Effect of Nimodipine on Platelet Function in Patients With Subarachnoid Hemorrhage

Seppo Juvela, MD, Markku Kaste, MD, and Matti Hillbom, MD

We studied platelet function in 41 patients with subarachnoid hemorrhage who were random-
ized to receive either nimodipine or placebo in a double-blind fashion. Nimodipine was given
to 21 patients, intravenously for 7–10 days and then orally until 21 days after the subarachnoid
hemorrhage. The other 20 patients received placebo in a similar manner. Nimodipine did not
significantly influence platelet aggregability. For the first 1–5 days after the subarachnoid
hemorrhage, nimodipine treatment did not have any notable effect on adenosine diphosphate-
induced platelet thromboxane B2 release, but a significant \((p<0.05)\) inhibitory effect was
observed thereafter. During intravenous administration, nimodipine prevented the increase in
thromboxane release otherwise observed after subarachnoid hemorrhage. Concomitant with
the decrease in thromboxane release, nimodipine increased the platelet count both before and
after surgery so that the capacity for thromboxane formation per liter of blood decreased less
than expected on the basis of thromboxane release per 10^7 platelets. Our study suggests that
nimodipine might diminish the chance of cerebral ischemia by inhibiting platelet thromboxane
release. (Stroke 1990;21:1283–1288)

delayed ischemic deterioration is an impor-
tant cause of disability and death in
patients with subarachnoid hemorrhage
(SAH) who have survived the primary insult.1–4 The
pathogenesis of cerebral ischemia and cerebral artery
vasospasm is obscure and may be precipitated by
many factors.2,4

Recently, calcium channel blocking agents have
received much attention in the prevention of cerebral
vasospasm and ischemia. It has been assumed that
the contraction of cerebral arterial smooth muscle
cells, which is calcium dependent, can be inhibited
after SAH by preventing the influx of extracellular
calcium.2,5 Platelet-derived thromboxane may be
associated with cerebral ischemia after SAH because
thromboxane is an effective vasoconstrictor and
platelet aggregating agent.6

We studied, in a double-blind manner, adenosine
diphosphate (ADP)–induced platelet aggregability
and the associated release of thromboxane in
selected SAH patients who were randomized to
receive nimodipine or placebo.

Subjects and Methods

We included 41 patients admitted ≤96 hours after
the onset of SAH to the Department of Neurosurgery
at the Helsinki University Central Hospital who had
been enrolled in a prospective double-blind placebo-
controlled study of nimodipine after aneurysmal
SAH.7 Twenty-one patients received nimodipine, and
the other 20 received a placebo administered in a
similar manner.

Patients who had used nonsteroidal anti-inflam-
matory drugs during the 2 weeks before admission were
excluded from the study. No patient had salicylates in
the urine on admission, and following admission no
nonsteroidal anti-inflammatory drugs were given.

Patients who were operated on were routinely given
4 mg i.m. betamethasone every 6 hours, starting the
day before surgery and continuing until 6 days after
surgery, in diminishing doses. The patient's clinical
grade on admission and before surgery was classified
according to Hunt and Hess.8

The SAH was verified by computed tomography
(CT) in 40 patients and by lumbar puncture and
surgery in one patient. All CT examinations were
performed ≤48 hours after the onset of SAH either
before referral in the primary hospital or on admis-
sion. The amount of subarachnoid blood on the CT
scan at admission was categorized according to
Fisher et al9 as 1) no evidence of subarachnoid blood,
2) diffuse deposits or a thin layer in the fissures and
vertical cisterns, or 3) localized clots or a thick layer
in the fissures and vertical cisterns.

Thirty-eight patients were operated on. The median time from SAH (day 0) to surgery was 5.0
(range 0.7–23) days because of variation in the timing
of surgery for supratentorial aneurysms in a second study.10

The initial dose of nimodipine or placebo was 0.25
\(\mu g/kg/min\) by continuous infusion administered via
an infusion pump. After 2 hours, the dose was
increased to 0.5 \(\mu g/kg/min\), which was maintained
until 7–10 days after the onset of SAH and for at least
3 days after surgery if the patient was operated on \(\geq 8\)
days from SAH. After intravenous administration,
nimodipine or placebo was administered orally for up
to 21 days after the SAH. The oral dose was 60-mg
tables every 4 hours.

From one to six blood samples were drawn from
each patient for platelet function studies. The mean
time of the first sample (early phase, at the beginning
of treatment) was 3.0 (range 1–5) days after SAH,
that of the second sample (intermediate phase, at the
end of intravenous administration) was 8.6 (range 7–10)
days, and that of the third sample (late phase, during
oral administration) was 14.5 (range 11–18)
days. Three patients were sampled only after the
early phase. Not all patients with an early-phase
sample had samples during the intermediate or late
phases due to death, coincidence of the sampling
time and a weekend, or discharge to other hospitals.
Blood samples were taken 4 hours after the oral
administration of nimodipine or placebo. Postopera-
tive samples were collected \(\geq 2\) days after surgery to
decrease the effect of medication associated with
anesthesia. The first sample during each phase was
included in the analysis of platelet aggregability, but
these were not always the same samples used for the
analysis of thromboxane release since the latter was
determined only from samples showing irreversible
(secondary-phase) platelet aggregation. Accordingly,
in some patients different samples served for the
analyses of platelet aggregability and thromboxane
release.

To study the release of thromboxane from platelets
(measured as the concentration of the stable metabo-
lite thromboxane \(B_2 [TXB_2]\), we applied the method
of ADP-induced platelet aggregation11 described in
detail elsewhere.12 We used 8 \(\mu M\) ADP on the basis of
our earlier observation.12 ADP is believed to be a
physiological inducer of platelet aggregation.13 TXB2
formation in 11 blood was calculated as the product of
TXB2 release and the blood platelet count. This
variable reflects the capacity of blood to release thromboxane. Platelet studies were performed by one
laboratory technician who was blinded to the case
histories of the patients.

A neurologic examination was performed daily
after admission to record deterioration in the level of
consciousness and development of neurologic defi-
cits. CT scans were obtained on admission, after
clinical deterioration, and on discharge. By delayed
ischemic deterioration with fixed neurologic deficit
we mean the gradual development of totally or
partially irreversible focal neurologic signs and/or
deterioration in the level of consciousness not due to
intracerebral hematoma, rebleeding, hydrocephalus,
clipping of an arterial branch along with the aneu-
rysms, infection, or serum electrolyte disorders. These
causes of deterioration were excluded by CT, routine
postoperative angiography, laboratory investigations,
or autopsy.

Outcome was assessed at 6 months according to
the three-point Glasgow Outcome Scale14 as inde-
pendent state (good recovery or moderate disability),
dependent state (severe disability or persistent veget-
ative state), or death.

The data were analyzed using BMDP.15 Fisher's
exact two-tailed test and the sign test were used to
compare platelet aggregability between and within
treatment groups. The results of TXB2 release and
formation capacity were analyzed after logarithmic
transformation, which was necessary due to their
skewed distributions. TXB2 values and timing of
surgery are given as median±standard error of the
median (SE). Other interval scale values are ex-
pressed as mean±standard error of the mean (SEM)
or mean±standard deviation (SD). We compared the

treatment groups during each phase using Student's or
Welch's \(t\) tests. In patients without missing data, the
effect of time after SAH, treatment group, and possi-
bile confounding factors (delayed ischemic deterio-
ration, amount of subarachnoid blood seen on the
admission CT scan, age, sex, and clinical grade on
admission) were compared using repeated-measures
analyzes of variance and covariance.

Results

The treatment groups did not differ by baseline
characteristics (Tables 1 and 2). The timing of sur-
gery was uniformly distributed over days 1 to 10 after
SAH. The interval between the onset of SAH and
the initiation of intravenous nimodipine or placebo aver-
egaged 1.9 (range 0.7–4.4) days. The time of blood
sampling did not differ according to treatment group.
Outcome tended to be somewhat better in the nimo-
dipine group (Table 2).

Nimodipine had no significant effect on platelet
aggregability (data not shown); 74% of aggregations
were irreversible during the early phase. Aggregabil-
ity increased according to time after SAH, so that all
aggregations were irreversible from the end of the
first week on. Irreversible (secondary-phase) platelet
aggregation was verified from the aggregation curves.
The aggregation curves of the patients (measured as
the maximal percentage change in light transmitt-
ance within 5 minutes) did not differ between groups
(data not shown), and there were no differences
between groups when preoperative and postopera-
tive samples were analyzed separately (data not
shown).

Mean±SEM platelet counts of the nimodipine

group were 208.3±12.4, 305.5±21.3, and 358.7±
25.6×10⁹/l during the early, intermediate, and late
phases, respectively. Corresponding values for the
placebo group were 212.4±13.1, 271.1±17.8, and
284.5±25.2×10⁹/l, respectively. During the late
phase, the platelet count was significantly higher
thromboxane B2 release was significantly higher ($p<0.05$) in the five patients who deteriorated due to preoperative cerebral ischemia than in the other patients during all phases. Median±SE TXB2 release of those with preoperative cerebral ischemia were 2,008.0±96.6, 5,150.5±1,437.2, and 8,251.3±2,789.0 fmol/10^7 platelets during the early, intermediate, and late phases, respectively. Corresponding values for the patients without ischemia were 1,516.5±257.9, 2,354.0±553.5, and 1,811.5±649.2 fmol/10^7 platelets, respectively. The four patients who deteriorated due to postoperative cerebral ischemia had significantly greater ($p<0.05$) TXB2 release (8,190.0±2,617.0 fmol/10^7 platelets) during the late phase.

There was no significant difference in the occurrence of delayed ischemic deterioration with fixed neurologic deficit between groups, probably because of the small number of patients. In both groups two patients deteriorated due to postoperative ischemia, and two patients in the nimodipine group and three in the placebo group deteriorated due to preoperative ischemia.

Among patients without cerebral ischemia nimodipine significantly ($p<0.05$) inhibited platelet TXB2 release from the early phase on, while no significant effect could be detected in the patients who developed ischemia because they were too few. However, patients who deteriorated due to ischemia and received nimodipine also had lower TXB2 release than patients with ischemia who received placebo.

### Table 1. Demographic Characteristics of 41 Patients With Aneurysmal Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Treatment group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio (male:female)</td>
<td>Nimodipine (n=21)</td>
<td>Placebo (n=20)</td>
</tr>
<tr>
<td>No.</td>
<td>8:13</td>
<td>13:7</td>
</tr>
<tr>
<td>Age (mean±SD yr)</td>
<td>42.3±9.7</td>
<td>43.8±11.1</td>
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<tr>
<td>Hypertension</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Clinical grade* on admission</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>I</td>
<td>19.0</td>
<td>20.0</td>
</tr>
<tr>
<td>II</td>
<td>38.1</td>
<td>40.0</td>
</tr>
<tr>
<td>III</td>
<td>38.1</td>
<td>30.0</td>
</tr>
<tr>
<td>IV</td>
<td>4.8</td>
<td>10.0</td>
</tr>
<tr>
<td>Location of ruptured aneurysm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Anterior communicating artery</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Pericallosal artery</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Vertebrobasilar artery</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Subarachnoid blood on CT scan* at admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Thin layer</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Thick layer</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Intraventricular bleeding</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Intracerebral hematoma ≤30 mm in diameter</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

*Hypertension, repeated blood pressure readings of >160/95 mm Hg before onset or use of antihypertensive medication.
TABLE 2. Surgical Treatment and Outcome of 41 Patients With Aneurysmal Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Nimodipine (n=21)</th>
<th>Placebo (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Surgery</td>
<td>20</td>
<td>95.2</td>
</tr>
<tr>
<td>Clinical gradea before surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>7</td>
<td>35.0</td>
</tr>
<tr>
<td>II</td>
<td>4</td>
<td>20.0</td>
</tr>
<tr>
<td>III</td>
<td>8</td>
<td>40.0</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>V</td>
<td>1</td>
<td>5.0</td>
</tr>
<tr>
<td>Days to surgery (median±SE)</td>
<td>4.0±0.9</td>
<td>5.5±1.4</td>
</tr>
<tr>
<td>Rebleeding</td>
<td>1</td>
<td>4.8</td>
</tr>
<tr>
<td>Delayed ischemic deterioration</td>
<td>4</td>
<td>19.0</td>
</tr>
<tr>
<td>Outcome14 at 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent</td>
<td>16</td>
<td>76.2</td>
</tr>
<tr>
<td>Dependent</td>
<td>4</td>
<td>19.0</td>
</tr>
<tr>
<td>Dead</td>
<td>1</td>
<td>4.8</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rebleeding</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Delayed ischemic deterioration</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Independent, good recovery or moderate disability; dependent, severe disability or persistent vegetative state.

after the early phase. Median±SE TXB₂ release in patients with cerebral ischemia receiving nimodipine was 2,008.0±877.0, 3,103.0±466.4, and 5,935.5±2,817.0 fmol/10⁷ platelets during the early, intermediate, and late phases, respectively. Corresponding values for patients with ischemia receiving placebo were 1,840.8±510.5, 4,796.0±1,864.8, and 10,567.0±0 fmol/10⁷ platelets (range 9,357.0-11,609.5 fmol/10⁷ platelets, n=3 in this last group).

The TXB₂ formation capacity was significantly higher (p<0.05) in patients with preoperative ischemia than in other patients during the early phase and significantly higher (p<0.05) in patients with postoperative ischemia than in patients without cerebral ischemia during the late phase. Platelet count, platelet aggregability, and aggregation percentage did not differ according to the presence of cerebral ischemia.

Discussion

Recent double-blind placebo-controlled studies have demonstrated a beneficial effect of nimodipine in the prevention of cerebral ischemic symptoms and cerebral infarctions after SAH.⁷,₁⁶-⁻¹⁹ Nimodipine, a 1,4-dihydropyridine, seems to decrease the incidence and severity of ischemic neurologic deficits without preventing the narrowing of major cerebral arteries visualized by angiography.¹⁸⁻²² Accordingly, there must also be mechanisms other than vasospasm to cause deficits.

Calcium channel blocking agents may exert their effects by dilating leptomeningeal collateral arteries (not visualized in angiography),²⁻²⁵ by antiplatelet effects,²³⁻²⁴ or by preventing the entrance of lethal amounts of extracellular calcium into the cells.⁵⁻²⁵ Nifedipine has been shown to decrease platelet function after a single 20-mg dose in patients with coronary disease.²³ Nicardipine and acetylsalicylic acid given simultaneously in low doses have an additional antiaggregatory effect on platelets.²⁴

In an animal experiment, nimodipine decreased TXB₂ concentration in the arterial wall after exposure to a periartrial hematoma.²⁶ In another exper-

TABLE 3. Release of Thromboxane B₂ From Platelets in Patients According to Time After Aneurysmal SAH and Treatment

<table>
<thead>
<tr>
<th>Samples</th>
<th>Nimodipine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Median±SE</td>
</tr>
<tr>
<td>Early phase</td>
<td>16</td>
<td>1,739.3±306.3</td>
</tr>
<tr>
<td>Intermediate phase</td>
<td>15</td>
<td>2,193.5±421.9*</td>
</tr>
<tr>
<td>Late phase</td>
<td>14</td>
<td>1,930.5±831.2</td>
</tr>
<tr>
<td>Preoperative</td>
<td>13</td>
<td>1,935.0±306.3</td>
</tr>
<tr>
<td>Postoperative</td>
<td>8</td>
<td>1,417.3±654.9</td>
</tr>
</tbody>
</table>

Samples showing reversible platelet aggregation have been excluded. SAH, subarachnoid hemorrhage. Values are fmol/10⁷ platelets. Early phase, 1–5 (mean 3.0) days after SAH; intermediate phase, 7–10 (mean 8.6) days after SAH; late phase, 11–18 (mean 14.5) days after SAH. *p<0.05 different from placebo by Student's t test.
TABLE 4. Capacity of Blood to Form Thromboxane B2 in Patients According to Time After Aneurysmal SAH and Treatment

<table>
<thead>
<tr>
<th></th>
<th>Early phase</th>
<th>Intermediate phase</th>
<th>Late phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nimodipine</td>
<td>Placebo</td>
<td>Nimodipine</td>
</tr>
<tr>
<td>All</td>
<td>n Median±SE</td>
<td>n Median±SE</td>
<td>n Median±SE</td>
</tr>
<tr>
<td>All</td>
<td>16</td>
<td>35.1±8.7</td>
<td>15</td>
</tr>
<tr>
<td>Preoperative</td>
<td>13</td>
<td>32.7±8.5</td>
<td>5</td>
</tr>
<tr>
<td>Postoperative</td>
<td>8</td>
<td>39.4±17.4</td>
<td>12</td>
</tr>
</tbody>
</table>

Samples showing reversible platelet aggregation have been excluded. SAH, subarachnoid hemorrhage. Values are nmol/L. Early phase, 1–5 (mean 3.0) days after SAH; intermediate phase, 7–10 (mean 8.6) days after SAH; late phase, 11–18 (mean 14.5) days after SAH.

Nimodipine in the post-SAH increase of TXB2 release was inhibited by intravenous nimodipine treatment, although platelet aggregability was not decreased. Nimodipine decreased TXB2 release significantly in those patients who did not deteriorate due to ischemia and less markedly in those who developed cerebral ischemia.

The effect of nimodipine on TXB2 release was less remarkable when the drug was given orally. The maximal serum concentration of nimodipine occurs approximately 1 hour after an oral dose. Since we took blood samples approximately 4 hours after oral administration of the drug, we do not know whether low serum concentrations explain the modest effect of treatment with oral nimodipine on platelet TXB2 release.

We do not know why the platelet count was increased more in the nimodipine group than in the placebo group. This could be associated with a negative feedback mechanism compensating for the decreased TXB2 release due to nimodipine. Increased platelet TXB2 release after SAH could be one mechanism involved in the prevention of rebleeding. If this is the case, an increase in the platelet count could compensate for the decreased TXB2 release induced by nimodipine and maintain effective hemostasis after SAH. In spite of the increased platelet count in the nimodipine group, capacity of the blood to form TXB2 tended to remain lower in the nimodipine group than in the placebo group after the early phase.

The majority of patients will not suffer, although they do increase their thromboxane release. Those who have an exceptionally high thromboxane release may develop ischemic symptoms, which may be ameliorated by nimodipine. The mechanism by which nimodipine acts on platelet TXB2 release is unknown, but it could be by inhibiting calcium influx into platelets, which can inhibit the phospholipase A2 activity necessary for thromboxane production from arachidonic acid. If thromboxane release is decreased by nimodipine, vasocostriction of the resistant vessels and platelet aggregability may be attenuated, leading to better local and collateral circulations.

In conclusion, we observed decreased platelet TXB2 release caused by nimodipine treatment in patients with SAH. Accordingly, nimodipine may increase cerebral blood flow and decrease delayed cerebral ischemia via antplatelet effects.

Acknowledgment
We would like to thank Mrs. Saija Heinonen for skillful technical assistance.

References


**KEY WORDS**: nimodipine • subarachnoid hemorrhage • platelet aggregation • thromboxane B2
Effect of nimodipine on platelet function in patients with subarachnoid hemorrhage.
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Stroke. 1990;21:1283-1288
doi: 10.1161/01.STR.21.9.1283

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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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