Effect of cilostazol on cerebral arteries in secondary prevention of ischemic stroke

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Abstract: Objective To compare the effects of cilostazol on cerebral arteries and cerebrovascular blood flow in secondary prevention of ischemic stroke, with those of aspirin. **Methods** Sixty-eight patients who had ischemic stroke during the recent 1-6 months were recruited and randomized into cilostazol or aspirin group. Cerebrovascular condition was assessed by magnetic resonance angiography (MRA) and transcranial doppler ultrasonography (TCD) at the beginning of the study and after 12-month medication. **Results** During the clinical follow-up, ischemic stroke recurred in 2 patients in cilostazol group, while in aspirin group, one case of ischemic stroke recurrence and one case of acute myocardial infarction were found. MRA revealed that in aspirin group, the percentages of patients experiencing aggravation and attenuation of cerebrovascular condition were 3.3% and 6.7%, respectively, while in aspirin group, they were 3.3% and 10%, respectively. Moreover, TCD revealed that 26.9% of the patients in aspirin group and 14.3% of the patients in cilostazol group experienced aggravation of cerebrovascular condition. However, the systolic peak flow velocity of the previously abnormal arteries increased by 42.9% after 12-month medication of cilostazol, which was significantly higher than that after aspirin medication (27.5%) ($P = 0.04$). Furthermore, as a major side effect of antiplatelet therapy, the frequency of bleeding was much less in cilostazol group (0 case in cilostazol group vs 5 in aspirin, $P < 0.05$). **Conclusion** Cilostazol is as effective as aspirin in preventing the aggravation of cerebral arteries in secondary prevention of ischemic stroke. Besides, it is more safe. Cilostazol can increase the systolic peak flow velocity of cerebral arteries, which may improve the blood supply of focal ischemia.

Keywords: cilostazol; aspirin; stroke, ischemic; magnetic resonance angiography; transcranial doppler ultrasonography

1 Introduction

Antiplatelet therapy plays an important role in secondary prevention of ischemic stroke. As an antiplatelet agent, although aspirin is widely used, the formation of drug resistance and the risk of bleeding^[1,2] have limited the clinical application of aspirin. Cilostazol has been shown to significantly reduce the risk of stroke recurrence while it does not induce the intracranial hemorrhage, thus it has drawn much

attention since the past few years.

In the Cilostazol Stroke Prevention Study (CSPS)^[3,4], a randomized, double-blind, and placebo-controlled trial was conducted, involving more than 1 000 Japanese patients, who had been diagnosed with ischemic stroke during the previous 1-6 months. Results have shown that cilostazol could significantly reduce the risk of the second stroke by 41.7%, compared with the placebo ($P = 0.015$). Cilostazol could also induce significant reductions on a number of combined endpoints, such as ischemic stroke, intracranial hemorrhage, myocardial infarction (MI), and vascular death. These results indicate that cilostazol may act as a vascular neuroprotector, but the clinical implications are limited due to the placebo, instead of aspirin, as the control.

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In the Trial of cilostazol in Symptomatic intracranial Stenosis (TOSS)^[5], which is another multicenter double-blind placebo-controlled trial, 135 patients with acute symptomatic stenosis in the M1 segment of middle cerebral artery or the basilar artery are randomized to cilostazol medication (200 mg per day) or placebo for 6 months, during which all the patients also receive aspirin medication. The results have shown that cilostazol and aspirin are tolerable and the co-effect in preventing the progression of symptomatic intracranial arterial stenosis (IAS) is superior to that of aspirin mono-therapy. However, this also fails to determine whether cilostazol is superior to aspirin in cerebrovascular restenosis prevention.

Besides the antiplatelet property, cilostazol also exerts other effects, such as vasodilation, inhibition of thrombosis, decrement of triglycerides, elevation of high density lipoprotein cholesterol, inhibition of vascular smooth muscle cell growth, and neuroprotection^[6-9]. It is hypothesized that cilostazol may play an important role in preventing the aggravation of cerebrovascular stenosis. Thus, the present study aims to compare the effects of cilostazol with those of aspirin on cerebral arteries and cerebrovascular blood flow in secondary prevention of ischemic stroke.

2 Materials and methods

2.1 Study design A total number of 68 patients were included in the present study. They were admitted to the 2nd Affiliated Hospital of Guangzhou Medical College between May 31, 2004 and December 30, 2005. Patients gave their informed consent for the study approved by ethics committees.

2.2 Participants The participants in this study were 18-75 years old, and all of them had ischemic stroke (modify Rankin Scale less than 4) during the previous 1-6 months, which had been confirmed by cranial computed tomography (CT) or magnetic resonance imaging/angiography (MRI/MRA).

The patients exhibiting any of the following symptoms were excluded from the study: (1) known hemorrhagic diathesis or recent major bleeding history; (2) anemia (hemoglobin $\leq$ 10 mg/dL) or thrombocytopenia (platelet $\leq$ 100 000/mm³); (3) chronic wasting disease; (4) nonatherosclerotic vascular disease such as vasculitis, or moyamoya disease; (5) severe stroke (National Institutes of Health stroke scale $\geq$ 16 at

recruitment); (6) serious complications (malignant tumors, liver cirrhosis, renal failure, or heart failure); (7) with a possibility of past or future cardiogenic cerebral embolism or any one of the following complications: mitral valve stenosis, prosthetic valve, endocarditis, acute myocardial infarction within 6 weeks after onset, ventricular aneurysm, intraventricular or intraatrial thrombosis, mitral valve prolapse, atrial fibrillation, and inborn myocardial disease; (8) contraindications to cilostazol.

2.3 Treatment allocation Participants randomly received either cilostazol (100 mg twice per day) or aspirin (100 mg once per day), both of which were supplied by Zhejiang Dazhong Pharmaceutical Company. The random order was determined by using a computerized random number generator. Among the 68 participants, 34 patients were randomly assigned to cilostazol group and 34 to aspirin group.

2.4 Cerebrovascular condition evaluation MRA was primarily used to assess the degree of angiostenosis, while TCD was performed to check the results of MRA. MRA images were obtained on a 1.5T MR Scanner (Magnetom Symphony, SIEMENS Medical System). All the cerebrovascular information was obtained using a 3 dimensional time-of-flight gradient-echo technique (echo time = 4.6 ms, repeat time = 36 ms, matrix size = 384 $\times$ 224, field of view = 16.0 $\times$ 16.0 cm²). TCD evaluation was performed by experienced sonographers according to standardized manual of operations. All the TCD studies were performed using a 2 MHz pulsed ultrasound probe (DWL, $\times$ 4 DOP). The studies on middle cerebral artery (MCA), anterior cerebral artery (ACA), terminal branch of internal cerebral artery (ICA C1 segment) and posterior cerebral artery (PCA) were based on the transtemporal approach. Besides, the transorbital approach was used for carotid siphon (C3 segment of the ICA) study, and the suboccipital approach through the foramen magnum was used for basilar artery (BA) evaluation. Both MRA and TCD were performed at the beginning of recruitment and at the end of the 12-month medication.

2.5 Clinical follow up Participants were followed up once per month, and Modify Rankin Scale (mRS), blood pressure (BP), respiration (R), heart rate (HR), and body mass index (BMI) were assessed. The adverse effects and clinical vas-

cular events were also observed. Laboratory tests including blood routine, urine routine, stool routine, liver function tests, renal function tests, plasma lipids and glucose detection were conducted at month 3 and 6, and at the end of the trial. The remaining amount of the studied drug was counted at each visit, and if the percentage of the remaining drug was more than 75% (poor compliance) or other antiplatelet agents were taken, the patients were excluded. When serious adverse effects happened, participants were also dropped out as decided by a physician who did not know the drug allocation. All the adverse effects were recorded, and their possible associations with the studied drugs were assessed.

2.6 Outcome measurement The primary outcome was to observe the cerebrovascular aggravation by MRA and the recurrence of clinical vascular events, such as ischemic stroke, MI, intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), transient ischemic attack (TIA), and death. The secondary outcome was to observe the aggravation of cerebral arteries detected by TCD.

After the follow-up evaluations, the raw MRA data of the patients were gathered as graphic information, and 2 researchers who were blind to the clinical information reviewed the data using the same types of monitors and software. The extent of cerebrovascular stenosis was classified into 4 grades according to the report of Rother^[10]: normal (no signal loss), mild (signal reduction: A < 50%, B ≥ 50%), moderate (complete signal loss. A: limited to stenosis, B: including poststenotic), and severe (signal loss, including poststenotic with signal rarefaction of distal vessels). Aggravation was defined as worsening of stenosis by 1 or more grades evaluated by MRA, compared with the baseline, whereas improvement was defined as attenuation of stenosis by 1 or more grades.

Aggravation of stenosis was identified by TCD as the following^[5,10]: (1) the change of the waveform to an occlusive pattern; or (2) an increase in the systolic peak flow velocity (>20 cm/s) by >20% on flow-up TCD compared with baseline value. Improvement was defined as: (1) change of the occlusive waveform to a stenotic pattern; or (2) a decrease in the systolic peak flow velocity (>20 cm/s) by >20%.

2.7 Statistical analysis Data were analyzed by unpaired

student's *t*-test for continuous variables and by χ^2 test for categorical variables. The baseline clinical and imaging characteristics of the participants who were prematurely terminated in the 2 groups, were also compared. $P < 0.05$ was considered as statistically significant. SPSS version 13.0 for window software was used for statistical analysis.

3 Results

3.1 Clinical outcome In general, patients in the 2 groups were well matched with age, gender, and clinical profiles, as shown in Table 1. In aspirin group, one case of ischemic stroke recurrence and one case of acute myocardial infarction were detected. In cilostazol group, 2 cases of ischemic stroke recurrence were detected. However, there was no statistical differences in the rate of vascular events between the 2 groups.

3.2 Adverse events and premature termination During the follow-up period, some adverse effects developed, including headache (14.7%), gastrointestinal disturbance (7.4%), dizziness (2.9%), and bleeding events (7.4%, including 1 intracerebral hemorrhage, 1 nasal bleeding, 1 gastrointestinal hemorrhage, 1 fecal occult blood and 1 vaginal bleeding). Headache developed more frequently in cilostazol group (23.5% in cilostazol vs 5.9% in aspirin, $P < 0.05$). Besides, 14.7% of the patients in aspirin group experienced bleeding, while no patient in cilostazol group did ($P < 0.05$). The incidences of other adverse events were not significantly different between the 2 groups.

Five clinical vascular events (3 ischemic stroke, 1 intracerebral hemorrhage, and 1 acute coronary event) occurred in the 2 groups. There were 7 (20.5%) participants prematurely terminated in cilostazol group and 6 (17.6%) in aspirin group. Two patients in aspirin group died of acute myocardial infarction and acute pancreatitis, respectively. There were totally 3 cases of ischemic stroke recurrence, among which 2 cases were in cilostazol group and 1 in aspirin group. As listed in Table 2, the number of premature termination was not significantly different between the 2 groups.

3.3 Changes of cerebral arteries Two estimators blindly reviewed the grades of arterial stenosis in 128 cases (68 baseline and 60 follow-up cases) in 1152 arteries (2 MCAs, 2

Table 1. Baseline clinical and angiographic characteristics of patients in cilostazol and aspirin groups

	Cilostazol (<i>n</i> = 34)	Aspirin (<i>n</i> = 34)	<i>P</i> value
Baseline characteristics			
Mean age (year)	59.44±10.63	62.06±11.12	0.98
Female (%)	22 (65.00)	22 (65.00)	1.00
Hypertension (%)	23 (68.00)	22 (65.00)	0.79
Diabetes mellitus (%)	2 (5.80)	4 (11.70)	0.67
Current smoker(%)	10 (29.40)	16 (47.10)	0.13
Hyperlipidemia (%)	15 (44.10)	16 (47.10)	0.81
Severity of stenosis			0.39
Normal (%)	34 (9.24)	22 (6.40)	
Mild stenosis (%)	292 (79.35)	282 (81.98)	
Moderate stenosis (%)	37 (10.05)	32 (9.30)	
Occlusion stenosis (%)	5 (1.36)	8 (2.33)	

Values indicate the number of patients.

Table 2. The adverse events and the causes of premature termination

	Cilostazol group (<i>n</i> = 34)	Aspirin group (<i>n</i> = 34)	<i>P</i> value
Adverse events			
Headache	8	2	0.04*
Dizziness	2	0	0.12
Gastrointestinal disturbance	3	2	0.50
Bleeding events	0	5	0.03*
Cardiac arrhythmias	8	5	0.36
The causes of premature termination			
Death	0	2	0.24
Acute coronary events	0	1	0.50
Intracerebral hemorrhage	0	1	0.50
Ischemic stroke	2	1	0.50
Other adverse events	2	0	0.25
Poor compliance	3	1	0.307

*: significant difference. Values indicate the number of patients.

ACAs, 2 PCAs, 2 ICAs and 1 BA in each case) with MRA. As shown in Table 3, the degree of arterial stenosis changed in 7 of the 60 patients (11.6%). Only 1 patient (3.3%) experienced aggravation in cilostazol group, and 1 patient in aspirin group. The improvement was found in 2 patients (6.7%) in cilostazol group and in 3 patients (10.0%) in aspirin group. The rates of aggravation and improvement were not significantly different between cilostazol and aspirin groups ($P = 0.90$).

TCD evaluations were conducted in 47 patients, and the results were similar and consistent with those of MRA. The aggravation of stenosis was detected in 3 of the total 21 patients (14.3%) in cilostazol group and 7 of 26 (26.9%) in aspirin group. Although the rate of aggravation was relatively lower in cilostazol group, there was no significant difference between the 2 groups ($P = 0.40$) in the rates of aggravation or improvement.

Table 3. The changes of arterial stenosis measured by MRA and TCD in aspirin and cilostazol groups.

	MRA outcome		TCD outcome	
	Cilostazol (%)	Aspirin (%)	Cilostazol (%)	Aspirin (%)
Improvement	2 (6.7)	3 (10.0)	7 (33.3)	10 (38.5)
Stationary	27 (90.0)	26 (90.0)	11 (52.4)	9 (34.6)
Aggravation	1 (3.3)	1 (3.3)	3 (14.3)	7 (26.9)
<i>P</i> value	0.90		0.40	

Values indicate the number of patients.

Table 4. The effects of cilostazol and aspirin on cerebrovascular systolic peak flow velocity (cm/s)

	Aspirin			Cilostazol		
	Initial (<i>n</i> = 26)	One year later (<i>n</i> = 26)	<i>P</i> value	Initial (<i>n</i> = 21)	One year later (<i>n</i> = 21)	<i>P</i> value
BA	67.39±31.99	64.87±23.81	0.55	54.96±22.33	59.00±38.71	0.32
RMCA	98.74±32.97	93.26±27.56	0.31	110.38±47.15	101.33±43.16	0.30
LMCA	132.9±75.50	116.5±56.88	0.15	109.90±31.92	106.10±39.59	0.56
RACA	82.25±21.72	78.52±19.04	0.31	77.40±15.41	75.90±16.87	0.67
LACA	83.74±25.65	82.70±28.16	0.86	83.90±21.21	81.10±22.16	0.50
RPCA	61.60±17.83	61.20±12.71	0.94	60.95±11.28	61.79±9.31	0.68
LPCA	73.20±22.38	69.20±20.26	0.54	60.25±9.98	57.13±11.82	0.23
RICA	100.17±32.37	96.50±27.22	0.47	108.94±44.26	103.41±42.78	0.54
LICA	143.85±79.57	123.4±61.61	0.23	111.75±33.10	104.12±33.49	0.28

As shown in Table 4, TCD method revealed that the systolic peak flow velocity of the cerebral artery exhibited a mild decrease in aspirin group, and a mild increase in some arteries in cilostazol group after one-year medication. However, neither group showed significant difference in the systolic peak flow velocity of the cerebral artery between the initial of medication and the end of medication (after 12 months).

According to Kwon and Sliwka's criteria^[5,10], the change of cerebrovascular systolic peak flow velocity was further analyzed in all the patients. TCD results showed that none of the arteries exhibiting normal systolic peak flow velocity at the initial of medication deteriorated later. However, among the 153 arteries (84 in cilostazol group and 69 in aspirin group) that exhibited abnormal systolic peak flow velocity at the initial of medication, 36 (42.9%) arteries showed an increase in systolic peak flow velocity in cilostazol group and 19 (27.5%) in aspirin group. There was a significant difference in the number of these abnormal arteries between the 2 groups, but

Table 5. The velocity change of arteries which exhibited abnormal systolic peak flow velocity

	Cilostazol (%)	Aspirin (%)	<i>P</i> value
Increase	36 (42.9)	19 (27.5)	0.04*
Decrease	13 (15.5)	15 (21.7)	0.32
Stationary	35 (41.7)	35 (50.7)	0.26

Values indicate the number of arteries. *: significant difference.

not in the number of abnormal arteries that exhibited decreasing or stationary systolic peak flow velocity (Table 5).

4 Discussion

Stroke is the leading cause of death and disability in China^[11], and also a leading cause of hospitalization in neurological department. The most common type of ischemic stroke is lacunar infarction, followed by atherothrombotic and cardioembolic infarction. The incidence, mortality, and cost of stroke may all increase with aging in Chinese population.

The strategy for secondary prevention of stroke is pri-

marily focused on controlling the vascular risk factors, including management of hypertension, lipid abnormalities, and smoking cessation. Antiplatelet therapy also plays an important role. The present study mainly aims to evaluate the efficacy of cilostazol, an inhibitor for phosphodiesterase-3, on cerebral arteries in the secondary prevention of ischemic stroke. Our major finding is that cilostazol is as effective as aspirin on preventing the aggravation of cerebral arteries in secondary prevention of ischemic stroke. Besides, it is more safe. Cilostazol can also increase systolic peak flow velocity of cerebral arteries, which may improve the blood supply of focal ischemia.

Meanwhile, side effects developed in the patients during the study, including headache, gastrointestinal disturbance, dizziness, bleeding, *etc.* Between the 2 groups, bleeding occurred more frequently in aspirin group and headache more frequently in cilostazol group. Our results suggest that cilostazol is more safe than aspirin in bleeding event and patients may benefit from the lower incidence of bleeding by using cilostazol. This result is quite consistent with a previous report^[12]. Besides, the occurrence of headache may be attributed to the vasodilation effect of cilostazol, which can be avoided or attenuated by reducing the dose at the beginning.

While digital subtraction angiography (DSA) is considered to be invasive, we used MRA instead to assess the degree of stenosis and analyze the changes of cerebral artery stenosis. TCD was further conducted to confirm the reliability of MRA results. Since there are no commonly accepted TCD criteria for the classification of cerebral artery stenosis, an elevation of the systolic peak flow velocity has a good correlation with DSA, especially in moderate and severe stenosis^[10]. Thus the systolic peak flow velocity detected by TCD was employed to assess the cerebral artery stenosis.

As revealed by MRA, there were no significant differences in the number of improved arteries or aggravated arteries between the 2 groups. Meanwhile, TCD results also indicate that the aggravation rate is relatively lower in cilostazol group, but with no statistical difference between the 2 groups. We further analyzed the changes of cerebrovascular systolic peak flow velocity of all the patients between the initial and

the end of medication (one year later). Of the arteries that exhibited abnormal systolic peak flow velocity at the initial of medication, cilostazol group showed more percentage with velocity increase than aspirin group did. The increase of blood velocity in cilostazol group may be due to the small-vessel dilation, which can improve the blood supply of focal ischemia. Since several studies have confirmed that cilostazol causes vasodilation of isolated and pressurized rabbit spinal arteriole^[13], we extrapolate that the elevation of the systolic peak flow in the cerebral microcirculation may be also due to the cilostazol-induced vasodilation of the arterioles feeding the central nervous system. Cilostazol has also been proved to dilate the pial arteries and inhibit the formation of thrombosis during focal ischemia in cat^[14]. In a rat model of focal cerebral ischemia, cilostazol improves cerebral blood velocity (CBV) and cerebral blood flow (CBF) in the peri-infarct area^[15]. Clinically, cilostazol could also reduce the risk of stroke with small-vessel etiology in the CSPS trial^[4,16]. The exact mechanisms of cilostazol in vascular smooth muscle still unknown^[13]. Presumably, inhibition in phosphodiesterase-3 and the corresponding cAMP increase in smooth muscles of arterioles are involved to some extent, because phosphodiesterase-3 is strongly expressed in these cells^[17].

In the investigations of TOSS^[5], co-treatment of cilostazol and aspirin induces the aggravation of symptomatic IAS in 3 (6.7%) out of the total 45 patients, and the improvement in 11 (24.4%) patients. In aspirin group, 15 (28.8%) patients experience symptomatic IAS aggravation and 8 (15.4%) patients experience improvement. In the present study, the vascular change of stenosis is relatively lower, which may be due to the different observed stroke phases. The study of TOSS addresses the acute phase of stroke (within 2 weeks after cerebral infarction), whereas our study deals with the sub-acute or chronic phase of brain infarction (1-6 months after cerebral infarction). It is possible that the cerebrovascular plasticity at the acute phase may differ from that at the chronic phase, in that the cerebrovascular plasticity at the acute phase may be more obvious than that at the chronic phase. On the other hand, the patient selection in the study of TOSS may be also responsible for this difference. In the study of TOSS, all the patients have acute symptomatic stenosis in the M1

segment of middle cerebral artery or the basilar artery, while in our study, only part of the patients are detected with vascular stenosis. The third explanation for the difference is the drug management. TOSS applies co-treatment of aspirin and cilostazol, whereas our study employs aspirin monotherapy. And co-treatment of aspirin and cilostazol may be superior to aspirin monotherapy in preventing the aggravation of symptomatic IAS.

However, there are 2 limitations in our study, that is, the small number of participants and the short period of the study. Further clinical trials on vascular events are required to confirm the efficacy of cilostazol on cerebrovascular restenosis prevention in ischemic stroke.

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西乐他唑在脑梗死二级预防中对脑血管的影响

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摘要: **目的** 观察西乐他唑与阿司匹林在脑梗死二级预防中对脑血管状况和脑血流的影响, 并作比较。**方法** 选取在近 1-6 个月内有脑梗死病史患者 68 例, 随机分配入西乐他唑和阿司匹林组。在入组时及用药 12 个月后, 应用核磁共振血管成像(MRA)和经颅多普勒超声(TCD)方法评价患者脑血管状况。**结果** 随访期间, 西乐他唑组有 2 例患者再发脑梗死, 而阿司匹林组有 1 例再发脑梗死, 1 例发生急性心肌梗死。MRA 检测发现, 西乐他唑组患者血管状况恶化和好转的比例分别为 3.3% 和 6.7%, 阿司匹林组分别为 3.3% 和 10.0%。TCD 检测显示西乐他唑和阿司匹林组患者血管状况恶化发生的比例分别为 14.3% 和 26.9%。以上结果两组间均无统计学差异。服用西乐他唑 12 个月后, 血流异常的血管中其收缩期血流峰值升高的比例高于阿司匹林组, 分别为 42.9% 和 27.5%。作为抗血小板治疗的主要副作用, 出血事件在西乐他唑组发生 0 例, 在阿司匹林组发生 5 例($P < 0.05$)。**结论** 西乐他唑在脑梗死二级预防中同阿司匹林一样有效且比阿司匹林更为安全。西乐他唑能升高脑血管峰值血流速度, 改善缺血灶血供。

关键词: 西乐他唑; 阿司匹林; 脑梗死; 核磁共振血管成像; 经颅多普勒超声