need attention? Are they controllable? The period of acute hypoxia is critical in determining the eventual extent of cellular damage. There are still very few methods of medical-surgical intervention that have been demonstrated to influence the immediate course of the evolving neuronal pathology. One of the major issues is the timing of intervention. Does increasing cerebral blood flow during the period of hypoxia and the related deficit in autoregulation have beneficial or deleterious consequences? Do the medical and surgical therapies that are presently widely used have significant impact on the acute course of the disease or on its long-term consequences? Restitution of function is the goal for those who recover from the acute episode. Do methods to enhance neuronal sprouting and axonal regeneration offer promises to reestablish or circumvent destroyed pathways? Do neural prostheses offer practical methods for electronic substitution of injured biological pathways? Each of these questions of clinical significance is surrounded by a host of questions that require information obtainable only from the basic science laboratory.

Answerable questions can now be posed by the cerebrovascular investigator both in basic and clinical areas. Research tools have been developed that provide the methodologies for addressing these questions. Competition for research funds is intense, but funds are available for high quality research. In many ways, the opportunity for important advances lies in our understanding of the forces that regulate cerebral circulation and neuronal metabolism. The outlook for the development of improved methods of diagnosis and therapy has never been greater.

"A leader is a person who can place himself at a time in the future and from that position govern his actions accordingly."

Philip H. Frohman, Architect, Washington National Cathedral

So it is with stroke research.

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Early Management of the Patient with Recent Aneurysmal Subarachnoid Hemorrhage

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ANNUALLY, more than 26,000 people in North America suffer an acute aneurysmal subarachnoid hemorrhage (SAH). At least half of the persons die or become disabled as a result of the illness. If we are going to improve these dismal statistics, we must improve our early diagnosis and management of SAH; the first few days are critical.

Diagnosis

One of the major problems in early management of SAH is delayed diagnosis. Approximately 25% of the patients with SAH are initially treated for another disease. SAH is commonly missed among less seriously ill appearing persons; those that walk into an emergency room or a physician’s office complaining of an unusually severe headache, often of sudden onset. These are the persons who are most likely to benefit from early medical or surgical treatment. As a consequence of misdiagnosis, critical early treatment for SAH is lost. Computed tomography of the brain (CT) is now readily available in most hospitals in North America. We should not be reluctant to use this highly sensitive technology in our evaluation of patients displaying symptoms that possibly represent SAH. Besides aiding the initial diagnosis of SAH, CT provides information about complications such as intracerebral hematoma, cerebral infarction or hydrocephalus. CT also facilitates prediction of overall outcome, survival and the development of vasospasm.

Consequences

Patients are at risk for a number of complications during the first days after SAH; they should be treated in a facility that has special expertise. The leading causes of death during the first few days after SAH are: 1) acute, often irreversible effects of the initial hemorrhage, 2) recurrent hemorrhage, and 3) cerebral vasospasm and infarction. Unfortunately, some patients are so severely injured that no medical or surgical therapy will improve outcome. However, some acute complications such as hydrocephalus, convulsions, intracranial hemorrhage, cardiac arrhythmias or electrolyte disturbances can be treated.

Medical Management

Definite advances in the treatment of SAH have appeared during the last decade. During this time, the standard management has been early medical treatment followed by intracranial operation at 7–14 days after the ictus. New data about medical therapies have
The risk of cerebral infarction can be reduced by correcting hyponatremia, as well as avoiding dehydration and fluid restriction. Calcium channel blocking drugs may further reduce the risks of vasospasm and cerebral infarction. Nimodipine has been the subject of a randomized, double-blind trial in approximately 120 patients. The frequency and severity of ischemic sequelae of vasospasm can be lessened by hypervolemic hemodilution and drug-induced hypertension. This therapy has been successful in reversing impending infarction but can be complicated by rerupture of a non-surgically treated aneurysm.

Antifibrinolytic drugs have been used in patients with SAH because no other medical therapy has been successful in reducing the risk of recurrent hemorrhage. This therapy is controversial. The recent Cooperative Aneurysm Surgery Study report and the randomized, double-blind Dutch-British trial have answered questions about the efficacy and the relative safety of antifibrinolytic drugs. However, new issues have been raised. Antifibrinolytic drugs do reduce the overall risk of rebleeding during the first two weeks after SAH. However, they do not prevent rebleeding during the first few days. A therapeutic response does not occur until 2-3 days after initiation of treatment. Unfortunately, this lag in therapeutic response corresponds to the period of highest risk for rebleeding. Shortening the delay in therapeutic response might improve the efficacy of antifibrinolytic drugs. In the past, antifibrinolytic drugs have been given as a continuous infusion, without a loading dose. Using this regimen, effective blood and cerebrospinal fluid levels are not reached for 2-3 days. A 5-10 gram bolus dose ofaminocaproic acid is followed by rapid therapeutic blood levels. A loading dose followed by a continuous infusion might allow more rapid achievement of therapeutic levels in cerebrospinal fluid. Thus a more marked reduction in rebleeding might be achieved. This treatment regimen deserves evaluation.

While antifibrinolytic drugs reduce the risk of early rebleeding, they do not reduce mortality since a proportional increase in ischemic sequelae is noted. Cerebral infarction is the leading cause of death among patients given antifibrinolytic drugs. In both recent studies, the rates of cerebral ischemia were similar in untreated and treated patients during the first week after SAH. Thereafter, ischemia was more frequent among patients given antifibrinolytic drugs. The mechanism of the effect of antifibrinolytic drugs on the development of the ischemic sequelae of SAH is not known. Shortening the duration of antifibrinolytic therapy might reduce ischemic complications. Careful fluid management with prevention of dehydration and avoiding simultaneous use of antihypertensive drugs may lower the risk of ischemia. Concomitant administration of calcium channel blocking drugs could also reduce ischemic sequelae of antifibrinolytic therapy.

Surgical Management

Surgical clipping of the aneurysmal neck prevents early and long-term rerupture. In the past, early intracranial operations were complicated by prohibitive morbidity and mortality. Because postoperative complications of surgery performed 10 or more days after SAH were few, delayed surgery became standard. Yet, many patients died while awaiting operation. Advances in operative technique have led some neurosurgeons to recommend early intervention. Several series have reported improved outcome with early operations. Early operation effectively eliminates the risk of rebleeding, and, with lavage of the subarachnoid space, may lower the likelihood of vasospasm. Early intervention may allow a more vigorous treatment of ischemic sequelae of vasospasm. Early operation also would avoid some of the complications of medical treatment. Hence, such early surgery has the potential to be extremely useful in some patients with recent SAH.

The optimal time for aneurysm surgery was recently studied. In an organizational tour de force, the International Cooperative Study on the Timing of Aneurysm Surgery enrolled 3521 patients hospitalized within three days of SAH. This study was the collaborative effort of 213 neurosurgeons with a special interest in aneurysm surgery who were at 68 medical centers in 15 countries. It was an intention-to-treat study; when the patient was admitted, surgeons stated the time of scheduled surgery. Patients were grouped into surgical intervals of 0-3, 4-6, 7-10, 11-14 and 15+ days after SAH. Day 0 is the day of SAH. Results of management were analyzed on the basis of outcomes assessed six months after SAH by investigators “blinded” to the time of surgery. While this was not a randomized trial, prognostic factors were similar in early and delayed surgical populations. The results of this study are now known:

Intracranial operations were performed in 83% of the patients. Operations were done in 92% of approximately 1600 patients who had surgery planned for days 0-3. However, 24% of patients originally scheduled for surgery for 11-14 days after SAH, and 38% of those with surgery scheduled at 15+ days, did not have surgery. Many of these patients died or had complications that contraindicated operation. Among patients who had surgery, post-operative results were superior with delayed surgery. These results held true regardless of the patients’ age or location of the aneurysm. Among alert patients, those operated within 48 hours of SAH did at least as well as those surgically treated two weeks after the ictus. Looking only at the
postoperative results, the conclusion would be that delayed operations are usually preferable to early operations.

Overall results of management, including those patients who did not reach surgery, give a much different picture. Outcomes among those patients with surgery planned within 3 days of SAH and those with surgery scheduled for 11–14 days were almost identical. The mortality was 20% and good outcomes were noted in 60%. Patients with operation planned for the interval 7–10 days after SAH did poorer than those operated upon at other times.

Early operation was not accompanied by a higher rate of surgical complications than delayed operation produced. Early operation significantly reduced morbidity and mortality secondary to rebleeding. However, similar to the response to antifibrinolytic drugs, the reduction in mortality due to rebleeding achieved by early operation was nullified by deaths due to cerebral ischemia. Early operation did not prevent vasospasm and cerebral infarction as a cause of neurological deterioration after SAH.

Summary

Despite its efficacy in preventing rebleeding, the anticipated strong trend in favor of early intracranial surgery has not been achieved. Early intracranial operation remains a useful choice in the management of recent SAH in good-risk patients, but patients must be carefully selected on an individual basis. Many patients will undoubtedly benefit from early surgery but it is not a panacea. Further investigation of surgical treatment in combination with improved preoperative and postoperative medical therapy will be required to ameliorate the outcome of SAH. In particular, the prevention and treatment of cerebral infarction deserves attention. The results of the antifibrinolytic and timing of intracranial surgery studies point to the need for an effective prevention treatment regimen for vasospasm. Further studies about the efficacy of calcium channel blocking drugs in prevention of ischemia after SAH are needed among patients given antifibrinolytic drugs or having early operation.

All the advances in treatment are predicated on prompt diagnosis of SAH in good-condition patients. The medical community needs to maintain a high degree of vigilance for the diagnosis of SAH in all patients complaining of a new, unusual or severe headache. Early referral to properly equipped and staffed medical facilities remains a keystone to effective treatment of SAH.

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