

Systematic assessment and meta-analysis of the efficacy and safety of fasudil in the treatment of cerebral vasospasm in patients with subarachnoid hemorrhage

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Abstract

Purpose Cerebral vasospasm (CVS) is a frequent and unpredictable complication in patients with subarachnoid hemorrhage (SAH) and often leads to poor outcomes. This study was aimed at evaluating the efficacy and safety of fasudil in the treatment of CVS in patients with SAH.

Methods A search was conducted using the full-text database of Chinese scientific journals, the Wanfang Database (January 1999 to November 2010), the Chinese Medical Association Digital Journal Database, PubMed, the Cochrane library, OVID, and EMBase (searching through November 2010).

Results A total of 8 studies met the inclusion criteria. The incidence rates of symptomatic CVS and CVS confirmed by angiography among the patients in the fasudil group were only 48% (odds ratio [OR]=0.48, 95% confidence interval [CI]: 0.32–0.72, $P=0.0005$) and 40% (OR=0.40, 95% CI: 0.24–0.67, $P=0.0004$) respectively of that of the

control group. The odds ratios of cerebral infarction for all cases and cerebral infarction for CVS cases in the fasudil group were only 50% (OR=0.50, 95% CI: 0.34–0.76, $P=0.0009$) and 43% (OR=0.43, 95% CI: 0.26–0.70, $P=0.0008$) respectively of that of the control group.

Conclusions Fasudil greatly reduces the occurrence of CVS and cerebral infarction in SAH patients, significantly improves the clinical outcomes of the patients (as assessed by the Glasgow Outcome Scale). Because of the limited number of trials and samples available for analysis, the conclusions from the present study still need to be validated with results from large randomized, controlled clinical trials.

Keywords Fasudil · Subarachnoid hemorrhage · Cerebral vasospasm · Clinical outcome · Meta-analysis

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Cerebral vasospasm (CVS) is a frequent and unpredictable complication in patients with subarachnoid hemorrhage (SAH) and often leads to adverse outcomes [1]. The current treatment for CVS primarily includes the prophylactic use of vasodilators, transluminal balloon angioplasty, and triple-H therapy (hypervolemia, hypertension, and hemodilution). According to reports on clinical trials and meta-analyses, although endothelin receptor antagonists, tirilazad, nimodipine, and nicardipine, as well as transluminal balloon angioplasty, were able to prevent or reverse CVS, they could not improve clinical outcomes among the patients [2–7]. Currently, sufficient evidence to support the efficacy and safety of triple-H therapy is lacking [8].

Recent basic and clinical studies indicate that Rho-kinase is an important target in the pathogenesis of

various vascular diseases [9, 10]. Increases in Rho-kinase activity lead to smooth muscle cell contraction, increased muscle fiber tension, and vascular contraction [9]. Through the inhibition of tumor necrosis factor (TNF)-induced IL-6 release [11], the Rho-kinase inhibitor fasudil performs the following actions: it inhibits the expression of tissue factors that are induced by TNF- α in vascular endothelial cells, activates the endogenous neural stem cells in the central nervous system, increases the levels of granulocyte colony-stimulating factor and astrocyte-stimulating factor, suppresses intracellular calcium release, dilates cerebral blood vessels, protects neurons, improves neurological function, inhibits ischemic cerebral injuries [12], and prevents and reverses CVS [11]. The results from one study [13–15] show that fasudil significantly improves the clinical outcome in SAH patients while preventing and reversing CVS. However, the results from other studies [16–18] do not fully support this finding. To date, no published reports have presented a systematic evaluation and meta-analysis of fasudil use in SAH treatment. Eight randomized, controlled clinical studies were included in the present study. CVS, cerebral infarction, and other indicators were assessed for efficacy analysis. A comprehensive study of the efficacy and safety of fasudil in the treatment of CVS among SAH patients was performed.

Materials and methods

Literature search strategy

The electronic databases searched in the present study included the full-text database of Chinese scientific journals, dissertations, and conference papers (for articles published from January 1994 to November 2010), the VIP journal index (January 1994 to November 2010), the Wanfang Database (January 1999 to November 2010), the Chinese Medical Association Digital Journal Database (through November 2010), PubMed (through November 2010), the Cochrane library (through November 2010), OVID (through November 2010), and EMBase (through November 2010). The Chinese search words used were “*fashudier/fasudil*” and “*nao xueguan jingluan/cerebral vasospasm*” or “*zhuwangmo xiaqiang chuxue/subarachnoid hemorrhage*,” and the English search words used were “*fasudil*” and “*cerebral vasospasm*” or “*vasospasm*” or “*subarachnoid hemorrhage*.” In the process of searching PubMed, the language restriction was removed. In addition, we carefully checked the studies that were included in the reference lists and satisfied the inclusion criteria of this study to identify any studies that were missed in the searches mentioned above.

Literature inclusion and exclusion criteria

The inclusion criteria were as follows:

1. Controlled, prospective clinical studies on fasudil use in the prevention and treatment of non-traumatic SAH
2. Studies that provided relevant calculated indicators and that could be used for data extraction for the meta-analysis

The excluded studies included the following:

1. Purely descriptive studies, such as reviews and summaries
2. Retrospective studies
3. Repeated published studies
4. Studies of questionable authenticity

Only the study methods and results in the original studies were considered in the present study, without considering sample size.

Data extraction

Based on the study objective, the following data were extracted: sample size, patient clinical classification, fasudil dosage, type and dosage of the control drug, drug administration starting time and duration, clinical assessment indicators (clinical outcomes and/or nervous system complications), assessment criteria and time, trial quality, and adverse responses.

Quality control

Two authors (G.J. Liu and Y.F. Wang) independently reviewed the literature and extracted the data following consistent standards. All of the authors participated in the discussions and decision-making processes when there was disagreement about the quality of a study. Studies that had complete data or were recently published were employed for the scalability report. The quality of all of the studies that were included in the analysis was assessed following the Jadad quality rating scale [19]. The authenticity of the studies was also evaluated. The present study did not mask the source of the studies or the affiliations of the authors.

Statistical processing

Meta-analyses were performed using Review Manager version 4.2 software provided by the Cochrane Collaboration Network. Cerebral infarction, Glasgow Outcome Scale (GOS), Glasgow Coma Scale (GCS), and other indicators were adopted as the indicators for efficacy analysis. The efficacy of fasudil and control drugs in terms of different outcome indicators was evaluated. Intent-to-treat (ITT) analysis was performed for those studies that provided data

on the patients who violated the treatment protocol. The existence of publication bias in the meta-analysis was evaluated for statistically significant outcome indicators through calculating their fail-safe numbers (N_{fs}). Stratified analyses were conducted for each outcome indicator.

A heterogeneity test was performed for the studies before a test for overall effect. The outcome indicators in the studies with heterogeneity and the possible reason for heterogeneity were further analyzed. Sensitivity analysis was performed for all outcome indicators, including stratified analysis of outcome indicators presented in low-quality literature with data from the low-quality literature included or excluded. Outcome indicators were also analyzed using the fixed effects model and the random effects model. The odds ratio (OR) was utilized as the effect assessment indicator for categorical variables, whereas the weighted mean difference (WMD) was adopted as the effect assessment indicator for continuous variables. The patient number needed to treat (NNT) was chosen as the clinical efficacy assessment indicator for categorical variables. When calculating the OR and WMD values for each outcome indicator, the 95% confidence interval (CI) was calculated as well. $P < 0.05$ was considered statistical significance.

Results

Literature search results

A total of 400 references were obtained in the preliminary search. Through reading of the titles, abstracts, and some full texts, the studies that were not relevant to the particular subject and those with repetitive or redundant reports were eliminated. Finally, 8 articles [13–18, 20, 21] were found to meet the criteria of this study. These 8 articles all reported controlled prospective clinical studies [13–18, 20, 21]. Among them, 6 studies reported that the patients were randomly distributed to the fasudil group and the control group [13, 15–18, 21], which was not specified in the other 2 studies [14, 20]. Nimodipine was the control for fasudil in 6 studies [13, 14, 16–18, 20, 21], with another study using a placebo as the control [15]. The final study used fasudil in addition to ozagrel in the treatment group, and ozagrel only was administered in the control group [14]. Six studies were confirmed to involve SAH caused by ruptured aneurysms [13–18], whereas the other 2 did not specify the details of the SAH mechanisms [20, 21]. A total of 843 patients were included in these 8 studies, and 71 patients (8.42%) were excluded from the analysis (69 cases because of protocol violation, and 2 were lost during the study period). The quality of all the studies that were included in the analysis was assessed according to the Jadad quality

rating scale [19]. Among the 8 reports, 7 can be considered high-quality literature [13–18, 21], but the remaining study scores as low-quality literature [20]. The clinical characteristics of these 8 trials are shown in Tables 1 and 2.

Meta-analysis results (fasudil group versus control group)

Complications

Cerebral vasospasm Four [14–16, 18] studies reported data from the patients with symptomatic vasospasm. The meta-analysis results indicated no statistically significant difference in the incidence rate of symptomatic vasospasm between the groups of patients ($P=0.19$). The cause of the heterogeneity among the references ($P(\chi^2)=0.03$) needs to be further analyzed. When the single reference with a relatively low-quality score was excluded [14], the meta-analysis showed that the incidence rate of symptomatic vasospasm of the fasudil group was only 48% of that of the control group (OR=0.48, 95% CI: 0.32–0.72, $P=0.0005$, $P(\chi^2)=0.64$; Table 3). Sensitivity analysis suggested that the heterogeneity within the group was caused by different study methods. The NNT results indicated that, compared with the control group, 1 of every 2 patients in the fasudil group avoided symptomatic vasospasm (see Table 5).

Four articles [15, 17, 18, 20] reported data on the patients with CVS confirmed by angiography 14 days after treatment. The meta-analysis results showed that the incidence rate of CVS confirmed by angiography 14 days after treatment in the fasudil group was only 40% of that of the control group (OR=0.40, 95% CI: 0.24–0.67, $P=0.0004$, $P(\chi^2)=0.29$). When the low-quality reference was excluded, the meta-analysis results demonstrated that the incidence rate of CVS confirmed by angiography 14 days after treatment in the fasudil group was only 45% of that of the control group (OR=0.45, 95% CI: 0.27–0.76, $P=0.003$, $P(\chi^2)=0.32$; Table 3). The NNT results indicated that compared with the control group, 1 out of every 3 patients in the fasudil group avoided angiography-confirmed CVS (see Table 5).

Cerebral infarction Five articles [13, 15–18] reported data from all cases with secondary cerebral infarction, whereas 2 references [14, 15] reported data from the CVS cases with cerebral infarction. The meta-analysis results showed that the OR of cerebral infarction for all cases in the fasudil group was only 50% of that of the control group (OR=0.50, 95% CI: 0.34–0.76, $P=0.0009$, $P(\chi^2)=0.67$), whereas the OR of cerebral infarction for CVS cases in the fasudil group was only 43% of that in the control group (OR=0.43, 95% CI: 0.26–0.70, $P=0.0008$, $P(\chi^2)=0.13$; Table 3). The NNT results indicated that, compared with the control group, 1 of every 2 patients in the fasudil group avoided cerebral

Table 1 The characteristics of the original literature included in the meta-analysis

Reference	Sample size (cases, fasudil group/control group)	Quality score	Age (years) ^a (fasudil group/control group)	Clinical classification	Drug and dosage of the fasudil group and the control group; treatment start time and duration
[15]	131/136	7	55±11/55±11	Hunt–Hess [22] Grades I–IV, Fisher Grades 2–4	AT877 ^b 30 mg×3 days; placebo 2 ml×3 days; started within 24 h of surgery, lasting for a total of 14 days
[14]	60/57	3	58±12.0/58±10.4	Hunt and Kosnik [23] Grades I–IV	Fasudil 30 mg×3 days, ozagrel 80 mg·days ⁻¹ ; ozagrel 80 mg·days ⁻¹ ; started immediately after surgery, for 14 days
[13]	48/48	4	54.7±11.3 /52.4±9.5	Hunt–Hess [22] Grades I–IV	Fasudil 30 mg×3 days, nimodipine 1–2 mg·h ⁻¹ ×24 h, edaravone 30 mg×2 days, methylprednisolone 30 mg·(kg·days) ⁻¹ ×7 days; control group: nimodipine 1–2 mg·h ⁻¹ ×24 h; started within 72 h of the onset of the disease, for a total of 14 days
[17]	10/10	6	50.8±9.6/51.2±10.5	Hunt–Hess [22] Grades I–IV	Fasudil 30 mg×3 days; Nimotop ^c 0.5–2 mg·h ⁻¹ ×24 h; started immediately after surgery, for a total of 14 days
[18]	37/35	5	47.9±12.50 /52.3±9.88	Hunt–Hess [22] Grades I–IV	Fasudil 30 mg×3 days; nimodipine 1 mg·h ⁻¹ ×24 h; started within 24 h of disease onset, for a total of 14 days
[16]	32/32	6	37–60 (ungrouped)	Hunt–Hess [22] Grades I–IV	Fasudil 30 mg×3 days; nimodipine 8 mg×3 days; started immediately after surgery, for a total of 14 days
[21]	38/38	3	33–67/31–63	Unspecified	Fasudil 30 mg×3 days; nimodipine 10 mg·days ⁻¹ ; started within 72 h of disease onset, for a total of 14 days
[20]	30/30	2	56±4.1/55±4.5	Unspecified	Fasudil 30 mg×3 days; nimodipine 7.5 μg–30 μg·(kg·h) ⁻¹ ×24 h; started within 72 h of disease onset, for a total of 14 days

^a Age (years) is expressed as mean ± standard deviation or a range from the minimum to the maximum value

^b AT877 is fasudil hydrochloride

^c Nimotop is an injectable nimodipine formulation manufactured by Bayer

infarction in all cases, whereas 1 out of every 3 patients in the fasudil group avoided cerebral infarction in CVS cases.

Clinical outcomes

Good outcomes Five articles [13–16, 18] reported data on patients with good recovery as assessed by GOS for all cases. The meta-analysis results indicated that the good recovery rate for all cases in the fasudil group was 1.58-fold higher than that of the control group (OR=1.58, 95% CI: 1.12–2.23, $P=0.009$, $P(\chi^2)=0.53$). The other 2 articles [14, 15] also reported data on patients with good recovery among the CVS cases. The meta-analysis results indicated that the good recovery rate for CVS cases in the fasudil group was 2.07-fold higher than that of the control group (OR=2.07, 95% CI: 1.20–3.59, $P=0.009$, $P(\chi^2)=0.35$; Table 3). The NNT results showed that, compared with the control group, 1 of every 2 patients in the fasudil group exhibited good recovery among all cases, whereas 1 out of 4 patients displayed good recovery among the CVS cases (see Table 5).

The meta-analysis results based on the GOS scores (for all cases [13–17] and CVS cases [13, 15, 17, 18]) indicated

that, compared with the control group under both conditions, the GOS scores of the fasudil group increased by an average of 0.25 points and 0.33 points respectively (all cases: WMD=0.25, 95% CI: 0.07–0.43, $P=0.006$, $P(\chi^2)=0.69$; CVS cases: WMD=0.33, 95% CI: 0.12–0.55, $P=0.002$, $P(\chi^2)=0.48$; Table 4). These results suggest that fasudil can significantly improve the clinical outcomes of patients as assessed according to the GOS.

The final 2 articles [13, 21] reported clinical outcome data on the basis of the author's self-formulated assessment criteria for therapeutic efficacy. The meta-analysis results showed that the number of patients with significant treatment effectiveness in the fasudil group was 2.5 times that of the control group (OR=2.50, 95% CI: 1.32–4.72, $P=0.005$, $P(\chi^2)=0.73$), whereas the difference in the total response rate between the groups was not statistically significant ($P>0.05$; Table 3). Compared with the control group, the NNT results indicated that 1 in every 4 patients of the fasudil group showed significant effectiveness (Table 5).

Adverse outcomes Four articles [13–15, 18] reported data on death, vegetative state, or severe disability through GOS assessment among all cases. The meta-analysis results

Table 2 Itemized studies evaluated for the meta-analysis

References	Clinical outcomes (time of evaluation)
[15]	Symptomatic vasospasm ^a (by self-formulated standards during the treatment period); CVS ^b (DSA on postoperative days 5–21); cerebral infarction ^c (CT on admission, immediately after surgery, and 1–2 weeks and 1 month after onset); clinical outcomes (GOS ^d 1 month after onset)
[14]	Symptomatic CVS (no specification); cerebral infarction (cranial CT on admission and after the onset of symptomatic CVS); clinical outcomes (GOS on discharge); adverse response (during treatment)
[13]	Symptomatic vasospasm and therapeutic effects ^e (by self-formulated effective standards, at the end of treatment); cerebral infarction (CT or MRI during the treatment period); clinical outcomes (GOS 1 month after surgery); mean blood flow velocity of the middle cerebral artery (TCD 1, 3, 7, and 14 days after treatment); level of consciousness (GCS during the treatment period)
[17]	CVS (DSA before surgery and 1 week after disease onset); cerebral infarction (CT before surgery, 48 h post-surgery, and 1 week and 1 month after onset); level of consciousness (GCS before surgery, before treatment, 1 week after treatment, at the end of treatment, and 1 month after onset)
[18]	Symptomatic vasospasm (standards of reference [15]); CVS (DSA before surgery and 7–17 days after onset); cerebral infarction (CT before surgery and within 48 h post-surgery, when focal symptoms and high risk of CVS occur); clinical outcomes (GOS 1 month after onset); level of consciousness (GCS, unknown)
[16]	Cerebral infarction (CT before treatment and 7 and 14 days after treatment); level of consciousness (GCS ^f before and after treatment); mean blood flow velocity of the middle cerebral artery (TCD before treatment and 1, 3, 5, 7, 10, and 14 days after treatment); therapeutic effects ^g (by self-formulated effective standards, at the end of treatment); adverse reactions (during the treatment period)
[20]	CVS (DSA upon the onset of symptomatic CVS and following completion of treatment); level of consciousness (GCS before treatment and on day 14 of the treatment)
[21]	Therapeutic effects (standards of reference [16], at the end of treatment); adverse reactions (during the treatment period)

CVS, cerebral vasospasm; DSA, digital subtraction angiography; CT, computed tomography; MRI, magnetic resonance imaging; TCD, transcranial color Doppler; GOS, Glasgow Outcome Scale; GCS, Glasgow Coma Scale

^a Symptomatic vasospasm: neurological deterioration, either temporary or permanent, was considered to be due to vasospasm when all other potential causes (such as surgery, hydrocephalus, intracranial rebleeding, seizure, infection, cardiopulmonary dysfunction, electrolyte imbalance, and metabolic disturbances) had been excluded [15]

^b CVS was divided into four grades, which included no contraction, mild contraction, moderate contraction between mild and severe, and severe contraction with diffuse hair-like changes [15]

^c Low-density areas on postoperative CT (between days 5 and 42) were classified into five grades: none; mild, or small lacunar-like low-density areas less than 1 cm in diameter (corrected for magnification); moderate, or low-density areas greater than 1 cm, but limited to territories of the branches of a major cerebral artery; severe, or low-density areas extending to the entire territory of a major cerebral artery; and larger [15]

^d GOS standards were as follows: good recovery 5 points, moderate disability 4 points, severe disability 3 points, vegetative state 2 points, and death 1 point [24]

^e Diagnostic criteria for symptomatic vasospasm: (1) progressive consciousness disorders; (2) occurrence or aggravation of signs; (3) new cerebral infarction on CT or MRI, excluding cerebral hemorrhage and electrolyte imbalance; and (4) TCD-determined mean blood velocity of the middle cerebral artery >120 cm/s [13]. Therapeutic effects: (1) excellent—complete resolution of clinical symptoms and signs, complete self-care, and reduction in the mean blood velocity of the middle cerebral artery >20%; (2) effective—relief of clinical symptoms and signs, partial self-care, and reduction in the mean blood velocity of the middle cerebral artery >10%; and (3) ineffective—aggravation or no improvement in clinical symptoms and signs and reduction in the mean blood velocity of the middle cerebral artery <10% [13]

^f GCS standards: patients whose clinical grade was I had GCS scores of 15 and were neurologically intact, apart from having cranial nerve palsy. Those of grade II had GCS scores of 15 and were neurologically intact, apart from having cranial nerve palsy with neck stiffness or headache, or both. Those of grade III had GCS scores of 13–14 and were with or without neurological deficits, and those of grade IV had GCS scores of 8–12 with or without neurological deficits. Finally, those of grade V had GCS scores of 3–7 and were in a coma with or without abnormal posturing [25]

^g Therapeutic effects: (1) excellent—no signs of nervous system dysfunction, no new cerebral infarction on CT, no vasospasm according to TCD or angiograph, and Hunt–Hess grade of II or less; (2) effective—neurological symptoms and signs are significantly improved, Hunt–Hess grade is decreased by one grade, there is no new cerebral infarction on CT, and TCD or DSA shows that CVS is improved after drug administration; (3) generating improvement—neurological symptoms are improved, Hunt–Hess grade is unchanged, there is no new cerebral infarction on CT, and TCD or DSA shows mild CVS or slight improvement after drug administration; and (4) ineffective—symptoms and signs of ischemic cerebrovascular disease, Hunt–Hess grade is increased, new cerebral infarction on CT, and CVS diagnosed by TCD or DSA [16]

showed that, compared with the control drug, fasudil slightly decreased the incidence of these adverse outcomes (OR=0.68, 95% CI: 0.45–1.02, $P=0.06$, $P(\chi^2)=0.64$). Two other articles [14, 15] reported data on death, vegetative state, or severe disability in CVS cases. The meta-analysis results showed that, compared with the control drug, fasudil significantly

decreased the occurrence of these adverse outcomes (OR=0.37, 95% CI: 0.18–0.76, $P=0.007$, $P(\chi^2)=0.22$; Table 3). The NNT results indicated that, compared with the control group, 1 in every 4 patients in the fasudil group avoided the occurrence of death, vegetative state, or severe disability, both among all cases and among CVS cases (Table 5).

Table 3 Results of the meta-analysis for categorical variables (fasudil group versus control group)

Outcome or subgroup title	Number of studies	$P(\chi^2)^*$	Fixed effects model		Random effects model	
			P	OR (95% CI)	P	OR (95% CI)
Symptomatic vasospasm [14–16, 18]	4	0.03	0.01	0.64 (0.45–0.92)	0.19	0.63 (0.31–1.26)
Symptomatic vasospasm	3	0.64	0.0005	0.48 (0.32–0.72)	0.0005	0.48 (0.32–0.72)
CVS confirmed by angiography						
14 days post-treatment [15, 17, 18, 20]	4	0.29	0.0004	0.40 (0.24–0.67)	0.03	0.43 (0.20–0.91)
14 days post-treatment ^a [15, 17, 18]	3	0.32	0.003	0.45 (0.27–0.76)	0.04	0.48 (0.24–0.97)
Cerebral infarction (on CT/MRI)						
All cases ^b [13, 15–18]	5	0.67	0.0009	0.50 (0.34–0.76)	0.001	0.51 (0.34–0.76)
CVS cases ^c [14, 15]	2	0.13	0.0008	0.43 (0.26–0.70)	0.03	0.38 (0.16–0.91)
Good recovery						
All cases ^b [13–16, 18]	5	0.53	0.009	1.58 (1.12–2.23)	0.01	1.57 (1.11–2.22)
CVS cases ^c [14, 15]	2	0.35	0.009	2.07 (1.20–3.59)	0.01	2.06 (1.18–3.58)
Therapeutic effect						
Excellent [13, 21]	2	0.73	0.005	2.50 (1.32–4.72)	0.005	2.49 (1.32–4.72)
Totally effective ^d [13, 21]	2	0.25	0.12	2.52 (0.80–7.98)	0.27	2.50 (0.50–12.54)
Death, vegetative state, or severe disability						
All cases ^b [13–15, 18]	4	0.64	0.06	0.68 (0.45–1.02)	0.07	0.68 (0.45–1.02)
CVS cases ^c [14, 15]	2	0.22	0.007	0.37 (0.18–0.76)	0.03	0.36 (0.14–0.91)
Adverse reactions [16, 18, 21]	3	0.74	0.61	0.83 (0.40–1.71)	0.60	0.82 (0.40–1.70)

OR, odds ratio; CI, confidence interval; CVS, cerebral vasospasm

* $P(\chi^2)$ is the probability value of the heterogeneity test within a group

^a Poor-quality studies were excluded

^b “All cases” refers to all of the patients who participated in the assessment of a given indicator

^c “CVS cases” refers to all cases excluding the patients with complications other than CVS

^d Total response rate = significantly effective + effective

Table 4 Results of the meta-analysis for continuous variables (fasudil group vs control group)

Outcome or subgroup title	Number of Studies	$P(\chi^2)^*$	Fixed effects model		Random effects model	
			P	WMD (95% CI)	P	WMD (95% CI)
GCS score						
2 weeks post-treatment [16–18, 20]	4	0.41	<0.00001	0.95 (0.67–1.22)	<0.00001	0.95 (0.67–1.22)
2 weeks post-treatment ^a [16–18]	3	0.43	0.0002	0.79 (0.37–1.18)	0.0002	0.78 (0.37–1.18)
GOS score						
All cases ^b [13–17]	5	0.69	0.006	0.25 (0.07–0.43)	0.006	0.25 (0.07–0.43)
CVS cases ^c [14, 15]	2	0.48	0.002	0.33 (0.12–0.55)	0.002	0.33 (0.12–0.55)
Blood flow velocity ^d (cm/s)						
2 weeks post-treatment [13, 16]	2	0.51	<0.00001	–12.14 (–17.45 to –6.83)	<0.00001	–12.14 (–17.45 to –6.83)

WMD, weighted mean difference; CI, confidence interval; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; CVS, cerebral vasospasm; TCD, transcranial color Doppler

* $P(\chi^2)$ is the probability value of the heterogeneity test within a group

^a Poor-quality studies were excluded

^b “All cases” refers to all of the patients who participated in the assessment of a given indicator

^c “CVS cases” refers to all cases excluding the patients with complications other than CVS

^d Blood flow velocity (cm/s) is the mean blood flow velocity in the middle cerebral artery, as determined by TCD

Table 5 The fail-safe number^a (N_{fs}) and the number of patients needed to treat (NNT)

Outcome or subgroup title	Trials (literature studies)	$\sum ZI$	N_{fs} (studies)	NNT (cases)
Symptomatic vasospasm [15, 16, 18]	3	13.303	62	1.905 \approx 2
CVS confirmed by angiography (14 days post-treatment) [15, 17, 18, 20]	4	17.893	114	1.974 \approx 2
CVS confirmed by angiography (14 days post-treatment ^b) [15, 17, 18]	3	10.698	39	3.278 \approx 3
Cerebral infarction (on CT/MRI, all cases ^c) [13, 15–18]	5	30.977	349	2.444 \approx 2
Cerebral infarction (on CT/MRI, CVS cases ^d) [14, 15]	2	13.640	67	2.625 \approx 3
Good recovery, all cases ^c [13–16, 18]	5	17.005	102	-1.848 \approx -2
Good recovery, CVS cases ^d [14, 15]	2	7.696	20	-4.194 \approx -4
Death, vegetative state, or severe disability, all cases ^c [13–15, 18]	4	5.189	6	3.869 \approx 4
Death, vegetative state, or severe disability, CVS cases ^d [14, 15]	2	9.270	30	3.808 \approx 4
Excellent results [13, 21]	2	8.173	23	-2.414 \approx -2

$NNT=1/(\text{control event rate}-\text{experiment event rate})$ [26]

NNT, number needed to treat; CVS, cerebral vasospasm; GOS, Glasgow Outcome Scale; CT, computerized tomography; MRI, magnetic resonance imaging

^aThe test validity was set at $P<0.05$. $N_{fs} = \left[(\sum ZI)^2 / 2.706 \right] - k$. $\sum ZI$ is the sum of statistics of a number of k trials under a test validity of $P<0.05$, k is the number of trials or studies included in the meta-analysis, and N_{fs} is the fail-safe number [27]

^bPoor quality studies were excluded

^c“All cases” refers to all of the patients who participated in the assessment of a given indicator

^d“CVS cases” refers to all cases excluding the patients with complications other than CVS

Level of consciousness

Four articles [16–18, 20] reported data on GCS scores 2 weeks after treatment. The meta-analysis results showed that, compared with the control group, the average GCS score of the patients in the fasudil group increased by 0.95 points (WMD=0.95, 95% CI: 0.67–1.22, $P<0.00001$, $P(\chi^2)=0.41$). The GCS scores of the fasudil group increased by an average of 0.79 points upon the exclusion of the low-quality article [20] (WMD=0.79, 95% CI: 0.37–1.18, $P=0.0002$, $P(\chi^2)=0.43$; Table 4). These results showed that, compared with the control group, the consciousness level significantly improved in the patients of the fasudil group.

Blood flow velocity

Two articles [13, 16] reported data on TCD-determined mean blood flow velocity in the middle cerebral artery of the patients 2 weeks after treatment. The meta-analysis results demonstrated that the mean blood flow velocity in the middle cerebral artery of the patients in the fasudil group decreased by 12.14 cm/s compared with the control group (WMD=-12.14, 95% CI: -17.45 to -6.83, $P<0.00001$, $P(\chi^2)=0.51$; Table 4).

Adverse responses

Three articles [16, 18, 21] reported data on adverse responses in patients. The meta-analysis showed no significant difference in the incidence rate of adverse responses between

the two groups during treatment ($P>0.05$). Another article [18] reported the changes in the systolic pressure of the patients before and after treatment. The meta-analysis results showed that, compared with the fasudil group, the systolic pressure decreased by 8.40 mmHg in the nimodipine group 60 min after the treatment (fasudil group/nimodipine group: WMD=8.40, 95% CI: 0.67–16.13, $P=0.03$; Table 3).

Sensitivity analysis

1. With the exclusion of a single low-quality article [20] or an article with a relatively low-quality score [14], the results of repeated meta-analysis showed that all outcome indicators (14 days after the treatment among the angiography-diagnosed CVS cases [15, 17, 18], GCS scores 2 weeks after the treatment [16–18], and symptomatic vasospasm [15, 16, 18]) remained statistically significant ($P<0.05$; Tables 3, 4).
2. Through analysis of the 18 indicators using the fixed effects model and the random effects model, the overall effectiveness values calculated from the two models were found to be largely consistent with their 95% CI values for all indicators except symptomatic vasospasm [14–16, 18] (the results of a small number of indicators using the random effects model were relatively conservative, and the results of most of the indicators from the two models were identical; Tables 3, 4).

The sensitivity analysis carried out using both methods described above showed that the meta-analysis results of

the majority of outcome indicators in this study are robust and reliable with relatively low sensitivity.

Publication bias

The fail-safe number (N_{fs}) of each outcome indicator is far greater than the number of trials included in the meta-analysis, which suggests that no publication bias exists in the meta-analysis described above (Table 5).

Discussion

The results of this study show the following:

1. Compared with the control drug, fasudil not only greatly reduces the odds ratio of symptomatic vasospasm, but also significantly lowers the odds ratio of angiography-diagnosed CVS in SAH patients.
2. Fasudil significantly reduces the odds ratio of cerebral infarction for all cases and for CVS cases in SAH patients.
3. More importantly, compared with the control drug, fasudil significantly increases the odds ratios of good recovery for all cases and for CVS cases (while significantly improving the GOS scores among all cases and CVS cases), significantly reduces the odds ratio of death, vegetative state, or severe disability among the CVS cases, and exhibits a trend of slightly decreasing the odds ratio of death, vegetative state, or severe disability among all cases.
4. Compared with nimodipine, fasudil significantly increases the GCS scores of patients 2 weeks after treatment.
5. Fasudil significantly reduces the mean blood flow velocity in the middle cerebral artery of patients.
6. Fasudil has similar adverse effects to nimodipine (the analysis of one article [18] indicated that, compared with the fasudil group, the systolic blood pressure in the nimodipine group was significantly reduced 60 min after treatment, and 1 patient withdrew from the trial because of the significantly lowered blood pressure).

The present study used the “Quality of Reporting of Meta-analyses” system formulated by Professor David Moher and others [28] at the University of Ottawa, Canada in 1999 as the standards for the development of research methods and guiding the research process. We not only searched the current major Chinese-language and English-language international electronic databases (with language restrictions removed during the PubMed search process), but also individually reviewed the studies in the reference lists of the articles that met the inclusion criteria of this study to include other studies that might have been missed in the process of the on-line literature search. We strictly assessed the quality and authenticity of the selected studies and also conducted

heterogeneity and sensitivity analyses on various outcome indicators. To highlight the therapeutic effects of fasudil on CVS, we conducted stratified analysis on some outcome indicators (for all cases and CVS cases). We calculated the fail-safe number to determine whether there was a publication bias for some outcome indicators to further demonstrate the credibility of the research results. Although the sample sizes of some trials were relatively small, the vast majority of the outcome indicators exhibited good literature homogeneity. In addition, most statistically significant outcome indicators had a narrow 95% CI range, which indicates relatively high credibility of the results. The results from this study showed that the homogeneity of the studies included in this research was relatively high, the meta-analysis results of the majority of the outcome indicators were robust and reliable with low sensitivity, and no publication bias was found in any of the 9 meta-analysis results (outcome indicators of categorized variables) with statistical significance.

The highlight of this study is that, based on the meta-analysis, fasudil was found to not only prevent and reverse CVS in SAH patients, but, most importantly, also significantly improve the clinical outcomes of the patients, as evaluated with the Glasgow Outcome Scale. This effect represents an advantage over endothelin receptor antagonists such as tirilazad, or nicardipine [3–6].

We were unable to obtain detailed data, including the number of surgery patients, surgical timing, surgical approach, and surgical outcome, for each patient in the fasudil and control groups. We did not have access to the clinical-level data of each patient before treatment. In addition, differences in the geographical regions, hospital levels, and the impacts of different basic and combined medications on the clinical outcomes of the patients in each trial were not considered (these factors may affect the results and conclusions of the meta-analysis). Therefore, research bias cannot be completely ruled out in this study. In addition, we could not control for publication bias because of the different diagnostic criteria of symptomatic cerebral vasospasm used by different authors. At the same time, owing to the limited number of trials and samples available for analysis, the conclusions from the present study still need to be further verified through large randomized, controlled clinical trials.

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