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

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CRD summary
This review evaluated the efficacy of triple-H (hypertension, hypervolaemia, haemodilution) therapy in reducing the occurrence of clinical vasospasm, delayed ischaemic neurological deficits, and death after subarachnoid haemorrhage. The authors’ concluded appropriately that a lack of evidence combined with limitations in the design of included studies preclude evaluation of the effects of triple-H prevention or any recommendations regarding its use.

Authors’ objectives
To evaluate the efficacy of hypertension, hypervolaemia and haemodilution (triple-H) therapy in reducing the occurrence of clinical vasospasm, delayed ischaemic neurological deficits (DINDs), and death after subarachnoid haemorrhage (SAH).

Searching
MEDLINE (from 1966 to 8 July 2001), EMBASE (from 1984 to 2 September 1999) and the Cochrane Controlled Trials Register (2001) were searched without any language restrictions; the search terms were reported. In addition, the reference lists of identified studies, recent review articles and a systematic review were examined.

Study selection
Study designs of evaluations included in the review
Full reports of comparative, prospective clinical trials published in peer-reviewed journals were eligible for inclusion. Reviews of records were excluded, as were conference abstracts, animal studies and data from review articles. Only one included study had more than 50 participants per treatment group.

Specific interventions included in the review
Studies evaluating the effectiveness of triple-H prevention (of longer than one day) compared with no triple-H prevention were eligible for inclusion. In the included studies, triple-H therapy lasted between 7 and 14 days.

Participants included in the review
Studies investigating adults suffering from spontaneous aneurysmal or presumably aneurysmal SAH, documented by computerised tomography scanning, cerebrospinal fluid examination or cerebral angiography, and who were at risk of developing cerebral vasospasm, were eligible for inclusion. The included studies examined patients suffering from aneurysmal SAH who underwent a surgical procedure for aneurysm repair. The participants had a mean age of 53 years old and were predominantly female (66%).

Outcomes assessed in the review
Primary studies were eligible for inclusion if they addressed at least one of the following: angiographically confirmed vasospasm, symptomatic vasospasm, DINDs (confirmed cerebral infarction), medical complications (pulmonary oedema or left ventricular failure), hospital length of stay, neurological outcome, or death. The outcome definitions used were those employed by the authors of the included primary studies. None of the included studies reported length of hospital stay as an outcome measure.

How were decisions on the relevance of primary studies made?
Two reviewers screened titles and abstracts to determine relevance to the review question.

Assessment of study quality
The authors assessed the internal validity of the primary studies using Jadad quality criteria. To assess external validity, they scored studies on the following: documentation of diagnosis of spontaneous, aneurysmal SAH; definition of start of triple-H prevention after SAH; definition of duration of triple-H prevention; target for therapy; target mentioned for controls; the duration of follow-up; and adverse events mentioned. Four reviewers independently assessed the internal validity of the included trials, with agreement reached by discussion in the case of discrepancy. The authors did not state how judgements of external validity were made.

**Data extraction**

Three reviewers independently extracted the data from the primary studies. Any discrepancies were resolved through discussion until a consensus was reached. Information were recorded on: patient characteristics, type and timing of aneurysm intervention; timing, regimen and monitoring of prophylactic therapy; type of clinical and/or neuroimaging follow-up; and any concomitant treatments during prevention therapy. Relative risk (RR) estimates of incidence data were calculated, together with 95% confidence intervals (CIs), for symptomatic vasospasm, DINDs and death.

**Methods of synthesis**

How were the studies combined?

Where appropriate, the studies were combined using a fixed-effect model; where significant (P>0.1) statistical heterogeneity was detected, a random-effects model was substituted. Three outcomes of the review (vasospasm, DINDs and death) were combined quantitatively in this way.

How were differences between studies investigated?

The authors implied that formal statistical tests were used to assess heterogeneity. The authors also used sensitivity analyses to investigate the impact of randomisation or treatment allocation concealment on the pooled RRs of symptomatic vasospasm, DINDs and death. Tabular presentation of participant and intervention characteristics and validity indicators allowed further investigation of between-study differences.

**Results of the review**

Four studies (n=488) were included in the review: two randomised controlled trials (n=112), and two cohort studies with historical and parallel designs (n=348 and n=28, respectively).

The included studies scored 0, 0, 1 and 2 according to the Jadad quality criteria, out of a maximum score of 5. For external validity, the studies were allocated scores of 2, 3, 3 and 6 out of a potential maximum score of 7. The authors of one randomised controlled trial conducted an intention-to-treat analysis.

Angiographically confirmed vasospasm (1 study): three cases (20%) were reported in the treatment group and nine cases (60%) in the control group.

Symptomatic vasospasm (4 studies): triple-H therapy conferred a protective effect against symptomatic vasospasm, with a combined RR of 0.45 (fixed-effect model, 95% CI: 0.32, 0.65). Trials without allocation concealment gave a slightly bigger treatment effect, with a RR of 0.4 (fixed-effect model, 95% CI: 0.26, 0.61).

DINDs (3 studies): the RR was 0.54 (95% CI: 0.2, 1.49). In the trial with allocation concealment, the RR was 1.75 (95% CI: 0.55, 5.53).

Medical complications (2 studies): one case of left ventricular failure (2%) was reported in the treatment group; two cases of hyponatraemia in each group were reported; and cerebral oedema was detected in 15% of those in the treatment group and 17% of those in the control group. Another trial reported re-bleeding in 13% of those who received preventive therapy compared with 18% of those who did not.

Neurological outcome (1 study): 33 individuals (80%) in the treatment group and 31 individuals (76%) in the control group were classified as attaining a good or excellent neurological outcome at 3 months' follow-up. Five cases of severe disability (12%) were reported in both groups at the same assessment point.
Death (3 studies): the overall mortality rate was reduced in those receiving the prophylactic regimen, with a combined RR of 0.68 (95% CI: 0.53, 0.87). The randomised trials showed more considerable reductions in mortality in the treated groups.

Authors' conclusions
There were insufficient good-quality trials to make recommendations for the use and optimal regimen of triple-H strategy as a prophylactic treatment after SAH.

CRD commentary
The review question and ensuing inclusion criteria were clearly reported. The literature search was adequate, but the authors did not report any attempts to locate unpublished material. Hence, the results may be affected by publication bias. The validity of the primary studies was thoroughly assessed and the steps taken to minimise bias in the review process were reported. Details of the included primary studies were well presented and the methods of quantitative synthesis were transparent. Whilst the results of statistical tests to assess heterogeneity were not presented, sensitivity analyses explored the impact of quality on effect sizes. Other potential sources of heterogeneity, such as specific regimen, duration of treatment or concomitant treatments, were not discussed. The review was hampered by the lack of trials and the authors' conclusions were appropriately cautious in view of the limited evidence available.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors highlighted the need for a well-designed randomised controlled trial of sufficient power and with clinically relevant and measurable outcomes to investigate the efficacy of triple-H therapy after SAH.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.