Effect of Nicardipine Prolonged-Release Implants on Cerebral Vasospasm and Clinical Outcome After Severe Aneurysmal Subarachnoid Hemorrhage

A Prospective, Randomized, Double-Blind Phase IIa Study

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Background and Purpose—The purpose of this study was to investigate the effect of nicardipine prolonged-release implants (NPRIs) on cerebral vasospasm and clinical outcome after severe subarachnoid hemorrhage.

Methods—Thirty-two patients with severe subarachnoid hemorrhage and undergoing aneurysm clipping were included into this single center, randomized, double-blind trial. Sixteen patients received NPRIs implanted into the basal cisterns in direct contact to the exposed proximal blood vessels; in 16 control patients, the basal cisterns were opened and washed out only without leaving implants. Angiography was performed preoperatively and at day 8.

Results—The incidence of angiographic vasospasm in proximal vessel segments was significantly reduced after implantation of NPRIs (73% control versus 7% NPRIs). Significant differences occurred also for the majority of distal vessel segments. Computed tomography scans revealed a lower incidence of delayed ischemic lesions (47% control versus 14% NPRIs). The NPRI group demonstrated more favorable modified Rankin and National Institute of Health Stroke scales as well as a significantly lower incidence of deaths (38% control versus 6% NPRIs).

Conclusions—Implantation of NPRIs reduces the incidence of cerebral vasospasm and delayed ischemic deficits and improves clinical outcome after severe subarachnoid hemorrhage. (Stroke. 2007;38:330-336.)

Key Words: nicardipine prolonged-release implants ▪ SAH ▪ stroke ▪ vasospasm

Cerebral vasospasm remains one of the most serious complications after aneurysmal subarachnoid hemorrhage (SAH). Over the past decades, several pharmacological approaches have been investigated for the prevention of cerebral vasospasm. Among those, the most prominent is the use of voltage-gated calcium channel antagonists such as nimodipine and nicardipine. Experimental data support the concept that voltage-gated calcium channel antagonists are capable of preventing cerebral vasospasm if administered in high enough doses to the vessel wall. However, when administered intravenously or orally, the doses necessary to exert maximum pharmacological effect cannot be achieved as a result of the side effects of the drug. Recently, this limitation in the delivery of voltage-gated calcium channel antagonists has been overcome by the introduction of nicardipine prolonged-release implants (NPRIs). These nicardipine-loaded polymers are implanted into the basal cisterns in close contact to the proximal cerebrovascular system at the time of aneurysm clipping and release the drug over 14 days. Thereby, nicardipine is delivered locally at a high and constant concentration to the cerebral blood vessel wall, at the same time avoiding systemic side effects.

The initial preclinical and clinical experiences with NPRIs have been promising and have failed to show toxicity. In a retrospective case series comparing 69 patients who received NPRIs after SAH with 28 patients with SAH who did not, Kasuya and coworkers suggested that the incidence of delayed ischemic neurologic deficits may be decreased and outcome after SAH may be improved by NPRIs. Consequently, in his editorial comment, MacDonald, keeping the limitation of a case series in mind, speculated that "the idea to..."
use nicardipine in high doses by local delivery could...represent a cure for vasospasm.” However, without randomization and blinding, evidence for the efficacy of NPRIs in preventing cerebral vasospasm has not been provided so far. Also, the lack of a quantitative and independent evaluation of standardized postoperative angiographic studies has raised some doubt in the vasoactivity of NPRIs. Therefore, the aim of the present study was to conduct a controlled, prospective, randomized, and double-blind phase II study to further address the efficacy of NPRIs in reducing the incidence of cerebral vasospasm and delayed ischemic deficits and improving clinical outcome after severe SAH.

Material and Methods
Nicardipine Prolonged-Release Implants
NPRIs used in this study have been previously characterized.4 NPRIs are rod-shaped polymers (2×10 mm) containing 4 mg nicardipine. Release kinetics and pattern of distribution of nicardipine have been characterized.4

Study Population and Management
The study was approved by the local Research Ethics Committee and Institutional Review Board. Thirty-two consecutive patients (age 18 to 70 years) with a severe SAH (ie, Hunt and Hess grade 3 to 4, Fisher grade 3) were included into the study. Further inclusion criteria were: (1) saccular aneurysm, (2) surgical clipping of the aneurysm location (Figure 1). By tailoring the implantation of NPRIs, analysis of the angiograms and computed tomography locally for patient management decisions only. To assess the efficacy of implants was chosen based on previous clinical experience in which 10 NPRIs was the maximum implanted and their safety had been documented.4 The pattern of NPRI distribution was dependent on aneurysm location (Figure 1). By tailoring the implantation of NPRIs, we aimed at reaching a maximum delivery of nicardipine to the vessel segments at highest risk for vasospasm. In contrast, the basal cisterns of patients in the control group were opened and washed out identically but were left without implantation of NPRIs. Only the operating surgeons (P.S., P.V.) were aware of the corresponding study arm. Investigators and medical staff taking care of the patients postoperatively were blind to the randomization.

Patients were assessed clinically by recording the Glasgow Coma Scale, modified Rankin and National Institute of Health Stroke scales during the monitoring period. For outcome determination, they were again seen 1 year after SAH. Angiography was performed preoperatively and at day 8±1 after SAH to evaluate the occurrence of angiographic vasospasm or earlier when clinical or transcranial Doppler suggested presence of vasospasm. If angiographic vasospasm was confirmed, hypervolemic/hemodilution/hypertensive therapy was initiated. Computed tomography was performed at least preoperatively to confirm the diagnosis of SAH, within 48 hours postoperatively to identify surgery related ischemic lesions, and at discharge.

Assessment of Cerebral Vasospasm
All angiograms and computed tomography scans were evaluated locally for patient management decisions only. To assess the efficacy of NPRIs, analysis of the angiograms and computed tomography scans was performed by an independent and blinded neuroradiologist (S.W.). Therefore, diameters of the proximal vessel segments (C1, M1, A1, P1, BA) were measured in the initial and follow-up angiograms. To overcome potential bias from angiograms with different magnifications, the following procedure was chosen: First, angiograms were optically 5X magnified to measure different vascular sections more precisely. Second, diameters (ie, the contrast agent filled compartment of the vessel) were measured digitally in absolute values. Third, a ratio was built between all intradural and one extradural proportion (C5) of the vessel tree, a procedure that had been established by Weir and coworkers.6 Fourth, these ratios were used to analyze vessel diameters independently from the original magnification used. Angiographic vasospasm was defined as a ≥35% reduction in diameter in at least one vessel segment. Changes in the diameter of distal vessel segments (M2+, A2+, P2+) were assessed using a qualitative grading system. Computed tomography analysis aimed at identifying delayed ischemic lesions (ie, not related to surgery) serving as surrogate marker for severe symptomatic vasospasm.

Assessment of Clinical Outcome
Outcome was assessed using the modified Rankin and the National Institute of Health Stroke scales 1 year after SAH. “Good outcome” was defined as NIH scale of 0 to 4 and modified Rankin scale of 0 to 2.
End Points of the Study

Primary end points of the study were the influence of NPRIs on angiographic vasospasm. Secondary end points were the incidence of delayed ischemic lesions on computed tomography scan and clinical outcome.

Statistical Analysis

Before study initiation, a power calculation was performed. According to this, to achieve a power of 94%, a sample size of 30 patients was required with the assumption of 50% incidence of vasospasm in the control group and 10% in the pellet group. Patients were randomized according to a predefined list with patients randomly assigned to one of the study arms. Patient characteristics are given as mean ± standard deviation. Side and intergroup differences of proximal vessel diameters were analyzed using repeated analysis of variance measurements. Side and intergroup differences of distal vessel diameters were measured using the Wilcoxon test. Insignificant side differences of distal vessels were tested for levels of agreement using the weighted kappa index. Because simple percentages of pairwise agreement would be insufficient, the kappa index corrects for the occurrence that can be expected by chance alone for 2 groups. The weighted kappa index allows comparison of disagreements of varying degree. Intergroup differences were measured using the U test from Mann–Whitney, the Student t test, the χ² test, and Fisher exact test, as applicable. Differences were considered significant when P value was <0.05.

Results

Study Population

During the 1-year study period, a total of 79 patients were admitted with the diagnosis of SAH. Forty-seven patients were excluded from the study: 27 patients were Hunt and Hess (H&H) grade I to II or V, aneurysms of 10 patients were coiled, 10 patients had perimesencephalic SAH, or no aneurysm was detectable. Mean age was 54±6 and 51±8 years for the control and NPRI groups, respectively (P=0.222, Student t test). In both groups, there was a predominance of female patients (75% control and 63% NPRI; P=0.703, χ² test). The proportion of smokers (57% control versus 60% NPRI; P=0.835, χ² test) and patients with arterial hypertension (36% control versus 31% NPRI; P=1.0, Fisher exact test) was equally distributed. The proportion of aneurysms located in the anterior circulation was similar (81% control versus 88% NPRI; P=1.0, Fisher exact test).

Toxicity

NPRIs were tolerated well and no drug-related adverse events were noticed. In particular, there was no significant difference in the incidence of central nervous system infection or hydrocephalus. No signs of cerebral hyperperfusion were observed in the NPRI group.

Illustrative Cases

Case No. 1

This is a 63-year-old female patient with a SAH grade III according to the H&H classification (Figure 2A). Digital subtraction angiography revealed a posterior communicating artery aneurysm on the left side (not shown). The patient was randomized to the control group. Several days postoperatively, the patient deteriorated and showed signs of symptomatic vasospasm. Digital subtraction angiography on day 7 revealed diffuse, severe vasospasm (Figure 2C).
tomography scan on day 8 demonstrated bilateral middle cerebral artery strokes (Figure 2D). By day 10, the patient developed intracranial hypertension that was refractory to therapy.

Case No. 2
This is a 45-year-old female patient with a SAH grade IV according to the H&H classification (Figure 3A). Digital subtraction angiography revealed an anterior communicating artery aneurysm (Figure 3B). The patient was randomized to the NPRI group. After the operation, the patient showed rapidly improving clinical scores. The day 8 angiogram failed to show angiographic vasospasm (Figure 3C). No ischemic lesions were documented on computed tomography scan at discharge (Figure 3D).

Nicardipine Prolonged-Release Implant and Cerebral Vasospasm
In total, 29 angiograms were available for analysis (n=15 control, n=14 NPRI). Three patients had to be excluded from the angiographic analysis: for 2 patients, either the pre- or postoperative angiogram was not accomplished (one control, one NPRI); one patient died on day 3 (NPRI).

First, we addressed the efficacy of NPRIs in preventing vasospasm of the proximal vessel segments. Their diameters were measured in absolute values in the initial and follow-up angiograms and relative diameter changes were calculated. Five hundred twenty-two vessel segments were examined. The analysis revealed that NPRIs significantly reduced the incidence of proximal angiographic vasospasm from 73% to 7% (P<0.05, χ² test) (Figure 4A). It is noteworthy that NPRIs induced a mild to moderate dilation of these vessel segments (Table 1). In contrast, an analysis of side to side differences revealed no relevant results, suggesting that the implants exerted efficacy also at sites distant from their implantation (Table 1). This was unexpected because we hypothesized that the lipophilic character of nicardipine would limit its efficacy to the site of implantation.

To further address the distant activity of NPRIs, we investigated their efficacy in preventing vasospasm of distal vessels. Using a qualitative grading system, the analysis revealed that also distal vessel segments were wider in the NPRI group when compared with controls (Table 2). This result confirmed that NPRIs exert vasoactivity on cerebral blood vessels beyond their site of implantation.

Finally, we aimed at determining the clinical relevance of this reduction of angiographic vasospasm. Therefore, we evaluated the incidence of nonsurgery-related, delayed ischemic lesions on computed tomography scans as a surrogate marker for severe, symptomatic vasospasm. As illustrated in Figure 4B, the prevention of cerebral vasospasm by NPRI successfully translated into a reduced incidence of delayed ischemic lesions, reaching almost statistical significance (P=0.054, 2-sided Fisher exact test).

Clinical Outcome
Mortality rates differed significantly in favor of the NPRI group. Although in the control group, 38% (n=6) of the patients died within the hospital stay, only 6% (n=1) did so...
in the NPRI group ($P=0.042$, 2-sided Fisher exact test). However, not only did less patients die in the NPRI group, but they also experienced a significantly better outcome after a mean follow-up period of 15 months (Table 3).

**Discussion**

The principal novel finding of the present study is that implantation of NPRIs after severe SAH reduces the incidence of both angiographic and symptomatic vasospasm. This beneficial effect on cerebral vasospasm translates into a reduced incidence of delayed cerebral ischemic lesions and, most importantly, an improved clinical outcome up to 1 year after SAH. NPRIs may represent a potent prophylaxis for cerebral vasospasm after severe SAH.

Voltage-gated calcium channel antagonists were among the first substances studied for the prevention of cerebral vasospasm. The underlying concept is that calcium-mediated smooth muscle cell contraction is the terminal step of the molecular signaling cascade(s) causing cerebral vasospasm.$^9,10$ Other reports have lately provided conflicting results on the significance of calcium-mediated vasoconstriction and have questioned the potential therapeutic value of voltage-gated calcium channel antagonists in the delayed phase of cerebral vasospasm.$^{10,11}$ The fact that in the present study, the local delivery of nicardipine through NPRIs resulted in prevention of vasospasm strengthens the significance of calcium-mediated smooth muscle cell contraction in cerebral vasospasm.

However, prevention of cerebral vasospasm with voltage-gated calcium channel antagonists seems to be achievable only by application of relatively high doses to the vessel wall. This is supported by studies in which nimodipine and nicardipine were administered systemically and yielded largely disappointing results in terms of prevention or reversal of cerebral vasospasm.$^{12–14}$ Only when administered at a higher dose did nicardipine prevent angiographic vasospasm.$^{14}$ However, at the same time, the therapeutic benefit was put off by the side effects accompanying the increase in dose.$^{14}$ Thus, voltage-gated calcium channel antagonists in principle seem to exert vasoreactivity after severe SAH but may not reach maximum pharmacological efficacy when administered systematically as a result of their side effects.

The local, high-dose delivery of voltage-gated calcium channel antagonists was a logical consequence. First attempts were made from both the luminal and extravascular side.$^{15,16}$ However, the drawback is the need for a continuous endovascular or intrathecal infusion system. As an alternative, the use of prolonged-release polymers implanted at the time of aneurysm clipping represents an elegant concept.$^{3,4}$ NPRIs are applied in direct contact to the wall of vessels at risk for developing vasospasm and continuously release a high dose of nicardipine over 14 days. They are implanted at the end of

**TABLE 1. Severity of Proximal Angiographic Vasospasm**

<table>
<thead>
<tr>
<th>Resulting Vessel Diameter</th>
<th>Treatment Groups</th>
<th>$P$ Value</th>
<th>$t$ test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control, $n=15$</td>
<td>NPRIs, $n=14$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1—side of implantation</td>
<td>87±19%</td>
<td>113±19%</td>
<td>0.0021</td>
</tr>
<tr>
<td>C1—contralateral side</td>
<td>85±28%</td>
<td>115±18%</td>
<td></td>
</tr>
<tr>
<td>$P$ value $t$ test</td>
<td>0.692</td>
<td>0.595</td>
<td></td>
</tr>
<tr>
<td>M1—side of implantation</td>
<td>75±28%</td>
<td>110±25%</td>
<td>0.0024</td>
</tr>
<tr>
<td>M1—contralateral side</td>
<td>75±35%</td>
<td>117±26%</td>
<td></td>
</tr>
<tr>
<td>$P$ value $t$ test</td>
<td>0.953</td>
<td>0.345</td>
<td></td>
</tr>
<tr>
<td>A1—side of implantation</td>
<td>62±25%</td>
<td>116±39%</td>
<td>0.0004</td>
</tr>
<tr>
<td>A1—contralateral side</td>
<td>79±35%</td>
<td>125±34%</td>
<td></td>
</tr>
<tr>
<td>$P$ value $t$ test</td>
<td>0.042</td>
<td>0.491</td>
<td></td>
</tr>
<tr>
<td>P1—side of implantation</td>
<td>88±26%</td>
<td>117±18%</td>
<td>0.0152</td>
</tr>
<tr>
<td>P1—contralateral side</td>
<td>81±22%</td>
<td>128±14%</td>
<td></td>
</tr>
<tr>
<td>$P$ value $t$ test</td>
<td>0.318</td>
<td>0.192</td>
<td></td>
</tr>
<tr>
<td>BA</td>
<td>88±36%</td>
<td>129±22%</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Proximal vessel diameters were measured bilaterally in absolute values on baseline and follow-up angiograms at predefined segments (C1, M1, A1, P1, BA). The given data represent the calculated relative values (%) of the resulting vessel diameter on the day 8 angiogram compared with baseline. No significant within-group differences were seen in either treatment group, except for the A1 segment of the control group. For intergroup differences, the vessel diameter of the implanted side (NPRI group) was compared with the mean vessel diameter from both sides of the control group. Differences are considered significant when $P<0.05$. 

![Figure 4](image-url)
surgery without the need for further interventions avoiding serious side effects. The results of the present study confirm the safety of NPRIs.

According to Figure 1, implantation of NPRIs was tailored to the individual aneurysm type. Considering the lipophilic character of nicardipine, we expected that NPRIs are effective primarily at vessel segments where direct contact exists. However, the data of the present study suggest that nicardipine exerts activity not only at the site of implantation, but also distant thereof. Both proximal and distant vessel segments were affected by NPRIs without side differences. We, therefore, presume that despite its lipophilic character, nicardipine is distributed within the subarachnoid space as previously suggested by radio cisternography.

So how does the NPRI system conceptually compare with upcoming pharmacological strategies specifically targeting molecular signaling pathways involved in the pathophysiology of cerebral vasospasm? Recently, statins and endothelin receptor antagonists have also demonstrated antivasospasm activity, conceptually questioning the need for a surgical solution using NPRIs. However, NPRIs remain highly attractive and carry several advantages: (1) the concept of inhibiting the common final pathway of vasoconstriction (ie, calcium influx) instead of focusing on a single putative target molecule in a potentially multifactorial pathology, (2) the lack of central nervous system-specific or systemic adverse events, and (3) the avoidance of long-term infusion of an expensive drug. In contrast, a drawback of NPRIs clearly is the need for surgery, which may restrict NPRIs to patients whose aneurysm is not amenable by endovascular means.

Given the current lack of an effective prophylaxis for cerebral vasospasm, the results of this study are encouraging. However, because of the limited number of patients and the single-center study design, the observed benefits of NPRIs need to be confirmed in further studies.

**TABLE 2. Incidence and Severity of Distal Angiographic Vasospasm**

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Control (n=15)</th>
<th>NPRIs (n=14)</th>
<th>P Value U test</th>
</tr>
</thead>
<tbody>
<tr>
<td>M2+ side of implantation</td>
<td>50</td>
<td>93</td>
<td>0.039</td>
</tr>
<tr>
<td>Contralateral side</td>
<td>53</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>A2+ side of implantation</td>
<td>40</td>
<td>71</td>
<td>0.026</td>
</tr>
<tr>
<td>Contralateral side</td>
<td>47</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>P2+ side of implantation</td>
<td>80</td>
<td>100</td>
<td>0.067</td>
</tr>
<tr>
<td>Contralateral side</td>
<td>73</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Weighted kappa (95% CI)</td>
<td>0.633 (0.437–0.841)</td>
<td>0.533 (0.224–0.842)</td>
<td></td>
</tr>
<tr>
<td>Weighted kappa (95% CI)</td>
<td>0.873 (0.739–1.005)</td>
<td>0.598 (0.263–0.934)</td>
<td></td>
</tr>
<tr>
<td>Weighted kappa (95% CI)</td>
<td>0.907 (0.724–1.092)</td>
<td>0.759 (0.316–1.0)</td>
<td></td>
</tr>
</tbody>
</table>

Distal vessel diameters were assessed qualitative on the day 8 angiogram according the grading system “wider, equal, mild, moderate, severe vasospasm” as compared with the baseline angiogram for distal vessel segments (M2+, A2+, P2+). For the analysis of within-group differences the Wilcoxon test, for intergroup differences, the U test from Mann–Whitney were used. For intergroup differences, the vessel diameter of the implanted side (NPRI group) was compared to the mean vessel diameter from both sides of the control group. Differences are considered significant when P<0.05.

**TABLE 3. One-Year Clinical Outcome**

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Control (%)</th>
<th>NPRIs (%)</th>
<th>P Value U test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified rankin scale 0–2 “good”</td>
<td>38.5 (n=5)</td>
<td>85 (n=11)</td>
<td></td>
</tr>
<tr>
<td>3–4 “moderate”</td>
<td>7.7 (n=1)</td>
<td>7.5 (n=1)</td>
<td></td>
</tr>
<tr>
<td>5–6 “poor”</td>
<td>53.8 (n=7)</td>
<td>7.5 (n=1)</td>
<td>0.0001</td>
</tr>
<tr>
<td>National Institutes of Health Stroke Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4 “good”</td>
<td>71 (n=7)</td>
<td>100 (n=11)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Outcome at 14.7±2.5 months after SAH. For the modified Rankin scale, 3 patients of the control group were not willing to participate versus 4 of the NPRI group. For analysis of the National Institutes of Health Stroke Scale, only survivors can be included that were willing to participate. For analysis of intergroup differences, the U test from Mann-Whitney was used. Differences are considered significant when P<0.05.

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**References**


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