


Case Report

Intra-arterial infusion of fasudil hydrochloride to treat post-traumatic cerebral vasospasm

Tomoaki Murakami,¹  Ryuichiro Kajikawa,¹ Hajime Nakamura,² Takeshi Nishida,¹ Kazuhiro Yoshimura,¹ Tomoyuki Yoshihara,¹ Koichiro Tsuruzono,¹ Akatsuki Wakayama,¹ and Haruhiko Kishima²

¹Department of Neurosurgery, Osaka Neurological Institute, Toyonaka City, ²Department of Neurosurgery, Osaka University Graduate School of Medicine, Suita, Japan

Background: The effect of intra-arterial infusion of fasudil hydrochloride in patients with post-traumatic cerebral vasospasm remains unclear. Here we report a case of intra-arterial infusion of fasudil hydrochloride for post-traumatic cerebral vasospasm.

Case presentation: A 47-year-old man was transferred to our hospital with a fractured skull and traumatic subarachnoid hemorrhage. As rhinorrhea of cerebrospinal fluid had not improved, repair surgery was carried out on day 4. Aphasia appeared on day 13. Magnetic resonance imaging and angiography showed an ischemic region in the left temporal lobe and vasospasm of the left middle cerebral artery. We immediately carried out angiography and diagnosed severe vasospasm of the M1 region of the left middle cerebral artery. After placing a microcatheter into the proximal middle cerebral artery, we injected fasudil hydrochloride intra-arterially. Vasospasm improved and aphasia resolved.

Conclusion: In this case, intra-arterial infusion of fasudil hydrochloride was effective against post-traumatic cerebral vasospasm.

Key words: Endovascular, fasudil hydrochloride, intra-arterial infusion, ischemic region, post-traumatic cerebral vasospasm

INTRODUCTION

POST-TRAUMATIC CEREBRAL VASOSPASM (PTV) has been reported since the 1960s, and often results in neurological deficit and poor outcome.¹ However, guidelines for the management of severe traumatic brain injury do not address strategies for treating PTV. We therefore treat patients with PTV according to the protocols for aneurysmal subarachnoid hemorrhage (aSAH). Although the efficacy of intra-arterial infusion of fasudil hydrochloride (IA-FH) for cerebral vasospasm has been recognized in patients with aSAH,² the efficacy of IA-FH in patients with PTV remains unclear. Here we report a case in which IA-FH was successfully used to treat PTV.

Corresponding: Tomoaki Murakami, MD, PhD, Department of Neurosurgery, Osaka Neurological Institute, 2-6-23 Shounai Takaramachi, Toyonaka City, Osaka 561-0836, Japan. E-mail: mmtmtmoaki@gmail.com.

Received 27 Nov, 2018; accepted 19 Mar, 2019; online publication 19 Apr, 2019

Funding Information

No funding information provided.

CASE REPORT

INTRA-ARTERIAL INFUSION OF fasudil hydrochloride for post-traumatic cerebral vasospasm is currently not covered by insurance in Japan. Ethics approval to administer IA-FH for post-traumatic cerebral vasospasm was therefore obtained from the Osaka Neurological Institute Institutional Review Board (Toyonaka City, Japan) (approval no. 10).

A 47-year-old man was transferred to our hospital from another hospital after diagnosis of traumatic SAH (tSAH), acute subdural hematoma, and skull fracture. Plain computed tomography of the head showed moderate SAH, right slight subdural hematoma, comminuted fracture of the right frontal bone, and fracture of the right frontal skull base (Fig. 1). Due to rhinorrhea of cerebrospinal fluid, the patient was treated with ceftriaxone sodium hydrate; as it had not improved by day 4, repair surgery was undertaken that day. Intraoperatively, the bone of the frontal base next to the crista galli showed a linear fracture with a tear in the underlying dura mater. We reconstructed this torn dura mater with periosteum and fibrin glue. Although the postoperative

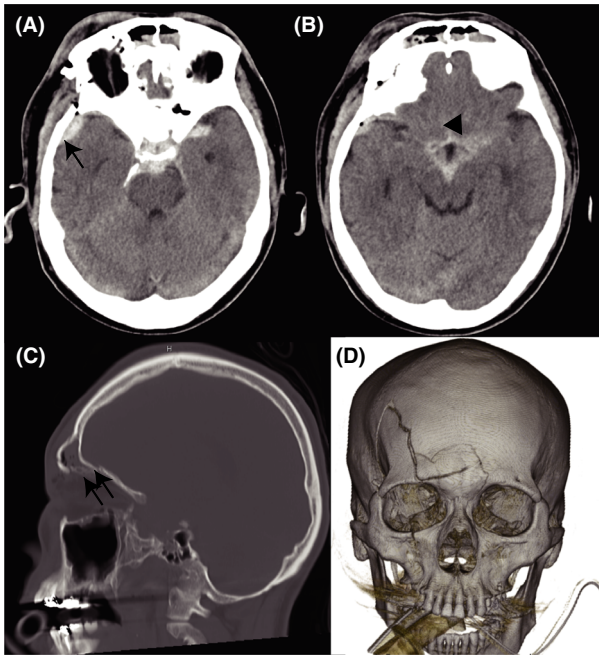


Fig. 1. Plain computed tomography on day 1 of admission of a 47-year-old man with post-traumatic cerebral vasospasm. A, Axial view shows right slight subdural hematoma (arrow) and subarachnoid hemorrhage. B, Axial view also shows subarachnoid hemorrhage in the (left > right) sylvian fissure (arrowhead). C, Sagittal bone window view shows fracture of the frontal skull base (double arrow) and fluid collection in the right frontal sinus. D, In the 3-D reconstruction of the bone window, comminuted fracture of the right frontal bone is apparent.

course was good, spike fever was observed on day 6. Examination of the cerebrospinal fluid revealed meningitis (cell count, 4,128/ μ L, 79% neutrophils). Administration of meropenem was started, in place of the ceftriaxone sodium hydrate. Fever resolved and inflammatory reactions appeared improved by day 9, and rehabilitation was then started.

On day 13, aphasia appeared and magnetic resonance imaging (MRI) was carried out. Diffusion-weighted imaging showed an ischemic region in the left temporal lobe (Fig. 2A). Magnetic resonance angiography revealed a spastic M1 region of the left middle cerebral artery (MCA; Fig. 2B). Angiography was therefore carried out immediately. Left common carotid artery angiography showed severe vasospasm of the M1 region of the left MCA (Fig. 2C), and neuroendovascular therapy was initiated for the vasospasm.

A 6-Fr Roadmaster guiding catheter (Goodman, Aichi, Japan) was placed in the left internal carotid artery (ICA). A microcatheter Excelsior SL-10STR (Stryker, Kalamazoo,

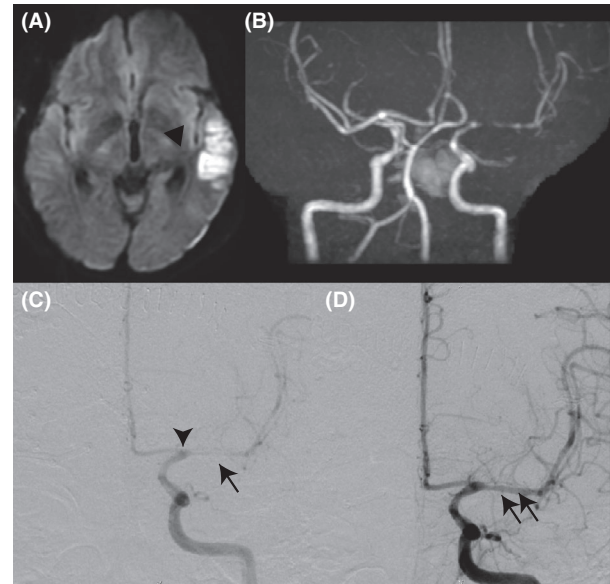


Fig. 2. Results of imaging of a 47-year-old man with post-traumatic cerebral vasospasm. A, Diffusion-weighted imaging on day 13 reveals a high-intensity area in the left temporal lobe. B, Frontal-view magnetic resonance angiography on day 13 shows M1 vasospasm in the left middle cerebral artery. C, Frontal-view internal carotid angiography (ICAG) of the left internal carotid artery before arterial infusion of fasudil hydrochloride shows M1 spasm in the left middle cerebral artery (arrow). A microcatheter Excelsior SL-10STR (Stryker, Kalamazoo, MI, USA) was placed into the proximal left middle cerebral artery (arrowhead). D, After intra-arterial injection of fasudil hydrochloride, left ICAG shows vasospasm is markedly improved (double arrow). Blood flow in the distal middle cerebral artery is improved on lateral view of the left ICAG.

MI, USA) was placed into the proximal left MCA using a microguidewire ASAHI CHIKAI 0.014-inch (ASAHI INTECC, Nagoya, Japan; Fig. 2C, arrowhead). We infused fasudil hydrochloride (FH; 30 mg) into the left MCA for 10 min. After the SL-10STR (Stryker) was placed into the top of the left ICA, we manually injected FH (15 mg) into the ICA for 5 min. As left internal carotid angiography showed improvement of vasospasm, we finished this treatment (Fig. 2D).

After this treatment, aphasia gradually improved. Although follow-up MRI after 1 week revealed a residual high-intensity area in the left temporal lobe, vasospasm of the MCA was ameliorated and the patient was discharged on day 20 (Fig. 3A,B). Aphasia resolved completely and follow-up MRI at 3 months postoperatively showed that the high-intensity area on a fluid-attenuated inversion recovery sequence was significantly reduced (Fig. 3C).

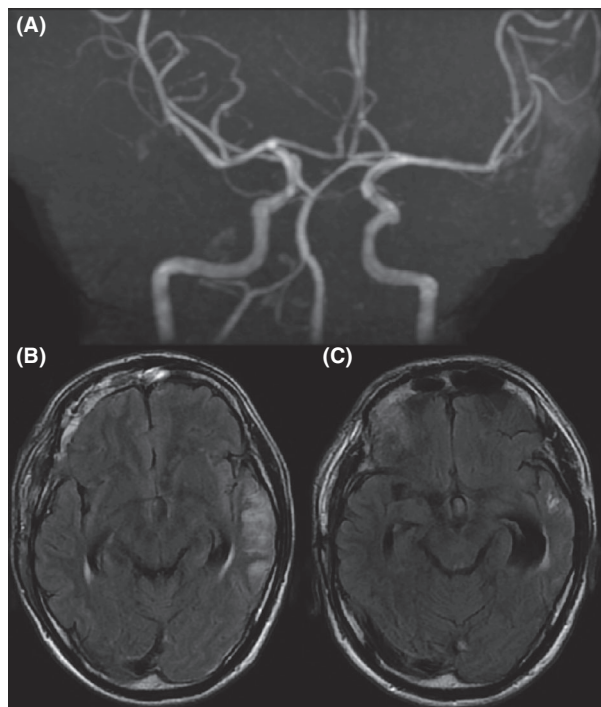


Fig. 3. Time-dependent changes in magnetic resonance imaging after treatment of a 47-year-old man with post-traumatic cerebral vasospasm. A, Magnetic resonance angiography shows vasospasm of the middle cerebral artery has entirely disappeared at 1 month. B, At 1 week, fluid-attenuated inversion recovery imaging shows a residual high-intensity area in the left temporal lobe. C, The high-intensity area on fluid-attenuated inversion recovery imaging had mostly disappeared by 3 months after the procedure.

DISCUSSION

POST-TRAUMATIC CEREBRAL VASOSPASM has previously been reported to occur in 19–68% of patients with tSAH, with only 3.9–16.6% developing neurological deficits. Severe neurological symptoms due to PTV also appear rare (0.8%). Onset of PTV was earlier and vasospasm duration was shorter compared to vasospasm secondary to aSAH.³ In our case, severe vasospasm of the left MCA occurred on day 13 and resulted in aphasia. Fortunately, aphasia improved after IA-FH.

Although the mechanisms underlying PTV have remained unclear, previous reports have suggested various possibilities. Stretching and mechanical hypothesis, SAH, and cortical spreading depolarization have been considered triggers for PTV.¹ In our case, more SAH was present in the left sylvian fissure than the right (Fig. 1B). Hence, as vasospasm occurred on the left side, this SAH might have triggered the PTV. In our case, we undertook repair surgery for rhinorrhea

of cerebrospinal fluid and the patient developed meningitis. Repair surgery associated with PTV is not well known, but some reports have suggested a relationship between meningitis and cerebral vasospasm.^{4,5} Cerebral vasospasm caused by meningitis has been indicated as the inflammatory mechanism, especially through interleukin-1 β , interleukin-6, and leucocytes in the cerebrospinal fluid.⁴ Because meningitis was also present in our case, not only the SAH, but also the meningitis might have been associated with the occurrence of PTV. Those reports also suggested that endovascular therapy was effective for cerebral vasospasm.^{4,5}

Intra-arterial infusion–vasodilator injection and percutaneous transluminal angioplasty (PTA) are currently the main modes of endovascular treatment for severe vasospasm.^{1,6} Although the opium alkaloid papaverine and the calcium channel blockers nimodipine, verapamil, and nicardipine have often been used as intra-arterially administered vasodilators for PTV, which agents are most suitable has not been established.¹ Little has been reported on the optimal treatment of PTV. As a result, the treatment for PTV has been considered in accordance with the treatment for vasospasm after aSAH. Intra-arterial infusion of papaverine has vasodilatory effects on spastic cerebral arteries. However, because the duration of effect is short, repeat injection is needed. Moreover, IA-papaverine has many complications such as increased ICP, hemorrhage, blindness, and brainstem dysfunction.⁶ Percutaneous transluminal angioplasty is a mechanical vasodilatation achieved by expanding the luminal caliber with a balloon catheter. It is more effective and continuous, compared with IA-vasodilators. However, as PTA has crucial complications such as dissection and rupture of the artery, procedural attention is warranted.⁷ In any case, IA-calcium channel blockers have also been reported as safe for treating vasospasm after aSAH.⁸ Fasudil hydrochloride is a rho-kinase inhibitor that offers powerful vasodilatory effects specific for the cerebral arteries and inhibits the action of free intracellular calcium ions, as opposed to calcium channel blockers such as nimodipine, verapamil, and nicardipine.^{2,8} Fasudil hydrochloride thus ameliorates hemodynamic status by increasing regional cerebral blood flow.³

In Japan, IA-FH had been the standard therapy for treating vasospasm after aSAH.⁹ Therefore, in our institute, we also decided to use IA-FH as the first-line treatment of severe vasospasm. In our case, we did not choose PTA because the lesions were so long that there might have been a risk of injury to the MCA. We therefore selected IA-FH first. As a result, in our case, vasospasm improved and no complications occurred. Because complications of IA-FH have rarely been reported, IA-FH has been accepted as safe. The only complication of IA-FH reported for cerebral vasospasm has been convulsion. Enomoto *et al.* recommended constant

pump infusion at a rate of 3 mg/min to prevent convulsions. Moreover, manual injection was significantly associated with the occurrence of convulsion.¹⁰ Although manual injections were used in our case, fortunately no convulsions were encountered. A 15- to 30-mg dose of FH should thus be injected intra-arterially to the affected artery for 5–10 min by infusion pump. Then, because the duration of effect can be transient,⁶ we should keep in mind that repeat injection is sometimes needed. One key limitation in the present case was that we could not definitively declare PTV as the pure cause of vasospasm, due to the potential influence of meningitis. After all, meningitis could have been involved in the pathology of cerebral vasospasm. Some controversy thus remains regarding whether IA-FH was effective for PTV alone. Further studies are needed to confirm the effectiveness of IA-FH purely for PTV.

CONCLUSION

WE HAVE REPORTED a case in which IA-FH was used to effectively treat PTV.

DISCLOSURE

Approval of the research protocol: N/A.

Informed consent: Informed consent was obtained from the patient for publication of this case report and any accompanying images.

Registry and registration no. of the study/trial: N/A.

Animal studies: N/A.

Conflict of interest: None declared.

REFERENCES

- 1 Perrein A, Petry L, Reis A, Baumann A, Mertes P, Audibert GJ. Cerebral vasospasm after traumatic brain injury: an update. *Minerva Anesthesiol.* 2015; 81: 1219–28.
- 2 Shibuya M, Suzuki Y, Sugita K *et al.* Effect of AT877 on cerebral vasospasm after aneurysmal subarachnoid hemorrhage Results of a prospective placebo-controlled double-blind trial. *J. Neurosurg.* 1992; 76: 571–7.
- 3 Kramer DR, Winer JL, Pease BA, Amar AP, Mack WJ. Cerebral vasospasm in traumatic brain injury. *Neurol. Res. Int.* 2013; 2013: 7.
- 4 Chaichana K, Riley LH 3rd, Tamargo RJ. Delayed cerebral vasospasm secondary to bacterial meningitis after lumbosacral spinal surgery: case report. *Neurosurgery* 2007; 60: E206–7.
- 5 Buechner D, Gelfand MS, Cleveland KO. Percutaneous transluminal angioplasty in a patient with vasospasm due to staphylococcal meningitis. *J. Neurosurg.* 2012; 117: 103–6.
- 6 Hyogo T. Endovascular treatment of cerebral vasospasm. *Jpn. J. Neurosurg.* 2002; 11: 777–82 (in Japanese).
- 7 Elliott JP, Newell DW, Lam DJ *et al.* Comparison of balloon angioplasty and papaverine infusion for the treatment of vasospasm following aneurysmal subarachnoid hemorrhage. *J. Neurosurg.* 1998; 88: 277–84.
- 8 Dabus G, Nogueira RG. Current options for the management of aneurysmal subarachnoid hemorrhage-induced cerebral vasospasm: a comprehensive review of the literature. *Interv. Neurol.* 2013; 2: 30–51.
- 9 Hayashi K, Hirao T, Sakai N *et al.* Current status of endovascular treatment for vasospasm following subarachnoid hemorrhage: analysis of JR-NET2. *Neurol. Med. Chir.* 2014; 54: 107–12.
- 10 Enomoto Y, Yoshimura S, Yamada K *et al.* Convulsion during intra-arterial infusion of fasudil hydrochloride for the treatment of cerebral vasospasm following subarachnoid hemorrhage. *Neurol. Med. Chir.* 2010; 50: 7–11.