Intraarterial Papaverine for the Treatment of Vasospasm

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Summary: The authors describe the use of intraarterial papaverine to treat vasospasm following subarachnoid hemorrhage. Two cases are reported: a 40-year-old woman with a posterior communicating artery aneurysm and a 67-year-old man with a posterior cerebral artery aneurysm. Both patients developed symptomatic, angiographically demonstrated vasospasm that responded to papaverine infusion.

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

After subarachnoid hemorrhage (SAH), delayed ischemic neurologic deficits caused by vasospasm can develop in up to 30% of patients (1, 2). A variety of therapies have been used to treat vasospasm, including pharmacologic agents and volume expansion to increase perfusion. Patient outcome has been improved with the use of hypervolemic, hypertensive therapy and calcium channel blockers. However, a significant number of patients still develop permanent deficits and continue to deteriorate (3, 4). Recently, balloon catheter dilatation of arteries narrowed by vasospasm has been used. Angioplasty shows promise in the treatment of a select group of patients with vasospasm involving the proximal cerebral circulation (5–9). However, the technique is able to dilate only more proximal vessels in the cerebral circulation successfully, and complications such as arterial rupture can occur (10). This study reports two cases in which direct arterial infusion of papaverine was used for the treatment of vasospasm. These patients had undergone maximal medical therapy and were not candidates for balloon angioplasty because of the location of vasospasm.

Case Histories

Case 1

A 40-year-old woman was brought to the emergency room with nausea, vomiting, and confusion. Admission work-up included a head computed tomography (CT) that showed extensive subarachnoid blood with large amounts of clot in the left sylvian fissure. Angiography demonstrated an 8-mm left posterior communicating aneurysm. The patient also developed neurogenic pulmonary edema and suffered an episode of ventricular tachycardia shortly after admission. Surgery was performed 1 day after hemorrhage. At the time the patient was comatose and showing some purposeful movements in response to pain stimulus (Grade IV, Hunt and Hess scale). At the time of aneurysm-clipping tissue plasminogen activator was instilled into the cisterns around the brain to help clear subarachnoid blood. The patient was treated with nimodipine, volume expansion, and hypertension for vasospasm.

On the first postoperative day, her eyes were open and she was moving all four extremities, although not following commands. She gradually deteriorated, and by the third postoperative day (4 days after SAH), she was much less responsive and did not move her right extremities, even to painful stimulus. CT scan showed some blood remaining in the sylvian fissure with adjacent edema along the margin of the temporal lobe. Angiography showed diffuse vasospasm of the left carotid territory, which included the left A1 and M1 segments of the anterior and middle cerebral arteries. Spasm was also seen in distal branches of both arteries. Mild spasm was noted in the right carotid and vertebrobasilar territories.

A coaxial catheter system utilizing a Tracker 18 catheter (Target Therapeutics, San Jose, CA) was advanced into the left M1 segment and 90 mg of papaverine were infused over 20 minutes. For first two infusions of papaverine in this patient, 120 mg of papaverine were diluted in 50 mL of normal saline. For all subsequent infusions used in this study, 300 mg of papaverine were mixed in 100 mL of normal saline. All the doses were administered by pump infusion. Digital angiography showed a mild response with some dilatation of the M1 segment. The catheter was withdrawn into the supraclinoid carotid to treat both the middle and anterior cerebral artery territories, where an additional 120 mg of papaverine were infused.

Angiography after papaverine infusion showed significant reversal of vasospasm in the left anterior and middle cerebral arteries (Figs. 1B and 1C). After papaverine infusion, the patient had two brief generalized seizures that were controlled with valium and dilantin. The next day (5th

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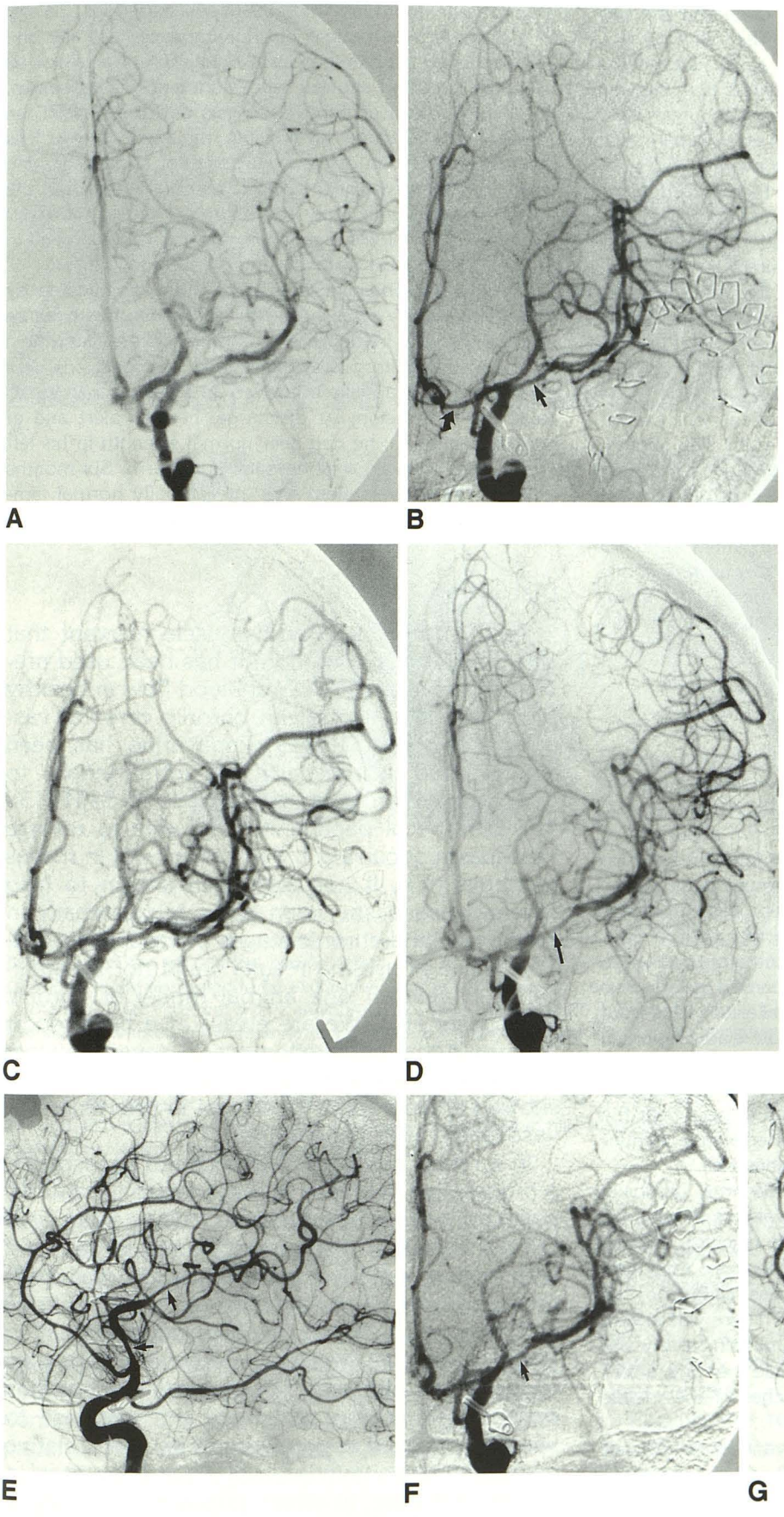

Fig. 1. Case 1, a 40-year-old woman after SAH from a left posterior communicating artery aneurysm.

A, Anteroposterior left internal carotid artery angiograms performed on the day of SAH. The double density in the region of the supraclinoid carotid is the posterior communicating artery aneurysm.

B and C, Anteroposterior views from left carotid angiogram performed 4 days after SAH; pretreatment (*B*) and post-treatment (*C*) with papaverine. Pre-papaverine treatment spasm is seen in the anterior and middle cerebral artery territories. Most notable are areas of spasm in the A1 segment (*curved arrow*) and in the M1 segment (*straight arrow*). Post-papaverine angiogram (*C*) demonstrates significant reversal of vasospasm best seen in the A1 and M1 segments.

D and E, Anteroposterior and lateral left internal carotid artery angiograms done 7 days post-SAH showing recurrent vasospasm 2 days after the initial treatment with papaverine. Spasm is again noted in the M1 segment (*arrow, D*).

E, Segments of the angular artery of the middle cerebral artery also show vasospasm (*arrows, E*). *F and G*, Anteroposterior and lateral left carotid angiograms done post-papaverine infusion on the same day as *D* and *E*. Significant response is again noted in the areas of vasospasm, with dilatation again noted in the M1 segment of the middle cerebral artery (*arrow, F*) and in the areas of vasospasm noted in the angular artery (*arrows, G*).

day post-SAH), the patient's eyes were open and she was moving her right side spontaneously. By the following day, however, she was more obtunded and again not moving her right side. Angiography was repeated and showed recurrent vasospasm in the same areas seen previously, although none of the segments appeared quite as narrowed as before the initial treatment with papaverine (Figs. 1D and 1E). A 5F Berenstein catheter was then placed in the internal carotid artery at the C1 level. As vasospasm was again present in both the anterior and middle cerebral artery territories, it was decided to infuse papaverine directly in the high cervical carotid via a 5F catheter rather than via a more complicated superselective coaxial system. Over 20 minutes, 300 mg of papaverine were infused. A significant response in the left anterior and middle cerebral arteries was again noted (Figs. 1F and 1G).

The day after the procedure, the patient was awake, following commands, and moving her right side spontaneously. At discharge to a rehabilitation facility (32nd postoperative day), she had good strength in all extremities and was following commands, but had an expressive aphasia. By 5 months after discharge, the patient's aphasia had cleared. She demonstrated mild problems with short-term memory and a left homonymous upper outer quadrantanopsia, but she was fully independent with her activities.

Case 2

A 67-year-old man presented with headache, nausea, vomiting, and neck stiffness. CT scan showed a moderate amount of subarachnoid blood diffusely in the cisternal spaces. At angiography, there was a 6-mm aneurysm of the right posterior cerebral artery at the junction between the P1 segment and the posterior communicating artery. In addition, the right internal carotid artery was chronically occluded and the left internal carotid artery had an 80% stenosis at its origin. No cross-filling via the anterior cerebral artery was seen when the left carotid artery was injected; instead, the right middle cerebral artery filled from the vertebral injection with antegrade flow via an enlarged right posterior communicating artery (Fig. 2A). The aneurysm was clipped at surgery and tissue plasminogen activator was instilled into the basal cisterns to help clear the SAH. Postoperatively, the patient remained awake, continued talking, and moved all four extremities well.

Over the next several days, he became gradually drowsy, and at 6 days after SAH, he was not moving his left extremities despite treatment with calcium channel blockers, hypertension, and volume expansion. Angiography demonstrated continued lack of cross-filling from the left carotid to the right carotid territory. There was severe vasospasm of the right posterior communicating artery and moderate vasospasm in the right middle cerebral artery with poor filling of the opercular branches of the middle cerebral artery.

A 5F Berenstein catheter was advanced in the left vertebral artery to the C1 level and 300 mg of papaverine were infused over 20 minutes. This resulted in significant angiographic improvement in the vasospasm (Figs. 2B and 2C). However, the patient did not improve clinically and had continued left hemiparesis. Angiography was repeated 24 hours later and showed redevelopment of vasospasm. A repeat infusion of papaverine was performed with the catheter at the same level using the same dose. This resulted in dilatation of the right posterior communicating artery and segments of the middle cerebral artery, but the response was significantly less than previously observed (Figs. 2D and 2E). No significant change was observed in the patient's clinical status during the next few days.

The patient's hospital course became complicated by severe respiratory disease due to congestive heart failure and hemophilus influenza pneumonia. This necessitated prolonged ventilatory support, and a tracheostomy was performed. He gradually improved and was discharged 65 days after admission. At discharge, he was alert and of normal mentation; he had near normal strength in his left leg, but had marked weakness in his left arm. Six months after his SAH, the patient was intellectually normal, ambulated with a brace, and had left arm paresis.

Discussion

Papaverine is a smooth muscle relaxant that causes arteriolar dilatation. It has been used previously to increase cerebral blood flow in healthy patients and patients with chronic cerebral vascular ischemia (11, 12). Papaverine has been administered intrathecally and intraarterially to treat vasospasm in animal models of SAH (13–16). Intrathecal papaverine was able to reverse vasospasm occurring 1 week after SAH in rhesus monkeys (13). It has also been shown to help reverse vasospasm when given intraarterially in both acute and chronic stages of vasospasm (14, 16). These promising results could not be duplicated in at least one animal model of chronic vasospasm (15). We are aware of a brief report of intraarterial papaverine use in seven patients with vasospasm (17). Four of the seven patients showed angiographic or clinical improvement of vasospasm after papaverine.

In a rabbit model of SAH-induced vasospasm, a progressive decrease in response to intraaterial papaverine was observed 3–5 days after SAH (18). This lack of response appeared to correlate with experimentally measured artery wall stiffness and loss of contractility to norepinephrine and potassium. These findings suggest that in later stages of vasospasm, when histologic changes are observed, artery wall damage has occurred. This may attenuate the response to vasodilators such as papaverine (18). This relative resistance to papaverine may have been seen in the second case, in which papaverine infused 7

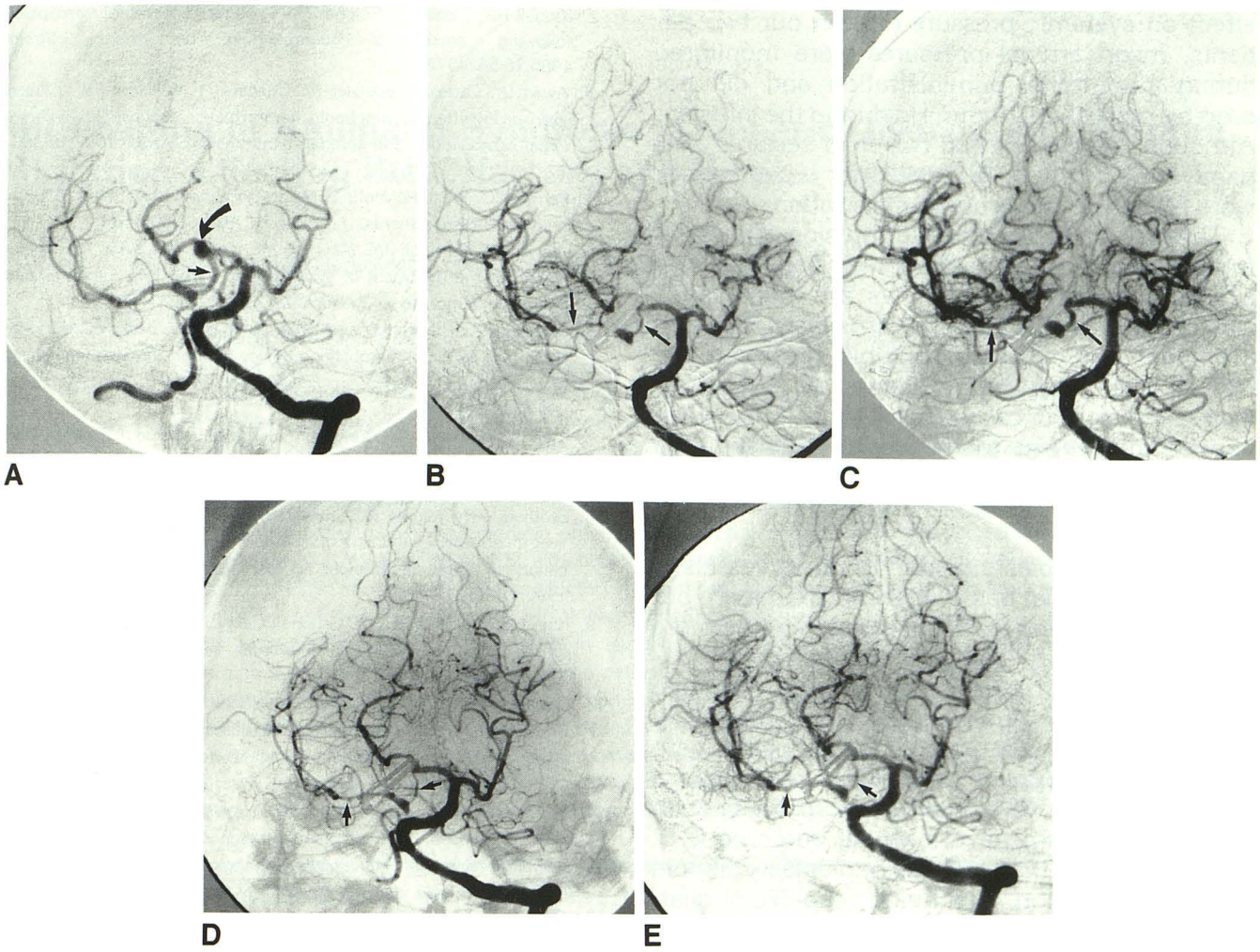

Fig. 2. Case 2, A 67-year-old man with SAH from a right posterior cerebral artery aneurysm.

A, Left vertebral angiogram in the anteroposterior projection. A posterior cerebral artery aneurysm is noted at the junction between the posterior communicating artery and the P1 segment (*curved arrow*). Because the right internal carotid artery was chronically occluded and the left internal carotid artery did not show evidence of cross-filling into the right carotid territory, supply of the right carotid territory was noted to be exclusively from a large posterior communicating artery (*straight arrow*).

B and C, Left vertebral artery angiogram in Towns projection done before (*B*) and after (*C*) papaverine infusion 6 days after SAH. Vasospasm is noted in the posterior communicating artery and right M1 segment per infustion (*arrows, B*). This is significantly reversed after papaverine infusion (*arrows, C*).

D and E, Left vertebral artery angiograms done 7 days after SAH before (*D*) and after (*E*) papaverine infusion. Severe spasm is again noted in the posterior communicating artery and the right middle cerebral artery M1 segment (*arrows, D*) 24 hours after the first infusion with papaverine. Papaverine was again infused and a mild dilatation was noted (*arrows, E*), although the response was not as dramatic as with the first infusion of papaverine.

days after SAH did not yield as good a vasodilatory response. Clearly, many subjects will be needed to evaluate the potential window of time for response to a vasodilator such as papaverine.

The vasodilatory effects of papaverine are transient and the vasospasm appears to reverse 24 hours after treatment (13, 16). These results are confirmed in the two cases reported here. Both patients had angiographically demonstrable recurrent vasospasm 24 hours after treatment, although the spasm had not returned completely to the stenosis seen prior to papaverine infusion. This suggests that recurrent infusion, as was done in these two cases, may be needed. Other alternatives, such as intrathecal administration via a shunt, may prove to be useful routes for continuous infusion.

Papaverine relaxes smooth muscle of larger blood vessels and also acts to reduce peripheral resistance, so that it can have a hypotensive

effect on systemic pressure (19). In our two patients, mean arterial pressures were monitored during intraarterial administration and did not drop by more then 20 mm Hg during the infusion. Although one patient had two brief seizures after papaverine infusion, it is not clear whether they were related to the drug administration.

The use of superselective infusion allows for more controlled administration of papaverine to a select territory where flows are significantly slowed. However, when the vasospasm is diffuse in nature and flows in multiple territories are slowed, there may be no advantage in superselective infusion. In cases such as this, rather than expose the patient to the additional risks of a superselective coaxial catheter system, a less selective arterial infusion may prove to be adequate.

Balloon angioplasty is able to dilate vessels in the more proximal basal cerebral circulation, but is not as well suited for vasodilatation of the more distal vasculature (5–9). Angiographically confirmed vasospasm is unfortunately not restricted to these proximal territories and is seen frequently in distal arteries (20). In addition, ischemic neurologic deficits appear to correlate more with a diffuse form of vasospasm, and patients with diffuse vasospasm have a worse outcome (21). While it is true that balloon angioplasty should improve circulation, a technique capable of dilating both proximal and distal arterial territories would be of benefit. Consideration should also be given to a combined therapeutic approach. For example, balloon dilatation may be of benefit in the management of those proximal arterial segments refractory to vasodilatation with papaverine.

In conclusion, intraarterial papaverine has been used to reverse angiographically demonstrated vasospasm in two patients with ischemic neurologic deficits after SAH. In one patient, a symptomatic improvement occurred after papaverine administration. In both patients, the observed dilatation in response to papaverine reversed to some degree 24 to 48 hours after its administration. Further evaluation will clearly be needed to establish the role of a smooth muscle vasodilator such as papaverine in the management of ischemia due to vasospasm.

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