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Experimental of Cerebral Vasospasm and Measure the Mean Blood Flow Velocity in the Middle Cerebral Artery

Byung-Rae Park†

Department of Radiological Science, Catholic University of Pusan, Busan 609-757, Korea

To determine the appropriate concentration of papaverine hydrochloride (PPV) for therapeutic intraarterial infusion against cerebral vasospasm and to measure the mean blood flow velocity of the middle cerebral artery in rabbits. Vasospasm was induced in the experimental groups (3 days after infusion; group 1, n=3, 7 days after infusion; group 2, n=3) and a control group (n=1) by placing a blood clot in the subarachnoid space around the top of the internal carotid siphon. PPV (5 mg/kg) was infused into the internal carotid artery. The vascular diameters of the internal carotid artery (ICA) and middle cerebral artery (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. After PPV infusion in both groups, vascular dilatation of about 20% was seen. The mean increase in blood flow velocity in the group 1 (30%) was smaller than in the group 2 (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. PPV infusion may be more effective in early stages of vasospasm when vascular walls have fewer histologic changes.

Key Words: Papaverine hydrochloride, Cerebral vasospasm, Blood flow velocity

INTRODUCTION

The superselective intraarterial infusion of papaverine is effective in the treatment of cerebral vasospasm after subarachnoid hemorrhage (Kassell et al., 1992; Livingston et al., 1993). Superselective infusion of 0.13% (10^{-2} mol/L) papaverine at a site just proximal to the narrowing vessels is considered sufficient to dilate the spastic arteries in most cases. But when papaverine is infused far from the spastic site because of difficulties in catheterization, or when relatively papaverine-resistant vasospasm exists (Vorkapic et al., 1991) a larger dose or higher concentration of papaverine may be needed to dilate the affected arteries. Hypertensive hypervolemic hemodilutional therapy and the use of calcium channel blockers may be effective in the treatment of vasospasm (Findlay et al., 1991). However, approximately 40% of patients with Percutaneous transluminal angioplasty has recently been performed in selective cases as an effective method of treatment for symptomatic vasospasm (Higashida et al., 1989; Takahashi et al., 1990). 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 (ACA) (Linskey et al., 1991). Papaverine hydrochloride (PPV), a potent vasodilator, has been used for the treatment of clinical and experimental cerebral vasospasm by intravenous or intrathecal administration.

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.

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†Corresponding author: Byung-Rae Park, Department of Radiological Science, Catholic University of Pusan, Busan 609-757, Korea.
Tel: 051-510-0583, Fax: 051-510-0588
e-mail: brpark@cup.ac.kr

MATERIALS AND METHODS

1. Experimental animals

The rabbits weighing 3.5 to 5.1 kg were divided into three groups: a group studied 3 days after surgically induced vasospasm (group 1, n=3); a group studied 7 days after surgery (group 2, n=3); and one monkey in whom no surgery was performed (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).

2. Vasospasm was induced according to the method and angiography

Fronto-temporal 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 4 mL of blood, was placed in the basal cistern. The dura was closed in a watertight fashion and the incision was closed in layers. After exposing the femoral artery, a 2.5F catheter was inserted and advanced into the proximal ICA under fluoroscopic monitoring with the use of a 0.025-inch guide wire. 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.

3. Infusion of papaverine hydrochloride

Infusion of PPV was performed with a Tracker-16 catheter via a transfemoral guiding catheter placed in the terminal part of the right ICA in 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 (4 mg/kg) was mixed with 15 to 25 mL normal saline at concentrations ranging from 1.5 to 2.0 mg/mL, with total doses ranging from 50 to 70 mg. In all animals, papaverine was given by slow continuous pump infusion for about 1 hours. 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.

4. Measurements of blood vessel diameter and blood flow velocity

The percentage of change in blood vessel diameter of the main arteries in 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 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.

5. Electron microscopic examination

The group 1 and 2 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 110 cm H_2O 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.

RESULTS

1. Angiograms and change in vascular diameter

Magnetic resonance T2-weighted imaging of coronal and sagital plane imaged 24 hours after PPV infusion rabbit brains (Fig. 1A and 1B). The carotid angiograms in rabbits showed the location of vascular diameter measurements of the supraclinoid portion of the ICA, MCA and ACA of rabbit brain. Angiogram of 3 days after induction of intracranial arterial and middle cerebral artery vasospasm (Fig. 1C), and after PPV infusion (Fig. 1D). The percentages of change in vessel diameter in each group after induction of

vasospasm and infusion of PPV are listed in Tables 1. 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. In the seventh-day group, the blood vessels were found to be more severely narrowed relative to the third-day group. 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. 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 (Fig. 1D and Tables 1). 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.

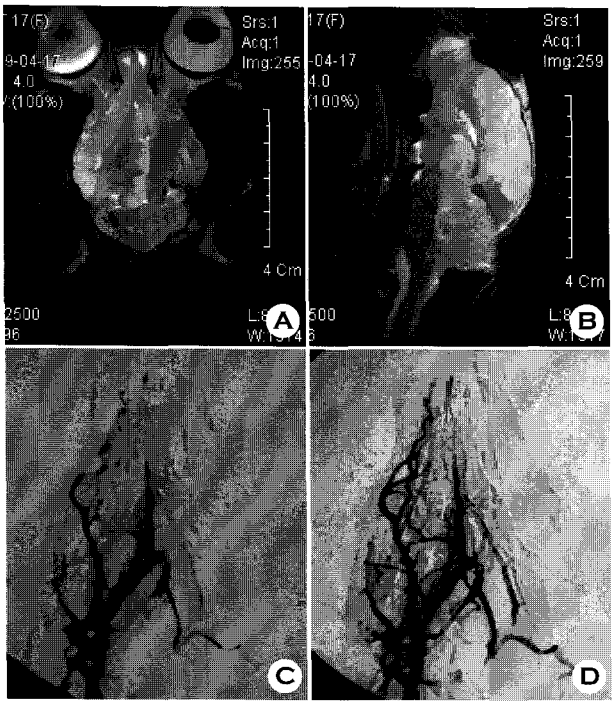

Fig. 1. Magnetic resonance T2-weighted imaging of coronal **(A)** and sagital **(B)** plane imaged 24 hours after PPV infusion rabbit brains. Angiogram shows location of vascular diameter mea- surements of the supraclinoid portion of the ICA, MCA and ACA of rabbit intraarterial. Angiogram of 3 days after induction of intracranial arterial and middle cerebral artery vasospasm **(C)**, and after PPV infusion **(D)**.

2. Mean blood flow velocity and blood pressure

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 2. 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. 2). All animals in the group studied 3 days after SAH induction showed only slight deterioration 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 subarachnoid hemorrhage (SAH) induction showed disturbance of consciousness and reduction in activity and appetite, with recovery occurring immediately after PPV infusion.

3. Electron microscopic 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. 2) 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

Table 1. Percentage of change in vascular diameter in third and seventh-day group

Rabbit	Supraclinoid portion of internal carotid artery				Sphenoidal portion of middle cerebral artery			
	After vasospasm		After PPV injection		After vasospasm		After PPV injection	
Groups	3 days	7 days	3 days	7 days	3 days	7 days	3 days	7 days
1	-26	-47	-11	-28	-28	-46	-7	-19
2	-25	-43	-9	-29	-29	-39	-7	-21
3	-31	-45	-13	-30	-36	-46	-9	-24
Mean	-27.33	-45.00	-11.00	-29.00	-31.00	-43.67	-7.67	-21.33

PPV; papaverine hydrochloride

Table 2. Change in mean blood flow velocity and blood pressure in third and seventh-day group

Rabbit	Mean blood flow velocity (cm/s) and blood pressure (mm Hg)					
	Before PPV		After PPV		After 24 hours	
Groups	3 days	7 days	3 days	7 days	3 days	7 days
1	30	60	18	32	33	58
	132/71	115/89	109/77	113/72		
2	28	56	22	40	31	49
	127/72	112/89	113/87	109/77		
3	40	60	32	44	30	51
	111/86	112/89	101/68	111/72		
Mean	32.7	58.7	24	38.7	31.33	52.67

PPV; papaverine hydrochloride

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. 2A). In the seventh-day group, however, marked corrugation of the intima and elastic lamina was noted (Fig. 2B). In the seventh-day group (Fig. 2B), 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.

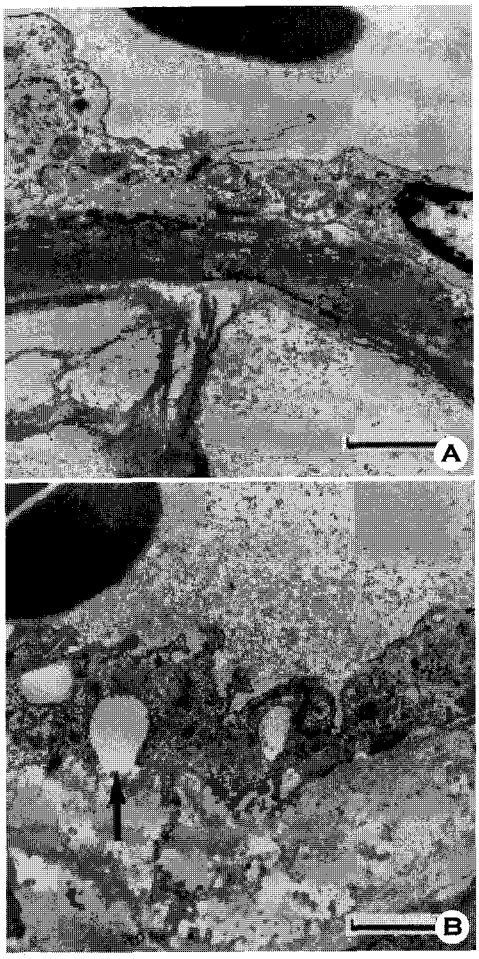

Fig. 2. Rabbits from third and seventh-day group. The internal elastic lamina shows corrugation and the adventitial layer shows thickening without inflammatory cells. Transmission electron micrographs of the ipsilateral middle cerebral artery in rabbits after infusion of varying concentrations of papaverine (bar represents 1 mm; original magnification ×8000) **(A)**. Rabbits 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. After infusion of papaverine, vacuole formation is seen in the endothelium (arrow) **(B)**.

DISCUSSION

Cerebral vasospasm after SAH has been treated with PPV administered intraarterially, and the clinical effectiveness of such therapy has been reported (Kaku et al., 1992; Kassel et al., 1992). Kaku et al, 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. 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. Clouston et al, 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-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 (Eckard et al., 1992) have not been identified. There was histologic 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 rabbits, the examined the angiographic and histologic changes in vasospastic vessels after intraarterial infusion of PPV. The 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. 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.

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.

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