Efficacy of Cilostazol in Prevention of Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Meta-Analysis

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Objectives: Cilostazol, a selective inhibitor of phosphodiesterase 3, may reduce symptomatic vasospasm and improve outcome in patients with aneurysmal subarachnoid hemorrhage considering its anti-platelet and vasodilatory effects. We aimed to analyze the effects of cilostazol on symptomatic vasospasm and clinical outcome among patients with aneurysmal subarachnoid hemorrhage (aSAH). *Patients and Methods:* We searched PubMed and Embase databases to identify 1) prospective randomized trials, and 2) retrospective trials, between May 2009 and May 2017, that investigated the effect of cilostazol in patients with aneurysmal aSAH. All patients were enrolled after repair of a ruptured aneurysm by clipping or endovascular coiling within 72 hours of aSAH. fixed-effect models were used to pool data. We used the I^2 statistic to measure heterogeneity between trials. *Results:* Five studies were included in our meta-analysis, comprised of 543 patients with aSAH (cilostazol [n=271]; placebo [n=272], mean age, 61.5 years [SD, 13.1]; women, 64.0%). Overall, cilostazol was associated with a decreased risk of symptomatic vasospasm (0.31, 95% CI 0.20 to 0.48; P <0.001), cerebral infarction (0.32, 95% CI 0.20 to 0.52; P <0.001) and poor outcome (0.40, 95% CI 0.25 to 0.62; P <0.001). We observed no evidence for publication bias. Statistical heterogeneity was not present in any analysis. *Conclusion:* Cilostazol is associated with a decreased risk of symptomatic vasospasm and may be clinically useful in the treatment of delayed cerebral vasospasm in patients with aSAH. Our results highlight the need for a large multi-center trial to confirm the observed association.

Key Words: Cilostazol—Aneurysmal subarachnoid hemorrhage—Vasospasm—Delayed Cerebral Ischemia.

Aneurysmal subarachnoid hemorrhage (aSAH) is associated with high mortality, with more than 60% of all deaths occurs in first 48 hours as a result of severity of initial hemorrhage or rebleeding.[1] Delayed cerebral ischemia (DCI) is a major and potentially preventable cause of morbidity and mortality in those patients who survives beyond 48 hours. Ischemia due to spasm of large arteries is considered a vital underlying mechanism for DCI. However, more recently, this association of angiographic spasm as a sole mechanism of DCI has been challenged due to a number of reasons.

Firstly, angiographically demonstrated vasospasm is common and seen in up to 70% of patients after aneurysmal rupture whereas only 20%-30% of patients develops symptoms of delayed ischemic injury and cerebral infarction demonstrated on neuroimaging can occur without spasm in corresponding vessels.[2] Secondly, Nimodipine, has been shown to improve functional outcome of patients with SAH but has not shown any significant effect on angiographic spasm.[3] Additionally, pharmacologic treatment that

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Received March 12, 2018; revision received June 5, 2018; accepted June 20, 2018.

Conflict of interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.06.027

reverses vasospasm may not prevent new neurologic deficit, development of cerebral infarction or outcome.[2,4]

Recent studies have proposed other pathophysiologic mechanisms such as early brain injury (EBI), microcirculatory dysfunction with loss of autoregulation, cortical spreading depolarization (CSD), and microthrombosis, that may contribute to the development of ischemic injury leading to delayed neurologic deficit, cerebral infarction and worsening of neurologic outcome.[5,6] Consequently, further prophylactic and therapeutic modalities are required to address these alternative mechanisms rather than focusing only on vasospasm.

Cilostazol is an anti-platelet and vasodilatory (selective inhibitor of phosphodiesterase-3) agent,[7] and has been shown to reduce symptomatic vasospasm after aSAH in animal models.[8] Besides being a potent vasodilator, Cilostazol has a number of other modulatory effects, that can influence the alternative mechanisms of delayed ischemic injury such as autoregulatory and cerebromicrovascular dysfunction, microvascular thrombosis[9] and EBI.[10,11]

Prior randomized clinical trials in human have shown inconsistent results for the efficacy of cilostazol for prevention of DCI following aSAH.[12–16] We aimed to conduct a meta-analysis of prior studies to evaluate the safety and efficacy of cilostazol for the prevention of cerebral vasospasm, delayed symptoms due cerebral ischemia and cerebral infarction following aneurysmal SAH.

Material and Methods

Study selection and data collection

We searched Pubmed, Embase databases to identify studies that assessed the effects of cilostazol in aSAH until May 2017 without language restrictions. The combination of following search terms was used: "cilostazol" and "subarachnoid hemorrhage." Two authors independently performed the review of the literature. The references of final articles were searched to find further studies. Article that did not meet our inclusion criteria were excluded. Inclusion criteria for the studies were (1) randomized/ controlled clinical trial or cohort studies; (2) Evaluation of the effect of cilostazol in aSAH; (3) Reporting of the risk estimates for symptomatic vasospasm or outcome. Data were extracted from the selected studies by two independent authors (H.S, A.D.) using a standardized form. The information included study name, publication year, region of the study, characteristics of patient population, number of patient treated with cilostazol, risk of symptomatic vasospasm, DCI and overall outcome in each group.

Outcome measures

The primary outcome was the incidence of DCI. Secondary outcomes were the incidence of cerebral infarction and poor outcome.

The definitions of the outcome measures were made according to the descriptions provided in the included studies. DCI was defined as any new unexplainable focal or global neurological deficit and decrease of at least 2 points on the Glasgow Coma Scale not explained by any identifiable medical conditions, regardless of cerebral vasospasm.

Cerebral infarction was determined by clinical and imaging studies. Poor outcome was defined as a modified Rankin Scale (mRS) of 3 to 6 determined during the follow-up in the study (Table 2).

Statistical analysis

Statistical analyses were performed by using the Review Manager (RevMan) Version 5.3 (Nordic Cochrane Centre, The Cochrane Collaboration, 2012, Copenhagen, Denmark). Random effects model was used for meta-analysis. Cochran *Q* test and I^2 test were used to detect heterogeneity. Significant heterogeneity was defined as either Q values greater than the chi-square critical value at alpha=0.1 level, or an I^2 value greater than 50%.

Results

Study selection and population

The PubMed and the EMBASE search revealed 112 and 322 hits, respectively. Review articles and meta-analyses were removed, and the remaining articles were subsequently evaluated for relevance based on title and abstract. Consequently, a total of 5 studies (4 randomized trials and 1 retrospective cohort studies, n=543) with a diagnosis of aSAH were ultimately included in this meta-analysis, including 271 patients (mean age 61.6±, 40% male) in cilostazol group and 272 patients (mean age 63.5±, 45% male) in placebo group. Table 1 demonstrates baseline characteristics and patients' demographics in these studies. No statistically significant difference was found for baseline factors including age, sex or initial Hunt and Hess score among the two groups.

Outcomes (Figure 1)

Symptomatic vasospasm

Symptomatic vasospasm was seen in 14% (38/271) of patients in cilostazol group and 34% (93/272) of patients in control group. Symptomatic vasospasm was significantly lower in patient treated with cilostazol as compared with control group. (OR 0.31, 95% CI 0.20 to 0.48; P <0.001; I^2 = 0%). No significant heterogeneity was seen across the studies.

Cerebral Infarction

Cerebral infarction was seen in 11% (30/271) of patients in cilostazol group and 27% (75/272) of patients in control group. Cerebral infarction was significantly lower in