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Efficacy of multiple intraarterial papaverine infusions for improvement in cerebral circulation time in patients with recurrent cerebral vasospasm

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Object. Cerebral vasospasm that is caused by aneurysmal subarachnoid hemorrhage and that is refractory to maximal medical management can be treated with selective intraarterial papaverine infusions. The effects of single papaverine treatments on cerebral circulation time are well known. The purpose of this study was to assess the efficacy of multiple, repeated papaverine infusions on the cerebral circulation time in patients with recurrent vasospasm.

Methods. A retrospective study was conducted in 17 patients who received multiple intraarterial papaverine infusions in 91 carotid artery (CA) territories for the treatment of cerebral vasospasm. Cerebral circulation times were measured from the first angiographic image, in which peak contrast was seen above the supraclinoid internal CA, to the peak filling of cortical veins. Glasgow Outcome Scale (GOS) scores assessed 12 months after discharge were reviewed. Cerebral circulation times in 16 CA territories were measured in a control group of 11 patients.

Seventeen patients received a total of 91 papaverine treatments. Prolonged cerebral circulation times improved after 90 (99%) of 91 papaverine treatments. The prepapaverine mean cerebral circulation time was 6.54 seconds (range 3.35–27 seconds) and the immediate postpapaverine mean cerebral circulation time was 4.19 seconds (range 2.1–12.6 seconds), an overall mean decrease of 2.35 seconds (36%, $p < 0.001$). Recurrent vasospasm reflected by prolonged cerebral circulation times continued to improve with subsequent papaverine infusions. Repeated infusions were just as successful quantitatively as the primary treatment (mean change 2.06 seconds). The mean cerebral circulation time in the control group was 5.21 seconds (range 4–6.8 seconds). In five patients a dramatic reversal of low-attenuation changes was detected on computerized tomography scans. The mean GOS score at 12 months after discharge was 3.4.

Conclusions. The preliminary results indicate that multiple intraarterial papaverine treatments consistently improve cerebral circulation times, even with repeated infusions in cases of recurrent vasospasm.

KEY WORDS • cerebral vasospasm • subarachnoid hemorrhage • papaverine • cerebral circulation time

CEREBRAL vasospasm caused by aneurysmal SAH continues to be a disabling disease associated with high risks of morbidity and death. Furthermore, it is the most common cause of delayed neurological deficits, affecting up to 30% of patients who survive the initial hemorrhage.[17,23] Current therapy for prevention and treatment of symptomatic vasospasm includes triple-H therapy,[1] Ca channel antagonists,[2] and early surgery with clot removal.[15] If, however, vasospasm is refractory to medical management, endovascular therapy, consisting of selective intraarterial papaverine infusions, transluminal balloon angioplasty, or a combination of these treatments, has been used.[8,25,35] The primary goal of endovascular treatment for symptomatic vasospasm is to increase CBF to prevent infarction.

Intraarterial papaverine infusions have been used to reverse angiographically and clinically evident vasospasm, with some success.[9,21,22,24,32,40] Papaverine improves CBF by dilating the proximal, intermediate, and distal cerebral arteries; effectively increases angiographically demonstrated vessel diameter;[32] improves mean circulation time;[31] and improves cerebral oxygenation.[9] Nevertheless, one of the major disadvantages of papaverine infusion is its transient nature, resulting in recurrent and/or persistent angiographically and clinically evident vasospasm that may require multiple repeated infusions despite a successful response to the initial treatment.[4,32,36] The purpose of this study was to assess the efficacy of multiple intraarterial papaverine infusions in patients with recurrent cerebral vasospasm by measuring cerebral circulation time.[13,31]

Abbreviations used in this paper: CA = carotid artery; CBF = cerebral blood flow; CT = computerized tomography; DS = digital subtraction; GOS = Glasgow Outcome Scale; ICA = internal CA; ICP = intracranial pressure; MCA = middle cerebral artery; rCBF = regional CBF; SAH = subarachnoid hemorrhage.

Clinical Material and Methods

Patient Population

Aneurysmal SAH databases covering the period from July 1996 to December 2002 were reviewed at two institutions: Westchester Medical Center, Valhalla, New York; and University of Utah Health Sciences Center, Salt Lake City, Utah. A total of 512 patients were admitted with a diagnosis of aneurysmal SAH. Of these, 115 patients (57 from Westchester Medical Center and 58 from University of Utah Health Sciences Center) received intraarterial papaverine infusions for symptomatic vasospasm. Seventeen of 115 patients (four treated at Westchester and 13 at the University of Utah) received multiple intraarterial papaverine infusions. Patients who received a single papaverine treatment were excluded from this study. The charts, operative records, radiographic studies, and angiograms were reviewed for the 17 patients in this series, whose ages ranged from 20 to 83 years (mean 52 years). The male/female ratio was 6:11.

Diagnosis and Evaluation of Vasospasm

All 17 patients exhibited symptomatic vasospasm that was refractory to maximal medical management with triple-H therapy and Ca channel blockers. Daily transcranial Doppler ultrasonography studies were performed as a routine noninvasive surveillance method for vasospasm. Clinical vasospasm was diagnosed after the occurrence of a new neurological deficit or a decreased level of consciousness not attributed to hydrocephalus. All patients who exhibited clinical vasospasm underwent cerebral angiography to confirm vasospasm with radiographic evidence.

Intraarterial Infusion of Papaverine

In all 17 patients the ruptured aneurysm was occluded from the cerebral circulation by using microsurgical clip ligation (14 patients), vessel wrapping (one patient), or coil embolization (two patients) prior to papaverine treatments. Intraarterial papaverine hydrochloride was infused into the supraclinoid segment of the CA. The mean total dose in each CA territory was 140 mg, with a range of 60 to 165 mg. The infusion was mixed with normal saline at a concentration of 0.3% and was typically administered at a rate of 3 ml/min. The rate of infusion was adjusted according to changes in ICP, which was monitored continuously through an external ventricular drain in all patients receiving papaverine.

Angiographic Evaluation of Cerebral Circulation Time

Using DS angiography, the cerebral circulation time was calculated before and after intraarterial papaverine infusions. The observed cerebral circulation time was measured based on the definition by Milburn, et al.,[31] which calculates the interval between the first image in which contrast material is visible above the supraclinoid ICA and the peak filling of the cortical parietal veins. The original tapes for each angiographic run were retrieved to view all the images used to calculate cerebral circulation time. The images were acquired at 3.8 frames/second for the first 5 seconds and one frame/second thereafter; this filming sequence requires interpolation of frame numbers to measure cerebral circulation time. As a control population, we studied 11 consecutive patients who underwent cerebral angiography for CA atherosclerotic disease who had no evidence of ipsilateral intracranial or extracranial stenosis, tumor, unruptured aneurysm, or vascular malformation. The comparison of cerebral circulation times before and after papaverine treatment was performed using paired Student t-tests. The level of statistical significance was selected at a probability value of less than 0.05.

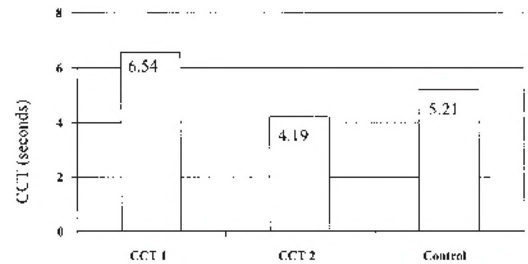

FIG. 1. Bar graph showing improvement in mean cerebral circulation time after intraarterial papaverine infusion in 91 treatments ($p < 0.001$). CCT1 = prepapaverine cerebral circulation time; CCT2 = postpapaverine cerebral circulation time.

Evaluation of Treatment

New neurological deficits caused by vasospasm and changes in the results of neurological examinations performed after papaverine treatment were documented. The initial admission Glasgow Coma Scale and GOS[19] scores at 12 months after discharge were documented. When available, unenhanced CT scans obtained before intraarterial papaverine infusion were compared with postpapaverine neuroimages; these images were evaluated for the reversal of low-attenuation changes.

Results

In this series, intraarterial papaverine infusions for the treatment of vasospasm were instituted in 115 (22.5%) of 512 of the patients with aneurysmal SAH. Of the patients who received intraarterial papaverine, 17 (14.8%) of 115 underwent multiple infusions; a total of 91 papaverine infusions were performed in these 17 patients (Table 1). In 16 patients papaverine infusions were administered in bilateral CA territories, whereas in one patient repeated papaverine infusions were given in a unilateral CA territory. The number of papaverine infusions per patient ranged from two to 11 (mean 5.35), and the number of repeated papaverine infusions administered in a CA territory (left or right ICA) ranged from two to seven.

Prolonged cerebral circulation times improved after 90 (99%) of 91 papaverine treatments. The prepapaverine mean cerebral circulation time was 6.54 seconds (range 3.35–27 seconds) and the immediate postpapaverine mean cerebral circulation time was 4.19 seconds (range 2.1–12.6 seconds), an overall decrease of 36% ($p < 0.001$; Fig. 1). The mean cerebral circulation time in the control group was 5.21 seconds (range 4–6.8 seconds).

Recurrent vasospasm was reflected by prolonged cerebral circulation times after previous successful papaverine infusions. In 15 cases, repeated papaverine infusions were given on consecutive days within a 24-hour period. In severe cases of diffuse cerebral vasospasm, papaverine was infused in bilateral CA territories. Twenty-seven CA territories were treated with a second infusion, 17 received a third treatment, 11 received a fourth treatment, four had a fifth treatment, two had a sixth treatment, and one had a seventh

TABLE 1
*Characteristics of 17 patients treated with multiple papaverine infusions for recurrent vasospasm**

		Grade or Score				Aneurysm Characteristics							
Case No.	Age (yrs), Sex	H & H	Fisher	Adm GCS	12-Mo GOS	Location	Tx	No. of Txs	Terri-tories	CCT1 (secs)	CCT2 (secs)	Post-SAH Day	Comment
1	60, M	II	2	14	4	lt MCA	clip ligation	2	lt ICA	5.86	3.20	5	
									lt ICA	4.27	2.93	6	
2	50, M	III	3	15	4	lt PCoA	clip ligation	2	lt ICA	6.80	5.73	5	
									lt ICA	5.87	5.60	6	
3	20, M	IV	3	5T	5	lt ICA bifurca-tion	clip ligation	5	lt ICA	7.60	4.00	4	improved low attenuation on CT scans, improved monoparesis
									rt ICA	7.34	4.00	5	
									lt ICA	3.73	3.46	5	
									lt ICA	5.34	3.46	7	
									lt ICA	6.13	4.00	11	
4	36, F	IV	3	10T	3	lt PCoA	wrapping	3	rt ICA	18.70	9.40	4	improved low attenuation on CT scans
									lt ICA	27.00	12.60	4	
									lt ICA	12.80	5.60	7	
5	34, F	IV	3	10T	4	ACoA	clip ligation	6	rt ICA	5.10	2.70	7	improved low attenuation on CT scans, increased ICP
									lt ICA	7.10	2.75	7	
									rt ICA	6.15	2.65	8	
									lt ICA	8.05	4.60	8	
									rt ICA	4.20	2.75	9	
									lt ICA	4.25	2.50	9	
6	75, F	IV	3	9T	3	ACoA	coil embol-ization	10	rt ICA	6.40	4.25	6	
									lt ICA	7.20	5.80	6	
									rt ICA	6.45	3.30	7	
									lt ICA	7.40	5.55	7	
									rt ICA	6.25	3.35	8	
									lt ICA	5.50	2.43	8	
									rt ICA	4.75	2.65	9	
									lt ICA	5.45	2.60	9	
									rt ICA	5.70	5.45	10	
									rt ICA	5.25	3.85	11	
7	50, F	III	2	15	5	lt MCA	clip ligation	2	lt ICA	6.25	5.10	4	improved aphasia, improved low attenuation on CT scans
									lt ICA	6.30	5.00	5	
8	82, M	IV	3	8T	3	ACoA	coil embol-ization	6	rt ICA	7.75	5.80	11	
									lt ICA	7.75	5.50	11	
									rt ICA	4.20	4.10	12	
									lt ICA	5.80	3.30	12	
									rt ICA	5.05	3.15	13	
									lt ICA	4.05	2.35	13	
9	47, M	II	3	15	4	lt MCA	clip ligation	6	rt ICA	5.00	3.10	7	improved aphasia, improved low attenuation on CT scans
									lt ICA	5.85	2.70	7	
									lt ICA	5.05	3.00	9	
									rt ICA	3.85	3.20	10	
									lt ICA	4.95	3.20	10	
									lt ICA	4.75	2.70	11	
10	53, F	IV	2	12	1	rt MCA	clip ligation	7	rt ICA	4.85	3.75	7	death: pulmonary embolus
									lt ICA	4.85	2.85	7	
									lt ICA	5.05	4.00	8	
									rt ICA	4.25	2.80	9	
									lt ICA	5.15	3.40	9	
									rt ICA	5.00	2.70	10	
									lt ICA	5.10	3.25	10	
11	38, F	III	3	13	4	BA	clip ligation	5	rt ICA	5.00	3.90	7	increased ICP
									lt ICA	6.10	2.10	7	
									rt ICA	5.05	2.40	8	
									lt ICA	4.05	2.60	8	
									lt ICA	4.05	2.95	9	
12	83, M	IV	3	14	1	ACoA	clip ligation	6	rt ICA	6.50	3.90	6	increased ICP, death: support withdrawn, lt MCA stroke
									rt ICA	8.55	3.30	11	
									lt ICA	6.75	2.75	11	
									rt ICA	7.80	4.10	12	
									lt ICA	6.00	3.50	12	
									rt ICA	7.75	4.40	13	

TABLE 1 *(continued)*

*Characteristics of 17 patients treated with multiple papaverine infusions for recurrent vasospasm**

		Grade or Score				Aneurysm Characteristics							
Case No.	Age (yrs), Sex	H & H	Fisher	Adm GCS	12-Mo GOS	Location	Tx	No. of Txs	Territories	CCT1 (secs)	CCT2 (secs)	Post-SAH Day	Comment
13	47, F	IV	3	7T	5	rt PCoA	clip ligation	9	rt ICA	4.85	4.70	6	
									lt ICA	9.50	5.80	6	
									rt ICA	6.10	4.10	7	
									lt ICA	6.85	5.60	7	
									rt ICA	6.80	4.50	8	
									lt ICA	8.55	5.55	8	
									rt ICA	7.60	5.00	9	
									lt ICA	6.85	5.30	9	
									rt ICA	6.05	3.90	10	
14	52, F	III	3	13	4	rt OphA	clip ligation	11	rt ICA	9.70	7.05	4	
									rt ICA	11.30	8.15	5	
									lt ICA	6.75	5.00	5	
									rt ICA	7.55	5.35	6	
									lt ICA	4.05	3.10	6	
									rt ICA	10.65	7.50	7	
									lt ICA	5.05	3.05	7	
									rt ICA	9.55	7.35	8	
									lt ICA	5.05	3.05	8	
									rt ICA	8.35	5.05	9	
									rt ICA	7.30	6.20	11	
15	47, F	II	3	15	3	ACoA	clip ligation	4	rt ICA	6.35	4.05	10	
									lt ICA	5.75	4.55	10	
									rt ICA	5.40	3.95	12	
									lt ICA	5.05	3.70	12	
16	60, F	III	3	12	1	ACoA	clip ligation	5	lt ICA	4.35	3.00	5	death: support withdrawn, bilat ACA infarcts
									lt ICA	3.35	3.60	6	
									lt ICA	4.00	2.70	7	
									lt ICA	6.30	4.00	10	
									lt ICA	5.70	4.30	11	
17	52, F	III	3	14	4	lt PCoA	clip ligation	2	lt ICA	8.30	5.70	8	transient aphasia from papaverine
									lt ICA	7.05	4.60	8	
mean					3.40					6.54	4.19		

* ACA = anterior cerebral artery; ACoA = anterior communicating artery; adm = admission; BA = basilar artery; GCS = Glasgow Coma Scale; H & H = Hunt and Hess; OphA = ophthalmic artery; PCoA = posterior communicating artery; Tx = treatment.

treatment. Repeated infusions were just as successful quantitatively as the first treatment (Table 2, Figs. 2 and 3). The mean improvement in cerebral circulation time during the first papaverine treatment was 2.95 seconds. The mean improvement in cerebral circulation time after subsequent papaverine treatments was 2.01 seconds for the second treatment, 2.12 seconds for the third treatment, 2.36 seconds for the fourth treatment, 1.5 seconds for the fifth treatment, 2.35 seconds for the sixth treatment, and 1.1 seconds for the seventh treatment.

Eight patients experienced improvement in their depressed level of consciousness after papaverine infusion. In one patient reversal of an upper-extremity monoparesis occurred, and in three patients there was improvement in vasospasm-induced aphasia. In five patients in whom an initial exacerbation of low-attenuation lesions was observed on CT scans, there was ultimately a reversal of radiographically identified changes after multiple infusions of intraarterial papaverine (Fig. 4).

In three patients the papaverine treatments were discontinued before delivery of the target dose was completed, when ICP increased during infusion. One patient experienced a transient, papaverine-induced aphasia with slowing detected on electroencephalography. No other complications from intraarterial papaverine infusions were noted.

The mean GOS score at 12 months after discharge was 3.4. Ten patients (59%) had a GOS score of 4 or 5 and were living independently at home. Four patients (24%) had a GOS score of 3 and were severely disabled. There were three deaths in our series of patients with refractory vaso-

TABLE 2

Change in cerebral circulation time after repeated intraarterial papaverine treatments

No. of Txs	No. of Territories	Mean CCT1 (secs)	Mean CCT2 (secs)	Reduction in Mean CCT After Tx (secs)
1	29	7.63	4.68	2.95
2	27	6.00	3.99	2.01
3	17	5.50	3.38	2.12
4	11	6.40	4.04	2.36
5	4	6.75	5.25	1.50
6	2	6.80	4.45	2.35
7	1	7.30	6.20	1.10
mean		6.63	4.57	2.06

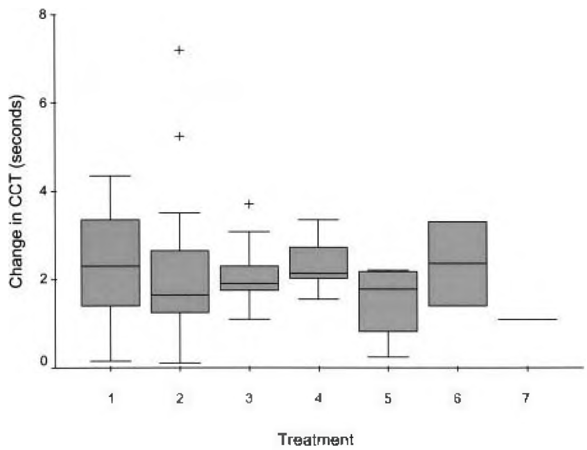

FIG. 2. Boxplot showing change in cerebral circulation time median (*line* within box), 25th- and 75th-percentile (lower and upper boundaries of box), and 5th- and 95th-percentile *(whiskers)* values.

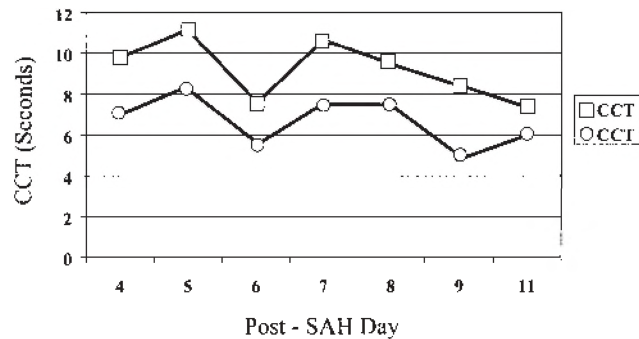

FIG. 3. Graph displaying results in an illustrative example (Case 14). The graph demonstrates repeated improvement of cerebral circulation time after multiple papaverine infusions in the right ICA territory.

spasm: one patient died of a massive pulmonary embolus, and the other two underwent withdrawal of care after suffering from debilitating cerebral infarcts (one in the left MCA distribution and one in the bilateral anterior cerebral artery distribution).

Discussion

Since the initial reports of Kaku, et al.,[21] and Kassell, et al.,[22] the use of intraarterial papaverine to treat symptomatic vasospasm induced by aneurysmal SAH has increased.[4,9,10,24,27,32] Papaverine is an alkaloid of the opium group that has potent vasodilating effects through direct action on smooth muscle. Although the mechanism is not completely understood, papaverine is thought to inhibit cyclic adenosine monophosphate and cyclic guanosine monophosphate phosphodiesterases in smooth muscles to increase intracellular levels of both substances.[26] It also may work by blocking Ca ion channels in the cell membrane and inhibiting the release of Ca from the intracellular space.[35]

Papaverine improves CBF by dilating the proximal, intermediate, and distal cerebral arteries, effectively increasing angiographically observed vessel diameter,[32] improving mean circulation time,[31] and improving cerebral oxygenation.[9] Nevertheless, its efficacy in improving neurological outcome remains inconclusive.[4,10,20–22,27] At various neurosurgical centers,[24,39] intraarterial papaverine continues to be a mainstay of endovascular treatment of vasospasm refractory to medical management. Even though the successful use of papaverine has been reported anecdotally, its clinical benefit and its precise role in treating vasospasm have yet to be determined in controlled prospective studies. Our data demonstrate that repeated papaverine infusions are as effective as the initial one.

Measurement of Cerebral Circulation Time

Assessments of rCBF can be performed using positron emission tomography, Xe-CT, or single-photon emission CT scanning; however, these modalities are not widely available. Cerebral circulation time, which can be readily calculated based on results of conventional angiography studies, is proportional to mean transit time and can be used to evaluate cerebral hemodynamics.[11,14] Cerebral circulation time measurements can be useful for evaluating cerebral vasospasm and rCBF.[34,37,38] Using both DS angiography and single-photon emission CT scanning, Ohkuma, et al.,[37] demonstrated an inverse correlation between cerebral circulation time and rCBF in patients with cerebral vasospasm. Thus, prolonged cerebral circulation time may correlate with decreased CBF.

The measurement of cerebral circulation time may also be useful for evaluating the effects of endovascular treatments, such as intraarterial papaverine infusion and/or angioplasty, in patients with cerebral vasospasm.[18,31,34] In our study, we have demonstrated that patients with clinically evident vasospasm exhibited a prolonged cerebral circulation time when compared with the control group. There was also a consistent decrease (36%) in cerebral circulation time after intraarterial papaverine infusion (Fig. 1); these results are consistent with previous reports.[18,31,34] Milburn, et al.,[31] showed a decrease in cerebral circulation time after intraarterial papaverine infusions in 58 of 59 CA territories in 27 patients. Iseda, et al.,[18] showed a decrease in cerebral circulation time in seven patients who received endovascular therapy (intraarterial papaverine alone or intraarterial papaverine and angioplasty), which correlated with improvements in CBF.

The methodology for measuring cerebral circulation time from angiography was originally described by Greitz.[13,14] Because not all images were filmed in our cases, we viewed the original tapes for each angiographic run. By viewing all the images, we could better define the start point and end point images to calculate a more accurate cerebral circulation time. One disadvantage of DS angiography is that the images are not acquired in real time. Therefore, the interpolation of frame numbers to calculate cerebral circulation time may introduce some degree of error (3.8 frames/second allows for < 0.3 second of error for each measurement).

Severe vasospasm in the posterior circulation that warranted endovascular therapy was observed in three patients in our series. Because cerebral circulation time measured in the vertebrobasilar circulation is different from that measured in the CA circulation,[12] the data from these treatments were not included in the present study.

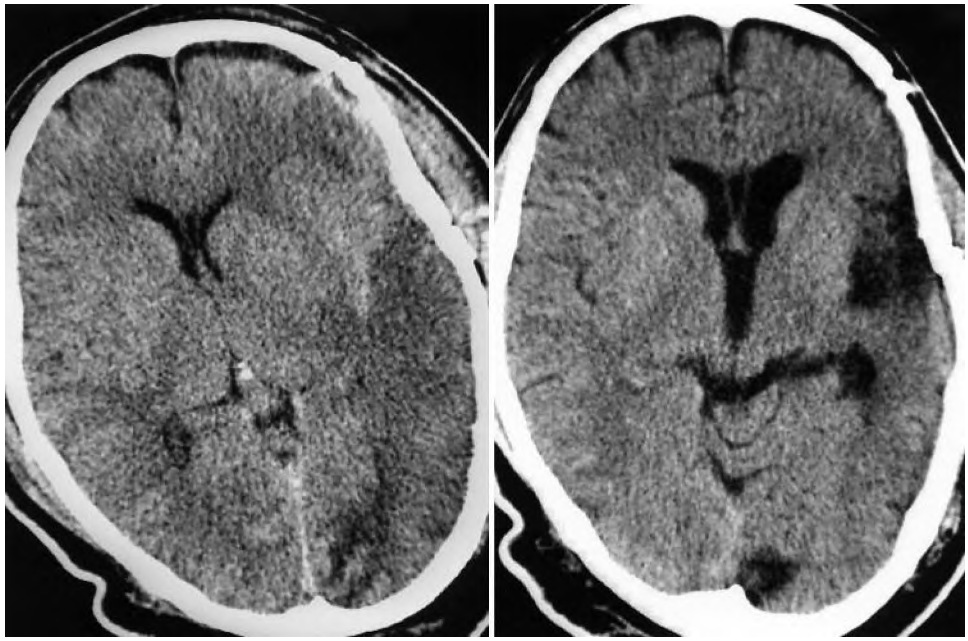

FIG. 4. Case 9. Axial CT scans obtained in a patient with SAH, demonstrating reversal of low-attenuation changes after multiple papaverine infusions. *Left:* Prepapaverine CT scan obtained on post-SAH Day 7. *Right:* Postpapaverine CT scan obtained on post-SAH Day 151.

Multiple Papaverine Infusions

The results from our study indicate that repeated intraarterial papaverine infusions consistently improve cerebral circulation time. Interestingly, each subsequent papaverine infusion achieved a similar magnitude of change, which demonstrates its efficacy on previously treated vessels (Table 2, Figs. 2 and 3). Overall, there was a consistent response to papaverine on repeated infusions (mean change 2.06 seconds).

This patient series represents those who have severe, diffuse, refractory cerebral vasospasm manifested by prolonged circulation times. It has been our practice to intervene aggressively with endovascular treatments at the earliest onset of clinical vasospasm that has become refractory to maximal medical management. Despite favorable angiographically confirmed responses after papaverine infusion, recurrent vasospasm occurs frequently within 24 to 48 hours.[22,27] Its origin is not well understood but is probably due to the relatively short halflife of papaverine. The actual effective halflife of smooth muscle relaxation after intraarterial papaverine infusion has not been determined in human cerebral arteries but was reported to be less than 1 hour in canine vasospasm models.[43] If the halflife is truly shorter, clinical improvement is likely attributable to the additive effect of triple-H therapy after cerebral vasodilation by papaverine treatment. There is some evidence that plasma levels of papaverine rise with continuous administration of the drug every 6 hours, which indicates a true halflife closer to 24 hours.[6] This rise in basal plasma papaverine levels may be an additional mechanism by which multiple papaverine treatments received on consecutive days were effective in some patients in this series.

Repeated papaverine infusions may be a method for treating recurrent vasospasm, especially when it is more diffuse and seen in more distal arteries in which angioplasty is not possible. Numaguchi, et al.,[36] reported that up to three infusions on consecutive days may be warranted if the patient's general condition allows. Studies of CBF before or after infusion may aid in identifying regions of ischemia that require treatment, and in assessing improvement posttreatment.[44] One of the major disadvantages of papaverine therapy, as seen in our series, is the transient nature of its effects, resulting in recurrent and/or persistent angiographically and clinically evident vasospasm that may require multiple infusions.[4,32,36]

Effects of Papaverine on the Microcirculation

One major factor affecting cerebral ischemia during cerebral vasospasm is the luminal narrowing of the large extraparenchymal arteries, which is often detected as angiographically confirmed vasospasm. In addition, vasospasm in the microcirculation, detected as prolonged peripheral cerebral circulation time (circulation time defined as the difference between the cortical segment of the rolandic artery and the rolandic vein), is also thought to be a factor contributing to cerebral ischemia. In some studies the investigators have suggested that vasospasm of the microcirculation plays a significant role in prolonging cerebral circulation time and decreasing rCBF.[34,37,38] Ohkuma, et al.,[37] measured both the proximal cerebral circulation time (circulation time through the extraparenchymal large arteries) and the peripheral time (circulation time through the intraparenchymal small vessels), and demonstrated that prolonged peripheral cerebral circulation time was associated with decreased rCBF in cases of severe angiographically confirmed vasospasm as well as in cases of absent or mild angiographically evident vasospasm. Compared with the overall circulation time, peripheral cerebral circulation time showed a stronger inverse correlation with rCBF. Prolonged peripheral cerebral circulation time may be related to impaired autoregulatory vasodilation or decreased luminal diameter in the microcirculation.

Complications of Intraarterial Papaverine Administration

The use of papaverine, however, is not without risk. Reported complications include rapid increases in ICP,[30] transient neurological deficits including mydriasis[16] and brainstem depression,[3,28] monocular blindness,[4] seizures,[4,27] thrombocytopenia,[33] precipitation of crystal emboli during infusion,[29] and paradoxical exacerbation of vasospasm leading to cerebral infarction.[5] Care should be taken when concentrations higher than 0.3% are used because the papaverine may form a precipitate when mixed with blood. All of our patients underwent ICP monitoring[7,30] during the papaverine infusions. In this series, three patients exhibited increases in ICP during the papaverine infusion, which necessitated discontinuation of the treatment. After cessation of the infusions, the ICP returned to normal values. One patient experienced transient aphasia during the papaverine infusion, which resolved after treatment was stopped.

Reversal of Low-Attenuation Lesions Identified on CT Scans

In this study, there were five patients in whom an initial exacerbation of low-attenuation lesions was observed on CT scans, with ultimate reversal of radiographically observed changes after multiple infusions of intraarterial papaverine (Fig. 4). We have previously reported this interesting phenomenon.[24] Although these areas of low attenuation appear to represent areas of impending infarction, they most likely denote areas of edematous ischemic brain. Ischemic cytotoxic edema seen on CT scans is caused by the influx of water content due to the lowered electrochemical potential of the neuronal plasma membrane.[41] This potential is a result of ischemia-induced depletion of adenosine triphosphate that leads to the inhibition of Na^+/K^+ adenosine triphosphatase activity, which leads, in turn, to increased intracellular Na^+ and decreased intracellular K^+. If CBF is restored in edematous ischemic brain before the tissue undergoes irreversible cell death, the low-attenuation areas seen on CT scans can be reversed.

With repeated papaverine infusions, regions of low attenuation may become exacerbated before they are reversed. This phenomenon may be caused by a combination of recurrent vasospasm and postreperfusion cerebral hyperemia. During the period of ischemia, metabolic vasodilator products such as H^+, K^+, or adenosine accumulate and contribute to increased CBF during reperfusion.[42] Intravascular fluid then extravasates into the extravascular space through leaky ischemic vessels and contributes to more edema. The presence of low-attenuation changes on CT scans in some cases may represent reversible ischemic changes and may not be a contraindication to intraarterial papaverine treatments. Nevertheless, one should be mindful of potential risks of reperfusion injury and hemorrhagic transformation after treatment in these situations.

Conclusions

Intraarterial papaverine retains a useful role in the treatment of severe diffuse cerebral vasospasm. Papaverine adds the potential benefit of treating both large and small distal intracranial vessel segments that are not amenable to angioplasty. Intraarterial papaverine is effective in decreasing prolonged cerebral circulation time. In cases of recurrent vasospasm, repeated papaverine infusions are as effective as the initial one in decreasing cerebral circulation time. Further studies are needed to compare improvement of cerebral circulation time with clinical outcome.

References

1. Awad IA, Carter LP, Spetzler RF, et al: Clinical vasospasm after subarachnoid hemorrhage: response to hypervolemic hemodilution and arterial hypertension. Stroke 18:365–372, 1987
2. Barker FG II, Ogilvy CS: Efficacy of prophylactic nimodipine for delayed ischemic deficit after subarachnoid hemorrhage: a metaanalysis. J Neurosurg 84:405–414, 1996
3. Barr JD, Mathis JM, Horton JA: Transient severe brain stem depression during intraarterial papaverine infusion for cerebral vasospasm. AJNR 15:719–723, 1994
4. Clouston JE, Numaguchi Y, Zoarski GH, et al: Intra-arterial papaverine infusion for cerebral vasospasm after subarachnoid hemorrhage. AJNR 16:27–38, 1995
5. Clyde BL, Firlik AD, Kaufmann AM, et al: Paradoxical aggravation of vasospasm with papaverine infusion following aneurysmal subarachnoid hemorrhage. Case report. J Neurosurg 84: 690–695, 1996
6. Cook P, James I: Drug therapy: cerebral vasodilators (first of two parts). N Engl J Med 305:1508–1513, 1981
7. Cross DT III, Moran CJ, Angtuaco EE, et al: Intracranial pressure monitoring during intraarterial papaverine infusion for cerebral vasospasm. AJNR 19:1319–1323, 1998
8. Eskridge JM, Newell DW, Winn HR: Endovascular treatment of vasospasm. Neurosurg Clin N Am 5:437–447, 1994
9. Fandino J, Kaku Y, Schuknecht B, et al: Improvement of cerebral oxygenation patterns and metabolic validation of superselective intraarterial infusion of papaverine for the treatment of cerebral vasospasm. J Neurosurg 89:93–100, 1998
10. Firlik KS, Kaufmann AM, Firlik AD, et al: Intra-arterial papaverine for the treatment of cerebral vasospasm following aneurysmal subarachnoid hemorrhage. Surg Neurol 51:66–74, 1999
11. Gado M, Eichling J, Grubb R, et al: Appraisal of the angiographic circulation time as an index of cerebral blood flow. Radiology 115:107–112, 1975
12. Greitz T: Evaluation of circulation time in angiography of the vertebral artery. Acta Radiol Diagn 9:300–309, 1969
13. Greitz T: Normal cerebral circulation time as determined by carotid angiography with sodium and methylglucamine diatrizoate (Urografin). Acta Radiol Diagn 7:331–336, 1968
14. Greitz T: A radiologic study of the brain circulation by rapid serial angiography of the carotid artery. Acta Radiol 46 (Suppl 140):1–123, 1956
15. Handa Y, Weir BKA, Nosko M, et al: The effect of timing of clot removal on chronic vasospasm in a primate model. J Neurosurg 67:558–564, 1987
16. Hendrix LE, Dion JE, Jenson ME, et al: Papverine-induced mydriasis. AJNR 15:716–718, 1994
17. Heros RC, Zervas NT, Varsos V: Cerebral vasospasm after subarachnoid hemorrhage: an update. Ann Neurol 14:599–608, 1983
18. Iseda T, Nakano S, Yoneyama T, et al: Angiographic cerebral circulation time before and after endovascular therapy for symptomatic vasospasm. Clin Radiol 55:679–683, 2000
19. Jennett B, Bond M: Assessment of outcome after severe brain damage. A practical scale. Lancet 1:480–484, 1975
20. Jin Y, Sagher O, Thai QA, et al: The effects of papaverine on phor-

bol dibutyrate-induced vasoconstriction in brain slice microvessels. J Neurosurg 81:574–578, 1994
21. Kaku Y, Yonekawa Y, Tsukahara T, et al: Superselective intraarterial infusion of papaverine for the treatment of cerebral vasospasm after subarachnoid hemorrhage. J Neurosurg 77:842–847, 1992
22. Kassell NF, Helm G, Simmons N, et al: Treatment of cerebral vasospasm with intra-arterial papaverine. J Neurosurg 77: 848–852, 1992
23. Kassell NF, Sasaki T, Colohan ART, et al: Cerebral vasospasm following aneurysmal subarachnoid hemorrhage. Stroke 16: 562–572, 1985
24. Liu JK, Tenner MS, Oestreich HM, et al: Reversal of radiographically impending stroke with multiple intraarterial papaverine infusions in severe diffuse cerebral vasospasm induced by subarachnoid hemorrhage. Acta Neurochir 143:1249–1256, 2001
25. Livingston K, Guterman LR, Hopkins LN: Intraarterial papaverine as an adjunct to transluminal angioplasty for vasospasm induced by subarachnoid hemorrhage. AJNR 14:346–347, 1993
26. Lugnier C, Stoclet JC: Inhibition by papaverine of cGMP and cAMP phosphodiesterases from the rat heart. Biochem Pharmacol 23:3071–3074, 1974
27. Marks MP, Steinberg GK, Lane B: Intraarterial papaverine for the treatment of vasospasm. AJNR 14:822–826, 1993
28. Mathis JM, DeNardo A, Jensen ME, et al: Transient neurologic events associated with intraarterial papaverine infusion for subarachnoid hemorrhage-induced vasospasm. AJNR 15: 1671–1674, 1994
29. Mathis JM, DeNardo AJ, Thibault L, et al: In vitro evaluation of papaverine hydrochloride incompatibilities: a simulation of intraarterial infusion for cerebral vasospasm. AJNR 15:1665–1670, 1994
30. McAuliffe W, Townsend M, Eskridge JM, et al: Intracranial pressure changes induced during papaverine infusion for treatment of vasospasm. J Neurosurg 83:430–434, 1995
31. Milburn JM, Moran CJ, Cross DT III, et al: Effect of intraarterial papaverine on cerebral circulation time. AJNR 18:1081–1085, 1997
32. Milburn JM, Moran CJ, Cross DT III, et al: Increase in diameters of vasospastic intracranial arteries by intraarterial papaverine administration. J Neurosurg 88:38–42, 1998
33. Miller JA, Cross DT, Moran CJ, et al: Severe thrombocytopenia following intraarterial papaverine administration for treatment of vasospasm. J Neurosurg 83:435–437, 1995
34. Minami H, Kuwamura K, Tamaki N: Intraarterial infusion of papaverine and change of cerebral hemodynamics in symptomatic cerebral vasospasm. Kobe J Med Sci 47:169–179, 2001
35. Newell DW, Elliott JP, Eskridge JM, et al: Endovascular therapy for aneurysmal vasospasm. Crit Care Clin 15:685–699, 1999
36. Numaguchi Y, Zoarski GH, Clouston JE, et al: Repeat intra-arterial papaverine for recurrent cerebral vasospasm after subarachnoid haemorrhage. Neuroradiology 39:751–759, 1997
37. Ohkuma H, Manabe H, Tanaka M, et al: Impact of cerebral microcirculatory changes on cerebral blood flow during cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Stroke 31: 1621–1627, 2000
38. Ohkuma H, Ogane K, Tanaka M, et al: Assessment of cerebral microcirculatory changes during cerebral vasospasm by analyzing cerebral circulation time on DSA images. Acta Neurochir Suppl 77:127–130, 2001
39. Polin RS, Hansen CA, German P, et al: Intra-arterially administered papaverine for the treatment of symptomatic cerebral vasospasm. Neurosurgery 42:1256–1267, 1998
40. Sawada M, Hashimoto N, Tsukahara T, et al: Effectiveness of intra-arterially infused papaverine solutions of various concentrations for the treatment of cerebral vasospasm. Acta Neurochir 139:706–711, 1997
41. Terent A, Ronquist G, Bergstrom K, et al: Ischemic edema in stroke. A parallel study with computed tomography and cerebrospinal fluid markers of disturbed brain cell metabolism. Stroke 12:33–40, 1981
42. Todd NV, Picozzi P, Crockard HA, et al: Reperfusion after cerebral ischemia: influence of duration of ischemia. Stroke 17: 460–466, 1986
43. Varsos VG, Liszczak TM, Han DH, et al: Delayed cerebral vasospasm is not reversible by aminophylline, nifedipine, or papaverine in a "two-hemorrhage" canine model. J Neurosurg 58:11–17, 1983
44. Yonas H: Cerebral blood measurements in vasospasm. Neurosurg Clin N Am 1:307–318, 1990

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