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Effectiveness of Intra-Arterially Infused Papaverine Solutions of Various Concentrations for the Treatment of Cerebral Vasospasm

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Summary

We evaluated the effect of intra-arterially infused papaverine solutions of various concentrations on cerebral vasospasm following subarachnoid haemorrhage. A total of 90 vascular territories in 46 patients with symptomatic cerebral vasospasm after subarachnoid haemorrhage were treated with intra-arterial infusions of papaverine. In all patients, papaverine was infused at the top of the internal carotid artery (ICA). Of the 90 vascular territories, 30 vascular territories in 14 patients were treated with an infusion of 0.1–0.2% (weight/volume) papaverine (Group 1), 30 vascular territories in 16 patients were treated with a 0.4% (w/v) papaverine infusion (Group 2), and 30 vascular territories in 16 patients were treated with an infusion of 0.8–2.0% (w/v) papaverine (Group 3). Among the three groups, we compared the vasodilatory effects of papaverine by assessing the angiographical and clinical improvements following the treatment. When 0.4% (w/v) papaverine was infused, 24 vascular territories (80%) were successfully dilated and 7 patients (44%) showed a marked reversal of neurological deficits due to vasospasm. Therefore, 80 mg/20 ml (0.4% (w/v)) papaverine infused over a 10-minute period proved to be a beneficial concentration. Transient focal neurological deficits due to the infusion of papaverine occurred in 1 Group 1 patient (7%), 1 Group 2 patient (6%), and 7 Group 3 patients (44%). Highly concentrated papaverine had a higher risk of temporary deterioration. In conclusion, the papaverine concentration of 0.4% (w/v) infused at the top of the ICA was a safe and adequate concentration for treating cerebral vasospasm.

Keywords: Cerebral vasospasm; concentration; papaverine; subarachnoid haemorrhage.

Introduction

The intra-arterial infusion of papaverine hydrochloride has been used to treat cerebral vasospasm after subarachnoid haemorrhage. Some previous studies of this treatment reported a relatively small number of patients with variable success rates [8, 9, 18, 19] and other reports have described complications associated with papaverine infusion [1–3, 6, 10, 13–15]. The doses and concentrations of papaverine used in the treatment are difficult to compare among reports, but the optimal concentration of intra-arterially infused papaverine and possible complications during this treatment must be determined to achieve better clinical results. The present study evaluated the effect of intra-arterially infused papaverine solutions of various concentrations for the treatment of cerebral vasospasm.

Clinical Materials and Methods

Patient Population

Between December 1993 and June 1996, 90 vascular territories in 46 patients with vasospasm after subarachnoid haemorrhage were treated with an intra-arterial infusion of papaverine. The patients' age ranged from 31 to 69 years. All patients had undergone early surgery to clip the aneurysm by Day 2 and received 3H therapy (hypertension, hypervolaemia, haemodilution) for the prevention of cerebral vasospasm.

Indication for Treatment

Postoperatively, transcranial Doppler (TCD) ultrasonography recordings of the middle cerebral artery (MCA) and/or anterior cerebral artery (ACA) were performed by the standard transtemporal approach. Indications for the use of papaverine infusion were: (a) the presence of neurological deficits attributed to vasospasm, not responding to maximal medical treatment with absence of computed tomographic (CT) evidence of recognizable cortical infarction in the territory to be treated, and (b) more than 120 cm/sec mean cerebral blood flow velocity or more than 30 cm/sec per day increase of mean flow velocity measured by TCD when patients were comatose. Thereafter, when cerebral angiography was performed, angiographic spasms were estimated. If there was a vasospasm responsible for ischaemic symptoms and causing more than 30% reduction in the vessel diameter on the angiogram, an infusion of papaverine was performed. Angiographic spasms were assessed subjectively by three nonblinded neurosurgeons independently. Initial admission arteriograms, without obvious vasospasm, were

used as a reference and were compared with pretreatment and posttreatment angiograms.

Intra-Arterial Infusion of Papaverine

A Tracker-18 catheter (Target Therapeutics, CA, USA) with a Radifocus 0.016" guidewire (Terumo, Tokyo, Japan) was introduced coaxially. The tip of the microcatheter was positioned at top of the internal carotid artery (ICA), and the infusion of papaverine was then performed. Neurological changes in the patients were checked during the procedure. Systemic blood pressure (SBP) during the papaverine infusion was maintained within the range of 130 to 160 mmHg by the use of dopamine and/or dobutamine in all patients so that the SBP would not be related to the effect of the infused papaverine. Papaverine diluted with normal saline was infused through the microcatheter using a power injector for a period of 10 minutes. Of the 90 vascular territories, 30 vascular territories in 14 patients were treated with the infusion of 0.1 to 0.2% (weight/volume (w/v)) papaverine concentration (Group 1), 30 vascular territories in 16 patients were treated with 0.4% (w/v) papaverine infusions (Group 2), and 30 vascular territories in 16 patients were treated with the infusions of 0.8 to 2.0% (w/v) papaverine concentration (Group 3). The assignment of patients into these three groups was performed at random. In Groups 1 and 3, the papaverine concentration used in each patient was determined in accord with the initial grade of each vasospasm. Table 1 shows the characteristics of the 46 patients on admission. The age and sex distribution was similar in the three groups. There were no significant differences in the grade of vasospasm before treatment among the groups. The infusion of papaverine was repeated a few times until the affected vessels were dilated to nearly normal caliber size. The interval between infusions was approximately 10 minutes. In some patients, the infusion procedure was terminated without evidence of any vasodilatory effect of papaverine. All procedures were performed via a transfemoral approach under local anaesthesia with systemic heparinization.

Evaluation of Vasodilation

Immediately after the completion of the infusion of papaverine, angiograms were performed to assess the degree of dilatation obtained. With the pretreatment stenosis as A% and the posttreatment stenosis as B%, the vasodilatory effect of papaverine (Z) was calculated by the following formula: $Z = (A - B)/A \times 100$ (%). The effect of papaverine was evaluated as follows; good when Z was more than 50%, fair when Z ranged from 30% to 50%, and poor when Z was less than 30%. A follow-up angiogram was performed two days after the procedure. If a recurrence of vasospasm was noted in the follow-up study, the infusion of papaverine at the same concentration was performed again.

As for data analysis, statistical analysis was performed by using Student's unpaired t-test. P values of 0.05 or less were considered to be statistically significant.

Results

Papaverine was infused selectively into 90 vascular territories in 46 patients. We divided the 90 vascular territories into three groups by the papaverine concentrations infused and compared the vasodilatory effects of papaverine among them. In Group 1, 4 vascular territories were treated at 0.1%, 10 vascular territories were treated at 0.15% and 16 vascular territories were treated at 0.2%. In Group 2, all 30 vascular territories were treated with 0.4% papaverine infusion. In Group 3, 7 vascular territories were treated with 0.8% papaverine, 7 vascular territories were treated with 1.2%, 8 vascular territories were treated with 1.6%, and 8 vascular territories were treated with 2.0% papaverine. Table 2 shows the angiographic

Table 1. *Characteristics of Patients Undergoing Papaverine Infusion as Treatment for Cerebral Vasospasm*

	Group 1	Group 2	Group 3
Papaverine concentration	0.1–0.2%	0.4%	0.8–2.0%
No. of vascular territories	30	30	30
No. of cases	14	16	16
Female	8 (58%)	10 (63%)	9 (56%)
Mean age	58	59	60
H & K grade[a]			
I	1 (7%)	1 (6%)	1 (6%)
II	4 (29%)	6 (38%)	5 (31%)
III	6 (43%)	7 (44%)	7 (44%)
IV	3 (21%)	2 (13%)	3 (19%)
Fisher group[b]			
1	0 (0%)	0 (0%)	0 (0%)
2	5 (36%)	4 (25%)	5 (31%)
3	7 (50%)	9 (56%)	8 (50%)
4	2 (14%)	3 (19%)	3 (19%)

[a] Hunt and Kosnik classification.
[b] Subarachnoid haemorrhage (SAH) grouping according to Fisher *et al.*

Table 2. *Angiographic Findings Before and After Infusion of Papaverine*

Group 1. 30 vascular territories, 14 patients 0.01–0.2% papaverine

	Severe	Moderate	Mild
Before	18	12	0
After	4	11	15

Group 2. 30 vascular territories, 16 patients 0.4% papaverine

	Severe	Moderate	Mild
Before	21	9	0
After	3	5	22

Group 3. 30 vascular territories, 16 patients 0.8–2.0% papaverine

	Severe	Moderate	Mild
Before	20	10	0
After	6	14	10

Table 3. *Vasodilatory Effects After Infusion of PPV*

	Good	Fair	Poor
Group 1	14 (47%)	7 (23%)	9 (30%)
Group 2	24 (80%)	3 (10%)	3 (10%)
Group 3	6 (20%)	7 (23%)	17 (57%)

PPV papaverine.

findings before and after the infusion of papaverine in each group, and Table 3 provides a comparison of the vasodilatory effects after papaverine infusion among the groups. The proportion of the good vasodilatory effects angiographically evaluated after treatment was 47% in Group 1, 80% in Group 2, and 20% in Group 3. There were significant differences in vasodilatory effects among the groups. As for clinical improvement after treatment among the three concentration groups, 3 of the 14 patients (21%) in Group 1, 7 of the 16 patients (44%) in Group 2, and 1 of the 16 patients (6%) in Group 3 showed a marked reversal of neurological deficits due to cerebral vasospasm. There were significant differences in clinical effects among the groups. The 0.4% (w/v) papaverine concentration (Group 2) was thus demonstrated to be a beneficial concentration for infusion at the top of the ICA.

There were no serious side effects due to the infusions of papaverine. Nine of the 46 patients (20%) developed focal neurological deficits during the infusion of papaverine, which all resolved within an hour. Papaverine treatment in these 9 patients was discontinued as soon as these neurological changes were noted. The total amount of papaverine given to these patients was 20 mg in 1 patient, 40 mg in 3, 60 mg in 2, 80 mg in 1, and 100 mg in 1, 120 mg in 1, respectively. Table 4 summarizes the characteristics of the 9 patients with neurological complications during the infusion of papaverine. These 9 complications occurred in 1 Group 1 patient (7%), 1 Group 2 patients (6%), and 7 Group 3 patients (44%). There was no significant difference in the incidence of complications between Group 1 and Group 2, but the differences between Group 3 and the other two groups were significant. The Group 3 infusion concentration (0.8–2.0% (w/v)) may cause temporary deterioration.

In 8 patients (17%) who were successfully dilated after papaverine infusion, a recurrence of arterial narrowing occurred within 7 days after the initial treatment. These 8 restenoses occurred in 4 (25%) of the 16 patients of Group 2 and in 4 (25%) of the 16 patients of Group 3, with no significant difference between them. All restenoses due to vasospasm showed improvements on the angiogram after the second infusion of papaverine.

Discussion

Papaverine is a potent smooth muscle relaxant that produces generalized arterial dilatation and smooth muscle relaxation [4]. Its pharmacological effect is mediated by elevated levels of intracellular cyclic adenosine monophosphate (cAMP) or cyclic guanosine 3,5′-monophosphate (cGMP) and is secondary to the inhibition of phosphodiesterase [16].

We have treated cerebral vasospasm patients after subarachnoid haemorrhage using superselective intra-arterial infusion of papaverine [8]. Kassell *et al.* [9] also reported the effectiveness of selective intra-arterial infusions of higher doses of papaverine for cerebral vasospasm. The optimal concentration of papaverine for cerebral infusion was not determined by these previous studies. In the present study, various concentrations of papaverine (0.1% to 2.0%) were administered and the vasodilatory effects were compared. The assignment of patients to the high and low dose groups was random without the investigators' bias. The initial papaverine concentration we used clinically for cerebral vasospasm was 40 mg diluted in 20 ml of saline (0.2% (w/v)), as determined by an in vitro experiment by Tsukahara *et al.* [17]. In our initial study, after 0.1% to 0.2% (w/v) papaverine was infused at the top of the ICA, the papaverine concentration was gradually increased to 2.0% (w/v) to achieve a sufficient concentration for the spastic vessels and to obtain a greater vasodilatory effect. Based on our clinical study, 80 mg/20 ml (0.4% (w/v)) over 10 minutes infused at the top of the ICA proved to be an adequate and safe concentration to obtain angiographic and clinical improvements.

There have been few other clinical studies regarding the optimal concentration of intra-arterially infused papaverine. In a clinical study, Kassell *et al.* [9] suggested 0.3% (300 mg/100 ml) papaverine as an optimal concentration for selective intra-arterial cerebral infusion. In an experimental study, Mathis *et al.* [12] evaluated the stability of diluted papaverin with respect to changes in papaverine concentrations in simulated cerebral vasospasms. Their results indicated that papaverine solutions at concentrations of 0.3% (w/v) or higher have the propensity to form precipi-

tates when mixed with serum, and these precipitates are diminished by dilutions that decrease the papaverine concentration to less than 0.3% (w/v). The in vitro experiments by Jin *et al.* [7] demonstrated that, during vasospasm, microvessels show a paradoxical response such as vasoconstriction to low concentrations of 50 μM papaverine.

Complications in the central nervous system during the intra-arterial infusion of papaverine for vasospasm have previously been reported [1–3, 6, 9, 10, 13–15]. In the present study, we encountered 9 patients with transient complications (Table 4). In 7 of these 9 patients, the papaverine concentration used was above 0.4% (w/v), a concentration which seemed to be optimal in the other patients of this series. This result indicates that concentrations of papaverine over 0.4% (w/v) may cause more complications. Previously identified complications during the intra-arterial infusion of papaverine include transient hemiparesis [9], mydriasis [6, 9], confusion [1, 9], seizure [2], tachycardia [10], hypotension [14], thrombocytopenia [15], increased intracranial pressure [14], exacerbated vasospasm [3], and reversible brain stem depression [1, 13]. Possible causes for complications during the intra-arterial infusion of papaverine include (a) primary toxic or neurodepressive effects of the papaverine itself, and (b) secondary embolic or ischaemic effects associated with precipitate formation. As yet, it has not been determined whether these complications result from the former or the latter cause. In previous experience with such complications, the direct neurodepressive effect of papaverine was suggested as the cause of complications, since the concentration of infused papaverine was 0.3%

Table 4. *Characteristics of Nine Patients with Complications During PPV Infusion*

Case no.	Age/Sex	H & K[a]	Fisher group	Interval days from SAH to PPV infusion	Neurological deficit and grade (GCS) at treatment	Vessels infused	Concentration (mg/ml) Total dose (mg)	Complication	Clinical result Early / Late[b]
1	41, M	II	3	4	Decreased LOC GCS 11	Bil. IC top	20/10 30	R. hemiplegia	No change / MD
2	48, F	I	2	11	Aphasic Decreased LOC GCS 13	R. IC top	80/20 40	L. upper limb paralysis Confusion	Mild improvement / GR
3	65, F	IV	2	8	Decreased LOC GCS 9	R. IC top	120/20 80	L. upper limb paresis Confusion	No change / GR
4	46, M	IV	4	7	L hemiparesis GCS 8	R. IC top	120/20 60	Mydriasis	No change / MD
5	40, M	II	3	3	L hemiparesis GCS 7	L. IC top	120/20 100	Mydriasis	No change / Died (DIC)
6	78, M	III	4	5	Decreased LOC GCS 10	R. IC top	120/20 40	Confusion	No change / GR
7	49, M	III	3	3	Decreased LOC GCS 10	Bil. IC top	160/20 40	Mydriasis	No change / GR
8	54, M	III	4	5	R hemisparesis GCS 6	R. IC top	200/20 40	Mydriasis	No change / Died (Sepsis)
9	46, F	II	3	7	Decreased LOC GCS 13	L. IC top	240/10 120	R. hemiplegia Confusion	No change / GR

PPV papaverine; *IC* internal carotid artery; *LOC* level of consciousness; *GCS* Glasgow Coma Scale score.

[a] Hunt and Kosnik classification.

[b] Glasgow Outcome Scale score; *GR* good recovery; *MD* moderate disability.

(w/v). All previous complications were transient and the neurotoxicity of papaverine could easily explain the transience of the symptoms. As for our present cases, in contrast, concentration-dependent precipitate formation may have been a major cause of the complications. There was no evidence of an embolus formed from precipitation on the follow-up angiogram obtained immediately after the onset of neurological deficits, however, we cannot exclude the possibility that an embolus occurred during the infusion and dissolved before the angiogram. Once papaverine crystals are formed, they could easily create significant distal emboli with ischaemic symptoms. These ischaemic symptoms might be transient because of the resuspension of the precipitate with time. However, complications also occurred in two of our patients despite the infusion of an optimal or low papaverine concentration. In this respect, we cannot entirely exclude embolus formation due to the procedure, such as by a migration of the microcatheter into the ICA top, although a direct neurotoxic effect of papaverine may be enhanced by the locally diminished cerebral blood flow secondary to vasospasm even at low papaverine concentrations.

Even in the group treated with 0.4% (w/v) papaverine, which was considered to be the optimal concentration in the present study, only 44% of the patients obtained clinical improvement despite an 80% rate of angiographic improvement. Kassell *et al.* [9] reported that 60% of their patients treated with papaverine who had angiographic improvement in vasospasm had no clinical benefit, and Clouston *et al.* [2] stated that 50% of their patients had no clinical benefit despite angiographic improvement. A more recent study demonstrated that only 52% of the patients showed objective clinical improvement despite a 76% rate of angiographic improvement [14]. It is difficult to explain the lack of clinical benefit in patients with cerebral vasospasm that responds angiographically with vasodilation following intra-arterial papaverine treatment. Some of these patients may have sustained an irreversible ischaemic injury prior to papaverine administration. One possible explanation for this discrepancy is that vasodilation in nonischaemic regions may steal cerebral blood flow from the affected vascular area. One study supporting this hypothesis reported that low-dose papaverine (10 mg) actually reduced the cerebral blood flow in ischaemic regions [5]. Another possibility for the lack of correlation is that the vasodilatory effect of papaverine may not last long since the timing of papaverine administration is too late. Moreover, the discrepancy between the angiographic and clinical effects of papaverine may be the result of paradoxical effects such as a vasoconstrictor response of papaverine at the microvascular level; such a mechanism was suggested in an experimental study by Jin *et al.* [7]. As evidence of this hypothesis, a recent clinical report demonstrated the angiographical finding of a paradoxical aggravation of vasospasm during intra-arterial papaverine treatment [3]. The cause for the discrepancy between the angiographic and clinical results after papaverine treatment remains to be elucidated. Further evaluation is needed to clearly establish the role of papaverine as a smooth muscle vasodilator for the treatment of cerebral vasospasm.

Conclusion

The intra-arterial infusion of papaverine is effective in the treatment of cerebral vasospasm. However, the infusion of highly concentrated papaverine may cause less vasodilatory effect and induce temporary deterioration due to papaverine. Based on our experience, 80 mg/20 ml (0.4% (w/v)) papaverine infused at the top of the ICA over a 10-minute period proved to be an adequate and safe concentration. Although the cause of complications during the intra-arterial infusion of papaverine for cerebral vasospasm remains unclear, appropriate attention to the papaverine concentration may help decrease the incidence of side effects and enhance clinical improvement.

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Comments

In the above dose escalation study Sawada *et al.* explored the optimum concentration of intra-arterially infused papaverine solutions for cerebral vasospasm after subarachnoid haemorrhage. The authors found taht 0.4% is the concentration of choice with an optimum ratio of effectiveness to risk. The present result provides some explanation for the variable effectiveness of intra-arterial papaverine as reported in the literature. At the optimum concentration of 0.4% a good angiographic response was obtained in 80% of patients. However, a corresponding clinical improvement was seen in only roughly half of the patients. This result stresses that the option of selective intra-arterial papaverine cannot replace optimum systemic prophylactic treatment.

H.-J. Steiger

The effect of intra-arterially injected papaverine hydrochloride of various concentrations upon vasospasm was studied in 46 patients suffering from aneurysmal subarachnoid haemorrhage. The authors defined 90 afflicted "vascular territories" to treat with selective arterial injection. Selection criteria for the treatment were the following: if MCA and/or ACA blood flow velocity exceeded either 120 cm/sec or a daily increase of 30 cm/sec; angiography and a CT were performed. In case of an arterial narrowing of more than 30% without an accompanying hypodensity in the appropriate brain area, papaverine infusion was performed selectively into the spastic segment. Results of treatment were assessed by angiography. A conclusion was drawn that 80 mg/20 ml infusion over 10 minutes into the "top" of the ICA is an adequate and safe treatment of vasospasm.

I am afraid the authors failed to define the relationship between vessel narrowing and clinical symptomatology. If they were treating increases in TCD blood flow velocity and arterial narrowing on angiography that did not cause hypodensity in the appropriate brain areas, they ought to speak about prevention of symptomatic vasospasm or otherwise they are treating clinically insignificant phenomena. However, they saw the development of transitory neurological deficits due to the treatment in 20% of patients.

T. Dóczi

Answer from the authors:

Although we have treated asymptomatic vasospasm, which indicated increases in TCD blood flow velocity and arterial narrowing on angiograms, we basically treated vasospasm causing clinical signs in the present study. To clarify this point, we added the criterion of the presence of neurological deficits attributed to vasospasm as an indication for papaverine treatment. We also treated patients with symptomatic vasospasm without an abnormal low density on CT scan in the territory to be treated. However, we had difficulties in assessing the clinical changes in several patients who were semicomatose or comatose under the influence of the primary brain damage. In these cases, we treated the patients based on the increases in TCD blood flow velocity and arterial narrowing on angiography.

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