MATERIALS AND METHODS

Patient selection and evaluation
Between January 2008 and December 2009, we studied 59 patients out of 125 patients admitted to our department of neurosurgery due to acute ischemic stroke. Patients who were receiving anticoagulation therapy (due to atrial fibrillation, valvular heart disease, deep venous thrombosis, pulmonary embolism, severe hepatic disease, renal disease, malignancy, or drug use) were excluded. We evaluated risk factors: age, sex, hypertension, diabetes mellitus, dyslipidemia, other cardiac diseases (including acute myocardial infarction and angina), and cigarette smoking. There were 32 male and 27 female patients, ranging from 19 to 82 years in age (mean, 65.3 years).

At emergency room we took each patient’s history and performed a physical examination, neurologic examination using the National Institutes of Health Stroke Scale (NIHSS), serologic evaluation, and radiological evaluation [brain CT, brain MRI, and magnetic resonance angiography (MRA)]. We classified our patients into two groups according to treatment modality. One group received treatment with recombinant tissue plasminogen activator (rt-PA) and/or intra-arterial thrombolysis, and the others received treatment with intravenous argatroban (the argatroban group). We graded their out-
comes using the modified Rankin Scale (mRS) and modified Glasgow Outcome Scale (GOS), which places the scores in reverse order. To analyze the initial NIHSS results, we divided the patients into three categories according to this baseline NIHSS score: mild (0-6), moderate (7-15), and severe (16 and above)\textsuperscript{28}.

D-dimer analysis

D-dimer levels of patients with AIS were evaluated at admission and after seven days of treatment. The D-dimer test is a latex-enhanced immunoturbidimetric test for quantitative determination of cross-linked fibrin degradation products in human plasma. The D-dimer value is considered abnormal when in excess of 250 μg/L (normal range, 63.8-246.4 μg/L).

Volumetric analysis of infarcted areas

We obtained CT and MRI scans and performed volumetric analyses using DWI. MRI studies used a Siemens Vision 3.0T MR scanner (Magnetom Verio, Siemens, Erlangen, Germany). The imaging protocol comprised DWI, T2-weighted, fluid-atenuated inversion recovery, conventional spin-echo T1- and T2-weighted images, and MRA.

We measured infarction volume using DWI. To calculate the infarction volume, we employed the following formula: \(A \times B \times C/2\), where \(A\) is the largest diameter and \(B\) is the perpendicular diameter of the ischemic lesion, as measured, and \(C\) is the sum of the thicknesses of the slices where the lesion was visible. One senior experienced neuroradiologist, performed the volumetric analyses.

The criteria used in the analysis of infarction volume have been previously reported\textsuperscript{42}. We classified patients into 6 subgroups by infarction volume: focal (volume estimation was difficult), multiple embolic (focal multiple lesions in both hemispheres where volumetric calculation was difficult), 1-19 mL, 20-49 mL, 50-199 mL, and >200 mL.

Treatment

AIS patients received intravenous rt-PA treatment (0.9 mg/kg) if they reached the hospital within 4.5 hours after ictus\textsuperscript{43}. For patients with persistent arterial occlusion without signs of early recanalization immediately after IV thrombolysis and for patients visiting the hospital more than 4.5 hours after symptom onset but within 6 hours, we administered combined (IV and IA) thrombolysis therapy, for early recanalization\textsuperscript{11,12,17,24,35,46}. The patients who visited the hospital between 6 and 48 hours after symptom onset underwent treatment with IV direct thrombin inhibitor (argatroban) for 7 days. During the first 2 days the argatroban 120 mg (60 mg/day) was administered continuously. And, then during the subsequent 5 days 10 mg of argatroban was injected per 12 hours\textsuperscript{20}.

Brain CTs were checked immediately after thrombolysis, upon any neurological deterioration associated with an NIHSS increase of 2 points over baseline, and at a conscious level of arm, leg, or eye movement\textsuperscript{7}.

Statistical analysis

Relationships between plasma D-dimer level, changes in D-dimer, treatment modality, and NIHSS, mRS, and GOS scores were evaluated using the Mann-Whitney test for comparisons between two subgroups. The Mann-Whitney test, Kruskal-Wallis test, and Pearson correlation were used to evaluate correlations between plasma D-dimer level, change of D-dimer level, infarction volume, and NIHSS, mRS, and GOS scores.

RESULTS

Patients

Table 1 presents the patients’ profiles. Via the NIHSS, we diagnosed mild stroke in 29 patients (49%), moderate stroke in 23 (40%), and severe stroke in 7 (11%). After 7 days of treatment, NIHSS scores showed 42 (71%) with mild, 15 (26%) with moderate, and 2 (3%) with severe strokes. Modified Rankin scale scores of these patients ranged from 0 to 5 (mean, 1.75±1.38). The thrombolysis group showed a significantly higher mean mRS scale score than the argatroban group had (3.0 vs. 1.5, \(p<0.005\)). The mean modified GOS of all patients in this study was 1.68±0.84.

D-dimer and treatment modality

Table 2 shows the plasma D-dimer levels at admission and after seven days of stroke therapy, by treatment modality. Patients treated with rt-PA or intra-arterial thrombolysis showed higher D-dimer levels at admission than patients receiving intravenous argatroban did (922.3 μg/L vs. 573.4 μg/L, \(p=0.016\)). The thrombolysis group showed significantly greater changes in D-dimer levels compared to the argatroban group (\(p=0.019\)).

D-dimer and volume of infarcted area

Fig. 1 presents the D-dimer and stroke volume data, describ-

<table>
<thead>
<tr>
<th>Table 1. Patients’ profiles</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>65.3±11.8 years</td>
</tr>
<tr>
<td><strong>Sex (male : female)</strong></td>
<td>32 : 27</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>7</td>
</tr>
<tr>
<td>Other cardiac condition</td>
<td>7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7</td>
</tr>
<tr>
<td>Cigarette smoke</td>
<td>18</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2</td>
</tr>
<tr>
<td><strong>Treatment modality</strong></td>
<td></td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>9</td>
</tr>
<tr>
<td>IV anticoagulant</td>
<td>50</td>
</tr>
</tbody>
</table>
Correlation between D-Dimer and Stroke Volume  
YW Park, et al.

Disseminated intravascular coagulation, surgery, trauma, or stroke (2,9,16,33,41). D-dimer, a marker of plasmin-mediated fibrin degradation, is cross-linked to fibrin degradation products (FDP) and indicates vessel occlusion. Plasmin splits the fibrin into FDP and D-dimers when the coagulation and fibrinolytic system is activated. A number of studies have shown that D-dimer, C-reactive protein, and other markers of hemostatic activation associate with a stroke diagnosis (5,18,19,21-23,28,31,35,39) and with progression and death in acute ischemic stroke (5,6,10,30,44). The report by Laskowitz et al. (22) suggests that a biomarker panel may add valuable and time-sensitive diagnostic information to early stroke evaluation and rapid identification of patients with suspected stroke, which would expand the availability of time-limited treatment strategies. Laskowitz et al. (22) also demonstrated that, for the evaluation of early ischemia, a strategy incorporating the current biomarker test in conjunction with noncontrast CT has significantly greater sensitivity than CT alone possesses.

Table 2. Plasma D-dimer levels at admission and after the 7th day of stroke therapy

<table>
<thead>
<tr>
<th>Thrombolysis subgroup (n=9)</th>
<th>Argatroban subgroup (n=50)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At admission (µg/L)</td>
<td>922.3</td>
<td>573.4</td>
</tr>
<tr>
<td>After 7 days (µg/L)</td>
<td>227.0</td>
<td>240.3</td>
</tr>
</tbody>
</table>

Value change after therapy (%)

<table>
<thead>
<tr>
<th></th>
<th>Thrombolysis subgroup</th>
<th>Argatroban subgroup</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal</td>
<td>922.3</td>
<td>573.4</td>
<td>0.016</td>
</tr>
<tr>
<td>Multiple emboli</td>
<td>227.0</td>
<td>240.3</td>
<td>0.792</td>
</tr>
<tr>
<td>1-19</td>
<td>57.1</td>
<td>34.1</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Fig. 1. The positive relationship between initial D-dimer and stroke volume.

Fig. 2. The changes of D-dimer level each stroke volume group.

D-dimer and neurological outcome

Table 3 shows D-dimer level comparisons between the two groups with regard to the outcome index (mRS, modified GOS, and NIHSS scores). Forty-two patients belonged to the good mRS score (0-2) group and 17 patients to the poor mRS score (3-6) group. The favorable modified GOS (1-2) group had 47 patients, and the unfavorable modified GOS (3-5) group had 12 patients. When we analyzed the final NIHSS scores, 42 patients were in the mildly impaired category (71%), 15 in the moderate category (26%), and 2 in the severe (3%). We found no correlation between the D-dimer of the groups and the clinical outcome groups (p>0.05).

DISCUSSION

Although most diagnostic approaches to the evaluation of acute stroke rely on neuroimaging techniques, an alternative strategy could be the evaluation of blood-borne biochemical markers of tissue injury. This approach has precedents in the triage and early management of other urgent medical conditions. For example, biomarkers such as troponin, CK-MB, D-dimer, and B-type natriuretic peptide play important roles in the evaluation of myocardial ischemia, pulmonary embolism, and congestive heart failure (13,32). In the correct clinical context, such a rapid, noninvasive test would help identify a patient population at risk for cerebral ischemia, who need rapid evaluation and triage. Furthermore, it could provide adjunctive diagnostic information for patients for whom physicians are contemplating acute intervention.

D-dimer can be elevated in any case with deep venous thrombosis, pulmonary thromboembolism, myocardial infarction, disseminated intravascular coagulation, surgery, trauma, or stroke (2,8,36,33,41). D-dimer, a marker of plasmin-mediated fibrin degradation, is cross-linked to fibrin degradation products (FDP) and indicates vessel occlusion. Plasmin splits the fibrin into FDP and D-dimers when the coagulation and fibrinolytic system is activated. A number of studies have shown that D-dimer, C-reactive protein, and other markers of hemostatic activation associate with a stroke diagnosis (1,8,19,21-23,28,31,33,35) and with progression and death in acute ischemic stroke (2,8,10,10,44). The report by Laskowitz et al. (22) suggests that a biomarker panel may add valuable and time-sensitive diagnostic information to early stroke evaluation and rapid identification of patients with suspected stroke, which would expand the availability of time-limited treatment strategies. Laskowitz et al. (22) also demonstrated that, for the evaluation of early ischemia, a strategy incorporating the current biomarker test in conjunction with noncontrast CT has significantly greater sensitivity than CT alone possesses.
They have demonstrated the usefulness of some serologic markers, such as D-dimer, brain natriuretic peptide, matrix metalloproteinase-9, and protein S100-beta, for detecting cerebral ischemic stroke.

Skoloudík et al. found that the D-dimer levels increase within 6 hours after stroke onset is greater in patients with large artery occlusion and in patients with cardioembolic stroke than it is in patients with lacunar stroke or in patients without arterial occlusion. Barber et al. showed D-dimer can help physicians target interventions for preventing early neurological deterioration after acute ischemic stroke. However, some studies postulated that D-dimer assessment cannot be used as an AIS index, with the exception of the cardioembolic subtype. In this study, D-dimer had a statistical correlation to infarct volume, and D-dimer value changes during stroke therapy appeared greater in patients receiving intravenous rt-PA (with or without intra-arterial thrombolysis) than in those receiving intravenous argatroban therapy.

Lövblad et al. provided evidence that infarction volume may be predictive of clinical severity and outcome. Also, infarction volume has shown significant correlations with NIHSS and brain injury scores. Our study assessed the relationship between clinical outcome and infarction volume in AIS patients. Compared to previous studies, our results showed similar correlations between infarction volume and mRS, GOS, and NIHSS scores. Infarct volume increase correlated with poor outcomes on the mRS and NIHSS (p<0.05) but showed weaker correlation with the modified GOS (p=0.077).

Baird et al. reported a high correlation between volume change and change in NIHSS score. Our study used DWI to check infarction volume change, comparing the volumes at the acute infarction onset and after 7 days. Only 24 (40%) of 59 patients showed reduced infarction volume on MRI during the follow-up period. Eighteen patients (30%) showed no change, 6 (10%) patients had an increased infarction volume, and 6 (10%) had a decreased volume. Hemorrhagic transformation of the infarcted area occurred in 5 patients (8%). Infarcted volume after seven days of treatment could not predict neurological outcome in our results. However, we found that patients with higher D-dimer levels were more likely to have high NIHSS scores upon admission (p=0.040) and after 7 days (p=0.015).

According to previous studies in the literature, such as the Trial of Org 10172 in Acute Stroke Treatment, the stroke subtype categories are atherothrombotic, cardioembolic, small-vessel occlusion or lacunar stroke of undetermined etiology, and stroke of other undetermined etiology. Moreover, Montaner et al. have confirmed the usefulness of a unique biomarker in the etiologic diagnosis of a stroke, especially a cardioembolic stroke. We did not analyze by etiologic stroke diagnosis, as previous studies did, but rather categorized patients into 6 groups by infarction volume. The 6 groups comprised patients with focal, multiple embolic, 1-19 mL, 20-49 mL, 50-199 mL, and >200 mL infarctions, whose D-dimer levels were 215.3 µg/L, 385.7 µg/L, 566.2 µg/L, 668.8 µg/L, 702.5 µg/L, and 844.0 µg/L, respectively (p<0.05), at admission. Average D-dimer levels after 7 days were 201.0 µg/L, 293.2 µg/L, 272.0 µg/L, 232.8 µg/L, 336.6 µg/L, and 180.0 µg/L, respectively. This is the first study assessing the relationship between the D-dimer levels and stroke volume in ischemic stroke patients. Although we did not consider stroke etiology, our results show that knowing the D-dimer level is helpful for predicting infarction volume.

This study has several limitations. First, explaining the measurable variables in volume by our volumetric analysis, particularly in the focal and multiple embolic subgroups, was difficult. Though relationships among the other subgroups in our study correlate positively with D-dimer level and AIS lesion volume, D-dimer level in the focal and multiple embolic subgroups trended toward lower values. Second, we did not take account of potential confounding variables, such as age, gender, and co-morbid medical condition (pneumonia, acute renal failure, GI bleeding). Although many factors can influence an AIS patient's outcome, D-dimer level showed less correlation with patient outcome in our results. However, our data supports a correlation between D-dimer level and infarction volume in acute ischemic strokes. In spite of the confounding factors, D-dimer level revealed a positive correlation with infarction volume in our results. Third, our patient group was relatively small and heterogeneous in age and therapeutic modality. Patients with various stroke therapies and various risk factors were included in this one study.

**CONCLUSION**

This study shows that D-dimer level significantly increases after the onset of an acute ischemic stroke and that the D-dimer level correlates positively with acute ischemic volume. D-dimer can be considered as a valuable marker for predicting infarction...
volume in acute ischemic strokes and treatment response.

References

Correlation between D-Dimer and Stroke Volume | YW Park, et al.