Evidence-based cerebral vasospasm management

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✓Cerebral vasospasm and delayed cerebral ischemia remain common complications of aneurysmal subarachnoid hemorrhage (SAH), and yet therapies for cerebral vasospasm are limited. Despite a large number of clinical trials, only calcium antagonists have strong evidence supporting their effectiveness. The purpose of this work was to perform a systematic review of the literature on the treatment of cerebral vasospasm.

A literature search for randomized controlled trials of therapies used for prevention or treatment of cerebral vasospasm and/or delayed cerebral ischemia was conducted, and 41 articles meeting the review criteria were found. Study characteristics and primary results of these articles are reviewed.

Key indicators of quality were poor when averaged across all studies, but have improved greatly over time. The only proven therapy for vasospasm is nimodipine. Tirilazad is not effective, and studies of hemodynamic maneuvers, magnesium, statin medications, endothelin antagonists, steroid drugs, anticoagulant/antiplatelet agents, and intrathecal fibrinolytic drugs have yielded inconclusive results.

The following conclusions were made: nimodipine is indicated after SAH and tirilazad is not effective. More study of hemodynamic maneuvers, the effectiveness of other calcium channel antagonists such as nicardipine delivered by other routes (for example intrathecally), magnesium, statin drugs, endothelin antagonists, and intrathecal fibrinolytic therapy is warranted. There is less enthusiasm for the study of steroid drugs and anticoagulant/antiplatelet agents because they entail more risks and investigations so far have shown little evidence of efficacy. The study of rescue therapy such as balloon angioplasty and intraarterial vasodilating agents will be difficult. The quality of clinical trials should be improved.

KEY WORDS • cerebral infarction • cerebral ischemia • cerebral vasospasm • intracranial aneurysm • subarachnoid hemorrhage

DELAYED cerebral ischemia and cerebral vasospasm remain the most common and debilitating neurological complications following aneurysmal SAH.⁵⁹ Twenty-five to 30% of patients who survive SAH from a ruptured intracranial aneurysm suffer from ischemic complications in the ensuing weeks, and 10 to 15% of patients with SAH die or experience permanent disability due to their ischemic deficits.^{25,34} Although there is some controversy regarding the correlation between cerebral vasospasm in large arteries and cerebral ischemia, vasospasm remains one of the primary causes of DINDs.^{41,56}

Proven therapeutic options for the treatment and/or prevention of delayed cerebral ischemia or cerebral vasospasm are few. Suarez, et al.,⁵⁹ summarized current treatment recommendations for vasospasm as consisting of prophylactic nimodipine; hypervolemia with induced hypertension, usually following the onset of vasospasm with neurological deficits; and a potential for balloon angioplasty or directed application of vasodilating agents.

Due to the emergence of the more rigorous principles of

evidence-based medicine, the need has arisen for a review of the available evidence on which to base the prevention and treatment of vasospasm in patients suffering from aneurysmal SAH. We have performed a systematic analysis of randomized controlled trials conducted specifically to evaluate prevention or treatment of delayed cerebral ischemia and/or cerebral vasospasm.

Materials and Methods

Search Strategy

In April 2006 we conducted a literature search of MEDLINE, the Cochrane Controlled Trials Registry, the Cochrane Stroke Trials Registry, and the National Institutes of Health/National Library of Medicine clinical trials registry, with no limitation for publication date or language. The Cochrane Controlled Trials Registry was searched using the key words “cerebral vasospasm” and “delayed cerebral ischemia.” The MEDLINE Web site (www.pubmed.com) was searched using the clinical query function optimized for therapy and broad search results. Search terms on MEDLINE were “cerebral vasospasm” and “delayed cerebral ischemia.” Both the Cochrane Stroke Trials Registry (<http://www.strokecenter.org/trials/index.aspx>) and the National Institutes of Health/National Library of

Abbreviations used in this paper: CI = confidence interval; CONSORT = Consolidated Standards of Reporting Trials; CT = computed tomography; DINDs = delayed ischemic neurological deficits; GOS = Glasgow Outcome Scale; NO = nitric oxide; RR = relative risk; SAH = subarachnoid hemorrhage.

Medicine clinical trials database (<http://clinicaltrials.gov>) were also searched for trials relevant to therapies for treatment and/or prevention of either cerebral vasospasm or delayed cerebral ischemia.

Article Selection Criteria

Randomized controlled trials of pharmacological or device-related therapies for prevention or treatment of cerebral vasospasm after nontraumatic aneurysmal SAH were included in the review. We only included work that would be classified as Level 1 evidence.⁸ Trials that lacked a control arm, presented data from a previously published paper, or focused on the incidence of vasospasm as a negative consequence of a therapy designed for another aspect of SAH (that is, tranexamic acid and antifibrinolytic therapy to prevent rebleeding) were not considered. Copies of all articles meeting the criteria were obtained and, if necessary, translated into English. Two authors read each paper and assessed whether it met the criteria for inclusion stated earlier.

Statistical Analysis

The RR with 95% CIs was calculated for outcome variables in papers in which sufficient data were provided but in which the authors did not complete the calculation themselves. The Newcombe–Wilson method was used for calculating CIs.⁴⁰ Values from articles in which the RR was reported with CIs calculated according to different or unreported methods are presented as originally described.

Results

Literature Search

The literature search produced 223 published articles. After applying our selection criteria, we found 41 randomized controlled trials conducted for prevention and/or treatment of cerebral vasospasm to be eligible for review.

Characteristics of Articles on Vasospasm Therapy

Characteristics of the studies are summarized in Table 1. There were slight increases in the numbers of studies published for each 5-year period during the time of investigation of calcium channel antagonists and tirilazad. Sample sizes have often been large, particularly considering the relative rarity of SAH, and this is due to the large number of multicenter trials. Sixteen different treatments have been tested, the most frequent being calcium channel antagonists and tirilazad. Most studies included patients with all grades of SAH. Specific information about the timing of surgery was often omitted. The studies included more patients undergoing clip placements than endovascular treatments, but the latter methods were developed only lately and have been included in more recent studies. In 66% of studies, patients received follow-up care for 3 or more months. Outcome measures, however, were quite variable. A randomization method was described in 54%, with stratification in multicenter studies in 52%. Patients were lost to follow up in 22% of the studies reviewed, intention-to-treat analysis was done in only 49%, the method of blinding was stated in 56%, and formal power calculations were described in only 37%. Baseline characteristics were described and well balanced in 61% of studies.

Summary of Primary Outcomes

Forest plots are presented (Fig. 1) for the RR associated with the outcome variables for all studies in which such results were given or could be calculated from the data. In the seven papers that were not included, the authors had presented their results in a manner that did not allow a calculation of the RR.^{16,18,21,28,29,48,52}

Specific Therapies

Calcium Channel Antagonists. We included 10 trials of calcium channel antagonists in which nimodipine or nicardipine were used. Trials of AT877 (fasudil) and magnesium are listed separately because these agents have mechanisms of action other than antagonism of voltage-gated calcium channels. Metaanalysis of these studies has been performed previously and does not need to be repeated here.^{5,49} There is reasonable evidence that oral nimodipine reduces delayed neurological deterioration due to vasospasm as well as infarct frequency and poor outcome, although the mortality rate is not decreased. Nicardipine, however, did not improve outcome. In the main study, 906 patients with recent aneurysmal SAH classified in all grades were randomized to receive either nicardipine or placebo.¹⁸ It was found that 32% of patients in the nicardipine group experienced delayed cerebral ischemia compared with 46% in the placebo group, a significant difference. Infarction rates were 129 (48%) of 267 treated patients and 148 (51%) of 289 in those given a placebo, which was not significantly different. Angiograms were obtained 7 to 11 days after SAH in 103 (23%) of 449 patients who received nicardipine and in 121 (26%) of 457 patients who received a placebo.

In this selected and thus potentially biased subset of patients, 33% of those treated with nicardipine had moderate to severe angiographic vasospasm compared with 51% in the placebo group. Outcome was identical between the groups, with 57% of patients attaining a good recovery and 18% dead. The possible conclusions are as follows: 1) vasospasm does not cause infarction or poor outcome; 2) nicardipine has detrimental effects; or 3) rescue therapy improves outcome in patients given a placebo to the same extent that nicardipine helps treated patients. We suggest that the latter conclusion is correct, because delayed cerebral ischemia was less common in the nicardipine-treated group. If nicardipine was detrimental, which would most likely be due to hypotension, then delayed cerebral ischemia should have been at least as common in the nicardipine group, and these patients should have undergone the same or more frequent use of induced hypertension and/or rescue therapy.

Hemodynamic Therapy. We found three randomized controlled trials that were also discussed in prior metaanalyses.^{50,61} The control group in the first study was treated with antihypertensive drugs, which was common practice at that time, but which is a treatment modality that could affect the difference between treated and control patients.⁵¹ Excluding this trial reduces the number of patients in whom hemodynamic therapy has been well studied to 146 (with 73 each in treatment and control groups).^{10,30} These trials did not show that hypervolemia improved outcome or reduced the incidence of delayed ischemia, and complications were more common in patients treated with hypervolemia. There

TABLE 1

*Literature review of characteristics of randomized clinical trials for prevention and/or treatment of vasospasm**

Characteristic	No. of Trials (%)	References
publication yr		
1980–1984	4 (10)	1,36,51,67
1985–1989	10 (24)	15,20,21,24,35,44–46,53,60
1990–1994	4 (10)	3,18,42,55
1995–1999	9 (22)	4,13,16,17,26,28,29,38,52
2000–2004	9 (22)	10,19,22,30,48,54,57,66,68
2005–present	5 (12)	7,32,62–64
no. of patients		
<50	8 (20)	7,10,32,38,48,51,63,66
50–99	7 (17)	20,22,30,35,36,45,62
100–249	14 (34)	1,3,4,13,15,16,19,21,24,42,44,57,67,68
250–500	5 (12)	52,54,55,60,64
>500	7 (17)	17,18,26,28,29,46,53
no. of centers		
one	17 (42)	7,10,22,30,32,35,36,38,42,45,48,51,57,62,66–68
multiple	24 (59)	1,3,4,13,15–21,24,26,28,29,44,46,52–55,60,63,64
duration of study		
not reported	10 (24)	7,13,15,21,32,36,45,48,66,67
1–2 yrs	25 (61)	3,4,16–20,22,24,26,28,29,35,38,42,44,46,51–55,60,62,63
>2 yrs	6 (15)	1,10,30,57,64,68
therapy evaluated		
magnesium sulfate	3 (7)	7,64,66
statin	2 (5)	32,62
endothelin antagonist	2 (5)	54,63
anticoagulant	3 (7)	19,57,68
NO donor	1 (2)	48
hemodynamic	3 (7)	10,30,51
aspirin	2 (5)	22,36
calcium antagonist	10 (24)	1,15,18,24,35,42,44–46,55
tirilazad mesylate	5 (12)	16,17,26,28,29
antioxidant	2 (5)	4,52
plasminogen activator	1 (2)	13
calcitonin gene-related peptide	1 (2)	3
steroid	3 (7)	20,21,38
thromboxane synthetase inhibitor	1 (2)	60
adrenergic-blocking agent	1 (2)	67
dipyridamole	1 (2)	53
clinical grade on admission		
all grades	19 (46)	3,4,7,13,17,18,20,22,26,28,29,35,46,51,53,57,62,64,67
WFNS I–IV ^{9†}	2 (5)	16,54
WFNS ≥ III	1 (2)	63
H & H I–III ²³	4 (10)	10,42,45,68,
H & H II–IV	3 (7)	48,52,66
H & H I–IV	7 (17)	19,21,24,30,36,38,55
Fisher 1–4 ¹⁴	1 (2)	32
H & H ≥ III	1 (2)	44
neurologically normal	1 (2)	1
≥30 on JCS	1 (2)	60
unknown	1 (2)	15
timing of op post–SAH		
NS	25 (61)	3,4,7,15–18,20,21,24,26,28,29,35,36,42,44,46,51,53,54,62,66–68
≤24 hrs	2 (5)	19,48
≤48 hrs	4 (10)	32,38,57,63
≤72 hrs	4 (10)	10,13,55,60
≤96 hrs	3 (7)	22,52,64
>96 hrs	2 (5)	30,45
after 24 hrs of drug delivery	1 (2)	1
type of op		
clip occlusion	30 (73)	1,3,4,10,13,15–18,20–22,24,26,29,30,35,36,38,42,44–46,51–53,55,60,63,67
endovascular coil insertion	1 (2)	19
either method	7 (17)	28,32,54,57,64,66,68
NS or implied	3 (7)	7,48,62
timing of therapy relative to op		
postop	12 (29)	3,10,13,19,22,30,38,48,55,57,60,63
preop	8 (20)	1,36,42,44,45,51,53,64
NS	14 (34)	7,15,16,18,20,26,32,35,46,52,54,62,66,68

Continued

TABLE 1 (continued)

*Literature review of characteristics of randomized clinical trials for prevention and/or treatment of vasospasm**

Characteristic	No. of Trials (%)	References
timing of therapy relative to op relative to SAH onset		
≤24 hrs	2 (5)	19,48
≤48 hrs	9 (22)	7,17,26,28,29,32,35,38,63
≤72 hrs	9 (22)	10,13,16,20,45,57,60,62,66,68
≤96 hrs	7 (17)	1,44,46,52,54,55,64
>96 hrs	4 (10)	4,18,22,30
NS	5 (12)	15,36,42,51,53
after onset of DINDs	3 (7)	3,21,24
duration of FU		
finished at discharge	13 (32)	1,15,20,24,32,38,45,48,51,62,63
0–3 mos	3 (7)	17,21,55
3 mos	19 (46)	3,4,7,13,16,18,26,28,29,35,44,46,52–54,57,60,64,66
>3 mos	8 (20)	10,19,30,36,42,67,68
review of cases in multicenter trials		
centralized	16 (39)	1,3,4,16–19,24,26,28,29,44,46,52,63,64
decentralized or NS	8 (20)	13,15,20,21,53–55,60
primary outcome variables assessed		
no single “primary outcome” described	7 (17)	20,21,38,48,60,67,68
vasospasm on angiography	2 (5)	13,63
vasospasm on TCD	1 (2)	62
clinical vasospasm	2 (5)	26,51
clinical vasospasm w/ documented arterial spasm	2 (5)	19,32
cerebral infarction	1 (2)	46
changes in CBF	1 (2)	30
DINDs	5 (12)	1,4,45,54,64
clinical outcome		
at 1 mo	1 (2)	55
at 3 mos	10 (24)	3,7,16,18,35,44,52,53,57,66
at 4 mos	1 (2)	22
at 6 mos	1 (2)	36
at ≥ 1 yr	2 (5)	10,42
deaths/severe deficits at discharge	2 (5)	15,24
death at 3 mos	3 (7)	17,28,29
quality-related characteristics		
method of randomization reported	22 (54)	2,4,10,13,16–19,22,26,28–30,35,38,44,46,52,55,57,62,64
patients lost to FU	9 (22)	17,18,26,28,29,53,54,63,68
intent-to-treat analysis reported	20 (49)	4,10,16–18,22,28–30,32,42,46,48,51,52,54,57,62,63,68
blinding method reported	23 (56)	1,4,10,13,18,19,21,22,24,26,28–30,35,44,46,48,52,55,62–64,67,68
explanation of power calculations reported	15 (37)	3,4,17,18,42,44,46,52–55,57,62–64
randomization stratified to equalize treat- ment btwn centers in multicenter trials	13 (32)	1,13,16–18,26,28,29,44,46,52,55,63
baseline characteristics well described & balanced	25 (61)	1,4,10,13,16–19,21,22,26,28–30,32,42,44,45,52,54,55,57,60, 62–64,68
sources of funding		
government	4 (10)	7,18,30,32
private	3 (7)	57,62,64
pharmaceutical company	14 (34)	1,3,16–18,26,28,29,32,44,46,52,54,63
none stated	21 (51)	4,10,13,15,19,20,22,24,35,36,38,42,45,48,51,53,55,60,66–68

* CBF = cerebral blood flow; FU = follow up; H & H = Hunt and Hess; JCS = Japan Coma Scale; NS = not specified; TCD = transcranial Doppler; WFNS = World Federation of Neurosurgical Societies.

† See Drake.

seems to be no evidence to support use of prophylactic hypervolemia in patients with aneurysmal SAH.

Magnesium. There were three studies of therapeutic magnesium infusions in patients with aneurysmal SAH.^{7,64,66} In the largest one, 283 patients were randomized within 4 days of SAH to receive intravenous magnesium sulfate (64 mmol/L/day, which is a standard toxemia dose) or intravenous saline.⁶⁴ The primary outcome, delayed cerebral ischemia, was reduced by 34% after infusion of magnesium (hazard ratio 0.66, 95% CI 0.38–1.14).

There also were favorable trends in the magnesium-treated group in terms of reduction in poor outcome at 3 months (23% risk reduction, risk ratio 0.77, 95% CI 0.54–1.09). There were two studies, which included 4066 and 45 patients.⁷ These studies provide some evidence for the safety and feasibility of maintaining elevated serum levels of magnesium.

Statins. There were two small studies in which patients with SAH were randomized to a group receiving a hydroxymethylglutaryl coenzyme A reductase inhibitor

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FIG. 1. Forest plot showing RRs of adverse outcome as defined in the particular study. CGRP = calcitonin gene-related peptide.

(statin; either simvastatin [19 patients] or pravastatin [40 patients]) and a group of 70 patients who received a placebo.^{32,62} Statin therapy was associated in both studies with a significant reduction in evidence of vasospasm on transcranial Doppler ultrasonography, and in the larger study, in which pravastatin was used, with reduced duration of severe vasospasm and a reduced overall mortality rate.⁶²

Endothelin Antagonists. A nonselective endothelin receptor antagonist, TAK-044, was compared with a placebo in a randomized blinded trial of 420 patients treated within 96 hours of SAH.⁵⁴ There was a trend toward a reduction in ischemic events in the treated patients (23% with placebo, 21% with TAK-044; not significant) but no significant differences in outcome or overall deaths. Patients receiving TAK-044 had significantly more hypotensive episodes necessitating increased use of vasopressor drugs (16% compared with 7% in the placebo group).

A small clinical trial of clazosentan, an endothelin A receptor-specific antagonist, was recently reported.⁶³ In this study, 32 patients with thick aneurysmal SAH were randomly allocated to receive placebo or clazosentan. Angiographically confirmed vasospasm occurred in 88% of those who received placebo but in 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 intraarterial infusions, and there was a trend toward reduction in the incidence of cerebral infarction in treated patients.

Intracisternal Fibrinolysis. Findlay, et al.,¹³ conducted the only randomized study of intracisternal fibrinolysis with tissue plasminogen activator. Although there was no significant effect on the prespecified primary end point of angiographically confirmed vasospasm, there was a trend for vasospasm to be less severe in treated patients. In the subset of patients with thick SAH on admission CT scans, there was a 56% reduction in the RR of severe vasospasm in the fibrinolysis-treated patients ($p = 0.02$).

Anticoagulation Therapy. The low-molecular-weight heparin enoxaparin has been studied in two randomized controlled trials. Wurm and colleagues⁶⁸ reported a remarkable reduction in cerebral infarction caused by vasospasm, from 28% in patients receiving placebo to 9% in treated patients, in association with reductions in the following phenomena: vasospasm, poor outcome at 1 year, shunt-dependent hydrocephalus, and intracranial hemorrhagic complications. In the second study, Siironen and colleagues⁵⁷ found no significant difference in outcome at 3 months between the group given a placebo and enoxaparin-treated patients on the GOS and modified Rankin Scale.

Other Treatments. Tirilazad was studied in four trials.^{17,26,28,29} Although a formal metaanalysis has not been published, we analyzed the raw data in the 3567 patients participating in these trials and found that the odds of poor outcome were 1.04 with tirilazad compared with placebo (95% CI 0.94–1.16). Steroid drugs were studied in three trials that included 256 patients.^{20,21,38} In two studies mineralocorticoids were used, which have different actions from the glucocorticoids that were used in the third study.²¹ On metaanalysis it was found that mineralocorticoid treatment reduced the risk of delayed ischemia (RR

0.65, 95% CI 0.33–1.27) and poor outcome (RR 0.33, 95% CI 0.03–3.02).¹¹ Side effects were higher with treatment (RR 1.75, 95% CI 1.03–2.95) when examining all three studies, and there was no significant effect on outcome.

There are only very limited data available for other treatments, such as aspirin,^{22,36} NO donors,⁴⁸ other antioxidants,^{4,52} calcitonin gene-related peptide,³ thromboxane synthase inhibitors,⁶⁰ adrenergic antagonists,⁶⁷ and dipyridamole.⁵³

Discussion

Quality of Studies

Guidelines for reporting the results of randomized control trials (CONSORT Statement) have been published.^{6,37} The guidelines include a checklist of 22 items that should be included in the published report of a clinical trial. Researchers evaluated SAH trials published between 1990 and 1999 in 10 major journals, and based on these guidelines, they concluded that the majority of studies on treatment strategies for SAH do not meet the requirements for proper methods.⁶⁵ This implies that treatment recommendations for SAH are based on weak evidence.

Table 1 characterizes the vasospasm literature on the basis of several of the key quality measures. The small size of many of these studies mitigated some common problems such as lack of follow-up review for patients. Only 22% of the studies reported any patients lost to follow up, and generally these losses were small and balanced between study arms. However, randomization methods were reported in only half (54%) of the papers, few (37%) gave information on power calculations, and measures taken to ensure blinding were well reported in only 56% of studies. Intention-to-treat analysis was used in 49% of papers and, importantly, in the majority of the nimodipine papers large numbers of patients were eliminated in blinded reviews after randomization. Reporting of baseline characteristics was problematic; there was a high degree of inconsistency in the variables reported, and in 39% of the papers these variables were not well described or were not balanced between treatment and control groups. No papers included a multivariate analysis to correct for imbalances in the baseline characteristics. Of the multicenter trials, only 52% report a method used to stratify the randomization of patients at each center to prevent center-specific treatment procedures from confounding the results. Other measures that are related to quality were disclosure of funding sources and identification of a primary outcome (Table 1). Funding sources were reported in only 49% of studies and a primary outcome was not identified either explicitly or implicitly in 17% of the papers.

It is important to consider that this review includes papers that were published as far back as the early 1980s, predating the CONSORT guidelines, and thus an evaluation based on modern criteria may seem unwarranted. Nevertheless, some clinical trials that guide current clinical practice (for example, trials of calcium channel antagonists) were published prior to the CONSORT guidelines. Additionally, there were discussions about the proper or-

ganization and reporting of clinical trials long before the CONSORT statement was issued. In the articles reviewed here, there were examples of improper reporting both before and after 1996, and thus there was not a dramatic shift in the quality of trials over this time. Therefore, close adherence to common reporting procedures is recommended and would improve the quality of randomized controlled trials of vasospasm therapy.

Prior Metaanalyses

The randomized trials of nimodipine and nicardipine have been subjected to at least two metaanalyses. Barker and Ogilvy⁵ included seven nimodipine studies in which 1202 patients were randomized. Nimodipine improved the odds of good and good plus fair outcome (odds ratios 1.9 and 1.7, respectively; $p < 0.005$ for both) and reduced the odds of neurological deficit and/or death attributed to vasospasm by 0.46 ($p < 0.008$). The finding of infarction on CT scans also was reduced by 0.58 ($p < 0.008$), although the mortality rate was not altered significantly. In the Cochrane collaboration, investigators reviewed 12 studies that included nimodipine, nicardipine, AT877, and magnesium, and made a somewhat weak recommendation for use of nimodipine by stating that the evidence in its favor was not proven beyond reasonable doubt, but that they recommended its use in view of the favorable benefit/toxicity ratio.⁴⁹ We would make a stronger recommendation for its use for at least 14 days after SAH in all cases, except in patients with no visible SAH on CT scans or who can be discharged home sooner. These investigators also stated that there is no evidence that nicardipine or AT877 have significant effects on outcome post-SAH, with which we concur, and which supports a recommendation that these drugs not be used for this indication at present.

Another method of vasospasm management subjected to metaanalysis was hemodynamic therapy; there are two metaanalyses of the three randomized trials.^{50,61} These studies focused on prophylactic hypervolemia, and the effects of induced hypertension and hemodilution could not be discerned. The works in question also were compromised by use of pharmacologically induced hypotension in the control group in one study⁵¹ and by different target hematocrits. Rinkel, et al.,⁵⁰ who analyzed the three studies included here, reported that hypervolemia did not improve outcome or reduce the incidence of delayed ischemia. In fact, complications were more common in patients treated with hypervolemia. The authors concluded that there was no evidence for effectiveness of prophylactic hypervolemia, and they recommended that more clinical trials of volume expansion therapy be conducted. Hemodynamic manipulations were used both prophylactically and therapeutically at most centers in the US in the 1990s. For example, in the four randomized trials of tirilazad conducted between 1991 and 1997, 63% of the approximately 3500 patients underwent prophylactic hemodynamic manipulations and 23% were treated with hemodynamic therapy.^{17,26,28,29} Any future trials of hemodynamic therapy would have to consider whether to address prophylactic or therapeutic aspects, and which maneuver or combination thereof to study, and would also have to take into account flexibility in treatment regimens that would be acceptable to neurosurgeons.

Other Treatments

The efficacy of magnesium is still in question. A randomized blinded clinical trial is underway (Intravenous Magnesium Sulfate in Aneurysmal Subarachnoid Hemorrhage Trial) and is scheduled to be completed in November 2007, with a total of 500 patients randomized. Although the clinical trial of magnesium for ischemic stroke did not demonstrate efficacy,³⁹ there are numerous potential beneficial effects of magnesium, including vasodilation and neuroprotection. The cost is low, the therapeutic index is broad, and administration is simple. In SAH, treatment can begin before onset of ischemia, so there is a compelling rationale for the Intravenous Magnesium Sulfate in Aneurysmal Subarachnoid Hemorrhage Trial. Whether to use therapeutic infusions is open to question at present.

The promising results of the two statin trials were corroborated by a retrospective cohort study of 20 patients with SAH who were admitted to the hospital while being treated with statins and 40 control cases of SAH.⁴³ Patients receiving statin therapy had a better functional outcome and were less likely to suffer delayed cerebral ischemia, although there was no effect on the mortality rate. However, Singhal, et al.,⁵⁸ noted in a similar retrospective observational study that patients with SAH who were admitted while undergoing statin therapy had an increased risk of vasospasm, and they speculated that this might be due to abrupt discontinuation of the drug on hospital admission for SAH. Statins have a host of biochemical effects that may benefit patients with SAH, including increasing endothelial nitric oxide synthase, enhancing bioavailability of NO, decreasing oxidative stress, inhibiting thrombogenesis, and reducing inflammation.³¹ Risks are low and definitive clinical trials are strongly recommended. We suggest awaiting results of these studies before initiating widespread use of statins.

There is much interest in trials of endothelin antagonists. Evidence obtained from experimental models of SAH and clinical studies of endothelin concentrations in humans with SAH support the suggestion that alterations in the vasoconstricting endothelin system might contribute to vasospasm.⁷⁰ Although results of the first study with a non-selective receptor antagonist were unimpressive,⁵⁴ the selective endothelin A receptor antagonist clazosentan was strikingly effective, albeit in a very small trial.⁶³ There are theoretical reasons why antagonists that are selective for the A receptor may be more effective against vasospasm. The results of a Phase IIb trial of clazosentan, in which patient recruitment stopped in November 2006 after approximately 400 patients were enrolled, should be available soon. Only bosentan is commercially available, but it is not recommended for use in patients with SAH at present.

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 spasmogen is in the clot, or they incite more of the reaction that causes vasospasm), and rate of clearance of SAH.^{12,47,69} Therefore, it is highly likely that if one could safely and effectively remove the hematoma quickly after the onset of SAH, then vasospasm would be reduced. Fibrinolytic therapy was

subjected to metaanalysis that included nine trials.² All but one study were nonrandomized, unblinded trials of the type that are known for a tendency to overestimate efficacy and underestimate side effects. The metaanalysis indicated that these treatments have a favorable impact on development of DINDs, GOS score, and overall mortality rate. However, the results of the only randomized control trial,¹³ although they were within the 95% CIs for the pooled analysis, were at odds with the nonrandomized studies. Fibrinolytic therapy shows promise for the prevention of vasospasm, but the current level of evidence is weak and a large randomized controlled trial is needed. We do use intracisternal fibrinolytic therapy in selected patients with SAH whose ruptured aneurysms are definitely occluded and who have persistent SAH after aneurysm treatment.

It seems unlikely that enoxaparin will have any significant, measurable effect on outcome after SAH. At present, there is little evidence that can serve as a rationale for using anticoagulant agents specifically for prevention of vasospasm. There might be more support for their use in the prevention of venous thromboembolic complications, but even here, the question is whether this benefit is offset by an increased risk of hemorrhage. This question has been addressed in a previous review focusing on anticoagulation therapy in the context of head and spinal cord injury.³³

Trials of tirilazad included the most patients ever studied in randomized controlled SAH trials.^{17,26,28,29} A formal metaanalysis of the studies has not been published, but we have analyzed the raw data from these trials and found no evidence of an effect on outcome. Analysis of effects on symptomatic vasospasm and infarction need to be completed. Metaanalysis of the three trials of steroid drugs for treatment of SAH found no evidence for efficacy, and instead there was a suggestion of increased complications.¹¹ It was recommended that additional studies be performed. We do not use glucocorticoid agents in patients with SAH, nor do we have much interest in such studies.

It is difficult to say whether to pursue antiplatelet therapy for SAH. The experimental data in support of its use are weak at present, and these drugs would probably be associated with an increased risk of intracranial hemorrhage.

Conclusions

The only proven therapy for vasospasm is nimodipine; tirilazad is not effective. More study of hemodynamic maneuvers, other calcium channel antagonists such as nicardipine delivered by other routes such as intrathecally,²⁷ magnesium, statin drugs, endothelin antagonists, and intrathecal fibrinolytic medications is warranted. There is less enthusiasm for the study of steroid drugs and anticoagulant/antiplatelet agents because they entail more risks, and studies so far have shown little evidence of efficacy. The study of rescue therapy such as balloon angioplasty and intraarterial vasodilating agents will be difficult. The quality of clinical trials should be improved.

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