Preoperative management of patients with ruptured intracranial aneurysms

JOSEPH RANSOHOFF, M.D., ALBERT GOODCOLD, M.D., AND M. VALLO BENJAMIN, M.D.

Departments of Neurosurgery and Neurology, New York University Medical Center, New York, New York

The authors report their experience with the use of an antifibrinolytic agent and hypotensive drugs in the prevention of rebleeding from recently ruptured intracranial aneurysms and conclude that both measures are of suggestive value. With further refinement in these techniques an additional reduction of early rebleeding may be expected. Secondary cerebral vasospasm remains the major obstacle to early recovery and definitive surgery for ruptured intracranial aneurysms.

KEY WORDS: aneurysm, management, hypotension, antifibrinolysis, epsilon-aminocaproic acid.

Three short-term problems face the patient with a bleeding intracranial aneurysm. First, he must survive the initial effects of the hemorrhage, which include destruction of brain by the force of arterial blood, intracerebral hematoma, and sharply increased intracranial pressure, factors which account for a high percentage of deaths in the first 24 hours after hemorrhage. Second, if he has survived in fairly good neurological condition (Grades I, II, and III), the most immediate hazard is the prospect of bleeding again. Third, there is the threat of cerebrovasospasm with subsequent ischemia and edema, particularly during the first 3 to 7 days after hemorrhage.

Drake has stated: "It is probably true that if we could learn how to keep a patient safe from rebleeding for a week or longer, especially in obtunded patients with cerebral symptoms, the problems of surgery of ruptured intracranial aneurysm would nearly be solved."

Two avenues of clinical investigation have recently received attention, both designed to reduce the incidence of early rebleeding. Norlén and Thulin reported the use of epsilon-aminocaproic acid (EACA) to control bleeding from vascular malformations during surgery. Mullan and Dawley treated 30 patients with aneurysmal hemorrhage with this drug, including those ineligible for surgery, or refusing or awaiting it; they reported two instances of rebleeding, one fatal. Fourteen of their patients underwent surgery at times ranging from a few days to 3 weeks. Patients with a systolic blood pressure over 175 mm Hg were also treated with hypotensive agents. While these authors commented that a great deal more work would have to be done with the use of antifibrinolytic agents, their results were certainly encouraging.

Use of hypotensive agents to prevent rebleeding in both normotensive and hypertensive individuals (as reported by Slosberg) was investigated by scientists under the
Comparative Treatment Study of Intracranial Aneurysms supported by the National Institute of Health. In the case of internal carotid aneurysms, where a large sample was collected, hypotensive treatment in the first week after hemorrhage was proven to be statistically superior to bedrest alone in terms of preventing rebleeding and lowering the overall mortality rate.\textsuperscript{11}

**Plan of Clinical Investigation**

As a member of the Comparative Treatment Study Group, we had gained experience with both hypotensive agents and EACA. We decided to review the cases of 50 patients with recent aneurysmal hemorrhage treated with either or both of these techniques (called Group A in this report), and for comparison to undertake a formal study of the combination of EACA and hypotension (Group B). The plan of our clinical investigation (Group B) was as follows:

1. All patients admitted to the New York University Medical Center (Bellevue Hospital, University Hospital, and Manhattan Veterans Administration Hospital) within 1 week of a proven subarachnoid hemorrhage from a proven intracranial aneurysm or aneurysms would be started on a regimen of EACA and hypotensive therapy.
2. This regimen would be continued at least through the 14th day following the hemorrhage, surgery being withheld except as an emergency procedure for the removal of a life-threatening hematoma.
3. No patient was to be excluded from this clinical trial, irrespective of condition on admission, location of aneurysm or aneurysms, concurrent medical disease, age, or sociological factors. Angiography was carried out within the first 12 hours of admission on all patients with a spontaneous subarachnoid hemorrhage.
4. Patients were graded on the basis of the widely accepted classification of Botterell, \textit{et al.}\textsuperscript{3}

**Antifibrinolytic Therapy**

Epsilon-aminocaproic acid (EACA) was administered intravenously or orally at a standard dosage of 24 gm per day after an initial "loading" dose of 6 gm. The oral dose was 3 gm every 3 hrs; the intravenous schedule was 1 gm every 1 hr.

**Hypotensive Therapy**

\textbf{Drugs.} Phenobarbital, 45 mg four times a day, was instituted orally or intramuscularly in all patients and maintained throughout the period of acute hypotensive therapy.

Aldomet (methyl dopa) 250 mg was started orally or intravenously within the first 12 hours after admission and repeated twice a day thereafter. This drug was increased as needed to a total daily dose of 3000 mg.

Diuuril (chlorothiazide), or hydrodiuril, was added in the great majority of cases to maintain adequate levels of hypotension. Dosages varied from 500 to 1500 mg per day in divided doses, initially intravenously and later orally. Potassium was replaced when blood levels fell below 3.5 mEq.

\textbf{Monitoring.} The patient's blood pressure was monitored with the use of the Arteriosonde Blood Pressure Monitor (Roche Electronics), which automatically records blood pressure via an external cuff utilizing the Doppler effect obtained from the brachial artery.

\textbf{Blood Pressure Levels.} Our goal was to maintain blood pressure at a level of 15\% below admission recordings for normotensive individuals. Patients with admission pressures between 140 and 170 mm Hg systolic were maintained at a 20\% reduction of pressure and those over 170 mm Hg systolic at a 25\% reduction. It is obvious that many patients exhibited abnormally high pressures on admission, which fell during the first 12 hours of hospitalization. We were generally satisfied, therefore, to observe pressures in the 90 to 100 mm of Hg systolic range during the period of acute therapy.

**Supportive Care**

Anticonvulsants were routinely administered, phenobarbital being used for its anticonvulsant effect as well as for the induction of hypotension. Corticosteroids were administered in patients with increasing intracranial pressure and papilledema as clinically indicated, at times supplemented by osmotic diuretics. Tracheostomy and assisted respiration were used as needed, as well as antibi-
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tics, gastric feedings, and other modalities of general supportive care in the neurologically ill patient. Temperature was controlled to maintain normothermia; hypothermia was not used.

Definition of Rebleeding

Lumbar puncture was carried out within the first 12 hours after admission to establish a baseline for future reference. Indications for repeat puncture included rapid deterioration of the state of consciousness, progression of neurological signs, seizures, increased headache, persistence of neck stiffness, or unexplained temperature elevations. Lumbar puncture was carried out on 2 consecutive days in patients suspected of rebleeding if the initial repuncture did not provide positive evidence of hemorrhage. Increased number of red cells, increased xanthochromia, or both were considered to be positive evidence of rebleeding.

Results

Group A: 50 Nonconsecutive Patients Treated with EACA, Hypotension, or Both

This initial group of patients was not treated for any set period following hemorrhage; therapy was not selected on any programmed basis nor were all patients admitted during this period subjected to these treatments. Thirty-five patients received EACA for periods varying from 3 to 26 days. Thirty patients received hypotensive drugs for periods of 6 to 45 days. Fifteen patients received both EACA and hypotensive drugs.

The main value of this group was that it served as a representative sample of the patient population seen in our medical center and documented the fact that the 50 Group B patients below were not accidentally or inadvertently a favorable sample. Other observations were also useful.

No thrombotic episodes were noted in the patients receiving EACA. No untoward effects were observed that could be attributed to the use of hypotensive agents in this group, although in our earlier experiences we had noted difficulties when the blood pressure had been dropped too precipitously in conjunction with increased intracranial pressure. Finally, the 15 patients who received both therapies appeared to tolerate the combination of drugs sufficiently well to allow us to study their combined effect in a more organized program. Since there were only 12 instances of rebleeding in this group; we were encouraged to pursue these therapies.

Group B: 50 Consecutive Patients Treated with EACA and Hypotension for 2 Weeks Following a Hemorrhage

Age distribution and aneurysmal sites were not significantly different in the total of 100 patients (Groups A and B) and those in Group B (Tables 1 and 2).

There was a higher percentage of Grade IV and V patients in the Group B series at the time of the institution of therapy because some of the sicker patients were not treated in the earlier (Group A) phase of this investigation (Table 3). As can be seen in Table 4, therapy was instituted within the first 3 days following the hemorrhage in three fourths of the patients, one fourth being ad-
TABLE 3
Clinical status of patients at time of institution of therapy

<table>
<thead>
<tr>
<th>Clinical Status</th>
<th>Groups A and B Rebleeding Cases</th>
<th>Group B Rebleeding Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Grade II</td>
<td>30</td>
<td>14</td>
</tr>
<tr>
<td>Grade III</td>
<td>45</td>
<td>17</td>
</tr>
<tr>
<td>Grade IV</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Grade V</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100</strong></td>
<td><strong>50</strong></td>
</tr>
</tbody>
</table>

mitred and treated between the 4th and 7th day after their hemorrhage.

Analysis of Rebleeding Episodes in Group B. Of passing interest is the fact that three of the six rebleeding episodes occurred in patients with anterior communicating aneurysms and two in patients with multiple aneurysms (Table 1). We are not able to attach any significance to the fact that in this small series no rebleeding was seen from the internal carotid aneurysms.

All of the six rebleeding episodes were in patients who had been started on therapy within 3 days after their initial hemorrhage (Table 4); three of the rebleeding episodes occurred during the first week of treatment (Table 5), one occurred in the 3rd week, and two beyond the 3rd week. One of the late hemorrhages occurred in an obtunded patient with a middle cerebral aneurysm who survived the second hemorrhage and whose aneurysm was eventually successfully ligated.

No surgical candidate in Grades I or II at the time of institution of therapy rebled (Table 3). Rebleeding did occur, however, in a patient with an anterior communicating aneurysm who had improved to a Grade II at the time of his fatal rebleeding episode on the 8th day after his initial ictus. He was on steroids for increased intracranial pressure and also had been hypertensive for a long time.

There were only two rebleeding episodes in 32 Grade I, II, and III patients.

Thus, six rebleeding episodes, five of them fatal, occurred in this group of 50 patients treated for a total of 306 patient days. One of the six was a possible candidate for surgical intervention at the time of the second hemorrhage.

Discussion

The results of our treatment in these patients, both the initial 50 and the subsequent 50 treated consecutively, cannot be considered to be of statistical significance. The number of patients is too small and there are obviously no control (untreated) patients available for the type of comparison necessary to unequivocally prove the value of hypotensive and antifibrinolytic therapy.

An excellent review of the extensive literature on the incidence of rebleeding from intracranial aneurysms is available in Pakarinen's monograph. The available figures cannot be compared with our results because only rarely are they correlated with the patient's clinical state, a factor of considerable importance if one is planning eventual surgical intervention. McKissock et al., however, reported 18 recurrent hemorrhages, 13 fatal, in a series of 55 middle cerebral aneurysms; all patients were considered Grade I or II in the first 2 weeks following admission to the hospital. This represents a 23% mortality rate. Drake has reported that of 61 Grade I or II patients on bedrest for 1 week before surgery, seven died of rebleeding. This represents an 11% loss of possible surgical candidates during the first week following hemorrhage.

Calculated in the same fashion, our statistics show the loss of no patients from the initial 15 in Grades I or II; however, one patient improved from a Grade III to a Grade II status and rebled fatally on day 8 after his initial hemorrhage. Considering the 26 patients who were eventually operated on as an elective procedure, the one dying of postop-

TABLE 4
Relationship of rebleeding to day that therapy was instituted following initial hemorrhage in 50 Group B patients

<table>
<thead>
<tr>
<th>Day After Hemorrhage</th>
<th>Group B</th>
<th>Rebleeding Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 3</td>
<td>37</td>
<td>6</td>
</tr>
<tr>
<td>4 to 7</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>50</strong></td>
<td><strong>6</strong></td>
</tr>
</tbody>
</table>
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erative infection and the two who made a good recovery without surgery (Table 6), we experienced one fatal and one nonfatal incidence of rebleeding in a total of 29 patients who eventually reached a Grade I or II status.

Mullah and Dawley's figure of two deaths in 30 patients from rebleeding is impressive; the clinical grade of these patients was not noted in this preliminary paper which represents the major report in the literature concerning the use of EACA alone.

Hypotension alone was used in the treatment of 109 cases of aneurysmal bleed reported in the Cooperative Aneurysm Study: 12 of these were listed as poor surgical candidates. There was a 48% mortality rate. Sahs concludes that in 46 "reasonable risk" patients, there is a suggestion that the incidence of rebleeding may have been diminished. Their overall 48% mortality rate can be compared with a 36% mortality in our 50 patients treated with both hypotension and EACA (Table 6).

Additional investigation into the mechanism and selection of antifibrinolytic drugs is surely warranted. EACA appears to act principally via inhibition of plasminogen activator substances occurring in blood and body tissues and to a lesser degree through its direct antiplasmin effect. Theoretically, therefore, EACA retards fibrin breakdown in an intra-aneurysmal clot and hence prevents rebleeding. It also has some effect on maintenance of fibrin in vitro. EACA has little effect, however, against plasmin and no effect whatsoever against other powerful intra- and extracellular proteolytic enzymes that attack fibrin. EACA given to dogs in doses sufficiently high to inhibit general plasma fibrinolysis did not inhibit local fibrinolysis in thrombin-induced intravascular clots. At best, therefore, EACA appears to offer incomplete protection against fibrinolysis.

A second series of questions relates to fibrin itself. How long can fibrin effectively seal a wound, in this case a defect in the dome of an aneurysm? Is there a difference between the fibrin laid down within the aneurysm itself and that which is applied from the extravascular tissues, i.e., arachnoid and dura? Crompton suggests that "the cellular and fibrinous infiltrate found in the walls of unruptured aneurysms... results in weakening of the aneurysm wall." Although there are many references in the literature stating that fibrin stimulates granulation tissue production, the effect of an excess or abnormally long persistence of fibrin on wound healing is not clear.

We must keep in mind that our goal is to develop a short-term regimen by which patients with an aneurysmal hemorrhage can be carried through the critical 2-to-3-week period and then be treated by elective surgical intervention. In these patients we are not interested in long-term "wound" healing. On this basis we believe additional attempts to stabilize fibrin are justified. Plasma factor XIII converts urea soluble fibrin to urea insoluble fibrin via the mechanism of cross linkage. Cross-linked fibrin is more resistant to fibrinolysis. The effect of excess factor

### Table 5

**Relationship of total days treatment to time of rebleeding in 50 Group B patients**

<table>
<thead>
<tr>
<th>Days of Treatment*</th>
<th>Group B</th>
<th>Rebleeding Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>less than 7</td>
<td>12</td>
<td>3 (3 fatal)</td>
</tr>
<tr>
<td>7 to 14</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>15 to 21</td>
<td>13</td>
<td>1 (1 fatal)</td>
</tr>
<tr>
<td>greater than 21</td>
<td>7</td>
<td>2 (1 fatal)</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>6</td>
</tr>
</tbody>
</table>

* These 50 patients received a total of 306 patient days of treatment during which time six incidents of rebleeding occurred on days 4, 5, 6, 20, 21, and 25 of treatment.

### Table 6

**Final outcome in 50 Group B patients**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead: rebleeding</td>
<td>5</td>
</tr>
<tr>
<td>Spasm and edema</td>
<td>10</td>
</tr>
<tr>
<td>Emergency craniotomy</td>
<td>2</td>
</tr>
<tr>
<td>Elective craniotomy</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
</tr>
<tr>
<td>Alive: elective craniotomy</td>
<td>25</td>
</tr>
<tr>
<td>Long-term hypotension</td>
<td>7 (2 excellent)</td>
</tr>
<tr>
<td>(5 incapacitated)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
</tr>
</tbody>
</table>

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XIII in the nondeficient subject is not known, and while it has been demonstrated in tissues,\textsuperscript{14} its distribution in the various compartments of the nervous system may be of importance from a therapeutic point of view. In those patients who do not come to surgery, factor XIII may have additional long-term value related to its positive effect on fibroblast formation.

Another area for investigation may be the use of proteinase inhibitors, potentially more effective than EACA and other synthetic inhibitors. Trasylol, an extract of bovine lung and salivary gland, is a "wide spectrum" proteinase inhibitor that has been used as an antifibrinolytic agent. Sicuteri\textsuperscript{14} administered trasylol to patients with subarachnoid hemorrhage with the implication that it entered the CSF and might reduce the irritative effects of blood in the subarachnoid space. Direct evidence as to the CNS distribution of this drug and similar large molecular weight polypeptides is, however, still lacking.

Our experience with the use of an antifibrinolytic agent and hypotensive drugs in the prevention of rebleeding from recently ruptured intracranial aneurysms leads us to the conclusion that both measures may be valuable. With further refinement in these techniques, an additional reduction of early rebleeding may be expected.

References


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Address reprint requests to: Joseph Ransohoff, M.D., 550 First Avenue, New York, New York 10016.

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