Effect of intraarterial verapamil on the diameter of vasospastic intracranial arteries in patients with cerebral vasospasm

Avi Mazumdar, M.D., Dennis J. Rivet, M.D., Colin P. Derdeyn, M.D., DeWitte T. Cross III, M.D., and Christopher J. Moran, M.D.

Interventional Neuroradiology Section, Mallinckrodt Institute of Radiology, and Departments of Neurological Surgery and Neurology, Washington University School of Medicine, St. Louis, Missouri

Object. This study was conducted to determine whether there is a change in intracranial arterial diameters after verapamil infusion for vasospasm and, if it is present, to determine whether the change occurs in proximal, intermediate, or distal vessels.

Methods. The authors measured arterial diameters in all patients treated with intraarterial verapamil at their institutions between August 2003 and September 2004. In all, 18 treatments were examined in 15 patients. Measurements were made before and after verapamil infusion in a blinded fashion with the aid of a magnification loupe at nine predetermined arterial sites on each angiogram. Baseline arterial measurements were made on each patient’s initial angiogram and on the angiogram demonstrating spasm prior to endovascular therapy as well in 14 of the patients. Charts were retrospectively reviewed to determine whether the patients benefited from intraarterial verapamil.

From the time of the initial angiogram to the time of vasospasm, there was a 21.6% decrease (p = 0.092) in proximal artery diameter, a 47.1% decrease (p < 0.05) in intermediate artery diameter, and a 12.4% decrease (p < 0.05) in distal artery diameter. There were no significant changes in the diameters of proximal, intermediate, or distal vessels after verapamil infusion (mean dose 7.4 mg, range 2.5–10 mg). After infusion of intraarterial verapamil, the proximal vessels showed a 1.1% decrease in diameter, the intermediate vessels showed a 9.4% increase, and the distal vessels showed a 3.3% decrease.

Conclusions. Administration of intraarterial verapamil does not cause a significant increase in the diameter of vasospastic vessels at the administered doses.

KEY WORDS • vasospasm • verapamil • intraarterial infusion • subarachnoid hemorrhage

Cerebral vasospasm is a major complication of aneurysmal SAH. Its effects peak from 4 to 12 days after the initial rupture, and it results in a marked increase in morbidity and mortality. Cerebral vasospasm that can be confirmed using angiography occurs to some degree in up to 70% of all patients with aneurysmal SAH, with approximately 14 to 40% of them developing clinical vasospasm. Some researchers have hypothesized that some microcirculatory vasospasm of penetrating vessels is smaller than can be shown by the highest resolution of angiography, which may explain changes in the mental status of patients with normal results on angiograms. Five to 20% of patients admitted for aneurysmal SAH die as a result of vasospasm. Vasospasm occurs primarily, but not exclusively, in large proximal vessels near the basilar cisterns and is related to the amount of blood surrounding the proximal cerebral vasculature, which was quantified by both the Fisher and Columbia scales for grading of SAH on CT scans.4,11,15,18

Having hypertension, smoking, using cocaine, and being between 40 and 59 years old also have been shown to be independent risk factors for vasospasm. Patients with vasospasm present with confusion, delirium, an altered level of consciousness, or focal neurological deficits, and they are at risk for the development of a delayed ischemic neurological deficit or diffuse cerebral edema. On pathological examination, red cell hemolysis appears to cause prolonged smooth-muscle contraction as well as vessel wall changes such as hypertrophy, hyperplasia, and fibrosis.

The pathogenesis of vasospasm is centered on inflammatory vasoconstriction secondary to surrounding hemorrhage as well as circulating factors primarily involving a superoxide free radical mechanism that results in an increase in intracellular protein kinase C and the subsequent release of intracellular calcium stores.

Medical treatment of cerebral vasospasm consists of hemodynamic augmentation therapy (hypervolemia, hypertension, hemodilution), the goal of which is to increase cerebral perfusion pressure and thus prevent ischemia. This is accomplished with intravenous fluid administration and often the use of inotropic agents or vasopressors. The treatments are usually monitored by tracking pulmonary capillary wedge pressure, central venous pressure, or mean arterial pressure. Complications of medical therapy

Abbreviations used in this paper: CT = computed tomography; ICA = internal carotid artery; ICP = intracranial pressure; SAH = subarachnoid hemorrhage.
are primarily cardiopulmonary in nature and include myocardial infarction, congestive heart failure, and pulmonary edema. Oral nimodipine has been shown to have a neuroprotective effect.

Endovascular treatments for vasospasm include angioplasty or intraarterial injection of vasodilators such as papaverine, verapamil, or nitroglycerin. Patients commonly undergo a diagnostic cerebral angiogram prior to endovascular therapy. Conventional cerebral angiography remains the gold standard for the diagnosis of vasospasm, although adjunctive diagnostic measures such as transcranial Doppler ultrasonography, CT angiography, and CT perfusion are also used.

The safety and efficacy of intraarterial angioplasty for the treatment of vasospasm has been demonstrated in numerous studies. However, many distal vessels are not amenable to such treatment.

Previous work with papaverine has shown that its administration results in an increase in the diameters of vasospastic vessels. However, because recent reports have shown cortical necrosis with intraarterial papaverine, other intraarterial agents have been used for the treatment of vasospasm. These include verapamil, nimodipine, and nicardipine.

The safety of intraarterial verapamil in the treatment of cardiovascular disease, its effects on ICP, and its vasodilatory effects have been reported in studies by other groups. On the basis of these studies, we used intraarterial verapamil in the treatment of cerebral vasospasm. We used methods that have previously been described with intraarterial papaverine to see whether intraarterial verapamil caused an increase in the diameter of vasospastic vessels as measured by angiography.

Clinical Material and Methods

The current study is a retrospective analysis of patients who received intraarterial verapamil between August 2003 and September 2004; it was approved by the institutional review board of the host institution. Vasospasm was diagnosed based on the results of angiographic studies obtained in all patients after aneurysmal SAH. All patients had undergone definitive treatment to secure the ruptured aneurysm, either craniotomy and clip occlusion or endovascular coil placement. We evaluated the outcomes for 18 verapamil treatments in 15 patients; 17 treatments were in the carotid distribution and one was in the posterior circulation. Six men and nine women received treatment (mean age 47.7 years). The ruptured aneurysms consisted of four anterior communicating artery lesions, three in the posterior communicating artery, three in the middle cerebral artery, one basilar tip aneurysm, three ophthalmic segment lesions, and one in the ICA terminus.

The dose of verapamil administered ranged from 2.5 to 10 mg (mean 7.4 mg). The dose was infused using a No. 5 French diagnostic angiographic catheter that was positioned in the ICA at the Cl–2 level, with hand injections performed for a period of approximately 5 to 10 minutes. All angiograms were evaluated using the digital subtraction technique. The patients’ neurological status, systemic blood pressure, heart rate, and, when available, ICP changes, were monitored continuously during the infusions. If a patient was being treated with vasopressors prior to the angiography, treatment was continued to maintain previously established mean arterial pressure goals throughout.

In the carotid (anterior) circulation, measurements were made at eight predetermined sites, which were chosen to represent the proximal, intermediate, and distal arteries (Fig. 1). On the lateral view, measurements were made of the supraclinoid ICA and the A, and the angular branches of the middle cerebral artery. On the anteroposterior view, measurements were made of the A, A, M, M, and M branches. In the vertebral (posterior) circulation, measurements were made at the midbasilar artery and the P, P, and P segments. Measurements were made in a blinded fashion by two observers.

All identifying patient data on the film was obscured with black tape. The organization of the films and selection of measurement positions were completed on a different day from when the actual measurements were taken. Arteries were measured with a magnification loupe graduated to 0.2 mm. The vessel diameters were recorded to the nearest 0.1 mm. Skull diameters, when available, were used to obtain relative measurements of arterial diameter to compensate for magnification effects that occur with digital subtraction angiography.

When skull diameters were not available, the cervical ICA, an aneurysm coil, or an aneurysm clip was used as a reference standard. The data were grouped into those of proximal (supraclinoid ICA or midbasilar artery), intermediate (A, M, P), and distal (A, A, M, M, angular, P, P) vessels. Measurements from within groups were pooled.

Patient charts and conscious sedation monitoring forms were reviewed retrospectively to determine whether administration of intraarterial verapamil resulted in a change in a patient’s blood pressure, heart rate, ICP, or neurological status.

Results

From the initial angiogram to the time of vasospasm, there was a 21.6% decrease (p = 0.092) in proximal artery diameter, a 47.1% decrease (p < 0.05) in intermediate artery diameter, and a 12.4% decrease (p < 0.05) in distal artery diameter.

In the proximal vessels, there was a 1.2% decrease (p = 0.717) in vessel diameter after verapamil infusion. In the intermediate and distal vessels, there was a 9.4% increase (p = 0.206) and a 3.3% decrease (p = 0.189) in vessel diameter after verapamil administration, respectively.

Retrospective chart review showed that in 14 cases, images were obtained within approximately 5 minutes after infusions of verapamil. In four cases, follow-up post-treatment images were obtained after a delay of between 15 and 33 minutes.

There was no significant change in blood pressure or ICP during the administration of intraarterial verapamil in 14 of 15 patients. In one patient, verapamil administration had to be terminated because of systemic hypotension that resolved after cessation of drug infusion.

Of the 15 patients who had angiograms for cerebral vasospasm, it was suspected clinically due to a global change in the level of consciousness in eight patients, aphasia or
dysphasia in six, and hemiparesis in one. Six of 15 patients improved clinically after intraarterial verapamil administration: one patient had improvement of an upper-extremity monoparesis, three had an improvement in aphasia, and two had a global improvement in level of consciousness. Eight patients showed no change after infusion. The condition of the remaining patient worsened despite verapamil therapy and hemodynamic augmentation.

Discussion

The significant morbidity associated with aneurysmal SAH extends beyond the treatment period of the underlying aneurysm. Vasospasm remains a major complication of aneurysmal SAH. A combination of early aneurysm treatment, oral nimodipine administration, and aggressive hemodynamic augmentation has reduced morbidity and mortality from aneurysmal SAH substantially. Endovascular therapy for cerebral vasospasm has also played a significant role at many centers.

Percutaneous transluminal angioplasty and intraarterial papaverine administration have been the mainstays of endovascular vasospasm treatment. Papaverine given intraarterially has been shown to increase the diameter of vasospastic vessels as well as improve cerebral circulation times. A study by Milburn, et al.,9 of treatment in 81 arterial territories for 34 patients showed that 300 mg of intraarterial papaverine administered for periods ranging from 15 to 60 minutes caused a mean increase in arterial diameter of 26.5%. Papaverine is thought to have a direct inhibitory effect on smooth-muscle contraction. Recent reports of cortical necrosis resulting from the use of intraarterial papaverine, however, have led to a search for alternative treatments.

There are numerous complications associated with papaverine, including increased ICP, transient neurological deficits, mydriasis, and respiratory depression (with verteobasilar infusion of papaverine).9

Angioplasty of proximal vessels is a well-established technique that has been shown to be effective by many re-
searchers. However, angioplasty of distal vessels is not possible. Many patients have tortuous vessels, which make access difficult. Angioplasty of intracranial vessels is associated with a risk of rupture. In addition, systemic anticoagulation therapy is necessary. Calcium channel blockers are a potential alternative to intraarterial papaverine for the treatment of vasospasm. Intraarterial verapamil has been used to treat vasospasm in the coronary circulation. In the setting of coronary angioplasty and stent placement, coronary vasospasm refractory to the use of nitroglycerin has been shown to be responsive to intraarterial verapamil administered in relatively low doses (1–1.5 mg). In addition, intraarterial verapamil has been shown to improve mechanically induced vasospasm in the carotid artery of a primate. In vitro animal experiments have shown that the cerebral vessels of mongrel dogs exhibit a dose-dependent vasodilatory effect with verapamil that develops gradually and stabilizes in 15 to 30 minutes. In the same animal model, a vasodilatory effect also has been shown with nifedipine and diltiazem, and this effect of verapamil was shown to be greater in the cerebral vessels than in peripheral vessels. Vasoconstriction induced by prostaglandins, which is a likely mechanism in patients with SAH, was reversed more readily with calcium channel blockers than with other vasodilatory agents. The effectiveness of intravenous and intracisternal injection of calcium channel blockers also has been shown in an in vivo animal model by using angiography. Intraarterial nifedipine and nicardipine have been shown to be effective in vasospasm treatment, as monitored using transcranial Doppler ultrasound and qualitative angiographic assessments.

A study by Feng, et al., has demonstrated the safety of intraarterial verapamil administration as well as its effect of increasing arterial diameter. Verapamil was given intraarterially to 29 patients in 34 procedures. Follow-up angiography was performed in 10 patients to determine the effect of the verapamil by measuring the diameter of the treated paracanoid ICA, M1, and A1 segments. The change in the diameter of the most spastic vessel was used to calculate the average change among these patients. The average dose was 2 mg, and the largest dose was 8 mg. Intraarterial verapamil was reported to increase arterial diameters of vasospastic segments 44 ± 9% without adverse hemodynamic effects.

Given the in vivo and in vitro animal data available as well as the coronary and preliminary clinical data in patients who were treated with intraarterial calcium channel blockers, intraarterial verapamil seems to be a promising avenue for endovascular vasospasm treatment. However, no rigorous quantitative angiographic evaluation of the vasodilatory effects of intraarterial verapamil has been performed regarding cranial circulation for vasospasm secondary to SAH.

Quantitative studies have shown that infusion of intraarterial papaverine results in increased diameter of vasospastic vessels. In our current study of intraarterial verapamil, we used the same methodology previously used to study intraarterial papaverine. We rigorously measured the diameter of proximal, intermediate, and distal vessels in the territory infused with verapamil at the time of presentation (baseline), at the time of vasospasm, and after verapamil infusion. This technique did not show a significant change in the diameter of proximal, intermediate, or distal vessels at the doses of verapamil used. Our methodology did demonstrate a robust change in vessel diameter from the initial angiogram to the angiogram obtained at the time of vasospasm.

Six of 15 patients showed some degree of clinical improvement within 24 hours after intraarterial verapamil administration. Because calcium antagonists have shown a greater and more sustained effect on small penetrating arterioles in an in vivo rat model, there may be a disparity between the clinical efficacy of calcium channel antagonists and their visualized angiographic effects in the patients.

There are many potential explanations for the discrepancy between our results with intraarterial verapamil and those published in other reports, including one about our experience with papaverine. We measured representative vessels in the entire treated distribution rather than only the most vasospastic segment. It is possible that the most vasospastic segments are more sensitive to intraarterial verapamil. The largest vasodilatory effect was seen in intermediate vessels. At our institution, severe proximal large-vessel spasm is usually treated with angioplasty of the involved segment rather than intraarterial calcium channel blockers. Our data support the prediction that due to the typical distribution of aneurysmal SAH in the basilar cisterns, proximal and intermediate arteries are most affected. The most vasospastic arterial segments in our study were the intermediate-size vessels, which showed a trend toward vasodilation after intraarterial verapamil. However, the degree of vessel dilation was not statistically significant.

There are strong animal data showing that the vasodilatory effect of calcium channel blockers on the cerebral vasculature is dose-dependent. Increasing the total amount of verapamil delivered, the concentration, and the rate at which it is administered may improve the vasodilatory effect by increasing the intraarterial concentration. Administering verapamil closer to the site of maximal vasospasm (for example, through a distal microcatheter rather than a proximal guide catheter) also may improve the vasodilatory effect. In addition, given that animal data indicate that large-vessel dilation peaks at 15 to 30 minutes after verapamil administration, whereas the effect on small vessels is more rapid, delayed imaging may better demonstrate the effect of intraarterial verapamil.

Because there are demonstrated effects of intraarterial calcium channel blockers on the coronary microcirculation as well as on small penetrating vessels in the brain, angiographic measurements of vessel caliber may not be adequate measures of the effect of these agents on patients with cerebral vasospasm. Quantification of cerebral blood flow to the treated distribution by using positron emission tomography, CT perfusion, or magnetic resonance perfusion may be a better surrogate measure for efficacy of treatment with intraarterial verapamil.

Conclusions

Given our inability to demonstrate a substantial angiographic effect of intraarterial verapamil administration in this population, we believe that rigorous studies demonstrating efficacy are necessary for intraarterial verapamil...
to become a mainstay in vasospasm treatment and justify the abandonment of papaverine, which has been demonstrated angiographically to be beneficial.

References

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