Efficacy and Safety of Nicardipine Prolonged-Release Implants for Preventing Vasospasm in Humans

Hidetoshi Kasuya, MD; Hideaki Onda, MD; Mikihiko Takeshita, MD; Yoshikazu Okada, MD; Tomokastu Hori, MD

Background and Purpose—Despite extensive investigative efforts, there are few treatments that can prevent vasospasm after subarachnoid hemorrhage. This study was conducted to examine the efficacy and safety of nicardipine prolonged-release implants (NPRI) for humans, which have already been proven in dogs.

Methods—Twenty consecutive subarachnoid hemorrhage patients with thick subarachnoid clot were treated with NPRI (a pellet of diameter 2 mm, length 10 mm, containing 4 mg of nicardipine) during surgery after clipping of their aneurysm. The number and location of pellets depended on the amount and site of subarachnoid clot on preoperative CT and on craniotomy.

Results—Two to 10 pellets were implanted in the cistern of the internal carotid, middle cerebral, and/or anterior cerebral artery, where thick clots existed and therefore vasospasm related to delayed ischemic neurological deficits was highly likely. Delayed ischemic neurological deficits and cerebral infarctions were seen in 1 patient. Angiography performed on days 7 to 12 revealed no vasospasm in any arteries near which NPRI were placed. No complications were experienced.

Conclusions—Vasospasm was completely prevented for the arteries in thick clot cisterns, when NPRI were placed adjacent to the arteries during surgery. This drug-delivery system offers a promising approach for preventing vasospasm. (Stroke. 2002;33:1011-1015.)

Key Words: copoly(lactic/glycolic acid) ▪ drug delivery systems ▪ nicardipine ▪ subarachnoid hemorrhage ▪ vasospasm, intracranial

Despite extensive investigative efforts, the pathogenesis and pathophysiology of delayed cerebral vasospasm after aneurysmal subarachnoid hemorrhage (SAH) remain far from clear. Vasospasm continues to be one of the primary causes of mortality and neurological morbidity and an important cause of cerebral ischemia and stroke, despite the establishment of early surgical obliteration of aneurysm.1,2 Although the treatments of intravascular volume expansion, hemodilution, induced hypertension, and the use of nimodipine have had substantial beneficial effects on delayed ischemic neurological deficits (DIND) due to vasospasm, these are not tolerated or are ineffective in some patients. They also do not represent treatment for preventing or reversing vasospasm per se. Transluminal cerebral angioplasty is very effective in reversing angiographically confirmed vasospasm, and anecdotal reports of its clinical utility are numerous.1 However, it is difficult to draw any conclusion regarding its superiority for the medical management of symptomatic vasospasm.3 Although the efficacy of intrathecal fibrinolytic therapy with tissue-type plasminogen activator or urokinase has been reported, it is technically complicated.4 Additional and alternative treatments for vasospasm that are less invasive and less complicated, particularly those specifically targeting the dilation of cerebral vessels, are now needed.1,2

We have developed a drug-delivery system using a vasodilating drug that can be implanted intracranially at the time of surgery for aneurysm clipping, without systemic side effects or side effects associated with long-term intrathecal drug administration through indwelling catheters.5–8 We previously reported the effectiveness and safety of nicardipine prolonged-release implants (NPRI) using copoly(lactic/glycolic acid) (PLGA), which significantly prevented vasospasm in dogs while maintaining an appropriate concentration of nicardipine in the cistern.7 We designed NPRI for humans, and this study was conducted to examine the effect of NPRI for preventing vasospasm in humans and to assess the safety of this drug delivery system.

Subjects and Methods

Development of NPRI for Humans

A rod-shaped pellet (2 mm in diameter, 10 mm in length, containing 4 mg of nicardipine) was prepared by heat compression. PLGA (PLG1600 ML; molecular weight 4000, lactic acid ratio 0.5) was purchased from Taki Co. A mixture of PLGA (900 mg) and nicardipine-free base (100 mg) was dissolved in dichloromethane (10 mL). The dichloromethane was evaporated with a rotary evaporator, and the resultant mass was dried further under vacuum. The dried powder (40 mg) was charged into a Teflon tube (2-mm inner diameter). The tube was set in a stainless steel cylinder kept at 35°C to 40°C. A pressure of 100 kg/cm² was applied between the upper and lower stainless steel dies. The compressed pellet was sterilized...
by γ-ray (Nippon Shosha Service). Nicardipine-free base was prepared as follows: nicardipine HCl (Sigma Chemical Co.) was dissolved in water. NaOH (5N) was added to the solution to shift the pH above 10. The nicardipine-free base was extracted with dichloromethane.

The release of nicardipine from the pellet was examined in a mixture of 0.02 mol/L phosphate buffer, pH 7.3, and saline (1:1, v/v) in a flask. The flask was shaken in a waterbath (37°C) at a frequency of 20 strokes/minute. Five milliliters of the release medium was withdrawn periodically and replaced with an equivalent volume of fresh buffer. The amount of nicardipine released was analyzed by high performance liquid chromatography (Hitachi L6000, Hitachi), under the following conditions: column, YMC-Pack ODS AM-312 (150×6.0-mm inner diameter); column temperature, 40°C; mobile phase, 10 mmol/L KH₂PO₄/acetonitrile (6:4); flow rate, 1.5 mL/min; detection, ultraviolet absorbance at 240 nm; internal standard, papaverine (obtained from Iwaki Pharmaceutical).

**Patient Population and Management**

Twenty consecutive patients were investigated in the Department of Neurosurgery, Tokyo Women’s Medical University. The study was approved by the University Ethical Committee, and informed consent was obtained by the principal investigator (H.K.). Table 1 lists the clinical aspects of the patients treated. Eligibility criteria were CT radiographic SAH group of 3rd and early craniotomy for clipping of aneurysm. Only that part of the blood clot necessary for exposure and clipping of the aneurysm was removed surgically. We started our protocol on October 1, 1999 and 20 patients were treated with NPRI, among 40 SAH patients hospitalized by July 31, 2000. No patient was excluded from the study. A frontotemporal craniotomy and a midline frontal craniotomy were performed for internal carotid artery and middle cerebral artery (MCA) aneurysms, and anterior communicating and distal anterior cerebral artery aneurysms, respectively. NPRI was placed in the cistern of the internal carotid artery, that of M1 (horizontal segment), M2 (insular segment), and/or M3 (opercular segment) of the MCA, and/or that of A1 (horizontal segment) and/or A2 (interhemispheric segment) of the anterior cerebral artery, where thick clots existed and therefore vasospasm related to DIND was highly likely. The number of pellets and location of the placement depended on the amount and site of subarachnoid clot in preoperative CT and on craniotomy. Cerebral vasospasm was assessed by angiography on days 7 to 12, DIND, and low-density area on CT. Deterioration in the level of consciousness, appearance of motor weakness, sensory deficit, or aphasia was recorded as DIND if there was no other explanation in the postoperative period. The cause of low-density areas on CT scans that appeared de novo postoperatively was investigated. When all other causes of low-density areas were excluded, for example, operative (brain retraction and use of vasospasm-related narrowing of vessels). The vessel diameters were measured bilaterally at M1 of the MCA and C5 (extradural pyramidal segment).

**Vessel Diameter Assessment**

Angiographically demonstrated vasospasm was classified into 4 grades: none; mild (minimal or mild change in vessel lumen); moderate (between mild and severe); and severe (threadlike and diffuse narrowing of vessels). The vessel diameters were measured bilaterally at M1 of the MCA and C5 (extradural pyramidal segment).

**Table 1. Characteristics of 20 Consecutive Patients With Thick Subarachnoid Hemorrhage (Fisher CT Group 3)^a**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female/male</td>
<td>12/8</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>-49</td>
<td>4</td>
</tr>
<tr>
<td>-59</td>
<td>3</td>
</tr>
<tr>
<td>-69</td>
<td>6</td>
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<tr>
<td>70+</td>
<td>7</td>
</tr>
<tr>
<td>Grade*</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>2, 3</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Subarachnoid blood on CT</td>
<td></td>
</tr>
<tr>
<td>Localized thick in unilateral SF</td>
<td>8</td>
</tr>
<tr>
<td>Localized thick in IHF</td>
<td>6</td>
</tr>
<tr>
<td>Diffuse thick</td>
<td>6</td>
</tr>
<tr>
<td>Ruptured aneurysm</td>
<td></td>
</tr>
<tr>
<td>ICPC</td>
<td>4</td>
</tr>
<tr>
<td>MCA</td>
<td>7</td>
</tr>
<tr>
<td>A1</td>
<td>1</td>
</tr>
<tr>
<td>AComA</td>
<td>6</td>
</tr>
<tr>
<td>AC distal</td>
<td>2</td>
</tr>
<tr>
<td>Day of surgery</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
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<tr>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Outcome†</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>11</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>5</td>
</tr>
<tr>
<td>Severely disability</td>
<td>1</td>
</tr>
<tr>
<td>Persistent vegetative</td>
<td>2</td>
</tr>
<tr>
<td>Death‡</td>
<td></td>
</tr>
</tbody>
</table>

ICPC indicates internal carotid posterior communicating; MCA, middle cerebral artery; AComA, anterior communicating artery; ACA, anterior cerebral artery; IHF, interhemispheric fissure; SF, Sylvian fissure. *Classification according to World Federation Neurological Society SAH grade.† Classification according to the Glasgow Outcome Scale.‡ Died from pulmonary embolism.

Statistical Analysis

All data were stored on a personal computer and analyzed using the Statview 4.5 software (Abacus Concepts). Comparison of M1/C5 ratios between preoperative and postoperative angiography was made using a paired t test. Probability values less than 0.05 were considered significant.
Results

In Vitro Study of NPRI for Humans

In the first 3 days, about 7% of the nicardipine was released; in the next 3 days, 46%. The amount of nicardipine released within the first 9 days was 62% of the total nicardipine content. After 6 days, the curve for cumulative release was less steep (Figure 1).

Effect of NPRI

Two pellets were implanted in 4 patients; 3 in 4; 4 in 4; 5 in 3; 8 in 1; 9 in 2; and 10 in 1. DIND and low-density areas were seen in a single patient (patient 1, Table 2). The other 19 patients presented neither DIND nor low-density areas. In angiography performed on days 7 to 12, 12 patients did not present cerebral vasospasm (Figure 3). Table 2 lists the 8 patients showing angiographical vasospasm. There was 1 patient with severe angiographical vasospasm that led to DIND and low-density areas on CT (patient 1, Table 2) (Figure 5). Moderate angiographical vasospasm was seen on the MCA at the pellet side (patient 3); the number of pellets was only 2, one of which was placed in the Sylvian fissure not adjacent to the MCA. In the other 6 patients, mild evidence of vasospasm was present on the arteries not adjacent to pellets, such as those on the other side of the craniotomy (patients 5 and 8) (Figure 4), more distal arteries (patients 4, 6, and 7), and the arteries not adjacent to pellets in the same cistern (patient 2). Vasospasm was not presented in any arteries to which NPRI were adjacently placed. Figure 2 shows the M1/C5 ratios in 13 SAH patients with unilateral placement of pellets on M1 (and M2). Patients received pellets adjacent to M1 in the Sylvian fissure with thick clots, where vasospasm related to DIND was highly expected. Pellets were not placed on the other side, mostly because of lack of a thick clot. The preoperative M1/C5 ratios were compared with those on days 7 to 12 in both sides. On the side of placement of pellets, the average ratio was significantly increased, whereas that of the other side did not change.

Discussion

In clinical reports of intrathecal nicardipine therapy, 2 mg of nicardipine was safely injected 3 times a day, or 4 mg twice a day, for an average of 10 days through cisternal drainage. The total amount of nicardipine used in humans (60 to 80 mg) was 8 to 10 times higher than that of the high-dose

TABLE 2. Eight Patients Showing Angiographical Vasospasm in 20 Consecutive Patients With Thick Subarachnoid Hemorrhage (Fisher CT Group 3)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Aneurysm</th>
<th>Craniotomy</th>
<th>Subarachnoid Clot</th>
<th>Placement of Pellets</th>
<th>Angiographical Vasospasm</th>
<th>Low-Density Area on CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>It A1</td>
<td>It frontotemporal</td>
<td>Diffuse thick</td>
<td>1-It IC, 1-rt IC, 1-IHF</td>
<td>Severe in bil M2, M3</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>AComA</td>
<td>midline bifrontal</td>
<td>Diffuse thick</td>
<td>1-It IC, 1-rt IC, 1-IHF</td>
<td>Mild in rt M2, bil A2</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>rt MCA</td>
<td>rt frontotemporal</td>
<td>Localized thick in rt SF</td>
<td>1-rt M1, 1-rt SF</td>
<td>Moderate in rt M1, M2, M3</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>rt MCA</td>
<td>rt frontotemporal</td>
<td>Localized thick in rt SF</td>
<td>1-rt IC, 2-rt M1, 1-rt M2</td>
<td>Mild in rt M3, bil A2</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>It ICPC</td>
<td>It frontotemporal</td>
<td>Diffuse thick</td>
<td>2-It M1, 2-It M2</td>
<td>Mild in rt M1, rt M2</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>AComA</td>
<td>midline bifrontal</td>
<td>Localized thick in IHF</td>
<td>1-rt A1, 2-bil A2</td>
<td>Mild in bil ACA distal</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>rt MCA</td>
<td>rt frontotemporal</td>
<td>Localized thick in rt SF</td>
<td>2-rt M1, 3-rt M2</td>
<td>Mild in rt M3</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>rt ICPC</td>
<td>rt frontotemporal</td>
<td>Localized thick in rt SF</td>
<td>2-rt M1, 2-rt M2, 1-rt M3</td>
<td>Mild in rt M1, It M2, rt A1</td>
<td>No</td>
</tr>
</tbody>
</table>

AComA indicates anterior communicating artery; MCA, middle cerebral artery; ICPC, internal carotid posterior communicating artery; ACA, anterior cerebral artery; DIND, delayed ischemic neurological deficits; IHF, interhemispheric fissure; SF, Sylvian fissure; rt, right; It, left; bil, bilateral.
group (8 mg) in our canine study. PLGA pellets with this amount of nicardipine can be implanted in human SAH patients. We applied 2 to 10 pellets (8 to 40 mg of nicardipine) in thick clot cisterns, and there was no vasospasm seen in the arteries adjacent to pellets. Less efficacy was found for arteries remote from the placement of pellets. This was expected from our in vitro result of high lipophilicity of nicardipine. Nicardipine was probably adsorbed to the clot and the arterial tissue near the pellets because of its high lipophilicity and did not affect the remote arteries, since nicardipine was not detected in any cerebrospinal fluid samples in our experimental model.7

No side effects were noted in SAH patients treated with NPRI, although chemical meningitis caused by PLGA was expected to some extent. PLGA implants showed no neuronal toxicity to brain tissue. The materials have a long history of usage in sutures and drug delivery systems, with a proven safety profile for parenteral applications.7,8 We expected that the disappearance of PLGA implants in the cistern would not take long in humans, similar to the results in dogs.7,8 Compared with the implantation of PLGA in the brain, inflammatory responses were milder, probably because of the cerebrospinal fluid circulation. Patients did not experience complications such as headache after injections of nicardipine, most likely because the drug works slowly and locally.

We stress that angiographical vasospasm did not appear on the arteries in the cisterns with thick clots, where vasospasm was highly expected, when pellets were placed adjacent to those arteries. Pre- and postoperative comparison revealed that the M1 was dilated instead of being contracted by the placement of pellets on M1 (and M2) in the Sylvian fissures with thick clots ($P=0.0146$). Blood localized in the subarachnoid space in sufficient amount at specific sites is the only important etiologic factor in vasospasm.9 Therefore vasospasm can be completely prevented in patients with localized thick clots. Although NPRI may not be indicated for patients with diffuse thick clot, NPRI could be placed in A1, the lower part of A2, M1, M2, and M3 on the side of craniotomy, A1 and M1 on the other side in patients with frontotemporal craniotomy, and bilateral A1, A2, M1, and M2 in patients with interhemispheric approach. When vasospasm in these parts of the arteries is prevented, DIND and/or infarction may not occur in most patients with diffuse

Figure 3. A 78-year-old female patient received 10 nicardipine prolonged-release implants along the right middle cerebral artery (MCA) (M1, M2, and M3) after clipping of right MCA aneurysm (preoperative angiography: middle, arrowhead). CT scan on admission showed thick hematoma in the right Sylvian fissure (top). Angiography on day 8 (bottom) shows no vasospasm, despite vasospasm being highly expected (arrows).

Figure 4. A 52-year-old male patient with localized thick clot in the right Sylvian fissure (top) from an right internal carotid posterior communicating artery aneurysm (preoperative angiography: middle, arrowhead). Two nicardipine prolonged-release implants were placed adjacent to M1, 2 to M2, and 1 to M3 after clipping through right frontotemporal craniotomy. The right middle cerebral artery (MCA) was slightly dilated on day 12 (bottom left, arrows), whereas the right anterior cerebral artery (A1) and left MCA showed mild evidence of vasospasm (bottom right, arrowheads). (Patient 8, Table 2).
thick clots. We believe it is possible that the infarctions in our series (patient 1, Table 2) could have been prevented if we had placed more pellets in appropriate cisterns.

Prevention or relief of narrowing of large cerebral arteries by calcium antagonists is controversial in clinical series of patients with SAH regardless of the route of administration, although treatment of vasospasm with calcium antagonists may constitute a reasonable approach in patients with SAH.14 A significant improvement in outcome related to DIND has generally not been associated with a reduction in angiographic vasospasm, which is explained by some beneficial influence due to neuronal protection from ischemia. It is also possible that calcium antagonists act principally on the smaller resistance vessels not visualized on angiography. Vasospasm may not be prevented by calcium channel blockers that regulate the influx of calcium ions through the cell membrane but are not involved in the intracellular regulatory mechanism of calcium.14 Complete prevention of vasospasm of conducting arteries by NPRI is in direct conflict with the above hypotheses. Our results suggested that nicardipine can prevent vasospasm completely if an appropriate concentration of nicardipine is maintained in the surrounding cistern by using the newly developed drug delivery system.7

This is probably explained by the mechanism that higher concentration of nicardipine might antagonize the Ca\(^{2+}\) influx through the receptor-operated Ca\(^{2+}\) channels as well as the voltage-dependent Ca\(^{2+}\) channels.15

Conclusions

Vasospasm was completely prevented in the arteries in cisterns with thick clots, where vasospasm was highly expected, by placing NPRI adjacent to the arteries during surgery. NPRI is an effective, simple, and safe prophylactic treatment for vasospasm when early craniotomy is chosen for obliterating ruptured aneurysms. Use of NPRI might be a promising approach for preventing vasospasm.

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References

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