Since its recognition more than 40 years ago, cerebral arterial vasospasm—exclusive of the initial hemorrhage—has remained a leading cause of morbidity and mortality in patients with ruptured intracranial aneurysms. At this time, there is little doubt that the presence and amount of blood within the basal subarachnoid cisterns foretell the development and degree of subsequent vasospasm. Angiographically demonstrated vasospasm has a typical temporal course, with onset occurring 3 to 5 days following hemorrhage, maximum narrowing 5 to 14 days after hemorrhage, and gradual resolution over 2 to 4 weeks posthemorrhage. Numerous therapies with well-defined risks have been used to prevent and treat vasospasm, resulting in variable success rates. Agents that have proved to reduce the relative risk of angiographically demonstrated vasospasm, when given intravenously, have failed to improve overall outcome.

Efficacy of controlled-release papaverine pellets in preventing symptomatic cerebral vasospasm

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Object. Vasospasm as a complication of subarachnoid hemorrhage is a major concern in clinical practice. The systemic drugs in current use are of limited value. Topical, intrathecal, or intraarterial papaverine administered during surgical or angiographic procedures is a potent vasodilating drug; however, hypotension limits its systemic application. Local application of papaverine in a biodegradable controlled- or sustained-release matrix is proposed for vasospasm prophylaxis to be used in patients scheduled for aneurysm surgery.

Methods. Controlled-release papaverine (PapaCR) drug pellets were prepared using the biodegradable aliphatic polyester poly(DL-lactide-co-glycolide) as the carrier matrix. In vitro tests were performed to determine drug kinetics. One hundred seventeen patients, 73 assigned to the control group and 44 assigned to the PapaCR-treated group, participated in this study. Patients who were deemed to be at high risk for the development of vasospasm were selected to participate in the study. During aneurysm surgery, drug pellets were placed in cisterns over arterial segments. In two patients, cerebrospinal fluid was sampled every 6 hours for the first 5 days through a lumbar catheter that had been inserted at the beginning of aneurysm surgery. The incidence of clinical vasospasm and Glasgow Outcome Scale scores in the patients were evaluated statistically.

The results of in vitro studies showed that effective local concentrations of papaverine could be maintained for more than 10 days. The first-degree drug-release profile was demonstrated using this design. In clinical studies no adverse effects due to the drug were seen. The PapaCR effectively prevented development of clinical vasospasm, and outcome scores were significantly better in patients in the treated group.

Conclusions. Local application of controlled- or sustained-release papaverine can be safely used in preventing vasospasm.

Key Words • vasospasm • drug delivery • papaverine

Abbreviations used in this paper: CSF = cerebrospinal fluid; CT = computerized tomography; GOS = Glasgow Outcome Scale; PapaCR = controlled-release papaverine; SAH = subarachnoid hemorrhage.
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Papaverine, a biodegradable drug for the treatment of vasospasm, was prepared in this study. Papaverine HCl (158 mg) and the polymer (1070 mg) (approximately 15:100 wt/wt) were dissolved in 5 ml dichloromethane and were continuously stirred until excess solvent had evaporated and a kneadable thick paste had been obtained. This mixture was then packed in Teflon molds preheated to 90˚C and kept at this temperature for 2 hours. To produce the final shape, 600 kg/cm² of pressure was applied using a stainless-steel cylinder while maintaining the temperature at 90˚C. After they had been cooled to room temperature, the resultant drug pellets appeared cylindrical in shape with a 4-mm diameter, a 2-mm height, and an average weight of 76.8 ± 4.1 mg. Each pellet contained 7.2 ± 1.8 mg of papaverine. The drug pellets were kept in a desiccation bottle at 18˚C until their use. Drug pellets were weighed, packed, and sterilized in dry air at 110˚C for 2 hours just before their use.

Clinical Material and Methods
Preparation of Sustained-Release Drugs
High-molecular-weight poly(DL-lactide-co-glycolide), a biodegradable carrier matrix (85:15 concentration, average molecular weight 90,100; Sigma Chemical Co., St. Louis, MO) was chosen for use in this experiment. Papaverine HCl (158 mg) and the polymer (1070 mg) (approximately 15:100 wt/wt) were dissolved in 5 ml dichloromethane and were continuously stirred until excess solvent had evaporated and a kneadable thick paste had been obtained. A mixture was then packed in Teflon molds preheated to 90˚C and kept at this temperature for 2 hours. To produce the final shape, 600 kg/cm² of pressure was applied using a stainless-steel cylinder while maintaining the temperature at 90˚C. After they had been cooled to room temperature, the resultant drug pellets appeared cylindrical in shape with a 4-mm diameter, a 2-mm height, and an average weight of 76.8 ± 4.1 mg. Each pellet contained 7.2 ± 1.8 mg of papaverine. The drug pellets were kept in a desiccation bottle at 18˚C until their use. Drug pellets were weighed, packed, and sterilized in dry air at 110˚C for 2 hours just before their use.

In Vitro Dissolution Studies
Dissolution tests were performed in a temperature-controlled chamber at 37˚C. Artificial CSF was used to simulate in vivo conditions. To prepare the artificial CSF, sodium chloride (7.25 g), potassium chloride (0.28 g), potassium dihydrogen phosphate (0.170 g), magnesium sulfate (MgSO4•7H2O, 0.5 g), calcium chloride (CaCl2•2H2O, 0.29 g), sodium bicarbonate (2.2 g), and dextrose (1.8 g) were added to deionized water to make a 1-L solution. This solution was purged by using a 5% CO2/95% O2 (vol/vol) gas mixture. All chemicals were obtained at their highest purity formulations and used as purchased.

Papaverine-loaded pellets (PapaCR) were put into a piece of gauze and placed at the bottom of a 75-ml flask that had been filled with artificial CSF, after which the flask was placed in a large beaker (Fig. 1). Artificial CSF flow was maintained at a rate of 0.25 ml/minute; overflow was sampled every hour for the 1st hour and every 6 hours thereafter for 15 days. Papaverine concentrations were measured using an ultraviolet spectrophotometer at 237 nm (model UV 160A double-beam spectrophotometer; Shimadzu, Kyoto, Japan). Calibration solutions were prepared with concentrations ranging from 2.5 × 10⁻³ to 2.5 × 10⁻¹ nM, and calibration curves were obtained at the beginning of each session.

Patient Selection
This prospective study was conducted in patients who were admitted to our clinic from September 1995 to May 1998 in whom angiography revealed an aneurysm. The protocol for this study was approved by the local ethics council, and written consent was obtained from patients or their first-degree relatives. Patients who were in the high-risk group for the development of vasospasm during the postoperative period (Fisher Grade 3 SAH on CT scan or angiographic or perioperative evidence of vasospasm) were included. For use as a control group, we included data from patients who did not take part in the study group but underwent surgery performed by the same surgical team and shared a similar distribution of age, day of surgery, clinical grade, and Fisher grade. During surgery, the sylvian, carotic, olfactory, lamina terminalis, and chiasmatic cisterns were routinely dissected and blood clots were aspirated as much as possible. Four to six pellets, each carrying 7.2 ± 1.8 mg of papaverine, were placed directly on media and carotid bifurcations, lateral to the carotid artery, on the posterior communicating and choroidal arteries, and on the anterior cerebral and anterior communicating arteries. A small piece of gelatin sponge was used to hold the drug disk in its place whenever necessary. Placements of the drug pellets were recorded on the patient chart. In patients with anterior communicating artery aneurysms, the opposite carotid and proximal sylvian cisterns were opened and a drug pellet was placed there too. An average of 38.4 ± 2.4 mg papaverine was used in each patient.

Development of focal signs and deterioration of consciousness during the first 2 weeks post-SAH were accepted as clinical signs of vasospasm. Glasgow Outcome Scale scores were assigned to patients following their 1-month follow-up examination.

Exclusion From Statistical Evaluations
Not all cases were used for statistical evaluation. Cases were excluded for several reasons. Surgical complications such as early rupture of aneurysm or the need for a long-term temporary clip application were deemed to be exclusion criteria. Incidental cases and cases in which patients did not undergo surgery within 2 weeks (14 days inclusive) post-SAH were accepted as late cases for review of vasospasm development, but were not taken into consideration for statistical analysis. Also excluded were patients with systemic complications but no abnormal findings on CT scans and those with cranial complications documented by CT scans.
Patient data were transferred to a spreadsheet (Excel 97; Microsoft Corp., Redmond, WA), and statistical evaluations of results were performed using commercially available statistical software programs (Matlab version 4.2 and Statistics Toolbox; The MathWorks, Inc., Natick, MA).

In two patients from the study group, lumbar drainage was applied preoperatively to relax the brain during surgery. In these two patients, CSF samples were obtained every 6 hours for 5 days to follow the in vivo release of the drug.

Results

In Vitro Dissolution Studies

Drug pellets prepared in one batch in the manner described earlier displayed identical release characteristics. There was an initial burst of drug discharge, followed by a steady release of papaverine for nearly 15 days (Fig. 2A). Statistical analysis demonstrated a second-degree polynomial fit for the cumulative drug release ($f = y_0 + ax + bx^2$, $r = 0.99869492$, $y_0 = 110 \pm 43$ [$p = 0.0135$], $a = 45 \pm 0.6$ [$p < 0.0001$], $b = -0.071 \pm 0.0015$ [$p < 0.0001$]; Fig. 2B). A first-degree kinetics—that is, a derivative of the cumulative drug-release curve for the released amount per unit time—was obtained.

In Vivo Dissolution Study

Papaverine concentrations measured from CSF samples obtained through a lumbar drainage catheter every 6 hours for 5 days were plotted on the same graph (Fig. 3). Sampling was discontinued because lumbar drainage was stopped on the 5th day. In accordance with the in vitro studies, an initial burst of drug was observed, followed by a steady discharge for 5 days.

Clinical Studies

One hundred seventeen patients, 73 assigned to the control and 44 assigned to the PapaCR treatment group, participated in this study. Fifteen patients from the PapaCR treatment group and four from the control group were excluded in accordance with the aforementioned exclusion criteria. None of the aneurysms was mycotic or traumatic. Fifty male and 48 female patients with a mean age of 49 ± 11 years were included. The control group consisted of 35 male patients with a mean age of 46 ± 11 years and 34 female patients with a mean age of 53 ± 12 years. The treatment study group was composed of 15 male patients with a mean age of 48 ± 9 years and 14 female patients with a mean age of 48 ± 13 years. Patients in both groups were treated under euvoletic conditions and, with the exception of standard medications, no specific vasospasm protection drugs such as calcium channel blockers were administered. Patients selected into the control and treatment groups were first tested for their distributions. Linear quantile–quantile plots of aneurysm location, Fisher grades, patient age, and timing of surgery for the two groups demonstrated that both groups shared the same distribution (Fig. 4). The means of Fisher and Yasargil grades, timing of surgery, aneurysm location, patient...
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ages, and outcome scores (GOS scores) in patients in the control group and those in the study group were compared using t-tests. Some of the results are given as box plots (Fig. 5), and the distribution of patients according to aneurysm location is shown in a bar graph (Fig. 6). Statistical tests supported the contention that the control and study groups were identical except for vasospasm incidence and outcome scores ($p < 0.001$). There was strong statistical evidence (that is, a very low significance level = $8.6 \times 10^{-4}$) of significant differences in patient outcomes between the control and treatment groups. In other words, clinical vasospasm was observed in only one patient in the PapaCR-treated group compared with 34 patients in the control group (Figs. 7–9). When outcome scores were taken into consideration, average GOS scores were $4.93 \pm 0.05$ in the PapaCR-treated group and $3.84 \pm 1.63$ in the control group.

Discussion

Vasospasm is a major complication of SAH, and sever-
al therapies have been tried to prevent it.$^{4,12,16,23}$ The problem with treatment arises because vasospasm occurs in a local vascular segment close to the primary site of the ruptured aneurysm, and systemic drugs have to be administered at high doses to obtain effective concentration in this region. Despite their known complications, invasive methods such as balloon angioplasty and intraluminal papaverine injection have been used as alternative vasospasm treatments; however, they cannot be used for pro-

**Fig. 4.** Quantile-quantile plots of timing of operation (date post-SAH; A) and patient age (B) distribution of patients. Linearity of the plots confirms that control and treatment groups shared similar distribution.

**Fig. 5.** Box plots demonstrating Fisher grades (A), timing of operation (B), and patient age (C) distributions of patients in the control and treatment groups.
phylaxis. Intrathecal administration of drugs has been proposed to avoid systemic side effects, but it is not feasible to maintain effective concentrations when using intermittent administration, and the continuous infusion method is inherently open to the possibility of infections and complications. Besides, vasospasm usually occurs in distal arteries and, hence, a high drug concentration around the cranial base would not effectively spread to distal branches to prevent vasospasm.

Implantable controlled- or prolonged-release forms of drugs are used to obtain high concentrations while avoiding systemic side effects. Several preliminary experimental studies have been reported in which spasm-preventing drugs were delivered in a controlled-release form. We chose papaverine for the vasodilating drug because it is readily available and its usage during vascular surgery is accepted as a safe and effective method to prevent vasospasm. As mentioned earlier, however, its topical use as a preventive medication is limited by its transient effect. In a canine SAH model, placement of drug pellets in the cisterns proved to be effective against vasospasm. The authors of the aforementioned study reported that drug pellets should be placed as close as possible to the arteries at risk. Our findings confirm this view: drug pellets placed directly on the distal arteries effectively prevented the development of clinical vasospasm in all but one case.

We have tested several different biodegradable drug-carrying matrices in vitro. We decided to use poly(DL-lactide-co-glycolide) because of its release characteristics and well-documented human applications. In our series, we saw no adverse effects caused by the use of poly(DL-lactide-co-glycolide). There was only one incidence of minor complication related to papaverine, in which the patient was allergic to analgesic drugs. In that case, there was a cross-sensitization to papaverine and a regimen of corticosteroids and antihistamines was administered for 2 weeks.

In the worst-case scenario, the drug may dissolve immediately. In this event the 38.4 mg of papaverine implanted in each patient would correspond to the amount safely given intrathecally without causing significant hypotension.

In our study, clinical signs of vasospasm appearing during a short postoperative period and the patient’s GOS scores at the 1-month follow-up examination were taken as evaluation criteria. All patients underwent postoperative CT examinations. Repeated angiography was not required to confirm vasospasm; instead, after excluding other causes, the timing, development rate, and nature of the symptoms were used in the diagnosis of clinical vasospasm. The results in our patient treatment group were in favor of PapaCR effectiveness. In our control group, the clinical vasospasm rate was significantly higher than that found in our general aneurysm population (78% compared with 32%, respectively). This finding might result from our selection criteria. In general, to avoid vasospasm, we prefer to delay surgery for 2 weeks if we are unable to operate during the early stage. On the other hand, in this study, patients who received PapaCR underwent surgery around their 6th day post-SAH, and the matching control patients were selected because they had a similar distribution of patient age, Fisher grade, and timing of operation. Patients who underwent surgery after 2 weeks post-SAH were excluded from the study. The similarity in distributions between the two groups was further confirmed by
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Fig. 8. Histograms displaying the relationship between presence of vasospasm and Fisher grades in control (A) and treatment (B) groups. Spasm + = vasospasm; spasm − = no vasospasm.

Fig. 9. Histograms demonstrating patient distribution according to the GOS scores. In the treatment group (B), all patients fully recovered (GOS score of 5), except two with minor deficits (GOS score of 4).

Conclusions

When placed on arteries during vascular surgery, pellets that release papaverine for 2 weeks can effectively prevent the development of vasospasm with no noticeable complication. More studies on larger series with placebo controls should be planned before such drugs are widely used.

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