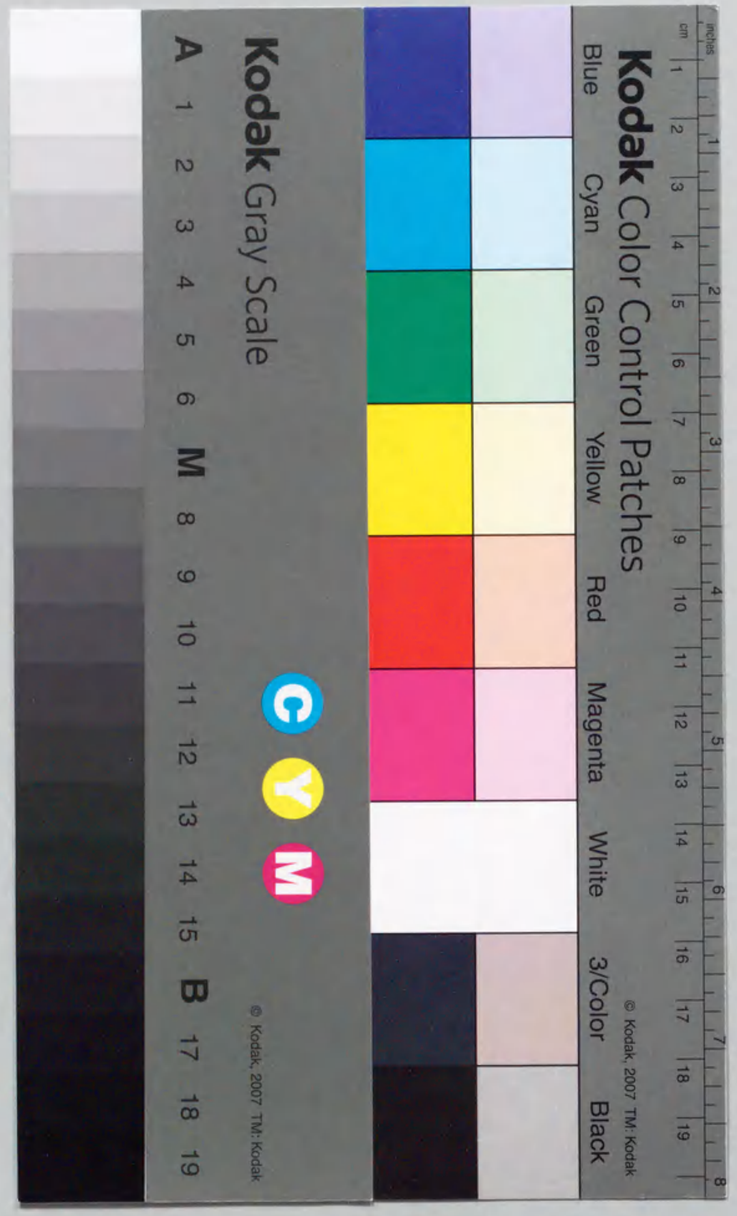

論　文　目　録

岐　阜　大　学

報告番号	乙第1008号	氏名	郭　泰彦

主　論　文

Intra-arterial infusion of papaverine for the treatment of cerebral vasospasm　1冊
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1）The endothelium-dependent response of human cerebral arteries and its changes after subarachnoid hemorrhage　1冊
平成2年発行　Cerebral Vasospasm, Tokyo ; University of Tokyo Press, pp227～230

2）Muscarinic cholinergic receptors in human and dog cerebrovascular endothelium　1冊
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3）Superselective intra-arterial infusion of papaverine for the treatment of cerebral vasospasm after subarchnoid hemorrhage　1冊
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5）Superselective intra-arterial infusion of papaverine for the treatment of cerebral vasospasm after subarachnoid hemorrhage　1冊
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主 論 文

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Intra-arterial Infusion of Papaverine for the Treatment of Cerebral Vasospasm

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Intra-arterial Infusion of Papaverine for the Treatment of Cerebral Vasospasm

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Cerebral vasospasm due to subarachnoid hemorrhage (SAH) remains a leading cause of morbidity and mortality in patients with ruptured intracranial aneurysm. The present report describes the successful treatment of cerebral vasospasm after subarachnoid hemorrhage with superselective intra-arterial infusion of papaverine hydrochloride (PPV) and the experimental background of this treatment. *In vitro* experiment demonstrated that 10^{-4} M PPV induced maximal dilatation of all the control (non-SAH) and SAH arteries obtained from autopsy cases. This result suggested that PPV can be applied clinically as a vasodilator for the spastic arteries after SAH. In a clinical study, during a 53-month period between August 1990 and December 1994, sixty vascular territories in 24 patients were treated with superselective intra-arterial infusion of PPV. 0.4% PPV was delivered through a microcatheter at a rate of 0.056 mℓ/sec, and a total of 10 mℓ was infused for each vascular territory. Fifty-five of 60 vascular territories (91.7%) were successfully dilated, and 16 of 24 patients (66.7%) showed improvement in neurological function after the procedure. In order to achieve better results, it may be essential to infuse PPV just proximal to the spastic arteries, and PPV should be infused as early as possible before the artery loses the ability to return to normal luminal diameter after SAH. Superselective intra-arterial infusion of PPV is an alternative method of treatment for symptomatic vasospasm.
Acta Sch Med Univ Gifu 43；488-497 (1995)
Key words : cerebral vasospasm, papaverine, angioplasty, subarachnoid hemorrhage

INTRODUCTION

Cerebral arterial vasospasm due to subarachnoid hemorrhage (SAH) remains a leading cause of morbidity and mortality in patients with ruptured intracranial aneurysm[1]. Despite numerous therapies having been proposed for this condition, they have achieved only limited success.

Percutaneous transluminal angioplasty (PTA) for the treatment of cerebral arterial vasospasm has recently been performed in selected cases, with generally favorable results in patients with symptomatic vasospasm refractory to conventional therapy[2)~4)]. Angioplasty balloon catheters currently available, however, have limited ability to selectively enter the narrowed branches at a bi- or trifurcation of the major branches, such as the distal middle cerebral artery (MCA), and sharply angled vessels, such as the anterior cerebral artery (ACA). We have treated such peripheral and spastic vessels with superselective intra-arterial infusion of papaverine hydrochloride.

Papaverine, a potent vasodilator, has been used for the treatment of experimental and clinical vasospasm by intravenous or intrathecal administration[5)~11)]. These attempts, however, have not shown sufficient therapeutic effect mainly for the following reasons. A drug administered into the cerebro-spinal fluid (CSF) pathways might not reach the target arteries, since the basal cistern is filled with thick clots after rupture of the aneurysm. If the drugs are administered into the venous system or into the major artery, a dose large enough to achieve a vasodilating effect would cause systemic hypotension, which might induce decreased regional cerebral blood flow. Recent advances in interventional neuroradiology have solved these problems and allowed the treatment of an intracranial artery by delivering vasodilating agents specifically to the selected artery. The present report describes the successful treatment of cerebral vasospasm after SAH with superselective intra-arterial infusion of papaverine.

1995年5月11日受理

Measurement of Arterial Responses *in vitro*

Materials and Methods

Cerebral arterial specimens (cortical branches of the middle cerebral artery with a diameter of 1 mm) were obtained from autopsy cases (TABLE 1). Cerebral arteries were carefully removed from the brain within 4 hours after death and rinsed in cold Krebs solution.

TABLE 1 Clinical profile of 8 autopsy cases.

Case	age	sex	Cause of death	Location of aneurysm	Day of death following SAH
SAH group					
1	34	M	SAH	right MCA	Day 3
2	49	F	SAH	Basilar tip	Day 11
3	58	F	SAH	right ICA	Day 16
4	81	M	SAH	right VA	Day 13
Control (non-SAH) group					
5	56	M	Brain tumor		
6	69	F	Myocardial infarction		
7	70	M	Brain tumor		
8	75	F	Brain tumor		

Abbreviations : SAH=subarachnoid hemorrhage ; MCA=middle cerebral artery ; ICA=internal carotid artery ; VA=vertebral artery

Ring segments of human cerebral artery (3 mm in length) were prepared and suspended between two L-shaped stainless-steel rods in an organ bath with 10 mℓ working volume of Krebs' solution, which was aerated with 95% O_2 and 5% CO_2. The pH of the solution ranged from 7.4 to 7.5. One rod was connected to a force-displacement transducer. The preparations were allowed to equilibrate at 37 ℃ for 60 min before use. Resting tension was adjusted to 400 mg. The contractile force was recorded isometrically using the force-displacement transducer and displayed on a polygraph. To confirm appropriate contractile activity in each specimen, the contractile response to 40 mM KCl was first obtained in each ring segment. Only the specimens that showed a good response to 40 mM KCl were used for the relaxation study. Precontractions were induced by 10^{-5} M serotonin. The relaxing effect of PPV (10^{-8}~10^{-4} M) was measured when the serotonin elicited contraction reached a plateau. Relaxation was expressed as a percentage of the amplitude of contraction.

Results

PPV (10^{-4} M) induced maximal dilatation of all the control and SAH arteries examined. In contrast, no acetylcholine-induced endothelium dependent relaxation was apparent (FIG. 1). ED50 of PPV were not statistically different between the control ($3.6\pm1.6\times10^{-6}$ M, n=4) and SAH arteries ($4.1\pm0.9\times10^{-6}$ M, n=4). As demonstrated in FIG. 2, the relaxing response to PPV was slower in SAH arteries than that in control arteries. These results suggest that PPV is one of the most potent vasodilators of spastic arteries after SAH, although the relaxing response of PPV is disturbed to some extent by SAH.

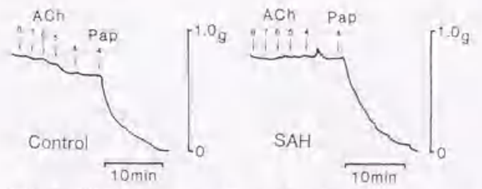

FIG. 1 Typical examples of relaxing response induced by 10^{-8} to 10^{-4}M acetylcholine (ACh) and 10^{-4}M papaverine (Pap) in a control cerebral artery and an artery after subarachnoid hemorrhage (SAH) obtained at autopsy. Numbers with arrows indicate the negative log molar concentration of ACh and Pap. Vertical bar indicate the contractile force of ring segment of a human cerebral artery.

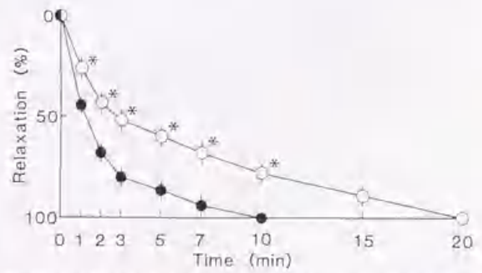

FIG. 2 Time course of relaxing responses to 10^{-4}M papaverine of control cerebral artery (●) and middle cerebral arteries after SAH (○). Values are mean±SEM for 4 cases in each group. Statistical comparison was performed by Student's t-test for unpaired observations.
*Significantly different from control group at $p<0.01$

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On the basis of this data, it was decided to treat spastic cerebral vessels with superselective intra-arterial infusion of PPV.

Clinical materials and Methods

Case materials

During a 53 month period between August, 1990 and December 1994, twenty-four patients, with ages ranging from 35 to 86 years, were treated. All cases involved cerebral vasospasm due to subarachnoid hemorrhage following aneurysm rupture, and all had undergone early surgery, i.e., clipping of an aneurysm by Day 2. TABLE 2 presents a clinical summary of the patients treated including age, sex, location of the aneurysm, neurological grade at admission, Fisher group on CT scan, interval from SAH to PPV infusion, and vessels treated.

Sixty vascular territories were treated; supraclinoid internal carotid artery 11 times, anterior cerebral artery 17 times, middle cerebral artery 29 times, basilar artery twice, and posterior cerebral artery 1 time.

In order to evaluate the effect of the therapy, angiographic vasospasm was graded as mild (minimal vessel changes), moderate (vessel narrowed by 25% to 50% compared to initial admission angiogram) or severe (vessel narrowed by >50% compared to initial admission angiogram). Initial admission angiograms, without obvious vasospasm, were used as a reference and were compared with pre-treatment and post-treatment angiograms. Overall angiographic response was graded as fair if all or most of the treated vessels improved by one angiographic grade (eg, severe to moderate or moderate to mild), good if the vessels responded by two grades (eg, severe to mild or moderate to normal), and excellent if the vessels with marked vasospasm normalized.

TABLE 2 Clinical summary of 24 patients treated with intra-arterial infusion of papaverine

Case No	Age (yrs)	Sex	Location of Aneurysm	Neurological grade*	Fisher** group	SAH to PPV infusion (days)	Neurological deficit	Vessels treated	Degree of vasospasm	Doses of PPV (mg)	Angiographical result	Early result	Outcome***
1	57	M	rt MCA	II	3	9	lt hemiparesis	rt-MCA	severe	6	excellent	improved	good recovery
2	47	F	A com	III	3	5	lt hemiparesis decreased LOC	bil.C1,M1 A1	moderate	8	good	improved	good recovery
3	35	F	rt IC-PC	III	3	4	paraparesis decreased LOC	bil.M1,A1 lt P-com	mild	12	fair	improved	good recovery
4	53	M	lt VA	IV	3	19	tetraparesis decreased LOC	rt C1,M1 M2	severe	6	excellent	improved	good recovery
5	86	F	lt IC-PC	II	3	10	decreased LOC	rt C1	moderate	6	unchanged	unchanged	moderate disability
6	67	F	basilar tip	IV	3	7	visual dist.	bil.P2,BA	moderate	6	unchanged	unchanged	moderate disability
7	41	M	lt IC bifurcation	III	3	5	decreased LOC	lt A1 bil.M1,M2	severe	6	excellent	improved	good recovery
8	64	M	A com	II	3	1	decreased LOC	lt C1,ACA bil.M1,M2	severe	20	good	improved	good recovery
9	53	F	rt MCA	IV	3	16	lt hemiparesis	rt C1 M1,M2	moderate	12	good	improved	good recovery
10	52	M	A com	III	4	9	decreased LOC	rt ACA	moderate	16	good	improved	good recovery
11	81	F	lt VA	III	3	12	decreased LOC	BA	moderate	12	good	improved	good recovery
12	64	M	rt IC-PC	III	3	8	decreased LOC	rt C1 rt M1,ACA	severe	20	excellent	unchanged	died
13	62	M	rt IC bifurcation	IV	3	17	decreased LOC	rt MCA	mild	20	fair	unchanged	severe disability
14	76	F	lt IC-PC	III	4	6	rt hemiparesis aphasia	lt MCA	moderate	40	unchanged	unchanged	moderate disability
15	73	F	lt IC-PC	IV	4	7	decreased LOC	rt MCA	mild	10	unchanged	unchanged	moderate disability
16	32	F	A com	II	3	8	paraparesis decreased LOC	bil.C1 bil.MCA,ACA	severe	80	excellent	improved	good recovery
17	74	F	lt IC-PC	II	2	13	decreased LOC	lt MCA	moderate	40	good	improved	good recovery
18	73	F	lt IC-PC	IV	3	9	lt hemiparesis decreased LOC	bil.MCA rt ACA	moderate	80	good	improved	good recovery
19	62	M	lt MCA	III	4	6	rt hemiparesis decreased LOC	lt MCA	mild	20	fair	unchanged	died
20	59	F	rt IC-PC	II	3	8	lt hemiparesis decreased LOC	lt MCA	moderate	40	good	improved	good recovery
21	73	F	unknown	II	3	13	lt hemiparesis decreased LOC	rt MCA	mild	40	fair	improved	good recovery
22	56	F	rt MCA	III	3	5	lt hemiparesis decreased LOC	rt MCA rt ACA	moderate	80	good	improved	good recovery
23	45	M	A com	II	2	8	paraparesis decreased LOC	bil.MCA bil.ACA	severe	120	fair	unchanged	moderate disability
24	45	M	rt IC-PC	III	4	8	lt hemiparesis decreased LOC	rt MCA rt ACA	moderate	80	good	improved	good recovery

Abbreviations: MCA=middle cerebral artery; A com=anterior communicating artery; IC=internal carotid artery; PC, P-com=posterior communicating artery; ACA=anterior cerebral artery; VA=vertebral artery; M1,M2=segments of the MCA; C1=segment of the IC; A1=segment of the ACA; LOC=level of consciousness; PPV=papaverine

*Hunt and Kosnik classification

**Subarachnoid hemorrhage grouping according to Fisher *et al.*

***Glasgow Outcome Scale score

Indication for Transluminal Angioplasty

The indications for transluminal angioplasty of cerebral vasospasm are: 1) new onset of an ischemic neurological deficit not attributable to other causes, 2) no evidence of infarction on CT scan, 3) the neurological deficit is not successfully treated by conventional medical and pharmacological therapies, 4) mean flow velocity in the affected vessel is greater than 100 cm/sec or the increase in mean flow velocity is greater than 30 cm/sec within 24 hours, measured by transcranial Doppler ultrasonography, and 5) vasospasm is seen angiographically in a location that could be responsible for the neurological deficit.

Interventional Neuroradiological Technique

Angioplasty of the intracranial vessels was performed in two steps, as follows: a silicone non-detachable balloon 0.9 mm in diameter before inflation (Dow-Corning, Japan) was used for dilatation of the first narrowed segment, for example, the supraclinoid segment of the internal carotid artery and the proximal MCA. A leak silicone balloon catheter or Tracker 18 catheter (Target Therapeutics Inc, San Jose) was then introduced into or just proximal to the site of vasospasm not accessible to the angioplasty balloon catheter, such as the distal MCA or ACA, for superselective infusion of papaverine. Papaverine was diluted with normal saline to a concentrations of 0.4%, and a total of 10 mℓ was infused at a rate of 0.056 mℓ/sec for each vascular territory, under monitoring by digital subtraction angiography. All procedures were performed via a transfemoral approach under local anesthesia with full heparinization. Continuous neurological assessment was performed throughout the procedure. Follow-up angiograms were obtained the following day, and 7 days after the procedure. All patients were maintained in an intensive care unit, and serial TCD velocity measurements were obtained before and after angioplasty.

Representative case reports

Case 1

This 57-year-old man presented with a SAH due to rupture of a right middle cerebral bifurcation aneurysm. He was in Hunt and Kosnik grade 2 on admission. The aneurysm was successfully clipped on Day 2. Seven days after clipping, he developed left hand weakness, which did not improve with induced hypertension and hypervolemia. Angiography performed within 6 hours of the onset of symptoms revealed severe vasospasm of the right M2 and M3 (FIG. 3A). A leak silicone balloon was introduced just proximal to the right M2, so that 6 mg of 0.4% papaverine, 0.5 mg of nicardipine, and 60000 IU of Urokinase could be superselectively infused (FIG. 4). Subsequently, the spastic vessels were successfully dilated (FIG. 3B), and it was judged as excellent angiographic response. The patient demonstrated immediate clinical improvement following the procedure by regaining the ability to move his left upper extremity. Follow up angiography obtained the following day and 7 days after the procedure demonstrated continued patency without evidence of recurrent stenosis (FIG. 3C, D). He was neurologically intact when

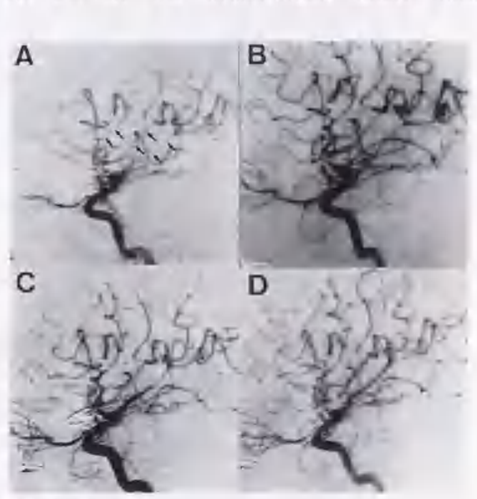

FIG. 3 Case 1
A: Right ICA angiogram, lateral view, demonstrating severe vasospasm of M2 and M3 (arrow).
B: Angiogram obtained following superselective infusion of papaverine showing return of normal luminal diameter of M2 and M3, with angiographic evidence of improved perfusion.
C: Angiogram obtained the day following the procedure showing continued patency.
D: Follow up angiogram on 7 days after the procedure demonstrating continued patency without evidence of recurrent stenosis.

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discharged 2 weeks later.

Case 7

This 41-year-old man presented with a SAH due to rupture of a left ICA bifurcation aneurysm. He was in Hunt and Kosnik grade III on admission. The aneurysm was successfully clipped on Day 1. Four days following surgery, his level of consciousness decreased rapidly and did not improve with conventional medical therapy. Angiography within 4 hours of the onset of symptoms revealed severe vasospasm of the left MCA and segmental vasospasm of the left A1.

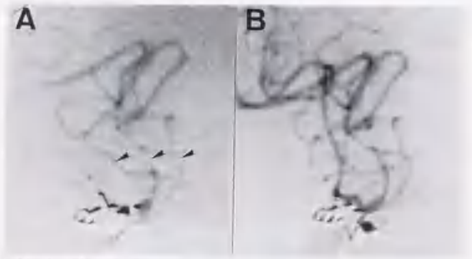

FIG. 4 Case 1
A : Superselective angiogram demonstrating severe vasospasm of M2 and M3 (arrowhead), a leak silicone balloon was introduced just proximal to M2.
B : Superselective angiogram obtained following infusion of papaverine showing return of normal luminal diameter of the spastic vessels.

Balloon angioplasty of the left supraclinoid segment of the internal carotid artery and the left proximal middle cerebral artery was performed. A tracker 18 catheter was then introduced just proximal to the spastic segment of A1, so that 6 mg of papaverine and 0.5 mg of nicardipine could be superselectively infused. All vessels were dilated with restoration of normal luminal diameter (FIG. 5), and it was judged as excellent angiographic response. He showed immediate improvement in level of consciousness, and was neurologically intact when discharged 1 month later.

Case 12

This 64-year-old man presented with a SAH due to rupture of a anterior communicating artery aneurysm. He was in Hunt and Kosnik grade III on admission. The aneurysm was successfully clipped on Day 1. Six days after clipping, he developed right hemiparesis and his level of consciousness decreased rapidly, which did not improve with conventional medical therapy. Angiography performed within 6 hours of the onset of symptoms revealed diffuse severe vasospasm of the anterior circulation (FIG. 6A). Balloon angioplasty of the left supraclinoid segment of the internal carotid artery and the left proximal middle cerebral artery was performed (FIG. 6B). A leak balloon catheter was then introduced just proximal to the spastic segment of M2 and supraclinoid segment of internal carotid artery, so that 40 mg of papaverine and 1 mg of nicardipine could be superselectively infused. All vessels were dilated with restoration of normal luminal diameter (FIG. 6C). In spite of excellent angiographic improvement, he consequently died of marked brain swelling 6 days later.

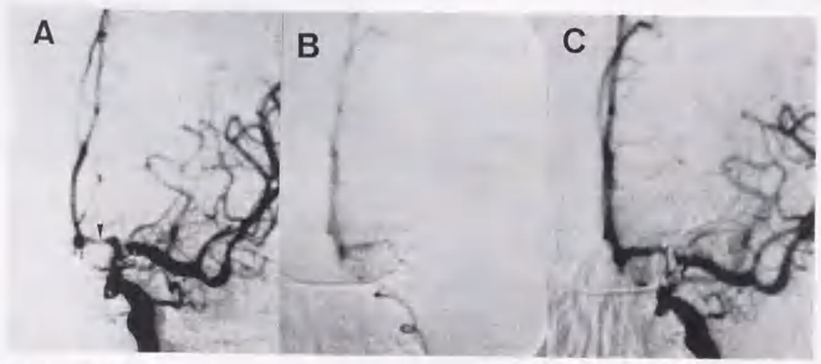

FIG. 5 Case 7
A : Left ICA angiogram demonstrating segmental vasospasm of A1 (arrowhead).
B : Superselective angiogram, a tracker 18 catheter was introduced just proximal to the spastic portion of A1.
C : Left ICA angiogram obtained following the procedure showing return of A1 to normal luminal diameter.

Case 24

This 45-year-old man presented with a SAH due to rupture of right ICA-posterior communicating bifurcation aneurysm. He was in Hunt and Kosnik grade III on admission. The aneurysm was successfully clipped on Day 1. Eight days following surgery, he developed marked reduction of consciousness level with mild left hemiparesis, which did not improve with conventional medical therapy. Angiography performed within 6 hours of the onset of symptoms revealed diffuse moderate vasospasm of the right MCA and ACA (FIG. 7A). A Tracker 18 catheter was first introduced to M1 portion (FIG. 7B), so that 40 mg of papaverine could be infused and the Tracker 18 catheter was then

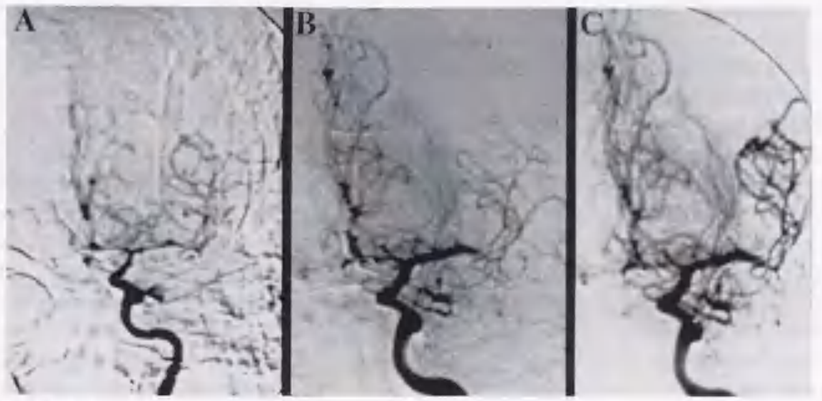

FIG. 6 Case 12
A : Left ICA angiogram demonstrating diffuse severe vasospasm of the anterior circulation.
B : Angiogram obtained following balloon angioplasty of the supraclinoid ICA and the proximal segment of the MCA.
C : Angiogram obtained after superselective infusion of papaverine demonstrating a normal luminal diameter of the entire vessel with evidence of improved perfusion.

FIG. 7 Case 24
A : Lateral view of right ICA angiogram demonstrating diffuse moderate vasospasm of MCA and ACA.
B : Superselective angiogram(A→P view), Tracker 18 catheter was introduced to M1 portion.
C : Selective angiogram(A→P view), Tracker 18 catheter was drew back to the tip of ICA.
D : Lateral view of right ICA angiogram obtained following superselective infusion of PPV showing a normal luminal diameter of the entire vessel with evidence of improved perfusion.

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drew back to the tip of ICA (FIG. 7C), so that 40 mg of papaverine could be infused. After infusion of papaverine, all vessels were dilated with restoration of normal luminal diameter (FIG. 7D), and it was judged as good angiographic response. He showed immediate improvement in level of consciousness, and was neurologically intact when discharged 2 weeks later.

Results

Angiographical results

Papaverine infusion was made into cervical internal carotid artery 3 times, supraclinoid internal carotid artery 11 times, selective A1 anterior cerebral artery 8 times, selective M1 middle cerebral artery 21 times, and basilar artery 2 times.

Overall angiographic improvement was noted in 20 of the 24 patients (83.3%) and 55 of 60 vascular territories (91.7%) were successfully dilated; excellent angiographic improvement in 5 cases, good in 10 cases, and fair in 5 cases. There was no improvement in 4 cases (16.7%). Vasospasm involved supraclinoid internal carotid artery showed improvement in 8 of 9 treatments, anterior cerebral artery vasospasm improved in all of 13 treatments with the best angiographic results obtained with superselective A1 infusion, middle cerebral artery vasospasm improved in 26 of 28 treatments, basilar artery vasospasm improved in one of 2 treatments, and there was no improvement in one vasospasm involved posterior cerebral artery. In 3 patients (Case 5, Case 14 and Case 15), superselective catheterization was not achieved due to atherosclerosis or coiling of the parent arteries, and papaverine was infused at the cervical internal carotid artery or cavernous internal carotid artery with the results of no angiographical improvement. Two cases (Case 16, Case 18) showed recurrence of angiographic vasospasm; Case 16 was treated with repeated infusion of papaverine and resulted in marked angiographic improvement, and Case 18 was treated conservatively and resulted in good outcome.

Clinical results

Sixteen of 24 patients (66.7%) showed improvement in neurological function after intra arterial infusion of papaverine. TABLE 2 presents the early results and late outcomes following treatment. Clinical results did not always show direct correlation with angiographic response. For example, two cases with excellent or fair angiographic improvement consequently died (Case 12, Case 19), while two cases with fair angiograpic improvement showed no change in clinical status (Case 13, Case 23).

Complications

Although this procedure had no effect on systemic arterial pressure, heart rate increased 10 to 20%, which continued for about 10 minutes after infusion of papaverine. Two patients had procedual complications. One patient suffered permanent monocular blindness because of papaverine infusion near the ophthalmic artery (Case 10). The other patient suffered transient unilateral oculomotor palsy (Case 20), and this symptom lasted over 1 month.

Discussion

Introduction of transluminal angioplasty contributed greatly to progress in the treatment of vasospasm. In 1984, Zubkov et al first reported the treatment of cerebral vasospasm after SAH using transluminal balloon angioplasty[4]. Subsequent reports have similarly described the application of this technique, in which generally favorable results were obtained in patients with symptomatic vasospasm refractory to conventional therapy[2,3]. However, the balloon catheter currently available has limited ability to access distally affected vessels and to access vessel origins that are short and sharply angled, such as the A1 segment of the anterior cerebral artery. Therefore, it was decided to treat such peripheral vessels by means of superselective infusion of a vasodilating agent. Essential criteria for choosing the vasodilating agents used for this treatment is that its vasodilating effect is not lost after SAH, and that it dilates the arteries constricted by multifactorial stimuli. Vasodilators such as substance P and acetylcholine, whose effect is endothelium-dependent, are not indicated, since endothelium-dependent relaxation is severely injured following SAH[10][12~14]. Nitrovasodilators such as nitroglycerine, sodium nitroprusside and nitric oxide (NO) are known to dilate the constricted arteries. Since these nitrovasodilators are inactivated by hemoglobin, however, they could not be used for the treatment of delayed vasospasm. Papaverine is an alkaloid of the opium group well known to cause vasodilatation of cerebral arteries through a direct action on smooth muscle, and it reduces the constriction of smooth muscle produced by a wide variety of stimuli. Although the precise molecular mechanism of action of papaverine is presently unknown, papaverine is thought to have its vasodilating effect by inhibition both cAMP and cGMP phosphodiesterase activity in the smooth muscle cell, and increasing intracellular cAMP and cGMP turnover[15~17]. In our *in vitro* experiment, papaverine (10^{-4} M) always induced a maximal amount of vasodilatation of control and spastic human arteries following SAH, whereas endothelium dependent vasodilatation, for example, was markedly disturbed in the arteries after SAH. We decided the concentration of papaverine to be used in the clinical trials on the basis of these *in vitro* data. If the drug is infused at a rate of 0.056 mℓ/sec into an artery with a diameter of 2 mm and a flow velocity of 100 cm/sec, the drug is attenuated 56.1 times in one second by blood flow. Since we used 0.4% papaverine ($Ca\ 60\times10^{-4}$ M papaverine) at a rate of 0.056 mℓ/sec, rough estimation suggests that the target artery received a submaximum (10^{-4} M) dose of papaverine during the infusion.

Several experimental and clinical trials have been performed to prevent or treat cerebral vasospasm using papaverine, although there is none report successfully treating cerebral vasospasm[6][8][9]. The reason for its limited effect in clinical studies can be categorized as follows; 1) the route of administration; When papaverine is applied topically, it relaxes cerebral arteries, as is sometimes observed during operations in the acute stage of SAH. Papaverine given into the CSF pathway, however, might not reach the target arteries, because thick clots in the basal cisterns prevents it from reaching them. Intravenous administration would require larger doses of papaverine to obtain sufficient relaxation of the spastic cerebral arteries. Such a high dose of papaverine might produce systemic hypotension, and a consequent decrease in regional cerebral blood flow. When papaverine is administered into the major cerebral arteries, such as the internal carotid artery or vertebral artery, larger doses are required or the spastic arteries do not receive a sufficient concentration. In fact, we did not achieve satisfactory results in 3 cases in our clinical series, because the catheters could not be introduced superselectively into the spastic arteries. In order to deliver a sufficient concentration of papaverine, it may be essential to infuse papaverine just proximal to the spastic arteries.

2) the timing of administration of papaverine; Morphological studies have revealed a number of organic changes in the cerebral arteries after SAH, such as endothelial damage, smooth muscle cell vacuolization, myonecrosis and subendothelial thickening[1]. Once the distensibility of the vessel wall is decreased with these morphological changes, it is not easy to dilate such vessels using any vasodilator.

Considering these clinical results, it is clear that the pathogenesis of cerebral vasospasm after SAH, at least in its initial stage, is arterial contraction which can be treated with vasodilating agents. Therefore, in order to achieve better results, papaverine should be infused as early as possible before the artery loses the ability to return to normal luminal diameter.

Despite the duration of action of papaverine in experimental vasospasm being reported to be rather short[5~8][18], vasospasm rarely recurs after superselective intra arterial infusion of papaverine in clinical cases when vasoconstrictive agents remained in the subarachnoid space and within the vascular wall. Although the reason for the lasting effect of papaverine is not clear, it was speculated that once an improvement in cerebral microcirculation is achieved, increased cerebral circulation can maintain normal luminal size and the dilated vessels no longer responded to vasoconstrictive agents because of decreased energy metabolism in the vascular wall after SAH.

In conclusion, superselective intra arterial infusion of papaverine allowed the successful treatment for symptomatic cerebral vasospasm following SAH.

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脳血管攣縮に対する塩酸パパベリンの超選択的動注療法

クモ膜下出血後に生じる脳血管攣縮は，種々の治療法が発達した今日においてもなお，その予後を悪化させる最大の因子の1つになっている。1984年にZubkovらが報告した本疾患に対するballoon angioplastyは，現在では有効な治療法として一般に認められつつある。しかしながら手技中の血管破裂の危険性やballoon catheterを誘導できる範囲に制約があることなどの問題点が存在する。そこでこれに代わる方法として，内皮細胞非依存性の強力な血管拡張物質である塩酸パパベリン（PPV）を超選択的に動注することにより，攣縮血管を拡張させる方法を考案した。本稿では，その理論的根拠となった*in vitro*の実験結果と臨床例の治療結果につき検討を加えた。

【*in vitro*の実験系における血管反応性の測定】剖検時に得られたヒト脳血管リング標本を使用した*in vitro*の実験系においては，くも膜下出血後の脳血管においてもcontrol（非クモ膜下出血）群と同様に，10^{-4} M（0.007%）のPPVにより最大弛緩反応が得られた。

【対象】1990年8月から1994年12月の間に治療した破裂脳動脈瘤によるクモ膜下出血症例で，原則として早期手術によるクリッピングが完了したもののうち症候性脳血管攣縮が出現した24症例（60血管領域）を対象とした。

【方法】実際の臨床例においては血流による薬剤の希釈が起こるため，0.4%の濃度のPPVを0.056 mℓ/secの速度で，できるだけ攣縮血管の近傍からマイクロカテーテルを用いて超選択的に注入した。

【結果】PPVの超選択的動注を行った24例中20例（83.3%）で血管撮影上攣縮血管の拡張が得られ，この内16例（66.7%）では臨床症状も速やかに改善した。症候性脳血管攣縮の再発は16例中2例（12.5%）に認められた。

【結論】PPVの超選択的動注は，クモ膜下出血後の脳血管攣縮に対する有効な治療法である。本法はballoon angioplastyに比し安全かつ簡便で，しかも広範囲の脳血管攣縮をその治療対象とすることが可能である。