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Intracranial Pressure Monitoring during Intraarterial Papaverine Infusion for Cerebral Vasospasm

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PURPOSE: **Intraarterial papaverine infusions are performed to reverse cerebral arterial vasospasm resulting from subarachnoid hemorrhage, but such infusions may lead to increases in intracranial pressure (ICP). This study was undertaken to determine when ICP monitoring is indicated during papaverine treatment.**

METHODS: **Seventy-eight vessels were treated in 51 sessions in 28 patients with symptomatic vasospasm. ICP, papaverine doses, and infusion rates were recorded during treatment sessions. The procedural data, Hunt and Hess scores, Fisher grades, Glasgow Coma Scale scores, and ages for all subjects were reviewed and analyzed retrospectively.**

RESULTS: **Baseline ICP ranged from 0 to 34 mm Hg. With typical papaverine doses of 300 mg per territory and infusion times ranging from 5 to 60 minutes per vessel, ICP increases above baseline during papaverine infusion ranged from 0 to 60 mm Hg. Significant (≥20 mm Hg) ICP increases during therapy were observed even in patients with low baseline ICP and with papaverine infused at the slowest rate. Patients with a baseline ICP of more than 15 mm Hg were much more likely to have significant ICP increases than were patients with a baseline ICP of 0 to 15 mm Hg. Hunt and Hess scores, Fisher grades, age, and Glasgow Coma Scale scores on admission and immediately before treatment did not correlate with ICP increases during papaverine infusion. Patients with ICP increases of more than 10 mm Hg during therapy were more likely to experience adverse clinical events than were patients with ICP increases of ≤10 mm Hg. Reduction in the rate of papaverine infusion, or termination of infusion, resulted in reversal of drug-induced ICP elevation.**

CONCLUSION: **ICP monitoring during intraarterial papaverine infusions for cerebral vasospasm is recommended for all patients and is particularly important for patients with elevated baseline ICP. Continuous ICP monitoring facilitates safe and time-efficient drug delivery.**

Patients with subarachnoid hemorrhage resulting from rupture of a cerebral aneurysm commonly experience arterial vasospasm (1–2). While cerebral vasospasm in such circumstances is most often asymptomatic or managed successfully by medical therapy, an estimated 10% of such events are refractory to conservative treatment, and these patients are referred for endovascular therapy (audience poll; Working Group in Interventional Neuroradiology Conference, Val d'Isere, France, 1997). Balloon angioplasty of cerebral vessels and intraarterial papaverine infusion are two current treatment options for endovascular vasospasm (3–12). Papaverine infusion in cerebral vessels is only rarely associated with complications, such as blindness, thrombocytopenia, and circulatory arrest (13–15), but it is not unusual for such therapy to provoke increases in intracranial pressure (ICP) (16). To determine whether ICP monitoring is required for all patients receiving intraarterial papaverine or whether ICP monitoring can be safely eliminated under certain circumstances, we undertook a retrospective analysis of our data.

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Methods

From 1992 to 1995, 39 patients were treated for cerebral vasospasm with intraarterial papaverine infusions. Twenty-eight had continuous ICP monitoring during therapy, made possible because ventriculostomy catheters or ICP monitors

had been placed prior to treatment. These 28 patients constitute the study group. Initially, no ICP monitors were placed solely for the purpose of ICP monitoring during papaverine therapy. Later, however, after it was observed that changes in ICP occurred fairly frequently during papaverine delivery, some ICP monitors were placed solely for use during papaverine delivery. Seventy-eight cerebral vessels (66 internal carotid arteries, eight vertebral arteries, three anterior cerebral arteries, and one middle cerebral artery) were infused in 51 sessions. Internal carotid and vertebral artery infusions were conducted through 5F diagnostic catheters positioned extracranially, while anterior and middle cerebral artery infusions were conducted through microcatheters positioned intracranially. Cerebral angioplasty complemented intraarterial papaverine therapy in 26 of 78 territories treated. Papaverine was mixed as 300 mg in 100 mL of normal saline and infused with an automatic pump. Infusion times ranged from 5 to 60 minutes, and infusion rates ranged from 100 to 400 mL/hr. Doses ranged from 100 to 600 mg per vessel, but were generally 300 mg per vessel. Patients did not receive anticoagulation treatment during infusion. ICP monitoring was done with fiber-optic monitors (Camino OLM, Camino Laboratories, San Diego, CA) or, for patients with hydrocephalus, with ventriculostomy catheters connected to pressure transducers. To protect patients from significant ICP elevations during therapy, papaverine infusions were generally stopped or slowed when ICP rose 20 mm Hg above baseline, when cerebral perfusion pressure (CPP) fell to below 60 mm Hg, or when adverse clinical events occurred. Records of ICP at baseline and during papaverine infusion, drug infusion rates, total doses, and the infusion positions were analyzed. Hunt and Hess scores, Fisher grades, Glasgow Coma Scale scores on admission and immediately before treatment, patients' ages, and adverse events were recorded for all subjects. The Fisher exact test was used for statistical analysis of the data.

Results

Table 1 lists data for all infusions, arranged in order of increasing ICP increments. Baseline ICP ranged from 0 to 34 mm Hg, with a mean of 14 mm Hg. The mean dose of papaverine infused per vessel was 294 mg, and the mean infusion time was 26 minutes. In 70 (90%) of 78 territories treated, ICP rose with papaverine infusion. The increase in ICP ranged from 0 to 60 mm Hg, and the mean increase was 12 mm Hg. The highest ICP recorded during papaverine infusion was 70 mm Hg, observed in a patient with a baseline ICP of 10 mm Hg. The 60 mm Hg increase in ICP observed in that patient was the highest increase in ICP observed in the series, and it occurred within 5 minutes at the fastest infusion rate, 400 mL/hr (20 mg/min). Even at the slowest infusion rate, 100 mL/hr (5 mg/min), increases in ICP of up to 30 mm Hg were observed during treatment.

We found a highly significant difference in responses to papaverine infusion between patients with elevated baseline ICP and those with normal baseline ICP. Elevations in ICP of at least 20 mm Hg were much more likely to occur during treatment in patients with elevated baseline ICP (>15 mm Hg) than in those with low baseline ICP (0–15 mm Hg) (P = .005). The significance of this finding became more striking (P = .001) when populations were further subdivided into definitely low (0–10 mm Hg) and definitely high (>20 mm Hg) baseline ICP (Table 2).

No relationship was established between ICP increase during papaverine infusion and patient's age (P = 1.00), Hunt and Hess score (P = 0.70), Fisher grade (P = 1.00), or Glasgow Coma Scale score at admission (P = 0.65) or immediately before treatment (P = 1.00) (Table 3).

Adverse effects of papaverine infusion in the study group, aside from increases in ICP, included agitation, mental status changes, chills, hypotension, seizure, aphasia, pupillary dysfunction, respiratory arrest, and hypertension (Table 1). Multiple adverse effects were seen in some patients, but all adverse effects were transient. They were observed in patients with normal or elevated baseline ICP, but were more frequent in patients with ICP increases of more than 10 mm Hg above baseline during papaverine infusion (P = .02; Table 4). There were no complications resulting from placement of ICP monitors.

Discussion

Increased ICP during papaverine infusion has been recognized previously, although the mechanism for this event is uncertain (16). One proposed explanation for ICP elevation is that papaverine infusions in cerebral vessels result in increased cerebral blood volume, perhaps primarily an effect of increased venous capacity (17, 18). Whatever the cause, it is clear from the above data that an ICP increase of some degree during papaverine infusion should be expected. Significant ICP increases can occur despite low baseline ICP and slow papaverine infusion rates, and such increases cannot be predicted in advance by the patient's age, presenting or pretreatment clinical state, or the amount of subarachnoid blood evident on the brain CT scan.

ICP elevations may decrease cerebral perfusion, the opposite of the desired effect of therapeutic papaverine infusions for cerebral vasospasm, and may be associated with other adverse clinical events (19–21). ICP elevations during papaverine infusion are closely linked to the rate of drug delivery. In this series, a reduction in the papaverine delivery rate or a cessation of the papaverine infusion, in those cases in which ICP rose significantly, was always followed by a decline in ICP toward baseline within 5 minutes. Continuous monitoring of ICP during infusions permitted timely recognition of significant ICP increases and appropriate reductions in papaverine infusion rates to avoid diminishing cerebral perfusion.

In this series, papaverine infusion rates were initially set to deliver the drug over variable time periods. Continuous ICP readings were compared with continuous mean arterial pressure readings to adjust initial infusion rates, if necessary. Early in our experience, we tended to terminate a papaverine infusion when ICP rose significantly. Later on, we tended to resume the papaverine infusion at a slower rate after a temporary cessation of the infusion allowed ICP to return to baseline. Five vessel infusions in this series were stopped before delivery of the desired papaverine dose because of increases in ICP.

Some patients had an elevated baseline ICP and, nonetheless, received papaverine infusions safely.

TABLE 1: Data for 78 vessels (in 28 patients with cerebral arterial vasospasm) treated with papavrine infusion

Vessel Infused	Dose, mg, per Vessel	Infusion Time, min	Baseline ICP, mm Hg	Maximum ICP, mm Hg	Increase in ICP, mm Hg; Adverse Events
1. LICA	300	15	16	16	0
2. RICA	300	15	16	16	0
3. LICA	300	15	14	14	0
4. RICA	300	15	14	14	0
5. LICA	300	15	13	13	0
6. RICA	300	20	10	10	0
7. LICA	300	20	10	10	0
8. RICA	300	30	15	15	0
9. RICA	300	19	15	16	1
10. LICA	300	60	10	12	2
11. RICA	300	15	13	16	3
12. LVERT	300	15	9	12	3
13. LICA	300	15	9	12	3
14. RICA	300	15	9	12	3
15. LICA	300	30	11	15	3, Agitation
16. LICA	200	40	8	12	4
17. RICA	600	30	28	32	4
18. LVERT	300	60	10	15	5
19. RICA	300	25	5	10	5
20. LICA	300	15	8	13	5
21. RICA	300	20	20	25	5
22. LICA	300	20	20	25	5
23. RICA	300	15	7	12	5
24. RICA	300	20	7	12	5
25. LICA	300	30	18	24	6
26. RICA	300	45	6	12	6
27. LICA	300	20	12	18	6, Chills, mental status changes
28. RICA	300	25	12	18	6
29. LICA	300	15	13	19	6
30. RACA	100	20	8	15	7
31. RICA	300	15	8	15	7
32. RICA	300	15	6	13	7
33. RICA	300	30	9	16	7, Agitation
34. LICA	300	30	9	16	7
35. LICA	600	60	8	16	8
36. RICA	300	30	8	16	8
37. LVERT	100	5	14	22	8, Arrest
38. RICA	300	15	10	18	8
39. RICA	300	30	17	25	8
40. RICA	300	25	17	26	9
41. LICA	300	15	8	17	9
42. RICA	300	60	20	30	10
43. LACA	300	30	30	40	10
44. RICA	300	15	15	25	10
45. RICA	300	15	9	19	10
46. LICA	300	20	7	17	10
47. RICA	300	40	34	46	12, Mental status changes
48. RVERT	300	25	9	21	12
49. RICA	300	30	20	33	13
50. RMCA	120	60	21	34	13
51. LICA	300	20	10	23	13, Seizure
52. RICA	300	30	0	14	14, Transient aphasia
53. RICA	300	20	19	34	15
54. LICA	300	20	15	30	15
55. RICA	300	30	23	38	15
56. RICA	300	20	10	25	15
57. RVERT	300	60	0	15	15
58. LICA	300	15	14	30	16
59. RICA	180	60	21	37	16
60. LICA	300	18	17	34	17
61. RICA	300	20	5	22	17, Hypotension, bradycardia
62. LICA	300	38	22	35	17, Pupillary dysfunction
63. LVERT	150	25	16	34	18, Hypotension
64. RICA	300	20	10	28	18
65. LVERT	300	30	20	40	20
66. RVERT	300	15	17	37	20
67. RICA	300	20	0	20	20
68. LICA	300	20	0	20	20
69. RICA	300	20	30	50	20
70. LICA	300	20	30	50	20
71. LICA	300	60	27	60	23
72. RICA	250	25	13	42	29, Pupillary dysfunction
73. RACA	300	60	30	60	30
74. RICA	150	10	21	52	31, Agitation
75. RICA	450	25	28	60	32, Transient aphasia
76. LICA	300	25	28	63	35
77. LICA	300	15	20	57	37
78. RICA	200	10	10	70	60, Hypertension, tachycardia, mental status changes
Average	293.59	26.03	14.12	25.77	11.56

Note.—ICP, intracranial pressure; RICA, right internal carotid artery; LICA, left internal carotid artery; RVERT, right vertebral artery; LVERT, left vertebral artery; RACA, right anterior cerebral artery; LACA, left anterior cerebral artery; RMCA, right middle cerebral artery.

TABLE 2: Increases in intracranial pressure (ICP) during papaverine infusion relative to baseline ICP

Baseline ICP	No. of Infusions with ICP Rise of <20 mm	No. of Infusions with ICP Rise of ≥20 mm
Low, ≤10 mm	42	5
High, ≥20 mm	5	9
Normal, 0–15 mm Hg	45	4
Elevated, >15 mm Hg	19	10

TABLE 3: Relationship of clinical parameter to increases in intracranial pressure during papaverine infusion

Clinical Parameter	No. of Patients with ICP Rise of <20 mm	No. of Patients with ICP Rise of ≥20
Hunt and Hess score 1–2	8	4
Hunt and Hess score 3–4	9	7
Fisher grade 1–2	4	3
Fisher grade 3–4	13	8
Admission GCS score 1–9	3	3
Admission GCS score 10–15	14	8
Pretreatment GCS score 1–9	10	6
Pretreatment GCS score 10–15	7	5
Age <50 y	8	6
Age ≥50 y	9	5

Note.—GCS, Glascow Coma Scale.

The group of patients most likely to have significant increases in ICP during therapy were those who had an elevated baseline ICP; papaverine therapy in such patients was geared toward maintaining cerebral perfusion pressure above 60 mm Hg.

An added benefit of continuous ICP monitoring is that it enables the practitioner to deliver papaverine doses as quickly as possible. Patients symptomatic with cerebral vasospasm require intensive care, and the shorter the time spent outside the ICU environment, the better. Slow preset infusion rates result in prolonged procedure times, particularly if three arterial territories are treated, with each territory requiring a 60-minute papaverine infusion. This type of protocol not only delays the patient's return to the ICU but also ties up an angiography suite for at least 3 hours. Since many patients tolerate more rapid infusions, papaverine delivery rates with continuous ICP monitoring may be initially set to treat a territory in 15 minutes then adjusted to deliver the drug more slowly should ICP significantly rise or CPP significantly fall.

In those situations in which ICP elevations associated with papaverine therapy are refractory to adjustments in drug delivery rates or to termination of papaverine therapy (an occurrence not observed in this series), or when aggressive papaverine therapy is indicated and ICP cannot be limited by papaverine delivery rate adjustments alone, one could attempt to lower ICP by administering intravenous mannitol. An attempt could also be made to lower ICP by intermittently allowing a ventriculostomy tube to drain. The effectiveness of these additional therapeutic maneuvers to lower ICP could probably be gauged best with continuous ICP monitoring.

TABLE 4: Relationship between adverse events and increase in intracranial pressure (ICP) during infusion

	No. of Infusions with Adverse Events	No. of Infusions without Adverse Events
No. of infusions with an ICP increase of ≤10 mm Hg	4	42
No. of infusions with an ICP increase of >10 mm Hg	10	22

The drawbacks to continuous ICP monitoring are the cost and potential complications of placing a pressure monitor or ventriculostomy in those patients in whom a means to measure ICP has not already been established. No ventriculostomy was placed solely for ICP monitoring for papaverine infusion, but some Camino bolts in this series were. Such additional costs are balanced against the risks of unrecognized ICP elevation and the potential consequences for the patient. Complications of Camino bolt placement, not observed in this series, are reported to be very low, from 0% to 0.6% (22, 23).

Conclusion

Optimal care could be rendered to patients with cerebral vasospasm by the use of continuous ICP monitoring during papaverine infusion. Papaverine delivery can be made both time-efficient and safe by obtaining baseline ICP and initially selecting an infusion rate to deliver the desired dose of papaverine over a short (eg, 15-minute) time interval, then stopping or slowing the papaverine infusion should the ICP rise more than 10 mm Hg above baseline or the CPP fall below 60 mm Hg. In this series, no predetermined papaverine infusion rate or baseline ICP guaranteed that a patient would not have a rise in ICP of more than 10 mm Hg during therapy. Symptoms such as agitation and tachypnea do not necessarily imply ICP elevation. It is not possible, by extrapolating from our data, to exclude any particular subgroup of patients from ICP monitoring during papaverine infusion by clinical means if the goal of such monitoring is to identify and reverse significant ICP elevation during therapy.

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