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Convulsion During Intra-arterial Infusion of Fasudil Hydrochloride for the Treatment of Cerebral Vasospasm Following Subarachnoid Hemorrhage

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Abstract

The incidence of convulsion and associated factors were retrospectively analyzed in 23 patients with symptomatic cerebral vasospasm following subarachnoid hemorrhage (SAH) who underwent a total of 31 intra-arterial infusion of fasudil hydrochloride (IAFH) procedures in 49 vessels. Fasudil hydrochloride was administered by superselective infusion via a microcatheter positioned at the proximal portion of the affected artery. Thirteen procedures were performed by manually controlled infusion of 30–75 mg fasudil hydrochloride (1.2–3.75 mg/ml) for approximately 10 minutes. Eighteen procedures were performed by continuous infusion of 60 mg fasudil hydrochloride (1.2 mg/ml) by infusion pump at a constant rate of 3 mg/min. Neurological improvement was observed after 18 of 22 procedures in patients with neurological deterioration due to vasospasm. Convulsion during IAFH developed in 4 patients, all treated by manual infusion ($p < 0.05$). The manual infusion method ($p < 0.05$) and infusion rate greater than 3 mg/min ($p < 0.01$) were significantly associated with the incidence of convulsion during IAFH. IAFH was effective for treating cerebral vasospasm following aneurysmal SAH. IAFH at a constant rate of 3 mg/min delivered by infusion pump improved the symptoms of cerebral vasospasm and prevented convulsions during IAFH.

Key words: cerebral vasospasm, convulsion, fasudil hydrochloride, intra-arterial infusion, subarachnoid hemorrhage

Introduction

Cerebral vasospasm following subarachnoid hemorrhage (SAH) remains a leading cause of morbidity and mortality in patients with ruptured intracranial aneurysm, despite various advances in treatment.[8,10,20] Percutaneous transluminal angioplasty (PTA) using a balloon catheter is useful for treating the proximal portion of large vessels, but has limited potential to treat peripheral vessels because of the risk of vessel rupture and the specialized skill required to perform endovascular techniques.[1,3,5,11,21] Fasudil hydrochloride is a potent vasodilating agent that inhibits the activity of a rho-kinase involved in the development of cerebral vasospasm.[14] Intravenous and intra-arterial administration of fasudil hydrochloride has been effective for cerebral vasospasm.[7,12,14,16–19] Complications associated with intravenous administration of fasudil hydrochloride have been reported in a small number of patients with temporary systemic hypotension.[12,16] In contrast, intra-arterial infusion of fasudil hydrochloride (IAFH) has only been associated with a single case of convulsion.[13]

The angiographic and clinical effects of IAFH were investigated in patients with cerebral vasospasm to identify the factors associated with convulsion.

Materials and Methods

Twenty-three patients, 14 women and 9 men aged 28–80 years (mean 57.3 years), with symptomatic cerebral vasospasm following aneurysmal SAH underwent a total of 31 IAFH procedures at our institute from July 2003 to June 2007. All patients underwent early surgery to clip the aneurysm of the anterior circulation by day 2, and had been receiving prophylactic hypertension, hypervolemia, and hemodilution therapy for up to 14 days after the onset of SAH. Patients were monitored for signs of

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neurological deterioration every 2 hours. The criteria for determining neurological deterioration included a decline of more than 2 points on the Glasgow Coma Scale and focal neurological deficit. The clinical condition on admission was graded according to the Hunt and Hess scale.[6] The severity of the SAH was classified based on the initial computed tomography (CT) scan, according to the Fisher scale.[4] Our study accorded with the Helsinki Declaration of 1975, as revised in 1983.

Neurological deterioration was the main indicator for IAFH. If neurological symptoms could not be observed, the indicator for IAFH was low focal cerebral blood flow on perfusion CT scans performed on day 7. If the patient showed neurological deterioration, angiographic vasospasm was evaluated with digital subtraction angiography, and IAFH initiated for the constricted vessels corresponding to the neurological symptoms. Patients were excluded if new infarction was detected by CT.

All procedures were performed under local anesthesia with systemic heparinization via the transfemoral approach. A 5 French guiding catheter was advanced to the cervical portion of the internal carotid artery. A microcatheter was placed at the proximal portion of the affected artery, such as the top of the internal carotid artery or the proximal portion of the middle cerebral artery, and superselective fasudil hydrochloride infusion was continued until the vessels were completely dilated or until further dilation could not be obtained. Patients were divided into the manual infusion group and the continuous infusion group. The manual infusion group consisted of 10 patients treated from July 2003 to December 2004: 30–75 mg fasudil hydrochloride was dissolved in saline to a final volume of 20–50 ml and concentration of 1.2–3.75 mg/ml (mean 1.6 mg/ml), and infused manually for about 10 minutes per vessel (mean 6.3 mg/min). The continuous infusion group consisted of 13 patients treated from January 2005 to June 2007: 60 mg fasudil hydrochloride was dissolved in saline for a total volume of 50 ml (1.2 mg/ml), and was infused at a constant rate of 3 mg/min by infusion pump. PTA was performed with a compliant balloon catheter for segmental vasospasm of large vessels.

The diameter of the most constricted point of the affected vessel after treatment was compared with the diameter on admission, by a single observer unaware of the protocol details. Overall angiographic response to the treatment was graded as follows: complete (complete dilation of the affected vessel), incomplete (partial or incomplete dilation of the affected vessel), and no change. The neurological effects of IAFH were assessed within 24 hours after treatment. Follow-up CT scans were assessed for new low density areas attributable to cerebral vasospasm 1–3 days after treatment. Clinical outcome was evaluated one month after SAH onset, using the modified Rankin scale (mRS).

Data are expressed as the mean ± standard deviation. Significant differences in continuous variables were determined using Student's t-test. Non-parametric data were compared using the Mann-Whitney U-test. Frequencies were compared using the 2-tailed chi-square test. Univariate logistic regression analysis was performed to assess the relationship between treatment variables and the incidence of convulsion. A two-tailed probability value of <0.05 was chosen as the threshold for statistical significance. Statistical analysis was performed using SPSS software, version 17.0 (SPSS Inc., Chicago, Ill., U.S.A.).

Results

The clinically characteristics of the 23 patients are listed in Table 1. There were no significant differences in any characteristic between the manual and continuous groups. Six of the patients required multiple treatments, so a total of 31 IAFH procedures were performed in 49 affected vessels. Twenty-two of the 31 procedures were performed after onset of neurological deterioration attributable to cerebral vasospasm. The clinical outcomes of IAFH are described in Table 2. Angiographic improvement was obtained in all 49 vessels, and neurological improvement was observed after 18 of the 22 procedures indicated for neurological deterioration. Favorable outcomes (mRS 0–1) were obtained in 13 patients. Newly developed low density areas on CT, assumed to be a result of cerebral vasospasm, were found in 5 of the 23 patients.

General clinical convulsion or simple partial seizure developed during 4 IAFH procedures. Convulsion appeared during infusion, and quickly disappeared with intravenous diazepam infusion in all cases, and did not influence the subsequent clinical course (Table 3). All cases of convulsion appeared during manual procedures. No other side effects were observed during IAFH, such as systemic hypotension, transient or permanent neurological deficits, visual disturbance, or pupil change. Multiple regression analysis revealed that manual infusion ($p < 0.05$) and infusion rate greater than 3 mg/ml ($p < 0.01$) were significantly associated with the incidence of convulsion during IAFH, although neither factor influenced the angiographic or clinical results.

Table 1 Characteristics of 23 patients treated with intra-arterial infusion of fasudil hydrochloride (IAFH)

Variable	Continuous infusion	Manual infusion	Total	p Value
No. of patients	n = 13	n = 10	n = 23	
Age, mean ± SD (yrs)	54.4 ± 13.2	61.1 ± 11.1	57.3 ± 12.5	0.210
Sex, females	8	6	14	0.940
Hunt and Hess grade				0.488
I	2	3	5	
II	7	4	11	
III	3	1	4	
IV	1	2	3	
Fisher scale				0.423
grade 2	1	2	3	
grade 3	12	8	20	
Location of aneurysm				0.068
ACA	0	2	2	
AcomA	2	4	6	
MCA	7	2	9	
ICA	4	2	6	
Affected vessels	n = 29	n = 20	n = 49	0.559
ACA	10	6	16	
MCA	18	14	32	
ICA	1	0	1	
Indication for IAFH (procedures)	n = 18	n = 13	n = 31	0.187
neurological deterioration	11	11	22	
low CBF on perfusion CT	7	2	9	

AcomA: anterior communicating artery, ACA: anterior cerebral artery, CBF: cerebral blood flow, CT: computed tomography, ICA: internal carotid artery, MCA: middle cerebral artery, SD: standard deviation.

Table 2 Clinical results of intra-arterial infusion of fasudil hydrochloride

	Continuous infusion	Manual infusion	Total	p Value
Results (procedures)	n = 18	n = 13	n = 31	
neurological improvement*	9/11	9/11	18/22	0.652
convulsion	0/18	4/13	4/31	< 0.05**
Angiographic effect (vessels)	n = 29	n = 20	n = 49	
complete dilation	22	13	35	0.401
incomplete dilation	7	7	14	
no change	0	0	0	
Clinical results (patients)	n = 13	n = 10	n = 23	
new LDA by vasospasm	3	2	5	0.859
favorable outcome (mRS 0–1)	6	7	13	0.472

*Data from the 22 procedures performed for neurological deterioration. **Based on two-tailed chi-square test. LDA: low density area, mRS: modified Rankin scale.

Discussion

Non-selective IAFH from the proximal carotid artery or vertebral artery obtained angiographic improvement of vasospasm in 16 of 24 affected vessels without adverse effects following aneurysmal SAH.[18] Subsequently, superselective IAFH using a microcatheter achieved angiographic improvement in 86.4% to 100% and symptom improvement in 44.1% to 81.8% of cases.[7,17,19] IAFH is believed to be safe because only one case of convulsion has so far been reported, although convulsion, transient or permanent neurological deficits, consciousness disturbance, visual disturbance, and pupil change have been reported during intra-arterial infusion of papaverine hydrochloride.[2,9,13,15] Superselective IAFH is thought to produce better clinical results than non-selective IAFH because fasudil hydrochlo-

Table 3 Clinical characteristics of patients who developed convulsion during intra-arterial infusion of fasudil hydrochloride

Case No.	Age (yrs)/ Sex	Hunt and Hess/Fisher scales	Days after the onset	Symptom	Side	Vessel infused	Concentration (mg/ml)	Total dose (mg)	Infusion rate (mg/min)	Angiographic improvement	mRS at 1 mo
1	45/M	IV/3	11	none	lt	ICA	1.5	60	6	complete	2
2	59/F	II/2	8	aphasia	rt	MCA	1.2	120	6	complete	0
					rt	ACA			6	complete	
3	70/F	I/2	7	aphasia	lt	ACA	1.5	60	6	complete	0
4	59/F	I/3	8	none	rt	MCA	2	60	6	complete	0

ACA: anterior cerebral artery, ICA: internal carotid artery, MCA: middle cerebral artery, mRS: modified Rankin scale one month after the onset of subarachnoid hemorrhage.

ride has a dose-dependent vasodilator effect.

Convulsion during IAFH occurred at a higher rate (4/31 procedures, 12.9%) in this study than previously reported, although the clinical efficacy of IAFH was similar. Convulsion disturbs the manipulation of the microcatheter, so the risk of this complication is important to reduce. In this study, the incidence of convulsion during IAFH was significantly associated with the manual infusion method and with infusion rate greater than 3 mg/ml. IAFH delivered by infusion pump at a constant rate of 3 mg/min prevented convulsion and improved the symptoms of cerebral vasospasm. However, this study was performed retrospectively in a small number of patients, and compared patient groups from different time periods. Therefore, whether manual infusion rate was really the only factor associated with increased seizures is difficult to conclude.

IAFH was an effective modality for treating cerebral vasospasm following aneurysmal SAH. The risk of convulsion during IAFH was apparently associated with infusion rate. IAFH at a constant rate of 3 mg/min delivered by infusion pump improved the symptoms of cerebral vasospasm and probably prevented convulsion during IAFH.

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Commentary

The authors report a significant adverse event of convulsions during intra-arterial infusion of rho kinase inhibitor fasudil hydrochloride administered for refractory cerebral vasospasm after subarachnoid hemorrhage. This occurred in 4 of 13 procedures of manual infusion of the drug, and in none of 18 procedures of similar superselective administration using continuous infusion of the drug at the described doses. The convulsions were easily arrested with intravenous diazepam in every instance, and did not result in any permanent morbidity, nor did they seem to impact the anecdotal benefit of fasudil infusion on vasospasm syndrome.

It is not clear what determined the decision to use manual versus continuous infusion in the respective patients, and hence whether other factors than fasudil administration mode predisposed to convulsion. It is also unclear if prophylactic anticonvulsants had been administered, and if this affected the prevalence of convulsion. Mechanisms of fasudil associated convulsion remain unknown, as this complication had only been documented/published in a single case previously. This complication should be sought prospectively in post-marketing studies of this drug, in common use in Japan for several years, but not approved or used widely in the United States. Until more information becomes available on this adverse event, we concur with the caution advocated by the authors to use the more careful continuous infusion of this drug via superselective intra-arterial route, rather than manual infusion. Prophylactic anticonvulsants would also seem prudent in this setting.

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Cerebral vasospasm remains one of the main factors resulting in morbidity and mortality after spontaneous intracranial subarachnoid hemorrhage. 3 H(N) therapy and high dose transvenous infusion of vasodilator agents are not always enough to prevent neurological deterioration or cerebral infarction after the arterial spasm has occurred. Superselective arterial injection of vasodilator agents has shown its priority in efficacy and safety. In our practice we have used nimodipine and papaverine injection via the microcatheter or guiding catheter in over 20 cases with rather satisfactory results. The authors have reinforced this viewpoint, announcing 71.4% complete dilation of the treated vessels after superselective arterial infusion of fasudil. The other contribution of this article is the assessment of the relationship between treatment variables and the incidence of convulsion. Although only limited cases were reviewed, all the 4 cases suffering from epileptic attack during therapy were related with a manual infusion rate of 6 mg/min, which gave us a deep impression that convulsion might be avoided if the infusion had been controlled at a lower rate. However, it would be interesting to know the detailed informations in the other 6

cases who did not suffer seizure in the manual group. Were there any other seizure-related problems? Manual injection might be at an uneven speed and the use of preventive anti-epileptic drugs or not is another confusing problem. As authors mentioned, the report had the attendant problems inherited from a retrospective study, therefore, prospective study with more cases is needed to further confirm their viewpoint.

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The authors investigated the complications associated with intra-arterial infusion of fasudil. This study showed that the occurrence of convulsion during this treatment was correlated with the administration rate of fasudil. This result provides very important and useful information for neurosurgeons. Therefore, this paper is excellent and recommended.

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