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Intraarterial Infusion of Papaverine in Experimental Cerebral Vasospasm

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PURPOSE: To determine the effectiveness of intraarterial infusion of papaverine hydrochloride (PPV) in an experimental model of cerebral vasospasm and to measure the mean blood flow velocity of the middle cerebral artery (MCA). **METHODS:** Seven Japanese monkeys were divided into three groups: those studied 3 days after surgery (the third-day group, $n = 3$); those studied 7 days after surgery (the seventh-day group, $n = 3$); and a control group ($n = 1$). Vasospasm was induced in the experimental groups by placing a blood clot in the subarachnoid space around the top of the internal carotid siphon. PPV (5 mg/kg) was infused (over 60 minutes) into the internal carotid artery (ICA). The vascular diameters of the ICA and MCA were measured on angiograms before and after infusion. The mean blood flow velocity in the MCA was measured on transcranial Doppler sonograms before and 24 hours after infusion. After fixation, the MCA was dissected out, stained, and examined microscopically. **RESULTS:** After vasospasm induction, both arteries were narrowed more than 30% in the third-day group and more than 50% in the seventh-day group. After PPV infusion in both groups, vascular dilatation of about 20% was seen. The mean increase in blood flow velocity in the third-day group (30%) was smaller than in the seventh-day group (70%). The mean blood flow velocity in the MCA decreased by about 30% in both groups, but increased again after 24 hours nearly to the level before PPV infusion. The intimal layer was more corrugated in the seventh-day group, and hypertrophy in the smooth muscle layer was also seen. Clinical examination showed no neurologic deficit in the third-day group 24 hours after PPV infusion; neurologic deficits were observed in the seventh-day group. **CONCLUSION:** PPV infusion may be more effective in early stages of vasospasm when vascular walls have fewer histologic changes.

Index terms: Drugs, intraarterial infusion; Vasospasm; Animal studies

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Intracranial arterial vasospasm caused by subarachnoid hemorrhage (SAH) is one of the major causes of morbidity and mortality after rupture of intracranial aneurysms (1–4). Angiographic arterial narrowing is observed in 40% to 70% of patients after SAH (5); clinical vasospasm is seen in 10% to 30% of patients with SAH (5, 6). If not treated, the vasospasm

causes major stroke or death in approximately 50% of patients (5, 6). Hypertensive hypervolemic hemodilutional therapy and the use of calcium channel blockers may be effective in the treatment of vasospasm (5). However, approximately 40% of patients with ischemic deficits caused by vasospasm do not respond to these treatments (5, 6). In this group of patients, many treatment trials have been carried out, but none has been fully effective (7–11).

Percutaneous transluminal angioplasty has recently been performed in selective cases as an effective method of treatment for symptomatic vasospasm (12–18). However, these balloon catheters have limited ability to enter selectively narrowed branches at a bifurcation or trifurcation of major branches, such as the distal middle cerebral artery (MCA), or of sharply angled vessels, such as the anterior cerebral artery

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(ACA) (13, 19). Papaverine hydrochloride (PPV), a potent vasodilator, has been used for the treatment of clinical and experimental cerebral vasospasm by intravenous or intrathecal administration (20, 21). Recently, PPV has also been administered intraarterially for the treatment of vasospasm (22–27). However, many of these attempts have not shown significant therapeutic effects. Recent advances in interventional neuroradiology have made it possible to treat vasospasm by delivering the vasodilating agents directly to the spastic intracranial artery.

In the present study, PPV was infused intraarterially in an experimental model of cerebral vasospasm. The effectiveness of the therapy was evaluated by measuring the blood vessel diameters of the internal carotid artery (ICA) and the MCA on angiograms and the mean blood flow velocity of the MCA. The histologic and clinical changes after PPV infusion were also evaluated.

Materials and Methods

All procedures were approved by the animal experimental committee of our institution.

Preparation of Experimental Animals

Seven male Japanese monkeys (*Macaca fuscata*) weighing 12 to 15 kg were divided into three groups: a group studied 3 days after surgically induced vasospasm (the third-day group, $n = 3$); a group studied 7 days after surgery (the seventh-day group, $n = 3$); and one monkey in whom no surgery was performed (the control group, $n = 1$). The animals were anesthetized by intramuscular administration of ketamine chloride (6 to 10 mg/kg) and atropine sulfate (1 mg/kg). They were then intubated transbronchially, and after stabilization by intravenous injection of pancuronium bromide (0.1 mg/kg), mechanical respiration was continued with room air.

Angiography

After exposing the femoral artery, a 4.5F catheter was inserted and advanced into the proximal ICA under fluoroscopic monitoring with the use of a 0.035-inch guidewire. Baseline and serial magnification angiograms were obtained before and after PPV infusion with the injection of 4 mL of nonionic contrast medium of 300 mg I/mL. The before and after PPV infusion angiographic studies were performed with the use of a 6.0F nylon catheter placed in the proximal ICA.

Induction of Vasospasm

Vasospasm was induced according to the method reported by Espinosa et al (28). Frontotemporal craniotomy

(right side) was performed and the sylvian fissure was split under an operating microscope. After identifying the ICA, MCA, and ACA, the subarachnoid space was exposed. The cerebrospinal fluid was drained and an autologous blood clot, prepared preoperatively from 5 mL of blood, was placed in the basal cistern. The dura was closed in a watertight fashion and the incision was closed in layers.

Intraarterial Infusion of Papaverine

PPV treatment was instituted after vasospasm was documented by diagnostic angiography. Infusion of PPV was performed with a Tracker-18 catheter (Target Therapeutics, Fremont, Calif) via a transfemoral guiding catheter placed in the terminal part of the right ICA (supraclinoid portion). Continuous intraarterial heparin administration was used to prevent thrombosis during infusion. PPV was administered only on the side in which clot-induced vasospasm was confirmed. Vasospasm on the opposite side was either almost invisible or less apparent than on the operated side. Papaverine (5 mg/kg) was mixed with 20 to 30 mL normal saline at concentrations ranging from 2.5 to 3.0 mg/mL, with total doses ranging from 60 to 80 mg. These concentrations were chosen on the basis of those routinely used clinically in our hospital. The amount of saline was determined by considering the weight of the animal so that a concentration equivalent to that in humans was obtained. Since the animals weighed only about 10 kg, less saline was used to avoid volume overload. In all animals, papaverine was given by slow continuous pump infusion for about 60 minutes. During administration, the arterial blood pressure was monitored. All experimental animals were examined neurologically before and after SAH, before and immediately after PPV infusion, and 24 hours after PPV infusion.

Measurements of Blood Vessel Diameter and Blood Flow Velocity

Blood vessel diameter before induction of vasospasm was specified as 100%. The percentage of change in blood vessel diameter of the main arteries (ICA and MCA) before and immediately after PPV infusion was calculated. Luminal dimensions were compared with baseline after vasospasm induction and before and after PPV infusion. The distances between tangent lines drawn across the C1 and M1 vessels (Fig 1) were measured independently by two radiologists both before and after treatment. The changes in the mean blood flow velocities of the MCA before and immediately after angiography and 24 hours after PPV infusion were measured with the use of transcranial Doppler sonography. Follow-up measurements of the lumen 24 hours after PPV infusion could not be performed.

After all experimental procedures, paralysis was reversed with intravenous injection of neostigmine methylsulfate (0.6 mg/kg) and atropine sulfate (0.02 mg/kg). Once spontaneous respiration was recovered, intubation was discontinued. An overdose of sodium pentobarbital

was injected intravenously to kill the animals for histologic study.

Histologic Study

After baseline angiography, one of the monkeys was killed for use as a control to study the normal structure of the vascular walls. The other six monkeys (the third-day group and the seventh-day group) were killed 24 hours after PPV infusion to study histologic changes in the vascular walls.

For light microscopic study, 500 mL of 10% formaldehyde solution was infused through the catheter into the brachiocephalic artery under 150 cm H₂O pressure. The brain with its vessels was removed. The vessels were then carefully dissected free. The horizontal portion of the right MCA was examined histologically. The blood vessels were sampled from roughly the same portion of all animals. The vessels were sectioned, stained by hematoxylin-eosin, and

examined under a light microscope. The specimens were examined by a pathologist and two neurosurgeons.

Results

Angiographic Findings

The baseline carotid angiograms obtained in all monkeys showed the arrangement and course of the ICA, MCA, and ACA to be much like that in humans (Figs 2A and 3A). In the second angiogram, taken 3 days after the vasospastic model was prepared, all of the main ipsilateral arteries looked remarkably narrow (Fig 2B). The percentages of change in vessel diameter in each group after induction of vasospasm and infusion of PPV are listed in Tables 1 and 2. Measurement and calculation of the vascular lumina of vasospastic vessels revealed about 30% decrease in diameter in the third-day group compared with that of baseline (Table 1). In the seventh-day group (Fig 3B), the blood vessels were found to be more severely narrowed relative to the third-day group (Fig 2B). Measurement and calculation of the vascular lumina of vasospastic vessels in the seventh-day group revealed about 50% decrease in diameter compared with that of baseline (Table 2). Although the spastic blood vessels were dilated after PPV infusion, the ACA and MCA in the seventh-day group were less dilated than those in the third-day group (Figs 2C and 3C and Tables 1 and 2). Evaluation of the ACA was precluded from this study because blood streaming is possible from the opposite side by way of the anterior communicating artery.



Fig 1. Angiogram shows location of vascular diameter measurements of C1, the supraclinoid portion of the ICA, and M1, the sphenoidal portion of the middle carotid artery. Curved arrows indicate measurement location of C1 and straight arrows indicate measurement location of M1.

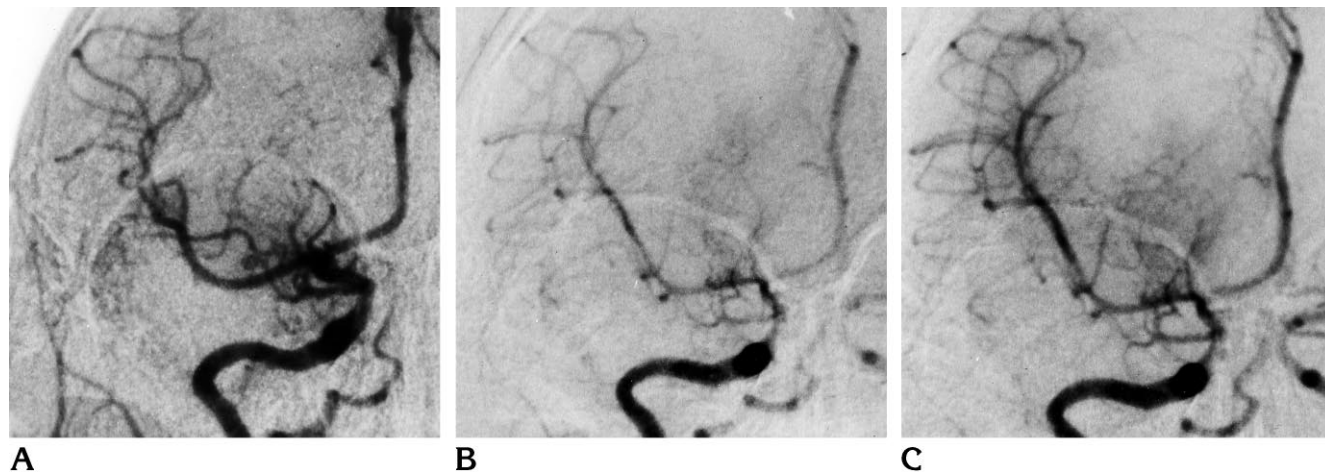


Fig 2. Angiograms of an animal from third-day group at baseline (A), 3 days after induction of SAH (B), and after PPV infusion (C).

Mean Flow Velocity as Determined by Transcranial Doppler Sonographic Findings

In both the third-day and the seventh-day groups, mean blood flow velocity was observed to be increased as compared with that before vasospasm induction but decreased rapidly after PPV administration. The mean blood flow velocity and blood pressure changes in each group before vasospasm induction and after PPV infusion are listed in Tables 3 and 4. Immediately after PPV infusion, the animals had a

mild blood pressure drop of 10 to 20 mm Hg. Twenty-four hours after infusion, mean blood flow velocity increased again in both groups, although the rate of increase in the third-day group was less than in the seventh-day group (Fig 4).

Clinical Evaluation

All animals in the group studied 3 days after SAH induction showed only slight deterioration

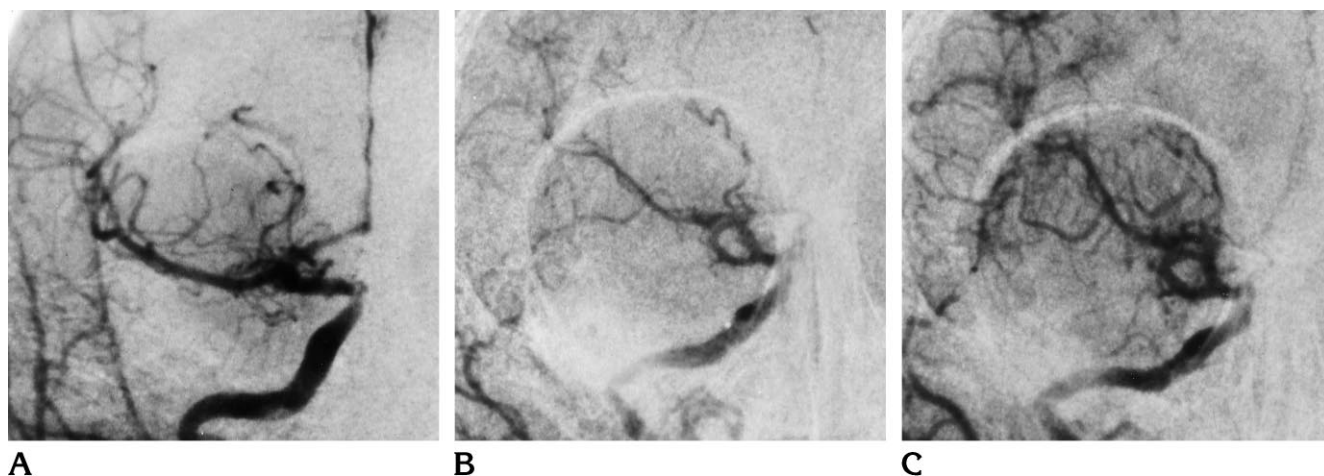


Fig 3. Angiograms of an animal from seventh-day group at baseline (A), 7 days after induction of SAH (B), and after PPV infusion (C).

TABLE 1: Percentage of change in vascular diameter in third-day group

Animal	C1 of ICA		M1 of MCA	
	After Vasospasm	After PPV Injection	After Vasospasm	After PPV Injection
1	-30	-10	-32	-8
2	-28	-9	-30	-6
3	-38	-17	-43	-8
Mean	-32	-12	-35	-8

Note—C1 indicates supraclinoid portion; ICA, internal carotid artery; M1, sphenoidal portion; and MCA, middle cerebral artery. The blood vessel diameter before the induction of vasospasm was specified as 100%.

TABLE 2: Percentage of change in vascular diameter in seventh-day group

Animal	C1 of ICA		M1 of MCA	
	After Vasospasm	After PPV Injection	After Vasospasm	After PPV Injection
1	-57	-30	-55	-29
2	-51	-34	-48	-23
3	-57	-35	-53	-32
Mean	-55	-33	-52	-28

Note—C1 indicates supraclinoid portion; ICA, internal carotid artery; M1, sphenoidal portion; and MCA, middle cerebral artery. The blood vessel diameter before the induction of vasospasm was specified as 100%.

TABLE 3: Change in mean blood flow velocity and blood pressure in third-day group

Animal	MFV (cm/s) and BP (mm Hg)		
	Before PPV	After PPV	After 24 hr
1	30 132/71	18 109/77	36
2	28 127/72	22 113/87	32
3	40 111/86	32 101/68	38
Mean	32.7	24	35.3

Note—MFV indicates mean blood flow velocity; BP, blood pressure.

TABLE 4: Change in mean blood flow velocity and blood pressure in seventh-day group

Animal	MFV (cm/s) and BP (mm Hg)		
	Before PPV	After PPV	After 24 hr
1	60 115/89	32 113/72	60
2	56 112/89	40 109/77	54
3	60 112/89	44 111/72	55
Mean	58.7	38.7	56.3

Note—MFV indicates mean blood flow velocity; BP, blood pressure.

of consciousness and reduction in appetite. The level of consciousness improved after PPV infusion. After 24 hours, no animal showed evidence of neurologic deficit. All animals in the group studied 7 days after SAH induction showed disturbance of consciousness and reduction in activity and appetite, with recovery occurring immediately after PPV infusion. However, 24 hours later, two animals had contralateral hemiparesis, and one had a slight neurologic deficit.

Histologic Findings

The M1 portion of the right MCA was examined in all animals. As seen under the light microscope, the control MCA after staining with hematoxylin-eosin (Fig 4A) showed no pathologic changes: the monolayer of endothelial cells with its oval configuration was arranged in normal fashion on the surface of the lumina; the internal elastic lamina showed a smooth and curved course without localized corrugation; and monocytes in the media showed regular arrangement with long, oval nuclei.

In the arterial wall of the spastic MCA on day

3 after vasospasm induction, slight corrugation of the intima and elastic lamina was noted (Fig 4B). In the seventh-day group, however, marked corrugation of the intima and elastic lamina was noted (Fig 4C). In the seventh-day group (Fig 4C), the endothelial cells on the intimal surface showed swelling with a rounded appearance, the medial layer showed marked thickening, and the smooth muscle cells were short and thick. Moreover, inflammatory changes were suggested in the adventitia in the seventh-day group, whereas no inflammatory cells or infiltration were observed in the intima and media in either of the experimental groups or of the control animal.

Discussion

Percutaneous transluminal angioplasty has contributed greatly to progress in the treatment of symptomatic vasospasm. In 1984, Zubkov et al (29) reported such treatment of symptomatic vasospasm after SAH. Since their report, many investigations into the efficacy of percutaneous transluminal angioplasty for symptomatic vasospasm due to SAH have been carried out (13–18). However, the balloon catheters currently available have limited ability to reach distally affected vessels or vessels whose origins are short and sharply angled.

Recently, cerebral vasospasm after SAH has been treated with PPV administered intraarterially, and the clinical effectiveness of such therapy has been reported (22–27). Kaku et al (22) treated 10 patients by using a combination of percutaneous transluminal angioplasty followed by superselective infusion of PPV with the dose ranging from 6 to 20 mg plus nicardipine or urokinase. Although eight (80%) of 10 patients showed early improvement, it is not possible to delineate the effect of PPV alone from this study because of the combination therapy. Kassel et al (23) treated 12 patients on 14 occasions, empirically deciding on a dose of approximately 300 mg of PPV given over 1 hour. Angiographic improvement was seen with eight (57%) of the 14 treatments, and dramatic reversal of profound neurologic deficit was seen in three (25%) of the 12 patients (23). Clouston et al (26) treated 14 patients on 19 occasions, using a PPV dose ranging from 150 to 600 mg (exceeding 400 mg on eight occasions). Angiographic improvement occurred in 18 (95%) of 19 treatments, and dramatic, acute clinical improve-

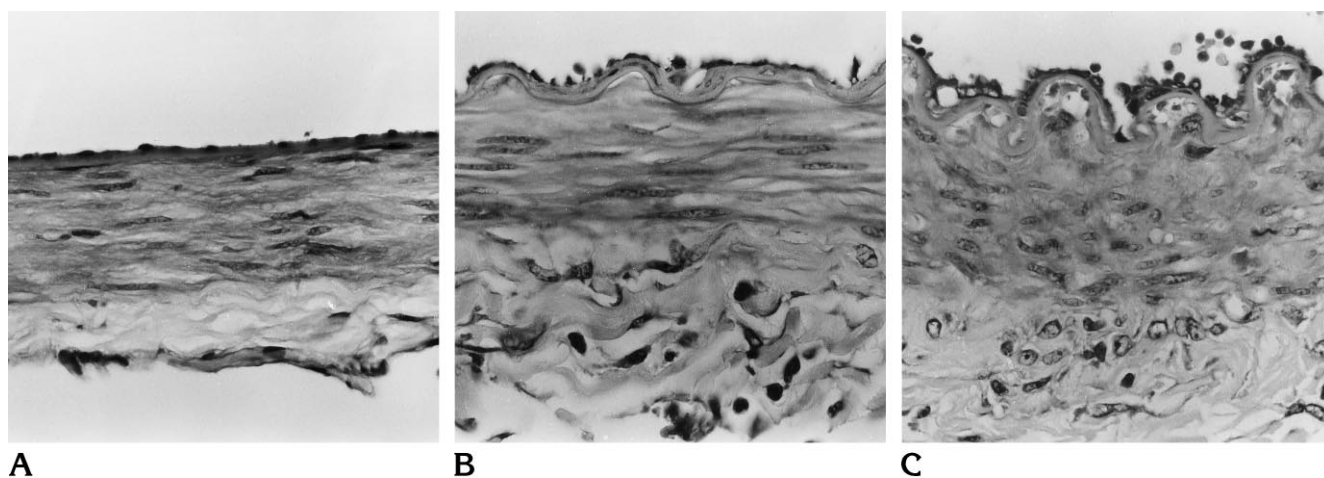


Fig 4. Light micrographs of the MCA (hematoxylin-eosin, original magnification $\times 40$).

A, Normal control animal. Medial layer shows a regular pattern. The internal elastic lamina does not show corrugation. Endothelial cells are seen in the intimal surface.

B, Animal from third-day group. The internal elastic lamina shows corrugation and the adventitial layer shows thickening without inflammatory cells.

C, Animal from seventh-day group. The spastic vessels show marked corrugation of intimal and internal elastic lamina. The endothelial cells show swelling. The medial and adventitial layers are thickened.

ment was seen in seven (50%) of 14 patients. The reasons for the ineffectiveness of PPV therapy in 20% to 50% of the cases in the reported studies (22–27) have not been identified.

PPV is an alkaloid of the opium group well known to cause vasodilatation of cerebral arteries through a direct action on smooth muscle, and to reduce the constriction of smooth muscle produced by a wide variety of stimuli (30). It is widely used to reverse mechanically induced local cerebral vasospasm (31). Although the exact molecular mechanism of action of PPV on smooth muscle is unknown, this drug is thought to act by inhibiting both cyclic adenosine monophosphate (cAMP) and cyclic guanosine 3',5'-monophosphate (cGMP) phosphodiesterase activity in smooth muscle cells and by increasing intracellular cAMP and cGMP turnover (32).

Tsukahara et al (33), using *in vitro* experiments, showed that a dose of 10^{-4} mol/L of PPV consistently induced a maximum amount of vasodilatation of control and spastic human arteries following SAH. Also, Kassel et al (23) reported that the optimum dose and duration of PPV infusion was 300 mg/100 mL infused over 60 minutes. On the basis of the results of the above studies, we used a 0.3% to 0.4% dose of PPV.

Bevan et al (34) were able to demonstrate angiographic narrowing of the MCA and ACA 5 days after experimental SAH with *in vitro* studies in monkeys. In that study, there was histo-

logic evidence of marked arterial wall damage, and loss of vasoconstrictive capacity was considered an index of cellular dysfunction. The greatest narrowing was associated with the greatest cellular change.

In the present experimental study with Japanese monkeys, we examined the angiographic and histologic changes in vasospastic vessels after intraarterial infusion of PPV. The Japanese monkeys were used as an experimental model because the course and distribution of intracranial vessels in these animals are similar to those in humans. We selected the third day and the seventh day after operation because there are some experimental data showing that cerebral arteries are resistant to intravenous or intraarterial vasodilator treatment 5 to 7 days after experimental SAH (21, 35, 36).

PPV was infused intraarterially into the contracted blood vessels, and the main arteries were observed to dilate. The arteries were less dilated in the group examined 7 days after SAH was induced than in the group examined 3 days after SAH induction, when the contracted blood vessels were less histologically abnormal. These results suggest that the smooth muscle layer of the media is more dilated 3 days after SAH than 7 days after. Contractility and elasticity of the blood vessels decrease with time, being less responsive to PPV 7 days after SAH.

The duration of vasodilating effectiveness of PPV is generally thought to be transient. Ac-

cording to experiments by Nagai et al (21), maximum dilatation was observed 10 minutes after arterial infusion in dogs, with vasodilatation lasting only 10 to 30 minutes. In another experimental report, in a canine model of vasospasm, 15 mg of intraarterial PPV significantly reversed angiographic vasospasm, but this effect disappeared after 2 hours (37). In our study, the main arteries were dilated by intraarterial infusion of PPV, but 24 hours after infusion, transcranial Doppler sonography showed the mean blood flow velocity to be increased again, suggesting that vasospastic blood vessels are temporarily dilated by PPV and that its effectiveness is transient.

Although the sample size in the present study is small, and the duration of the effectiveness of PPV appears to be temporary, the use of PPV may be more effective at an early stage in cerebral vasospasm when the pathologic changes are mild and reversible.

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