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Therapeutic Benefit of Cilostazol in Patients with Aneurysmal Subarachnoid Hemorrhage: a Meta-Analysis of Randomized and Nonrandomized Studies

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Abstract

Objective—To assess the effectiveness of cilostazol, a selective inhibitor of phosphodiesterase type III, in preventing cerebral ischemia related to cerebral vasospasm after aneurysmal subarachnoid hemorrhage (SAH).

Methods—A total of six clinical studies met the inclusion criteria and were included in the meta-analysis. We calculated pooled risk ratios (RR) and 95% confidence intervals (CI) using random-effects models. The primary endpoint was cerebral ischemia related to vasospasm. Secondary endpoints were angiographic vasospasm, new cerebral infarct, mortality, and death or disability at the final follow-up.

Results—A total of 136 (22%) of 618 subjects (38 and 98 assigned to cilostazol and control treatments, respectively) with SAH developed cerebral ischemia related to vasospasm. The risk of cerebral ischemia related to vasospasm was significantly lower in subjects assigned to cilostazol treatment (*RR* 0.43; 95% CI 0.31–0.60; $p< 0.001$). The risks of angiographic vasospasm (*RR* 0.67, 95% CI 0.54–0.84, $p< 0.001$) and new cerebral infarct (*RR* 0.37, 95% CI 0.24–0.57, $p< 0.001$) were significantly lower in subjects assigned to cilostazol treatment. There was a significantly lower rate of death or disability in subjects assigned to cilostazol treatment at follow-up (*PR* 0.55, 95% 0.39–0.78, $p = 0.001$).

Conclusion—The reduction in rates of cerebral ischemia related to vasospasm and death or disability at follow-up support further evaluation of oral cilostazol in patients with aneurysmal SAH in a large randomized clinical trial.

Keywords

Cilostazol; cerebral ischemia; subarachnoid hemorrhage; phosphodiesterase inhibitors; cerebral vasospasm

Introduction

Moderate to severe angiographic cerebral vasospasm occurs in almost 47% [1] and results in clinical symptoms in 38% [2] of patients with aneurysmal subarahnoid hemorrhagec in recent studies. Cerebral infarction occurred in 10% and 46% of patients with moderate and severe vasospasm in the Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After SAH (CONSCIOUS-1) study [3]. Death or disability was seen in 58% of patients who developed moderate to severe vasospasm in the CONSCIOUS-1 study [4]. The American Heart Association/American Stroke Association guidelines for the management of aneurysmal SAH acknowledge that cerebral ischemia especially that associated with arterial vasospasm, remains a major cause of death or disability in patients with aneurysmal SAH [5]. The guidelines also state that oral nimodipine is the only agent that has been shown to improve neurological outcomes (but not cerebral vasospasm) in patients with

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aneurysmal SAH (Class I; Level of Evidence A). The guidelines acknowledge that endothelin-1 antagonists [6], magnesium sulfate [7], and statin treatment [8] have failed to demonstrate clinically meaningful benefit in phase 3 clinical trials. Therefore, further strategies need to be evaluated for reducing the death or disability associated with cerebral vasospasm and cerebral ischemia.

Cilostazol, a phosphodiesterase III inhibitor, reduced cerebral vasospasm and cerebral ischemia associated with SAH in experimental studies [9,10] and small clinical studies [11,12] presumably by multiple mechanisms including: (1) increased release of nitric oxide levels from endothelial cells; (2) inhibition of vascular smooth muscle proliferation; (3) suppression of adhesion molecule expression on vascular membrane; and (4) inhibition of platelet-derived growth factor production. A previous meta-analysis of two randomized controlled trials and two quasi-randomized controlled trials [12] including 340 patients demonstrated that the incidence of cerebral ischemia related to vasospasm, vasospasm-related new cerebral infarctions, and poor outcome was significantly lower in the cilostazol treated group. Since that time, additional studies have been published with a larger number of patients [13].

Another more recent meta-analysis evaluated the effect of cilostazol on the rates of unfavorable outcome and demonstrated a reduction in rates of death or disability in patients with aneurysmal SAH [14], but other important endpoints such as cerebral vasospasm and cerebral ischemia were not studied. We performed this meta-analysis to provide more contemporary data on the efficacy of cilostazol on various endpoints in patients with aneurysmal SAH.

Methods

Study design

We performed a meta-analysis of both randomized and nonrandomized studies which investigated the therapeutic effect of cilostazol in patients with aneurysmal SAH. We performed a computerized literature search of MEDLINE and Cochrane databases on December 25, 2017.

Data extraction

Two independent authors searched databases using PICO questions (clinical trials, randomized studies, nonrandomized studies, cilostazol, SAH, or standardized medical management), and reviewed abstracts and articles to identify comprehensive studies keeping adequate study quality. For duplicate articles, we included those with the largest sample size or the most complete information. Data from the articles included in this study were extracted by two independent authors (MFI and SS) using a standardized form. The above-mentioned authors collected the following data from each study: name of the first author, publication year, study period, baseline characteristics of patients, and a number of patients and rates of outcomes of interest in each group. Three authors (AI, MFI, and AP) independently assessed the internal validity of the included studies by using the criteria list described by the Editorial Board of the Cochrane Back Review Group [15]. All disagreements were resolved by reaching consensus, and there was a complete agreement on abstracted results in the final dataset. We included randomized and nonrandomized studies if they enrolled patients with aneurysmal SAH, and cilostazol was administered in one of the treatment group. Trials that included less than 10 subjects, those who did not report the rates of angiographic vasospasm, cerebral infarcts, or functional outcome of patients were excluded. After careful evaluation and agreements among the reviewers, 15 studies were excluded (Supplemental Table 1).

Outcomes

The primary endpoint was the incidence of cerebral ischemia related to vasospasm. Secondary endpoints were angiographic vasospasm, new cerebral infarct, mortality, and death or disability in the final follow-up. Definition of cerebral ischemia related to vasospasm varied from study to study and the definitions are summarized in Table 1. Angiographic vasospasm was defined as a decrease in vessel diameter detected by digital subtraction, computerized tomographic, or magnetic resonance angiography. New cerebral infarct was identified on follow up computerized tomography (CT) or magnetic resonance imaging (MRI), regardless of any association with clinical symptoms. Death or disability was defined by modified Rankin Scale grades of three or greater at discharge, one, three, or six months (last follow up in the study). One study, Matsuda *et al.* [13], used Glasgow outcome scale at three months after onset of SAH to determine the clinical outcome, and the poor clinical outcome was defined by severe disability, vegetative state, and death. Another study by Murahashi *et al.* [16] did not provide the distribution of modified Rankin Scale in study subjects.

Statistical analysis

The relative risk and 95% confidence intervals were calculated using comprehensive meta-analysis 2.2.048; (Biostat Inc., Englewood, NJ, USA) for each endpoint in each of the included studies. We attempted to include

Table 1. Definition of cerebral ischemia related to vasospasm used in included studies

Trial	Definition
Matsuda *et al*. [13]	Development of new, focal neurological signs, deterioration in level of consciousness of at least two points on the Glasgow Coma Scale, or both, when the cause was felt to be ischemia attributable to vasospasm after other possible causes of worsening had been excluded.
Senbokuya *et al*. [11]	Development of a new focal or global neurological deficit or deterioration of at least two points on the Glasgow Coma Scale, which was not explained by initial hemorrhage, rebleeding, hydrocephalus, surgical complications, fever, infections, or electrolyte or metabolic disturbances and angiographic vasospasm on digital subtraction angiography or CT angiography regardless of presence of cerebral infarctions on CT or MRI scans.
Suzuki *et al*. [17]	Development of any unexplainable neurological deterioration other than rebleeding, intracerebral hematoma, hydrocephalus, brain edema, seizures, and metabolic disturbances such as hypoxia and hyponatremia. At least, CT scan was performed to exclude other pathological conditions. MR angiography, CT angiography, transcranial color sonography, and/or digital subtraction angiography were performed, if the surgeon thought it was necessary.
Yoshimoto *et al*. [18]	*Transient symptoms[Cilastazol group] defined as aphasia (two patients), right hemiparesis (one patient), and consciousness disturbances (one patient).[control group] confusion, aphasia, and right hemiparesis*Persistent symptoms[Cilastazol group] aphasia[Control group] deterioration of disturbed consciousness, aphasia, right hemiparesis, and agnosia.
Kimura *et al*. [20]	Development of a new focal or global neurological deficit or deterioration that was not explained by initial hemorrhage, rebleeding, hydrocephalus, surgical complications, fever, infections, electrolytes, or metabolic disturbances.
Murahashi *et al*. [19]	Not defined

every study, and studies in which specific endpoints were not reported were excluded only from the pooled analyses of that specific unreported endpoint. The pooled RRs were estimated using a random-effects model using the method described by DerSimonian and Laird [17]. We assessed heterogeneity and the magnitude of heterogeneity for each specific endpoint using the Cochran Q statistic and the I^2 measure (the percentage of total variability due to true between-study heterogeneity), respectively. Subgroup analyses by different study designs were performed. Sensitivity analyses were conducted by comparing the effect of sizes of all included studies using fixed-effects model. Risk of bias for randomized controlled trials and nonrandomized studies were also assessed using Newcastle–Ottawa scale. Risk of publication bias was also assessed by inspecting the asymmetry of funnel plot for outcomes of cerebral ischemia related to cerebral vasospasm and death or disability at follow-up.

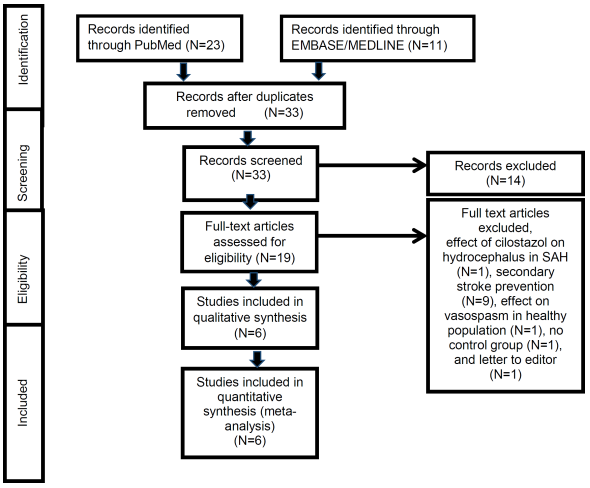

Figure 1. Flow-chart diagram presenting the selection of eligible studies.

Results

We initially identified 19 studies which evaluated the therapeutic effect of cilostazol in aneurysmal SAH patients. Ultimately, 6 clinical studies met the inclusion criteria and were included in the meta-analysis, 3 randomized [11,13,18], and 3 nonrandomized studies, [16,19,20] resulting in a total of 618 patients (Figure 1). A total of 587 subjects with aneurysmal SAH received surgical clip placement as a treatment procedure, and endovascular coil placement was performed in 31 subjects. The selected studies were published between 2008 and 2016. The characteristics of the individual trials included in the meta-analysis are provided in Table 2.

A total of 618 subjects included in the analysis, 136 (22%) subjects with aneurysmal SAH developed cerebral ischemia related to vasospasm. The proportion of subjects with cerebral ischemia related to vasospasm was significantly lower in those who were assigned to cilostazol treatment (*RR* 0.43; 95% CI 0.31–0.60; $p < 0.001$) (Figure 2). There was no heterogeneity between the trials (Cochran's Q statistic 2.79, *df* 5; $P = 732$, $I^2 = 0.000\%$). The risks of angiographic vasospasm were also lower in subjects who were assigned to cilostazol treatment (*RR* 0.67, 95% CI 0.54–0.84, $p < 0.001$) without any heterogeneity between the trials (Cochran's Q statistic 0.354, *df* 3; $P = 0.949$, $I^2 = 0.000\%$). The proportion of subjects who had new cerebral infarction was significantly lower in subjects who were assigned to cilostazol treatment (*RR* 0.37, 95% CI 0.24–0.57, $p < 0.001$, five studies included) without any heterogeneity between the trials (Cochran's Q statistic 0.506, *df* 4; $P = 0.973$, $I^2 = 0.000\%$). There was a lower rate of death or disability in the final follow-up in subjects who were assigned to cilostazol treatment (*RR* 0.55, 95% 0.39–0.78, $p = 0.001$, five studies included, see Figure 3) without any hetero-

Table 2. Characteristics of included studies

Trial name	Study type	Eligibility criteria	Cilostazol treated	Placebo/control treated	Treatment with cilostazol	Aneurysm treatment modality (surgical/endovascular)	Outcome
Matsuda *et al*. [13]	Randomized controlled trial	Age 20–80 years.Admitted within 24 hours after the ictus and received cilostazol within 48 hours of SAH onset.Surgical or endovascular aneurysm treatment.SAH diffuse (long axis ≥ 20 mm) or localized (long axis < 20 mm) thick (short axis ≥ 4 mm) subarachnoid clot on CT scan performed within 24 hours of SAH.Hunt and Hess grades 1–4	74	74	100 mg twice per day for 14 days	126/22	Glasgow Outcome Scale at three months
Senbokuya *et al*. [11]	Randomized controlled trial	Aneurysm in anterior circulation.Aneurysm treatment by surgery within 72 hours of SAH.Hunt and Kosnik grades 1–4.Cilostazol started by 96 hours after the onset of SAH and by 48 hours after surgery.	54	55	100 mg twice per day for 2 weeks	109/0	mRS after 1, 3, and 6 months, and length of hospitalization
Suzuki *et al*. [17]	Randomized controlled trial	Aneurysm treatment by surgery within 72 hours of SAH.Hunt and Hess grades 1–4.	49	51	100 mg twice per day for 2 weeks	100/0	mRS at discharge
Yoshimoto *et al*. [18]	Nonprospective with allocation according to time period of admission to the hospital, i.e., first year formed control group and second year formed cilostazol group	Early surgical or endovascular aneurysm treatment after the SAH onset(did not specify the duration, within couple of days).Cilostazol started within 24 hours after surgery.Hunt and Kosnik grades 1–4	26	24	200 mg/d for 2 weeks	41/9	mRS at discharge or one month
Kimura *et al*. [20]	Nonprospective with allocation according to time period of admission to the hospital, i.e., first two years formed control group and last two years formed cilostazol group	Aneurysm treatment by surgery within 72 hours of SAH.Hunt and Kosnik grades 1–5	62	68	100 mg twice per day for 2 weeks pluscombined enteraland parenteralnutrition	130/0	mRS at discharge
Murahashi *et al*. [19]	Nonprospective with allocation according to the admitting hospital, i.e, one hospital treated patient with cilostazol and other hospital formed control group	Aneurysm treatment by surgery within 72 hours of SAH.Hunt and Kosnik grades 1–5.Cilostazol started within 24 hours of aneurysm treatment	25	56	200 mg/d from day one after surgery for2 or4 weeks100 mg twice per day for two weeks	81/0	mRS (ascertainment time not provided)

mRS, modified Rankin scale; SAH, subarachnoid hemorrhage

geneity between the trials (Cochran's Q statistics 5.732, df 4; $P = 0.220$, $I^2 = 30.216\%$). One study could not be included in death or disability analysis due to lack of relevant data [16]. There was no difference in the risk of mortality in subjects assigned to cilostazol treatment (*RR* 0.40, 95% CI 95% 0.12–1.32, $p = 0.13$, four studies included).

Sensitivity analysis after exclusion of studies with high risk of bias including 470 patients showed the same effect of assignment to cilostazol treatment on risk of cerebral ischemia related to vasospasm (*RR* 0.46, 95% CI 0.31–0.66, $p < 0.001$). The risk for cerebral ischemia related to vasospasm was significantly lower in subjects who were assigned to cilostazol treatment (*RR* 0.42; 95% CI 0.29–0.57; $p < 0.001$) in the fixed-effects model. The risk reduction for cerebral ischemia related to vasospasm was similar in randomized (*RR* 0.46; 95% CI 0.31–0.70) and nonrandomized (*RR* 0.37; 95% CI 0.21–0.66) clinical trials. The risk reduction for death or disability in the final follow-up was similar in randomized (*RR* 0.40; 95% CI 0.25–0.62) and nonrandomized (*RR* 0.73; 95% CI 0.55–0.97) studies.

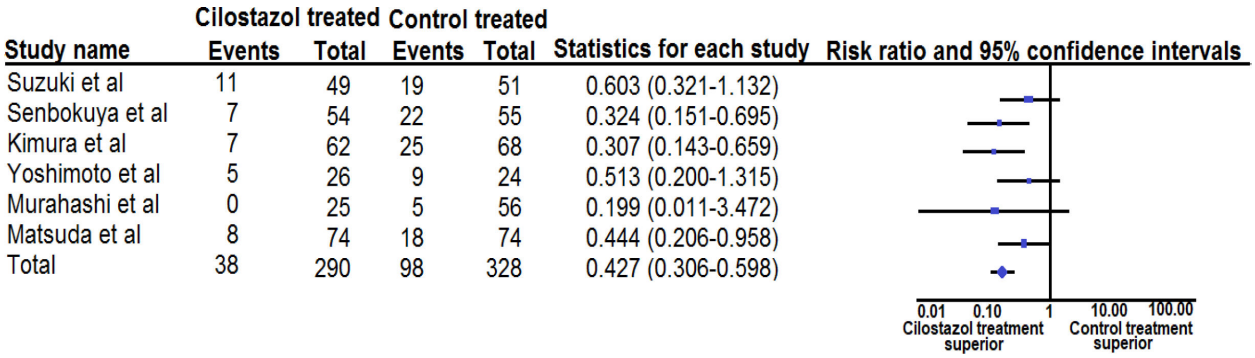

Figure 2. Risk ratio of cerebral ischemia related to vasospasm in subjects assigned to cilostazol and control treatments using random-effects model.

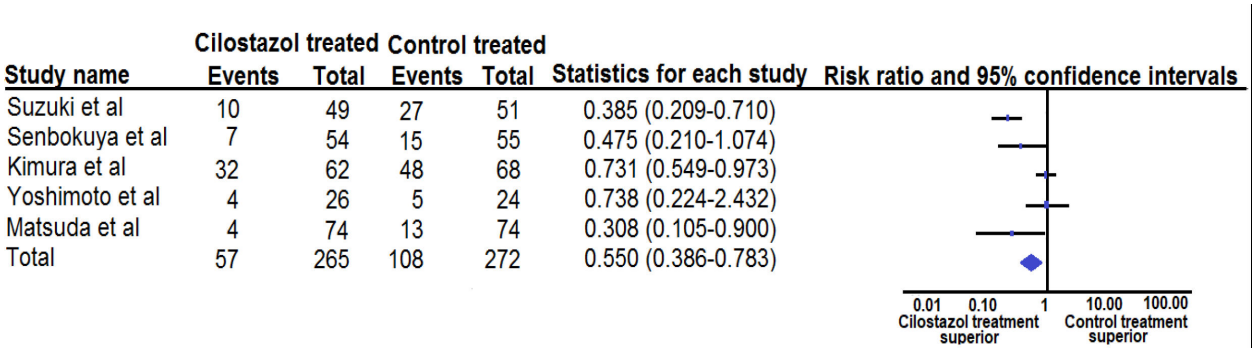

Figure 3. Risk ratio of death or disability in subjects assigned to cilostazol and control treatments using random-effects model.

Supplemental Tables 2 and 3 provide an assessment of the quality of randomized and nonrandomized clinical trials suggesting high-quality studies in most parameters assessed. Funnel plot inspection did not reveal evidence of asymmetry (publication bias) in studies reporting the outcomes of cerebral ischemia related to vasospasm (Figure 4) and death or disability in the final follow-up (Figure 5).

Discussion

The current meta-analysis demonstrated that cerebral ischemia related to vasospasm was significantly lower in aneurysmal SAH patients treated with cilostazol. The lower rates of cerebral ischemia appeared to be related to lower rates of vasospasm occurrence in patients treated with cilostazol. There was also a significant reduction in the rates of death or disability among SAH patients treated with cilostazol. The reduction in death or disability is most likely secondary to the reduction in vasospasm and cerebral ischemia in patients treated with cilostazol. The effect appeared to be consistent between randomized and nonrandomized clinical trials.

Oral cilostazol treatment appeared somewhat unique in preventing vasospasm, cerebral ischemia, and death or disability. The effect is somewhat different than nimodipine treatment where death or disability is reduced without any change in the rate of angiographic vasospasm [21]. The effect also differs than intravenous nicardipine and clazosentan treatment where there is a reduction in the rate of angiographic vasospasm without any reduction in death or disability [21–23]. The inability of certain agents such as intravenous nicardipine and clazosentan treatment to reduce the rates of death or disability despite the reduction in vasospasm has been attributed to several factors [1,24] including adverse events in the treated patients such as prominent hypotension or pulmonary complications, and continued micro thromboembolism. Cilostazol does not cause any hypotension and this may have a better safety profile in this patient population. Common side effects of cilostazol include a headache (the most common), diarrhea, severe heat

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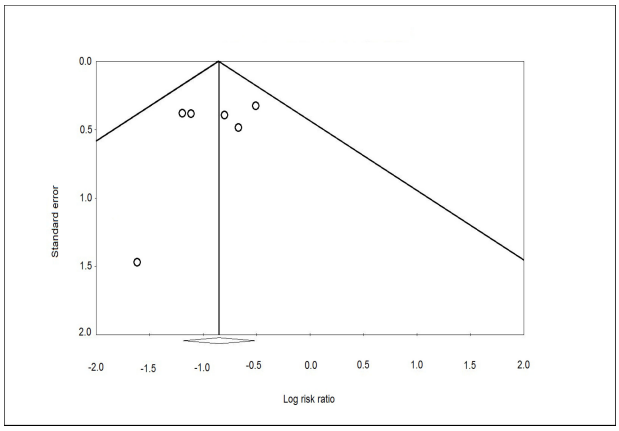

Figure 4. Funnel plot of the randomized and nonrandomized studies for the outcome of cerebral ischemia related to vasospasm using log risk ratio.

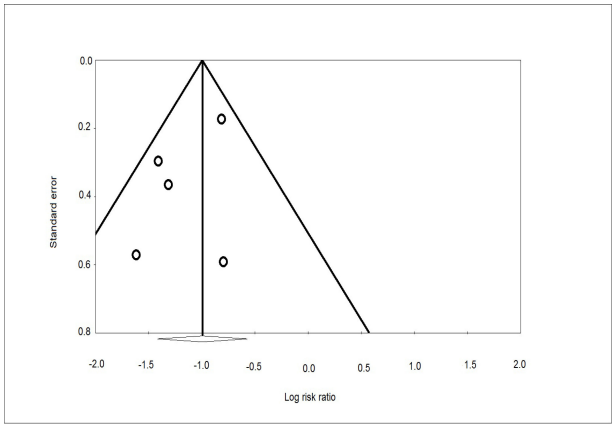

Figure 5. Funnel plot of the randomized and nonrandomized studies for the death and disability using log risk ratio.

intolerance, abnormal stools, increased heart rate, and palpitations. Two components of cerebral vasospasm and aneurysmal SAH that were not ameliorated by intravenous nicardipine and clazosentan treatment include smooth muscle and fibroblast proliferation in arterial wall and occurrence of micro thromboembolism. Smooth muscle and fibroblast proliferation has been observed in medium size cerebral arteries in experimental models of SAH [25,26]. Cilostazol inhibits smooth muscle and fibroblast proliferation in arterial wall [27–29] presumably due to inhibition of platelet derived growth factor. The occurrence of micro thromboembolism has been identified in 83% of patients with clinical vasospasm in previous studies [30–32]. Although not necessarily in the arteries with vasospasm, cilostazol has antiplatelet activity by reducing the catalysis of cyclic adenosine 3', 5'-monophosphate (cAMP) and cyclic guanosine 3', 5'-monophosphate (cGMP) [33]. A previous meta-analysis of randomized clinical trials evaluating the efficacy of antiplatelet agents in patients with SAH had found a trend toward lower rates of poor outcome (*RR* 0.79, 95% CI 0.62–1.01) [34]. Ticlopidine in one trial was associated with statistically significant fewer occurrences of a poor outcome (*RR* 0.37, 95% CI 95% CI 0.14–0.98).

Some limitations should be considered prior to interpretation of the results. There was heterogeneity in both definition and ascertainment of endpoints between the studies such as angiographic vasospasm, cerebral ischemia, and death or disability. Since the studies were performed in predominantly Japanese population, the issue regarding the applicability of results to North American and European population also needs to be considered [35,36]. There is some comparative data available based on randomized clinical trials (dose-finding studies) evaluating the therapeutic efficacy of clazosentan in North American and European patients [4] and Japanese and Korean patients [37] with SAH. The trial populations differed in regards the use of surgical treatment with all patients in Japanese and Korean patients and 45% of North American and European patients receiving surgical clip placement. The rate of moderate to severe angiographic vasospasm in placebo-treated groups was slightly higher in Japanese and Korean patients than North American and European patients (80% and 66%, respectively). The rate of composite endpoint of death from any cause within 6 weeks of SAH; new cerebral infarct due to vasospasm within 6 weeks of SAH; delayed ischemic neurological deficits due to vasospasm; and any rescue therapy within 14 days of SAH

was higher in Japanese and Korean patients than North American and European patients (47% and 31%, respectively) in placebo-treated groups. Therefore, the possibility that angiographic vasospasm and associated consequences are more prominent in Japanese and Korean patients cannot be excluded. The trials included in the meta-analysis are also a representation of patients receiving surgical clip placement for intracranial aneurysms. The risk of angiographic vasospasm and cerebral ischemia may be lower in patients undergoing coil placement for treatment of intracranial aneurysm [38,39] and the benefit of cilostazol may be lower among patients receiving coil placement.

The results of this meta-analysis support further evaluation of oral cilostazol as a treatment in patients with aneurysmal SAH in a large randomized clinical trial.

Acknowledgments

None.

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