Efficacy of prophylactic nimodipine for delayed ischemic deficit after subarachnoid hemorrhage: a metaanalysis
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Authors' objectives
The effectiveness of prophylactic nimodipine used in patients with subarachnoid haemorrhage (SAH).

Searching
MEDLINE was searched for articles published in any language (search dates and search strategy are not stated). Additional material was identified by examining reference lists of retrieved literature on nimodipine and vasospasm, and abstracts from recent neurosurgical meetings, and through personal communication with experts on vasospasm.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Nimodipine given in one or more of the following ways: intracisternal (during craniotomy), intravenous, or oral.

Treatment was given for more than 9 days and the outcome assessed between 9 days and 3 months (one group gave outcome data for 1 year).

Participants included in the review
Patients who had experienced subarachnoid haemorrhage. Patients were classified into one or more of the Hunt and Hess grades from I to V.

Outcomes assessed in the review
Glasgow Outcome Scale (GOS); overall mortality; deficit or mortality attributed to vasospasm or delayed ischaemic deficit (DID); mortality attributed to vasospasm or DID; cerebral infarction rate, as assessed by computerised tomography (CT); deficit or mortality attributed to rebleeding; mortality attributed to rebleeding.

How were decisions on the relevance of primary studies made?
The authors do not state how decisions were made but certain inclusion criteria had to be met. These were: random allocation between groups, and the outcome given should be for patients treated with and without prophylactic nimodipine. Studies using a historical control or dose-finding without a placebo control group were excluded, as were studies limited to patients with established symptomatic vasospasm. Studies of nicardipine, diltiazem or other calcium antagonists were also excluded.

Assessment of study quality
The validity of the studies is addressed by narrative discussion. All but one trial were described as prospective, placebo-controlled, and double-blind. The trial not meeting this criteria was the smallest of the included studies, contributing 20 of the 1,202 patients analysed. One study did not allow the calculation of the good plus fair outcome, while another did not supply outcomes for all patients and was omitted from the overall outcome meta-analysis. The authors do not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.

Data extraction
The data were independently extracted from trials by each author (2 people), and any discordant results (found in 3 of 56 end points) were resolved by discussion. Patient outcome was graded using the GOS, studies not reporting outcome in this way were converted to GOS by the authors. The radiographic infarction (assessed by CT) was analysed as the
rate of ‘hypodense areas consistent with infarct from vasospasm’ in one trial, as the rate of ‘definite infarcts’ in a second trial, and as ‘total infarcts’ in a third. Hunt and Hess values were calculated for patient groups where this was not stated in the original study. These values were based on reported entry criteria.

Methods of synthesis
How were the studies combined?
The treatment effect of nimodipine was expressed for each study as the conditional maximum likelihood with 99% confidence intervals (CIs). Fisher's exact test was used for statistical analysis of the data. Where possible, intention to treat analysis was performed to include patients with protocol violations.

Meta-analyses were performed using a random-effects model. A continuity correction of 0.5 was added to all cell values to prevent infinite odds ratios (ORs) and sampling variances. Fixed-effect analyses were also performed as a comparison: data were grouped as stratified 2x2 tables and an exact common OR was calculated with 99% CIs.

Where statistical significance was demonstrated, the number of patients needed-to-treat was calculated as the inverse of the absolute risk reduction using the meta-analysis OR and pooled baseline rates from the included placebo groups. Meta-regression was performed using least-squares linear regression with studies weighted by the inverse of the variance of their effect size. Power calculations used a standard formula assuming balanced sample sizes in treated and control groups. All probability values were 2-tailed and p<0.01 was taken as the significance level in the meta-analysis.

How were differences between studies investigated?
Cochran's Q test was employed for the random-effects model (where p(Q) exceeded 0.10 the studies were considered combinable). Zelen's exact test for the fixed-effect meta-analysis was also performed.

Results of the review
Seven studies were included and combined to determine the following outcome measures.

Good outcome versus all other grades (6 studies; 1,086 participants). Good or fair outcome versus other grades (4 studies; 1,016 participants).

Overall mortality (6 studies; 1,132 participants). Deficit or mortality attributed to vasospasm or DID (7 studies; 1,202 participants). Mortality attributed to vasospasm or DID (6 studies; 1,048 participants).

Cerebral infarction rate, as assessed by CT (3 studies; 921 participants).

Deficit or mortality attributed to rebleeding (3 studies; 842 participants).

Mortality attributed to rebleeding (4 studies; 958 participants).

All results are expressed as ORs with 99% CIs, significance level, and homogeneity test (Q) given in parentheses.

Good outcome versus all other grades: 1.86 (99% CI: 1.07, 3.25, p=0.004; p(Q)=0.11).

Good or fair outcome versus all other grades: 1.67 (99% CI: 1.13, 2.46, p=0.0007; p(Q)=0.43).

Overall mortality: 0.73 (99% CI: 0.42, 1.25, p=0.1; p(Q)=0.22).

Deficit or mortality attributed to vasospasm or DID: 0.46 (99% CI: 0.31, 0.68, p<0.00001; p(Q)=0.64).

Mortality attributed to vasospasm or DID: 0.50 (99% CI: 0.26, 0.97, p=0.007; p(Q)=0.55).

Cerebral infarction rate: 0.58 (99% CI: 0.38, 0.90, p=0.001; p(Q)=0.96).

Deficit or mortality attributed to rebleeding: 0.80 (99% CI: 0.2, 3.02, p=0.67; p(Q)=0.08).
Mortality attributed to rebleeding: 0.82 (99% CI: 0.3, 2.4, p=0.62; p(Q)=0.19).

Other than the first 3 analyses all other analyses were regarded as exploratory.

Publication bias. A funnel plot shows that the meta-analysis may be affected by publication bias. Further analysis to gauge the magnitude of this bias suggests that with the exception of the cerebral infarction analysis, the meta-analyses that showed positive treatment effects were unlikely to have been affected by publication bias.

Jackknife analysis. The main analysis (good outcome versus all other grades) was tested to determine if the single large trial unfairly dominated the meta-analysis, resulting in unrepresentation of the smaller trials. The Jackknife analysis suggests that the meta-analysis is independent of the single large trial (OR range: 1.60 - 2.15).

Meta-regression. The main meta-analysis showed some degree of heterogeneity. This was explained by studies that recruited patients with more severe SAH which reported lower overall odds of good outcome (p=0.005).

Fixed-effect models. All meta-analyses were repeated using the fixed-effect model. There were no significant differences between the two models with the exception that the homogeneity test for the primary analysis in the fixed-effect model fell below the nominal level of 0.10.

Authors' conclusions
Only one of the 7 included trials had a statistically-significant result at the p<0.01 level, even though the meta-analysis confirmed the significant efficacy of the prophylactic nimodipine in improving outcome after SAH under the conditions of the trials. The evidence for the use of nimodipine should, therefore, be considered as strong.

CRD commentary
The review is rigorous in terms of its methodological content and analysis. Readers should be confident in the conclusions drawn by the authors based on the included studies. However, it should be noted that there is no significant effect on the two outcomes of mortality due to rebleeding, and deficit or mortality due to rebleeding. For completeness, it would have been useful to know the time period over which databases were searched, specific patient details (e.g. age and sex), and how comprehensive the validity assessment was.

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