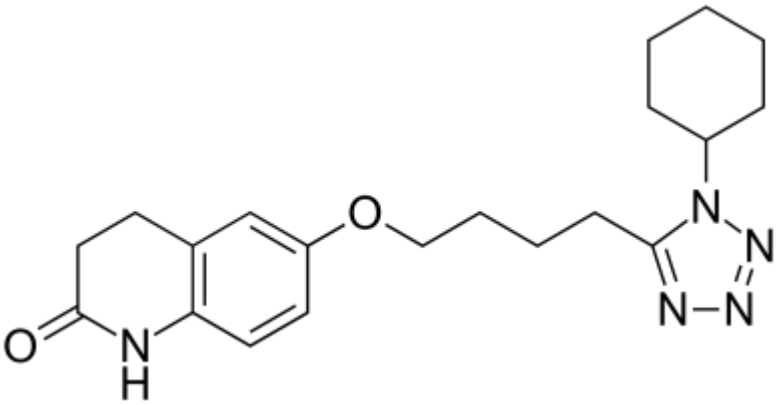
Cilostazol

- Japanese Nationwide Questionnaire Survey on the Treatment and Management of Subarachnoid Hemorrhage Due to Ruptured Cerebral Aneurysm
- Emerging Advances in the Management of Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage: A Narrative Review
- Spinal Drainage and Combined Pharmacotherapy as Potential Strategies to Improve Outcomes for Patients with Poor-Grade Subarachnoid Hemorrhage Treated with Clipping or Coiling but Not Receiving Nimodipine
- Characteristics of Cerebral Infarction Due to Anterior Cerebral Artery Dissection: A Review of 16 Cases
- Antithrombotic Therapy in Carotid Artery and Intracranial Artery Stent
- Bilateral Middle Cerebellar Peduncle Sign in a Patient with Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy and Coronavirus Disease 2019
- Randomized Controlled Trial of Cilostazol Addition for In-Stent Restenosis After Carotid Artery Stenting
- Impact of Clazosentan on Vasospasm Reduction and Functional Recovery after Aneurysmal Subarachnoid Hemorrhage



Cilostazol, is a antiplatelet drug that inhibits phosphodiesterase 3.

Application of cilostazol was reported to ameliorate vasospasm and improve outcomes in series and clinical trials. But the effectiveness and feasibility of cilostazol on aneurysmal subarachnoid hemorrhage remained controversial.

Kim et al. from the Asan Medical Center retrospectively analyzed the data of 427 patients with unruptured intracranial aneurysms who underwent endovascular treatment between July 2011 and June 2014. When clopidogrel resistance was confirmed via platelet reactivity unit (PRU) assay after dual antiplatelet therapy (aspirin plus clopidogrel) administration for 5 days, triple antiplatelet therapy with cilostazol was administered (Group I, 274 patients). The other group was placed on standard dual antiplatelet therapy (Group II, 153 patients). All patients underwent magnetic resonance diffusion-weighted imaging within 2 days after endovascular coiling.

No significant associations with the occurrence of a thromboembolic event and microembolic event were found between the groups. The occurrence of thromboembolic and microembolic events showed no statistical difference between groups I and II ($p = 0.725$ for thromboembolic events and $p = 0.109$

for microembolic events). Also, the PRU value and the occurrence of microembolic events, using a PRU cutoff value of 240, showed no statistical difference (p = 0.114 in group I and 0.064 in group II). There was significant increase in microembolic events after the use of a stent-assisted endovascular procedure. As the PRU value increased, there was a trend toward an increase in the mean number of microembolic lesions without statistical significance.

Even though there is a presumed anti-thromboembolic effect for clopidogrel resistance in other literature, the clinical efficacy of adjustment of additional cilostazol for endovascular coiling of unruptured aneurysms may be limited due to the unspecified cutoff value of the PRU assay for evaluating the resistance [1].

Systematic reviews

2021

A total of 454 articles were identified using the search criteria. Six articles were selected for systematic review and the 4 randomized controlled trials were included in the meta-analysis. The pooled odds ratio for symptomatic vasospasm, new-onset infarct, and angiographic vasospasm was 0.35 (95% confidence interval [CI], 0.21-0.59; P < 0.0001), 0.38 (95% CI, 0.21-0.66; P = 0.0007) and 0.49 (95% CI, 0.31-0.80; P = 0.004), respectively. The pooled risk ratio for unfavorable outcome was 0.52 (95% CI, 0.37-0.74; P = 0.0003).

Cilostazol decreases the prevalence of symptomatic vasospasm, new-onset infarct, and angiographic vasospasm when administered after aSAH. Trial sequential analysis increased the precision of our results because the defined thresholds of effect were met by the available studies. However, further studies involving patients from other geographic areas are required to confirm the generalization of the results [2]

2019

Shan et al., performed a systematic review to clarify this issue.

PubMed, Ovid and Cochrane library database were systematically searched up to May 2018 for eligible publications in English. Quality assessment was conducted for included studies. Meta-analysis was conducted to evaluate the overall effect on events of interest. Subgroup analyses and sensitivity analyses were used to check whether the results were robust. Publication bias was evaluated with the funnel plot.

Pooled analyses found cilostazol significantly reduced incidences of severe angiographic vasospasm ($p = 0.0001$), symptomatic vasospasm ($p < 0.00001$), new cerebral infarction ($p < 0.00001$) and the poor outcome ($p < 0.0001$). Subgroup and sensitivity analyses achieved consistent results. There was no statistical difference between cilostazol and the control group in reducing mortality ($p = 0.07$). But sensitivity analysis changed the result after excluding one study. Under the prescribed dosage, complication was few and non-lethal.

Cilostazol was effective and safe to reduce incidences of severe angiographic vasospasm, symptomatic vasospasm, new cerebral infarction and poor outcome in patients after aneurysmal subarachnoid hemorrhage. However, its effect on mortality and the interactive effect with nimodipine

warranted further research [3].

Case series

Beneficial for patients with atherothrombosis. In contrast to other anti-platelet drugs such as aspirin and thienopyridines, little information is available on the relationship between platelet responses to cilostazol and clinical outcomes.

Ikeda et al. from the Ehime University Graduate School of Medicine in Japan, conducted a prospective study on patients with cerebral infarction who were treated with cilostazol. The platelet response to cilostazol was assessed with a new assay for the phosphorylation of vasodilator-stimulated phosphoprotein (VASP) subsequent to the pharmacological action of cilostazol. Patients were followed up for 2 years and the relationship between VASP assay results and the recurrence of thrombotic events was examined. We also investigated the effects of CYP3A5 and CYP2C19 genotypes involved in the metabolism of cilostazol on the platelet response to cilostazol.

Among the 142 patients enrolled, 130 completed the 2-year follow-up and the recurrence of thrombotic events was noted in 8 (6.2%). VASP phosphorylation levels were significantly lower in patients with than in those without recurrence. The combined genotype of CYP3A5*1/*3 and CYP2C19*1/*1 was associated with a low level of VASP phosphorylation, while either genotype was not. A multivariate analysis showed that high residual platelet reactivity during the cilostazol treatment, which was defined by a low response of platelet VASP phosphorylation to cilostazol, was an independent risk factor for the recurrence of thrombotic events.

A low platelet response to cilostazol determined by a new platelet assay was associated with the recurrence of thrombotic events in patients with cerebral infarction [4].

Experimental models

established an experimental model using normal and diabetic rats at 12 months of age. The diabetic rats were assigned to 4 different diet groups, distinguished by whether they were fed plain rat feed, or the same feed supplemented by 1 of 3 antiplatelet drugs (cilostazol, aspirin, or clopidogrel: all 0.1%) for 2 weeks, and the carotid artery was perforated by an embolization coil (“carotid coil model”). We monitored the process by which vascular endothelial cells formed the new endothelium on the surface of the coil by sampling and evaluating the region at 1, 2, and 4 weeks after placement. This repair process was also compared among 3 groups treated with different antiplatelet drugs (i.e. aspirin, clopidogrel, and cilostazol). One-way analysis of variance tests were performed to evaluate the differences in vascular thickness between groups, and $P < .05$ was considered statistically significant.

Results: The diabetic rats showed delayed neoendothelialization and marked intimal hyperplasia. Cilostazol and clopidogrel effectively counteracted this delayed endothelial repair process. Flk1 immunostaining revealed greater expression in the diabetic rats administered cilostazol, second only to normal rats, suggesting that this agent acted to recruit EPCs.

Conclusion: Neoendothelialization is delayed when vascular endothelial cells fail to function normally, which consequently leads to the formation of hyperplastic tissue. Cilostazol may remedy this dysfunction by recruiting EPCs to the site of injury [5].

1)
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