Fibrinolytic parameters as an admission prognostic marker of head injury in patients who talk and deteriorate

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Because it has been difficult to predict the outcome of patients with head injury in the early period after admission, a clinical study was undertaken to evaluate if the fibrinolytic parameters could be reliable indicators of outcome. Seventy patients presenting with head injury without obvious trauma in other regions were studied, and plasma levels of α2-plasmin inhibitor–plasmin complex (PIC) and D-dimer on admission (within 2 hours postinjury) were assessed. Plasma levels of both PIC and D-dimer were elevated and correlated well to patient outcomes. When plasma PIC levels were higher than 15 μg/ml or D-dimer levels were higher than 5 μg/ml, 92% of patients died regardless of their consciousness level on admission, whereas all patients made good recoveries when their PIC levels were less than 2 μg/ml or D-dimer levels were less than 1 μg/ml. Therefore, plasma levels of both PIC and D-dimer on admission were revealed to be reliable prognostic markers of head injury. Using these markers, patients with poor outcomes (progressive brain injury), such as “talk and deteriorate” types, could be readily identified on admission.

Key Words • head injury • prognosis • fibrinolysis • talk and deteriorate • α2-plasmin inhibitor–plasmin complex • D-dimer

The prognosis for severe head injury has been based on the results of computerized tomography (CT) scanning as well as neurological examination. Recently, other modalities have been used to evaluate the impaired function of the damaged brain, including magnetic resonance imaging, cerebral perfusion pressure, cerebral venous oxygen saturation in the jugular veins, and cerebral blood flow.5,10,14,22 None of these, however, has been established as a reliable indicator to predict the outcome of patients at the time of admission, which indicates that none could be used successfully to quantitate the extent of the brain damage.

It is well established that patients with severe head injuries develop abnormalities in the coagulation or fibrinolytic system.3,9,17,19,25 The brain contains high concentrations of tissue factor that, if released into the circulation or exposed to the bloodstream posttrauma, trigger the activation of the extrinsic coagulation pathway.13,14,24,27 Several reports have indicated that patients exhibiting a hypercoagulable state on admission had severe brain damage and subsequently a worse outcome. A strong association between a coagulopathy on admission and a poor neurological outcome has recently been confirmed by data obtained from the National Traumatic Coma Data Bank. These results indicate that the extent of the activation of the coagulation system, which is indeed determined by the amounts of tissue factor released from the damaged brain tissue, could be a reliable marker of the extent of the brain damage.7,13,16,17,25 Such a hypercoagulable state after head injury is frequently followed by an elevation of fibrinolysis.1,2,3,6,9,11 Many possible mechanisms for the initiation of fibrinolysis after coagulation have been identified, such as conformational alteration of native plasminogen to a more susceptible form after binding to fibrin, or fibrin-specific enhancement of plasminogen activation by tissue plasminogen activator, although precise mechanisms remain to be established. In the present study we examined whether fibrinolytic parameters could be indicators of the extent of the brain damage, which may correlate with the patients’ outcomes. We conducted this study particularly to distinguish poor outcome patients with progressive brain injury such as the “talk and deteriorate” type in the early period after admission before they deteriorate, from those with a good recovery.3,11,15,25

Results obtained in the present study indicate that the fibrinolytic parameters of α2-plasmin inhibitor–plasmin complex (PIC) or D-dimer fraction of fibrin/fibrinogen degradation products (FDPs) could be reliable indicators of patients’ outcomes. These may be better markers than those of the coagulation system, which are sometimes influenced by other factors, such as intracranial hemorrhage, that are unrelated to the brain damage.

Clinical Material and Methods

Patient Population

Seventy consecutive patients admitted with head injury to the department of neurosurgery of Seirei-Mikatahara hospital during a period of 2 years were studied. All
patients studied were admitted to the hospital within 2 hours after injury. Patients showing obvious trauma in regions other than the head were omitted from the study. Patients found to have abnormalities other than neurological deficits and disturbance of consciousness on physical examination, chest x-ray films, or in routine laboratory examinations were also omitted. Patients younger than 16 years of age were omitted; the mean age of the patients was 55.4 years, ranging from 17 to 85 years; 43 patients were male. All patients received careful neurological evaluations performed by at least two specialized neurosurgeons and underwent cranial CT scanning on admission. All patients had brain contusion, and its severity was assessed according to the Glasgow Coma Scale (GCS) score at admission. The GCS scores ranged from 3 to 14.

Assay of Fibrinolytic Parameters

Blood samples were collected on admission from the patients’ antecubital vein by means of a venous puncture performed by a neurosurgeon. Plasma levels of PIC and D-dimer fraction were measured using the enzyme-linked immunosorbent assay (PIC by Teijin Enzyme Immunoassay; Teijin Co., Tokyo, Japan; D-dimer by Dimertest Enzyme Immunoassay; Fuji Revio Co., Tokyo, Japan).

Statistical Analysis

Patients were divided according to the Glasgow Outcome Scale (GOS) score at discharge into three subgroups: Group 1, good recovery or moderate disability (32 of 70); Group 2, severe disability or vegetative (eight of 70); and Group 3, dead (30 of 70). The parameters of fibrinolysis tested on admission were compared between these subgroups. Statistical analysis of the results was performed by one-way analysis of variance. A probability value of less than 0.05 was considered to be statistically significant.

Results

In all patients with head injury, plasma levels of both PIC and D-dimer were much higher than the normal range (PIC < 0.3 μg/ml; D-dimer 0.2 μg/ml). Plasma PIC levels in each group were as follows: 5.7 ± 2.8 μg/ml (Group 1), 9.5 ± 4.4 μg/ml (Group 2), and 18.6 ± 11.8 μg/ml (Group 3), respectively. The PIC levels in Group 3 were significantly higher than those in Group 2 (p < 0.05) and Group 1 (p < 0.0001). The PIC levels in Group 2 were significantly higher than those in Group 1 (p < 0.05) (Fig. 1A). When plasma PIC levels were higher than 15 μg/ml, 11 (92%) of 12 patients died, and no patient experienced good recovery or moderate disability. In contrast, when plasma PIC levels were lower than 2 μg/ml, all patients experienced either good recovery or moderate disability, regardless of their GCS score on admission (Fig. 1B).

Plasma D-dimer levels in each group were as follows: 1.6 ± 1.3 μg/ml (Group 1), 6.3 ± 4.9 μg/ml (Group 2) and 21.6 ± 19.8 μg/ml (Group 3), respectively. The D-dimer levels in Group 3 were significantly higher than those in Group 2 (p < 0.05) or Group 1 (p < 0.0001). The D-dimer levels in Group 2 were significantly higher than those in Group 1 (p < 0.0005) (Fig. 2A). When plasma D-dimer levels were higher than 5 μg/ml, 23 (92%) of 25 patients died, and no patient experienced good recovery or moderate disability. When plasma D-dimer levels were...
less than 1 μg/ml, all patients had good recovery or moderate disability, regardless of GCS score on admission (Fig. 2B). Three patients were diagnosed with disseminated intravascular coagulation (DIC) on admission and all had severe brain contusion (data not shown). Because they did not have obvious trauma in regions other than the head as was the case in other patients, we believe that the disseminated intravascular coagulation (DIC) stage was induced by severe brain contusion. Minor bleeding from severe head injuries was seen in most of the patients, and CT scanning revealed massive subdural hematoma (SDH) in 26 of 70 patients. In any type of hematoma, no significant correlation was seen between its size and fibrinolytic parameters in patients (data not shown).

In relation to consciousness, there was no inverse correlation between D-dimer and GCS score on admission (Fig. 3). Five patients in Group 3 (17%) were talk and deteriorate types whose GCS scores ranged from 10 to 14 (Table 1). Plasma PIC and D-dimer levels in the patients who talked and deteriorated on admission were 14.7 ± 6.6 and 16.6 ± 1.9 μg/ml, respectively, which are comparable to those in patients who did not and who died (26.6 ± 6.7 and 20.7 ± 4 μg/ml, respectively) (Table 2). There was no significant difference in these levels between those patients who talked and deteriorated and those who did not and who died. Plasma levels of both PIC and D-dimer in the talk and deteriorate patients on admission were significantly higher than those of the patients with good recovery whose verbal GCS scores were higher than 3.

**Discussion**

The present study, which was conducted in small numbers of patients, demonstrated that the fibrinolytic parameters found on admission could be reliable indicators of the outcome of head injury: when plasma D-dimer levels were higher than 5 μg/ml or plasma PIC levels were higher than 15 μg/ml, 92% of patients died regardless of their consciousness levels on admission. In contrast, all patients recovered well when their PIC levels were less than 2 μg/ml or D-dimer levels were less than 1 μg/ml. These values, therefore, were reliable indicators for predicting patient outcome regardless of their consciousness levels on admission.

Plasmin is the main enzyme involved in fibrinolysis and is generated by activation of its zymogen form by plasminogen activators. Plasmin, which is indeed responsible for dissolution of fibrin clots, is inactivated rapidly by its specific inhibitor (α2-PI, which forms a high-molecular-weight complex (PIC) in the absence of fibrin. The appearance of PIC in plasma, therefore, directly indicates the generation of plasmin in the vasculature. An indicator of fibrinolysis, D-dimer is a fragment of degradation products of cross-linked fibrins. Unlike ordinary FDPs, generation of D-dimer is direct evidence of fibrin formation and its dissolution by plasmin. These two parameters (PIC and D-dimer), the latter of which could be a reliable indicator of fibrinolysis after fibrin formation, directly indicate the activation of fibrinolysis.

The prognosis for head-injured patients has been estimated based on consciousness level and CT findings on admission.29 Previous reports have shown that the outcome of head injury is related to findings on CT scans or to GCS scores.16,24,38 In our cases, however, GCS scores were not well related to outcome in many patients. Four patients whose GCS scores were less than 5 recovered...
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well, and five patients who were talk and deteriorate types died. The GCS scores and CT scans, therefore, turned out to be unreliable indicators of patient outcome. Several investigators have confirmed that patients with head injuries develop coagulation and fibrinolysis disturbances, but few reports have evaluated the usefulness of these phenomena as predictors of outcome on admission.

In the present study we clearly demonstrate that plasma PIC or D-dimer levels in Group 3 were significantly higher than those in Group 2, and that PIC or D-dimer levels in Group 2 were significantly higher than those in Group 1. When plasma D-dimer levels were higher than 5 µg/ml or plasma PICs were higher than 15 µg/ml, 92% of patients died and when their PIC levels were less than 2 µg/ml or D-dimer levels were less than 1 µg/ml, all patients recovered. These results indicate that these values could let us predict specifically the outcome of these patients. Five of 30 patients who died were the talk and deteriorate type. Although they could speak on arrival, they fell into a deep coma within 4 hours of admission (Table 1). Plasma PIC and D-dimer levels obtained on admission in these patients were not different from those of the patients who did not talk and deteriorate and who died. These results indicate that fibrinolytic activities in patients with head injury are well correlated to the extent of brain damage regardless of their consciousness levels on admission.

There were several exceptions in our study. In four patients who died, plasma D-dimer levels were between 1 and 2 µg/ml. Autopsy or operative findings, however, revealed that the direct cause of death was not brain contusion but massive SDH caused by a lacerated bridging vein or sagittal sinus. The low plasma levels of these parameters, therefore, seems to have accurately indicated their mild brain contusion. Using these values we may know the extent of the brain damage and select the appropriate treatment. For example, when the plasma D-dimer level in a comatose patient with massive SDH is less than

![Graph showing the relationship between plasma D-dimer levels and GCS scores.](image)

**TABLE 1**

Characteristics of five talk and deteriorate patients and their plasma levels of PIC and D-dimer on admission

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Admission GCS</th>
<th>Time of Blood Collection (hrs)</th>
<th>GCS at Time of Blood Collection</th>
<th>Time of Deterioration (hrs)</th>
<th>Parameter (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>&lt;1</td>
<td>13</td>
<td>3</td>
<td>21.5 15.2</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>&lt;1</td>
<td>10</td>
<td>3</td>
<td>14.7 11.8</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>1</td>
<td>14</td>
<td>4</td>
<td>17.5 27.1</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>&lt;1</td>
<td>12</td>
<td>2</td>
<td>12.8 3.8</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>&lt;1</td>
<td>10</td>
<td>2</td>
<td>13.8 6.9</td>
</tr>
</tbody>
</table>

**TABLE 2**

Comparison of plasma levels of PIC and D-dimer and outcome in patients who could speak on admission (verbal GCS 3–5)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Talk &amp; Deteriorate</th>
<th>Good Recovery</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer (µg/ml)</td>
<td>15.0 ± 5.9</td>
<td>0.8 ± 0.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PIC (µg/ml)</td>
<td>16.1 ± 1.6</td>
<td>2.3 ± 0.4</td>
<td>&lt;0.0001</td>
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</tbody>
</table>

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2 μg/ml on admission, it seems to be worthwhile to remove the hematoma and stop bleeding immediately because the brain contusion is probably mild. When plasma D-dimer levels in patients with head injury are greater than 5 μg/ml on admission, immediate decompressive therapy should be recommended, because the outcome would be poor even if the patients could speak on admission. The convenience of D-dimer level assays is also an advantage. Although we may calculate the extent of brain damage precisely by monitoring cerebral perfusion pressure, cerebral venous oxygen saturation in jugular veins, or cerebral blood flow, it takes time to collect these data. In contrast, it takes only a few minutes to detect plasma D-dimer levels by a latex aggregation test, which is indeed essential for emergency situations.

Conclusions

Plasma levels of D-dimer and PIC were well correlated to the extent of brain damage in patients with head injury. Using these values, we may rapidly predict the outcome of head-injured patients.

References


Manuscript received June 17, 1996. Accepted in final form December 13, 1996.

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