Influence of Timing of Admission After Aneurysmal Subarachnoid Hemorrhage On Overall Outcome

Report of the Cooperative Aneurysm Study

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SUMMARY The overall management results after aneurysmal rupture were studied in 158 patients admitted to the hospital on day 0-3 and 175 patients admitted on day 4-7 following subarachnoid hemorrhage. In this series surgery was planned no sooner than 12 days following the ictus. Despite effective medical and surgical therapy overall results were disappointing: 3 months following the initial hemorrhage only 43% of patients in the 0-3 day group and 53% of patients in the 4-7 day group were capable of independent functional living. Patients admitted on days 4-7 also had a lower mortality rate, re-bleed less frequently, and had lower postoperative mortality and morbidity than those admitted on days 0-3. For reasons not well defined, time of admission following aneurysmal SAH has an important influence on outcome. Accordingly, in evaluating outcome for patients with ruptured aneurysms treated with different therapeutic modalities, time of admission must be carefully controlled.

IN RECENT YEARS interest has again centered on early intracranial operation for ruptured saccular aneurysms.1 Not only is the role of early surgery debatable, but proponents disagree about its optimal timing. An initial step in evaluating the efficacy of early operation is comparison of results of management between series of patients admitted in similar time periods after subarachnoid hemorrhage (SAH) but having operation at different intervals following the ictus. The abundant literature describing surgical results is of little assistance because it addresses only outcome for patients having operation rather than the overall management results relevant to the population at risk. Unfortunately, reports of overall treatment from time of SAH until convalescence are scarce and those which do exist are difficult to compare because of differences in grading neurological status, interval between SAH and admission and operation, timing of ensuing examinations, and other important parameters.

This report presents the results of management of a series of patients admitted within 7 days of SAH (day 0 is the day of hemorrhage) for whom surgery was planned no sooner than 12 days after the bleed, and compares the outcomes among patients admitted on days 0 to 3 with those patients admitted on days 4 to 7.

Patient Material and Methods

This study is based on 511 patients with verified aneurysmal SAH admitted to 11 participating institutions of the Cooperative Aneurysm Study (CAS) from July, 1974, until July, 1977 (Appendix). All patients were randomized to preoperative care with or without fluid restriction. The degree of fluid restriction did not influence the outcome. 6 The 183 men and 328 women were admitted to the study within 7 calendar days of the most recent SAH, after confirmation of a ruptured aneurysm by the presence of bloody cerebrospinal fluid (CSF) on lumbar puncture and angiographic demonstration of one or more aneurysms. Aneurysms arose from the internal carotid artery in 113 patients, middle cerebral artery in 71 patients, anterior cerebral artery in 169 patients and vertebrobasilar arteries in 39 patients. Multiple aneurysms were found in 119 patients.

On admission, the neurological status was characterized as good (equivalent to Hunt’s grades I, IA, II and III) or poor (equivalent to Hunt’s grades IV and V) (table 1). Among the patients admitted on days 0 to 3, 76% (190/250) were in good condition, while 84% (219/262) of those admitted on days 4 to 7 were in good condition (table 1). In all patients planned time of operation was at least 12 days after the last SAH. During the interval, patients were treated with bed rest, sedatives, analgesics, anticonvulsants and antifibrinolytic agents — either aminocaproic acid in a daily dosage of 36 grams or tranexamic acid in a daily dosage of 12 grams. While mannitol and corticosteroids were administered as needed, antihypertensive drugs were not routinely used.

Ultimately, 158 patients admitted on days 0 to 3 and 175 patients admitted on days 4 to 7 had surgery. Intracranial operations were performed upon 141 patients admitted on days 0 to 3 and upon 143 patients admitted on days 4 to 7. The remainder of the patients had carotid ligation. The median time of carotid artery ligation or intracranial operation was 16 days, operations were performed from 12 to 76 days after the ictus. If antifibrinolytic therapy was continued after 14 days following the hemorrhage, the dosage was tapered before being discontinued.

Occurrence of re-bleeding, change in neurological condition, and survival status were recorded 14 and 90
days after SAH. Re-bleeding was suspected if the patient developed a new or severe headache or had a rapid change in neurological status. This was confirmed by appearance of fresh blood on CSF examination or at necropsy. The 90-day neurological status of surviving patients was considered favorable if the patient had no symptoms or minimal residual impairment and unfavorable if the patient had persistent major neurological deficits or required nursing care.

Results

The 249 patients admitted on days 0 to 3 and 262 patients admitted on days 4 to 7 were comparable in the percentage of those having intracranial operation or carotid artery ligation, in the interval from SAH until operation and in their condition at time of operation (table 1). Good condition on admission was found in 76% (190/249) of patients admitted on days 0 to 3 and in 84% (219/262) of the patients admitted on days 4 to 7. The 14-day survival differed between the two groups, 87% (216/249) of those patients admitted on days 0 to 3 survived compared to 93% (244/262) of those patients admitted on days 4 to 7.

As can be seen from table 2, overall results were better for patients admitted on days 4 to 7 than on days 0 to 3. At evaluation 90 days after the SAH, approximately 43% (108/249) of all patients admitted on days 0 to 3 had a favorable outcome and 34% (85/249) were dead, while in patients admitted on days 4 to 7, 53% (138/262) had a favorable outcome and 24% (62/262) were dead. This pattern of a more favorable outcome and lower mortality for all patients was the same for the subgroups of patients admitted in good or poor neurological status.

Re-bleeding within 14 days of the most recent SAH was higher in patients admitted on days 0 to 3 than in those admitted on days 4 to 7 for all patients (12% vs 5%) as well as the sub-groups admitted in good neurological status (10% vs 5%) and those admitted in poor neurological status (20% vs 5%) (table 3).

In those patients subjected to surgery, either carotid ligation or an intracranial procedure, favorable outcome was more likely, and the mortality was lower in the 4 to 7 day group (table 4).

Discussion

In this study the results in terms of a favorable outcome, mortality, and re-bleeding for patients admitted in either good or poor neurological status were consistently worse for those admitted to neuro-surgical or neurological units on days 0 to 3 after the most recent subarachnoid hemorrhage than those admitted on days 4 to 7. Those patients admitted in poor condition had a worse outcome than those admitted with good neurological status, for both the 0 to 3 and 4 to 7 day groups. These results are consistent with previous reports. Alvord and Thorn, in a series of patients treated conservatively, noted that the probability of living 90 days after aneurysm rupture was approximately 54% if the patient was admitted on days 0 to 3 after hemorrhage, 66% if the patient was admitted on days 4 to 8, 70% if the patient was admitted on day 9 to 14 and 80% if the patient was admitted on day 15 to 21.9. In this series the 90 day mortality of 34% in patients admitted on day 0 to 3 was lower than the 46% natural mortality of the disease.

Discussion

In this study the results in terms of a favorable outcome, mortality, and re-bleeding for patients admitted in either good or poor neurological status were consistently worse for those admitted to neuro-surgical or neurological units on days 0 to 3 after the most recent subarachnoid hemorrhage than those admitted on days 4 to 7. Those patients admitted in poor condition had a worse outcome than those admitted with good neurological status, for both the 0 to 3 and 4 to 7 day groups. These results are consistent with previous reports. Alvord and Thorn, in a series of patients treated conservatively, noted that the probability of living 90 days after aneurysm rupture was approximately 54% if the patient was admitted on days 0 to 3 after hemorrhage, 66% if the patient was admitted on days 4 to 8, 70% if the patient was admitted on day 9 to 14 and 80% if the patient was admitted on day 15 to 21.9. In this series the 90 day mortality of 34% in patients admitted on day 0 to 3 was lower than the 46% natural mortality of the disease.

Table 1. Comparison of Patients Admitted on Days 0 to 3 After Subarachnoid Hemorrhage With Those Admitted on Days 4 to 7

<table>
<thead>
<tr>
<th>Condition on admission</th>
<th>Days 0-3</th>
<th>Days 4-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>190 (76%)</td>
<td>219 (84%)*</td>
</tr>
<tr>
<td>Poor</td>
<td>59</td>
<td>43</td>
</tr>
<tr>
<td>Survival until day 15</td>
<td>216 (87%)</td>
<td>244 (93%)**</td>
</tr>
<tr>
<td>Operative treatment</td>
<td>161 (65%)</td>
<td>174 (66%)</td>
</tr>
<tr>
<td>Intracranial operation</td>
<td>139 (56%)</td>
<td>142 (54%)</td>
</tr>
<tr>
<td>Carotid artery ligation</td>
<td>22 (9%)</td>
<td>32 (12%)</td>
</tr>
<tr>
<td>Good condition at time of operation</td>
<td>141 (88%)</td>
<td>154 (89%)</td>
</tr>
<tr>
<td>Good condition at intracranial operation</td>
<td>120 (86%)</td>
<td>123 (87%)</td>
</tr>
<tr>
<td>Good condition at carotid artery operation</td>
<td>21 (95%)</td>
<td>31 (97%)</td>
</tr>
<tr>
<td>Median interval to operation</td>
<td>16 days</td>
<td>16 days (12-76)*</td>
</tr>
<tr>
<td>Median interval to carotid artery ligation</td>
<td>16 days</td>
<td>15 days (13-24)</td>
</tr>
</tbody>
</table>

* p = 0.061, **p = 0.024
† Range + % of operated patients.

Re-bleeding within 14 days of the most recent SAH was higher in patients admitted on days 0 to 3 than in those admitted on days 4 to 7 for all patients (12% vs 5%) as well as the sub-groups admitted in good neurological status (10% vs 5%) and those admitted in poor neurological status (20% vs 5%) (table 3).

In those patients subjected to surgery, either carotid ligation or an intracranial procedure, favorable outcome was more likely, and the mortality was lower in the 4 to 7 day group (table 4).

Table 2. Overall Results 90 Days After SAH Among Patients Admitted on Days 0-3 and 4-7

<table>
<thead>
<tr>
<th>Condition on admission</th>
<th>Days 0-3</th>
<th>Days 4-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable outcome</td>
<td>97 (51%)</td>
<td>126 (55%)</td>
</tr>
<tr>
<td>Dead</td>
<td>52 (27%)</td>
<td>40 (18%)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition on admission</th>
<th>Days 0-3</th>
<th>Days 4-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable outcome</td>
<td>11 (19%)</td>
<td>12 (28%)</td>
</tr>
<tr>
<td>Dead</td>
<td>33 (56%)</td>
<td>22 (51%)</td>
</tr>
</tbody>
</table>

All patients on admission

<table>
<thead>
<tr>
<th>Days 0-3</th>
<th>Days 4-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable outcome</td>
<td>108/249 (43%)</td>
</tr>
<tr>
<td>Dead</td>
<td>85/249 (34%)</td>
</tr>
</tbody>
</table>

*p < 0.05
**p < 0.05 Mantel-Haenszel test.

Table 3. Incidence of Rebleeding Within 14 Days of SAH in Patients Admitted on Days 0-3 and 4-7

<table>
<thead>
<tr>
<th>Admission Status</th>
<th>Days 0-3</th>
<th>Days 4-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>19/190 (10%)</td>
<td>12/219 (5%)</td>
</tr>
<tr>
<td>Poor</td>
<td>12/59 (20%)</td>
<td>2/43 (5%)*</td>
</tr>
<tr>
<td>Total</td>
<td>31/249 (12%)</td>
<td>14/262 (5%)**</td>
</tr>
</tbody>
</table>

*p < 0.06
**p < 0.102 Mantel-Haenszel test.
treated conservatively. The results were similar for those patients admitted in day 4 to 7.

In either the 0 to 3 or 4 to 7 day groups, patients in good neurological status on admission fared better in both favorable outcome and survival than those admitted in poor neurological status. Patients admitted in poor condition had a proportionately higher mortality rate. A possible explanation for this is that the initial insult of a subarachnoid hemorrhage often produces profound alterations in neurological function, but, unless there is structural disruption of parenchyma from intracerebral hematoma, the potential for significant recovery exists. Often patients will improve dramatically in the first several days following subarachnoid hemorrhage. If impairments do not resolve over time, the chances increase that brain injury is irreparable. The reasons patients admitted on days 0 to 3 do worse than those admitted on days 4 to 7 are more elusive. The re-bleeding rate is higher in the 0 to 3 day group, and remains so even when consideration is made for the fact that these patients are exposed to a greater number days of risk than the 4 to 7 group. Results of surgery in patients admitted on days 0 to 3 were worse than those admitted on days 4 to 7 even though the timing of surgery and the condition of the patients were the same in both groups. Possibly, the patients who present to specialized neurological centers soon after their hemorrhage are in certain ways more ill, have more friable aneurysms, or have had more severe hemorrhages, than patients who present later. Some support for this is found in a recent report where those patients whose SAH was initially misdiagnosed and whose admission was therefore delayed had a better prognosis. An alternative and remote possibility is that the treatment modalities employed adversely affected outcome.

The patients in this series were provided with contemporary medical and surgical therapy in established neurosurgical units. Re-bleeding was effectively reduced in the first 2 weeks with medical therapy as evidenced by the 8.8% re-bleed rate compared with a rate of 22.6% expected without therapy. Surgery was performed in an acceptable manner as evidenced by the 11.5% postoperative mortality rate which is similar to the results of other surgical centers. However, the over-all results of management were a disappointment — only 43% of the patients admitted on days 0 to 3 were capable of an independent functional existence 3 months later. Despite adequate medical and surgical therapy an unacceptable number of patients continues to die or be disabled as a result of re-bleeding, medical and surgical complications, and in particular, as a consequence of vasospasm. One approach in attempting to improve results is a renewed interest in early intracranial surgery. However, part of the difficulty in evaluating this approach is the difference in time from hemorrhage to admission in various series.

The events which occur in the first several hours or days subsequent to rupture of an intracranial aneurysm have a profound influence on ultimate outcome. In addition, the time from SAH to admission is an important parameter in predicting outcome. Accordingly, in studying the results of different treatment programs in patients following SAH, comparison should be made of groups admitted at similar intervals following the ictus.

While the role of early surgery in improving the prognoses for patients with aneurysmsal SAH has yet to be defined, it must be assumed that early management of patients is essential if advances are to be made in improving overall results. Accordingly, greater emphasis must be placed on referring patients to specialized units at the earliest time possible, regardless of a particular philosophy of timing of surgery.

### References

8. Nibbelink DW, Torner JC, Burmeister LF: Fluid restriction in...

APPENDIX
Participating Investigators and Centers
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