 6.98 ± 7.46 μg/ml in the deep vein thrombosis–negative and deep vein thrombosis–positive groups, respectively. The lower limb motor index scores significantly correlated with D-dimer levels regardless of the time between the onset of spinal cord injury and D-dimer testing. Patients with trauma had significantly increased D-dimer levels compared with patients without trauma.
Conclusion: Although D-dimer levels have limitations with regard to the positive prediction of acute spinal cord injury, it is a useful screening parameter for deep vein thrombosis. Trauma and lower limb motor weakness should be considered when analyzing D-dimer levels.

Key Words: Spinal Cord Injury, D-Dimer, Motor Index Score, Deep Vein Thrombosis

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What Is Known

- D-dimer is a fibrin degradation product originating from fibrinolysis of a blood clot. D-dimer levels are increased by infection, paralysis, and trauma, which are common comorbidities in acute spinal cord injury patients.

What Is New

- Over time after acute spinal cord injury, D-dimer levels decrease. Lower motor index scores, as opposed to the total motor index scores, correlated with D-dimer levels. No statistically significant correlation was found between the severity of paralysis and the occurrence of DVT.

Venous thromboembolism is a serious life-threatening event.[1] Motor weakness, venous stasis, trauma, immobility, and major surgery promote the occurrence of thromboembolic events. These comorbidities are commonly accompanied by spinal cord injury (SCI). Thus, screening for thromboembolism has been established as a preventive strategy against serious adverse events in patients with acute SCIs.[2,3] The D-dimer test is simple, fast, and less invasive and thus has been established as a common screening test for deep vein thrombosis (DVT).[4] D-dimer is a specific product of fibrin clot degradation; thus, the D-dimer test has a high specificity for fibrin production and stabilization as the main component of thrombosis. D-dimer level measurements as a screening test for venous thromboembolism are commonly performed in the acute stage of SCI because it provides good negative prediction of thromboembolic disorders.[5–7]

However, factors that follow SCI affect D-dimer levels, making it difficult to accurately analyze D-dimer concentration. Thus, D-dimer levels exceeding the normal range do not necessarily mean that patients have a venous thromboembolism. Therefore, understanding and analyzing D-dimer levels properly and the effect of various factors on D-dimer levels are important. Trauma and motor weakness decrease the blood stream velocity and caused a hypercoagulable state, thus promoting thromboembolic events. However, no study has investigated the effects of comorbidities post-SCI on D-dimer concentration. Therefore, the relationship between comorbidities after SCI, namely trauma (defined as a spinal fracture caused by external force) and motor weakness, and D-dimer levels after SCI were investigated.

METHODS

In this study, a retrospective chart review was conducted for all inpatients with SCI who were transferred to the rehabilitation center for inpatient rehabilitation, between 2017 and 2018. The institutional review board approved this study and waived the need for written informed consent in this study. This study conforms to all the strengthening the reporting of

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observational studies in epidemiology statement guidelines and reports the required information accordingly (see Supplemental Checklist, Supplemental Digital Content 1, http://links.lww.com/PHM/A940). The inclusion criteria were as follows: (*a*) acute SCI onset within the previous 3 mos and (*b*) D-dimer level and duplex ultrasonography assessments. The exclusion criteria were as follows: (*a*) elderly patients, (*b*) SCI patients admitted for the treatment of comorbidities other than SCI, and (*c*) patients who did no undergo D-dimer and duplex ultrasonography assessments.

The D-dimer test and duplex ultrasonography were performed as DVT screening tests at the time of transfer to the rehabilitation center. D-dimer levels were measured using the latex agglutination method, in which HemosIL D-dimer HS was used. All patients were assessed with duplex ultrasonography (LOGIQ E9; GE Healthcare, IL) of both lower limbs by expert physicians. After diagnosis of DVT by duplex ultrasonography, patients were assigned to either the DVT-positive or DVT-negative group.

The main difference with our study in comparison with others was that the motor score was used as a measure of impairment. The American Spinal Injury Association (ASIA) upper and lower limb motor scores more accurately represent the impairment and mobility compared with a single motor score or ASIA grade.[8] Moreover, ASIA motor score relates well to the Functional Independence Measure score as indicator of patient disability.[9] Therefore, we analyzed the correlation between the level of D-dimer and separate ASIA motor score to indicate the degree of disability more accurately. There are several studies to examine the relationship between D-dimer and DVT within SCI. However, acute SCI patients often have factors influencing D-dimer values. Therefore, in interpreting the clinical significance of the D-dimer level, it is important to study the relationship between DVT and factors that influence D-dimer level. Considering this, we designed this research as follows.

The motor index score was calculated by adding the muscle score of each key muscle group in the upper and lower limbs, in accordance with the guideline of the ASIA.[10] The mean time between the onset of SCI and the D-dimer testing (interval) was calculated to analyze the change in D-dimer levels over time. Patients with traumatic spinal fracture caused by external force were defined as traumatic SCI patients. However, osteoporotic compression spinal fractures were not defined as a trauma. Patients with SCI that did not occur as the result of trauma were classified as nontraumatic SCI patients.

Statistical Analyses

Data input and statistical calculation were performed using SPSS Version 23.0 (SPSS Inc, Chicago, IL). D-dimer values were compared between the DVT-positive and DVT-negative groups by analysis of variance to minimize the effect of the interval on D-dimer levels. The effect of trauma on D-dimer levels was also analyzed using analysis of covariance to minimize the effect of the interval. The correlation between the occurrence of DVT and multiple factors, namely age, interval, D-dimer level, and motor score, was analyzed using Spearman correlation. The correlation between each factor and D-dimer level was analyzed using Pearson correlation.

RESULTS

Forty-five patients without pharmacological thromboembolic thromboprophylaxis 5–90 days after the onset of injury were enrolled in the study (Table 1). Fourteen patients (31%) were diagnosed as having DVT using ultrasonography examination. The patients' mean ± SD age was 60.47 ± 17.41 yrs. The mean ± SD interval was 27.33 ± 21.16 days. The mean ± SD

TABLE 1. Demographic data of the patients

		DVT			
	Total (N = 45)	**DVT-Positive (n = 14)**	**DVT-Negative (n = 31)**	***P*[a]**	***P*[b]**
Age	60.47 ± 17.41	65.6 ± 14	58.1 ± 18.5	0.18	—
Interval, d	27.33 ± 21.16	23.7 ± 21.6	29 ± 21.1	0.45	—
D-dimer, ug/ml	3.65 ± 5.17	7 ± 7.5	2.2 ± 2.7	0.03[c]	<0.01[d]
U/E motor score	34.93 ± 17.63	35.8 ± 17.7	34.5 ± 17.9	0.83	0.96
L/E motor score	17.89 ± 15.44	12.9 ± 15.2	20.1 ± 15.2	0.15	0.16
Total motor score	52.82 ± 25.93	48.7 ± 23.5	54.7 ± 15.2	0.48	0.37
Pathology					
CSM		**24.4% (n = 11)**			
Spinal tumor		**13.3% (n = 6)**			
Disc herniation		**2.2% (n = 1)**			
Osteoporotic compression fx.		**8.9% (n = 4)**			
Spinal fracture		**35.6% (n = 16)**			
Spinal cord infarct		**8.9% (n = 5)**			
EDH		**2.2% (n = 1)**			
Epidural abscess		**2.2% (n = 1)**			

Interval refers to the time from injury to D-dimer testing.

[a] *T* test.

[b] Analysis of covariance controlling for the effect of interval.

[c] $P < 0.05$.

[d] $P < 0.01$.

D-dimer level was 2.15 ± 2.74 μg/ml in the DVT-negative group and 6.98 ± 7.46 μg/ml in the DVT-positive group (Fig. 1). The pathologies of the SCIs are summarized in Table 1.

D-dimer levels decreased as the time between D-dimer testing the onset of SCI increased. Thus, D-dimer levels showed a negative correlation with the time of the test (Fig. 1B). However, if the patient had a DVT, the interval did not affect the D-dimer level, but the occurrence of DVT itself had an effect.

The total motor index score and motor index score of the upper limbs did not correlate with D-dimer levels; however, the motor index score of the lower limbs was significantly correlated with D-dimer levels (Table 2, Fig. 1). The greater degree of motor weakness in the lower limbs, the greater the increase in D-dimer levels. However, each motor score did not show a significant correlation with the occurrence of DVT. Thus, no statistically significant correlation was found between the severity of paralysis and the occurrence of DVT (Table 2). When the cutoff D-dimer level was set at 2.20 μg/ml for DVT, the sensitivity was 0.64% and the specificity was 0.69%.

Age did not significantly correlate with D-dimer levels or the occurrence of DVT (Table 2). The mean ± SD D-dimer levels of the patients with traumatic SCI (n = 17) and nontraumatic SCI (n = 28) were 5.54 ± 7.0 and 2.51 ± 3.23 μg/ml, respectively. Traumatic SCI significantly affected D-dimer levels compared with nontraumatic SCI (P = 0.006).

DISCUSSION

D-dimer levels were shown to be negatively correlated with the interval. However, regardless of the interval, the DVT-positive group showed significantly higher D-dimer levels than the DVT-negative group. The lower limb motor index score showed a significant correlation with D-dimer levels regardless of the interval. However, the lower, upper, and total index motor severity scores were not significantly correlated with the occurrence of DVT. Traumatic SCI patients were found to have elevated D-dimer levels.

D-dimer as a biological marker has shown high specificity for fibrin formation and stability.[11] The latex agglutination method can be used for quantitative and rapid testing.[12] Thus, the D-dimer test can be used to diagnose venous thromboembolic events. However, D-dimer levels are increased in various medical issues, including trauma, immobility, infection, and recent surgery.[4] Accordingly, D-dimer levels are usually higher normal in patients with acute stage SCIs. Roussi et al.[7] and Stein et al.[13] reported normal D-dimer levels in only 31% of patients with SCIs. Moreover, all DVT-positive patients had elevated D-dimer levels. As such, the analysis of D-dimer levels is difficult in patients with acute SCIs. In Korean patients in the acute rehabilitation unit who had SCIs without pharmacologic thromboembolic thromboprophylaxis, the incidence of DVT was 27.6%,[14] which is similar to the 31% incidence of DVT in acute SCI found in this study.

Lower motor weakness had a significant effect on D-dimers levels of patients with acute SCI as compared with general motor function deterioration. If venous stasis caused by motor weakness is a major factor of DVT, the severity of generalized motor weakness should correlate with increased fibrin production and maintain the resulting increase in D-dimer levels. However, the lower index motor score only showed a significant correlation with D-dimer levels. Thus, the discrepancy between the upper and lower motor functions was speculated to

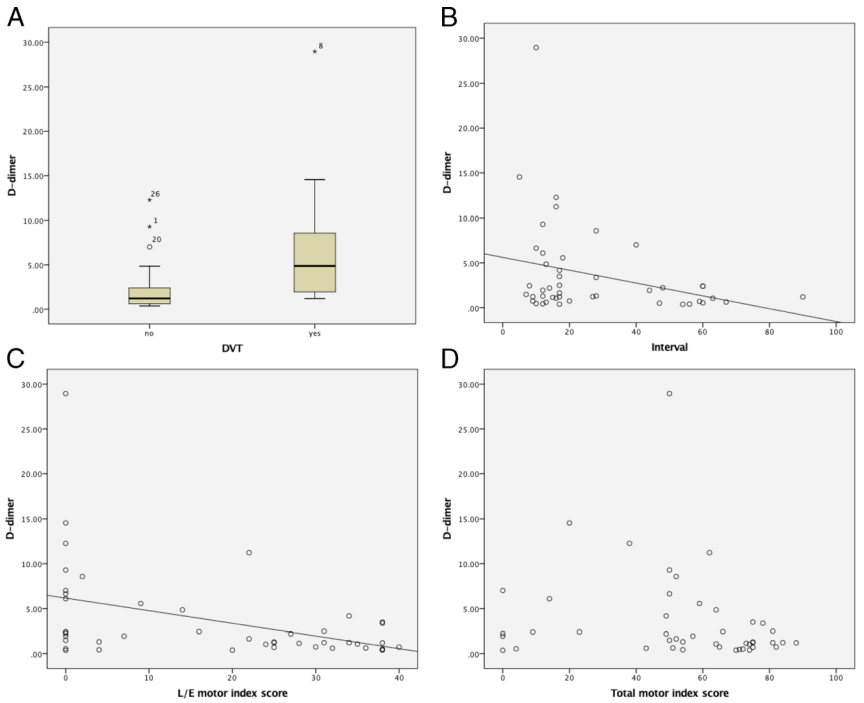

FIGURE 1. The mean ± SD D-dimer level is 2.15 ± 2.74 μg/ml in the DVT-negative group and 6.98 ± 7.46 μg/ml in the DVT-positive group (A). The DVT-positive group shows a statistically significant increase in D-dimer level. The D-dimer level decreased according to the interval (B). However, this decrease is not statistically significant. The lower limb motor index score and D-dimer level show a statistically significant negative correlation (C). The total motor index score does not show a statistical correlation with D-dimer level (D). Interval refers to the time from injury to D-dimer testing.

TABLE 2. Correlation coefficient *R* between the D-dimer levels and the comorbidities in acute spinal cord injury

	Interval	D-Dimer	DVT	U/E Motor Index Score	L/E Motor Index Score	Total Motor Index Score
Age	−0.138	0.132	0.170	−0.040	0.139	0.056
Interval, d	1	−0.293	−0.102	−0.348[a]	0.021	−0.224
D-dimer, ug/ml		1	0.510[b]	0.091	−0.419[b]	−0.188
DVT			1.000	0.053	−0.169	−0.187
U/E motor index score				1	0.226	0.815[b]
L/E motor index score					1	0.749[b]
Total motor index score						1

Interval refers to the time from injury to D-dimer testing.

R, correlation coefficient.

[a]$P < 0.05$.

[b]$P < 0.01$.

maximize the venous stasis in the lower limbs, promoting the occurrence of DVT. In a previous study, patients with paraplegia showed higher D-dimer levels than patients with tetraplegia.[15] Duplex ultrasonography has a high sensitivity and specificity for DVT of the lower limbs.[16,17] Detection of DVT in distal and peripheral small vessels showed low sensitivity (60%) and specificity (50%–70%). Moreover, 44% of patients with pulmonary embolism did not have DVT.[18] Thus, if D-dimer levels are higher and motor weakness of the lower limbs is severe in patients with acute SCI, physicians should pay attention not only to venous thromboembolism within the lower limbs but also to pulmonary embolism.

A systemic review reported that the incidence of DVT in patients with acute SCIs was highest during the first 2 wks after injury.[19] Thus, screening tests for DVT are recommended in the acute rehabilitation state of patients with SCIs. However, in trauma, elevated D-dimer levels are related with not only increased fibrinogen levels but also an elevated white blood cell count and low hematocrit count.[20,21] Previous research reported that increased D-dimer levels were maintained for more than 2 wks after trauma.[22] This study also showed that patients with trauma had higher D-dimer levels than those without trauma. However, trauma did not show any significant difference in the occurrence of DVT. Tissue injury after trauma can cause a false increase in D-dimer levels. Therefore, patients with trauma require more careful analysis of D-dimer levels.

This study has several limitations. It did not conduct pulmonary embolism evaluations; as such, only D-dimer values were interpreted during DVT diagnosis, not the entire venous thromboembolism. The D-dimer test was not performed consistently but at different time points during transformation to the rehabilitation center. Therefore, the correlation between D-dimer level and the comorbidities of SCI was statistically analyzed to minimize the effect of the interval by using analysis of covariance.

Although D-dimer levels are limited with regard to the positive prediction of DVT in the acute stage of SCI, it is a valid screening tool for early detection of venous thromboembolism. Lower limb motor function and trauma have a significant effect on D-dimer levels. Thus, these effects should be considered in the analysis of the D-dimer assay in the screening test for patients with acute SCI.

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