Intraarterial Papaverine Infusion for Cerebral Vasospasm after Subarachnoid Hemorrhage

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PURPOSE: To evaluate the techniques and efficacy of intracranial intraarterial papaverine infusion for symptomatic vasospasm after subarachnoid hemorrhage caused by aneurysm rupture. **METHODS:** Papaverine was infused on 19 occasions in 14 patients, 6 hours to 2 days after spasm became apparent clinically. Sixty vascular territories were treated. Infusion was made into the supraclinoid internal carotid artery 20 times, cavernous internal carotid artery once, selective A1 anterior cerebral artery 8 times, M1 middle cerebral artery 7 times, and basilar artery 3 times. Papaverine doses ranged from 150 to 600 mg and exceeded 400 mg on 8 occasions. **RESULTS:** Angiographic improvement occurred in 18 (95%) of the 19 treatment sessions: results were excellent in 3 sessions, moderate in 8, and mild in 7. The best angiographic results often were obtained with superselective infusion, although angiographic results did not always correlate with clinical response. Seven (50%) of the 14 treated patients showed dramatic acute clinical improvement within 24 hours of papaverine therapy, and there was no clinical evidence of recurrent vasospasm in these patients. Recurrence of angiographic vasoconstriction was demonstrated in three patients; one showed marked clinical improvement after a second treatment. There were no episodes of systemic hypotension in any of the cases. Monocular blindness developed in one patient because of papaverine infusion near the ophthalmic artery. **CONCLUSIONS:** Papaverine was effective in dilating narrowed arteries in most patients with symptomatic vasospasm caused by subarachnoid hemorrhage. This series showed encouraging clinical results with no recurrence of neurologic deterioration in those patients who responded well to papaverine. Superselective infusion appears to be indicated in some cases for adequate papaverine delivery.

Index terms: Vasospasm; Subarachnoid space, hemorrhage; Drugs, intraarterial injection; Interventional neuroradiology

It has been shown that vasospasm is the leading cause of disability and death after intracranial aneurysm rupture, but the pathogenesis of the arterial narrowing is not completely understood (1–12), and the best form of treatment is not yet clear (5, 7–9, 12–23). Unresolved issues in the treatment of vasospasm include indications and timing for treatment, conservative versus interventional therapy, angioplasty versus intraarterial vasodilators, drugs, doses and site of administration of vasodilators, and the size of target vessels (1, 3–5, 8, 9, 13–22).

Intracranial angioplasty with nondetachable silicone balloons and intracranial intraarterial papaverine infusion have been used in a number of institutions; however, the reported experience remains modest (13–23). Currently, there are no reported prospective trials for either mode of therapy, so the apparent benefits of each have yet to be proved and comparison of the advantages and disadvantages of each technique is difficult with the limited available data.

This report describes our experience with the use of intracranial intraarterial papaverine in 14 patients and evaluates techniques used and efficacy.

Materials and Methods

Patient clinical data and method of analysis are shown in the Table. Intracranial intraarterial papaverine was administered on 19 occasions in 14 patients with subarachnoid hemorrhage caused by intracranial aneurysm rupture. Treatment was undertaken 1 to 16 days after subarachnoid hemorrhage and 6 hours to 2 days after spasm manifested clinically. All patients' aneurysms had been successfully obliterated 0 to 15 days before papaverine therapy, 12 by surgical clipping and 2 by endovascular coil embolization. In the surgical group, after the aneurysm was clipped, the accessible cisterns were opened and all possible clot removed. No cisternal papaverine or fibrinolytics were used. After aneurysm treatment, all patients were maintained moderately hypervolemic, and all received calcium channel blockers from the time of hospital admission. When a clinical diagnosis of vasospasm was made, maximal hypervolemic hypertensive therapy was instituted in all cases.

Indications for papaverine treatment were: (a) the presence of neurologic deficits attributed to vasospasm, not responding to maximal medical treatment, and (b) absence of computed tomographic (CT) evidence of recognizable cortical infarction in the territory to be treated. Patients were not excluded if they had an ischemic infarct remote from the proposed treatment area. Only one patient had a preexisting infarct in a territory treated with papaverine. Preprocedure CT showed a small, ill-defined hypodense area in the internal capsule region, which subsequently matured into a symptomatic lacunar infarct.

Patients' neurologic deficits could be divided into the following groups: (a) a focal neurologic deficit in one patient; (b) a combination of focal deficit plus reduced conscious level in nine patients; and (c) reduced consciousness level without focal deficit in four patients.

Sixty vascular territories were treated: the supraclinoid internal carotid artery 8 times, anterior cerebral artery 23 times, middle cerebral artery 20 times, basilar artery 3 times, and posterior cerebral artery 6 times. Infusion was made into the supraclinoid internal carotid artery 20 times, cavernous internal carotid artery once, selective A1 anterior cerebral artery 8 times, selective M1 middle cerebral artery 7 times, and basilar artery 3 times.

Angiographic spasm was assessed subjectively by three nonblinded neuroradiologists and graded by consensus as either mild, moderate, or severe. Initial admission arteriograms, without obvious vasospasm, were used as a reference and were compared with pretreatment and posttreatment angiograms. Overall angiographic response was graded as mild if all or most of the treated vessels improved by one angiographic grade (eg, severe to moderate or moderate to mild), moderate if the vessels responded by two grades (eg, severe to mild or moderate to normal), and excellent if vessels with marked spasm normalized.

Papaverine treatment was instituted immediately after diagnostic angiography. Infusion of papaverine was performed using Tracker 18 or Tracker 10 catheters (Target Therapeutics, Fremont, Calif) via a transfemoral guiding

catheter placed in the cervical internal carotid artery or vertebral artery. One patient was treated via an axillary approach. Patients were fully heparinized throughout the procedure, and topical nitrates were applied at the commencement of the treatment.

Papaverine was mixed with normal saline at concentrations ranging from 3 to 5 mg/mL, with total doses ranging from 150 to 600 mg. In the first 3 patients, 300 mg of papaverine at a concentration of 3 mg/mL was given by slow continuous pump infusion over 45 to 60 minutes. In the next 11 patients, papaverine with concentrations ranging from 3 to 5 mg/mL was given by manual injection. Brisk 0.2- to 1-mL injections were made at a dose rate of 1 to 2 mL/min with the larger 1-mL boluses delivered if reflux was desired to treat the vessel origin, proximal to the catheter tip. A closed system was used, with a three-way stopcock, a 60-mL reservoir syringe, and a 1-mL syringe for injection. With increasing experience, severe anterior or middle cerebral artery spasm was treated first with supraclinoid internal carotid artery infusion, followed by superselective catheterization of A1 anterior cerebral or M1 middle cerebral artery. Supraclinoid internal carotid artery doses ranged from 100 to 450 mg but were typically between 150 and 300 mg. Superselective A1 or M1 doses ranged from 30 to 300 mg but were typically between 70 and 200 mg, and basilar artery doses ranged from 100 to 150 mg. The maximum total dose exceeded 400 mg on 8 occasions.

Early clinical response was assessed within the first 24 hours after completion of papaverine treatment, and late assessment was made according to the Glasgow Outcome Scale (7) at the latest available follow-up, ranging from 2 to 12 months.

Results

Detailed results are listed in the Table.

Angiographic Results

Overall angiographic improvement was noted in 18 (95%) of the 19 treatment sessions: excellent in 3 sessions, moderate in 8, and mild in 7. There was no improvement in one patient.

Supraclinoid internal carotid artery spasm showed improvement in 6 of 8 treatments. Anterior cerebral artery spasm improved in 21 of 23 treatments, with the best angiographic results obtained with superselective A1 infusion. Superselective catheter placement was difficult for severe anterior cerebral artery spasm but was enhanced after initial supraclinoid internal carotid artery infusion of papaverine, which typically resulted in dilatation of the proximal A1 segment. Superselective papaverine infusion into the A1 segment often caused dilatation of the contralateral anterior cerebral artery, pre-

Fourteen patients treated with intraarterial papaverine infusion

Patient	Age, y/Sex	Aneurysm Location (Days between Subarachnoid Hemorrhage and Aneurysm Obliteration)	Neurologic Grade on Admission*	Fisher Grade† of Admission CT	Days between Subarachnoid Hemorrhage and Papaverine Infusion	Days between Onset of New Signs and Papaverine Infusion	Neurologic Deficit and Grade (GCS) at Treatment	Vascular Territories Treated (Degree of Spasm)‡	Infusion Site and Dose	Overall Angiographic Response	Clinical Result Early	Clinical Result Late§
1	39/F	L MCA (1)	IV, 9T	2	1	1	Decreased LOC R hemiparesis GCS 10	L ICA(2+) L ACA(2+) L MCA(2+)	L SICA 300 mg	Excellent	Marked improvement Unchanged hemiparesis GCS 14	Good recovery
2	39/M	L ICA bifurcation coiled day 7	IV, 5	4	8	No new signs Treated during coil embolization	Decreased LOC R hemiparesis GCS 5	L ICA(3+)	L SICA 300 mg	None	No change	Moderate disability
3	69/F	ACoA (1)	IV, 9T	3	4	2	Decreased LOC R hemiparesis GCS 8T	L ACA(2+)	L cavernous ICA 300 mg	Mild	Marked improvement Resolved hemiparesis GCS 13	Good recovery
4	54/F	R PCoA (1)	III, 13	4	15	1	L hemiparesis GCS 14	R ICA(3+) R ACA(3+)	R SICA 70 mg R A1 60 mg	Moderate	Marked improvement Resolved hemiparesis GCS 15	Good recovery
5	56/F	R PCoA (1)	III, 14	3	9	1	Decreased LOC L hemiparesis GCS 8	R MCA(3+) R ACA(3+)	R M1 70 mg R SICA 300 mg	Moderate	No change GCS 15	Moderate disability
6	33/F	L PCoA (1)	II, 15	3	4	1	Decreased LOC R hemiparesis Dysphasia GCS 10	R MCA(1+) L ACA(2+) L MCA(1+) R ICA(1+)	L A1 100 mg R SICA 450 mg	Excellent	No change	Good recovery
7	54/F	Basilar tip and L ICA Coiled day 1	IV, 7T	4	6	2	Decreased LOC R hemiparesis GCS 13	R ACA(2+) R MCA(3+) L ACA(2+) L MCA(3+)	L SICA 225 mg	Mild	Further decline GCS 11	Moderate disability

(Table continues)

Note.—ACA indicates anterior cerebral artery; ACoA, anterior communicating artery; BA, basilar artery; GCS, Glasgow coma score; ICA, internal carotid artery; LOC, level of consciousness; MCA, middle cerebral artery; PCoA, posterior communicating artery; SICA, supraclinoid internal carotid artery; and T, intubated.

* Hunt and Hess and Glasgow coma score.
† Amount and distribution of subarachnoid blood on CT (25).
‡ 1+ indicates mild; 2+, moderate; and 3+, severe.
§ Glasgow outcome score (7).

Table continued

Patient	Age, y/Sex	Aneurysm Location (Days between Subarachnoid Hemorrhage and Aneurysm Obliteration)	Neurologic Grade on Admission*	Fisher Grade† of Admission CT	Days between Subarachnoid Hemorrhage and Papaverine Infusion	Days between Onset of New Signs and Papaverine Infusion	Neurologic Deficit and Grade (GCS) at Treatment	Vascular Territories Treated (Degree of Spasm)‡	Infusion Site and Dose	Overall Angiographic Response	Clinical Result Early	Clinical Result Late§
8	55/M	ACoA (2)	III, 14	3	4	2	Decreased LOC Intermittent hemiparesis GCS 10T	R ACA(3+) R MCA(1+)	R SICA 150 mg	Moderate	No change	
8–2nd treatment					13	1	Declining LOC GCS 6T	R MCA(1+) L ACA(3+) L MCA(1+)	R SICA 100 mg R A1 150 mg L SICA 225 mg	Moderate	No change	Vegetative survival
9	71/F	R PCoA (1)	IV, 6T	4	16	1	Decreased LOC Aphasic GCS 11	R ACA(3+) L ACA(2+)	R SICA 100 mg R A1 200 mg	Moderate Improved speech	Marked improvement GCS 14	Severely disabled
10	65/F	R PCoA (1)	II, 15	4	5	1	Decreased LOC L hemiparesis GCS 12	R ACA(1+) R MCA(2+) L ACA(1+) L SICA 100 mg	R SICA 100 mg R M1 150 mg R A1 100 mg	Mild GCS 15	Marked improvement Resolved hemiparesis	Good recovery
11	31/F	L PCoA R cavernous ICA (1)	II, 14	3	6	1	Decreased LOC GCS 10	R ICA(2+) R ACA(3+) R MCA(3+) L ICA(3+) L ACA(3+) L MCA(3+) BA (3+) R PCA(3+) L PCA(3+)	R SICA 100 mg R M1 80 mg L SICA 150 mg BA 100 mg	Mild	Further decline GCS 7T	
11–2nd treatment					7	2	Worsening LOC GCS 7T	R ICA(2+) R ACA(3+) R MCA(3+) L ICA(3+) L ACA(3+) L MCA(3+) BA (3+) R PCA(3+) L PCA(3+)	R SICA 150 mg L SICA 150 mg BA 150 mg	Moderate	Marked improvement GCS 14	Good recovery

Table continued

Patient	Age, y/Sex	Aneurysm Location (Days between Subarachnoid Hemorrhage and Aneurysm Obliteration)	Neurologic Grade on Admission*	Fisher Grade† of Admission CT	Days between Subarachnoid Hemorrhage and Papaverine Infusion	Days between Onset of New Signs and Papaverine Infusion	Neurologic Deficit and Grade (GCS) at Treatment	Vascular Territories Treated (Degree of Spasm)‡	Infusion Site and Dose	Overall Angiographic Response	Clinical Result Early	Clinical Result Late§
12	75/F	R pericallosal (1)	IV, 11	4	4	1	Decreased LOC R hemiparesis GCS 7T	L ACA(2+) L MCA(1+)	L SICA 200 mg L M1 100 mg L A1 30 mg	Mild	No change	
12–2nd treatment					5	2	Remains 7T	R PCA(2+)	Basilar 150 mg	Mild	No change	Severely disabled
13	44/F	ACoA (1)	II, 14	3	1	6 hours	Decreased LOC L hemiparesis GCS 10T	L PCA(2+) R ACA(2+) R MCA(2+)	R SICA 200 mg	Excellent	Further decline GCS 8	
13–2nd treatment					3	2	GCS 6	R MCA(2+) L ACA(3+) L MCA(3+)	R M1 200 mg L SICA 200 mg L A1 200 mg	Moderate	Further decline GCS 4	
13–3rd treatment					4	3	GCS 4	R MCA(2+)	R M1 200 mg	Mild	Mild improvement GCS 6	Died
14	54,F	R P Co A (1)	II, 14	4	3	12 hrs	Decreased LOC	L ACA(3+) R ICA(1+)	L A1 300 mg R SICA 180 mg	Moderate	Marked improvement GCS	Good recovery
							GCS 11	R ACA(2+) R MCA(3+)	R M1 120 mg	14		

Note.—ACA indicates anterior cerebral artery; ACoA, anterior communicating artery; BA, basilar artery; GCS, Glasgow coma score; ICA, internal carotid artery; LOC, level of consciousness; MCA, middle cerebral artery; PCoA, posterior communicating artery; SICA, supraclinoid internal artery; and T, intubated.

* Hunt and Hess and Glasgow coma score.

† Amount and distribution of subarachnoid blood on CT (25).

‡ 1+ indicates mild; 2+, moderate; and 3+, severe.
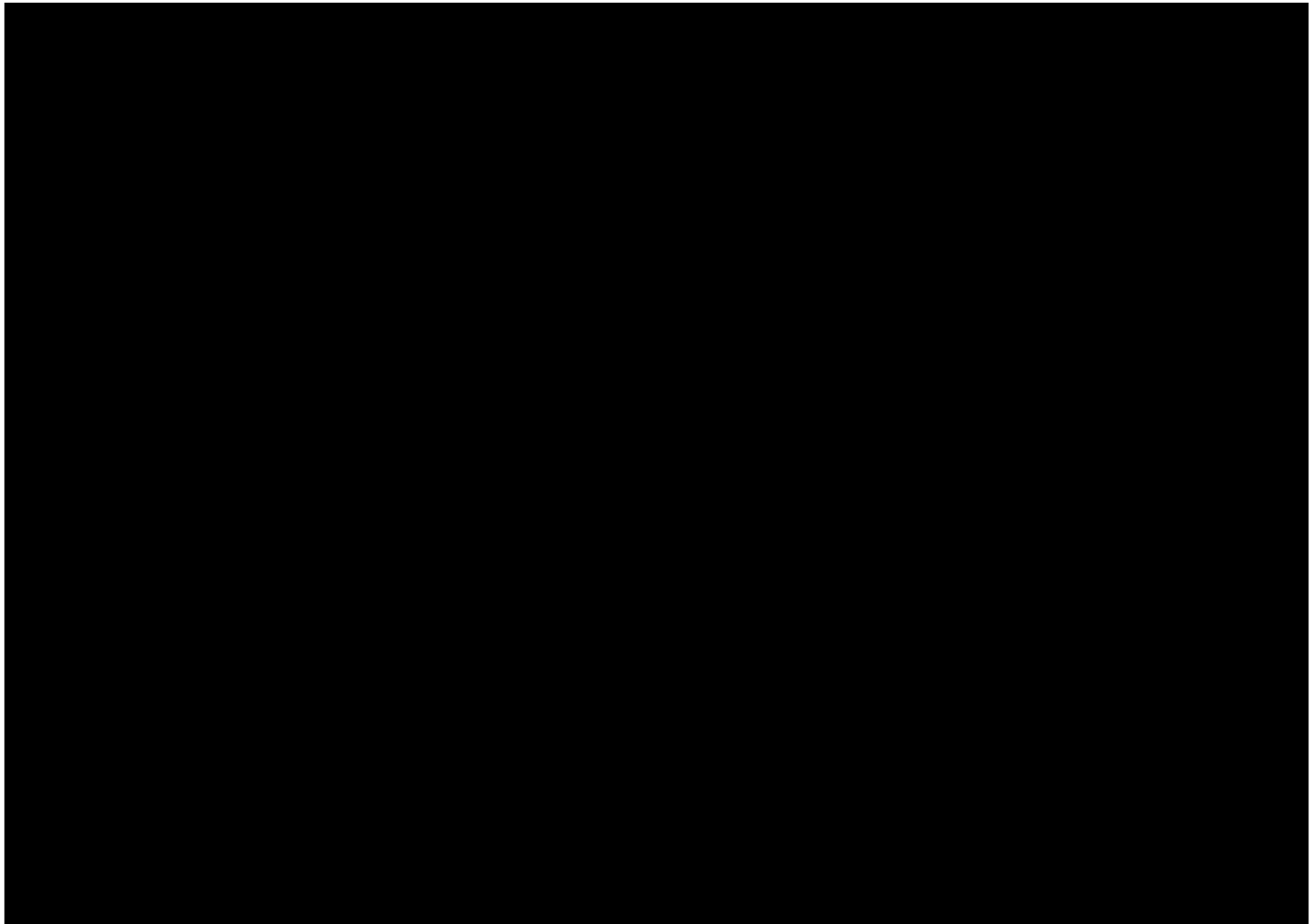
§ Glasgow outcome score (1).

Fig 1. Patient 9. A 71-year-old woman in whom decreased consciousness level and dysphasia developed after clipping of a right posterior communicating artery. *A* and *B*, Oblique views of bilateral internal carotid angiograms demonstrate moderate to severe vasospasm, especially in the anterior cerebral arteries bilaterally, with poor distal opacification (*arrowheads*).

C, After infusion of 100 mg of papaverine in the right supraclinoid internal carotid artery, the A1 segment shows dilatation (*arrow*), but the distal anterior cerebral artery remains extremely narrowed (*arrowhead*). Significant vasodilation is noted in the middle cerebral artery.

D, Superselective infusion of 100 mg papaverine into the right anterior cerebral artery results in significant vasodilatation.

E, and *F*, Oblique views of bilateral internal carotid angiograms. Good angiographic improvement of spasm is shown. Spasm in the left anterior cerebral artery is also alleviated, probably because of papaverine crossing the anterior communicating artery.

G, Posteroanterior projection of left internal carotid angiogram demonstrates good cross filling of right anterior cerebral artery (*arrow*), which was not seen before papaverine infusion, confirming significant reversal of spasm of left A1 and the anterior communicating artery. Marked clinical response was noted with improved consciousness level and speech.

sumably by crossflow through the anterior communicating artery; this obviated superselective catheterization of the contralateral A1 (Fig 1). Middle cerebral arterial spasm responded well in 19 of the 20 treatments, basilar artery spasm improved on all 3 occasions, and posterior cerebral artery spasm in all 6 treatments.

Follow-up angiography was performed on five patients, four because of failure to improve and one for routine follow-up. Three showed recurrent vasospasm (patients 8, 11, and 13). One showed no recurrence of vasospasm in the previously treated carotid territory but had basilar territory spasm, which was treated (patient
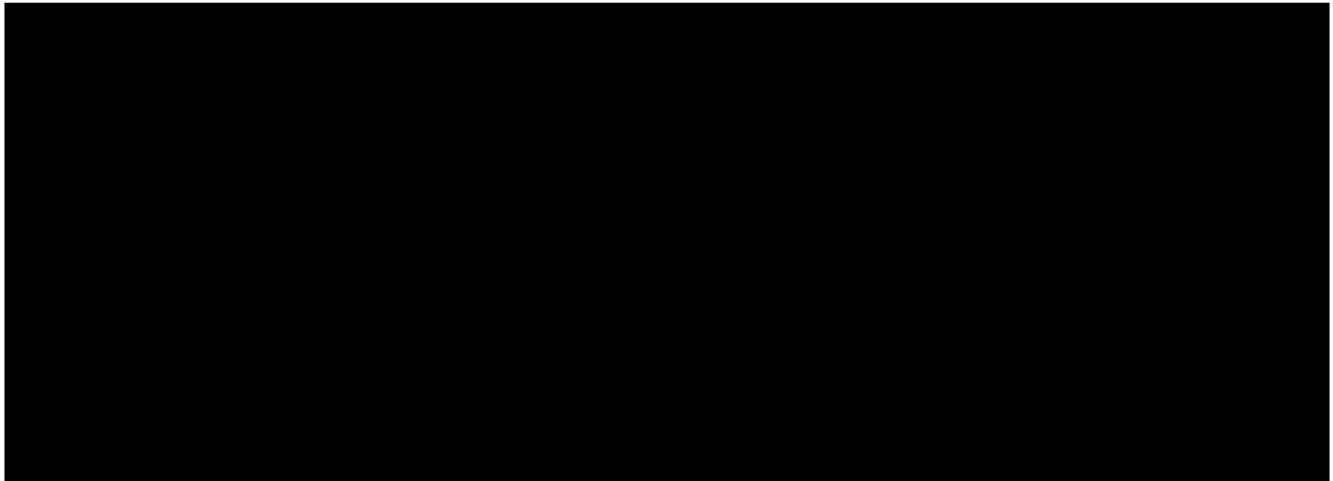
Fig 2. Patient 14. A 54-year-old woman developed marked reduction of consciousness level and agitation without focal neurologic deficit after clipping of a right posterior communicating artery aneurysm.

A, Posteroanterior right internal carotid angiogram demonstrates moderate spasm in M1 and M2 middle cerebral artery and A1 and A2 anterior cerebral artery (*arrowheads*). Mild spasm is also noted in the supraclinoid internal carotid artery at the clip site (*arrow*).

B, After papaverine infusion, 120 mg in the M1 segment and 180 mg in the supraclinoid internal carotid artery, there is significant vasodilatation, especially in the middle cerebral artery. Focal spasm at the clip site persists (*arrow*).

C, Follow-up angiogram 15 hours later. Focal spasm of the supraclinoid internal carotid artery is much less obvious (*arrow*). There has been marked clinical improvement by this time, and she became fully alert and oriented within the next 24 hours.

12). The 5th patient was the only one in whom repeat angiography was performed after early marked neurologic improvement; further angiographic improvement was shown 1 day after papaverine treatment (patient 14) (Fig 2).

Clinical Results

Seven (50%) of the 14 patients showed marked acute clinical improvement (patients 1, 3, 4, 9, 10, 11, and 14) within 24 hours of papaverine therapy, although patient 11 responded only after a second treatment. Clinical outcome according to pretreatment neurologic groups was as follows: (*a*) complete early recovery in the single patient with focal neurologic deficit only (patient 4); (*b*) complete early recovery or marked early improvement in 4 of the 9 patients with focal deficits plus reduced conscious level (patients 1, 3, 9, and 10); (*c*) excellent early recovery in 2 of the 4 patients with reduced consciousness level without focal signs (patients 11 and 14).

Late follow-up showed good recovery in seven patients, moderate disability in three, severe disability in two, and vegetative survival in one, according to the Glasgow Outcome Scale. One patient died.

Clinical results did not show direct correlation with angiographic response. For example, three patients with moderate to excellent angiographic improvement showed no change in clinical status (patients 5, 6, and 13), and two patients with a mild angiographic improvement had dramatic clinical recovery (patients 3 and 10).

Likewise in this series, there was no apparent correlation between clinical outcome and elapsed time from subarachnoid hemorrhage or surgery, Fisher grade of admission CT, duration of new neurologic symptoms (although all were treated within 2 days), dose or site of infusion of papaverine, or distribution of angiographic spasm.

There was no early or late clinical deterioration in any of the patients who showed acute marked neurologic improvement after papaverine treatment; that is, recurrence of clinical vasospasm was not seen in any of the patients who showed initial positive response.

Four patients had repeat treatment: three were treated twice, and one was treated three times. Only one patient (patient 11) showed excellent clinical improvement after repeat treatment (Fig 3).

One patient (patient 13) demonstrated particularly aggressive vasospasm. She was treated three times over 4 days, with spasm progressing to affect more vessels between the first and second treatments and recurring after
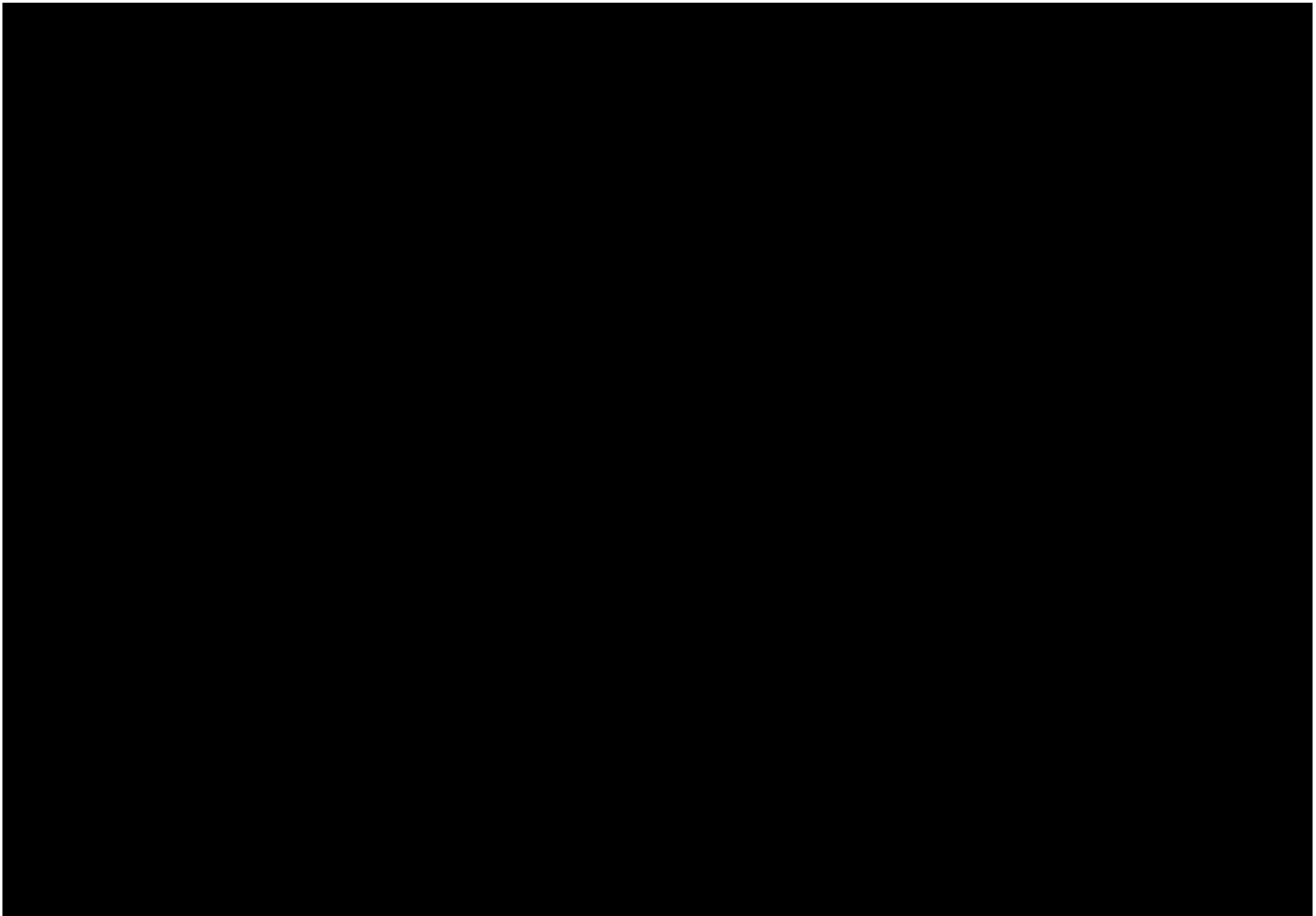
Fig 3. Patient 11. A 31-year-old woman in whom depressed consciousness level developed after clipping of a left posterior communicating artery. *A–C*, Bilateral internal carotid and left vertebral angiograms show severe spasm bilaterally in the supraclinoid internal carotid artery, anterior cerebral artery, middle cerebral artery, posterior cerebral artery, and basilar artery arteries (*arrowheads*). An incidental aneurysm is also noted at the cavernous segment of right carotid artery.

D–F, After papaverine infusion, 80 mg in the right M1 middle cerebral artery, 100 mg in the right supraclinoid internal carotid artery, 150 mg in the left supraclinoid internal carotid artery, and 100 mg in the basilar artery, significant reversal of spasm is seen. Despite this, the patient's general condition continued to worsen. Repeat angiogram the next day showed recurrence of spasm similar to that noted on the preceding day. Papaverine infusion was repeated in a similar fashion but with higher dose to basilar artery (150 mg) and resulted in significant angiographic improvement, as occurred previously. After the second treatment, she showed marked clinical improvement and by the next morning was following commands and had normal power bilaterally.

each successful treatment. She did not ever show lasting clinical improvement after papaverine and died several days later.

All cases had multiple follow-up CT examinations after papaverine treatment, and none showed evidence of hemorrhage.

Complications

There were no episodes of systemic hypotension during or after papaverine treatment despite the use of high doses in several patients.

Three patients had procedural complications. One patient (patient 3) suffered permanent monocular blindness and had an ophthalmologic diagnosis of orbital infarction. Her papaverine therapy was via a transaxillary approach, necessitated by vascular anatomy related to an abdominal aortic aneurysm. Optimal Tracker catheter placement was not possible, and papaverine infusion was performed in the cavernous internal carotid artery. Three hundred milligrams of papaverine was administered over 1 hour, using continuous pump infusion. Prepapaverine and postpapaverine angiograms showed no change in the ophthalmic artery; however, chemosis, midriasis, and blindness developed shortly after the

procedure, despite marked improvement of her neurologic condition.

One patient (patient 8) suffered an internal carotid artery dissection during guiding catheter placement. Tortuous vessels made positioning of the guiding catheter in the cervical internal carotid artery difficult and a flow-limiting dissection occurred. He was heparinized and suffered no neurologic decline related to this dissection.

One patient (patient 13), who had no previous seizure history, had a generalized tonic-clonic seizure after infusion of 200 mg of papaverine. The ictus was brief and readily controlled with intravenous diazepam.

Discussion

Background

The International Cooperative Study on the Timing of Aneurysm Surgery (7) ranked vasospasm as the leading cause of major morbidity and mortality in patients with ruptured intracranial aneurysms. Angiographic arterial narrowing is demonstrated in 40% to 70% of patients after subarachnoid hemorrhage. Clinical vasospasm is seen in 20% to 30% of patients, typically occurring between days 2 to 17 and causing major stroke or death in approximately 50% of patients if not treated (5, 12, 24). Hypertensive hypervolemic hemodilutional therapy and the use of calcium channel blockers are effective in the treatment of vasospasm; however, approximately 40% of patients in whom ischemic deficits caused by vasospasm develop do not respond to this treatment and either remain stable with reduced neurologic function or continue to decline (9). For this group of patients, balloon angioplasty and intraarterial vasodilator infusion have been advocated by different authors, based on differing hypotheses regarding the pathogenesis of vasospasm (1–20). Angiographic arterial narrowing has been attributed to abnormal smooth muscle activity, both vasoconstriction and loss of vasodilating ability, and cytoarchitectural changes, which affect the intima, media, and adventitia (2, 4–6, 9–12, 25). Recently, it has been strongly advocated that clinical vasospasm is caused by profound and sustained muscle spasm rather than by structural wall changes and that it is responsive to vasodilator therapy (8, 9).

Balloon Angioplasty

There are several published series concerning percutaneous transluminal angioplasty for refractory vasospasm (13–17, 22, 26, 27). The initial series by Zubkov et al (13) is the largest with 33 patients. Improvement was noted after angioplasty; however, detailed data were not presented.

Higashida et al (16) treated 28 patients using a nondetachable silicone balloon (ITC, South San Francisco, Calif) and reported acute neurologic improvement in 17 (60.7%). Newell et al (15) treated 10 patients, with 8 (80%) showing improvement and 4 (40%) showing acute dramatic clinical response.

The issue of distal vessel involvement is discussed in several of the balloon angioplasty series (10, 13, 14, 16, 18, 22). Zubkov et al felt that only the basal segments required treatment, believing that these were the only pathologically narrowed vessels (13). Although this is true in some cases, Brothers et al observed persisting lumenal narrowing distal to angioplastied segments in patients with severe diffuse spasm. They proposed that treatment of branches beyond the circle of Willis is likely to be very important (22).

Although elegant technical solutions to improve branch access have been developed (22), superselective catheterization can be a problem during balloon angioplasty, particularly in accessing the anterior cerebral artery and branches beyond the basal cisterns (17). It is noteworthy that although middle cerebral and basilar artery territory deficits may dominate the clinical picture, anterior cerebral artery ischemia can be responsible for lower extremity signs and abulia (psychomotor retardation without long tract signs) (28).

In experienced hands, balloon angioplasty has a good safety record; however, complications have been described, including delayed thrombosis at an angioplasty site, fatal vessel rupture, fatal intracranial hemorrhage attributed to reperfusion of an infarcted area, and rebleeding from an unprotected aneurysm following proximal vessel dilatation (14–16, 29).

Intraarterial Papaverine

More recently, the successful use of intraarterial papaverine for the treatment of vasospasm has been reported (18–21, 23). These

studies have shown that satisfactory vasodilation can be achieved in many cases, which is highly suggestive that the arterial narrowing early in the course of symptomatic human vasospasm is predominantly caused by smooth muscle contraction rather than by cytoarchitectural changes or loss of distensibility of the vessel wall.

Intraarterial vasodilators have been advocated for several reasons: (*a*) there are instances when a spastic segment will not allow passage of the balloon catheter, (*b*) branch access, including the A1 anterior cerebral artery, is difficult, (*c*) balloon angioplasty does not treat distal or perforating vessels, and (*d*) there are specific risks of angioplasty as outlined above (14, 15, 17–21).

Kassell et al (19) treated 12 patients on 14 occasions, empirically deciding on a dose of approximately 300 mg of papaverine given over 1 hour. Angiographic improvement was seen with 8 (57%) of the 14 treatments, and dramatic reversal of profound neurologic deficits was seen in 3 (25%) of the 12 patients.

Kaku et al (18) treated 10 patients using a combination of balloon angioplasty followed by superselective infusion of papaverine with the dose ranging from 6 to 20 mg plus nicardipine; urokinase was also administered in 2 patients. Although 8 (80%) of 10 patients showed early improvement, it is not possible to delineate the effect of papaverine alone in this series because of the combination therapy.

Recurrence of ischemic symptoms with recurrent arterial narrowing is considered one of the major drawbacks of this technique. This situation does occur in a significant number of cases (19, 20). Also of concern are those patients who show no clinical response despite a good angiographic result. Delay in initiation of papaverine treatment, inadequate doses, and inadequate duration of treatment have been suggested as possible mechanisms (19, 20).

Analysis of Current Series

This series of patients showed that almost all constricted arteries could be successfully dilated with intraarterial papaverine. Seven (50%) of the 14 patients showed dramatic acute clinical improvement, which compares favorably with the published results for balloon angioplasty and papaverine infusion (14–16, 19), although all series are small and only superficial comparisons can be made. The long-term outcome appears satisfactory as compared with earlier series; however, the long-term results are also affected by many other variables, such as intracerebral hemorrhage, brain edema, hydrocephalus, metabolic derangement, and iatrogenic complications.

The elapsed time from subarachnoid hemorrhage to treatment had no bearing on the effectiveness of papaverine in this group of patients, which strongly suggests that even quite late neurologic decline is caused by vasodilator-responsive vasospasm rather than by nonresponsive spasm or cytoarchitectural wall changes. Although there was no obvious correlation between duration of new neurologic signs and outcome, it still seems prudent to treat with papaverine as early as possible, with the aim of preventing irreversible ischemic damage (17).

There appear to be two separate patient subgroups in this series. One group responded very well to papaverine without further clinical decline, indicating no recurrence of clinical vasospasm. A second group of patients showed recurring recalcitrant spasm that resisted multiple papaverine treatments. There is currently no obvious method of recognizing and excluding the latter group from treatment. Group categorization is further complicated by the response shown by patient 11, who had a dramatic acute recovery after a second treatment for recurrent vasospasm. This case raises the question of whether all nonresponders should be restudied and retreated at least once in the hope of increasing the neurologic salvage rate.

Our current protocol is to treat patients with refractory clinical vasospasm at the earliest opportunity. If there is poor clinical response by day 1 after treatment, patients are restudied and retreated was required. If recurrent spasm becomes an obvious problem as more patients are seen, combination therapy with papaverine and balloon angioplasty may offer a solution, as previously suggested (18, 20).

The disparity between angiographic and clinical results highlights one of the major problems encountered with endovascular therapy for vasospasm: deciding which vessels require treatment. Angiographically visible arterial spasm occurs in the distal vessels as well as in the basal segments. These distal vessels usually show good vasodilatation after papaverine, a result that could not be achieved with balloon angioplasty alone. Further, it seems likely that

small and perforating arteries, along with the proximal larger arteries, play a role in clinical vasospasm and that they will respond to papaverine (3, 14). This treatment of entire arterial territories may increase the likelihood of clinical recovery, as seen in two patients who had a remarkable clinical response in spite of only mild angiographic gain (patients 3 and 10). Likewise, consideration should be given to liberal treatment of multiple regions if there is poor angiographic correlation with neurologic deficits. Cerebral blood flow studies may help clarify regions of ischemia that require treatment (17, 30, 31).

This series differs from earlier reports in that superselective infusion was used more frequently, although no obvious correlation was found between clinical response and the site of papaverine administration. Despite this result, superselective catheter placement may be important in many cases to ensure adequate delivery of papaverine to target territories. Several examples were seen where there was no papaverine effect on a severely constricted artery because the drug was diverted into vessels with lower resistance. Additionally, when papaverine preferentially flows into these more patent vessels, they usually vasodilate (as shown in Fig 1C), and this causes further flow reduction through the spastic arteries. This problem can be remedied by superselective papaverine infusion into the severely narrowed vessel. There were no obvious complications directly attributable to this superselective technique.

With increasing experience, we used higher doses of papaverine, usually because of the need to treat multiple territories and the desire to infuse reasonable doses into each territory. No obvious relationship was found between increased papaverine dose and clinical outcome. The ideal dose is not yet defined.

The complication of monocular blindness after papaverine infusion in patient 3 is difficult to explain. Kassell et al (19) also described a single case of transient pupillary dilatation that resolved after papaverine infusion was ceased. Accordingly, it may be prudent to infuse papaverine distal to the ophthalmic artery. The brief, rapidly controlled generalized seizure that occurred in one patient during papaverine infusion also is difficult to explain. This seizure may have been caused by the papaverine infusion—seizures during papaverine therapy have been previously reported (20).

Conclusion

Intraarterial papaverine infusion was effective in dilating spastic arteries in most patients with symptomatic vasospasm after subarachnoid hemorrhage. This small series showed encouraging clinical results with no recurrence of neurologic deterioration in those patients who responded well to papaverine. Superselective infusion appears to be indicated in some cases for adequate papaverine delivery, although further study is needed to assess its role overall.

Prospective trials are required to assess the efficacy of papaverine, balloon angioplasty, or a combination of both and to decide the best way to use them in patients with clinical vasospasm. It is also necessary to ensure that these treatments are improving the natural history of this disorder.
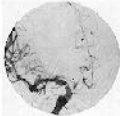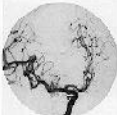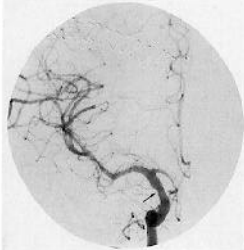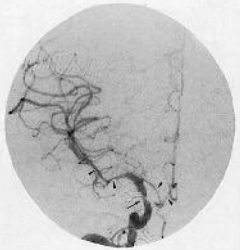
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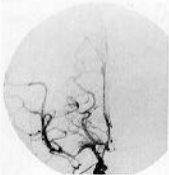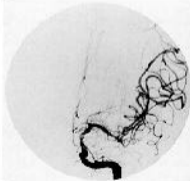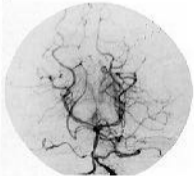31. Yonas H. Cerebral blood measurements in vasospasm. *Neurosurg Clin N Am* 1990;1:307–318

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