Reduced platelet aggregability and thromboxane release after rebleeding in patients with subarachnoid hemorrhage

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Serial blood samples were obtained from 80 patients with subarachnoid hemorrhage (SAH) to study adenosine diphosphate-induced platelet aggregation and associated thromboxane B2 release. The goal of the investigation was to detect whether reduced platelet function is involved in rebleeds. Seventeen patients (21%) suffered a rebleed, six of whom experiencing their first rebleed within 24 hours after SAH. Therefore, most platelet function studies were performed after rebleeds. Thromboxane release was lower in patients with rebleeds than in the others, both before and after rebleeding, although statistical significance was reached only in samples collected after rebleeds. Patients rebleeding within 24 hours after SAH had lower platelet aggregability (p = 0.037) than patients without a rebleed in the samples taken within 3 days after SAH. The results suggest that reduced platelet aggregability and thromboxane release are involved in rebleeds following primary SAH.

Key Words • platelet aggregation • rebleeding • subarachnoid hemorrhage • thromboxane release

Reduced platelet aggregability has been reported after subarachnoid hemorrhage (SAH); however, it is not known whether this precedes or follows SAH and an association with rebleeding remains a possibility. Platelets accumulate on the intimal surface of arteries after experimental SAH, which could lead to fewer remaining active platelets in the circulation. This can be detected as reduced platelet function after SAH, and may be one reason why rebleeding occurs most frequently during the 1st day after primary SAH, when the platelet plug and fibrin are mainly responsible for hemostasis.

We studied adenosine diphosphate (ADP)-induced platelet aggregation and the associated thromboxane release (measured as the stable metabolite thromboxane B2) after SAH by serial blood sampling from 80 patients with SAH, beginning 1 day after admission. The purpose of this study was to determine whether reduced platelet function is impaired before or after rebleeding.

Clinical Material and Methods

Patient Presentation

This prospective study included 80 patients (45 men and 35 women) with a median age of 44.2 years (range 22 to 65 years). These patients were admitted within 96 hours after the onset of SAH between February, 1985, and September, 1986, to the Department of Neurosurgery, Helsinki University Central Hospital.

The patients and their relatives were asked about the use of steroids, nonsteroidal anti-inflammatory drugs, and other drugs, and their urine was screened for salicylates. Medication with nonsteroidal anti-inflammatory drugs or its absence was confirmed by case history, urine analysis, and platelet aggregation studies. Fifty patients (63%) had not received acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs for at least 2 weeks prior to admission. After admission, patients were not given these drugs; however, patients undergoing operations routinely received 4 mg betamethasone intramuscularly every 6 hours, starting the day before surgery and continuing until the 6th postoperative day with diminished doses. Twenty-three patients (29%) were considered to have hypertension either because they had used antihypertensive medications or because their pre-SAHI blood pressure readings had repeatedly exceeded 160/95 mm Hg prior to admission.

Grades for the 80 patients on admission, according to the classification of Hunt and Hess, were as follows: 15 patients were in Grade I, 28 in Grade II, 23 in Grade III, 12 in Grade IV, and two in Grade V. The preoperative grades of the 66 patients who were operated on were as follows: 26 patients were in Grade I, 13 in Grade II, 22 in Grade III, two in Grade IV, and three in Grade V.
Neuroradiological Findings

In 77 patients SAH was verified by computerized tomography (CT). Three patients were diagnosed by lumbar puncture and operation; in two of these the CT scan failed to demonstrate bleeding. Eighteen patients (23%) had an intracerebral hematoma at least 1 cm in diameter, and 17 (21%) had an intraventricular extension of the bleeding.

The location of the ruptured aneurysm was as follows: the internal carotid artery in 19 patients; the anterior communicating artery in 22; the pericallosal artery in three; the middle cerebral artery in 29; and the basilar artery in five. In two patients, CT demonstrated SAH and suggested the presence of an aneurysm in the posterior fossa; however, this was not confirmed on carotid angiography. In both of these older patients, CT scans revealed rebleeding.

Timing of Surgery

Sixty-six patients (82.5%) were operated on. The median time from SAH (Day 0) to the operation was 5.0 days (range 0.3 to 23 days). Fifty percent of patients were operated on within 3 to 9 days after SAH. The variation in timing of surgery was due to a randomized study to evaluate this factor in a series of supratentorial aneurysms.16 Forty-eight patients in Grades I to III on admission were randomly assigned according to that study protocol: 16 were operated on within 3 days from SAH, 14 on Days 4 to 7 after SAH, and 18 at least 8 days after SAH. Eighteen patients were not operated on according to the randomized timing study for the following reasons: four patients underwent emergency operations necessitated by intracerebral space-occupying hematomas, six were admitted too late for randomization, three were not in Grades I to III on admission (they improved later), and five patients had aneurysms of the verteobasilar region.

Clinical Monitoring and Outcome

Neurological examinations were carried out daily after admission. Deterioration in the level of consciousness, development of neurological deficits, and blood pressure readings were recorded. A CT scan was performed on admission, after clinical deterioration, and on discharge. Rebleeding was suspected if there was a sudden deterioration in the patient’s clinical status (such as that typically seen with SAH) or disturbed consciousness other than seizure. Rebleeds were verified by CT and/or autopsy; lumbar puncture was not used for verification.

Delayed cerebral ischemia with a fixed neurological deficit was determined by the gradual development of totally or partially irreversible focal signs and/or deterioration in the level of consciousness. For this diagnosis intracerebral hematoma, rebleed, hydrocephalus, clipping of an arterial branch together with the aneurysm, infection, and serum electrolyte disorders were excluded as causes of deterioration by CT and routine postoperative angiography and/or at autopsy and by laboratory investigations.

Outcome was assessed in three categories at discharge and at 1 year after SAH, according to the Glasgow Outcome Scale;10 independent state (good recovery or moderate disability); dependent state (severe disability or persistent vegetative); and death.

Blood Sampling

Blood samples for analysis of platelet function were collected with a frequency of 1 sample every 1 to 4 days on weekdays from the 1st day after admission until discharge or death. One to seven samples were taken from each patient. Because thromboxane is released from platelets during irreversible aggregation, thromboxane B2 levels were determined only from samples showing irreversible (secondary phase) platelet aggregation.

Laboratory Studies

The method of ADP-induced platelet aggregation18 was applied in the study of platelet thromboxane release. Briefly, blood samples were collected with minimal stasis from patients after an overnight fast. Samples

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TABLE 1

Clinical summary of 80 patients in this series*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Without Rebleed</th>
<th>With Rebleed</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>total cases</td>
<td>63</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>sex ratio (M:F)†</td>
<td>35:28</td>
<td>10:7</td>
<td>NS‡</td>
</tr>
<tr>
<td>mean age (yrs)†</td>
<td>43.4 ± 11.0</td>
<td>45.1 ± 8.9</td>
<td>NS§</td>
</tr>
<tr>
<td>hypertension</td>
<td>18 (28.6%)</td>
<td>5 (29.4%)</td>
<td>NS§</td>
</tr>
<tr>
<td>NSAID's</td>
<td>22 (34.9%)</td>
<td>8 (47.1%)</td>
<td>NS§</td>
</tr>
<tr>
<td>IVH</td>
<td>10 (15.8%)</td>
<td>7 (41.2%)</td>
<td>0.043‡</td>
</tr>
<tr>
<td>ICH</td>
<td>12 (19.0%)</td>
<td>6 (35.3%)</td>
<td>NS§</td>
</tr>
<tr>
<td>clinical grade on admission</td>
<td></td>
<td></td>
<td>0.064†</td>
</tr>
<tr>
<td>I–II</td>
<td>37 (58.7%)</td>
<td>6 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>19 (30.2%)</td>
<td>4 (22.2%)</td>
<td></td>
</tr>
<tr>
<td>IV–V</td>
<td>7 (11.1%)</td>
<td>7 (40.7%)</td>
<td></td>
</tr>
<tr>
<td>no. of surgical cases</td>
<td>61 (96.8%)</td>
<td>5 (29.4%)</td>
<td>&lt;0.0001‡</td>
</tr>
<tr>
<td>prop clinical grade</td>
<td></td>
<td></td>
<td>NS§</td>
</tr>
<tr>
<td>I–II</td>
<td>36 (59.0%)</td>
<td>3 (60.0%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>20 (32.8%)</td>
<td>2 (40.0%)</td>
<td></td>
</tr>
<tr>
<td>IV–V</td>
<td>5 (8.2%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>delayed ischemia</td>
<td>12 (19.0%)</td>
<td>3 (16.7%)</td>
<td>NS§</td>
</tr>
<tr>
<td>outcome at 1 yr</td>
<td></td>
<td></td>
<td>&lt;0.0001‡</td>
</tr>
<tr>
<td>independent</td>
<td>51 (80.9%)</td>
<td>5 (29.4%)</td>
<td></td>
</tr>
<tr>
<td>dependent</td>
<td>9 (14.3%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>dead</td>
<td>3 (4.8%)</td>
<td>12 (70.6%)</td>
<td></td>
</tr>
</tbody>
</table>

*NSAID's = use of nonsteroidal anti-inflammatory drugs prior to admission; IVH = intraventricular hemorrhage (one patient without a CT scan on admission); ICH = intracerebral hemorrhage greater than 10 mm in diameter; NS = no significant difference. Clinical grade is according to Hunt and Hess and outcome is based on the Glasgow Outcome Scale.10 Percentages are of the total 80 patients except for preoperative clinical grade, which relates to the 66 surgical patients.

† Ages are given as means ± standard deviation.
‡ Values are derived from Fisher’s exact two-tailed test.
§ Values are derived from Student’s t-test.
‖ Values are derived from a Mann-Whitney U-test.
Thromboxane release in subarachnoid hemorrhage

were drawn from an antecubital vein into tubes containing ethylenediaminetetra-acetic acid and into plastic tubes containing 3.8% citrate for a final volume ratio of 1:10 (citrated blood was used for platelet function studies). The amount of anticoagulant was adjusted according to the packed cell volume to be the same in each case. Platelet-rich plasma (PRP) was prepared by centrifugation of blood at 330 G for 10 minutes, and platelet-poor plasma (PPP) by centrifugation of blood at 1500 G for 10 minutes. Platelet count of PRP was adjusted to $200 \times 10^3 \mu l^{-1}$ by autologous PPP. All procedures were performed at room temperature, but aggregation was not started until the samples were warmed to 37°C.

Two hours after blood sampling, platelet aggregation was measured with a dual-channel aggregometer. Aggregation was induced in PRP by adding 8 $\mu M$ ADP with continuous stirring by a magnetic stirrer at 1200 rpm for 5 minutes, then stopped by adding 1 N HCl (final concentration 0.1 mol/liter). We chose to use ADP as it is believed to be a physiological aggregation inducer; a volume of 8 $\mu M$ ADP was selected on the basis of our earlier observations.

Immediately after the addition of 1 N HCl, the tubes were transferred to an ice bath. The amount of thromboxane B$_2$ released during aggregation was measured directly from the plasma by a double antibody radioimmunoassay technique using a standardized kit. All platelet studies were performed by one laboratory technician who was blinded to the patient's history.

Statistical Analysis

Because blood samples from patients in the series were collected on different post-SAH days, the data were reorganized and analyzed by the BMDP data manager computer software program and statistical package (1988 version). For each patient the results for samples taken on the day nearest to the 2nd (range 1 to 3 days, 50 samples), 5th (4 to 6 days, 57 samples), 8th (7 to 9 days, 48 samples), and 12th (10 to 14 days, 50 samples) days after SAH were included in the statistical comparisons. In order to abolish the effect of surgical stress on the results, this reorganization was done separately for: 1) all samples, and 2) for only preoperative samples. Complete data were not available for all the patients for various reasons: death, admission more than 3 days after SAH, coincidence of the sampling time interval and a weekend, or discharge to another hospital.

For analysis of thromboxane release this reorganization was repeated only for samples with irreversible aggregation. The results of thromboxane B$_2$ release were analyzed after logarithmic transformation, which was required due to a skewed distribution.

The patients with and without a rebleed were compared by Student's or Welch's t-tests in studies of aggregation percentage and thromboxane release. The effects of time on the results were analyzed by the sign test, the paired t-test, or the Wilcoxon signed rank test. Nonparametric statistical significances were calculated according to the Mann-Whitney U test and Fisher's exact test. All tests were two-tailed.

Aggregation percentages are expressed as means ± standard error of means, and thromboxane B$_2$ values as medians and ranges.

Results

Occurrences of Rebleeding

Seventeen patients (21%) suffered a rebleed. Six patients had their first rebleed within 24 hours after primary SAH. In the remaining group, rebleeds occurred from 4 to 11 days after SAH, with two patients suffering rebleeds in the 4th week. Four patients had two rebleeds and three suffered three rebleeds.

Of the six rebleeds occurring in the 1st 24 hours after the primary SAH, four were diagnosed by clinical symptoms of acute deterioration and two by CT scanning. Three of the six patients died due to the rebleed. Of the 21 rebleeds occurring more than 24 hours after SAH, 12 were diagnosed by CT scanning, five by autopsy, three by acute clinical deterioration with loss of consciousness but without verification by CT scan, and one by extravasation of contrast medium during angiography.

Eight (27%) of the 30 patients who had taken non-steroidal anti-inflammatory drugs prior to admission had at least one rebleed after admission as did nine (18%) of the 50 patients who had not used those drugs, the difference not being significant (p = 0.40). One of the 30 patients with previous intake of these drugs and five of the 50 patients without drug intake had rebleeds within 24 hours after SAH, suggesting that previous medication of anti-inflammatory drugs did not influence the occurrence of early rebleeds. Most patients receiving nonsteroidal anti-inflammatory drugs used analgesics to relieve the symptoms of primary SAH.

The occurrence of rebleeding was not associated with sex, age, or previous hypertension (Table 1). Generally, patients with a rebleed were in poorer condition on admission to our institution; some had deteriorated in the hospital of first admission or during transportation. Due to their poor clinical condition, surgery was performed less often in these patients (five of 17 cases, 29.4%) than in those without rebleeding (61 of 63 cases, 96.8%). Also, presence of intraventricular hemorrhage on entry CT scans was more common in patients with a rebleed (seven of 17 cases, 41.2%) than in those without (10 of 62 cases, 16.1%) (p = 0.043). Delayed ischemia with a fixed neurological deficit was equally common in both groups (17.6% in the rebleed group and 19% in those without rebleeds) (Table 1).

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* Dual-channel aggregometer manufactured by Chronolog Corp., Havertown, Pennsylvania.
† Radioimmunoassay kit supplied by New England Nuclear Co., Boston, Massachusetts.
TABLE 2
Platelet aggregability and % aggregation in patients with SAH

<table>
<thead>
<tr>
<th>Study &amp; Group</th>
<th>0 to 3 Days</th>
<th>4 to 6 Days</th>
<th>7 to 9 Days</th>
<th>10 to 14 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>aggregability†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no rebleed</td>
<td>20.7 (74)</td>
<td>27.2 (93)</td>
<td>24.1 (96)</td>
<td>27.0 (100)</td>
</tr>
<tr>
<td>rebleed</td>
<td>3.4 (43)</td>
<td>6.0 (100)</td>
<td>5.0 (100)</td>
<td>4.0 (100)</td>
</tr>
<tr>
<td>% aggregation‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no rebleed</td>
<td>64.3 ± 2.5</td>
<td>67.2 ± 2.6</td>
<td>64.9 ± 3.2</td>
<td>78.4 ± 3.5</td>
</tr>
<tr>
<td>rebleed</td>
<td>59.6 ± 5.6</td>
<td>57.8 ± 7.4</td>
<td>63.4 ± 5.7</td>
<td>60.8 ± 15.2</td>
</tr>
</tbody>
</table>

* Data from patients without prior use of nonsteroidal anti-inflammatory drugs, according to time after primary SAH and presence of rebleeding. SAH = subarachnoid hemorrhage.
† Aggregability values = ratio of patients with reversible aggregation to patients with reversible aggregation. Numbers in parentheses are percentage of patients with irreversible aggregation. Early rebleed = rebleed within 24 hours after primary bleed; value derived using Fisher's exact two-tailed test, significant difference between early rebleeding and no rebleeding, p = 0.037.
‡ Aggregation is measured as the maximum percentage change in light transmittance within 5 minutes after addition of 8 μM adenosine diphosphate to the test tube. Data are means ± standard errors of the means.

Platelet Aggregability

A decreased platelet aggregability was found in samples drawn within the first 6 days post-SAH from patients previously using nonsteroidal anti-inflammatory drugs. After exclusion of these samples the aggregability was found to be lower during the first 3 days after SAH than thereafter (difference between 0 to 3 and 4 to 6 days; sign test of 22 samples, p = 0.031). We did not find significant statistical differences in aggregability between the patients with and without rebleeding, except that in samples drawn within 3 days post-SAH, irreversible aggregation was less common in patients with an early rebleed (occurring within 24 hours after the primary SAH) than in patients without a rebleed (p = 0.037) (Table 2).

Only one (20%) of five patients with a rebleed during the 1st day post-SAH compared to 20 (74%) of 27 without a rebleed had irreversible platelet aggregation. In later rebleeds, a comparable effect was not seen, which could be explained by the smaller number of patients with a rebleed and by the increasing aggregation with time after SAH. The aggregation curves of the patients (measured as the maximum percentage change in light transmittance within 5 minutes after addition of 8 μM ADP) did not differ according to the presence or absence of rebleeding (Table 2).

Thromboxane Release

Since thromboxane is released from ADP-stimulated platelets during the secondary phase of platelet aggregation (irreversible aggregation), we excluded from our analysis irreversible aggregations and samples from patients with previous use of nonsteroidal anti-inflammatory drugs. Thromboxane B₂ release increased significantly with time in samples drawn from 16 patients between Days 0 to 3 and Days 4 to 6 (p = 0.044). As a whole, thromboxane release in patients with rebleeding was significantly decreased in samples drawn from 7 to 9 days after SAH (p = 0.033) (Table 3).

Thromboxane B₂ release in four patients with samples drawn before rebleeding, within 4 to 6 days post-SAH, was lower than that of patients without rebleeding; however, a statistically significant difference was not achieved, possibly because of the small number of rebleeds (Table 3).

In three patients suffering rebleeds 4 to 6 days after SAH, thromboxane B₂ release in samples taken between 7 to 9 days post-SAH was lower than in corresponding samples from patients without rebleeding (p = 0.051).

TABLE 3
Median platelet aggregation-induced thromboxane B₂ release and formation capacity

<table>
<thead>
<tr>
<th>Study &amp; Group</th>
<th>Occurrence of Rebleed after SAH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 to 3 Days</td>
</tr>
<tr>
<td>thromboxane B₂ release (fmol/10⁷ platelets)</td>
<td></td>
</tr>
<tr>
<td>no rebleeding</td>
<td>1230 (405–4409)</td>
</tr>
<tr>
<td>rebleeding</td>
<td>1936 (779–2248)</td>
</tr>
<tr>
<td>pre-rebleeding (4 samples)</td>
<td>1504 (463–2124)</td>
</tr>
<tr>
<td>post-rebleeding (3 samples)</td>
<td></td>
</tr>
<tr>
<td>thromboxane B₂ formation capacity (nmol/liter)</td>
<td></td>
</tr>
<tr>
<td>no rebleeding</td>
<td>26.9 (8.1–88.2)</td>
</tr>
<tr>
<td>rebleeding</td>
<td>21.9 (11.8–31.2)</td>
</tr>
<tr>
<td>pre-rebleeding (4 samples)</td>
<td></td>
</tr>
<tr>
<td>post-rebleeding (3 samples)</td>
<td></td>
</tr>
</tbody>
</table>

* Data from patients with reversible aggregation were excluded. Values represent the median results; numbers in parentheses denote the range.
† Significant difference between rebleeding and no rebleeding: Welch's t-test, p = 0.033; post-rebleeding, Student's t-test, p = 0.031.
‡ Significant difference between rebleeding and no rebleeding: Student's t-test, p = 0.026; post-rebleeding, Student's t-test, p = 0.0005.

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The thromboxane release had probably increased by that time in the latter group (Table 3). When only preoperative thromboxane B₂ values in three patients with rebleeds (median 1562 fmol/10⁷ platelets, range 486 to 2297 fmol/10⁷ platelets) were compared at the same time interval to seven patients without rebleeds (median 3809 fmol/10⁷ platelets, range 1206 to 6492 fmol/10⁷ platelets), the difference was less apparent, probably due to the small number of patients. However, there remained a trend toward lower thromboxane B₂ release in patients with a rebleed (p = 0.088).

Thromboxane Formation Capacity

The thromboxane B₂ release in a liter of blood was determined by the release per 10⁷ platelets and the platelet count in whole blood. When the capacity of blood to form thromboxane was calculated in this way, the results showed a pattern similar to that for thromboxane B₂ release (adjusted to 10⁷ platelets) except that the formation capacity was clearly lower after rebleeding in samples taken 7 to 9 days post-SAH (p = 0.0005) (Table 3). Preoperative thromboxane B₂ formation capacity in a liter of blood at this same time interval was significantly lower in three patients after rebleed (median 14.4 nmol/liter, range 13.3 to 30.8 nmol/liter) than in seven patients without rebleed (median 81.9 nmol/liter, range 51.1 to 201.3 nmol/liter) (p = 0.0014).

Patient Outcome

As expected, patients with rebleeding had a significantly poorer outcome than the other patients (p < 0.0001) (Table 1). Death occurred in 12 (70.6%) of the 17 patients with rebleeding (nine due to a rebleed and three due to delayed ischemia), compared to only three (4.8%) of 63 patients with no rebleeding (two due to delayed ischemia and one due to the primary bleed). Previous use of nonsteroidal anti-inflammatory drugs did not have an effect on the outcome.

Discussion

The risk of rebleeding is greatest on the day of initial SAH,¹¹⁻¹² possibly within 6 hours after SAH.²⁹ This may be due to an insufficient platelet-fibrin plug, although no evidence of this has emerged so far. The other possible peak in the occurrence of rebleeds is at 1 week after SAH,¹³⁻¹₁,²² which may be due to increased fibrinolytic activity of blood.

Coagulation and Fibrinolytic Activity

Ettinger¹ showed both increased coagulability and activation of fibrinolytic mechanisms of blood within the first 48 hours from SAH, but three patients in his series with later rebleeding did not have increased fibrinolysis. Utley and Buckell²⁰ demonstrated longer thromboplastin generation and recalcification times and a tendency toward increased blood fibrinolytic activity in patients with rebleeding 0 to 6 days after SAH; however, it was not known if these changes occurred before rebleeding. Fibrinolytic activity in cerebrospinal fluid (CSF) increases gradually for the first 10 days after SAH,¹³⁻¹⁴ which may explain the efficiency of antifibrinolytic agents in diminishing the occurrence of late rebleeding.¹³⁻²¹ Recently, Kasuya, et al.,¹⁴ showed a strong activation of the coagulation system in CSF in the early stage of SAH. Fibrinopeptide A and bradykinin concentrations decreased rapidly after the 1st day post-SAH.

Platelet Function

Platelets are responsible for primary hemostasis after hemorrhage and, thereafter, coagulation factors and collagen secure the scar.¹³ To our knowledge, only one study concerning platelet function in SAH has been reported.¹⁹ In that study a reduced aggregability and aggregation percentage was observed after SAH, but these parameters did not predict a possible later rebleeding. Decreased platelet function after primary SAH might explain "ultra-early" rebleeding occurring within the first few hours after SAH on the basis of an unstable platelet plug after the primary bleed.²³ Thereafter, a plug of platelets and fibrin decreases the risk of rebleeding for a few days.

Thromboxane Release

Thromboxane A₂, released by platelets, is a potent vasoconstrictor and platelet aggregating agent. A labile bicyclic compound formed from prostaglandin endoperoxides, thromboxane A₂ has a half-life of about 30 seconds and is rapidly hydrolysed to its stable biologically inactive metabolite, thromboxane B₂.¹⁵ Measurements of thromboxane B₂ are used as an indicator of thromboxane A₂ production.

In the present study, platelet aggregability and thromboxane release were decreased after rebleeding. Because nonsteroidal anti-inflammatory drugs decrease platelet aggregability and thromboxane release, patients with previous use of these drugs were excluded from analysis in order to abolish the confounding effect of these drugs on the results. Many rebleeds occurred during the first few hours after the primary bleed and may have been caused by decreased platelet aggregability. This possibility is supported by the observation that in all patients aggregability was lowest within 3 days after SAH and especially low after early rebleeding.

Reduced thromboxane release during platelet aggregation might be involved in rebleeding. In patients with pre-rebleed samples collected 4 to 6 days after SAH, the level of thromboxane release was lower than in patients without a rebleed, although a statistically significant difference was not achieved perhaps due to the small number of patients with a rebleed. A significant difference was observed only after rebleeds in samples collected 7 to 9 days after SAH, one possible explanation being that thromboxane release and formation capacity had time to increase in patients without rebleeds while in patients with rebleeds thromboxane

release remained lower. The difference between patients with and without rebleeds was clearer.

The most active platelets might be adherent to the endothelium near the aneurysm, leading to liberation of vasoactive agents like thromboxane and serotonin. This in turn may cause vasoconstriction and increased platelet aggregability in the local circulation, and thus be involved in the prevention of rebleeds in spite of decreased platelet function in the systemic circulation. The other mechanism in preventing rebleeds might be liberation of thromboxane into the CSF from platelets during SAH. It has been shown that thromboxane concentrations in the CSF are greatest within a few days from SAH. Thromboxane might tighten the plug in spite of the fibrinolytic effect of CSF.

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