Recently, intensive research has been undertaken to improve the clinical outcome of patients with spontaneous subarachnoid hemorrhage (SAH). Rebleeding in particular has been well investigated and it is now recognized that early operation can prevent rebleeding that occurs within the first several days of onset. However, ultra-early rebleeding, which may occur prior to early operation, remains a serious problem by worsening the clinical outcome of patients with SAH. To date, few reports have focused on ultra-early rebleeding and none of these has comprehensively assessed its risk factors from various standpoints, including the use of multivariate analysis. Despite the fact that all patients admitted to our hospital within 24 hours of their last SAH were scheduled for early operation (within 24 hours after admission), a number of these patients died from ultra-early rebleeding before the operation could take place. This unfortunate situation provided us with the impetus to conduct the current study.

The purpose of this study was to assess the possible risk factors associated with SAH patients at the time of admission that could indicate their propensity for ultra-early rebleeding despite scheduling of early operation and to explore possible methods to prevent such rebleeding. For this purpose, we reviewed the records of 179 patients who were admitted to the hospital within 24 hours after their last attack of SAH. On the basis of these records we determined the incidence of, and risk factors for, the occurrence of rebleeding between admission and early operation (ultra-early rebleeding) in patients with spontaneous subarachnoid hemorrhage (SAH), the authors reviewed the cases of 179 patients admitted within 24 hours after their last attack of SAH. Thirty-one (17.3%) of these patients had ultra-early rebleeding despite scheduling of early operation (within 24 hours after admission). The incidence of rebleeding significantly decreased as the time interval between the last attack and admission increased. Patients with rebleeding before admission, high systolic blood pressure, intracerebral or intraventricular hematoma, those in poor neurological condition on admission, and those who underwent angiography within 6 hours of the last SAH were significantly more likely to have ultra-early rebleeding than those without these factors. The incidence of rebleeding also significantly increased as levels of enhancement of platelet sensitivity and thrombin-antithrombin complex increased. Multivariate analysis revealed that the following three factors were independently associated with ultra-early rebleeding: the level of enhancement of platelet sensitivity; the time interval between the last attack and admission; and the level of thrombin-antithrombin complex. On the basis of these findings, the authors suggest that many of the risk factors for ultra-early rebleeding are interrelated. A particularly high risk of ultra-early rebleeding was observed in those patients 1) who had platelet hypoaggregability; 2) who were admitted shortly after their last SAH; and 3) whose thrombin-antithrombin complex levels were extremely high and were thus in severe clinical condition.

**Key Words** • subarachnoid hemorrhage • rebleeding • risk factor • platelet aggregation • blood coagulation

**Clinical Material and Methods**

**Definition of Ultra-Early Rebleeding**

Ultra-early rebleeding is defined as recurrent SAH appearing between admission and early operation, that is, between the first CT at admission and a second CT following angiography for early operation. Whether patients had recurrent SAH was determined by monitoring clinical signs and reviewing CT scans. Patients exhibiting clinical signs of SAH, such as sudden headache and loss of con-
consciousness, two or more times within 2 weeks before admission, were regarded as having had rebleeding before admission.

**Patient Selection**

Between January 1990 and December 1994, 247 patients were diagnosed with SAH by CT scanning or lumbar puncture at our hospital. Sixty-eight of these patients were excluded from the study: 44 who were admitted more than 24 hours after their last SAH attack, 12 patients in whom it could not be determined whether ultra-early rebleeding or rebleeding before admission occurred, and 12 who were not scheduled for early operation due to old age or lack of peak V on recording of brainstem auditory evoked potentials (BAEPs). In all patients given a Hunt and Hess grade of V, BAEPs were recorded on admission (15 Hz–100 dB click sounds, 2000 stimulations). Patients whose bilateral BAEP recordings showed no peak V were not scheduled for early operation. The records of the remaining 179 patients (71 men and 108 women), all of whom were admitted within 24 hours after their last SAH and were scheduled for early operation on admission, were reviewed.

**Data Collection**

Immediately after admission, efforts were made to keep the systolic blood pressure below 150 mm Hg in each patient by administration of calcium channel blockers. The clinical status of patients was graded using the Hunt and Hess classification. All patients who were not comatose were mildly sedated with diazepam and pentazocine after neurological examination. Medical history, including information on episodes of rebleeding prior to admission, was obtained from the patients or their families. All patients underwent CT scanning within 1/2 hour after admission. The amount of clot in the subarachnoid space appearing on the CT scan was classified into one of four groups: 1) none = no evidence of clot detected in the subarachnoid space; 2) mild = a diffuse or localized thin clot found in the basal cisterns; 3) moderate = a localized thick clot found in the basal cisterns; or 4) severe = a diffuse thick clot found in the basal cisterns. All patients were scheduled for early operation within 24 hours after admission and generally for cerebral angiography just prior to operation. However, cerebral angiography was not performed within 6 hours after the last attack of SAH to avoid rebleeding except in cases with intracerebral and/or intraventricular hematoma. A second CT scan was performed in all patients to verify whether or not rebleeding had occurred. One hundred seventy-two of the 179 patients underwent a second CT study immediately after angiography; the remaining seven patients, who could not undergo angiography because of severe rebleeding, underwent a second CT scan just after rebleeding.

Although all 179 patients were originally scheduled for early operation on admission, 24 patients were unable to undergo the procedure, 13 were rescheduled for delayed operation after angiography because of the complexity of the surgical treatment, and 11 had no peak V on BAEP recordings after severe rebleeding after admission. The remaining 155 patients underwent early operation immediately after obtaining a second CT scan following angiography.

**Blood Sampling**

Within an hour of admission, blood was carefully drawn from all patients for laboratory examination using a multiple-syringe technique to avoid any artificial activation of the hemostatic system. Table 1 lists all of the tests performed and the hemostatic parameters assessed in this study, along with the tests’ purposes. The first milliliter of blood drawn from the patient was tested for platelet counts.
Rebleeding in SAH

(using the S-PLUS JR counter; Coulter, Hialeah, FL). The next 4.5 ml was carefully placed into a plastic tube containing 0.5 ml of 3.1% citrated buffer and was used to determine platelet aggregability within 1 hour after blood collection. The last 9 ml was transferred into a prechilled plastic tube containing 1 ml of 3.1% citrated buffer, and the plasma was used to determine prothrombin time, activated partial thromboplastin time, and fibrinogen levels. The remaining plasma was stored frozen at −70˚C until batch analyses of other hemostatic parameters were performed.

Laboratory Studies

Enhancement of platelet sensitivity (EPS) was defined as the lowest concentration of adenosine diphosphate to produce complete second-wave aggregation. This was determined using an aggregometer (PAM-8T; Mebanix, Tokyo, Japan) with the modified method reported by Fishman, et al.5 Several hemostatic assays were performed: clot-based assays to determine prothrombin time (Thromboplastin C; Baxter-Dade, Miami, FL), activated partial thromboplastin time (Actin; Baxter-Dade), and fibrinogen levels (Fibrinogen Determination Set; Baxter-Dade); chromogenic substrate assays to determine the activities of antithrombin III, plasminogen (Berichrom; Behringwerke, Marburg, Germany), and α2-antiplasmin (Testzym; Daiichi, Tokyo, Japan); an enzyme immunoassay to estimate the amount of thrombin–antithrombin complex (Enzygnost TAT; Behringwerke) and plasmin–α2-antiplasmin complex (α2PI complex; Teijin, Tokyo, Japan); and a latex photometric immunoassay to determine D-dimer levels (LPIA; Iatron, Tokyo, Japan). All assays were completed within 1 month after blood collection.

Clinical Outcome

Outcome was assessed by clinical follow up of at least 3 months’ duration. All patients were placed into one of five mutually exclusive categories using Glasgow Outcome Scale17 scores: 1) good recovery; 2) moderate disability; 3) severe disability; 4) persistent vegetative state; or 5) death.

Statistical Analysis

Cochran–Armitage’s method2 was used to assess the tendency for the incidence of ultra-early rebleeding to change in relation to the patient’s neurological grade on admission, the amount of subarachnoid clot on the initial CT, the patient’s clinical outcome, and levels of EPS and thrombin–antithrombin complex. The analysis of variance in linear regression was used to determine the correlations between the time of admission after the last attack and the patient’s neurological grade, the amount of subarachnoid clot, and levels of EPS and thrombin–antithrombin complex. The chi-square test or Fisher’s exact probability method was used to test the associations between the incidence of rebleeding and neurological grade, presence of intracerebral or intraventricular hematoma, rebleeding before admission, and angiography. Student’s t-test or Welch’s t-test was used to determine the significance of the differences in hemostatic parameters and systolic blood pressure at admission between patients with and without rebleeding and the differences in time of admission after the last attack between patients with and without intracerebral or intraventricular hematoma. Ryan’s method29 was used to determine the significance of the differences in the incidence of rebleeding among sites of aneurysm and levels of systolic blood pressure. Multiple logistic regression analysis was used to identify the independent factors predicting ultra-early rebleeding. Values were expressed as means ± standard error of the means. For all tests, probability values of less than 0.05 were considered to indicate statistical significance.

Results

Incidence of Ultra-Early Rebleeding

Of the 179 patients, 11 men and 20 women (17.3%) had ultra-early rebleeding after admission despite being scheduled for early operation within 24 hours after admission. There was no significant difference in mean age or sex ratio between patients with and without rebleeding. Figure 1 shows the numbers of patients with ultra-early rebleeding according to the time elapsed between the last SAH attack before admission and ultra-early rebleeding after admission. Twenty-seven (87.1%) of the 31 patients had rebleeding within 6 hours of their last attack.

Univariate Analysis of Risk Factors for Ultra-Early Rebleeding

Time Interval Between Last Attack and Admission. Because we planned to focus on predictors of ultra-early rebleeding applicable to patients with SAH at the time of admission, we assessed the relationship of ultra-early rebleeding to the time interval between the last attack and admission instead of the interval between the last attack and ultra-early rebleeding after admission. The patients were divided into four groups based on this time interval, as shown in Table 2. The incidence of ultra-early rebleeding significantly decreased as the interval between the last attack and admission increased. No patients admitted more than 6 hours after their last attack had rebleeding after admission. For the 172 patients who underwent angi-
ogy, the time interval between admission and completion of a second CT scan was 12.7 ± 0.5 hours. There was no significant difference in the time interval from admission to the second CT among the four groups classified according to the interval between the last attack and admission.

**Rebleeding Before Admission.** Thirty-three (18.4%) of the 179 patients had rebleeding before admission. The incidence of ultra-early rebleeding in patients who had rebleeding before admission (36.4%) was significantly higher than in those with no rebleeding before admission (13.0%). However, it is important to note that patients with rebleeding before admission arrived at the hospital significantly earlier than the other patients (Table 3).

**Blood Pressure on Admission.** All of the patients were divided into three groups based on their systolic blood pressure at admission (Table 3). The incidence rate of ultra-early rebleeding in patients with extremely elevated systolic blood pressure (> 200 mm Hg) (55.6%) was significantly higher than that in the other two groups. However, systolic blood pressure was significantly higher in patients with a shorter interval to admission. In each of the four groups classified according to time of admission (0–1, 1–2, 2–6, and 6–24 hours) after the last attack, no significant difference was found in systolic blood pressure between patients with and without ultra-early rebleeding.

**Neurological Grade on Admission.** The neurological severity at admission of the 179 patients is shown in Table 3. The incidence of ultra-early rebleeding significantly increased with the severity of neurological grade. However, the interval from the last attack to admission became significantly shorter as the neurological severity grew worse (Table 3). As shown in Fig. 2, in two of the four groups classified by time of admission (0–1 and 1–2 hours) after the last attack, the incidence of ultra-early rebleeding in patients classified with poor Hunt and Hess grades (Grade IV or V) was significantly higher than in those with good grades (Grade I or II).

**Computerized Tomography Findings.** The amounts of clot in the subarachnoid space demonstrated on initial CT scans are shown in Table 3. There was no significant association between the incidence of ultra-early rebleeding and the amount of clot. Initial CT revealed intracerebral hematoma in 57 and massive intraventricular hematoma in 31 patients. The incidence of ultra-early rebleeding in patients with intracerebral hematoma (26.3%) was significantly higher than in those without intracerebral hematoma. The incidence of ultra-early rebleeding in patients with intraventricular hematoma (35.5%) was also significantly higher than in those without intraventricular hematoma. There was no significant difference in the time interval from the last SAH to admission between patients with intracerebral or intraventricular hematoma and those without these respective hematomas (Table 3).

---

**Table 2**

<table>
<thead>
<tr>
<th>Time Between Last Attack &amp; Admission</th>
<th>Ultra-Early Rebleed</th>
<th>Total Cases</th>
<th>Incidence of Rebleed*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1 hrs</td>
<td>Yes: 24, No: 58</td>
<td>82</td>
<td>29.3%</td>
</tr>
<tr>
<td>1–2 hrs</td>
<td>Yes: 5, No: 23</td>
<td>28</td>
<td>17.9%</td>
</tr>
<tr>
<td>2–6 hrs</td>
<td>Yes: 2, No: 44</td>
<td>46</td>
<td>4.3%</td>
</tr>
<tr>
<td>6–24 hrs</td>
<td>Yes: 0, No: 23</td>
<td>23</td>
<td>0.0%</td>
</tr>
<tr>
<td><strong>total</strong></td>
<td>Yes: 31, No: 148</td>
<td>179</td>
<td>17.3%</td>
</tr>
</tbody>
</table>

* The incidence of ultra-early rebleeding significantly decreased as the interval between the last attack and admission was extended (Cochran–Armitage’s method).

**Table 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ultra-Early Rebleed</th>
<th>Total Cases</th>
<th>Incidence of Rebleed</th>
<th>Time Between Last SAH &amp; Admission (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>12</td>
<td>21</td>
<td>33</td>
<td>36.4%†</td>
</tr>
<tr>
<td>no</td>
<td>19</td>
<td>127</td>
<td>146</td>
<td>13.0%‡</td>
</tr>
<tr>
<td>yes</td>
<td>15</td>
<td>42</td>
<td>57</td>
<td>26.3%†</td>
</tr>
<tr>
<td>no</td>
<td>16</td>
<td>106</td>
<td>122</td>
<td>13.1%§</td>
</tr>
<tr>
<td>yes</td>
<td>11</td>
<td>20</td>
<td>31</td>
<td>35.5%†</td>
</tr>
<tr>
<td>no</td>
<td>20</td>
<td>128</td>
<td>148</td>
<td>13.5%‡</td>
</tr>
<tr>
<td>yes</td>
<td>7</td>
<td>53</td>
<td>60</td>
<td>11.7%§</td>
</tr>
<tr>
<td>no</td>
<td>6</td>
<td>39</td>
<td>45</td>
<td>13.3%‡</td>
</tr>
<tr>
<td>yes</td>
<td>8</td>
<td>40</td>
<td>48</td>
<td>16.7%§</td>
</tr>
<tr>
<td>no</td>
<td>9</td>
<td>1</td>
<td>10</td>
<td>10.0%‡</td>
</tr>
<tr>
<td>yes</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>33.3%§</td>
</tr>
<tr>
<td>no</td>
<td>6</td>
<td>1</td>
<td>7</td>
<td>85.7%§</td>
</tr>
<tr>
<td>yes</td>
<td>8</td>
<td>10</td>
<td>18</td>
<td>44.4%‡</td>
</tr>
<tr>
<td>no</td>
<td>23</td>
<td>138</td>
<td>161</td>
<td>14.3%§</td>
</tr>
<tr>
<td><strong>total</strong></td>
<td>31</td>
<td>148</td>
<td>179</td>
<td>17.3%§</td>
</tr>
</tbody>
</table>

* Values shown for the time interval between the last SAH and admission are means ± standard error of the means. ACA = anterior cerebral artery; ACoA = anterior communicating artery; ICA = internal carotid artery; MCA = middle cerebral artery; SAH = subarachnoid hemorrhage; VBA = vertebrobasilar system.
† The incidence of ultra-early rebleeding in these patients was significantly higher than in the other group (chi-square test or Fisher’s exact probability method).
‡ Patients in this group were admitted significantly earlier after the last attack and admission with an increase in systolic blood pressure on admission or with the severity of neurological grade (analysis of variance in linear regression).
§ There was a significant decrease in the time interval between the last attack and admission with an increase in systolic blood pressure on admission or with the severity of neurological grade (analysis of variance in linear regression).
** The incidence of ultra-early rebleeding was significantly higher than in any of the other groups (Ryan’s method).

---

Y. Fujii, et al.
Site of Aneurysm. The sites of cerebral aneurysms are listed in Table 3. Unknowns include patients for whom cerebral angiography failed to determine the site of aneurysmal rupture and those who could not undergo angiography because of severe rebleeding. There was no significant association between the incidence of rebleeding and site of aneurysm.

Emergency Angiography. Of the 179 patients, 18 underwent emergency angiography within 6 hours after the last SAH because of critical illness due to intracerebral or intraventricular hematoma (Table 3). Eight of these 18 patients had rebleeding during procedures related to angiography. The incidence of rebleeding in patients undergoing emergency angiography (44.4%) was significantly higher than in those who did not undergo the procedure (14.3%). There was a significant difference in the time interval to admission from the last attack between patients who did and did not undergo emergency angiography.

Hemostatic Parameters. Table 4 shows the differences in hemostatic parameters between patients with and without ultra-early rebleeding. Among blood coagulation parameters, only thrombin–antithrombin complex levels were significantly higher in patients with ultra-early rebleeding than in those without ultra-early rebleeding. In the fibrinolytic system no significant difference was found in any parameter between patients with or without rebleeding. In the platelet system, the level of EPS was significantly higher in patients with ultra-early rebleeding than in patients without rebleeding. In addition, the incidence of ultra-early rebleeding significantly increased as levels of thrombin–antithrombin complex and EPS increased (Table 5). Although the time interval between the last attack and admission grew significantly shorter as the level of thrombin–antithrombin complex increased, no significant association was found between this interval and the level of EPS.

Multivariate Analysis of Risk Factors for Ultra-Early Rebleeding

Due to the presence of interrelations among risk factors for ultra-early rebleeding, we used multiple logistic regression analysis to determine which risk factors were independently associated with ultra-early rebleeding (Table 6). In this analysis, each of the factors was classified as shown in Tables 2, 3, and 5. The analysis revealed that only three variables were independently related to ultra-early rebleeding. The level of EPS was the strongest predictor of ultra-early rebleeding; the next strongest predictor was the time interval between the last attack and admission; and the third independent predictor was the level of thrombin–antithrombin complex.

Relationship of Ultra-Early Rebleeding to Clinical Outcome

Of the 148 patients without ultra-early rebleeding, 76 made a good recovery (51.4%), 13 suffered moderate disability (8.8%), 21 severe disability (14.2%), 12 persistent vegetative state (8.1%), and 26 died (17.6%). Of the 31 patients who experienced ultra-early rebleeding, five made a good recovery (16.1%), one had moderate disability (3.2%), two severe disability (6.5%), three persistent vegetative state (9.7%), and 20 died (64.5%). There was a significant relationship between ultra-early rebleeding and clinical outcome: mortality in patients with ultra-early rebleeding was significantly higher than in patients without ultra-early rebleeding.

Discussion

Our study revealed that ultra-early rebleeding was not rare (17.3%), despite scheduling of early operation and

| TABLE 4 | Differences in hemostatic parameters between patients with and without ultra-early rebleeding after admission |
| --- | --- | --- | --- |
| Parameters | Normal Range | Yes (31 cases) | No (148 cases) |
| blood coagulation system | | | |
| prothrombin time (sec) | 10.6–13.9 | 11.6 ± 0.1 | 11.8 ± 0.1 |
| activated partial thrombo- | 25.4–34.4 | 25.3 ± 0.4 | 25.8 ± 0.2 |
| plastin time (sec) | | | |
| fibrinogen (mg/dl) | 150–380 | 262 ± 15 | 281 ± 6 |
| antithrombin III (%) | 87–113 | 104 ± 2 | 105 ± 1 |
| thrombin–antithrombin III | <5.0 | 141.5 ± 29.3† | 66.8 ± 7.4 |
| fibrinolytic system | | | |
| plasminogen (%) | 80–109 | 100 ± 3 | 101 ± 1 |
| α2-antiplasmin (%) | 85–120 | 92 ± 2 | 95 ± 1 |
| D-dimer (μg/ml) | <0.15 | 3.7 ± 1.1 | 2.4 ± 0.3 |
| plasmin–α2-antiplasmin | <1.0 | 3.8 ± 0.8 | 2.4 ± 0.3 |
| complex (μg/ml) | | | |
| platelet system | | | |
| platelet (104/mm3) | 15.0–36.0 | 24.0 ± 1.1 | 23.9 ± 0.5 |
| enhancement of platelet | 1.0–4.0 | 5.0 ± 0.6† | 3.5 ± 0.2 |
| sensitivity (μmol) | | | |

* Values are expressed as means ± standard error of the means.
† Significantly different from patients without rebleeding (Student’s or Welch’s t-test).
that the mortality of patients with ultra-early rebleeding was extremely high (64.5%). If ultra-early rebleeding can be prevented, it is clear that the overall clinical outcome for SAH patients will be dramatically improved. For this reason our study addressed risk factors for ultra-early rebleeding which might be applicable to patients with SAH at admission.

Risk Factors for Ultra-Early Rebleeding After Admission

Short Time Interval Between Last Attack and Admission. Patients who were admitted with a shorter interval from the last SAH attack were more likely to have ultra-early rebleeding after admission. The majority of ultra-early rebleeding episodes occurred within 6 hours after the last attack of SAH. Multivariate analysis demonstrated that the time interval between the last attack and admission was the second strongest independent predictor of ultra-early rebleeding. Ando and colleagues1,18 and Inagawa and associates4,19 reported that the majority of rebleeding episodes occurred within 6 hours of SAH onset, and Hillman, et al.13 claimed that no less than 9.6% of all patients admitted within 6 hours (particularly those admitted within 1 hour after the last attack) are at high risk of rebleeding after admission.

Rebleeding Before Admission. Patients with rebleeding before admission were more likely to have ultra-early rebleeding after admission than those who did not experience rebleeding before admission. Hijdra and associates11 claimed that the risk of further rebleeding was significantly increased in survivors of a first rebleeding. Thus, an episode of rebleeding before admission may be a risk factor for ultra-early rebleeding after admission, although not an independent predictor of rebleeding.

High Systolic Blood Pressure on Admission. Patients with extremely high systolic blood pressure (>200 mm Hg) at admission were at high risk for ultra-early rebleeding; this finding was similar to that of a previous study of the incidence of recurrent hemorrhage in the first several weeks after the initial hemorrhage.33 However, high systolic blood pressure cannot be used to predict rebleeding independently but rather through its interrelationships with the other factors, particularly the time interval between the attack and admission. Although high systolic blood pressure on admission may be a risk factor for ultra-early rebleeding after admission, although not an independent predictor of rebleeding.

Poor Neurological Grade on Admission. The incidence of ultra-early rebleeding increased with the severity of neurological grade on admission; this finding was similar to those of previous studies of recurrent SAH during the first several weeks after an initial SAH.25,28,31 Although patients with poor neurological grades were likely to be transferred to our hospital earlier than those with good neurological grades, the incidence of rebleeding within 2 hours after the last attack in patients with poor neurological grades was significantly higher than in those with good grades. Hence, a poor neurological grade on admission appears to be a risk factor for ultra-early rebleeding, although not an independent one.

Intracerebral and/or Intraventricular Hematoma. Our study revealed no relationship between the amount of sub-

<table>
<thead>
<tr>
<th>TABLE 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relationship between the incidence of ultra-early rebleeding and levels of thrombin–antithrombin complex and enhancement of platelet sensitivity*</td>
</tr>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>thrombin–antithrombin complex (ng/ml)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>enhancement of platelet sensitivity (µmol)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>total</td>
</tr>
</tbody>
</table>

* Values are expressed as means ± standard error of the means. SAH = subarachnoid hemorrhage.
† There was a significant decrease in the time interval between the last attack and admission with an increase in levels of thrombin–antithrombin complex (analysis of variance in linear regression).
‡ These variables are independent risk factors for ultra-early rebleeding.

<table>
<thead>
<tr>
<th>TABLE 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation of risk factors for ultra-early rebleeding by multiple logistic regression analysis</td>
</tr>
<tr>
<td>Variables*</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>interval to admission‡</td>
</tr>
<tr>
<td>rebleed before admission</td>
</tr>
<tr>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>neurological grade</td>
</tr>
<tr>
<td>amount of clot</td>
</tr>
<tr>
<td>intracerebral hematoma</td>
</tr>
<tr>
<td>intraventricular hematoma</td>
</tr>
<tr>
<td>emergency angiography</td>
</tr>
<tr>
<td>TAT level‡</td>
</tr>
<tr>
<td>EPS level‡</td>
</tr>
</tbody>
</table>

* CI = confidence interval; EPS = enhancement of platelet sensitivity; TAT = thrombin–antithrombin complex.
† Time interval between the last attack and admission.
‡ These variables are independent risk factors for ultra-early rebleeding.
Rebleeding in SAH

arachnoid clot and the incidence of ultra-early rebleeding; this finding was comparable to those of previous stud-
ies\textsuperscript{10,11,15,26} of rebleeding within several weeks after SAH attack. However, patients with intracerebral or intraventric-
tricular hematoma were more likely to have ultra-early rebleeding after admission than those without the respec-
tive hematomas. Previous studies have claimed that the risk of rebleeding was very high for patients with intra-
cerebral hematoma\textsuperscript{1} or intraventricular hematoma\textsuperscript{19,25} on entry CT scans. Although the reason why patients with
these kinds of hematomas are at high risk of rebleeding is unclear, the presence of intracerebral or intraventricular
hematoma on the initial CT scan appears to be a risk fac-
tor for ultra-early rebleeding, although it is not an inde-
pendent predictor of rebleeding.

Emergency Angiography. Komiyama, \textit{et al.},\textsuperscript{23} reviewed 14 of their own cases and 202 cases in the literature with
rebleeding during angiography and found that the major-
ity of rebleeding episodes occurred within 6 hours of the
last SAH. Ingawaga and associates\textsuperscript{14,15} claimed that the rate of rerupture during angiography performed within 6 hours of initial SAH is approximately twofold higher than that within 6 hours for the total series and that the angio-
graphic procedure itself carries the risk of provoking
rebleeding. The present study also demonstrated that pa-
tients undergoing angiography within 6 hours of the last
attack of SAH had a high likelihood of rebleeding during
procedures related to angiography. Hence, patients who
have to undergo emergency angiography appear to be
at risk of ultra-early rebleeding. However, it is unclear
whether emergency angiography itself may affect the occurrence of rebleeding because it was interrelated with
many of the other risk factors, particularly the time inter-
val between the last attack and admission, the presence of
intracerebral or intraventricular hematoma, and the sever-
ity of neurological deficit. The multivariate analysis we
performed could not verify that emergency angiography
was an independent risk factor for ultra-early rebleeding.

High Levels of Thrombin–Antithrombin Complex and EPS. In our previous studies,\textsuperscript{7,8} we demonstrated that certain changes in the hemostatic system, particularly
in platelet function, were closely related to development
of spontaneous intracerebral hemorrhage. In this study,
detailed analyses of the hemostatic system were per-
fomed to test the hypothesis that impaired hemostasis,
such as hypocoagulability, hyperfibrinolysis, and hypo-
aggregability, might be involved in the mechanism of
ultra-early rebleeding. We found that the levels of throm-
bin–antithrombin complex and EPS in patients with ultra-
early rebleeding were significantly higher than in those
without rebleeding and that the incidence of ultra-early
rebleeding became greater with increases in these levels.
We previously reported that thrombin–antithrombin com-
plex levels were abnormally elevated in association with the severity of neurological grade, the amount of clot,
and the presence of intracerebral and/or intraventricular
hematoma.\textsuperscript{6} Thus, the level of thrombin–antithrombin complex appears to coincide with the severity of the clin-
ical status of patients with SAH. This may be why multi-
ivariate analysis demonstrated that the level of thron-
bin–antithrombin complex was an independent predictor
of ultra-early rebleeding and that the severity of neurolog-
ic grade and the presence of intracerebral and/or intra-
ventricular hematoma, each of which was also a risk fac-
tor for rebleeding on univariate analysis, were not inde-
pendently associated with rebleeding. On the other hand,
our previous study demonstrated that platelet aggrega-
bility, that is, EPS level, was unrelated to the severity of
neurological grades or findings of CT examination. In this
study, EPS level was the strongest independent predictor
of ultra-early rebleeding. Hence, reduced platelet aggrega-
bility rather than hypocoagulability or hyperfibrinoly-
sis may be involved in the mechanism of ultra-early rebleeding.

Although no study has comprehensively assessed the
status of the hemostatic system, including the thrombin–
antithrombin complex, in SAH patients with rebleeding,
two studies have focused on platelet function in patients
with rebleeding.\textsuperscript{18,34} In those studies, however, only a very small number of SAH patients were examined, and no
significant difference in platelet aggregability between
patients with and without rebleeding or association be-
 tween the incidence of rebleeding and platelet aggregable-
cy could be found. Thus, the present study is the first to
demonstrate an independent association between the inci-
dence of ultra-early rebleeding and platelet hypoaggrega-
bility and thrombin–antithrombin complex levels.

Possibility of Prevention of Ultra-Early Rebleeding

Hillman, \textit{et al.},\textsuperscript{12} have indicated the necessity of devel-
op ing complementary pharmacological tools to prevent
ultra-early rebleeding from abruptly terminating the pa-
tient’s life. Administration of agents that improve hy-
poaggregability, if available, rather than antifibrinolytic
agents may prevent ultra-early rebleeding, because plate-
let aggregability appears to be involved in the mechanism
of the rebleeding. On the other hand, magnetic resonance
angiography may be able to reduce the incidence of ultra-
early rebleeding because it is a rapid method of obtaining
cerebral panangiograms, thus reducing the interval
between admission and clipping, and because it is a non-
invasive examination and much less stressful than con-
tventional angiography.

Summary

Thirty-one (17.3\%) of the 179 patients admitted within
24 hours of the last SAH attack had ultra-early rebleed-
ing after admission despite scheduling of early operation
within 24 hours after admission. Although many risk fac-
tors were associated with ultra-early rebleeding, a par-
ticularly high risk of rebleeding was observed in those
patients who had platelet hypoaggregability; who were
admitted shortly after their last SAH; and whose throm-
bin–antithrombin complex levels were extremely high
and, thus, were in severe clinical condition.

Acknowledgments

We express our gratitude to Drs. Senji Hayashi and Kazuo Endo
for their statistical assistance and to Dr. Hoyu Takahashi for his
valuable suggestions concerning hematological findings. We also
thank Ms. Noriko Sakai for her laboratory assistance, Ms. Chikako
Shino for her help in retrieving patient records, and Ms. Tomoe
Fujita for her editorial assistance.
References


Address reprint requests to: Yukihiko Fujii, M.D., Department of Neurosurgery, Kuwana Hospital, 6-4 Furukawa-cho, Niigata, 950, Japan.