Recent investigations have shown the significance of subarachnoid blood on a patient’s first computerized tomography (CT) scan after head injury. In a large European head injury study, it was shown that 33% of moderate-to-severe head injury patients demonstrate a traumatic subarachnoid hemorrhage (tSAH) on an early CT scan and that these patients have a significantly worse outcome than those who do not show tSAH on CT scanning. The appearance of tSAH seems to be an important and independent factor in predicting unfavorable outcome in head injury. Recent publications have suggested similarities between tSAH and aneurysmal (a)SAH. Pathophysiological mechanisms similar to those seen in aSAH, such as vasospasm, could contribute to secondary ischemic damage, leading to a worsened outcome in these patients.

The beneficial results observed in the subgroup of patients with a tSAH in the European nimodipine head injury trial, HIT II, indicated the need for further investigations of patients with tSAH. We now report the results of a prospective, randomized, multicenter, double-blind, placebo-controlled study involving 123 patients with a tSAH visible on CT scanning.

**Clinical Material and Methods**

**Patient Population**

One hundred twenty-three patients between 16 and 70 years of age in whom a tSAH was demonstrated on an initial postinjury CT scan were admitted to 21 German centers between January and October 1994. (The participating centers and investigators are listed in the Appendix.) Patients were entered in the study within 12 hours after head injury regardless of the patient’s level of consciousness. Eligible patients received either a sequential course of intravenous and oral nimodipine or placebo treatment for 3 weeks. Patients were closely monitored using clinical neurology, computerized tomography, laboratory, and transcranial Doppler ultrasound parameters.

Patients treated with nimodipine had a significantly less unfavorable outcome (death, vegetative survival, or severe disability) at 6 months than placebo-treated patients (25% vs. 46%, p = 0.02). The relative reduction in unfavorable outcome in the nimodipine-treated group was even higher (55%, p = 0.002) when only patients who complied with the protocol were considered.

**Key Words** • head injury • subarachnoid hemorrhage • computerized tomography • vasospasm • nimodipine • clinical trial
Nimodipine treatment of traumatic SAH

formed at entry into the trial and daily throughout hospitalization until the end of the 3rd week.

Computerized tomography scanning was performed four times: on admission, within 24 hours of hospitalization, on approximately the 3rd day, and after 3 weeks. The main reasons for obtaining follow-up CT scans were to study the occurrence of ischemic lesions, postoperative complications, and evolution of contusional defects and ventricular size.

A review committee composed of three neurosurgeons assessed all CT scans for the presence of tSAH under blinded conditions. The CT scans were graded by the amount and distribution of blood and by the thickness of the clot according to the criteria established by Fisher, et al.7

Transcranial Doppler (TCD) ultrasound examination was performed to measure intracranial arterial blood flow velocities (BFVs). This examination was conducted daily for 3 weeks. Flow velocities were considered normal when the mean velocity was below 80 cm/second, elevated when it increased up to 119 cm/second, compatible with vasospasm if the mean velocity reached or exceeded 120 cm/second at least once during the observation period, and compatible with severe vasospasm if it once reached or exceeded 160 cm/second.8,9

Intracranial pressure (ICP) was monitored at the discretion of each investigator. The criteria for surgical procedures were also the prerogative of each neurosurgeon. Hematological and biochemical laboratory evaluations were performed on admission and repeatedly during hospitalization.

Follow-Up Evaluation

Outcome was assessed 6 months after the head injury according to the Glasgow Outcome Scale (GOS). Outcome was dichotomized according to the following scheme: good recovery and moderate disability were considered favorable outcomes; severe disability, vegetative survival, and death were deemed unfavorable outcomes. The Disability Rating Scale20 and the Barthel Index21 were also used to verify the statements of the investigators regarding outcome. Additionally, the presence of posttraumatic epilepsy (seizures not related to the acute phase) was investigated.

Data Management

A remote data entry system (“Quest,” First Line Medical, Technilogix B.V., Alphen aan den Rijn, The Netherlands) was used for the management of data. Each participating center was provided with a notebook computer on which a program containing a case-record form was installed. A plausibility check was incorporated into the program. Study data were transferred via modem using the MediciNet network (a public-packet switched X-25 network operated by British Telecom, Bedford, England) to the administrative office handling the study.

Statistical Analysis

The two treatment groups were compared for baseline conditions and for findings based on CT and TCD ultrasound. Differences between the treatment groups were assessed using Fisher’s exact two-tailed test and odds ratios with 95% confidence interval (CI) calculations based on GOS results at 6 months. All other analyses were conducted on an exploratory basis. Prognostic factors, such as age, neurological score on entry, and additional CT findings, were tested separately because they were believed to be factors that might interact with the results of the treatment.

Results

Demographic Data

The data at baseline showed the overall comparability of the two treatment groups despite a slight difference in age and initial neurological scoring (Table 1). The mean age of the tSAH patients was 45 years. Eighty percent of the patients were male. Falls were the main cause of the head injuries (47%), followed by traffic accidents (34%). Twenty-four percent of patients sustained major multiple injuries. Forty-five percent of patients were intubated at the site at which the injury occurred. Twenty-five percent of the patients sustained a mild injury (GCS score >12) as assessed on admission to the hospital; on average, these were older patients (mean age 51 years).

Patients were admitted to the study hospital an average of 2 hours after injury, and test-drug therapy was initiated an average of 6.5 hours later.

Computerized Tomography Findings

The first CT scan after injury was obtained an average of 2 hours after trauma. The review committee of the study could not confirm the presence of tSAH on the first CT scan in 26 cases and, therefore, these injuries were classified as Fisher’s Grade 1. The distribution of patients with respect to the amount of blood and to Fisher grade is presented in Table 2. Traumatic SAH was seen at the convexity of the cerebral hemispheres in 67% of cases and at the basal cisterns in 40%. A combined finding was observed in 28% of patients. The most frequently associated CT lesions were contusions, which were seen in 72% of cases, followed by subdural hematoma in 40% of cases.

Hypodense areas compatible with cerebral infarction were observed by the investigators on follow-up CT scans...
in 14 patients (22%) in the placebo group and in four patients (7%) in the nimodipine group (p = 0.025).

**Transcranial Doppler Blood Flow Velocities**

In five patients no TCD monitoring was possible due to thickness of the skull. The mean BFV was always less than 80 cm/second in 31% of patients; it increased up to 119 cm/second in 41% of patients, and in 29% of patients it reached or exceeded values of 120 cm/second at least once during the observation period (Table 3). Eight percent of patients sustained mean BFV values reaching or exceeding 160 cm/second. More placebo-treated patients had BFV values compatible with vasospasm. Flow velocity increases were more pronounced in the middle cerebral artery (MCA). The time course of BFVs was similar in both treatment groups for those patients who had increased values. The time course of the mean MCA BFV of patients who had measurements that reached or exceeded 120 cm/second at least once during the observation period (Table 3). Increased BFVs compatible with vasospasm (≥ 120 cm/sec) were observed in 50% of patients who developed hypodensities on follow-up CT scans. Six percent of patients who entered the study with a mild head injury (GCS score > 12) developed BFVs compatible with vasospasm.

**Amount of Blood and TCD Flow Velocities**

An association between elevated TCD flow velocities and the amount of subarachnoid blood on the initial CT scan was found in patients with extensive bleeding. Only placebo-treated patients were considered so as to eliminate the possible effect of nimodipine. Twenty-seven percent of patients with a small amount of blood, 25% of patients with a moderate amount of blood, and 46% of patients with extensive tSAH on CT scanning had increased values (≥ 120 cm/second). According to Fisher’s grading system, 14% of placebo-treated patients in Grade 2 had an increase of BFV that was greater than or equal to 120 cm/second, 40% in Grade 3, and 57% in Grade 4.

**Blood Intracranial Pressures**

Eighteen percent of patients treated with nimodipine experienced drops in systolic blood pressure below 90 mm Hg during the first 48 hours of observation, compared to 13% of placebo-treated patients. Nimodipine treatment was associated with a decrease in blood pressure measuring almost 5 mm Hg systolic and 3 mm Hg diastolic when compared to placebo within the first 11 days of hospitalization (Fig. 2). However, this difference was not judged to have clinical relevance. Comedication in both groups was similar. Intracranial pressure measurements were performed in 40 patients (33%). In 34 of these patients (85%), ICP values were in excess of 20 mm Hg at least once. This was seen more frequently in placebo-treated patients (Fig. 3).

**Patient Outcome**

Two patients were lost to follow-up review at 6 months. Nimodipine treatment reduced the incidence of death, vegetative survival, and severe disability (Table 4). These patterns of outcome were shifted toward good recovery when compared to the placebo-treated group. The difference in unfavorable outcome between the two treatment groups is significant (p = 0.02; odds ratio 0.39, 95% CI 0.18–0.86). This represents a relative reduction in unfavorable outcome of 46% with nimodipine treatment. In patients complying with all protocol criteria (excluding the 26 patients whose tSAH could not be confirmed by the review committee, two patients who received commercial nimodipine, one patient who entered the study later than 12 hours after injury, and the two patients lost to follow-up review), 60% of placebo-treated patients had an unfavorable outcome compared to 27% of nimodipine-treated patients (Table 5: p = 0.002; odds ratio 0.25, 95% CI 0.1–0.61). The relative reduction in unfavorable outcome in these patients who, in the opinion of the study’s review committee, had an unequivocal tSAH on the first CT scan was 55%. Although there was an imbalance regarding predictors in the two arms of this study, this did not affect the treatment results. A stepwise logistic regression analysis of the overall and protocol-compliant groups showed that the treatment effect remained significant under all relevant
Nimodipine treatment of traumatic SAH

As shown in Table 7, patients with a moderate-to-extensive amount of blood, those with Fisher Grades 3 and 4, and those whose BFV as measured by TCD ultrasound was elevated benefitted more markedly from nimodipine treatment.

Of the patients who entered the study with a GCS score greater than 12, unfavorable outcome occurred in 18% of cases (three of 17) treated with placebo and in 8% (one of 13) of cases treated with nimodipine.

Posttraumatic Epilepsy

Six-month survivors who had been treated with nimodipine had a lower incidence of posttraumatic epilepsy than placebo-treated patients. This event was observed in 4% of the nimodipine-treated patients compared to 13% of the placebo group.

Adverse Events

Twenty-one adverse events (10 for nimodipine, 11 for placebo) were reported in 17 patients (10 of whom were given nimodipine and seven given placebo). Permanent

---

**TABLE 4**
Outcome at 6 months after injury in 121 patients with traumatic subarachnoid hemorrhage*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo Group (61 patients)</th>
<th>Nimodipine Group (60 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Percent</td>
</tr>
<tr>
<td>unfavorable outcome</td>
<td>28</td>
<td>46</td>
</tr>
<tr>
<td>death</td>
<td>16</td>
<td>26</td>
</tr>
<tr>
<td>vegetative survival</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>severe disability</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>favorable outcome</td>
<td>33</td>
<td>54</td>
</tr>
<tr>
<td>moderate disability</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>good recovery</td>
<td>30</td>
<td>49</td>
</tr>
</tbody>
</table>

* Outcome determined according to the Glasgow Outcome Scale.11

**TABLE 5**
Outcome at 6 months after injury in 92 protocol-compliant patients with traumatic subarachnoid hemorrhage*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo Group (47 patients)</th>
<th>Nimodipine Group (45 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Percent</td>
</tr>
<tr>
<td>unfavorable outcome</td>
<td>28</td>
<td>60</td>
</tr>
<tr>
<td>death</td>
<td>16</td>
<td>34</td>
</tr>
<tr>
<td>vegetative survival</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>severe disability</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>favorable outcome</td>
<td>19</td>
<td>40</td>
</tr>
<tr>
<td>moderate disability</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>good recovery</td>
<td>17</td>
<td>36</td>
</tr>
</tbody>
</table>

* Outcome determined according to the Glasgow Outcome Scale.11 For an explanation of protocol-compliant patients, see text.
discontinuation of test-drug therapy due to adverse events occurred in three nimodipine- and two placebo-treated patients. Hypotension was the most frequently reported adverse event. It was observed in five nimodipine- and two placebo-treated patients. Three of the five nimodipine- and one of the two placebo-treated patients had an unfavorable outcome. However, the hypotensive events themselves were not considered serious by the investigators. Of those patients who experienced a drop in systolic blood pressure below 90 mm Hg during the first 48 hours, 44% (four of nine) of nimodipine-treated patients had an unfavorable outcome, whereas 71% (five of seven) of the placebo group did so. The second most frequently reported adverse event was an increase in pancreatic and liver enzymes, which was described in three patients given placebo and one given nimodipine.

![Chart showing systolic blood pressure curves using the means and standard errors of the means during the 3 weeks of the trial in patients treated either with nimodipine or placebo. Note that the intervals in the y-axis are in 5-mm Hg steps.](image)

**TABLE 6**
Stepwise logistic regression analyses with outcome measurement in all study patients and in protocol-compliant patients with traumatic subarachnoid hemorrhage*  

<table>
<thead>
<tr>
<th>Factor</th>
<th>All Study Patients (121 patients)</th>
<th>Protocol-Compliant Patients (92 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>age</td>
<td>0.44</td>
<td>0.19–0.98</td>
</tr>
<tr>
<td>amount of blood</td>
<td>0.37</td>
<td>0.15–0.89</td>
</tr>
<tr>
<td>Fisher grade</td>
<td>0.33</td>
<td>0.14–0.80</td>
</tr>
<tr>
<td>BFV</td>
<td>0.40</td>
<td>0.18–0.92</td>
</tr>
<tr>
<td>GCS score</td>
<td>0.34</td>
<td>0.15–0.76</td>
</tr>
</tbody>
</table>

* These analyses include outcome as dependent variable and treatment + age (continuous), + amount of blood (categorical), + Fisher grades (categorical), + Doppler BFV (binary: < 120, ≥ 120 cm/second), and + Glasgow Coma Scale score at entry to the study (binary: ≤ 12, > 12 points) as independent variables. Excluded from study groups are two patients lost to follow-up evaluation. Other exclusions made to form the protocol-compliant group are provided in text. Abbreviations: BFV = blood flow velocity; CI = confidence interval; GCS = Glasgow Coma Scale; OR = odds ratio.

**TABLE 7**
Unfavorable outcome at 6 months after injury in various subgroups of patients with traumatic subarachnoid hemorrhage*  

<table>
<thead>
<tr>
<th>Unfavorable Outcome</th>
<th>Placebo Group</th>
<th>Nimodipine Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Percent</td>
<td>No.</td>
</tr>
<tr>
<td>amount of blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>small</td>
<td>2 of 10</td>
<td>3 of 17</td>
</tr>
<tr>
<td>moderate</td>
<td>14 of 23</td>
<td>5 of 21</td>
</tr>
<tr>
<td>extensive</td>
<td>12 of 14</td>
<td>5 of 10</td>
</tr>
<tr>
<td>Fisher grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0 of 14</td>
<td>2 of 12</td>
</tr>
<tr>
<td>2</td>
<td>6 of 19</td>
<td>6 of 19</td>
</tr>
<tr>
<td>3</td>
<td>15 of 21</td>
<td>5 of 25</td>
</tr>
<tr>
<td>4</td>
<td>7 of 7</td>
<td>2 of 4</td>
</tr>
<tr>
<td>TCD ultrasound measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80 cm/sec</td>
<td>4 of 16</td>
<td>3 of 20</td>
</tr>
<tr>
<td>80–&lt;120 cm/sec</td>
<td>12 of 22</td>
<td>5 of 26</td>
</tr>
<tr>
<td>≥120 cm/sec</td>
<td>12 of 22</td>
<td>5 of 12</td>
</tr>
</tbody>
</table>

* Unfavorable outcome: death, vegetative survival, and severe disability, based on the Glasgow Outcome Scale.11 Abbreviation: TCD = transcranial Doppler.
The incidence of pancreatic and hepatic enzyme values outside normal ranges did not differ between the treatment groups and was considered to be disease related.

**Discussion**

The results of this study indicate that nimodipine treatment in patients who have a tSAH visible on CT scanning is associated with a significant decrease in unfavorable outcome in this group of head injury patients.

Until recently, not much attention was paid to the issue of tSAH. In the analysis of the population of the European nimodipine head injury study, HIT II, however, the subgroup of patients in whom a tSAH was identified on the first CT scan after injury emerged as a clearly distinguishable subgroup of individuals with regard to clinical aspects and prognosis.

The findings of the current study provide evidence for the reduction of unfavorable outcome in patients who have a tSAH visible on CT scanning after injury when treated with nimodipine for a period of 3 weeks. The relative reduction of unfavorable outcome was 46% in the overall population studied, and 55% when only those patients were taken into account who, in the opinion of the study's review committee, had an unequivocal tSAH visible on the first CT scan after injury. Nimodipine-treated patients had a reduction in mortality, vegetative state, and severe disability. This decrease in unfavorable outcome was also observed in those patients who were classified as mildly injured and treated with nimodipine (8% vs. 18%).

The most frequent location of blood observed on the first CT scan after injury was the convexity of the cerebral hemispheres; this was related to the presence of contusions and subdural hematoma. The basal cisterns were less frequently involved. The strong association with contusions and subdural hematoma seen in this study confirms previous observations and might indicate the source of bleeding in these patients. Another relatively frequent finding in association with tSAH was the presence of blood at the tentorium. Blood may accumulate at this location; however, a subdural bleeding at this location cannot be excluded, especially in cases in which blood cannot be seen in the adjacent cisterns. As expected, TCD-measured BFVs that were compatible with vasospasm were seen more frequently in patients with extensive bleeding and in the presence of thick clots. It was also shown that the BFV curve in the group of patients who developed vasospasm showed a very similar shape to that seen in spontaneous SAH, with a peak at the end of the 2nd week after injury. This was observed in patients with different degrees of vasospasm. An earlier maximum peak of BFVs, which has been described in a Swiss report, could not be seen. This finding confirms observations recently reported in relation to TCD results in head injury and, especially, in tSAH. The incidence of unfavorable outcome among those patients who remained within normal BFV limits was relatively low. This changed dramatically when increases in mean BFVs over 80 cm/second were detected. Worse outcomes were seen in those patients who had BFVs that were compatible with vasospasm, which were observed in almost 30% of patients.

In our series we found that 22% of patients assigned to receive placebo had a hypodensity compatible with post-traumatic ischemia on follow-up CT scans. In 50% of these patients TCD values compatible with some degree of vasospasm were found, and this mechanism may well...
have contributed to the complication. Recent publications have already suggested that pathophysiological mechanisms similar to those seen in aSAH might be involved in tSAH.\(^1,3,17,22,26\) Therefore it seems reasonable that a therapeutic modality such as that used in treating aSAH might benefit patients with tSAH.

It is known that vasospasm after spontaneous SAH cannot be avoided by treatment with calcium antagonists,\(^3,4,18–20\) but its incidence and severity might possibly be lowered. In this series, fewer patients given nimodipine developed vasospasm than those given placebo. Although a decrease in vasospasm of the cerebral arteries and an improvement in collateral blood flow might be involved as a mechanism of action of nimodipine, the more favorable outcome of tSAH patients who received nimodipine might also be due to elevated ischemic tolerance on a cellular level induced by the calcium antagonist. Accordingly, this might explain the significantly different occurrence of hypodensities compatible with posttraumatic cerebral infarction on the follow-up CT scans in the two groups. It was also interesting to observe a reduction in late posttraumatic seizures in survivors who had been treated with nimodipine.

**Conclusions**

Nimodipine treatment proved to be safe and well tolerated. The incidence of reported adverse events was relatively low and not significantly different between the two treatment groups.

Finally, as reported earlier,\(^5,12\) we found that identification of tSAH on the first CT scan after head injury permits those patients who are at a high risk for an unfavorable outcome to be identified. The introduction of nimodipine treatment might represent a clear step forward in the pharmacological therapy of these head-injured patients.

**Appendix**

**Participants in the German tSAH Study Group**

Clinical centers participating in this study:

- Universitätssklinik Bochum, Bochum
  Investigators: A. Harders, M. Hardenack, and K. Schmieder
- Universitätsklinikum Essen, Essen
  Investigators: H. A. Trost and H. Hellwig
- Krankenhaus Merheim, Cologne
  Investigators: E. M. Buchholz, T. Klein, and R. Peters
- Krankenhaus Berlin-Neukölln, Berlin
  Investigators: J. Zierski and J. Veelken
- Rheinisch-Westfälische Technische Hochschule, Aachen
  Investigators: J. M. Gilsbach, L. Mayfrank, and H. Bassiouni
- Universität Regensburg, Regensburg
  Investigators: A. Brawanski and M. Holzschuh
- Städtische Kliniken, Duisburg
  Investigators: W. E. Hassler, V. Rohde, P. Ziebell, and N. Emonds
- Georg-August-Universität, Göttingen
  Investigators: E. Markakis, H. Kolenda, and B. Zimmerer
- Städtische Kliniken, Dortmund
  Investigator: T. Scharphuis
- Städtische Kliniken, Kassel
  Investigators: H. R. Egert, A. Wilkowski, and J. W. May
- Krankenhaus der Barnbarmherzigen Brüder, Trier
  Investigators: K. Faulhauer, J. Lauer, and J. Paulus
- Städtische Kliniken, Chemnitz
  Investigators: J. Schöche and A. Raabe
- Klinikum Schwerin, Schwerin
  Investigators: D. Salger and G. Schibalski
- Martin-Luther-Universität, Halle
  Investigators: W. Burkert, N. Rainov, and V. Heidecke
- Medizinische Hochschule, Erfurt

---

A. Harders, et al.
Nimodipine treatment of traumatic SAH


References