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Research Article

# CILOSTAZOL FOR STROKE IN SMALL VESSEL DISEASE : SYSTEMATIC REVIEW OF CURRENT LITERATURE

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**ABSTRACT**

**Introduction:** Cerebral small vessel disease (SVD) is accounted for 25% of ischemic stroke pathology. Cilostazol is a therapeutic option for secondary ischemic stroke prevention, especially in subgroups with high risks for hemorrhagic events. The available evidence is limited for optimal management of stroke in cerebral SVD. **Objective:** This systematic review aimed to identify the effectiveness of cilostazole for stroke in SVD **Method:** This systematic research was done by two authors using mainly PubMed and Cochrane as a database. The terms used to search the literature were "Cilostazol", "Small Vessel Infarction", "Lacunar Infarction", "Ischemic Stroke", and "Clinical Trial". We measure the quality of the clinical trials using Jadad Score. If the trial manage to meet the 3 important features then the jadad score of the trial will be 3. **Results:** The journal from PubMed and Cohrane was up to 3848 journals that were screened. Reviewers then begin to screening on the journals, exclude all of the irrelevant, and duplication study and make sure the inclusion and exclusion criteria were fulfilled. The result was 3 RCT studies. All studies have a good Jadad score. All of the comparison used in the studies is aspirin except for the study of Han, et al. (2014), that compare cilostazol with placebo. All of the subject that were used is above the age of 30 y.o. and the length of treatment is above 3 months. Each of the outcomes in all of the RCT studies is different, but their aims are to measure the effectiveness or the efficacy of cilostazol. Huang, et al (2008) have the most subject (720 subjects) and Lee, et al (2017), have the least subject (80 subjects). **Conclusion:** Cilostazol is proved to be effective in treating various conditions in ischemic stroke, i.e.: improved endothelial function, restored an inverse correlation between FMD and baseline L-arginine levels, decreased cerebral arterial pulsatility in patients with WMH, increases circulating EPCs and decreases small-dense LDL, reduced MPV, NIHSS, and mRS.

**Key words:** cilostazol, stroke, small vessel disease.

## INTRODUCTION

Ischemic stroke is accountable for 75% of all stroke cases [1]. Identify the risk factors is important to minimizing the disease burden [2]. Cerebral small vessel disease (SVD) is accounted for 25% of ischemic stroke pathology [3,4]. The definition of cerebral SVD refers to a group of pathological processes affecting the small arteries, arterioles, venules, and capillaries of the brain [5]. Two main mechanisms have been identified: (1) age-related and hypertension-related small vessel arteriopathy in the subcortical area and (2) cerebral amyloid angiopathy (CAA) that affects superficial cortical area [6]. SVD is known to occur in relation to hypertension, diabetes, smoking, radiation therapy and in a range of inherited and genetic disorders, autoimmune disorders, connective tissue disorders, and infections [7]. It also causes dementia, mood disturbance and gait problems [8].

The radiological characteristics of these processes on the brain parenchyma are mainly lesions located in the subcortical area, white matter lesions (WML, leukoaraiosis), intracerebral hemorrhages (ICHs) and cerebral microbleeds (CMBs) [9]. Different with the large cerebral artery disease, small vessels are not easily visualized [10]. Management of cerebral SVD is challenging because of the many unknown mechanism [11]. Traditional vascular risk factors do not entirely explain the variance in cerebral SVD [12]. Clinical consequences are varying from symptomatic to asymptomatic (silent brain infarction) [13].

Cilostazol is an antiplatelet agent that increases the cyclic adenosine monophosphate (cAMP) levels in platelets via inhibition of phosphodiesterase (PDE) [14]. Experimentally, cilostazol may enhance white matter regeneration after ischemia, improved motor and cognitive function and reduced infarct size as compared with aspirin [15]. Moreover, cilostazol has an endothelial protective effect and prevents blood brain barrier disruption in the ischemic brain [16,17]. Cilostazol also inhibits phosphodiesterase in vascular smooth muscle cells and thereby exerts its vasodilator effect without significant changes in blood pressure and pulse rate [18]. The anti-platelet and vasodilative effects of cilostazol are believed to underlie its preventive effect on recurrent stroke. It is also considered to be effective in promoting recovery from functional damage of the endothelium in cerebral penetrating arterioles. Cilostazol also promotes brain cell survival [19].

Cilostazol is indicated to treat the symptoms of intermittent claudication and increase walking distance in patients with peripheral arterial disease (PAD) [20]. Cilostazol is also supposed to be a therapeutic option for secondary ischemic stroke prevention, especially in subgroups with high risks for hemorrhagic events [21,22]. It is often preferred over aspirin or thienopyridines due to its comparable efficacy and more favourable safety profile [23,24]. The available evidence is limited for optimal management of stroke in cerebral SVD. This systematic review aimed to identify the effectiveness of cilostazole for stroke in SVD.

## METHODS

This systematic research was conducted by three authors using mainly PubMed and Cochrane as a database. The terms used to search the literature were "Cilostazol", "Small Vessel Infarction", "Lacunar Infarction", "Ischemic Stroke", and "Clinical Trial". The literature is eliminated if published over 10 years, not using english as the main language, and if the study is not a randomized controlled trial or RCT. The inclusion criteria for the literature are conducted in human with stroke or infarct and used cilostazol for the therapy. In this research, trials can be done using cilostazol as monotherapy drug or can be compared to other drug or placebo. We concerned only on the trials that measure the effectiveness of cilostazol or measure the efficacy between cilostazol and other drugs.

The appraisal process was done by three reviewers independently. We measure the quality of the clinical trials using Jadad Score. The maximum score for each clinical trials is 5. Jadad Score had 3 important features which are “randomized”, “double - blind”, “withdrawals, or “drop out status” to assess the trial. If the trial manage to meet the 3 important features then the jadad score of the trial will be 3. The other 2 points are about “appropriate randomized” and “appropriate blinding”. High quality randomized controlled trial (RCT) is substantial because it can assign the quality of the systematic review [25].

**RESULTS**

The journal from PubMed and Cohrane was up to 3848 journals that were screened. From further screening on the journals, specially the title and abstract that focus on the efficacy of cilostazol and the type of the study is RCT still 256 journals remained. Reviewers then begin to exclude all of the irrelevant and duplication study and make sure the inclusion and exclusion criteria were fulfilled. The result was 3 RCT studies. Figure 1 showed the study selection process that was done by the two reviewers. The diagram was made using PRISMA as a guidance while conduct the assessment. PRISMA or (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) is a list of the fundamenal points to specify transparent systematic review and meta analysis [26].

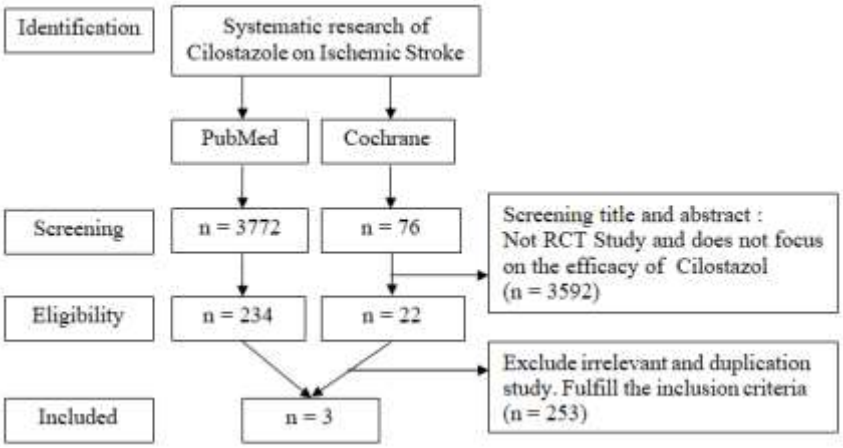


**Fig.1 : Guideline Selection Process**

The 3 RCT studies then started to be appraising the quality using Jadad Score. All of the RCT studies are published using English as the main language, and published within the last 10 years. There is only one RCT study that published in 2008. The other two RCT studies are published in 2014 and 2017. The entire literature studies that were appraised using Jadad Score have a good quality studies. The quality of the study is good if the Jadad Score ≥3. In the table 2. The quality of the studies can be seen more specifically.

**Table 2: Quality of Study by Using Jadad Score**

| Author (Year) | Was the study described as randomized? | Was the method used to generate the sequence of randomization described and appropriate? | Was the study described as double blind? | Was the method of double blinding described any appropriate? | Was there a description of withdrawal and dropout? | Total Score |
|---|---|---|---|---|---|---|
| Huang, et al. (2008) [27] | Yes | Yes | Yes | No | Yes | 4 |
| Ueno, et al. (2011) [28] | Yes | Yes | No | No | Yes | 3 |
| Han, et al. (2014) [29] | Yes | No | Yes | Yes | No | 3 |
| Haungsaithong, et al. (2015) [30] | Yes | Yes | No | No | Yes | 3 |
| Fujimoto, et al. (2016) [31] | Yes | Yes | No | No | Yes | 3 |
| Lee, et al. (2017) [16] | Yes | Yes | Yes | Yes | Yes | 5 |

In the table 3, all of the comparison used is aspirin except for the study of Han, et al (2014), that compare cilostazol with placebo. All of the subject that were used is greater than the age of 30 y.o. and the length of treatment is above 3 months. Each of the outcome in all of the RCT studies is different, but their aims are to measure the effectiveness or the efficacy of cilostazol. Huang, et al (2008) has the most subject (720 subjects) and Lee, et al (2017), have the least subject (80 subjects).

**Table 3: Summary of Selected Studies.**

| Authors (Year) | Type of Stroke | Intervention | Comparison | Subjects Baseline (Age) | Length of Treatment | Outcome Measure |
|---|---|---|---|---|---|---|
| Huang, et al. (2008) [27] | Ischemic Stroke | Cilostazol | Aspirin | 720 subjects (mean : 60.2 years) | 12 – 18 Months | The recurrence of stroke (ischaemic stroke, haemorrhagic stroke, subarachnoid haemorrhage) during trial period. |
| Ueno, et | Ischemic | Cilostazol 100 mg | Aspirin 100 mg/day | 49 subjects | 16 | Change in EPCs, PCs, platelet |

| | | | | | | |
|---|---|---|---|---|---|---|
| al. (2011) [28] | Stroke | b.i.d for a week, increased to 200 mg for the rest of the trial | | (Cilostazol group : 64.8 ± 8.5; Aspirin : 66.3 ± 6.6) | weeks | activation, lipid parameter (LDL-cholesterol, triacyglycerol, HDL-cholesterol, and small dense LDL-cholesterol) |
| Han, et al. (2014) [29] | Acute Lacunar Infarction | Cilostazol 100 mg b.i.d | Placebo b.i.d | 203 subjects (≥45 years) | 90 days | TCD PI and Volume of (WMH). |
| Haungsaithong, et al. (2015) [30] | Ischemic Stroke | Cilostazol 200 mg/day | Aspirin 81 mg/day, clopidogrel 75 mg/day, aspirin 50 mg/day + dipyridamole 200 mg/day | 21 subjects (60.0 years) | 4 weeks | MPV, NIHHS score, mRS |
| Fujimoto, et al. (2016) [31] | Non cardio-embolic ischemic stroke | Group C : Cilostazol 100 mg b.i.d + conventional antitrombotic* | Group A : Conventional antithrombotic* with/without aspirin (100-200 mg/day) | 311 subjects (Group A : 72.1 ± 10.8 years; Group C : 71.9 ± 10.6 years) | 3 months | NIHHS score, neurological deterioration, stroke recurrence, cardiovascular events, death |
| Lee, et al. (2017) [16] | Acute Cerebral Ischemic | Cilostazol | Aspirin | 80 subjects (≥30 years) | 3 months | Changes of FMD and corelation with L – Arginine levels. |

TCD PI: Transcranial Doppler Pulsatility Index, WMH: Volume of White Mater Hyperintensities, FMD: Flow Mediated Dilation, b.i.d: twice daily; MPV: Mean Platelet Volume, NIHHS: National Institute of Health Stroke Scale, EPCs: Endothelial Progenitor Cells, PCs: Progenitor cells, LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein

* Intravenous ozagrel sodium (160 mg/day), argatroban (60 mg/day during the initial 48 hours and 20 mg/d during the following 5 days) with or without oral aspirin (100 - 200 mg/d), during the first 7 hospital days

**Table 4: The result of selected study.**

| Authors (Year) | Results |
|---|---|
| Huang, et al. (2008) [27] | The estimated risk of primary endpoint in cilostazol group vs aspirin group, was 0.62 (95% CI 0.30-1.26; p: 0.185). Brain bleeding events were significantly more common in the aspirin group than in the cilostazol group (7 vs 1, p=0.034). |
| Ueno, et al. (2011) [28] | EPCs were significantly higher in the cilostazol group (p: 0.001 vs 0 weeks, p: 0.015 vs 4 weeks) than aspirin group (p: 0.24 vs 0 weeks, p: 0.40 vs 4 weeks) at 16 weeks, while PCs were already significantly higher at 4 weeks in the cilostazol group. The cilostazole group showed significantly less small dens LDL- and higher HDL-cholesterol than the aspirin gorup at both 4 and 16 weeks. |
| Han, et al. (2014) [29] | There was a significant decrease of TCD PIs at 90-day study from baseline in the cilostazol group (p = 0.02). The mean WMH volume was 11.57 cm(3) (0.13-68.45, median 4.86) and the mean MCA PI was 0.95 (0.62-1.50). The changes in PIs from the baseline to 14 days and to 90 days were 0.09 (-0.21 to 0.33) and 0.10 (-0.22 to 0.36). Cilostazol decreased the TCD PIs significantly at the 90-day point in patients with WMH volumes ≤ 4.9 cm(3) (p = 0.002). |
| Haungsaithong, et al. (2015) [30] | At 4-week, every type of antiplatelets reduced MPV, NIHSS, and mRS. Clopidogrel significantly reduced NIHSS score (p = 0.003), and it produced the greatest reduction in MPV compared to others. |
| Fujimoto, et al. (2016) [31] | A good outcome at 3 months after admission was observed more frequently in Group C than in Group A patients (68% vs. 56%, p: 0.0253). In the multivariate analysis, cilostazol (OR: 1.99; 95% CI: 1.05-3.77; p: 0.0353) was positively associated with a good outcome. |
| Lee, et al. (2017) [16] | There was a significant increase of FMD values in cilostazol group (7.9 ± 2.4 to 8.9 ± 2.3%, p = 0.001) and not in aspirin group (8.5 ± 2.6 to 9.3 ± 2.8%, p = 0.108). In the multiple regression analysis performed in cilostazol group, serum L–arginine levels were inversely correlated with FMD at T1 (ß = −0.050, SE: 0.012, p < 0.001) with age, total cholesterol levels, and C-reactive protein as confounders. While T0 FMD values in both aspirin and cilostazol groups did not show any correlation with serum L-arginine levels, the correlation is restored in the cilostazol group at T1 (r = 0.467, p = 0.007), while such is not shown in the aspirin group. |

TCD PI: Transcranial Doppler Pulsatility Index, WMH: Volume of White Mater Hyperintensities, FMD: Flow Mediated Dilation, b.i.d: twice daily; MPV: Mean Platelet Volume, NIHHS: National Institute of Health Stroke Scale, EPCs: Endothelial Progenitor Cells, PCs: Progenitor cells, LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein

## DISCUSSION

The problems in managing lacunar infarction in patients with SVD are: (1) should we give anti thrombotic to this patients, (2) is there any higher risk of bleeding. The cornerstone of managing brain infarction is to prevent further vessel occlusion. Anti thrombotic medication is the mainstay of the treatment. The choice of anti platelet in lacunar infarction is not easy. Limited previous trials focus on cerebral SVD. The management of traditional vascular risk factors is mandatory.

Hypertension is the most important risk factor for stroke. Previous studies showed the benefits of lowering BP for secondary stroke prevention. The data for its benefit in SVD are limited. The Secondary Prevention of Small Subcortical Strokes (SPS3) trial is the study to determine the best method for secondary prevention in patients with lacunar infarction. This study showed that there is no benefit in reducing the blood pressure for prevention further lacunar infarction (hazard ratio [HR], 0.81; 95% CI, 0.64-1.03). The benefit of blood pressure reductions remains uncertain. The result of cohort study showed that decreased diastolic BP was associated with decreased gray matter volume and cognitive impairment in older subjects .

Statin is beneficial in ischemic stroke patients, but previous studies do not focus in patients with lacunar infarction. Single study (Regression of Cerebral Artery Stenosis study) showed that statin use was associated with less WMH progression. Other potential target for SVD worsened prevention is tha agent that lowering homocystein. Homocystein is proven as risk factor for vascular damage. The sub goup analysis of MRI in VITATOPS study showed that B-vitamins were associated with a reduced WMH.

Antiplatelets are the main treatment for in non-cardioembolic stroke. Most of the studies did not focus on lacunar infarction. The SPS3 trial is the study that focuses on lacunar infarction. The SPS3 study did not show any benefit of combination of clopidogrel and aspirin. The dual anti platelet did not significantly reduce the risk of recurrent stroke and significantly increases the risk of bleeding.

The high risk of bleeding is the primary concern when using antiplatelets in cerebral SVD. Cilostazol is very promising anti platelet for cerebral SVD. The previous studies showed that cilostazol had fewer risk of bleeding compared with aspirin. The other benefit of cilostazol is its endothelial protective effect and prevents blood-brain barrier disruption. Previous trial with cilostazol for Prevention of Secondary Stroke study showed significant difference between the cilostazol and aspirin groups to the incidence of hemorrhagic stroke in patients with lacunar stroke.

## CONCLUSION

Cilostazol is proved to be effective in treating various conditions in ischemic stroke, i.e.: improved endothelial function, restored an inverse correlation between FMD and baseline L-arginine levels, decreased cerebral arterial pulsatility in patients with WMH, increases circulating EPCs and decreases small-dense LDL, reduced MPV, NIHSS, and mRS. Unfortunately, there is no significant difference in the rate of recurrence of stroke between patients with ischaemic stroke who were randomly assigned to take either cilostazol or aspirin. Early oral cilostazol in the acute phase appears to be associated with a good outcome in patients with progressive stroke.

## AUTHOR CONTRIBUTION

All three authors involved during systematic research and appraising the quality of journal. SCK contributed in the process of drafting manuscript. RDLRS works in manuscript revision. and RTP works in journal submission

## CONFLICTS OF INTEREST

Nothing to declare.

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