D-Dimer as an Independent Predictor for Poor Outcome After Aneurysmal Subarachnoid Hemorrhage

Seppo Juvela, MD, PhD; Jari Siironen, MD, PhD

Background and Purpose—After aneurysmal subarachnoid hemorrhage (SAH), elevated d-dimer levels have been associated with poor clinical condition and outcome. We tested prospectively whether d-dimer values affect outcome after SAH independently of severity of bleeding.

Methods—Previous diseases, and clinical as well as radiological variables, were recorded for 136 patients with SAH admitted within 48 hours after bleeding. Plasma d-dimer was measured in the morning after aneurysm occlusion and at discharge 10 to 12 days after SAH. Factors predicting poor outcome according to the Glasgow Outcome Scale at 3 months after SAH and appearance of cerebral infarction were tested with multiple logistic regression.

Results—Patients with poor outcome had higher d-dimer values than did those with favorable outcome: after surgery, a median 1250 (25th and 75th percentiles 675 and 2900) µg/L versus 720 (330 and 600) µg/L (P=0.001); and at discharge, 1150 (624 and 2875) µg/L versus 360 (330 and 600) µg/L (P<0.001), respectively. In repeated-measures ANOVA, d-dimer decreased more rapidly (P=0.022) in those with favorable outcome. After simultaneous adjustment for several factors affecting outcome, plasma d-dimer after surgery remained a significant predictor for poor outcome (odds ratio, 1.63 per mg/L; 95% CI, 1.03 to 2.60; P=0.038) but neither for delayed ischemia nor, on follow-up computed tomography in survivors, for cerebral infarction.

Conclusions—Elevated plasma D-dimer after admission independently predicts poor outcome, suggesting that prolonged excess thrombin generation may impair outcome. Repeated high plasma D-dimer values can be useful in discovering patients at increased risk for poor outcome. (Stroke. 2006;37:1451-1456.)

Key Words: coagulation ■ dimers ■ fibrinolysis ■ outcome ■ subarachnoid hemorrhage

Aneurysmal subarachnoid hemorrhage (SAH) is a serious disease with high rates of case fatality (≈40%) and morbidity.1,2 During aneurysm rupture, blood contacts the extravascular matrix, leading to an activation of both blood coagulation and fibrinolysis. After aneurysm rupture, high levels of markers of thrombin generation (thrombin–antithrombin complex and prothrombin fragments 1+2) and particularly of the fibrin degradation product d-dimer (marker of thrombin generation and cross-linked fibrin turnover) in plasma correlate with poor clinical condition and outcome.3–6 Elevated plasma d-dimer levels after SAH and surgery may also predict delayed cerebral ischemia4 and cerebral infarction.5 However, what has remained unclear is whether d-dimer, independently of severity of bleeding as assessed with clinical and radiological variables, is a risk factor for poor outcome.

We recently published the results of univariate association of d-dimer with patients’ clinical condition and outcome taking into account elapsed time after SAH.8 After that study, we continued to collect more patients to improve power of the study. In this study, plasma d-dimer, the most stable parameter of coagulation and fibrinolysis,6,7 was obtained on the first postoperative day after aneurysm surgery as well as at discharge from hospital to investigate whether elevated levels, independent of known risk factors, lead to increased risk for poor outcome and, in survivors, for occurrence of permanent cerebral ischemic lesions.

Patients and Methods

Patient Population
This prospective study included 136 consecutive patients (69 men and 67 women; 23.2 to 75.7 years of age; mean 50.2 years) with aneurysmal SAH who were admitted to our hospital within 48 hours after bleeding and whose aneurysms were occluded. After admission, patients and family members were interviewed with a structured questionnaire for previous diseases, medication, and health habits. Of the 44 (32%) patients with a history of hypertension (pre-SAH blood pressure readings >140/90 mm Hg or use of antihypertensive medication), 10 (7%) had values >160/95 mm Hg. Two (1%) patients had diabetes mellitus, 6 (4%) had coronary heart disease, and 27 (20%) had used nonsteroidal anti-inflammatory drugs before SAH.

Clinical Monitoring, Treatment, and Outcome
Each patient’s clinical condition on admission and during blood sampling was scored according to the World Federation of
Neurological Societies (WFNS) Grading Scale.\textsuperscript{5} All ruptured aneurysms were occluded within a mean 24 hours after bleeding (median 22; range 5 to 60 hours) by open surgery. During surgery, 39 (29%) patients underwent temporary occlusion of the proximal artery (mean 7.6 and median 5.0 minutes; in 9 patients, >10 minutes). Bolus administration of thiopental (5 to 10 mg/kg) and elevation of mean blood pressure were used routinely before temporary artery occlusion. Mannitol use was routine in all operations. Permanent artery occlusion was visible on angiography in 5 (4%) patients: clipping of the aneurysm together with the artery (in 3) or trapping or proximal clipping of a fusiform aneurysm (in 2).

Nimodipine treatment was started after admission and continued until 21 days after SAH. No hypertensive, hypervolemic, nor endovascular vasospasm therapy was routine but was used if ischemic symptoms occurred. Patients who underwent surgery received betamethasone routinely, 4 mg every 6 hours, starting before surgery and continuing until the sixth postoperative day.

Neurological examinations took place daily after admission. Delayed cerebral ischemia (reversible ischemic neurological deficit and fixed ischemic neurological deficit) was determined as a gradual development of focal neurological signs or deterioration in consciousness (decrease of $\geq 1$ point in motor response of Glasgow Coma Scale)\textsuperscript{6} for no known reason, for example, intracerebral hematoma (ICH), rebleed, hydrocephalus. Causes of poor clinical condition were determined by repeated computed tomography (CT) scanning, routine postoperative angiograms, autopsies, or laboratory investigations.

CT scans were routinely performed on admission, on the first postoperative day, at discharge, and at 3 months; scans were repeated if clinical deterioration occurred. The amount of subarachnoid blood on the CT scan at admission was categorized according to Fisher et al.\textsuperscript{7} Seventeen patients (13%) showed moderate to severe and 54 (40%) showed slight (small amount of blood in occipital horns or in the third or fourth ventricle) intraventricular hemorrhage (IVH).

Outcome was assessed at 3 months after SAH according to the Glasgow Outcome Scale (GOS) and modified Rankin Scale.\textsuperscript{8} A planned follow-up CT scan at 3 months after SAH was available for 125 (92%) patients to reveal occurrence of permanent hypodense areas consistent with cerebral infarction. Of the 11 cases with a missing CT scan, 8 had died during follow-up.

The hypodense lesions, none of which were visible on the CT scan at admission, appeared on follow-up scans of 80 (64%) patients. Causes of lesions on CT were grouped as follows: group 1: lesion in the same area as a previous ICH (n=8 patients) or lesion attributable to damage to a penetrating artery during surgery (n=8), temporary or permanent occlusion of the proximal artery of a saccular aneurysm (n=10) or other reasons (spatial pressure during surgery, angiographic complication, or cardiovascualar embolus; n=12), or multiple causes (n=5); group 2: lesion assumed to result from delayed cerebral ischemia after exclusion of other causes and appearing later than on the first postoperative CT scan (n=37 patients). On follow-up CT scans of 56 patients, lesions were small (<20 mm in diameter).

\section*{D-Dimer Analysis}

Both SAH\textsuperscript{4–6} and aneurysm surgery\textsuperscript{5,9} separately raise plasma D-dimer values. Postoperatively at 3 days after SAH, D-dimer levels are highest and show a high correlation with outcome and delayed cerebral ischemia.\textsuperscript{4,6} For this reason, our routine fasting blood samples in the morning were collected twice: (1) within 12 to 24 hours after aneurysm occlusion (mean±SD: 42±13 hours; median 40 hours after SAH), and (2) at discharge 10.3±1.2 (median 11) days after SAH.

Free-flowing blood was collected into polypropylene tubes containing the anticoagulant and processed essentially as reported previously.\textsuperscript{3} Sodium citrate (3.2%; 0.11 mol/L), at a ratio of 1 volume to 9 volumes of blood, served as the anticoagulant. D-dimers were measured with a quantitative latex assay (Tinaquant; Roche Diagnostics GmbH). According to the manufacturer, the intra-assay and interassay coefficients of variation have been <8.3%.

\section*{Statistical Analysis}

Data were analyzed with the SPSS for Windows (release 12.0.1.2003; SPSS Inc). For univariate statistics, conventional statistical tests were used. Association of continuous variables was tested by Spearman rank ($\tau$) correlation coefficients.

The effect of elapsed time after SAH and grouping variables on D-dimer values (expressed as median with the 25th and 75th percentiles or interquartile range) were compared by repeated-measures ANOVA. For this analysis, values for D-dimer were analyzed after logarithmic transformation to obtain the normal distribution and equality of variances between different groups. Odds ratios (ORs) and 95% CIs of risk factors, including their interactions, for poor outcome and for ischemic lesions on the follow-up CT scan were analyzed by unconditional logistic regression. A 2-tailed $P$ value <0.05 was considered significant.

\section*{Results}

Plasma D-dimer values on the first postoperative day (median 800 $\mu$g/L; 25th to 75th percentile range; 380 to 1705 $\mu$g/L; mean±SD; 1265±1157 $\mu$g/L) significantly ($t_r=0.577$; $P<0.001$) correlated with D-dimer values at discharge (430; 340 to 800 $\mu$g/L; 931±1179 $\mu$g/L). The decline in D-dimer values with elapsed time after SAH was also significant ($P<0.001$). Elevated plasma D-dimer levels (≥500 $\mu$g/L) on the first postoperative day compared with normal levels by baseline characteristics are shown in Table 1. Patients with elevated D-dimer levels were older and were more likely to have used antihypertensive medication. Cigarette smokers had lower D-dimer levels than did others because current cigarette smokers were significantly ($P=0.019$) younger than noncurrent smokers (47.7±10.9 years versus 53.2±14.3 years).

WFNS and IVH grades on admission, as well as outcome scales, correlated with plasma D-dimer levels both after surgery and particularly at discharge, when D-dimer also correlated with occurrence of early rebleeding, Fisher grade, and admission hyperglycemia (Table 2). D-dimer levels also predicted later occurrence of a shunt-dependent hydrocephalus. Poor-grade patients were quite frequently treated with ventriculostomy (17 patients) and later with a permanent shunt (9 patients) to improve cerebral perfusion pressure, although ventricle size was not necessarily significantly increased. Chronic shunt-dependent hydrocephalus was seen in 18 patients (13%).

Plasma D-dimer levels after surgery did not predict delayed cerebral ischemia, but at discharge, the levels were higher ($P=0.038$) in those with ischemia (632; 370 to 1456 $\mu$g/L) than in those without ischemia (406; 350 to 700 $\mu$g/L), although severity of symptoms was not significantly associated with D-dimer levels ($t_r=0.163$; $P=0.087$). Occurrence of ischemic lesions on the CT scan at 3 months did not associate with D-dimer levels after surgery (753; 350 to 1581 $\mu$g/L for those with a lesion and 1000; 370 to 1733 $\mu$g/L for those without a lesion). However, D-dimer levels were elevated ($P=0.05$) at discharge in those with an ischemic lesion compared with those without (492; 350 to 944 versus 364; 330 to 637 $\mu$g/L). The cause of the ischemic lesion did not seem to
associate with d-dimer levels at discharge (Table 2), but lesion size did (P=0.040).

When, for each patient, only the most important cause of poor outcome or clinical deterioration was taken into account, d-dimer levels after surgery were significantly (P=0.007) associated only with severe initial bleeding compared with those without any deterioration (900; 600 to 2686 µg/L; n=28 versus 563; 340 to 1000 µg/L; n=48). Plasma d-dimer values did not associate significantly with location of ruptured aneurysm, number of aneurysms (r=−0.105; P=0.22), timing of surgery (r=−0.04; P=0.62), or with duration (r=0.03; P=0.37) or number of episodes (r=0.08; P=0.33) of temporary proximal artery occlusion, permanent artery occlusion (P=0.38), or number of blood transfusion units (r=0.13; P=0.13; data not shown).

Plasma d-dimer values both on the first postoperative day and at discharge were highly correlated with outcome scales (Table 2). Particularly, those who had died or were severely disabled according to GOS (poor outcome or clinical deterioration was taken into account, D-dimer levels after surgery were significantly (P=0.007) associated only with severe initial bleeding compared with those without any deterioration (900; 600 to 2686 µg/L; n=28 versus 563; 340 to 1000 µg/L; n=48). Plasma d-dimer values did not associate significantly with location of ruptured aneurysm, number of aneurysms (r=−0.105; P=0.22), timing of surgery (r=−0.04; P=0.62), or with duration (r=0.03; P=0.37) or number of episodes (r=0.08; P=0.33) of temporary proximal artery occlusion, permanent artery occlusion (P=0.38), or number of blood transfusion units (r=0.13; P=0.13; data not shown).

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When d-dimer levels were tested according to GOS at 3 months (between factor: poor outcome versus independent state), with covariates being IVH (no/yes) and WFNS both on admission and during blood sampling (grade 1 versus others), d-dimer levels still were significantly higher in those with a poor outcome (P<0.001). In this analysis, IVH and WFNS as well as their interaction with elapsed time after SAH had no noticeable effect on the significant association between outcome and d-dimer levels. Interaction between outcome and elapsed time had a significant (P=0.028) effect on d-dimer level.

Table 3 shows that several variables obtained soon after admission predicted poor outcome in univariate analysis. In multivariate analysis (model I), the significance of Fisher grades, early rebleeding, and plasma glucose as predictors decreased because these variables significantly correlated with patient age and with occurrence of IVH or ICH. Significant independent risk factors for poor outcome were best predicted by patient age, occurrence of IVH or ICH, plasma d-dimer after surgery, and almost significantly (P=0.075) with WFNS grade >1. After additional simultaneous adjustment for gender, history of hypertension, occurrence of rebleeding, duration of temporary or permanent occlusion of the proximal artery during surgery, and for amount of subarachnoid blood, plasma d-dimer after surgery remained a significant predictor for a poor outcome (OR, 1.63; 95% CI, 1.03 to 2.60 per mg/L; P=0.038).

When the dichotomous WFNS variable was replaced by a 3-category WFNS grade (I, II–III, and IV–V) in multivariate model I of Table 3, plasma d-dimer after surgery remained a significant predictor for a poor outcome (OR, 1.60 per mg/L; 95% CI, 1.03 to 2.50). When adjustment for delayed cerebral ischemia, the significance of d-dimer increased, suggesting that the association of d-dimer with outcome was not attributable to symptomatic vasospasm (Table 3; model II).

D-Dimer level after surgery was not a risk factor for ischemic lesion on the follow-up CT (1.00; 0.72 to 1.39 per mg/L) or for symptomatic delayed cerebral ischemia (1.03; 0.74 to 1.42 per mg/L). Significant independent risk factors for ischemic lesions on the follow-up CT scan at 3...
months were WFNS grade >1 on admission (OR, 2.49; 95% CI, 1.03 to 6.04; P=0.043), a thick layer or localized subarachnoid clots on the initial CT scan (4.79; 1.95 to 11.80; P=0.001), and history of hypertension (3.65; 1.35 to 9.88; P=0.011).

**Discussion**

On the basis of this study, elevated plasma d-dimer values after early surgery, and particularly if persisting for 1 to 2 weeks after SAH, independent of severity of bleeding and several confounding factors predict poor outcome. Patients with prolonged blood hypercoagulability seem to recover less well than expected based on other prognostic factors. On the other hand, d-dimer values do not independently predict occurrence of delayed cerebral ischemia or permanent ischemic lesions visible on CT scans.

Outcome after SAH is determined principally by severity of initial bleeding. After SAH, the possibility of poor outcome rises because of disease-associated (delayed ischemia, rebleeding, and hydrocephalus) and treatment-associated (temporary or permanent proximal artery clipping, etc.) factors. Aneurysm rupture frequently also causes stress hyperglycemia, which, independent of severity of bleeding or of metabolic syndrome, elevates risk for poor outcome.

Outcome after SAH is thus probably determined by multiple independent factors.

After SAH, endothelial injury and intimal platelet accumulation are the earliest arterial wall changes. A sudden rise in intracranial pressure, but neither subarachnoid blood amount nor acute arterial hypertension, is responsible for the acute blood-arterial wall barrier disruption after experimental SAH. Tissue factor may be released through disrupted endothelium, leading to abrupt thrombin generation and coagulation activation. Because elevated d-dimer, the most stable parameter of coagulation and fibrinolysis, seems to predict independently poor outcome after SAH, it is possible that prolonged excess thrombin generation and cross-linked fibrin turnover may impair cerebral circulation after aneurysm rupture. Increased d-dimer levels may reflect ongoing thrombus formation within cerebral vessels or may be a marker of systemic hypercoagulability. d-dimer may also be an epiphenomenon of severe SAH. Among patients with brain infarction, d-dimer level at hospital admission has been considered an independent risk factor for progressing ischemic stroke.

In our patient population, d-dimer values after SAH correlated with severity of bleeding, plasma glucose values, and patient age but not with body mass index or history of hypertension. Thus, elevated d-dimer levels and increased blood coagulability after SAH are likely attributable to severe aneurysm rupture itself and only in part can be explained by stress reaction, surgery, or metabolic syndrome. This aneurysm rupture–induced increase in blood coagulability seems to be so marked that enoxaparin, a low–molecular weight heparin at a dose of 40 mg once daily for 10 days had no effect on outcome, occurrence of post-SAH cerebral infarction, or d-dimer levels. This fact did not cause bias in our study because all patients...
underwent surgery usually on an emergency basis and because neither temporary nor permanent parent artery clipping nor amount of blood transfusion units had any significant effect on the association between D-dimer values and poor outcome. Furthermore, we included in the present study only postoperative samples. In our previous article, the effect of microsurgery for ruptured aneurysm on D-dimer levels was modest (increase from 1289/11006–1812/9262 g/L at admission to 1450/11006–1308/9262 g/L after surgery; P=0.067) when compared with the effect of SAH.6 D-Dimer levels are also elevated because of venous thromboembolism, but we had only 3 cases with symptomatic deep venous thrombosis, of whom only 1 had symptoms during blood sampling at discharge. No pulmonary emboli occurred within the first 2 weeks after SAH. Some of the patients in poor clinical condition may have had asymptomatic deep venous thrombosis, but this is unlikely to have affected early-phase D-dimer levels. Furthermore, clinical condition was taken into account in our statistical analyses.

A reactant inflammatory process did not explain the association between D-dimer levels and outcome. The first samples were drawn during the early phase after SAH. For the first patients, C-reactive protein, fibrinogen, and leucocyte count were also analyzed simultaneously.6 In this subset of patients, none of these acute-phase reactants but only D-dimer was a nearly significant predictor for poor outcome (univariate OR, 2.48; 95% CI, 0.96 to 6.38 per mg/L; P=0.060). In our previous SAH study, the acute-phase reactants fibrinogen and C-reactive protein did not correlate with coagulation activity or fibrinolysis except for plasminogen activator inhibitor-1 activity.6 Furthermore, routine measurements of coagulation such as activated partial thromboplastin time and prothrombin time failed to correlate with D-dimer or outcome.

In conclusion, we found that D-dimer, which can act as a marker for fibrinolysis or hypercoagulability, independent of severity of bleeding was associated with outcome. However, this study could not show a causal relationship between increased blood coagulability and poor outcome. What also remains unknown is whether safer anticoagulants than those available nowadays, or whether induced hypertension, hemodilution, or hypervolemia started soon after aneurysm rupture, can reduce blood coagulability and thus improve cerebral blood circulation and outcome.

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References

TABLE 3. Risk Factors for Poor Outcome After SAH

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate OR (95% CI)</th>
<th>Model I OR (95% CI)</th>
<th>Model II OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>1.06 (1.02–1.09)†</td>
<td>1.05 (1.01–1.09)*</td>
<td>1.04 (0.99–1.08)</td>
</tr>
<tr>
<td>Rebleeding</td>
<td>10.50 (2.07–53.23)†</td>
<td></td>
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<tr>
<td>Plasma glucose (per mmol/L)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>At admission</td>
<td>1.36 (1.14–1.63)†</td>
<td>1.60 (1.05–2.45)*</td>
<td>1.60 (1.05–2.45)*</td>
</tr>
<tr>
<td>Fasting value after surgery</td>
<td>1.48 (1.05–2.08)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma D-dimer (per mg/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After surgery</td>
<td>1.71 (1.23–2.36)†</td>
<td>1.60 (1.05–2.45)*</td>
<td>1.60 (1.05–2.45)*</td>
</tr>
<tr>
<td>WFNS grade &gt;1 on admission</td>
<td>5.52 (2.39–12.71)†</td>
<td>2.46 (0.91–6.65)</td>
<td>2.46 (0.91–6.65)</td>
</tr>
<tr>
<td>Fisher grade on admission, thick layer or localized clots</td>
<td>3.20 (1.14–8.97)*</td>
<td>1.58 (0.54–4.62)</td>
<td>1.58 (0.54–4.62)</td>
</tr>
<tr>
<td>IVH</td>
<td>14.01 (4.60–42.68)†</td>
<td>13.28 (3.59–49.13)†</td>
<td>21.47 (4.67–98.80)†</td>
</tr>
<tr>
<td>ICH</td>
<td>3.49 (1.23–9.88)*</td>
<td>6.03 (1.54–23.57)†</td>
<td>8.18 (1.89–35.39)†</td>
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<tr>
<td>Delayed cerebral ischemia</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>RIND</td>
<td>2.32 (0.69–7.84)</td>
<td>1.10 (0.19–6.35)</td>
<td></td>
</tr>
<tr>
<td>FIND</td>
<td>3.71 (1.46–9.45)†</td>
<td>7.64 (1.86–31.39)†</td>
<td></td>
</tr>
</tbody>
</table>

Poor outcome was defined as severe disability or worse by GOS. ORs represent comparisons with patients without a risk factor, or those with WFNS grade I or with thin layer of blood in Fisher scale (reference categories of independent variables).

*P<0.05; †P<0.01.

RIND indicates reversible ischemic neurological deficit; FIND, fixed ischemic neurological deficit.


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