Efficacy of prophylactic nimodipine for delayed ischemic deficit after subarachnoid hemorrhage: a metaanalysis

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The authors report findings from a metaanalysis of all published randomized trials of prophylactic nimodipine used in patients who have experienced subarachnoid hemorrhage (SAH). Seven trials were included with a total of 1202 patients suitable for evaluation. Eight outcome measures were examined, including good versus other outcome, good or fair outcome versus other outcome, overall mortality, deficit and/or death attributed to vasospasm, infarction rate as judged by computerized tomography (CT), and deficit and/or death from rebleeding.

Nimodipine improved outcome according to all measures examined. The odds of good and of good plus fair outcomes were improved by ratios of 1.86:1 and 1.67:1, respectively, for nimodipine versus control (p < 0.005 for both measures). The odds of deficit and/or mortality attributed to vasospasm and CT-assessed infarction rate were reduced by ratios of 0.46:1 to 0.58:1 in the nimodipine group (p < 0.008 for all measures). Overall mortality was slightly reduced in the nimodipine group, but the trend was not statistically significant. The rebleeding rate was not increased by nimodipine. A metregression yielded findings indicating that the treatment effect of nimodipine in individual trials was positively correlated with the severity of SAH in enrolled patients.

Although the majority of individual trials examined did not have statistically significant results at the p < 0.01 level according to most outcome measures, the metaanalyses confirmed the significant efficacy of prophylactic nimodipine in improving outcome after SAH under the conditions used in these trials.

KEY WORDS • delayed ischemic deficit • metaanalysis • nimodipine • subarachnoid hemorrhage • vasospasm

Delayed ischemic deficit (DID) following subarachnoid hemorrhage (SAH) is a major source of morbidity and mortality after rupture of an intracranial aneurysm, despite recent improvements in diagnosis and therapy. Once symptomatic cerebral vasospasm is established, treatments currently available do not provide a good outcome for all patients.

Several drugs have been evaluated in clinical trials as prophylactic agents against DID after SAH, including nimodipine. Nimodipine has been widely used as a prophylactic agent against DID following SAH because several randomized trials reported efficacy in this setting. More recently, trials of prophylactic nimodipine and nicardipine, another calcium antagonist, reported no significant improvement in outcome in the treated groups, and a retrospective study using a historical control group failed to demonstrate any outcome improvement with calcium antagonists when all patients were treated with prophylactic expansion of intravascular volume. These investigators later indicated that they and other surgeons in their geographic area have stopped using calcium antagonists for DID prophylaxis. Because several prospective randomized trials that address the potential efficacy of prophylactic nimodipine after SAH have now been published, we performed a metaanalysis to assist in judging the strength or weakness of the evidence backing the routine use of nimodipine in this setting.

Clinical Material and Methods

Selection of Trials for Metaanalysis

Clinical trials of prophylactic nimodipine use after SAH were identified by means of a search of the MEDLINE database without limitation by language, by examination of abstracts from recent neurosurgical meetings, by personal communication with experts on vasospasm, and by reviewing reference lists of trials and of review articles on nimodipine and vasospasm. Trials comparing the outcome between groups of patients treated or not treated with prophylactic nimodipine, with random allocation between groups, were considered eligible for inclusion in this metaanalysis. Trials using historical control groups, a dose-finding study that did not include a placebo control group, and one controlled trial limited to patients with established symptomatic vasospasm were excluded. Trials of nicardipine, dilti-
azem,28 or other calcium antagonists34,33,75,76 were excluded. Eligibility for inclusion was based solely on trial methodology, without consideration of trial size or results.

**Data Extraction and Definition of Outcome Measures**

Data were independently extracted from trial reports by each author; discordant results (noted in three of 56 endpoints) were resolved by discussion. Patient outcome was graded using the Glasgow Outcome Scale (GOS).46 Some trials reported outcome using the GOS61,67,69 results of other trials51,56,68 were converted to the GOS in the following manner. For the trial reported by Philippon, et al.,58 we equated “survival without deficit” with good outcome; we could not quantify good plus fair outcome for the entire group. For the trial reported by Messeter and colleagues56 we followed a similar procedure, but their information on the severity of deficits also allowed calculation of good plus fair outcome. We equated the “good versus poor (any intellectual or neurological deficit)” outcome scale used by Mee and coworkers51,58 with “good versus all other outcomes”; we could not quantify the good plus fair outcome for this trial. The trial reported by Allen and coworkers3 did not supply outcomes for all patients and was omitted from the overall outcome metaanalyses.

Deficit and death due to DID (or vasospasm) and to rebleeding were analyzed as scored by the original investigators. The radiographic (as assessed by computerized tomography (CT)) infarction rate was analyzed as the rate of “hypodense areas consistent with infarct from vasospasm” in one trial (Table 767), as the rate of “definite infarcts” in a second trial (the diagnosis required confirmation by CT, autopsy, or at operation60), and as “total infarcts” in a third trial (Table 561; the diagnosis required a hypodense area on late follow-up CT in a region where there had not been a previous hematoma).

Hunt and Hess43 grades for enrolled patients were provided in most trial reports.56,60,61,67,68 For the trials lacking these scores3,51,69 we supplied the values shown in Table 1 for comparison purposes, based on reported entry criteria.

**Data Analysis**

The treatment effect of nimodipine was expressed for each study as the conditional maximum likelihood odds ratio7 with an exact 99% confidence interval (CI) using commercially available software (StatXact-Turbo; Cytel Software, Cambridge, MA). Statistical inference was based on Fisher’s exact test. When possible we performed an “intent to treat” analysis, in which patients with protocol violations were not excluded from treatment efficacy calculations.

Metaanalyses were performed using the random-effects method,18 which has been shown to be more conservative than the fixed-effects method.9 A continuity correction (0.5) was added to all cell values to avoid infinite odds ratios and sampling variances. Fixed-effects metaanalyses were performed for comparison: data were grouped as stratified 2×2 tables and an exact common odds ratio52 was calculated (using StatXact Turbo) with a 99% CI.

The homogeneity of treatment effect between studies was assessed using Cochran’s Q test.16 Homogeneity tests assess the validity of combining results from different experiments (that is, trials). For a metaanalysis containing n studies, Q is distributed as the chi-square statistic with n–1 degrees of freedom. We denote the upper-tail area for Q in the appropriate chi-square distribution as p(Q). Larger p(Q) values reflect more homogeneous effect sizes between studies. When p(Q) exceeded 0.10, we considered the studies to be combinable.9 Homogeneity was assessed with Zelen’s exact test83 for fixed-effects metaanalyses.

For metaanalyses demonstrating statistically significant treatment effects, the number of patients needed to treat18 to prevent one adverse outcome was calculated as the inverse of the absolute risk reduction using the metaanalysis odds ratio and pooled baseline rates from the included placebo groups. Metaanalysis46 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 formula31 assuming balanced sample sizes in treated and control groups.

All probability values were two-tailed. We considered a treatment difference at the p < 0.01 level to be significant in the metaanalyses and regarded other analyses as exploratory.

**Results**

**Eligible Trials and Methodological Characteristics**

We identified seven published trials3,51,56,60,67,69 and one unpublished trial9 that met the criteria for inclusion (random allocation of patients between treated and untreated
groups). We were not able to obtain the raw data from the unpublished trial and therefore excluded it. Characteristics of the seven trials included in the metaanalysis are summarized in Table 1. The seven trials enrolled 1255 patients, of whom 53 (4.2%) were excluded from analysis by investigators, principally because of protocol violations.

All trials specified random allocation of patients between treatment with or without nimodipine. All trials but one56 were described as prospective, placebo-controlled, and double blind. The trial that did not specify these methodological attributes56 was the smallest of the seven, contributing 20 of the 1202 patients analyzed (1.7%). Other characteristics of the seven trials included in the metaanalysis are summarized in Table 1. The seven trials enrolled 1255 patients, of whom 53 (4.2%) were excluded from analysis by investigators, principally because of protocol violations.

The aspect in which the most heterogeneity between trials was noted was the neurological grade required for entry. One trial was limited to patients in Grades I, II, or III,56,60,68 and three trials enrolled patients in Grades I, II, or III.3,61,69 Two trials enrolled patients in all grades3,51,69 and one trial was limited to high-grade patients.67

Nimodipine was given orally in five trials,3,51,67,69 of which one trial reported intracisternal administration at operation in some patients.51 Another trial specified use of intravenous nimodipine for at least 7 days, followed by oral dosing.60 Nimodipine was given intracisternally at operation and intravenously in the postoperative period in yet another trial.67 All trials called for at least 9 days’ treatment, with six of seven trials requiring treatment for 21 days (Table 1). Outcome was assessed between 21 days and 3 months, with one group also providing outcome data at 1 year.61 One trial did not specify the time before outcome assessment.56

Patient Outcome

Overall Morbidity and Mortality. We performed three metaanalyses based on overall patient outcome (Table 2).

The first metaanalysis was based on our specified principal outcome measure, good outcome versus all other grades (GOS 1 vs. GOS 2 or higher). Six studies contained data applicable to this analysis; one of these67 demonstrated improved outcome at a nominal significance level of p < 0.01 (Fig. 1 left). The metaanalysis demonstrated a higher chance of good outcome with nimodipine (p = 0.004; odds ratio 1.86, 99% CI 1.07–3.25, p(Q) = 0.11). Assuming a 52% good outcome rate in placebo-treated patients, one additional good outcome should occur for every seven patients treated with nimodipine.

The second metaanalysis based on an overall outcome measure compared the chances of good or fair outcome (GOS 1 or 2) versus all other outcomes. Four studies contributed to this metaanalysis, one of which69 demonstrated improvement with nimodipine at the p < 0.01 level (Fig. 1 right). The metaanalysis demonstrated a higher chance of good or fair outcome with nimodipine (p = 0.0007; odds ratio 1.67, 99% CI 1.13–2.46, p(Q) = 0.43). Assuming a 64% good or fair outcome rate in placebo-treated patients, one additional good or fair outcome should occur for every 10 patients treated with nimodipine.

The third metaanalysis was based on overall patient mortality. Six studies contributed to this analysis, none of which demonstrated a significant effect of treatment at the p < 0.01 level (Fig. 2 left). The metaanalysis showed a slight decrease in mortality with nimodipine; the decrease was not statistically significant (p = 0.1; odds ratio 0.73, 99% CI 0.42–1.25, p(Q) = 0.22).

Morbidity and Mortality Attributed to DID. We performed two metaanalyses that focused on adverse outcomes directly attributed to DID (Table 2). The first of these metaanalyses (Fig. 2 right) focused on deficit or death attributed to DID or vasospasm. Seven studies contributed to the analysis; no individual study displayed a significant effect of treatment at the p < 0.01 level. The metaanalysis showed a significant decrease in deficit or death attributed to DID or vasospasm in the nimodipine-treated patients (p < 0.0001; odds ratio 0.46, 99% CI 0.31–0.68, p(Q) = 0.64). Assuming a 28% rate of deficit or death attributed to DID or vasospasm in placebo-treat-
Nimodipine is favored over placebo (p = 0.001). The odds ratio 0.58 and 99% CI (0.38–0.90) for the metaanalysis. Nimodipine shows the treatment effect (odds ratio 0.46) and 99% CI (0.21–0.82) for the metaanalysis. Nimodipine is favored over placebo, but the trend is not statistically significant (p = 0.67). Right: Chart showing the results of the metaanalysis of mortality attributed to rebleeding. A negative log odds ratio denotes lower mortality attributed to rebleeding with nimodipine treatment (odds ratio < 1). The last line shows the treatment effect (odds ratio 0.50, 99% CI 0.26–0.97, p(Q) = 0.55). Assuming a 9.7% vasospasm-attributed mortality rate in placebo-treated patients, one fewer vasospasm-attributed death should occur for every 22 patients treated with nimodipine.

The second metaanalysis (Fig. 3 left) focused on the mortality attributed to DID or vasospasm. Of the six contributing studies, one60 showed a decrease in vasospasm-associated mortality with nimodipine treatment that was significant at the p = 0.01 level. The metaanalysis demonstrated a decrease in vasospasm-associated mortality with nimodipine treatment that was statistically significant (p = 0.007; odds ratio 0.50, 99% CI 0.26–0.97, p(Q) = 0.55). Assuming a 9.7% vasospasm-attributed mortality rate in placebo-treated patients, one fewer vasospasm-attributed death should occur for every 22 patients treated with nimodipine.

Radiographic Infarction Rate. Three studies contained data on the probability of infarction as assessed using CT scans. None demonstrated a significant treatment effect at the p < 0.01 level. The metaanalysis (Fig. 3 right) showed a significant reduction in radiographic infarction rate with nimodipine (p = 0.001; odds ratio 0.58, 99% CI 0.38–0.90, p(Q) = 0.96). Assuming a 32% radiographic infarction rate in placebo-treated patients, one fewer radiographic infarction should occur for every 10 patients treated with nimodipine.

Rebleeding. Two metaanalyses were performed to assess the effect of nimodipine on rebleeding rates (Table 2). The first (Fig. 4 left) focused on permanent deficit or death from rebleeding. Three studies contributed to the analysis, none of which showed a significant effect of treatment at
Metaanalysis of nimodipine after SAH

The metaanalysis demonstrated a slight trend toward less frequent deficit or death from rebleeding in the nimodipine-treated group, but with a wide CI (p = 0.67; odds ratio = 0.80, 99% CI 0.2–3.02). A considerable, apparent heterogeneity in treatment effect between studies was also demonstrated (p(Q) = 0.08).

The second metaanalysis focused on death from rebleeding (Fig. 4 right). Four studies contributed; none showed a significant effect of treatment at the p < 0.01 level. The metaanalysis showed a trend toward less frequent death from rebleeding in the nimodipine-treated group that was not statistically significant (p = 0.62; odds ratio = 0.82, 99% CI 0.3–2.4, p(Q) = 0.19).

Publication Bias

Metaanalyses are potentially vulnerable to a form of bias known as publication bias. Results of studies that are small in size and fail to show a "statistically significant" effect of treatment have been shown to be less likely to be published. This can cause bias because trials that fail to show a beneficial treatment effect are less likely to be included in the metaanalysis.

A funnel plot is one method of demonstrating publication bias. In a scatterplot of treatment effect versus trial size, a collection of trials influenced by publication bias will tend to have fewer trials near the origin than expected (small trials with small effect sizes, hence not reaching "statistical significance"). Figure 5 shows a funnel plot for our primary metaanalysis (good versus all other outcomes). Although the data are sparse because of the small number of trials, the region near the origin appears underpopulated, suggesting that the metaanalysis may be affected by publication bias. (Note that the smallest study had a large size showing no effect of treatment that must exist to offset completely the treatment effect suggested by the metaanalysis.)

With the possible exception of the CT infarction analysis, the metaanalyses that showed significant treatment effects appear unlikely to have been markedly affected by publication bias.

Jackknife Analysis

When a metaanalysis includes one trial that is much larger than the others, the metaanalysis may not be truly representative of the results of the smaller trials. Although this is not necessarily a source of bias, it is desirable to know whether a metaanalysis is markedly influenced by the results of a single trial. Because our main effect measure (good vs. all other outcomes) showed some heterogeneity between studies (p(Q) = 0.11), and one of the included trials contributed nearly half of the total patients in the analysis, we tested for a dominant effect on the metaanalysis caused by the results of any single trial.

Figure 6 displays the results of a jackknife analysis on our main metaanalysis. In this analysis, each trial included in the overall metaanalysis is deleted in turn, and a metaanalysis is performed on the remaining trials. The effect size suggested by our principal metaanalysis was stable with respect to this procedure, varying by less than one standard error as each trial was omitted in turn (jackknife odds ratio range 1.60–2.15).

Metaregression: Treatment Effect and Severity of SAH

As noted above, our principal measure of treatment effect (good vs. all other outcomes) showed some heterogeneity between studies. One potential explanatory variable that also varied between studies was the severity of SAH sustained by enrolled patients. We performed a
ment effect estimate from the main metaanalysis, and the two vertical dotted lines denote the treatment effect and 99% CI, respectively, for the metaanalysis omitting the study shown to the left. The last line shows the treatment effect estimate from the main metaanalysis ± one standard error. Jackknife treatment effect estimates varied by less than one standard error from the main metaanalysis treatment effect estimate.

Metaanalysis of treatment effect versus the mean Hunt and Hess grade for enrolled patients in each study to explore this possible correlation. The results of the metaregression were highly significant (trials enrolling patients with more severe grades of SAH tended to show a larger treatment effect; p = 0.004, data not shown). However, because not every trial reported Hunt and Hess grades for enrolled patients, this analysis involved extrapolation of Hunt and Hess grades from the grading systems reported by investigators, a potential source of bias. Because patient outcome is strongly correlated with the clinical measures of severity of SAH at presenta-

tional level of 0.10 for the fixed-effects analysis. Table 4 considers, we prespecified our principal outcome measure as good versus all other outcomes and regarded the other significant differences in the treatment effect between trial sub-
groups.

Fixed-Effects Models

We repeated all metaanalyses using a fixed-effects model. There were no significant differences between the conclusions of random-effects and fixed-effects models, except that the homogeneity test for the primary metaanalysis (good vs. other outcomes) fell below our nominal level of 0.10 for the fixed-effects analysis. Table 4 allows a direct comparison between random-effects and fixed-effects models for all analyses performed.

Discussion

Although the results of the individual trials included in this metaanalysis support the use of nimodipine as a prophylactic agent against DID after SAH, some recent reports have called this practice into question. Future clinical trials of prophylaxis against DID are likely to test novel agents such as tirilazad rather than nimodipine. To estimate the potential benefit of prophylactic nimodipine treatment after SAH, we conducted a quantitative review of the results of randomized nimodipine trials.

Metaanalysis is a quantitative technique for combining results from several independent experiments, such as randomized clinical trials. A metaanalysis can sometimes provide an “overall estimate” of the magnitude of a given treatment’s efficacy. If the differences between studies are so great that it seems unreasonable to combine their results, metaanalytic techniques may help distinguish important differences between subgroups of trials.

We analyzed results from seven trials in which post-
SAH patients were randomly allocated to treatment with or without prophylactic nimodipine. Six trials used similar methodology (prospective, randomized, placebo-controlled, double-blind studies); the seventh trial, which did specify that treatment was randomly allocated, was small (1.7% of all patients enrolled). The trials were similar in dosage regimen and length of treatment course.

We performed metaanalyses on eight outcome mea-
sures. To avoid the complicated adjustments of significance levels necessary when multiple endpoints are considered, we prespecified our principal outcome measure as good versus all other outcomes and regarded the other
Potential Sources of Bias

Analyses as exploratory. We chose good patient outcome as our principal endpoint to reflect the treatment effect of nimodipine for all patient subgroups. Another endpoint such as reduction of poor outcome caused by DID would have been more sensitive, but the possibility that overall outcome might be the same or worse for treated patients would not be excluded. For example, in the Cardiac Arrhythmia Suppression Trial,12 patients treated with some antiarrhythmic drugs after myocardial infarction were found to have a decrease in arrhythmias,12 but mortality was actually higher in the treated group.4,13,27

Only one of the six trials included in our primary metaanalysis demonstrated a significant (p < 0.01) increase in overall good outcome with nimodipine. If the p < 0.05 level had been chosen for significance tests, two of the six trials would have shown significant benefit. A simple vote-counting method might conclude that because only one or two of six trials showed a significant treatment effect, the likelihood of efficacy should be low. In fact, the metaanalysis demonstrated that prophylactic nimodipine is effective in increasing the odds of good outcome after SAH. Efficacy was both statistically significant (p = 0.004) and clinically significant in magnitude, with one additional good outcome expected for every seven patients treated.

Potential Sources of Bias

Metaanalyses are vulnerable to biases common to all observational studies. A metaanalysis presupposes that the included trials were unbiased. Although we have no independent means of confirming the quality of the trials included in our metaanalysis, their design and conduct seem to have been sound.

The process of extracting data from published reports can also result in bias.14,29 Two independent data extractions resulted in few disagreements (three of 56 endpoints), and these were readily resolved by discussion. None affected the principal metaanalysis. Because our main conclusion was robust against the frank omission of individual trials, we suggest that variation between our interpretation of published reports and the actual raw data, to which we did not have access, is not likely to have affected our conclusions.

Another form of bias peculiar to metaanalysis is publication bias, the combined tendency of authors and editors not to publish small studies with small or absent treatment effects. A metaanalysis of antibiotic prophylaxis trials for craniotomy3 suggested the presence of publication bias in the neurosurgical literature, as has been formally demonstrated for other fields of medicine.7,14,22,23,26,29 A funnel plot suggested that the present metaanalysis might be affected by publication bias, we estimated that 31 negative trials (enrolling over 5300 patients) would have to exist in unpublished form to nullify the treatment effect observed in our principal metaanalysis. To address another potential source of bias, we demonstrated with jackknife analysis that the metaanalysis does not simply reflect disparate results from any one individual trial.

**Metaregression and Other Exploratory Analyses**

Because we noted treatment effect differences between trials in our principal metaanalysis, we explored the relationship between severity of SAH and nimodipine treatment effect with a metaregression. Trials enrolling patients with more severe grades of SAH, as reflected by poorer outcome in the placebo-treated patient group, showed more benefit from nimodipine treatment.

We do not wish to imply that nimodipine might be less effective for individual patients with less severe grades of SAH. To explore this possibility, individual patient data would need to be analyzed because other differences between trials enrolling patients with differing SAH severities could account for the observed heterogeneity of treatment efficacy. As well, differences in observed good outcome rates in enrolled patients could reflect differences between trials in areas other than the severity of SAH. We suggest that analysts of future trials of DID prophylaxis consider reporting a treatment effect analysis stratified by the severity of SAH. Because only one of the seven trials we examined reported results stratified by Hunt and Hess grade, we could not explore this hypothesis further with subgroup metaanalyses. Another implication of these findings for trial design is that trials limited to high-grade patients may have more sensitivity in testing new treatments.

In our other exploratory metaanalyses, nimodipine showed significant benefit in increasing the odds of good or fair outcome and in reducing the odds of radiographically detectable infarction and of permanent deficit and/or death from DID. No significant effect on overall mortality or rebleeding-associated death or deficit was demonstrated, although favorable trends were noted.

We had planned to perform a metaanalysis on the effect of nimodipine on arteriographic vasospasm, as demonstrated in vitro by Peroutka and coworkers and in vivo by Haley, et al., with nicardipine treatment. Unfortunate-
ly, only two trials reported results of arteriograms obtained after the start of nimodipine treatment. One of these trials was limited to high-grade patients; the second trial was relatively small, and repeat angiography was reported in only 60% of patients. A third trial reported significant (p < 0.0001) alleviation of arteriographic vasospasm in nimodipine-treated patients when compared with the placebo-treated group from the randomized trial pooled with historical controls that had not received nimodipine. Given the limitations of the available data, and because nimodipine’s potential effect on arteriographic vasospasm is less important in clinical decision making than its effects on patient outcome, we declined to perform this metaanalysis.

Other Metaanalyses and Retrospective Trials

Other metaanalyses of nimodipine prophylaxis after SAH have been reported. Tettenborn and Dycka reported results of a metaanalysis of good and fair versus other outcomes that included a trial of nimodipine in patients with established vasospasm. The investigators, who were affiliated with the European manufacturer of nimodipine, appear to have had access to unpublished data from some trials. Di Mascio, et al, also included the trial of nimodipine in established vasospasm in their metaanalysis. The inclusion of this trial may have constituted a bias in favor of nimodipine. A more serious criticism is that these investigators adjusted for incomplete reporting of trial results by combining disparate outcome measures into a single metaanalysis. We avoided this potential source of bias by analyzing multiple endpoints, adopting relatively uniform criteria for each. Our metaanalysis differs from that reported by Dorsch in excluding trials using historical control groups. Other novel features of our metaanalysis include use of the more conservative random-effects model rather than a fixed-effects model, tests for publication bias and the potential undue influence of single large trials or outlying trials, and the metaregression of effect size versus severity of SAH. However, our basic conclusion that nimodipine prophylaxis is effective agrees with the prior investigators’ results.

As randomized clinical trials are performed more frequently in neurosurgery, metaanalysis will offer one approach for maximizing the usefulness of trial data in assisting with clinical decisions. If results from several different trials can be combined in a metaanalysis, the conclusions can be more confidently applied to patients with similar clinical scenarios at other centers. For nimodipine prophylaxis after SAH, outcome improvement with treatment was relatively homogeneous between studies for a variety of outcome measures. However, metaanalyses do not allow extrapolation of trial results to clinical scenarios not tested in the original trials. Although recent metaanalyses have indicated that intravenous magnesium administration reduced mortality after myocardial infarction, a subsequent, very large randomized trial showed no benefit from magnesium given under conditions different from those previously tested. Thus because none of the trials included in our metaanalysis specified the routine use of prophylactic hypervolemic hypertensive therapy, we cannot predict the efficacy of nimodipine in this setting.

We can, however, use the metaanalysis estimate of nimodipine treatment effect to calculate the necessary sample size for a randomized trial to test nimodipine efficacy with given baseline conditions. If SAH treatment with prophylactic hypervolemia and without nimodipine results in a good outcome rate of 67.5%, good outcome would be predicted in 74.5% of nimodipine-treated patients (metaregression estimated odds ratio 1.41). A prospective randomized trial enrolling over 1700 patients would be required to detect this difference with 90% power and a two-sided type I error of p < 0.05. Similarly, to detect the predicted decline in the CT-assessed infarction rate from 29% in untreated patients to 19.5% with nimodipine would require randomization of 850 patients. To conclude that hypervolemic treatment abolishes the efficacy of nimodipine because of the negative results of a considerably smaller retrospective trial is probably unwarranted.

Conclusions

The efficacy of prophylactic nimodipine in improving outcome after SAH was demonstrated by metaanalysis of seven published randomized trials. The benefit from nimodipine was both clinically and statistically significant. The analysis did not appear to be substantially weakened by extensive publication bias or by the undue influence of any single trial. The evidence in favor of routine prophylactic use of nimodipine after SAH is strong, and isolated retrospective trials that fail to confirm efficacy under specific conditions should not weigh heavily in decisions regarding its use.

Disclosure

The authors have no financial interest in, or connection with, the manufacturers of nimodipine.

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