Cooperative Study of Intracranial Aneurysms and Subarachnoid Hemorrhage. Report on a Randomized Treatment Study

I. Introduction

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Abstract: Introduction

Fifteen institutions participated in a cooperative study for treatment of single ruptured intracranial aneurysms. Between June, 1963, and February, 1970, 1,005 protocols were submitted to the Central Registry. All patients had a single ruptured aneurysm on the internal carotid, middle cerebral, anterior cerebral-anterior communicating or vertebral-basilar arteries. The four treatments allocated randomly were regulated bed rest, drug-induced hypotension, carotid ligation, and intracranial surgery. This study was an attempt to provide the relative merits of these several modes of therapy.

Additional Key Words: randomized study, cooperative aneurysm study, treatment of intracranial aneurysms

Phase I was the report on a data-collection study which covered a series of observations of patients with cerebral aneurysms and other disorders producing spontaneous subarachnoid hemorrhage extending over a period of eight years. During that interval, 6,368 cases were reported to the Central Registry. From these, 3,265 aneurysm cases were identified. A group of 2,951 patients bled from a ruptured aneurysm, and in 314 patients the aneurysm had not bled. This group incorporated seriously ill and poor risk patients. The report was entitled "Intracranial Aneurysms and Subarachnoid Hemorrhage," by Drs. Sahn, Perret, Locksley and Nishioka, and was published in monograph form in 1969. The gross mortality of patients managed conservatively ranged from 36% in the middle cerebral to 42% in the anterior cerebral-anterior communicating group.

Of those patients subjected to intracranial surgery the following mortality rates occurred: years 1956 to 1957, 33%; 1958, 30%; 1959, 36%; 1960, 34%; 1961 to 1964, 26%.

These statistics were questioned because of the possible variety of skills which were applied at various centers for both good-risk and poor-risk patients. It became evident after the project was under way that a randomized treatment study was indicated to provide more information concerning the relative merits of various modes of therapy.

Treatment of saccular aneurysms is a complex problem which involves variables such as age and sex, specific aneurysm sites, elapsed time since hemorrhage, and clinical condition of the patient. These and probably other factors influence the natural outcome of a ruptured aneurysm and have considerable impact on the prognosis of medical and surgical treatment. At the commencement of the original study, many of the group anticipated this problem and recognized the greater efficiency and scientific validity of a treatment study which, by proper design, would attempt to obviate factors of individual selection and also carefully define each mode of treatment according to standards most commonly employed. At that time, however, there existed such strongly conflicting and impressionistic opinions regarding treatment that the compromises and cooperation needed for a well-designed study of treatment were not immediately forthcoming. However, over a period of four or five years of individual and collective study, there evolved a more widespread awareness of the necessity for such a study and conviction as to its feasibility.

By December, 1961, an ad hoc committee devised a plan for a controlled comparative study of medical and surgical treatments of bleeding intracranial aneurysms. This was designated Phase II. Six months
later the detailed program was accepted in principle. A nucleus of ten centers proceeded with the proposed format, and began to submit protocols on June 15, 1963. The participating centers are listed elsewhere in this publication (Objectives and Design of Randomized Aneurysm Study. Stroke 5: 552-556 [July-Aug] 1974). The program was continued until February 1, 1970.

Patients meeting the criteria for admission to the study were allocated randomly to one of four treatment categories. These included regulated bed rest, drug-induced hypotension with regulated bed rest, carotid ligation, and intracranial surgery.

The sites chosen for study were single aneurysms located on the internal carotid, middle cerebral, and anterior cerebral-anterior communicating arteries, plus aneurysms of the posterior portion of the circle of Willis. Intervals from last bleed to allocated treatment were subdivided into three time periods as follows: (1) within seven days following the last bleed; (2) eight to 21 days after the hemorrhage, and (3) 22 to 92 days. An original estimate of 1,000 cases was indicated to answer the question regarding which treatment would be most favorable. A statistical method utilizing sequential analysis was considered by our statistician to be most efficient in terms of number of cases, time, and effort. These determinations were monitored closely in order to assess any factors responsible for any statistically significant undesirable outcome.

Case registrations were forwarded to the Central Registry from 1963 through the first six weeks of 1970. During this period, a total of 1,665 cases was available, from which 660 were excluded (table 1). The remaining 1,005 cases were randomly allocated among the four treatment categories. In this group, 33 cases were disqualified after allocation of treatment, leaving a total of 972 for detailed analysis of comparative treatments.

The mere fact that a patient was allocated randomly to a treatment category does not necessarily mean that such treatment was actually carried out on that particular patient. For example, a patient assigned to intracranial surgery might not have received such definitive treatment for a number of reasons. This problem will be discussed in detail in the sections that follow, but the reader should be aware at onset that the "allocated treatment" could not be followed according to protocol in all instances.

**TABLE 1**

<table>
<thead>
<tr>
<th>Case Registrations Excluded</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died before randomization</td>
<td>101</td>
</tr>
<tr>
<td>Multiple aneurysms</td>
<td>300</td>
</tr>
<tr>
<td>Arteriovenous anomaly in addition to aneurysm</td>
<td>13</td>
</tr>
<tr>
<td>Intracranial mass lesion requiring immediate surgery</td>
<td>49</td>
</tr>
<tr>
<td>Inability to obtain comprehensive treatment permit</td>
<td>147</td>
</tr>
<tr>
<td>Unrelated disease sufficiently compromising to hypotensive or surgical treatments</td>
<td>25</td>
</tr>
<tr>
<td>Previous aneurysm treatment other than bed rest</td>
<td>7</td>
</tr>
<tr>
<td>Aneurysm of posterior circle</td>
<td>13</td>
</tr>
<tr>
<td>Patient set aside according to pre-arranged schedule</td>
<td>4</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>660</td>
</tr>
</tbody>
</table>

The following subjects will appear at intervals in STROKE, although not necessarily in the order listed: Objectives and Design of Randomized Aneurysm Study Intracranial Surgery Regulated Bed Rest Drug-Induced Hypotension Carotid Ligation Follow-Up Studies Statistical Analyses

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