Systematic review of the prevention of delayed ischemic neurological deficits with hypertension, hypervolemia, and hemodilution therapy following subarachnoid hemorrhage

MIRIAM M. TREGGIARI, M.D., M.P.H., BERNHARD WALDER, M.D., PETER M. SUTER, M.D., AND JACQUES-ANDRÉ ROMAND, M.D.

Division of Surgical Intensive Care, Department of Anesthesia, Pharmacology, and Surgical Intensive Care, University Hospitals, Geneva, Switzerland

Object. There is uncertainty about the efficacy of hypertension, hypervolemia, and hemodilution (triple-H) therapy in reducing the occurrence of delayed ischemic neurological deficits (DINDs) and death after subarachnoid hemorrhage. The authors therefore conducted a systematic review to evaluate the efficacy of triple-H prevention in decreasing the rate of clinical vasospasm, DINDs, and death.

Methods. The authors systematically reviewed studies identified based on a MEDLINE, EMBASE, and COCHRANE Register search of articles published between 1966 and 2001, and reference lists of identified articles. An independent assessment of each study’s methodological quality, population, intervention, and outcomes (rates of symptomatic vasospasm, DINDs, and death) was performed. Summary relative risk estimates were calculated for the main outcomes using fixed- or random-effect models, as appropriate.

Only four prospective, comparative studies with a total of 488 patients were identified. The median internal validity score was 0.5 (range 0–2); the median external validity score was 3 (range 2–6). Compared with no prevention, triple-H therapy was associated with a reduced risk of symptomatic vasospasm (relative risk [RR] 0.45, 95% confidence interval [CI] 0.32–0.65), but not DIND (RR 0.54, 95% CI 0.2–1.49). The risk of death was higher (RR 0.68, 95% CI 0.53–0.87). Sensitivity analyses including only randomized, controlled trials showed no evidence of statistically significant results for these major end points.

Conclusions. The paucity of information and important limitations in the design of the studies analyzed preclude evaluation of the efficacy of triple-H prevention and formulation of any recommendations regarding its use for the prevention of cerebral vasospasm.

KEY WORDS • cerebral aneurysm • intracranial vasospasm • delayed ischemic neurological deficit • triple-H therapy

The occurrence of DINDs constitutes a major complication of aneurysmal SAH and has been associated with increased mortality rates in the first 2 weeks after SAH, as well as permanent disability in one third of cases. Although symptoms are not always present, intracranial vasospasm has been demonstrated on neuroimaging in as many as 70% of all patients presenting with aneurysmal SAH.2

The combination of induced hypertension, hypervolemia, and hemodilution (also known as triple-H therapy) is often initiated to prevent cerebral vasospasm. This strategy was first described more than 20 years ago,13,26 and is widely used, particularly in North America.27 The efficacy of triple-H therapy, however, in preventing the onset of cerebral vasospasm, and improving ischemic deficits or survival, remains uncertain because conflicting results have been reported.14,28,33 In addition, medical complications can result from triple-H prophylaxis that may offset its overall benefits. Indeed, triple-H therapy may be responsible for potentially life-threatening complications, such as pulmonary edema, myocardial ischemia, hyponatremia, renal medullary washout, indwelling catheter-related complications, and, eventually, bleeding from another aneurysm in the setting of multiple locations, hemorrhagic infarction, and cerebral edema.4,29,32

The aim of this systematic review was to search for data from comparative clinical trials on triple-H prevention after aneurysmal SAH, to appraise the data critically, and to investigate the strength of evidence of the efficacy of this approach in preventing vasospasm and delayed cerebral ischemia, as well as evidence of its harm.

Clinical Material and Methods

Search Strategy

We searched MEDLINE (PubMed, NLM Grateful Med, and KnowledgeFinder 4.19) for articles published between 1966 and July 8, 2001, EMBASE between 1984 and September 2, 1999, and the central COCHRANE Controlled Trial Register for 2001. All searches were without language restriction, and the following terms were used: “cerebral aneurysm,” “intracranial aneurysm,” “subarachnoid hemorrhage,” “delayed cerebral ischemia,” “neurologic deficits,” “cerebral vasospasm,” “volume expansion therapy,” “hy-
Triple-H preventive therapy after subarachnoid hemorrhage

pertensive,” “hypervolemic,” “hemodilution,” “hyperdynamic,” and “triple H therapy.” These words were linked using the following combinations: “cerebral aneurysm” or “intracranial aneurysm” or “subarachnoid hemorrhage” and “delayed cerebral ischemia” or “neurologic deficits” or “cerebral vasospasm,” and “volume expansion therapy” or “hypertensive” or “hypervolemic” or “hemodilution” or “hyperdynamic” or “triple H therapy.” Reference lists from the retrieved reports, recent review articles, and a systematic review were checked for completeness.

Inclusion Criteria, End Points, and Definitions

The papers included had to be full reports on adults who were suffering from spontaneous aneurysmal or presumably aneurysmal SAH documented by CT scanning, cerebrospinal fluid examination, or cerebral angiography, and who were at risk of developing cerebral vasospasm. The studies had to evaluate the administration of triple-H prevention compared with no triple-H prevention and had to be published in peer-reviewed journals. The minimum duration of triple-H therapy had to be longer than 1 day. For the purpose of our study, we used the definitions of triple-H prevention established by the authors of the articles we identified. To reduce the likelihood of bias and overestimation of efficacy, only comparative, prospective clinical trials were included. The definition of a prospective trial was as follows: trial said to be prospective by the original authors, or, in the absence of the expression “prospective,” there was a detailed methodological description in which clear inclusion and exclusion criteria were required. A review of records was regarded as retrospective. Abstracts from scientific meetings, animal studies, and data from review articles were not considered.

Seven clinical outcomes of primary interest were defined in a pre hoc conference: 1) angiographically confirmed vasospasm; 2) symptomatic vasospasm; 3) DINDs (that is, confirmed cerebral infarction); 4) medical complications (pulmonary edema, left ventricular failure); 5) hospital length of stay; 6) neurological outcome; and 7) death. The definitions of symptomatic vasospasm, DIND, angiographic vasospasm, cerebral infarction, and medical complications were used as described by the authors of each study. The reports we included had to characterize at least one of these outcomes.

Data Extraction

Two authors (M.T. and B.W.) screened the titles and abstracts of all reports retrieved, and all papers that did not explicitly meet our predefined inclusion criteria were excluded at this stage. Data abstraction of all remaining reports was done by three investigators (M.T., B.W., and J.A.R.) independently and in triplicate. Discrepancies were resolved by discussion among all investigators to reach a consensus. For data extraction the following criteria were used. The number of patients included who were then randomized and used for the analysis was recorded. If the number of analyzed but not the number of included patients was mentioned, it was assumed that the number of patients analyzed corresponded to the number of patients included (the best-case scenario).

Patient Characteristics. We identified age, sex, initial neurological severity score (Hunt and Hess grade, World Federation of Neurosurgical Societies score), and the initial CT findings (Fisher score).

Type and Timing of Aneurysm Intervention. We noted neurosurgical and neuroimaging procedures, early (< 7 days) or late (≥ 7 days) intervention, and additional measures used (for example, clot removal, application of subarachnoid papaverine, carotid branch sympathectomy, placement of recombinant tissue plasminogen activator, or ventricular drainage).

Timing of Prophylactic Therapy. We noted the time of initiation of prevention in relation to SAH or hospital admission and the duration of preventive therapy.

Regimen of Prophylactic Therapy. The volume of daily fluids, type of fluid administered, type and dose of vasoressor or inotropic drugs used, and blood derivative transfusions were identified.

Monitoring of Prophylactic Therapy. The invasive arterial pressure, CVP, pulmonary capillary occlusion pressure, cardiac output, intracranial pressure monitoring, urine output, plasma protein level, hematocrit, and duration of monitoring.

Type of Clinical and/or Neuroimaging Follow Up. Clinical neurological monitoring (Glasgow Coma Scale, pupil reactivity, neurologic deficits), the frequency of clinical examinations, type and frequency of neuroimaging assessment (CT scans, transcranial Doppler velocity, angiography), and duration of follow up were evaluated.

Concomitant Treatments During Prevention. Use of nimodipine, intracisternal fibrinolysis, or other treatments was noted.

Validity Assessments

Internal Validity. We decided to include randomized trials only, because randomized treatment assignments can provide a reliable and unbiased estimate of treatment effect. The quality of the methodology of randomized controlled trials was assessed using the Oxford score, values for which range from 0 to 5, maximum 5 points, minimum 0. All investigators independently assigned a score to the trials included in this study, and, in case of a discrepancy in the assigned scores, an agreement was reached by discussion.

Our search strategy was expected to retrieve only a few randomized trials that would have strictly met our inclusion criteria. Therefore, a pre hoc decision was made that in case our search selected fewer than five randomized controlled trials, then prospective comparative trials without concealment of allocation would also be included. We are aware that in comparative trials without proper randomization, there is a risk of selection bias that may lead to overestimation of a treatment effect size. To account for the potential bias introduced by the inclusion of prospective, comparative studies in addition to randomized controlled trials, we planned to perform a sensitivity analysis also, which would include only randomized controlled trials.

External Validity. To maximize the homogeneity of the data, we generated a scoring system for external validity that ranged from 0 (poorest quality) to 7 (highest quality). This external validity score included the following items, which were categorized as yes or no: a) documentation of the diagnosis of spontaneous, aneurysmal SAH (confirmed...
with angiography, CT angiography, or surgery); b) definition of the start of triple-H prevention after SAH; c) definition of the duration of triple-H prevention; d) target for triple-H prevention (arbitrary definition for the purpose of this study: CVP ≥ 8 mm Hg or pulmonary capillary occlusion pressure ≥ 12 mm Hg; hematocrit < 0.35; mean arterial pressure ≥ 70 mm Hg; and systolic arterial pressure ≥ 120 mm Hg); e) target mentioned for the control group; f) duration of follow up, at least during hospitalization; and g) adverse effects mentioned.

Data Analysis

The RR estimates of incidence data, comparing patients receiving triple-H therapy with those receiving no prophylaxis, were calculated for symptomatic vasospasm, DIND, and death, with a 95% CI (RevMan version 4.0; Cochrane Library, Oxford, England).21 For combined data, a fixed-effect model was used when there was homogeneity (p > 0.1); otherwise, a random effects model was used.3

Results

Characteristics of Trials Identified

A total of 465 articles were located from all sources, with 136 reports mentioning the use of triple-H therapy (Fig. 1). Fourteen reports that were not originally written in English have been translated (12 Japanese, one French, and one Italian). In 49 trials in which triple-H therapy was administered, 191,4,8–10,14–18,20,22–24,28,31,33,35,36 were prospective; 12 of these pertained to prevention of vasospasm with triple-H therapy.4,8–10,14,17,23,24,28,33,35,36 Four studies14,28,35,36 were prospective, controlled, comparative trials in which the effect of prevention compared with no prevention on symptomatic vasospasm was examined; these were included in the analysis (Table 1).

Two trials28,36 were published in neurosurgical journals and two14,35 appeared in a neurological journal. Two were randomized controlled trials,14,28 one used a historical cohort study design,35 and one used a parallel cohort design36 (Table 2). The size of the trials was small (≤ 50 patients), with the exception of one study.35 The median internal validity (Oxford) score was 0.5 (range 0–2), whereas the median external validity score was 3 (range 2–6).

Altogether, the four trials included 488 patients suffering from aneurysmal SAH, who underwent a surgical procedure for aneurysm repair. In two trials, surgery was performed within 7 days after hospital admission;14,36 in the other two it was performed at Day 7 or later.28,35 The patients’ mean age was 53 years (range 31–66 years) and 34% were men. The clinical neurological evaluation at admission was performed using Hunt and Hess grading in three trials;14,28,35 it included patients who were classified in Grade I to IV (Table 1). In one trial an additional CT scan was obtained at admission.36 The time elapsed from bleeding to hospital admission was 3 days or less in one trial,14 from 2 to 7 days in another36 and it was not reported in the remaining two studies.

Qualitative and Quantitative Analysis

In three investigations the type and intensity of neurological monitoring performed during the study protocol were described, and in one trial additional serial transcranial Doppler and xenon cerebral blood flow measurements were performed.14 In one trial angiography was performed when cerebral vasospasm was suspected based on clinical findings.28

Of the seven clinical outcomes of primary interest, four were analyzed qualitatively (Table 3) and three quantitatively. Only two trials reported either angiographically confirmed vasospasm,28 which was measured at the carotid, middle cerebral, and anterior cerebral arteries, or medical complications and neurological outcome.14 The type of medical complications recorded included cardiovascular (hypertension, arrhythmia, congestive heart failure), metabolic (hyponatremia, hyperglycemia), and infectious (pneumonia, urinary tract, bacteremia, meningitis/vasculitis) events. Lennihan, et al., reported the occurrence of hyponatremia (two cases in both groups) and cerebral edema (15% of patients who received preventive therapy compared with 17% of those who did not). In one trial in which a surgical protocol of late aneurysm clipping was used, rebleeding...
was reported in 13% of the patients who received preventive therapy and in 18% of those who did not. The length of hospital stay was never reported.

Symptomatic vasospasm and DIND were defined as “a focal neurologic deficit or deterioration in the level of consciousness, with either confirmation of infarction on a CT scan or exclusion of other possible causes of deterioration, such as rebleeding, surgical complication, hydrocephalus, cerebral edema, electrolyte disorder, infection or seizure” in the trial by Lennihan and colleagues. Rosenwasser, et al., judged symptomatic vasospasm by the development of either altered mental status or a focal deficit. Vermeij, et al., differentiated between probable or definite delayed ischemia, defined as gradual development of focal neurological signs with or without deterioration of the level of consciousness, based on CT scans or autopsy confirmation.

Yano, et al., indicated that “the diagnosis of delayed cerebral ischemia was based solely on the development of a new neurologic deficit, which was not attributable to an intraoperative complication, hemorrhage, or hydrocephalus as determined by CT scan, or a metabolic disturbance diagnosed by electrolyte and arterial blood gas analysis.”

Symptomatic vasospasm developed in 14% of the patients who received preventive therapy compared with 31% of those who did not (Table 4). The combined estimate of the RR demonstrated a protective effect of prevention (RR 0.45, 95% CI 0.32–0.65). In three trials in which DINDs were reported, this outcome occurred in 13% of the patients who received the prophylactic regimen and in 26% of the patients who did not (Table 5). The combined estimate of the RR was not statistically significant for prophylaxis compared with no prophylaxis (RR 0.54, 95% CI 0.20–1.49).

The overall mortality rate in patients who received the prophylactic regimen compared with those who did not was 28 and 41%, respectively, in the three trials in which this end point was reported (Table 6). The combined estimate of the RR was not statistically significant for prophylaxis compared with no prophylaxis (RR 0.68, 95% CI 0.53–0.87). The mortality rate was evaluated 14 days after the event in one study and at 3 months in the other two.

**Sensitivity Analysis**

The development of symptomatic vasospasm in patients who received the prophylactic regimen compared with those who did not was 20 and 30%, respectively, in studies without concealment of allocation (combined estimate of the RR 0.4, 95% CI 0.26–0.61; fixed-effects model).

The development of DIND in patients who received the prophylactic regimen compared with those who did not was 17 and 10%, respectively, in studies in which the allocation was concealed (combined estimate of the RR 1.75, 95% CI 0.55–5.53; random-effects model), and 12 and 30%, respectively, in the two trials without concealment of allocation (combined estimate of the RR 0.4, 95% CI 0.25–0.61; fixed-effects model).

The mortality rate in patients who received the prophylactic regimen compared with those who did not was 7 and 18%, respectively, in the randomized trials (combined estimate of RR 0.4, 95% CI 0.14–0.16; fixed-effects model), and 34 and 48%, respectively, in the one nonrandomized trial by Lennihan and colleagues.

---

**TABLE 1**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Group (no. of patients)</th>
<th>Duration of Therapy (days)</th>
<th>Targets for Triple-H Therapy</th>
<th>Targets for Control Group</th>
<th>Concomitant Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenwasser, et al., 1983</td>
<td>only patients w/ arterial hypertension</td>
<td>7-10</td>
<td>systolic arterial pressure (&gt;120 mm Hg), pulmonary artery occlusion pressure (7–13 mm Hg), CVP (5 mm Hg), pulmonary artery diastolic pressure (14 mm Hg)</td>
<td>fluid intake (NA)</td>
<td>fluid intake (NA)</td>
</tr>
<tr>
<td>Teasdale, et al., 1993</td>
<td>H &amp; H Grade</td>
<td>110</td>
<td>200 ml/min of anesthesia for ventilation</td>
<td>2 L fluid intake, fludrocortisone</td>
<td>2 L fluid intake, fludrocortisone</td>
</tr>
<tr>
<td>Lennihan, et al., 2000</td>
<td>10 kg BW, fluids intake (3 L/day/70 kg BW), (4.3 L/day/70 kg BW)</td>
<td>14</td>
<td>nimodipine, steroids, nifedipine</td>
<td>fluid intake (NA)</td>
<td>fluid intake (NA)</td>
</tr>
</tbody>
</table>

* BW = body weight, GCS = Glasgow Coma Scale, H & H = Hunt and Hess, NA = not available.
trial in which this outcome was reported (RR 0.71, 95% CI 0.55–0.92).

Conclusions in the Original Studies

In three studies (75%), the authors concluded from their data that prevention with triple-H therapy was useful. Rosenwasser, et al., reported that their patients experienced a decreased incidence of clinically confirmed vasospasm with early institution of volume expansion. Yano, et al., stated that hyperdynamic and hypertensive/hypervolemic therapies are the first choice as prophylactic treatment of delayed cerebral ischemia after SAH. Vermeij, et al., concluded that patient outcome improved as the result of a change in the medical treatment strategy. In the study by Lennihan, et al., the usefulness of such prevention was questioned; those authors concluded that prophylactic hypervolemia does not increase cerebral blood flow and is unlikely to confer any additional benefit over normovolemic therapy.

Discussion

The main finding of our systematic review is that, despite the widespread use of triple-H therapy to prevent vasospasm after SAH, only a few prospective, comparative trials addressed the question of its efficacy and harm. Furthermore, in our systematic search we identified major limitations related to inadequate internal and external validity of these trials, and small study samples for randomized controlled trials.

Internal Validity

To what extent were the inferences drawn on study participants valid for the source population? Only four prospective, controlled trials, which included 243 patients who received triple-H prevention and 245 who did not, were available. Overall, the four trials had a low internal validity, scoring between 0 and 2 on the Oxford scale, because of the absence of randomization, incomplete description of the randomization procedure, performance of only a pseudo-randomization, or failure of blinding (two studies) and the absence of descriptions of dropouts (three studies) (Table 2).

In a sensitivity analysis, in which we investigated randomized and nonrandomized trials separately, we found major differences between the two: when only randomized trials were considered, there were no differences between the intervention and the control groups in any of the three end points of interest: symptomatic vasospasm, DIND, and death. This could be related to the small sample of randomized patients, and, importantly, to the well-described over-estimation of efficacy in nonrandomized trials. Another

more, in our systematic search we identified major limitations related to inadequate internal and external validity of these trials, and small study samples for randomized controlled trials.

* ITT = intention-to-treat; Tx = treatment.

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Patients/ Group</th>
<th>ITT Analysis</th>
<th>Randomization</th>
<th>Blinding</th>
<th>Drop-Outs</th>
<th>Oxford Score</th>
<th>Diagnosis</th>
<th>Initiation of Tx</th>
<th>Duration of Tx</th>
<th>Target for Triple-H Group</th>
<th>Target for Control Group</th>
<th>Follow Up</th>
<th>Adverse Effects</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenwasser, et al., 1983</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>1</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>3</td>
</tr>
<tr>
<td>Yano, et al., 1993</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>0</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>3</td>
</tr>
<tr>
<td>Vermeij, et al., 1998</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>0</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Lennihan, et al., 2000</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>2</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>6</td>
</tr>
</tbody>
</table>

* Help needed in activities of daily living.
source of bias derives from the lack of blinding. Although in this setting blinding may be difficult, its lack raises concerns of an overestimation of the treatment effect size.19

External Validity

To what extent are the results from these trials generalizable, that is, are the patients included in these studies representative of the target population of patients with SAH? With the exception of one trial,14 the external validity was inadequate (Table 2). The design of most trials was incomplete, and did not even meet very moderate targets of triple-H prevention (CVP ≥ 8 mm Hg or pulmonary artery occlusion pressure ≥ 12 mm Hg; hematocrit < 0.35; mean arterial pressure ≥ 70 mm Hg; and systolic arterial pressure ≥ 120 mm Hg). The absence of minimal common targets for comparison of prevention and no prevention complicates the task of making inferences about the true parameters.

The great variability in the study protocols further complicates the interpretation of these results (Table 1). The regimens of prophylaxis administration varied widely among the studies analyzed. Fluid loads ranged from 1.9 to 3 L/day, with various combinations of crystalloid and colloid solutions. Hematocrit levels varied from 0.29 to 0.45. Drugs used to enhance the hemodynamic variables, concomitant treatments, and overall management were also nonuniform across studies. Therefore, it is difficult, if not impossible, to establish whether the effects attributed to the triple-H therapy resulted in outcomes that differed depending on the addition of other treatments, or a specific component of the regimen. In a previous systematic review in which more restrictive selection criteria were used (only randomized controlled trials) to evaluate circulatory volume expansion after SAH, the authors drew similar conclusions.7 Furthermore, in only one trial14 was the occurrence of serious adverse effects (for example, cerebral edema and congestive heart failure) reported (Table 2). The lack of quantification of side effects in the other studies is of concern for the relevance of their findings.

Research Agenda for Triple-H Prophylaxis

The question of the efficacy of triple-H therapy in preventing vasospasm and delayed cerebral ischemia and its adverse effects cannot be answered based on the available scientific literature. Our study emphasizes the need for a well-designed, randomized controlled trial, which would be sufficiently powered for patient-relevant outcomes (for example, DIND), to investigate the efficacy and harm of triple-H prevention in a defined patient population, after clipping and/or coil placement in ruptured cerebral aneurysms. An ideal end point must be measurable, sensitive, and clinically relevant. Although the use of a surrogate end point such as the onset of clinical vasospasm easily lends itself to the introduction of bias and is not suitable, death would be too restrictive as an end point, given the rarity of this occurrence and the existence of other important functional outcomes. In particular, clinically relevant and measurable outcomes such as neurological outcome at 3 or 6 months and neuroimaging confirmed cerebral infarction could be considered meaningful end points. Also important, consideration must be given to the treatment algorithms for the active treatment and comparison groups. The groups need to be treated in a sufficiently different way to detect the expected difference, if this truly exists. Finally, blinding of this trial will be difficult to implement, and therefore, measures must be taken to compensate for the difficulty in concealing treatment allocation. At least the evaluation and adjudication of the outcomes, conducted in an objective and measurable manner, must be performed by investigators in a blinded fashion. It is highly likely that such a study will be based on a multicenter design.

Conclusions

We found only a few trials in which the efficacy and side effects of triple-H therapy to prevent DIND were investigated. These studies had important methodological limita-

### Table 4

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Prevention</th>
<th>Control</th>
<th>RR</th>
<th>95% CI (fixed-effects model)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenberg, et al., 1983*</td>
<td>3 of 15</td>
<td>9 of 15</td>
<td>0.33</td>
<td>0.11–0.99</td>
<td>12.0</td>
</tr>
<tr>
<td>Yano, et al., 1993</td>
<td>3 of 15</td>
<td>9 of 13</td>
<td>0.29</td>
<td>0.10–0.85</td>
<td>12.8</td>
</tr>
<tr>
<td>Vermeij, et al., 1998</td>
<td>20 of 172</td>
<td>49 of 176</td>
<td>0.4</td>
<td>0.26–0.67</td>
<td>64.5</td>
</tr>
<tr>
<td>Lennihan, et al., 2000*</td>
<td>8 of 41</td>
<td>8 of 41</td>
<td>1.00</td>
<td>0.42–2.41</td>
<td>10.7</td>
</tr>
<tr>
<td>Total</td>
<td>34 of 243</td>
<td>75 of 245</td>
<td>0.45</td>
<td>0.32–0.65</td>
<td>100.0</td>
</tr>
</tbody>
</table>

* Randomized controlled trial.

### Table 5

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Prevention</th>
<th>Control</th>
<th>RR</th>
<th>95% CI (random-effects model)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yano, et al., 1993</td>
<td>2 of 15</td>
<td>8 of 13</td>
<td>0.22</td>
<td>0.06–0.84</td>
<td>26.0</td>
</tr>
<tr>
<td>Vermeij, et al., 1998</td>
<td>20 of 172</td>
<td>49 of 176</td>
<td>0.42</td>
<td>0.26–0.67</td>
<td>44.1</td>
</tr>
<tr>
<td>Lennihan, et al., 2000*</td>
<td>7 of 41</td>
<td>4 of 41</td>
<td>1.75</td>
<td>0.55–5.53</td>
<td>30.0</td>
</tr>
<tr>
<td>Total</td>
<td>29 of 228</td>
<td>61 of 230</td>
<td>0.54</td>
<td>0.20–1.49</td>
<td>100.0</td>
</tr>
</tbody>
</table>

* Randomized controlled trial.
tions. Our search revealed that there is insufficient “evidence-based medicine” data to make recommendations for the use and optimal regimen of triple-H strategy as a prophylactic treatment after SAH.

References


Manuscript received August 2, 2002. Accepted in final form February 5, 2003.

Address reprint requests to: Miriam M. Treggiari, M.D., Surgical Intensive Care, Geneva University Hospital, CH-1211 Geneva 14, Switzerland. email: treggmm@u.washington.edu.