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Effect of cilostazol in patients with aneurysmal subarachnoid hemorrhage: A systematic review and meta-analysis

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ABSTRACT

Previous studies with small sample size have shown that cilostazol can reduce the risk of cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage (SAH). The purpose of this study was to determine whether cilostazol is effective in patients with aneurysmal SAH. Studies investigating the effect of cilostazol in patients with aneurysmal SAH were identified using Embase.com without language or publication-type restrictions. We used the random-effect model to combine data. Pooled risk ratios (RR) and 95% confidence intervals (CI) were calculated. Two randomized controlled trials and two quasi-randomized controlled trials with a total of 340 patients were included. The incidence of symptomatic vasospasm (RR = 0.47; 95% CI, 0.31–0.72; $p < 0.001$), severe vasospasm (RR = 0.48; 95% CI, 0.28–0.82; $p = 0.007$), vasospasm-related new cerebral infarctions (RR = 0.38; 95% CI, 0.22–0.67; $p = 0.001$), and poor outcome (RR = 0.57; 95% CI, 0.37–0.88; $p = 0.011$) were significantly lower in the cilostazol group. The numbers needed to treat for these outcomes were 6.4, 6.3, 5.7, and 5.4, respectively. Mortality rate differences between the two groups were insignificant. No statistical heterogeneity was found for all outcomes. These results show that cilostazol can decrease the incidence of symptomatic vasospasm, severe vasospasm, vasospasm-related new cerebral infarctions, and poor outcome in patients with aneurysmal SAH.

1. Introduction

Subarachnoid hemorrhage (SAH) is a stroke subtype. Although it accounts for only 5% of all strokes, it generally occurs at a fairly young age with a relative high rate of morbidity and mortality [1]. Cerebral vasospasm and vasospasm-related cerebral infarction are common and serious complications in patients with aneurysmal SAH, and are important causes of death and dependency [2,3].

A Cochrane review showed that oral administration of nimodipine likely reduces the risk of cerebral ischemia and poor outcome after aneurysmal SAH, but the evidence for other calcium antagonists is inconclusive [4]. An updated systematic review that investigated the effects of statins in patients with aneurysmal SAH also showed no significant results [5]. Observational studies suggested that antiplatelet agents may reduce the risk of secondary ischemia and poor outcome after aneurysmal SAH [6], but randomized controlled trials (RCTs) and the Cochrane review failed to show any significant results [7]. However, studies that investigated the effect of cilostazol on aneurysmal SAH were not included in this Cochrane review.

Cilostazol, a selective inhibitor of phosphodiesterase 3, is an antiplatelet agent marketed in Japan that is used to treat the ischemic symptoms of peripheral vascular disease. Unlike other antiplatelet agents, cilostazol not only inhibits the platelet aggregation, but also has effects of direct vasodilatation [8] and anti-inflammation [9]. Moreover, cilostazol is more effective than aspirin in the secondary prevention of ischemic stroke without increasing the risk of bleeding complications [10]. Both animal studies and clinical studies have shown that cilostazol can reduce the risk of cerebral vasospasm in patients with aneurysmal SAH [9,11]. However, the sample sizes of previous studies were small, and there has been no relevant systematic review regarding this topic. We performed a systematic literature review of all clinical controlled trials to evaluate the effect of cilostazol in patients with aneurysmal SAH.

2. Methods

2.1. Search strategy

Studies that investigated the effect of cilostazol in aneurysmal SAH were identified until August 10, 2013 through electronic searches in Embase.com, which includes records from Medline and Embase, without language or publication-type restrictions. Search results were limited to human. The search strategy (Table 1S, Supplementary materials) combined the terms "cilostazol" and "subarachnoid hemorrhage." Two authors (P.P.N. and Y.Y.) independently performed the literature search. The references of identified articles were screened to find further studies.

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2.2. Study selection and eligibility criteria

Two authors (P.P.N. and G.Y.) independently screened the articles that were retrieved using the search strategy. Articles that failed to meet our inclusion criteria were excluded after reading the title, keywords, and abstract. Articles that were not excluded in the initial screen were evaluated by reading the full text. For duplicate articles, we included those with the largest sample size or the most complete information. Any disagreements were resolved by discussion.

Inclusion criteria for the studies were the following: (1) randomized controlled clinical trial or controlled clinical trial; (2) study that investigated the effect of cilostazol in patients with aneurysmal SAH; (3) study that reported the incidence of vasospasm, the incidence of cerebral infarction, or functional outcome of patients; and (4) rational diagnosis methods for aneurysmal SAH and cerebral infarction were described.

2.3. Data collection

Data from the articles included in this study were extracted by two independent authors (Y.Q.X. and Z.N.G.) using a standardized form. The following information were extracted from each study: name of the first author, publication year, study period, country or geographical origin of investigation, baseline characteristics of patients, number of patient in each group, and outcome data in each group. All disagreements were resolved by consensus.

2.4. Assessment of risk of bias for the included studies

Two authors (G.Y. and Y.Q.X.) 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 [12]. Twelve criteria that reflect the risk of bias were included in this appraisal system. Each criterion can be scored as yes, unclear, or no, where yes indicates the criterion has been met and therefore suggests a low risk of bias. Studies that meet at least 6 of the 12 criteria and have no serious flaws (e.g., 80% dropout rate in one group) can be defined as having a "low risk of bias."

2.5. Outcome measures

The primary outcome was the incidence of symptomatic vasospasm. Secondary outcomes were the incidence of severe vasospasm, incidence of vasospasm-related new cerebral infarctions, incidence of poor outcome, and mortality. The definitions of the outcome measures were made according to the descriptions provided in the included studies.

Symptomatic vasospasm was defined as any new unexplainable focal or global neurological deficit or a decrease of at least 2 points on the Glasgow Coma Scale (not associated with rebleeding, intracerebral hematoma, hydrocephalus, metabolic disturbances, fever, or infection), regardless of cerebral vasospasm. Vasospasm-related new cerebral infarction was defined as new follow-up computerized tomography (CT) or magnetic resonance imaging (MRI) lesions not attributable to other causes, regardless of any association with symptoms. Severe vasospasm was defined as >50% decrease in vessel diameter detected by digital subtraction angiography (DSA), computerized tomography angiography (CTA), or magnetic resonance angiography (MRA). Poor functional outcome was defined as a modified Rankin Scale (mRS) of 3 to 6 determined during the follow-up in the study.

2.6. Statistical analysis

STATA, version 12.0 (Stata Corporation, College Station, Texas) was used for all statistical analyses. The risk ratio (RR) and 95% confidence interval (CI) were used as the measure of effect of interest. We measured statistical heterogeneity using the Q statistic and I^2 statistic. Heterogeneity existed if the Q statistic was $p^Q < 0.1$ [13,14]. I^2 statistic is expressed as a value between 0% and 100% that represents heterogeneity as absent to extreme. Because only a few studies with low numbers of patients were included, the DerSimonian–Laird random-effect model was used in all analyses [5]. The number needed to treat (NNT) for each outcome was calculated. Subgroup analyses by different study designs were performed. Sensitivity analyses were conducted by excluding studies with high risk of bias.

3. Results

3.1. Studies included in the meta-analysis

According to our search strategies, 222 articles were initially identified. Ultimately, three articles written in English [11,15,16] and one article written in Japanese [17] with a total of 340 patients were included in this analysis. Two studies were RCTs [11,16] and two were quasi-randomized controlled trials (q-RCTs) [15,17]. The selected studies were published between 2009 and 2013. There were no significant differences in any of the characteristics between the two groups in the studies. Postoperative management was also uniform between the two groups for each study. The baseline characteristics of all qualified studies (Table 1), outcome data (Table 2), and main results of this meta-analysis (Table 3, Fig. 1) are presented. The risk of bias is also illustrated (Table 2S, Supplementary materials).

3.2. Assessment of risk of bias for the included studies

The results for the risk of bias assessment are presented in Table 2S. The four included studies were judged to have low risk of bias because ≥6 items were met for each of them. However, the two q-RCTs just met 6 of the 12 items. In the study by Senbokuya et al., six patients (11.11%) of the cilostazol group dropped out because of adverse events. However, the authors included these six patients in the cilostazol group analyses.

3.3. Quantitative data synthesis

3.3.1. Symptomatic vasospasm

All studies reported the incidence of symptomatic vasospasm. Using a random-effect model to combine data, the number of patients who had symptomatic vasospasm was significantly higher in the control group (55/186, 29.57%) than in the cilostazol group (23/154, 14.94%) (RR = 0.47, 95% CI = 0.31–0.72, $p < 0.001$), with no statistical heterogeneity showed by the Q statistic ($p = 0.586$) and I^2 statistic (0.0%). The NNT for this outcome is 6.4 (95% CI = 4.9–12.1). The significant difference was essentially unchanged after excluding the two q-RCTs (RR = 0.46, 95% CI = 0.25–0.84, $p = 0.012$). No statistical heterogeneity was found between the two RCTs ($p^Q = 0.216$, $I^2 = 34.5\%$).

3.3.2. Severe vasospasm

Yoshimoto et al. reported the incidence of severe vasospasm between 7 and 9 days (or when any neurological deterioration was detected) after the onset of SAH detected by cerebral angiography. Senbokuya N et al. and Murahashi et al. reported the incidence of severe vasospasm between 7 and 10 days after the onset of SAH detected by CTA or DSA. All of them used the definition of >50% decrease in vessel diameter for severe vasospasm. Using a random-effect model to combine data, the number of patients who had severe vasospasm was significantly higher in the control group (41/135, 30.37%) (RR = 0.48, 95% CI = 0.28–0.82, $p = 0.007$) than in the cilostazol group (16/105, 15.24%). The NNT for this outcome is 6.3 (95% CI = 4.6–18.3). Data on severe vasospasm did not indicate statistical heterogeneity ($p^Q = 0.347$, $I^2 = 5.5\%$). The RR was essentially unchanged after excluding the two q-RCTs (RR = 0.42, 95% CI = 0.22–0.80, $p = 0.008$).

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