Delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: the role of coagulation and fibrinolysis
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Chapter 7

Effect of nimodipine on outcome in patients with traumatic subarachnoid hemorrhage: a systematic review

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Abstract

Background and purpose
Despite several randomised controlled trials, there is still much debate whether nimodipine improves outcome in patients with traumatic subarachnoid haemorrhage. A 2003 Cochrane review reported improved outcome with nimodipine in these patients; however, because the results of Head Injury Trial (HIT) 4 were only partly presented there is still discussion whether patients with traumatic subarachnoid haemorrhage should be treated with this drug. Here, we present data from all head-injury trials, including previously unpublished results from HIT 4.

Methods
We systematically searched PubMed and EMBASE databases using the following combinations of variables: “nimodipine” or “calcium antagonist” with “traumatic subarachnoid haemorrhage”, “head injury”, “head trauma”, “brain injury”, or “brain trauma”. Bayer AG and all principal investigators or corresponding authors of the identified studies were contacted for additional information.

Results
Five manuscripts were identified, describing the results of four trials. We obtained additional data from HIT 1, 2, and 4. In total, 1074 patients with traumatic subarachnoid haemorrhage were included. The occurrence of poor outcome was similar in patients treated with nimodipine (39%) and those treated with placebo (40%); odds ratio was 0.88 (95% CI 0.51–1.54). Mortality rates did not differ between nimodipine (26%) and placebo (27%) treated patients (odds ratio 0.95; 95% CI 0.71–1.26).

Conclusion
Our results do not lend support to the finding of a beneficial effect of nimodipine on outcome in patients with traumatic subarachnoid haemorrhage as reported in an earlier Cochrane review.
Introduction

In patients with aneurysmal subarachnoid hemorrhage, nimodipine has been shown to be effective in the prevention of ischaemic complications after hemorrhage resulting in improved outcome. Since nimodipine is believed to have neuroprotective properties, the drug was suggested to be of potential benefit in patients with traumatic head injury.

The first report on nimodipine treatment in patients with severe head injury dates from 1984. The first randomised controlled trials investigating the effect of nimodipine in head injury the Head Injury Trials (HIT) 1 and 2 were published in the early 1990s. In the overall analysis of these studies, no reduction in poor outcome was shown. However, in a subgroup analysis of HIT 2, a possible beneficial effect was noted in patients with traumatic subarachnoid haemorrhage. Because of these findings, HIT 3 was initiated in which only head-injury patients with traumatic subarachnoid haemorrhage were included. The HIT 3 study showed a small but significant beneficial effect in nimodipine-treated patients. To confirm this favourable effect in a much larger group of patients, HIT 4 was started. Unexpectedly, HIT 4 showed a significant increase in poor outcome in nimodipine-treated patients. Possibly because of this disappointing result, the results of HIT 4 have never been published in detail, but some of the results were presented at a conference.

In 2003, a Cochrane review on the effects of calcium antagonists on outcome in patients with head injury was published, which concluded that there is no beneficial effect of nimodipine on outcome in head-injury patients. However, in the subgroup of patients with traumatic subarachnoid haemorrhage nimodipine was shown to improve outcome.

Because the results of HIT 4 were only partly presented, there is still much debate as to whether patients with traumatic subarachnoid haemorrhage should be treated with nimodipine. Here we present for the first time the data of all head-injury trials, including previously unpublished results from the HIT 4 trial.

Methods

Search strategy and selection criteria of studies
We systematically searched the electronic PubMed and EMBASE databases up to 2006 (week 10) for the following combinations of variables: “nimodipine” or “calcium antagonist” with “traumatic subarachnoid hemorrhage”, “head injury”, “head trauma”, “brain injury”, or “brain trauma”. Randomised controlled studies from the English, German, and French published work were included. Animal studies were excluded. Bayer AG and all principal investigators or corresponding authors of the identified studies were contacted for additional information. All randomised controlled trials investigating the effect of the calcium antagonist nimodipine
in patients with head injury were included, irrespective of dose, route of administration, and duration of treatment.

The Glasgow outcome scale was measured 6 months after head injury. Primary outcome was a poor outcome, defined as death, vegetative state, or severe disability. Favourable outcome was defined as moderate disability and good recovery. Secondary outcome was mortality.

Methodological quality
One of the investigators (MDIV) assessed the methodological quality of the studies by means of the Jadad scale. This scale is a validated 5 point scale in which the following items are assessed: randomisation (0–2 points), double-blinding (0–2 points), and withdrawals and drop-outs after randomisation (0–1 point). Higher values on the Jadad scale represent higher quality studies. All trials scoring 1 or 2 points for randomisation were included in the analysis.

Statistical analysis
Data were analysed according to the intention-to-treat principle and processed in Review Manager 4.2 as supplied by the Cochrane Collaboration. Odds ratios for poor outcome were calculated with a random-effects model because of possible heterogeneity between studies. Mortality odds ratios were calculated with a χ² analysis because only crude mortality rates were available. Statistical uncertainty was expressed by 95% CIs.

Role of the funding source
There was no external funding source or sponsor involved in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had responsibility for the final decision to submit for publication.

Results
By searching the electronic databases of PubMed and EMBASE five manuscripts were identified, describing the results of four trials. The principal investigators of HIT 1 and 2 were contacted for additional data on outcome and access was granted to both original datasets. For HIT 3, only published data were available. Bayer AG was contacted for the data of HIT 4, but they advised us to contact the principal investigator of HIT 4. The principal investigator of HIT 4 granted us permission to analyse and publish the results of HIT 4, which were described in a table of the pooled outcome scores of all patients of all four HITs. Finally, the corresponding author of the study by Pillai and co-workers was contacted for additional data. However, the original data were unavailable.
In HIT 1, 352 patients with head injury were included.\textsuperscript{3} The presence of traumatic subarachnoid hemorrhage was not registered during the study, but was assessed afterwards by a panel of four observers.\textsuperscript{9} CT scans could be retrieved for 257 patients, of whom traumatic subarachnoid hemorrhage was present in 71 (36 placebo patients, 35 nimodipine patients).

In HIT 2, 852 patients with head injury were enrolled.\textsuperscript{4} The presence of traumatic subarachnoid hemorrhage was assessed by the investigators and afterwards reassessed by a review committee. Although the participating investigators identified traumatic subarachnoid hemorrhage in 149 placebo patients and in 119 nimodipine patients, the review committee identified traumatic subarachnoid hemorrhage in 145 placebo patients and in 123 nimodipine patients.

In HIT 3 only head-injury patients with traumatic subarachnoid hemorrhage were enrolled.\textsuperscript{5} In total 123 patients were randomised. A review committee could not confirm the presence of traumatic subarachnoid hemorrhage in 26 patients. However, these cases were included for the intention-to-treat analysis. Of these 123 patients, two patients were lost to follow-up at 6 months.

In HIT 4, 592 patients were enrolled, of whom 577 were valid for the intention-to-treat analysis (287 placebo patients, 290 nimodipine patients; unpublished data). Why 15 patients were excluded for the intention-to-treat analysis is not known. A CT scan review committee identified traumatic subarachnoid hemorrhage in 525 patients (259 placebo patients, 266 nimodipine patients). The HIT 4 data, which were released earlier at a conference where data of the CT scan review committee were shown, were used for the Cochrane review. For the present systematic review we used the data of the HIT 4 intention-to-treat analysis, thus including 577 patients instead of 525 patients.

In the study by Pillai and co-workers, 97 patients with severe diffuse head injury were enrolled, of whom 39 had traumatic subarachnoid hemorrhage on CT scan.\textsuperscript{10} Of these 39 patients, follow-up was missing in two. Therefore Glasgow outcome scores at 6 months were available for 37 patients (18 placebo patients, 19 nimodipine patients).

In total, 1074 head-injury patients with traumatic subarachnoid hemorrhage were included for this systematic review. In the primary analysis, the effect of nimodipine on the incidence

| Table 1. Glasgow Outcome Scale of head injury patients with traumatic subarachnoid hemorrhage. Data are number (%). |
|---|---|---|---|---|---|---|
| Glasgow Outcome Scale | HIT-1 (n=71) | HIT-2 (n=268) | HIT-3 (n=121) | HIT-4 (n=577) | Pillai et al. (n=37) |
| Poor outcome | 25 (69) | 26 (74) | 83 (56) | 53 (45) | 28 (46) | 15 (25) | 75 (26) | 98 (34) | 11 (61) | 13 (68) |
| Favourable outcome | 11 (31) | 9 (26) | 66 (44) | 66 (55) | 33 (54) | 45 (75) | 212 (74) | 192 (66) | 7 (39) | 6 (32) |
| Total | 36 | 35 | 149 | 119 | 61 | 60 | 287 | 290 | 18 | 19 |
of poor outcome was studied. For this analysis all five studies supplied data on the incidence of poor outcome as well as unpublished data of HIT 4.4,5,9,10 Table 1 and the figure show the dichotomised Glasgow outcome scores. The occurrence of poor outcome was similar in nimodipine and placebo-treated patients (39% in the nimodipine group and 40% in the placebo group: odds ratio 0.88 (95% CI 0.51–1.54)).

**Figure.** Comparison of nimodipine versus placebo for the odds of poor outcome defined as death, vegetative state, or dependency on the Glasgow outcome scale at 6 months after head injury.

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>OR (random) 95% CI</th>
<th>Weight %</th>
<th>OR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIT1</td>
<td>26/35</td>
<td>25/36</td>
<td>15.11 [0.45, 3.59]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIT2</td>
<td>53/119</td>
<td>83/149</td>
<td>25.77 [0.39, 1.04]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIT3</td>
<td>15/60</td>
<td>28/61</td>
<td>19.80 [0.18, 0.85]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIT4</td>
<td>98/290</td>
<td>75/287</td>
<td>28.30 [1.01, 2.06]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pillai</td>
<td>13/19</td>
<td>11/18</td>
<td>11.02 [0.36, 5.34]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>523</td>
<td>551</td>
<td>100.00 [0.51, 1.54]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 205 (Treatment), 222 (Control)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for heterogeneity: Chi² = 13.35, df = 4 (P = 0.010), I² = 70.0%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 0.44 (P = 0.66)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

In the secondary analysis, we studied the effect of nimodipine on the incidence of mortality. No data on mortality were available in the study of Pillai and coworkers.10 Pooled mortality rates of all four HIT studies including all patients valid for intention-to-treat analysis are listed in table 2. Thus, for the secondary analysis, data for 1037 patients were available. The mortality rates were similar in nimodipine and placebo-treated patients (26% in the nimodipine group and 27% in the placebo group: odds ratio 0.95 (95% CI 0.71–1.26)).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Nimodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>390 (73.2)</td>
<td>374 (74.2)</td>
</tr>
<tr>
<td>Death</td>
<td>143 (26.8)</td>
<td>130 (25.8)</td>
</tr>
<tr>
<td>Total</td>
<td>533</td>
<td>504</td>
</tr>
</tbody>
</table>

The methodological quality of the included studies was assessed with the use of the Jadad scale (table 3). The CT scans of HIT 1 were assessed afterwards by a panel of observers who were unaware of drug allocation and outcome (G Teasdale, personal communication). The Jadad score for HIT 4 was based on limited data. The median score was 3 (range 2–5). As all trials scored 1 or 2 points for randomisation, no studies were excluded for this systematic review.
Effect of nimodipine in traumatic SAH

Discussion

The occurrence of poor outcome and mortality rates did not differ between patients treated with nimodipine and those treated with placebo. Our results contrast with those of the Cochrane review published in 2003, which showed that nimodipine significantly reduced poor outcome and mortality in patients with traumatic subarachnoid hemorrhage. The present analysis differs in three aspects from the Cochrane analysis. First, we restudied the original data of HIT 1 so that mortality rates of HIT 1 could be included in the present analysis. Second, we managed to obtain additional data from the HIT 4 study and included these data in the analysis of all patients with traumatic subarachnoid hemorrhage. Interestingly, in the Cochrane review, the HIT 4 data were only included in the overall analysis of patients with traumatic head injury and not in the subgroup analysis of patients with traumatic subarachnoid hemorrhage. This is remarkable since HIT 4 only included patients with traumatic subarachnoid hemorrhage. Therefore, the Cochrane review was based on less than half of the patients of our review. We also included the results of an additional study.

By contrast with patients with traumatic subarachnoid hemorrhage, nimodipine has been proven to improve outcome in patients with aneurysmal subarachnoid haemorrhage.\(^1\) Several factors can explain the difference in effect of nimodipine on outcome in patients with aneurysmal compared with traumatic subarachnoid hemorrhage. Aneurysmal and traumatic subarachnoid hemorrhages are different entities. In patients with aneurysmal subarachnoid hemorrhage, delayed cerebral ischemia can occur in the weeks after the hemorrhage. Patients who have delayed cerebral ischemia have an increased risk of poor outcome. This delayed cerebral ischeemia is less common in traumatic subarachnoid hemorrhage than in aneurysmal subarachnoid hemorrhage.\(^11,12\) Nimodipine is probably only eff ective for delayed cerebral ischemia and might therefore be effective only in patients with aneurysmal subarachnoid hemorrhage. For a long time, the beneficial effects of nimodipine in subarachnoid hemorrhage have been attributed to a beneficial effect on vasospasm. However, nimodipine exerts a fibrinolytic effect in patients with aneurysmal subarachnoid hemorrhage, an effect which was also observed in other calcium antagonists from the dihydropyridine group.\(^13\) Therefore, nimodipine exerts a beneficial profibrinolytic effect in patients with aneurysmal

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Table 3. Methodological quality of the included studies using the Jadad-scale.

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomisation (0-2 points)</th>
<th>Double-blinding (0-2 points)</th>
<th>Withdrawals / drop-outs (1 point)</th>
<th>Total (0-5 points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIT 1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>HIT 2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>HIT 3</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>HIT 4*</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Pillai</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

* Based on limited data
subarachnoid hemorrhage and this could be the mechanism by which the incidence of delayed cerebral ischemia is decreased. In patients with traumatic subarachnoid hemorrhage the profibrinolytic effect might not be beneficial, but even deleterious by inducing cerebral and systemic hemorrhages.

The Jadad scale was used to assess the methodological quality of the included papers. The Jadad score of HIT 4 was based on a limited number of data. With the available data of HIT 4, the Jadad score was 2. Therefore the largest study in this systematic review probably had the lowest quality score. Often, lower quality trials tend to have more positive results, but this was not found in this analysis.

In this systematic review including 1074 patients with traumatic subarachnoid hemorrhage, we could not confirm the beneficial effects of nimodipine shown in a previous review, which included 460 patients with this condition.

Acknowledgments

We thank Prof. Sir G. Teasdale and Prof. R. Braakman, principal investigators of HIT 1 and 2, respectively, for permission to study the original data of these trials. We also thank Prof. V.J. Farrell, principal investigator of HIT 4, for permission to use and publish parts of the results of HIT 4.
References


