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Efficacy and Safety of Fasudil in Patients With Subarachnoid Hemorrhage: Final Results of a Randomized Trial of Fasudil Versus Nimodipine

Jizong ZHAO,[1] Dingbiao ZHOU,[2] Jing GUO,[3] Zuyuan REN,[4] Liangfu ZHOU,[5] Shuo WANG,[1] Yan ZHANG,[1] Bainan XU,[2] Kuiming ZHAO,[3] Renzhi WANG,[4] Ying MAO,[5] Bin XU,[5] and Xiaolin ZHANG[6]; the Fasudil Aneurysmal Subarachnoid Hemorrhage Study Group

[1]*Department of Neurosurgery, Capital Medical University Affiliated Beijing Tiantan Hospital, Beijing, PRC;*
[2]*Department of Neurosurgery, General Hospital of the PLA, Beijing, PRC;*
[3]*Department of Neurosurgery, China-Japan Friendship Hospital, Beijing, PRC;*
[4]*Department of Neurosurgery, Peking Union Medical College Hospital, Beijing, PRC;*
[5]*Department of Neurosurgery, Shanghai Medical University Affiliated Huashan Hospital, Shanghai, PRC;*
[6]*Asahi Kasei Corporation Beijing Office, Beijing, PRC*

Abstract

Fasudil is believed to be at least equally effective as nimodipine for the prevention of cerebral vasospasm and subsequent ischemic injury in patients undergoing surgery for subarachnoid hemorrhage (SAH). We report the final results of a randomized, open trial to compare the efficacy and safety of fasudil with nimodipine. A total of 63 patients undergoing surgery for SAH received fasudil and 66 received nimodipine between 1998 and 2004. Symptomatic vasospasm, low density areas on computed tomography (CT), clinical outcomes, and adverse events were all recorded, and the results were compared between the fasudil and nimodipine groups. Absence of symptomatic vasospasm, occurrence of low density areas associated with vasospasm on CT, and occurrence of adverse events were similar between the two groups. The clinical outcomes were more favorable in the fasudil group than in the nimodipine group ($p = 0.040$). The proportion of patients with good clinical outcome was 74.5% (41/55) in the fasudil group and 61.7% (37/60) in the nimodipine group. There were no serious adverse events reported in the fasudil group. The present results suggest that fasudil is equally or more effective than nimodipine for the prevention of cerebral vasospasm and subsequent ischemic injury in patients undergoing surgery for SAH.

Key words: subarachnoid hemorrhage, cerebral vasospasm, fasudil, nimodipine, Rho-kinase inhibitor

Introduction

Cerebral vasospasm and the resulting cerebral ischemic injury occurring after subarachnoid hemorrhage (SAH) are still responsible for considerable morbidity and mortality. However, the mechanisms contributing to the development of vasospasm and occurrence of cerebral ischemic injury after SAH have not been fully elucidated. The development of vasospasm is thought to be related to a number of pathological processes, including smooth muscle cell contraction, endothelial damage, changes in vascular responsiveness, and inflammatory reactions.[3,8,18,21] Numerous factors, such as hemodynamic dysfunction including arterial narrowing, endothelial injury, and hyperviscosity and inflammatory responses including leukocyte infiltration and production of O_2^-, have been put forward to account for the causes of cerebral ischemic injury.[1,6,9,11–13]

Activation of the Rho-kinase pathway has been observed when cerebral ischemic injury occurs.[4,7,10]

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Rho-kinase is thought to play a role in the mechanisms underlying the occurrence of hemodynamic dysfunction, such as vasoconstriction, endothelial injury, and hyperviscosity, and inflammatory processes, such as leukocyte infiltration and production of O_2^-.[5,11,13,17] Fasudil and its active metabolite, hydroxyfasudil, are Rho-kinase inhibitors,[15,22] and are thought to prevent hemodynamic dysfunction and inflammatory processes through the inhibition of Rho-kinase.[11,13] Fasudil has shown clinical effectiveness in preventing cerebral vasospasm and subsequent ischemic injury in patients undergoing surgery for SAH.[16] Fasudil was launched for that indication and has been widely used in Japan since 1995.[19,20]

Interim results of a randomized trial of fasudil versus nimodipine have shown that fasudil is at least equally potent compared with nimodipine for the prevention of cerebral vasospasm and subsequent ischemic injury in patients undergoing surgery for SAH in the People's Republic of China.[23] Here we report the final results of this trial to evaluate the efficacy and safety of fasudil.

Patients and Methods

This randomized, open trial compared the efficacy and safety of fasudil with those of nimodipine in patients undergoing surgery for SAH. A total of 129 patients were enrolled at 5 neurosurgical institutions in the People's Republic of China between October 1998 and March 2004. This study was approved by the ethical committee at each institution. Patients ranged in age from 20 to 70 years and underwent surgery for ruptured aneurysms within 7 days after SAH. Entry requirements included a baseline Hunt and Hess grades I to IV. Table 1 lists inclusion and exclusion criteria. Comparison of the demographic and background data of patients, including Hunt and Hess grade, Fisher grade, and timing of surgery, found no statistically significant differences between 63 patients receiving fasudil and 66 patients receiving nimodipine (Table 2).

Patients were randomly assigned to the fasudil (Eril Injection; Asahi Kasei Pharma Corporation, Tokyo) or nimodipine group, and treatment with fasudil or nimodipine was started within 24 hours after aneurysm surgery and continued for 14 consecutive days. Fasudil (30 mg) was prescribed for intravenous administration over 30 minutes three times a day. Nimodipine was administered intravenously at a dose of 0.5–1 mg/hr for 2 hours and thereafter continued at a dose of 1–2 mg/hr.

Patients were followed daily for one month after SAH. Deterioration in level of consciousness, appearance of motor weakness, sensory deficit, or aphasia was recorded as symptomatic vasospasm if there was no other explanation in the postoperative period. Low density areas on computed tomography (CT) were evaluated as none, mild (distinctive infarction with diameter smaller than 1 cm), moderate (moderate infarction with diameter greater than 1 cm to infarction of the distribution of one blood vessel), high (multiple, small moderate infarctions), or severe (large scale infarction extending over the dis-

Table 1 Inclusion and exclusion criteria

Inclusion criteria
20 to 70 years of age
surgery for ruptured aneurysm within 7 days after SAH
Hunt and Hess grades I–IV
Fisher grades 1–4
first-time surgery patient
Exclusion criteria
severe cerebrovascular, hepatorenal, or metabolic disease (such as diabetes)
women who are pregnant or of child-bearing potential

SAH: subarachnoid hemorrhage.

Table 2 Baseline characteristics of patients

Factor	Fasudil group	Nimodipine group	p Value
Total patients	63	66	
Sex			0.217
male	21	29	
female	42	37	
Age (years)*	48.7 ± 11.9	51.4 ± 10.7	0.180
Hunt and Hess grade			0.113
I	8	3	
II	34	33	
III	17	27	
IV	4	3	
Day of operation*	3.8 ± 2.1	3.4 ± 2.3	0.248
Prior cerebrovascular episodes	8	11	0.525
Fisher grade			0.107
1	3	1	
2	9	7	
3	47	48	
4	4	9	
Complications	23	33	0.122
High blood pressure	19	31	0.050
Diabetes	3	3	0.953
Arteriosclerosis	5	3	0.425
Chronic lung disease	1	1	0.973
Gastroduodenal ulcer	0	2	0.164
Other	4	8	0.259

Values represent the number of patients unless otherwise indicated. *Values are expressed mean ± standard deviation.

tributions of two to three blood vessels or infarction of the distribution of the middle cerebral artery). Clinical outcome was assessed at one month after SAH according to the Glasgow Outcome Scale (good recovery, moderate disability, severe disability, persistent vegetative state, or death).

Characteristics at baseline were compared using the Wilcoxon rank sum test and the Student's t-test. Adverse events were compared using the χ^2 test. Comparisons of efficacy between groups were made using the Cochran-Mantel-Haenszel test, the Wilcoxon rank sum test, and the χ^2 test. Tests were two sided, with a significance level of $p < 0.05$.

Results

The efficacy of fasudil and nimodipine would be at least partly masked if all patients who deteriorated from causes other than vasospasm were included in the study, so this analysis did not include 11 patients whose outcomes were worsened by causes other than vasospasm. Two patients were excluded because of violation of the treatment protocol. The remaining 116 patients (56 in the fasudil group and 60 in the nimodipine group) were included in the analysis of efficacy.

Symptomatic vasospasm occurred in 8/56 patients (14.3%) in the fasudil group and in 14/58 patients (24.1%) in the nimodipine group, showing no significant difference between the two groups ($p = 0.244$). The occurrence of low density areas associated with vasospasm on CT was similar between the fasudil and nimodipine groups ($p = 0.948$) (Table 3). CT evidence of cerebral infarction was found in 12/55 patients (21.8%) in the fasudil group and in 14/59 patients (23.7%) in the nimodipine group.

Clinical outcomes were more favorable in the fasudil group than in the nimodipine group ($p = 0.040$) (Table 4). Good clinical outcome was achieved in 41/55 patients (74.5%) in the fasudil group and in 37/60 patients (61.7%) in the nimodipine group. Adverse events were observed in 7/63 patients (11.1%) in the fasudil group, and in 12/66 patients (18.2%) in the nimodipine group, with no significant difference between the two groups ($p = 0.257$) (Table 5). Blood biochemistry abnormalities occurred in 10 patients in the fasudil group. Other adverse events (e.g., confusion, hypotension, and facial flushing) did not occur in patients taking fasudil.

Table 3 Incidence of low density areas on computed tomography scans

Degree of low density area	Fasudil group (n = 55)	Nimodipine group (n = 59)
None	43	45
Mild	6	10
Moderate	4	4
High	1	0
Severe	1	0

Values represent the number of patients.

Table 4 Clinical outcome observed one month after subarachnoid hemorrhage

Outcome	Fasudil group (n = 55)	Nimodipine group (n = 60)
Good recovery	41 (74.5)	37 (61.7)
Moderate disability	8 (14.6)	11 (18.3)
Severe disability	6 (10.9)	6 (10.0)
Vegetative state	0 (0.0)	4 (6.7)
Death	0 (0.0)	2 (3.3)

Values represent the number of patients and percentage (in parentheses) of the total within each group.

Table 5 Adverse events

Adverse event	Fasudil group (n = 63)	Nimodipine group (n = 66)
Total	7 (11.1)	12 (18.2)
Confusion	0 (0.0)	1 (1.5)
AST increased	2 (3.2)	3 (4.5)
ALT increased	4 (6.3)	4 (6.1)
γ-GTP increased	2 (3.2)	4 (6.1)
ALP increased	2 (3.2)	0 (0.0)
TG increased	0 (0.0)	1 (1.5)
Hypotension	0 (0.0)	1 (1.5)
Flushing	0 (0.0)	2 (3.0)

Values represent number of patients and percentage (in parentheses) of the total within each group. ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, GTP: glutamyl transpeptidase, TG: triglycerides.

Discussion

The present clinical trial showed that the absence of symptomatic vasospasm and occurrence of low density areas associated with vasospasm on CT were similar between the fasudil and nimodipine groups. In contrast, the clinical outcomes were more favorable in the fasudil group than in nimodipine group. These results suggest that fasudil is more effective in preventing cerebral ischemic injury associated with vasospasm than nimodipine.

Previous studies demonstrated that fasudil, but

not calcium entry blockers including nimodipine, reversed chronic cerebral vasospasm induced in a two-hemorrhage canine model via systemic administration.[2] Nimodipine did not decrease blood viscosity, whereas fasudil prevented hyperviscosity in a rat model of cerebral ischemia.[6] In addition, recent findings on fasudil, such as amelioration of endothelial damage/dysfunction, inhibition of leukocyte infiltration, and inhibition of the production of O_2^- in neutrophils, offer further evidence on the efficaciousness of fasudil in preventing cerebral ischemic injury.[1,11,12,14] These results suggest that the favorable clinical outcomes attributable to fasudil may be due, at least in part, to reductions in various forms of secondary brain damage after the onset of cerebral vasospasm, and that this reduction in secondary brain damage may be the reason why the clinical outcomes were more favorable in the fasudil group than in the nimodipine group.

The present clinical trial compared the efficacy of fasudil with nimodipine. The absence of symptomatic vasospasm and the occurrence of low density areas associated with vasospasm on CT were similar between the two groups. Since this trial was not a placebo-controlled trial, we could not evaluate whether fasudil or nimodipine reduced the incidence of low density areas associated with vasospasm on CT or symptomatic vasospasm. In a prospective, placebo-controlled, double-blind phase III trial in Japan, fasudil reduced the incidence of low density areas associated with vasospasm on CT, the incidence of symptomatic vasospasm, and the number of patients with clinical outcomes associated with vasospasm.[16] In a post-marketing surveillance (PMS) study in Japan, the occurrence of low density areas, the absence of symptomatic vasospasm, and clinical outcomes were similar between patients treated with fasudil in the phase III trial and the patients in the PMS study.[19] The PMS study described the efficacy of fasudil in a large number of patients undergoing surgery for SAH, as demonstrated in the phase III trial. From these results, fasudil administration is thought to prevent the occurrence of symptomatic vasospasm and low density areas on CT, as well as to improve clinical outcomes.

The frequency of adverse events was 11.1% in the fasudil group, with no significant difference compared with the occurrence of adverse events (18.2%) in the nimodipine group. Only blood biochemistry abnormalities (10 cases) occurred in the fasudil group; and these adverse events were generally mild to moderate in severity before ameliorating. In contrast, one patient treated with nimodipine was discontinued from treatment due to hypotension.

The phase III trial and the PMS study in Japan found no differences in the occurrence of adverse events between the fasudil-treated groups and the placebo group.[19] Fasudil is a potent vasodilator, and as such, the question arose whether the potent vasodilatory action of fasudil can cause intracranial bleeding and hypotension in patients with SAH. There was no significant difference in the incidence of intracranial bleeding and hypotension between the fasudil-treated groups and the placebo group.[19] These clinical studies of fasudil demonstrate that increased risks of intracranial bleeding are absent or extremely low; and the risk of hypotension is extremely low. However, higher doses may lower blood pressure, especially in dehydrated patients. Both daily water balance and normovolemic state must be carefully maintained in patients.

There were several limitations in the present study. First, this trial did not use any type of blinded protocol. Second, following the fasudil treatment regimen, treatment for both fasudil and nimodipine was started after aneurysm surgery. Third, details of the episodes of symptomatic vasospasm (for example, rate of transient or permanent symptoms), and the morbidity and mortality due to vasospasm were not recorded. Fourth, details of intracerebral and/or intraventricular hemorrhage in patients with Fisher grade 4 SAH and the impact of the presence of intracerebral and/or intraventricular hemorrhage were not recorded. Further evaluation, for example, using a blinded trial or the details of symptomatic vasospasm or the details of intracerebral and/or intraventricular hemorrhage, may help to more concretely define the efficacy of fasudil for cerebral vasospasm and subsequent ischemic injury in patients with SAH.

The present clinical trial showed that absence of symptomatic vasospasm, occurrence of low density areas associated with vasospasm on CT, and occurrence of adverse events were similar between the fasudil and nimodipine groups. The clinical outcomes were more favorable in the fasudil group than in the nimodipine group. The present results suggest that fasudil is equally or more effective than nimodipine in the prevention of cerebral vasospasm and subsequent ischemic injury in patients undergoing surgery for SAH.

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References

1) Arai M, Sasaki Y, Nozaki R: Inhibition by the protein kinase inhibitor HA1077 of the activation of NADPH oxidase in human neutrophils. *Biochem Pharmacol* 46: 1487–1490, 1993
2) Asano T, Ikegaki I, Satoh S, Suzuki Y, Shibuya M, Takayasu M, Hidaka H: Mechanism of action of a novel antivasospasm drug, HA1077. *J Pharmacol Exp Ther* 241: 1033–1040, 1987
3) Dumont AS, Dumont RJ, Chow MM, Lin CL, Calisaneller T, Ley KF, Kassell NF, Lee KS: Cerebral vasospasm after subarachnoid hemorrhage: Putative role of inflammation. *Neurosurgery* 53: 123–135, 2003
4) Feske SK, Sorond FA, Henderson GV, Seto M, Hitomi A, Kawasaki K, Sasaki Y, Asano T, Liao JK: Increased leukocyte ROCK activity in patients after acute ischemic stroke. *Brain Res* 1257: 89–93, 2009
5) Higashi M, Shimokawa H, Hattori T, Hiroki J, Mukai Y, Morikawa K, Ichiki T, Takahashi S, Takeshita A: Long-term inhibition of Rho-kinase suppresses angiotensin II-induced cardiovascular hypertrophy in rats in vivo. *Circ Res* 93: 767–775, 2003
6) Hitomi A, Satoh S, Ikegaki I, Suzuki Y, Shibuya M, Asano T: Hemorheological abnormalities in experimental cerebral ischemia and effects of protein kinase inhibitor on blood fluidity. *Life Sci* 67: 1929–1939, 2000
7) Kawasaki K, Yano K, Sasaki K, Tawara S, Ikegaki I, Satoh S, Ohtsuka Y, Yoshino Y, Kuriyama H, Asano T, Seto M: Correspondence between neurological deficit, cerebral infarct size, and Rho-kinase activity in a rat cerebral thrombosis model. *J Mol Neurosci* 39: 59–68, 2009
8) Osuka K, Suzuki Y, Tanazawa T, Hattori K, Yamamoto N, Takayasu M, Shibuya M, Yoshida J: Interleukin-6 and development of vasospasm after subarachnoid haemorrhage. *Acta Neurochir (Wien)* 140: 943–951, 1998
9) Rikitake Y, Kim HH, Huang Z, Seto M, Yano K, Asano T, Moskowitz MA, Liao JK: Inhibition of Rho kinase (ROCK) leads to increased cerebral blood flow and stroke protection. *Stroke* 36: 2251–2257, 2005
10) Sato M, Tani E, Fujikawa H, Kaibuchi K: Involvement of Rho-kinase-mediated phosphorylation of myosin light chain in enhancement of cerebral vasospasm. *Circ Res* 87: 195–200, 2000
11) Satoh S, Hitomi A, Ikegaki I, Kawasaki K, Nakazono O, Iwasaki M, Mohri M, Asano T: Amelioration of endothelial damage/dysfunction is a possible mechanism for the neuroprotective effects of Rho-kinase inhibitors against ischemic brain damage. *Brain Res Bull* 81: 191–195, 2010
12) Satoh S, Kobayashi T, Hitomi A, Ikegami I, Suzuki Y, Shibuya M, Yoshida J, Asano T: Inhibition of neutrophil migration by a protein kinase inhibitor for the treatment of ischemic brain infarction. *Jpn J Pharmacol* 80: 41–48, 1999
13) Satoh S, Toshima Y, Hitomi A, Ikegami I, Seto M, Asano T: Wide therapeutic time window for Rho-kinase inhibition therapy in ischemic brain damage in a rat cerebral thrombosis model. *Brain Res* 1193: 102–108, 2008
14) Satoh S, Yamaguchi T, Hitomi A, Sato N, Shiraiwa K, Ikegaki I, Asano T, Shimokawa H: Fasudil attenuates interstitial fibrosis in rat kidneys with unilateral ureteral obstruction. *Eur J Pharmacol* 455: 169–174, 2002
15) Shibuya M, Hirai S, Seto M, Satoh S, Ohtomo E: Effects of fasudil in acute ischemic stroke: Results of a prospective placebo-controlled double-blind trial. *J Neurol Sci* 238: 31–39, 2005
16) Shibuya M, Suzuki Y, Sugita K, Saito I, Sasaki T, Takakura K, Nagata I, Kikuchi H, Takemae T, Hidaka H, Nakashima M: Effect of AT877 on cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *J Neurosurg* 76: 571–577, 1992
17) Shimokawa H, Takeshita A: Rho-kinase is an important therapeutic target in cardiovascular medicine. *Arterioscler Thromb Vasc Biol* 25: 1767–1775, 2005
18) Suzuki Y, Satoh S, Kimura M, Oyama H, Asano T, Shibuya M, Sugita K: Effects of vasopressin and oxytocin on canine cerebral circulation in vivo. *J Neurosurg* 77: 424–431, 1992
19) Suzuki Y, Shibuya M, Satoh S, Sugimoto Y, Takakura K: A postmarketing surveillance study of fasudil treatment after aneurysmal subarachnoid hemorrhage. *Surg Neurol* 68: 126–132, 2007
20) Suzuki Y, Shibuya M, Satoh S, Sugiyama H, Seto M, Takakura K: Safety and efficacy of fasudil monotherapy and fasudil-ozagrel combination therapy in patients with subarachnoid hemorrhage: Sub-analysis of the post-marketing surveillance study. *Neurol Med Chir (Tokyo)* 48: 241–248, 2008
21) Takizawa T, Tada T, Kitazawa K, Tanaka Y, Hongo K, Kameko M, Uemura K: Inflammatory cytokine cascade released by leukocytes in cerebrospinal fluid after subarachnoid hemorrhage. *Neurol Res* 23: 724–730, 2001
22) Yano K, Kawasaki K, Hattori T, Tawara S, Toshima Y, Ikegaki I, Sasaki Y, Satoh S, Asano T, Seto M: Demonstration of elevation and localization of Rho-kinase activity in the brain of a rat model of cerebral infarction. *Eur J Pharmacol* 594: 77–83, 2008
23) Zhao J, Zhou D, Guo J, Ren Z, Zhou L, Wang S, Xu B, Wang R: Effect of fasudil hydrochloride, a protein kinase inhibitor, on cerebral vasospasm and delayed cerebral ischemic symptoms after aneurysmal subarachnoid hemorrhage. *Neurol Med Chir (Tokyo)* 46: 421–428, 2006

Address reprint requests to: Xiaolin Zhang, MD, Asahi Kasei Corporation Beijing Office, Room No. 1407, New China Insurance Tower, Chao Yang District, Beijing 100022, PRC.