Intra-arterial Papaverine Treatment for Cerebral Vasospasm: Our Experience and Review of the Literature

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Abstract

We described the techniques and efficacy of intra-arterial papaverine hydrochloride infusion (IA-PAP) for symptomatic vasospasm due to aneurysmal subarachnoid hemorrhage based on our experience and review of the literature. Angiographic improvement occurred almost always, but only 50% of patients who presented with acute symptoms showed remarkable clinical improvement after the first, second, or third IA-PAP. Recurrent vasospasm after IA-PAP frequently occurred and this seems to be an apparent source of controversy regarding its efficacy. Review of the literature indicates that IA-PAP may be most effective in combination with percutaneous transluminal angioplasty. Further controlled studies should be conducted regarding papaverine's true efficacy including most effective papaverine concentration and rate of infusion, maximum total dose, site of infusion, timing of treatment, and selection of patients.

Key words: vasospasm, drugs, intra-arterial infusion, subarachnoid hemorrhage

Introduction

Angiographic vasospasm is known to occur in approximately 70% of patients between 4–9 days after aneurysmal subarachnoid hemorrhage (SAH). Clinical vasospasm associated with decreased level of consciousness and/or neurological deficits develops in 20–30% of these patients. Forty percent to 50% of these patients develop major strokes or death if left untreated.^{11,26,27)} Various vasodilators have been investigated to treat this condition^{1,3,16,17,19,29,31,43,46,50,52,53,59,63)} but no single agent has been proven to be significantly effective. Hypertensive hypervolemic, hemodilutional therapy and calcium channel blockers have achieved limited success.¹¹⁾ Many reports have been published regarding percutaneous transluminal angioplasty (PTA) for the treatment of cerebral vasospasm.^{6,10,12,20,30,47,51,62)} Approximately 40–60% of patients have shown early objective improvement after PTA in experienced hands.^{10,12,20,30,47)}

Over the last several years, intra-arterial papaverine hydrochloride infusion (IA-PAP) has been utilized to treat cerebral vasospasm induced by SAH.^{7,23–25,28,33,34,36,37,39,48,49,54,61)} However, its efficacy is

controversial and many issues including optimal indications, timing of treatment, papaverine dose and concentration, and delivery method, etc., seem to remain poorly defined.

In this report, we would like to summarize our experience with IA-PAP and to review how this treatment is currently positioned in the literature.

Materials and Methods

A total of 28 patients received IA-PAP for arterial vasospasm between February 1992 and September 1997. There were two groups of patients who underwent IA-PAP. The majority (Group A) consisted of 24 patients who presented with acute deterioration of level of consciousness with or without neurological deficits after clipping aneurysms. Thirty-six treatment sessions were given to these patients; 15 received only one IA-PAP treatment and six received a second, and three had a third treatment on consecutive days. IA-PAP was begun 1 to 16 days following SAH and 6 hours to 2 days after clinical manifestations of spasm for these patients. The second group (Group B) consisted of four patients who presented with no acute symptoms, but with continu-

ous deterioration or with lack of clinical improvement after aneurysmal surgery and whose angiograms showed vasospasm. Three of them received a single treatment and one had a repeat treatment the next day. All 28 patients had a Fisher grade²³ 3 or 4 SAH on admission and Glasgow Coma Scale score ranging from 5–14. All patients in both groups were maintained as hypervolemic hypertensive and had received calcium channel blockers. Using a microcatheter, papaverine was infused into the supraclinoid internal carotid artery (ICA) or basilar artery, or more distally into the anterior (ACA), middle (MCA), or posterior cerebral arteries (PCA). For most treatment sessions, papaverine was mixed with normal saline at concentrations ranging from 3–6 mg/ml (0.3–0.6%). In one session for the treatment of severe ACA spasm, 10 mg/ml (1%) was used. The total dose per treatment ranged from 300 mg to 600 mg and exceeded 400 mg on 15 occasions. Papaverine was injected manually using a combination of brisk pulsatile and slow infusion, at 1–2 ml/min. The ICA or basilar artery doses ranged from 100–450 mg but were typically between 100–300 mg. ACA, MCA, or PCA doses ranged from 30–300 mg, but were typically between 70–200 mg. Cerebral blood flow (CBF) study was performed using xenon-computed tomography (CT) in three patients; one had the study before and after IA-PAP and two received the studies only after IA-PAP.

Results

Angiographic improvement of vasospasm was noted in 35 (97%) of the 36 sessions in Group A patients and in all five sessions in Group B patients. Of the Group A patients, objective clinical improvement was noted in 15 (63%) of the 24 patients but dramatic clinical improvement was noted in eight (33%), including improved level of consciousness with an increase of more than 3 points in Glasgow Coma Scale score. Among the remainder of 16 who did not demonstrate dramatic clinical improvement, nine had repeat second or third infusions. Of these nine patients, three showed remarkable improvement after a second treatment and one had marked improvement after a third infusion. After combining all treatment sessions for the 24 Group A patients, 12 (50%) showed dramatic clinical improvement. None of the four Group B patients showed early clinical improvement after the first or second infusion.

The late outcome of the 28 patients was evaluated according to Glasgow Outcome Scale.²¹ Seventeen of the 24 patients (in Group A) recovered either with a condition of good recovery ($n = 11$) or moderate disability ($n = 6$). The other six patients suffered se-

vere disability ($n = 5$) or remained in a vegetative condition ($n = 1$). One patient died. Among the four patients (in Group B), only one patient improved to a moderate recovery condition and the rest suffered severe disability ($n = 2$) and vegetative conditions ($n = 1$).

Angiographic recurrence of spasm was noted within 24 hours after IA-PAP for all patients who did not respond to the first and second treatments. Three patients underwent follow-up angiography after remarkable clinical improvement and all showed no significant recurrence of vasospasm angiographically. Most importantly, in all patients who showed remarkable clinical improvement there was no further deterioration of symptoms and they continuously improved to good recovery or moderate disability status according to the Glasgow Outcome Scale.

Xenon-CT CBF study was performed before and after IA-PAP in one patient who showed remarkable clinical improvement. Diffusely decreased CBF was seen bilaterally, but especially in the left hemisphere prior to IA-PAP. Despite remarkable angiographic and clinical improvement, xenon-CT 15 hours after IA-PAP demonstrated overall worsening of CBF mixed with decreased and increased (hyperemic) areas (Fig. 1). She continued to improve to good recovery condition without recurrence of symptoms. In the other two older patients whose xenon-CT was not obtained prior to IA-PAP due to their poor cooperation, CBF on xenon-CT next day after papaverine infusion showed diffusely decreased CBF in both hemispheres mixed with a focal area of profound hyperemia. Neither patient showed significant immediate clinical improvement after IA-PAP but one of them gradually improved to the condition of moderate recovery. His follow-up xenon-CT 10 days after the initial study showed decreased size of the previously noted focal profound hyperemic area.

A procedure-related complication occurred in one patient in our early experience, who developed monocular blindness despite marked improvement of clinical symptoms. This occurred because of inadvertent administration of papaverine close to the origin of the ophthalmic artery. Brief tonic/clonic seizures also occurred in one patient. One patient developed psychomotor depression during selective infusion of papaverine into the ACA. This phenomenon was observed during both first and second treatments but resolved soon after the catheter was withdrawn from the ACA. None of our patients developed systemic hypotension even with the use of relatively large doses of papaverine. Intracranial pressure (ICP) was often transiently increased, but it was not recorded at the time of many of the treatments.

Fig. 1 A 50-year-old female who presented with acute deterioration of the level of consciousness 7 days after clipping of an anterior communicating artery aneurysm. *upper left:* Left internal carotid angiogram, lateral view, demonstrating diffuse spasm in the middle (MCA) and anterior cerebral artery (ACA) branches. The right carotid angiogram showed mild diffuse spasm (not shown). *upper right:* Xenon-computed tomography (CT) cerebral blood flow (CBF) study prior to intra-arterial papaverine hydrochloride infusion (IA-PAP) showing diffusely decreased CBF in both hemispheres (arrows), especially in the left hemisphere. *lower left:* Angiogram after IA-PAP (infusion of 150 mg of 0.6% papaverine) at the ACA-MCA junction showing a remarkable improvement in caliber of MCA and ACA. Spasm of right MCA and ACA also improved after the infusion of 150 mg into the right MCA (not shown). *lower right:* Xenon-CT study 15 hours after IA-PAP revealed mixed low (arrows) and hyperemic (arrowheads) CBF patterns bilaterally. Despite this overall worsening of the CBF pattern, the patient's level of consciousness was remarkably improved.

Discussion

Papaverine is an alkaloid of the opium group which

induces vasodilatation of the cerebral and coronary arteries by its direct action on smooth muscle. It is thought to act by inhibiting both cyclic adenosine

monophosphate (cAMP) and cyclic guanosine 3,5 monophosphate (cGMP) phosphodiesterase activity in smooth muscle cells, and by increasing intracellular cAMP and cGMP turnover.⁵⁾

Although papaverine has been used to treat cerebral vasospasm in animals or in humans with intravenous, intrathecal, or cisternal administration,^{29,50,52)} these methods have never become popular.

Since IA-PAP treatment was introduced by Kaku et al.²³⁾ and Kassell et al.²⁵⁾ in 1992, many other authors have described its efficacy for cerebral arterial vasospasm of various etiologies.^{7,9,14,24,28,33,34,36,37,39,44,48,49,54,55,61)} However, despite its wider acceptance, it has still not been well validated by a controlled study. Kaku et al.²³⁾ treated 10 patients using a combination of balloon angioplasty followed by IA-PAP resulting in an 80% clinical improvement. Due to combination therapy and lack of detailed description of the degree of improvement, the exact effect of papaverine is unknown. They experienced no recurrence of spasm. Kassell et al.²⁵⁾ reported 12 patients treated only with IA-PAP. Only three (25%) showed dramatic clinical improvement. Two of them showed recurrence of vasospasm and both improved significantly after the second papaverine infusion. Yoshimura et al.⁶¹⁾ reported that 15 (79%) of their 19 patients improved clinically after superselective IA-PAP but they did not mention the degree of improvement or the prevalence of recurrence. Kinoshita et al.²⁸⁾ reported clinical improvement in 12 (63%) of their 19 patients treated with IA-PAP but eight (67%) of the 12 patients demonstrated angiographic and clinical recurrence. Thus, the efficacy of IA-PAP varies in the literature, probably due to difference in the evaluation criteria and method of administration, and its true efficacy is unknown.

As described above, we achieved remarkable improvement in 12 (50%) of Group A patients after one, two, or three treatments. Since only eight (33%) of the 24 patients responded remarkably after first treatment without clinical recurrence, we presume the other 16 (67%) of the 24 had recurrent or persistent vasospasm. From the data of Kinoshita et al.²⁸⁾ and ours, the recurrence of angiographic vasospasm seems to occur in more than two-thirds of patients after IA-PAP treatment. Although more patients will be salvaged by the second or the third treatment in consecutive days after failure of initial treatment as described above, it is apparent that recurrence of vasospasm is an annoying problem of IA-PAP.

The etiology of recurrent vasospasm after IA-PAP is probably due to the relatively short half-life of papaverine.^{2,8,29,41,45,56)} The actual effective half-life of papaverine for smooth muscle relaxation has not

been determined but is estimated to be less than one hour.^{45,56)} However, the plasma papaverine levels have been noted to rise continually throughout a 4 day administration cycle.⁸⁾ This may explain why repeat papaverine treatment in consecutive days was effective in some patients in our series. It is quite a mystery why some patients respond to IA-PAP dramatically and others do not. There is currently no apparent method of recognizing and excluding the latter group of patients. Most authors agree that it is prudent to initiate IA-PAP as soon as clinical vasospasm manifests. This is supported by animal studies by Vorkapic et al.,⁵⁷⁾ Macdonald et al.,³⁵⁾ and Fujiwara et al.,¹⁵⁾ showing that papaverine infusion may be more effective in the early stages of vasospasm before structural changes occur in vascular walls. Although the number of Group B patients is small, we presume there will be no merit to perform IA-PAP in patients who do not present with acute symptoms even though their angiograms show vasospasm.

At present, the typical papaverine concentration in reported series is 0.2–0.3%, produced by diluting 200–300 mg papaverine in 100 ml normal saline. Most investigators used less than 300 mg for one vascular territory infused over 20–30 minutes with the maximum dose to be 600 mg or less. Mathis et al.³⁸⁾ reported in their *in-vitro* study that papaverine in concentrations of 0.3% (300 mg/100 ml of normal saline) or greater formed a precipitate when mixed with human serum. They also warned that these precipitates may lead to micro-embolic complications. However, such complications seem less likely to occur because papaverine is rapidly diluted upon entering the bloodstream. We recently increased the concentration to 0.5% to 0.6% to try to maximize the effectiveness of IA-PAP, and to decrease the time of catheter placement in spastic arteries. We have not experienced complications using these concentrations. In their study using rats, Yoshimura et al.⁶⁰⁾ recommended a papaverine concentration of less than 0.8% because papaverine at higher concentrations caused arterial wall damage attributed to its high acidity. Maximum safe concentrations of papaverine and maximum safe total dose in humans should be determined by further studies.

Most investigators have infused papaverine at the intracranial portion of the ICA distal to the ophthalmic artery or in the distal vertebral artery. Although no statistical analysis has been conducted among reported series regarding infusion sites vs. efficacy, it seems to us prudent to infuse papaverine at the site of vasospasm using a microcatheter. In our experience, it is quite common to experience vasospasm in the ACA territory. In such a situation,

infusion in the carotid artery or in the MCA may result in further flow reduction of the ACA due to preferential infusion of papaverine into the MCA which necessitates selective infusion in the ACA. When selective catheterization of ACA is difficult, infusion at the ACA-MCA bifurcation often dilates the proximal A₁-ACA and facilitates subsequent successful catheter advancement into the ACA.

Developing a safe and successful treatment of vasospasm without recurrence is a challenging task and several strategies may be effective. The combination of PTA and IA-PAP is reasonable since PTA seems to provide more sustained effect than IA-PAP.^{23,25,33)} There is a 2–5% risk of mortality associated with PTA due to arterial rupture or delayed thrombosis^{10,20,47)} and this technique should be reserved for treating vasospasm of ICA and vertebrobasilar arteries, and only the proximal segments of MCA, PCA, and possibly ACA. Papaverine can be infused prior to or after angioplasty in order to treat more distal spasm.

CBF study before and after IA-PAP or PTA has been advocated to help clarify the regions of ischemia that require treatment and assess improvement after treatment.^{30,32,51,58)} Firlik *et al.*¹²⁾ recently reported inconsistent improvement in clinical outcome and CBF after IA-PAP compared to the long-lasting effect by PTA. It is quite an enigma why the CBF findings did not match the clinical condition in one of our patients who showed remarkable improvement after IA-PAP (Fig. 1). Jin *et al.*²²⁾ determined that paradoxical vasoconstriction can occur in cerebral microvessel territories, especially when they are exposed to low concentration papaverine. Further investigation is needed to clarify this phenomenon.

The occurrence of profound hyperemia after IA-PAP as seen in our patients was reported by Fogarty-Mack *et al.*¹⁴⁾ This may be due to deranged autoregulatory function in a previously hypotensive area, and such hyperemia occurring after papaverine infusion is potentially deleterious and may account for transient increases in ICP.^{10,40)} Therefore, close monitoring of ICP during IA-PAP is recommended.

Various other adverse effects, mainly transient, have been reported with IA-PAP. Transient mydriasis seems to be a common phenomenon, particularly when the catheter tip is proximal to the ophthalmic artery.¹⁸⁾ Respiratory arrest can occur with the injection in the distal vertebral artery or proximal basilar artery, probably due to depression of medullary respiratory and cardiovascular centers.⁴⁾ Careful cardiopulmonary monitoring is essential in IA-PAP of the vertebrobasilar system. Transient tonic-clonic

seizure as occurred in one of our patients was also experienced by Marks *et al.*³⁶⁾ The etiology of this is unknown but crystal precipitation, paradoxical arterial constriction, or focal hyperemia may be responsible. An episode of psychomotor depression which occurred in one of our patients in two different sessions was probably due to the blockage of the spastic ACA by the catheter necessitating rapid infusion with a high concentration of papaverine. A single case of transient thrombocytopenia has been reported following IA-PAP.⁴²⁾

Various other antispasmodic agents have recently been investigated to prevent or treat cerebral vasospasm. These include oral administration of endothelin receptor antagonists, intrathecal injection of tissue plasminogen activator, and intraarterial injection of nitroglycerine, nitric oxide, or amrinone.^{1,43,46,59,63)}

In summary, the effectiveness of IA-PAP for symptomatic vasospasm varies among reported series, but it was at least 50% after single or multiple treatments in our series. Furthermore, all patients who showed remarkable clinical recovery of acute neurological deficits demonstrated continued clinical improvement. Recurrence of vasospasm after IA-PAP is common, and further investigation is needed to determine ways to sustain the papaverine effect. Combination of IA-PAP with PTA is technically more complex, but may improve treatment outcomes without an unacceptable risk of complications.

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