Evidence-based Treatment of Subarachnoid Hemorrhage: Current Status and Future Possibilities

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INTRODUCTION

Aneurysmal subarachnoid hemorrhage (SAH) affects approximately 30,000 Americans each year. The incidence approximates 6 to 16 per 100,000 persons per year, with some geographic variation throughout the world. There has been a modest decline in incidence over time, in contrast to more marked decreases in incidence of other types of stroke (such as ischemic stroke and intracerebral hemorrhage), which is consistent with epidemiological data indicating that the avoidance of risk factors for ischemic stroke and intracerebral hemorrhage, mainly hypertension, and possibly cigarette smoking, diabetes, and abnormal serum lipids, can reduce the incidence of the disease.

Guidelines for the management of aneurysmal SAH were published in 1994.[47] There have been numerous advances in diagnosis and management of aneurysmal SAH since that time, as well as some notable failures of extensively-tested drugs. This review summarizes some of these advances.

Materials and Methods

For this review, I searched the Cochrane Stroke Group Trials Register, the Cochrane Controlled Trials Register, and Medline for publications on aneurysmal subarachnoid hemorrhage. It became evident that the literature could be only partly reviewed due to the large number of relevant studies. The Cochrane Central Registry of Controlled Trials alone includes approximately 250 entries since 1994. Many issues are not addressed here, particularly those investigated in small numbers of patients from only one center. These include such things as postoperative fever management strategies using various cooling devices, cardiac dysfunction after SAH, and numerous small studies of treatments for vasospasm such as lidocaine, edaravone, and acetylsalicylic acid to name a few. The evidence provided was scored roughly according to the standard criteria for scientific merit and graded according to this assessment (*Table 28.1*).[12] The limitations of this review are that it is not exhaustive and that it was conducted by this author only. Thus, it falls short of a traditional systematic review or what would be required for formal development of guidelines for management.

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RESULTS

Epidemiology

The previous guidelines suggested that population-based mortality from SAH had declined since 1970. This continues to occur in most[69] but not all[60,64] studies. Whether the decrease is due to a decline in SAH incidence, case-fatality rate, or both depends on the study. A population-based stroke registry in the Auckland region of New Zealand determined the incidence of SAH and the 28-day case fatality rate in the periods from 1981 to 1983 and 1991 to 1993.[69] The incidence of SAH declined over these times from 15 to 11 per 100,000, although case fatality rates did not change. Evidence for a decline in incidence or mortality from SAH was not found in the Oxfordshire stroke registry or in one region of Finland.[60,64] This would probably constitute Level 2 evidence to support a reduction in SAH mortality. The reasons for reduced incidence, if any, were speculated to include cessation of smoking and control of hypertension. No epidemiological or data otherwise are available as yet to determine the impact of risk factor modification on the incidence of aneurysm formation and of SAH. Such studies would be very difficult to do, in part because of the low frequency of aneurysms and the impossibility of diagnosing them noninvasively.

The second comment in the previous guidelines was that hospital mortality was lower than community mortality. Several studies, constituting Level 3 to 5 evidence, have been published that seem to support this contention.[65] Among patients who underwent aneurysm clipping between 1995 and 1999, 12,023 patients were studied to determine if the volume of cases a hospital treated affected outcome.[13] Hospitals were divided into quartiles based on treatment volumes. Higher volume hospitals had lower mortalities for emergency (15 versus 9%, $P < 0.001$) and elective (9 versus 5%, $P < 0.001$) aneurysm surgery. Factors known or suggested to affect the prognosis of patients undergoing surgery for aneurysms, such as age, could be adjusted for. On the other hand, the most

TABLE 28.1. Levels of Evidence and Grading of Recommendations for Treatment of Patients with Aneurysmal Subarachnoid Hemorrhage

Levels of Evidence	
Level 1: Data from randomized trials with low false-positive (α) and low false-negative (β) errors (high power)	
Level 2: Data from randomized trials high false-positive (α) and high false-negative (β) errors	
Level 3: Data from nonrandomized concurrent cohort studies	
Level 4: Data from nonrandomized cohort studies	
Level 5: Data from anecdotal case series	
Strength of Cumulative Data	
Grade A: Supported by level 1 evidence	
Grade B: Supported by level 2 evidence	
Grade C: Supported by level 3, 4 or 5 evidence	
Degrees of Certainty	
Standards	Accepted principles of patient management that reflect a high degree of clinical certainty, usually based on level evidence but could be based on strong Level 2 evidence if the issue is not able to be tested practically in a randomized trial. Weak or contradictory Level 1 studies, however, might not lead to a standard
Guidelines	Are diagnostic or treatment strategies that reflect a moderate degree of clinical certainty, usually based on Level 2 evidence or abundant Level 3, 4 or 5 evidence
Options	Diagnostic and treatment strategies not covered by standards and guidelines, the appropriate strategy is uncertain, usually based on Level 3, 4 or 5 evidence

commonly cited risk factor for poor outcome, which is hypertension, was unknown and the database did not determine whether or not surgery was performed for unruptured or ruptured aneurysms. Analysis of 16,399 hospitalizations for SAH in 18 states included 9290 patients admitted through an emergency department.[14] Hospitals were divided into quartiles based on the volume of patients treated. Mortality at the hospitals in the highest quartile had mortality 1.4 times lower (95% confidence interval, 1.2–1.6) than at those in the lowest quartile. This analysis was adjusted for patient age and preexisting hypertension. These analyses seem to confirm the obvious, which, simply stated, would be that practice makes perfect. Hospitals treating more patients would be likely to have more resources and equipment, medical staff more experienced in treating such cases and physicians more facile with the complexities sometimes encountered in these cases. Indeed, analysis of other surgical procedures have produced similar findings.[5,9] On the other hand, there are very serious flaws in these analyses. In some studies, it could not be excluded that unsalvageable patients were kept at low volume hospitals and not transferred to high volume hospitals, which would bias against low volume institutions. Also, unless all of the factors affecting the outcome of such patients are known and can be adjusted for, one cannot be sure that the patients at large and small volume hospitals would otherwise have had the same outcome. None of the reports know all the factors that affect the prognosis after SAH, including age, neurological grade on admission, amount of blood on admission computed tomography, location and size of the aneurysm, presence of intracerebral and/or intraventricular hemorrhage, preexisting hypertension, and time from SAH to admission.[13,35]

Diagnosis

Misdiagnosis continues to occur at a rate not disimilar to that previously reported.[47] Fifty-six out of 482 SAH (12%) patients admitted to an urban university tertiary care hospital were misdiagnosed at their first contact with a medical professional. The diagnosis was more likely to be missed in patients who had normal mental status when first seen. The incorrect diagnoses were migraine or tension headache (36%), viral syndrome, musculoskeletal pain, sinusitis, and hypertension. If the diagnosis was missed, then the risk of death or severe disability was higher at 1 year. The most commonly cited figures are that cranial computed tomography (CT) within 1 day of SAH will detect 92% of cases, but this data is decades old.[35] There are few large studies of how often SAH is present, but undetectable with modern, high-resolution, multidetector CT, but it is probably lower than 1%.[6] In terms of lumbar puncture detection of SAH, the problem of lack of an appropriate spectrophotometric assay of properly centrifuged cerebrospinal fluid persists. The ready availability of CT, catheter angiography, and physicians eager to inter-

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vene, regardless of whether the detected aneurysm has ruptured or not, at least in the populated areas of the United States, makes the impetus for development of this test low.

The main imaging advance has been CT angiography. Several groups have described prospective evaluations of protocols in which CT angiography is used first to assess patients with SAH.[7,15,16,32,33] Boet et al.[7] used CT angiography initially in 90 patients with aneurysms. About one-quarter of the patients were operated on based on CT angiography alone. This percentage is probably higher now at some other institutions due partly to improvement in the CT scanners. I personally operate on virtually all ruptured aneurysms on the basis of CT angiography alone, a situation that developed as I became completely comfortable with the idea of not having a catheter angiogram before surgery. CT angiography often gives superior anatomic detail to biplane but not necessarily rotational catheter angiography. CT angiography is faster, safer, easier, and less risky.

Hoh et al.[32] prospectively used CT angiography in the evaluation of 109 patients with ruptured aneurysms. Eighty-eight (81%) of patients were treated based on the CT angiography alone. Five with negative CT angiograms underwent catheter angiography that also did not show a source of hemorrhage and 16 (15%) had catheter angiography. The authors concluded that most patients with SAH could be managed with CT angiography alone. The technology is improving so quickly that reviews of the sensitivity and specificity of CT angiography cite percentages that are probably lower than what can be achieved with advanced, multislice CT scanners, so the following figures should take that into consideration.[79] van Gelder completed a systematic review of CT angiography for aneurysm detection and found the sensitivity ranged from 53% for 2 mm aneurysms to 95% for 7 mm aneurysms.[74] Specificity was 99%. Another comprehensive review of 21 references found CTA to have a sensitivity of 93% and specificity of 885 among 1251 patients.[10] In patients with SAH, one needs to take into account that there is about a 70% chance that there is an aneurysm responsible and that the consequences of missing a ruptured aneurysm are potentially catastrophic. These translate into a high pretest likelihood of aneurysm and the need for a test with high sensitivity, although the latter can be accomplished by first performing CT angiography and then only catheter angiography if the CT angiography is unrevealing. CT angiography was about 90% sensitive to detecting ruptured aneurysms, which is not high enough, so catheter angiography is still recommended if the CT angiogram doesn't show the cause of SAH or in other cases in which the aneurysm is particularly complex or the CT distribution of clot doesn't fit with the identified lesion. This is, however, based thus far on only Level 4 to 5 evidence and would represent an option.

TREATMENT

Some issues discussed in the previous guidelines, such as the timing of surgery, although not addressed by any new data, seem irrelevant today. No new data have addressed timing of treatment of ruptured aneurysms. But, rightly or wrongly, neurosurgeons in the United States would be reluctant to randomize patients to delayed aneurysm treatment. A Cochrane review identified only one randomized, controlled trial of the timing of aneursym surgery, which showed that patients operated on early had better outcome although the confidence intervals were wide and all patients were good grade.[53,78] A randomized trial of timing of treatment in poor grade patients was recommended. This author would put this low on the list of priorities.

Clipping Versus Coiling

There are two randomized trials. The international subarachnoid aneurysm trial (ISAT) randomized 2143 patients with ruptured aneurysms to clipping or coiling. Of 801 patients undergoing coiling, 190 were dependent or dead at 1 year (24%), compared with 243 out of 793 (31%) of those undergoing clipping.[50] This was equivalent to a 23% relative and 7% absolute risk reduction in patients who were coiled. The most important limitations of ISAT were whether or not the results were generalizable to different populations of SAH patients, whether or not the outcome measure was appropriate, the experience of the surgeons, and how durable the results of coiling are. Eighty-eight percent of the randomized cases were World Federation of Neurological Surgeons (WFNS) Grade 1 or 2, 52% of aneurysms were under 5 mm in size, and 97% were anterior circulation. This sample is biased to small, anterior circulation aneurysms in good-grade patients and thus, not generalizable to the SAH population as a whole. Nevertheless, these results should be valid for this type of case. The main reason for concern even in this subset of SAH patients is that the endovascular treatment was done by physicians with at least 30 aneurysms coiled, whereas neurosurgeons were not required to provide any outcome figures before being permitted to operate on patients in the study. It was suggested that the neurosurgery may not have been the best technically that could be done.[4] This is consistent with the finding that 31% of surgically-treated patients had a modified Rankin score of 3 to 6 at 1 year, which is worse than other series of similar predominately good grade patients with small anterior circulation aneurysms.[40,41] On the other hand, a randomized trial that included a similar subset of good-grade SAH patients from various sites around the world but more patients from the United States, reported that 35% of patients had Rankin scores of 3 to 6 at 3 months.[67] Regarding the outcome measure used, the significant difference between groups was based in part on more clipped patients reporting that they had symptoms that significantly changed their lives and prevented them from coping fully

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such that they needed help looking after themselves. Other cutpoints in the scale would not have yielded a significant difference between groups. On the other hand, in every category of bad outcome, there were more clipped patients and in every good outcome category, there were more coiled patients.

A single-center Finnish study randomized 109 consecutive SAH patients to surgery (n = 57) or endovascular (n = 52) treatment.[38] At 1 year, there was good outcome or moderate disability in 43 operated and 41 endovascularly-treated patients. Death occurred in nine operated and seven coiled patients, with none of these differences being significant. Patients with good recovery who underwent surgery and coiling were not distinguishable by neuropsychological testing. Magnetic resonance imaging scans showed more superficial retraction and ischemic lesions in the territory of the ruptured aneurysm in the surgery group. Survival was also equal at a mean follow-up period of 39 months in each group, and there were no late rebleeds.

In summary, outcome is slightly better with coiling than with surgery, although this is based on a single randomized trial that would be considered Level 1 evidence. The lack of other studies would probably make this only a Grade B strength of cumulative data and a guideline or an option. Late rebleeding after coiling was not common, but there is no other long-term follow-up data available, and the coil manufacturers are unlikely to be very interested in spending money to obtain long-term follow-up data. Rebleeding occurred in 26 (2.5%) coiled and 10 (1%) clipped patients by 1 year in ISAT. The outcomes noted above incorporate these rebleeds. Cerebral infarcts are less common after coiling than surgery and infarction is strongly associated with poor outcome.[38,39] Endovascular techniques are improving. It seems likely that, for suitable aneurysms, coiling will become the preferred mode of treatment. Whether or not this will end up being based on Level 1 evidence with Grade A strength is uncertain because such a randomized study would require thousands of patients and at least 5 years of follow-up data. Because coils are already approved for use and new designs can be relatively easily approved through the 510(k) mechanism, the device manufacturers do not need to fund such a study. It also is difficult to get endovascular and surgical practitioners to agree on the design of a trial that would have to be funded by the only other source with enough money, the National Institutes of Health.

Long-term Durability of Treatment

There is little to add to the long-term surgical follow-up studies cited in the previous guidelines.[47] Eight out of 644 (1%) patients treated by Sundt et al.[66] rebled at unspecified times after surgery. In Yaşargil's[82] series of 1012 patients, 11 (1%) rebled over an unspecified time after surgical clipping. New aneurysm formation in patients with previous SAH doesn't seem to be especially rare. CT angiography was performed in 610 patients who had had SAH a mean of 9 years earlier.[77] One hundred twenty-nine aneurysms were detected in 96 (16%) patients. Twenty-four aneurysms (19%) were at the site of the previously ruptured aneurysm and 105 (81%) were at different locations. A series of 715 aneurysms were clipped, probably mostly after they had ruptured.[21] All patients underwent postoperative angiography and 28 partially-clipped aneurysms were identified. One patient rebled over a mean follow-up period of 8 years, giving a risk of rebleeding of 0.4 to 0.8% per year.

Another series of 1170 patients with SAH from aneurysms that were treated by clipping (n = 727) or coiling (n = 443) detected 11 rebleeds (1%) a mean of 10 months (range, 21 h–48 mo) after treatment.[2] Seven of these patients had postoperative angiograms showing complete occlusion of the aneurysm, three by clipping and four by coiling.

Intraoperative Management

Avoidance of intraoperative hypotension was previously recommended based on Level 4 to 5 evidence.[47] Neuroprotective strategies and induced hypertension were insufficiently studied to make specific recommendations. In an important new study by Todd et al,[67] 1001 patients with SAH who were WFNS Grades 1 to 3 were randomized to undergo aneurysm clipping with intraoperative hypothermia (33°C) or normothermia (36.5°C). Outcome on the Glasgow outcome score at 3 months was not significantly different between the groups (6% dead in each group; good recovery in 66% of hypothermia versus 63% of normothermia patients, $P = 0.32$). Significantly more patients in the hypothermia group developed postoperative bacteremia (5 versus 3%, $P = 0.05$). This study provides an example of some of the problems about clinical trials in SAH discussed below. Considering that intraoperative hypothermia could only reduce detrimental events occurring intraoperatively and that events that are of sufficient magnitude to be detected by the Glasgow outcome score are uncommon compared with the contribution of other factors that affect the outcome after SAH, the sample size required to detect a benefit is enormous. The investigators did collect other endpoints such as length of intensive care stay, but these were also not different between groups. Neuropsychological testing and postoperative imaging results may provide some critically important additional insights.

Antifibrinolytics

Rebleeding occurs acutely in up to 10% of patients within the first 24 hours after SAH.[25,31] There are many reasons why patients may not be able to have their aneurysms obliterated immediately after they have been diagnosed. In such cases, a method to prevent rebleeding might improve their chances of survival. The most common approach has been to use antifibrinolytic drugs, which have been studied in

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several randomized trials. The results have been subjected to meta-analysis.[57] The best data were derived from three trials that randomized 1041 patients to antifibrinolytic treatment or placebo. The odds of death, vegetative state, or severe disability were not altered by treatment (odds ratio, 1.12; 95% confidence interval, 0.88–1.43). Rebleeding was significantly reduced by antifibrinolytics, but this was completely balanced by an increased risk of cerebral ischemia. It was hypothesized that a short course of antifibrinolytic therapy that was stopped as soon as the aneurysm was clipped or coiled, in addition to modern vasospasm management with hemodynamic therapy and nimodipine, could reduce rebleeding, but not increase ischemia and improve outcome. An unblinded, randomized trial of 505 patients with SAH (254 treated with tranexamic acid and 251 controls) found no beneficial effect of treatment on outcome measured by the Glasgow outcome scale at 6 months.[30] Treatment was only given for a maximum of 72 hours. There was no increase in permanent delayed ischemic deficits. The Cochrane review concluded that the evidence does not support the routine use of antifibrinolytic drugs. This is based on Level 1 evidence and must come close to being a standard. The increase in cerebral ischemia in SAH patients treated with antifibrinolytics has usually been ascribed to inhibition of clot clearance leading to more severe, persistent vasospasm. I speculate that these could be arterial thromboembolic complications, based on the results of the recombinant Factor 7 study for prevention of rebleeding after intracerebral hemorrhage which reported an increase in cerebral ischemic events in treated patients.[48]

Two reasons the problem of rebleeding is of interest currently are the advent of other agents to prevent rebleeding and, in the United States, the issue of regionalization of treatment of aneurysmal SAH. The latter issue is addressed above. Regarding other drugs, Mayer et al.[48] reported the blinded, random assignment of 399 patients with intracerebral hemorrhage to treatment with recombinant Factor 7 to prevent rebleeding or to placebo. Factor 7 treatment reduced the mean increase in hematoma volume at 24 hours from 29% in the placebo group to 11 to 16% in the treated groups ($P = 0.01$). Importantly, this was associated with a significant reduction in risk of death at 3 months from 29% of placebo-treated patients to 18% in the treated cases ($P = 0.02$). Although not significant, there were more serious thromboembolic complications in the Factor 7-treated patients (7 versus 2% in the placebo group, $P = 0.12$). These were mostly myocardial or cerebral infarction. This has generated interest in the use of Factor 7 to prevent early rebleeding after aneurysm rupture.

Hemodynamic Therapy

Treggiari et al.[68] performed a systematic review of trials of prevention of symptomatic vasospasm with hypertension, hemidilution, and hypervolemia. They identified four prospective, comparative studies that included 488 patients.[42,59,75,81] Two were randomized and controlled.[42,59] Whether or not the results are applicable to current patients is questionable, in part because in two of the trials, including the largest one of 348 patients, surgery was not performed until 7 or more days after SAH. Most of the hemodynamic maneuvers used are not commonly used today, including antihypertensives in the control group in one study[59] and fludrocortisone as treatment compared to fluid restriction in the controls in another.[75] Treatment was associated with a reduction in risk of symptomatic vasospasm and death, but not of delayed ischemic neurological deficit. This could be due to detrimental effects of treatments used in the controls (antihypertensives, fluid restriction) rather to, or in addition to, any therapeutic benefit in treated patients.

A subsequent systematic review excluded two studies included in the review above because one used historical controls[75] and the other study did not specifically study hypervolemia.[81] They did include another trial of 32 patients that randomized patients to normovolemia or hypervolemic, hypertensive hemodilution therapy.[19,56] It is evident that hemodynamic therapy has only been studied using methods deemed necessary to generate Level 1 or 2 evidence in a very small number of patients (73 treated and 73 controls). Analysis of these trials found that hypervolemia did not improve outcome or reduce the incidence of delayed ischaemia. Complications were more common in patients treated with hypervolemia. The authors concluded that there was no evidence for the use of hypervolemia in patients with aneurysmal SAH and they recommended that more clinical trials of volume expansion therapy be conducted. Hemodynamic manipulations are used both prophylactically and therapeutically at most centers in the United States. In the four randomized trials of tirilazad conducted between 1991 and 1997, 63% of the approximately 3500 patients received prophylactic hemodynamic manipulations and 23% had hemodynamic therapy.[26,34,40,41] Such trials would have to consider whether or not to address prophylactic or therapeutic aspects and which maneuver or combination thereof to study. Hemodynamic management would then be a guideline based on a preponderance of Level 2 and lower evidence.

Anticonvulsants

The risk of seizures associated with or occurring within a few weeks of aneurysmal SAH is 5 to 8%.[3] I conducted multivariate analysis of prognostic factors for outcome among the approximately 3550 patients entered into the randomized trials of tirilazad between 1991 and 1997.[26,34,40,41] All patients had ruptured aneurysms and 90% of patients underwent surgical clipping of the aneurysm. This analysis found that independent factors associated with poor outcome were increasing age, worse admission neurological grade, preexisting hypertension, posterior circulation aneu-

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rysm, larger aneurysm, presence of intracerebral hemorrhage, systolic hypertension on admission, fever 8 days after SAH, vasospasm, use of prophylactic hypervolemia, and use of anticonvulsants.[58] The main anticonvulsant used was phenytoin, which was administered to 53% of patients in these studies. This usual and previously undescribed association was explored in further detailed analysis that confirmed an association of phenytoin use and poor outcome. Another group of investigators subsequently reported an association between phenytoin burden (average serum phenytoin multiplied by the number of days between the first and last levels obtained in the first 14 days after SAH) and worse functional outcome in 527 SAH patients.[52] Both of these analyses are observational and not based on randomization of patients to or not to treatment with anticonvulsants. Thus, it is always possible that some other unidentified factor that is different between treated and untreated patients accounts for the different outcomes, but, because it was not identified, it was not adjusted for. If one wants the real answer, one has to randomize and blind. The literature contains examples in which observational studies suggested a favorable effect that was not confirmed in randomized studies, including steroids for head injury.[18] Kent[37] cited the example of hormone replacement where biochemical and observational epidemiological studies suggested that the cardiovascular protective effects were so substantial that it would be unethical to randomize postmenopausal women in a study comparing hormone treatment to placebo. Two randomized studies, however, showed that hormone replacement actually increased the risk of cardiovascular complications.

Steroids

Some fundamental treatments that neurosurgeons use, such as perioperative steroids around the time of craniotomy for clipping of ruptured aneurysms, have never been adequately studied.[20] A Cochrane review identified three randomized trials of steroids in SAH patients.[20] Two trials used fludrocortisone[28,51] and one used hydrocortisone.[29] The overall analysis showed a trend to reduce the relative risk of delayed ischemia and poor outcome with fludrocortisone, although the confidence intervals were wide and included the possibility of lack of benefit. Adverse effects were significantly increased by steroid treatment and there was no overall significant effect on outcome. Complications of treatment included hyperglycemia, hypotension, and gastrointestinal bleeding. The conclusion was that there was no evidence for a beneficial or adverse effect of corticosteroids in SAH patients. This would be Level 2 evidence and would leave the use of perioperative steroids as an optional treatment.

It is worth considering a recent blinded trial that randomized 10,008 patients with head injury who had a Glasgow coma score of 14 or less within 8 hours of injury and were 16 years of age or older. They were treated with methylprednisolone (2 g intravenous bolus followed by 0.4 g/hour for 48 hours) or placebo. Death was more likely to occur at 2 weeks and 6 months (placebo, 22%; steroids, 26%; relative risk, 1.15) after injury.[18] These results from a powerful, randomized trial did not support the findings of a systematic review of steroids in head injury that suggested that corticosteroids decreased the risk of death after head injury by 1 to 2%.[1]

Magnesium

There are several small studies of therapeutic magnesium infusions in patients with aneurysmal SAH that include enough patients to support the safety of magnesium.[11,72,76] There are numerous potential beneficial effects of magnesium, including vasodilation and neuroprotection. This is a very attractive therapy because it is inexpensive, easy to administer, and has an excellent safety profile based on administration to women with toxemia. The vasodilatory action was studied by giving a 5g intravenous bolus of magnesium sulfate to 14 patients with SAH and comparing transcranial Doppler velocities before and after infusion.[8] Placebo patients infused with saline were also studied. Serum magnesium was doubled, but this did not affect mean Doppler flow velocities, although it did decrease mean arterial blood pressure. It takes hours for alterations in serum magnesium to be reflected in the cerebrospinal fluid. If vasodilation is dependent on increasing cerebrospinal fluid magnesium, adequate time may not have elapsed in this study.

The largest study thus far randomized 283 patients within 4 days of SAH to receive intravenous magnesium sulfate, 64 mmol/L per day, which is a standard toxemia dose.[73] The primary outcome, delayed cerebral ischemia, was reduced by magnesium by 34% (hazard ratio, 0.66; 95% confidence interval, 0.38–1.14). There were also favorable trends in the magnesium group in terms of reduced poor outcome. More study is needed.

Statins

Other agents undergoing clinical trials at present include hydroxymethylglutaryl coenzyme A reductase inhibitors (statins). There are two small studies that randomized patients with SAH to receive a statin (simvastatin [n = 19], pravastatin [n = 40]), or placebo [n = 60]).[44,70] In both studies, statin therapy was associated with a significant reduction in transcranial Doppler ultrasound evidence of vasospasm. In the larger study, it was associated with reduced duration of severe vasospasm and reduced overall mortality.[70] These very promising results were corroborated by a retrospective cohort study of 20 SAH patients who were admitted to hospital on statins and 40 SAH controls.[54] These investigators found that patients on statins had better functional outcome and were less likely to develop delayed cerebral ischemia although there was no effect on mortality. Singhal et al.,[63] however, noted in a similar retrospective, observational study that

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patients with SAH who were admitted on statins had an increased risk of vasospasm and they speculated that this might be due to abrupt discontinuation of the drug upon admission to hospital for SAH.

At present, everything touched by statins seems to turn to gold. They have a host of biochemical effects that may benefit SAH patients, including increasing endothelial nitric oxide synthase, enhancing bioavailability of nitric oxide, decreasing oxidative stress, inhibiting thrombogenesis and reducing inflammation.[43] They clearly need to be studied in clinical trials.

Endothelin Antagonists

The other major development in the treatment of vasospasm involves endothelin antagonists. Evidence from experimental models of SAH and clinical studies of endothelin concentrations in humans with SAH suggest that alterations in the vasoconstricting endothelin system might contribute to vasospasm.[85] TAK-044, an endothelin receptor antagonist, was compared with placebo in a randomized, blinded trial of 420 patients treated within 96 hours of SAH.[61] There was a trend towards reduced ischemic events in the treated patients (23% with placebo, 21% with TAK-044, not significant), but no significant differences in outcome or mortality overall. Patients receiving TAK-044 had significantly more hypotensive episodes (16 versus 7% in the placebo group), necessitating increased use of pressors. TAK-044 is an antagonist of both the A and B types of endothelin receptors. There are theoretical reasons why antagonists that are selective for the A receptor may be more effective against vasospasm and indeed, results of a small clinical trial of clazosentan, an A receptor specific antagonist, were recently reported.[71] Thirty-two patients with thick aneurysmal SAH were randomly allocated to receive placebo or clazosentan. Angiographic vasospasm occurred in 88% of placebo, but only 40% of clazosentan-treated patients ($P = 0.008$). Furthermore, the severity of vasospasm was reduced by clazosentan, reversal of established vasospasm was documented angiographically after selective intra-arterial infusions, and there was a trend towards reduction in the incidence of cerebral infarction in treated patients. These promising results are being investigated in a larger clinical trial.

Other Treatment

The biggest failure was of tirilazad, which was studied in five randomized trials that included more than 3500 patients from around the world. One metaanalysis suggested that tirilazad reduced the death rate from 17% of placebo-treated patients to 13% of treated patients ($P = 0.024$; odds ratio, 0.75; 95% confidence interval, 0.59–0.96), but this seemed to be based on some subgroups.[17] Detailed analysis of the entire dataset from the four largest trials failed to demonstrate any robust and logical (consistent across studies for a subgroup, evidence of dose-response) clinical benefit in any subgroup. The drug was not approved for use in the United States. Reasons for failure include inadequate dosing due to induction of liver enzymes by concomitant anticonvulsant use, too short a course of treatment (10 d), inability to discern clinically-important effects due to the ceiling effect of the Glasgow outcome scale, lack of effect due to sequestration of the lipophilic drug in the endothelium without penetration into the smooth muscle and/or cerebrospinal fluid, and true lack of efficacy in humans (but efficacy in flawed animal models).

Findlay et al.[22] conducted a small, 100-patient randomized, blinded study of intraoperative, intracisternal fibrinolysis with tissue plasminogen activator for lysis of SAH and prevention of vasospasm. Although there was no significant effect on the prespecified primary endpoint of angiographic vasospasm, there was a trend for the severity of vasospasm to be less in treated patients. In the subset of patients with thick SAH on admission CT scan, there was a 56% relative risk reduction in severe vasospasm in the fibrinolysis-treated patients ($P = 0.02$). There is abundant experimental and clinical evidence to support the hypothesis that vasospasm is related in a dose-response fashion to the location, volume, density (denser clots have more of whatever the spasmogen is in the clot or they incite more of the reaction that causes vasospasm), and rate of clearance of SAH.[23,55,84] Therefore, fibrinolytic therapy almost certainly prevents vasospasm. The limitations are that a single dose administered intraoperatively may not effectively diffuse to clear away all the clot fast enough and that hemorrhage may be precipitated by the treatment. The available evidence for its use, however, is Level 2 at present.

The other promising treatment is intrathecal nicardipine. Kasuya et al.[36] conducted a nonrandomized cohort study of 97 patients, of whom 69 had surgery and placement of subarachnoid nicardipine pellets within 72 hours of SAH. The dose ranged from 8 to 40 mg nicardipine. Delayed ischemia developed in four (6%) out of 69 patients treated with nicardipine and three (11%) out of 28 untreated patients. Little can be said scientifically about efficacy because this was not a blinded, randomized study, but no safety issues were reported. Vasospasm almost certainly begins as smooth muscle contraction and cerebrovascular smooth muscle is largely dependent, although not exclusively, for contraction on influx of calcium through voltage-gated calcium channels that are blocked by nicardipine. Nicardipine was already studied as an intravenous agent for prevention of vasospasm and there was evidence that high doses decreased vasospasm by transcranial Doppler and angiography criteria.[27] It did not affect outcome, however, and this was suggested to be because it caused hypotension that was detrimental to the patient. Because use of therapeutic hemodynamic maneuvers was higher in the placebo group, another explanation is that

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rescue therapy is equally effective as nicardipine at reducing delayed ischemia from vasospasm. For these reasons, I think this treatment is worth further study.

Finally, the low molecular weight heparin, enoxaparin, has been studied in two randomized, blinded studies. One reported a remarkable reduction in cerebral infarction from vasospasm from 28% in placebo to 9% in treated patients in association with reductions in vasospasm, poor outcome at 1 year, shunt-dependent hydrocephalus, and intracranial hemorrhagic complications.[80] The second study found no significant difference between placebo and enoxaparin treated patients in outcome at 3 months on the Glasgow outcome and modified Rankin scales.[62] Enoxaparin treatment was associated with more intracranial hemorrhagic complications. There is little rationale for using anticoagulants specifically to prevent some neurological complication of SAH. They might be useful, however, for preventing venous thromboembolic complications, but the question after SAH is whether this benefit is offset by an increased risk of hemorrhage. This question has been addressed in a review applying to head injury.[45] These patients generally should have intermittent pneumatic compression devices used on the lower extremities. Most studies used thigh-high compression, so whether or not the calf-only devices work as well is unknown. Prophylactic doses of anticoagulants probably carry only a small risk of causing bleeding when started 2 or 3 days after surgery, based on Level 2 data. This author recommended compression devices immediately and subcutaneous heparin starting after surgery or coiling if the postoperative imaging does not show concerning postoperative hemorrhage. The heparin is stopped before removing ventricular drains or performing other surgeries and then resumed later.

A summary of the above would be that magnesium, statins, endothelin antagonists, intrathecal nicardipine and intracisternal fibrinolysis all would be options at present.

Outcome Measures

The failure of the tirilazad trials with enormous cost and the ultimate restructuring of the entire drug company, as well as the failure of multiple neuroprotective drugs to improve outcome in patients with ischemic stroke, may have dampened enthusiasm for further studies. But, as can be seen above, there are a number of promising treatments that beg for further study. The question is how to best study these. Some specific limitations of the previous studies can be avoided, but designing new studies always raises a whole new set of questions to which only a best guess answer can be given. One issue is the endpoint chosen. This author estimated that using patient-based outcomes such as the Glasgow outcome scale, a trial would have to randomize approximately 5000 patients to demonstrate a significant improvement in outcome, even for a treatment that, for example, completely cured vasospasm.[46] Instead of assigning a common set of outcomes as being favorable for all patients, some trials used a prognosis-adjusted endpoint.[49] For example, in the surgical trial in intracerebral hemorrhage, patients who would be predicted to have a good outcome were assigned a good outcome if they made a good recovery or were moderately disabled on the Glasgow outcome scale. In patients predicted to have a poor outcome, good outcome included these categories plus the upper level of severe disability. Under some circumstances, this can increase trial power and reduce the sample sizes by 30 to 40%.[83] There are other approaches, including Bayesian adaptive trial designs and using surrogate endpoints instead of patient-based clinical outcomes. Fisher et al.[24] suggested that if the therapeutic maneuver was effective against the surrogate endpoint, then it could be licensed for use in patients in a bigger clinical trial. The power of human ingenuity is the only limitation and it is hardly a barrier. From the above information, it is remarkable to consider the advances made since the guidelines were published a little over a decade ago. Hopefully, the next decade will see vasospasm cured and effective neuroprotective treatments developed.

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