Efficacy and Safety of Cilostazol Therapy in Ischemic Stroke: A Meta-analysis

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Background: Antiplatelet therapy is recommended for patients who have experienced ischemic stroke. We performed a meta-analysis to compare the efficacy and safety of cilostazol with other antiplatelet therapies in patients with ischemic stroke. *Methods:* PubMed, EMBASE, MEDLINE, and the Cochrane Library were searched for randomized controlled trials published in English from May 1999 to May 2013. Clinical outcomes were compared by pooled and meta-regression analyses. *Results:* Nine studies involving 6328 patients satisfied our inclusion criteria. Stroke recurrence (including hemorrhagic and ischemic) with cilostazol use was 5.3% (157) versus 8.3% (248) in control group (risk ratio .63 [.52-.76], 95% confidence interval [CI]). Poststroke intracranial hemorrhage was .5% (16) with cilostazol versus 1.6% (46) in control group (risk ratio .36 [.21-.63], 95% CI). Poststroke extracranial bleeding complications occurred in 2.4% (66) of the patients taking cilostazol versus 3.9% (108) in control group (risk ratio .62 [.46-.83], 95% CI). No significant difference in cerebrovascular events (nonfatal stroke, intracranial hemorrhage, and transient ischemic attack) was found between the cilostazol group (8.2%, 246) versus control group (12.0%, 360; risk ratio .71 [.50-1.01], 95% CI). In addition, the cilostazol therapy brought about a nonsignificant reduction of cardiac adverse events (heart failure, myocardial infarction, and angina pectoris) comparing with control groups, with 3.8% (99) of the cilostazol group versus 4.7% (123) of control group (risk ratio, .81 [.62-1.04], 95% CI). *Conclusions:* Cilostazol, alone or in combination with aspirin, significantly reduces stroke recurrence, poststroke intracranial hemorrhage, and extracranial bleeding in patients with a prior ischemic stroke as compared with other antiplatelet therapies. **Key Words:** Ischemic stroke—antiplatelet therapy—cilostazol—hemorrhage—meta-analysis.

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Recurrent cerebrovascular events are among the leading impediment to recovery from ischemic stroke.[1] Antiplatelet therapies are the mainstay of prevention of recurrent stroke for patients who have experienced an ischemic cerebral injury.[2,3] Aspirin alone is the most highly recommended antiplatelet therapy but poses a significant risk of hemorrhage and is not entirely protective. Recurrent ischemic events occur in approximately 10%-20% of aspirin-treated patients within 5 years after the initial event.[4-6] Only clopidogrel was reported with marginal reduction in stroke recurrence and risk of serious vascular events by the comparisons with aspirin among several antiplatelet regimens.[7,8] In addition, dual-antiplatelet therapy (clopidogrel plus aspirin) was associated with a significant trend to increase moderate bleeding,[7] the combination of 2 antiplatelet drugs failed to improve stroke prevention rates owing to the increased risk of bleeding events associated with their long-term use.[9,10]

Cilostazol, a selective inhibitor of cyclic nucleotide phosphodiesterase 3, increases activated intracellular Cyclic Adenosine monophosphate (cAMP) concentrations and thus inhibits platelet aggregation.[11] It also contributes to vasodilation and inhibits vascular smooth muscle cell proliferation.[12]Cilostazol is recommended as a first-line treatment for intermittent claudication due to peripheral vascular disease by the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guidelines.[13] A recent study also showed that addition of cilostazol to conventional dual-antiplatelet therapy (aspirin and clopidogrel) leads to significantly lower platelet reactivity and a decrease in thromboembolic events in patients undergoing percutaneous coronary interventions.[14] We propose that cilostazol may be an important adjunct, or possibly even single therapy, in the prevention of recurrent cerebrovascular events.

In this meta-analysis of 9 randomized controlled trials (RCTs) on patients with previous stroke, we investigate if there are significant differences in efficacy and safety between cilostazol and other conventional antiplatelet regimens.

Methods

Search Strategy

We searched PubMed, EMBASE, MEDLINE, the Cochrane Library, ClinicalTrials.gov, and the Cochrane Central Register of Controlled Trials for RCTs or meta-analysis from 1985 to May 2013. The search terms included were "cilostazol," "aspirin," "clopidogrel," "dipyridamole," "ticlopidine," "prasugrel," "triflusal," "glycoprotein IIb/IIIa receptor antagonists," "anti-platelet therapy," "phosphodiesterase 3 inhibitor," "ischemic stroke," "transient ischemic attack," "stroke prevention," and "randomized controlled trials." Relevant clinical trials composed in English were eligible for inclusion regardless of the published status (published, unpublished, in press, or in progress). If needed, the authors were contacted for further data. The search was restricted to clinical trials conducted with human subjects.

Inclusion Criteria

We included the clinical trials satisfying the following criteria:

(1) Prospective controlled clinical studies, which compared the effect of cilostazol and conventional treatment or placebo on poststroke patients.
(2) Patient age less than 85 years and with a clinical diagnosis of stroke, had been confirmed with neuroimaging.
(3) Case fatality and clinical events responsible for prognosis were described precisely for both cilostazol and control groups.
(4) Randomized trials with a sample size greater than 60.
(5) Trials with end points consisting of stroke recurrence and other clinical outcomes.

We used a modified augmented Jadad scale[15,16] (Table S1 in Appendix) to assess the methodologic quality of each study included. The modified augmented Jadad questionnaire used is comprised of 10 areas, each addressing 3 primary quality factors (randomization, blinding, and reported withdrawals)[16] and 7 additional methodologic factors (exclusion criteria, intervention used, control used, and data reporting).[15] The process of quality assessment was executed by 2 reviewers independently.

Study Selection and Data Extraction

According to the previously mentioned criteria, 2 reviewers independently selected studies to be included in the meta-analysis. If a discrepancy was found between the 2 reviewers' assessments, it was resolved by group discussion. If any data were duplicated or shared among studies, the earlier published or more detailed study was used.

The extracted data included study characteristics (participants, interventions, comparisons, outcomes, and study design, study duration, and type of control), report characteristics (years considered, language, and publication status), indicators of treatment efficacy including recurrent stroke, cerebrovascular events (nonfatal stroke, intracranial hemorrhage, and transient ischemic attack), cardiac adverse events (heart failure, myocardial infarction, and angina pectoris), and indicators of treatment safety including intracranial hemorrhage, extracranial bleeding complications, and tolerable and intolerable adverse events. This review was carried out and reported based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement issued in 2009[17] (Figure S1 in Appendix).