Cognitive effect of cilostazol in post stroke cognitive impairment: a prospective study

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Research article

Keywords: Cilostazol, post stroke cognitive impairment, vascular cognitive impairment, vascular dementia

Posted Date: May 13th, 2019

DOI: https://doi.org/10.21203/rs.2.9552/v1

Abstract

Background Whether antiplatelet agents have a preventive effect on cognitive function after ischemic stroke remains unknown. This study examined the potential effect of cilostazol, an antiplatelet agent and cyclic adenosine monophosphate phosphodiesterase 3 inhibitor, on cognitive impairment after stroke in an Asian population. Methods A total of 45 patients using cilostazol (100 mg) twice per day were enrolled as the study group and 45 patients using aspirin (100 mg) or clopidogrel (75 mg) daily were enrolled as the control group. Mini-mental state examination and Cognitive Assessment Screening Instrument were administered at the start of the study and after 6 months. Multiple logistic regression analysis was used to estimate the association between the cognitive change and cilostazol use. Results Overall, 60-70% of the patients improved their cognition after 6 months follow up. No significant differences were observed in the cognitive change between the cilostazol and control groups. However, the cilostazol group appeared to perform better in the fluency, language and judgment subdomains. Conclusions In the current study, the clinical course of post stroke cognitive changes was described. Although cilostazol did not make a significant difference in cognitive change after ischemic stroke, it may improve fluency, language and judgment subdomains. These findings should be examined further in randomized clinical trials.

Background

Cognitive impairment and dementia represent a substantial burden on society [1]. After Alzheimer's disease (AD), vascular dementia (VaD) is the second most common type of dementia [2]. After a stroke, as many as two-thirds of patients experience cognitive impairment or decline. The presence of cognitive impairment is associated with a substantial increase in the risk of developing dementia [3]. A 15 year follow up study found that the prevalence of post stroke cognitive impairment was 22% and it remained persistently high over time [4]. Methods for stopping or delaying the onset of cognitive impairment following a stroke have become an important issue.

The term vascular cognitive impairment (VCI) encompasses all forms of cognitive impairment of a vascular origin (including stroke), ranging from mild cognitive impairment to VaD [5]. VCI is utilized to better study the full cognitive burden of cerebrovascular illness. Generally, the pathogenesis of VCI includes reduced cerebral blood flow, endothelial dysfunction, inflammation, oxidative stress, blood brain barrier dysfunction and amyloid deposition, which induce cerebral microinfarcts, microbleeding, white matter lesions, gliosis and brain atrophy [6]. Amyloid load in the brain and permanent inflammation have been previously reported as the most important factors associated with post stroke cognitive decline [7]. Amyloid load is also associated with white matter hyperintensities, which are considered to reflect cerebral small-vessel disease [8].

Cilostazol is a phosphodiesterase III inhibitor and an antiplatelet with fewer bleeding risks than aspirin in patients with small-vessel disease [9]. It can increase cyclic adenosine monophosphate levels in cells, which can lead to inhibition of platelet aggregation, protective effects in endothelial cells, vasodilation in

smooth muscle cells and neuroprotective effects as an antioxidant and antiapoptosis agent [10]. In a rat model of chronic cerebral hypoperfusion, cilostazol improved performance in neurobehavior tests, attenuated neuroinflammation and reduced white matter disintegration [11]. Saito *et al.* supposed that cilostazol exhibits pleiotropic capabilities against dementia by suppressing amyloid-β (Aβ) production in neurons, enhancing Aβ clearance through the perivascular drainage system and inhibiting platelet aggregation [12]. Our previous study found that cilostazol slowed cognitive decline when added to the drug regimen of patients with mild dementia who were already receiving donepezil [13]. Another study using the Taiwan Health Insurance Database, reported that patients using cilostazol had a significantly decreased incidence of all causes of dementia with dose-dependent effect [14]. Therefore, cilostazol is potentially useful for the treatment of VCI and a prospective clinical trial is needed. For these reasons, the current study was developed as a pilot study to examine the effects of cilostazol on VCI beyond stroke prevention.

Methods

Patients

A prospective study was conducted at Kaohsiung Municipal Ta-Tung Hospital and Hsiao-Kang Hospital in southern Taiwan. Patients aged >50 years with a diagnosis of stroke, and reported cognitive impairment after stroke were recruited from the outpatient departments. The diagnosis of stroke was based on a clinical neurological examination together with neuroimaging. The experimental group (Case) in the current study were patients using cilostazol (100 mg twice daily) as an antiplatelet drug for secondary prevention of stroke, while the Control group were patients using aspirin (100 mg daily) or clopidogrel (75 mg daily). Patients who had an active diagnosis of drug or alcohol abuse or dependence, delirium, or were unable to complete the neuropsychiatric assessment and receive regular follow up were excluded. Patients with a clinical diagnosis of AD, those aged >75 years with a medial temporal lobe atrophy (MTA) [15] score of ≥3 and those aged <75 years with an MTA score of ≥2 were excluded from the study. Also, patients with recurrent stroke during the follow up period were excluded.

Evaluation

Demographic data, including age, gender and education were collected as well as the patient's medical history, including hypertension, diabetes mellitus and peripheral arterial occlusive disease (PAOD). Brain magnetic resonance imaging (MRI) was performed at the start of the study. A set of comprehensive neuropsychological assessments, including mini-mental state examination (MMSE), Cognitive Assessment Screening Instrument (CASI) and clinical dementia rating sum of boxes (CDR-SB) were performed at the beginning of the study and at 6 months. These assessments were performed by a senior neuropsychologist and an experienced physician based on information provided by a knowledgeable collateral source (usually a spouse or adult child). Patients with a second MMSE or CASI score equal to or higher than their first MMSE or CASI score (ΔMMSE or CASI score ≥0) were considered as having an

improved cognitive change, whereas those with a lower second score were considered as having a declined cognitive change. Similarly, patients with a second CDR-SB score lower than or equal to their first CDR-SB score (ΔCDR-SB score ≤0) were considered as having an improved global status change, whereas patients with a higher score were considered as having a declined global status change.

The current study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-E(II)20160075) and written informed consent was obtained from all patients or their legal representatives prior to their inclusion within the study.

Statistical analysis

Data was presented as the mean ± standard deviation (SD) or proportion. The chi-squared test was used for categorical data, and the Student's t-test was used for continuous data. Multiple logistic regression models were conducted to calculate the odds ratios (ORs) and 95% confidence intervals for the association between cognitive or global status change and cilostazol use. This model was adjusted for age, sexfand educational level. Analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). A two-tailed P-value <0.05 was considered to indicate a statistically significant difference.

Results

A total of 90 patients who completed the full 6 months follow up were included in the statistical analysis; there were 45 patients in each group (cilostazol and control). The mean age of all participants was 69.8±11.8 years (range 50–94) and 71.9% of the participants were male. The average number of years education the patients had received was 7.8±4.9 (range 0–19). The baseline CASI score was 72.00±21.2; the baseline MMSE was 20.9±6.7; and the baseline CDR-SB was 2.7±3.2. The proportion of patients with PAOD, hypertension and diabetes mellitus were 28.7%, 73% and 39.3%, respectively.

At baseline there were no significant differences in age, gender, education level, proportion of diabetes or hypertension between the cilostazol and control groups (Table 1). However, there were a significantly higher number of patients with PAOD in the cilostazol group. This group also had a higher number of elderly patients and a worse cognitive performance, although these differences were not significant (Table 1).

After 6 months, 67.1% of all patients had an improved CASI score, 69.7% had an improved MMSE score and 72.9% had an improved CDR-SB score. However, no significant differences were observed in the cognitive (MMSE, CASI) and global status (CDR-SB) changes between the cilostazol group and the control group (Table 2). However, age was a significant predictor for cognitive change. The risk of having cognitive decline was 1.05-fold each year (adjusted p=0.048 for ΔMMSE).

Since there are different domains of cognitive performance, factors for CASI subdomain change were further examined by multivariate regression analysis (Table 3). However, this revealed no significant

differences between the cilostazol treated group and the control group. Age was a statistically significant predictor of remote memory, orientation and language domain decline (adjusted p=0.008, 0.002 and 0.004, respectively). Sex was also associated with cognitive subdomain changes. Males had a significantly lower risk of decline in remote memory and abstract domain compared with females (OR=0.06 and 0.21; adjusted p=0.021 and 0.019, respectively). Although no statistically significant differences were observed, the ratio of improvement was higher in the cilostazol group compared with the control group in the subdomains of verbal fluency, language and judgment (Table 4).

Discussion

In the current study, the clinical course of post stroke cognitive changes was described. A total of 67.1% of patients improved their CASI score, 69.7% improved their MMSE score and 72.9% improved their CDR-SB score at 6 months follow up. There was no significant difference in the cognitive and global status change between the cilostazol and control groups. However, the cilostazol group seemed to perform better in the subdomains of fluency, language and judgment. To the best of our knowledge, this is the first study to provide an objective neuropsychological assessment of post stroke cognitive change in Taiwanese patients and to explore the role of cilostazol in cognitive change after ischemic stroke.

In the current study, more than 60% of patients improved their cognitive performance and more than 70% improved their global status after 6 months. In a 2-year follow up study, Oh *et al.* reported an s-shape curve for changes in post-stroke cognitive impairment, which was characterized by a steep decline in the first 3 months, a steep increase between 3 and 6 months, and then a gradual decrease after 6 months [16]. This was comparable to the present study, where cognition also improved at 6 months. A study conducted by Britta *et al.* also demonstrated that cognition improved significantly between 2 and 6 months after stroke [17]. Therefore, even a cognitive decline may develop post stroke, a proportion of patients with cognitive impairment improve in a period in which acute changes have stabilized. However, these results should be interpreted carefully as different psychometrics, as well as the age of participants, comorbidities, stroke severity and cognitive dysfunction prior to stroke, can all affect the results [3, 18].

Although no significant differences in the overall outcome of cognitive change were noted between the cilostazol and control groups after 6 months follow up, cilostazol may be considered as “non-inferior” for post stroke cognitive change due to inherent bias. There was higher rate of PAOD in the cilostazol group; according to the national health insurance guidelines of Taiwan, cilostazol is suggested for the reduction of symptoms of intermittent claudication in individuals with PAOD. Therefore, a higher number of PAOD patients were recruited into the cilostazol group. Low ankle-brachial index or PAOD are associated with worse cognitive function [19]. Nonsignificant poorer cognitive function and older age at baseline were also noted in the cilostazol group. To combat this, a randomized case control study should be conducted in the future.

In the present study, the cilostazol group seemed to perform better in the subdomains of fluency, language and judgment, although there were no significant differences. The authors suppose that

fluency, language function in CASI and judgment are associated with frontal lobe function [20, 21]; white matter changes are also more abundant in the frontal region [22]. Cilostazol could protect against white matter injury [11], which could bring the benefits to patients. In addition, cilostazol has been shown to increase regional cerebral blood flow in the right anterior cingulate lobe [23]. These findings suggest that cilostazol might have a protective effect on these specific cognitive functions.

Age was found to be a predictor of cognitive change, which was in line with prior reports [24]. Compared with males, females had increased decline of remote and abstract thinking function after stroke. According to a review study [25], sex difference does exist in dementia of a vascular origin. Males are at greater risk of developing VaD, but strokes tend to be more severe in females [26]. Risk factors for VaD are more common in males, but they have a more severe impact in females [27]. In addition, female sex is a stronger predictor of pre-stroke dementia, which may be a sign or cause of a primary degenerative pathology [28]. Females are also more likely to experience poststroke depression, which is another risk factor for dementia [29].

The current study had some limitations that should be addressed. First, the number of participants was small. Second, it remains uncertain whether a 6 months study period is sufficient for assessing cognitive changes. Third, the diagnosis of AD or mixed type cognitive impairment cannot be totally excluded, however the MTA score was used to try and avoid this. A high MTA-score is very sensitive for the diagnosis of AD and is present in the vast majority of patients with AD [15]. Patients with a high MTA score were not included in the current study. Another limitation is that the present study did not include data on other potential risks for cognitive impairment (e.g. medicine or lifestyle factors), and no adjustments were made for medical history. However, there is no consistent data for its association with progressive decline [30]. Finally, at present there is no consensus on the definition of “improved” or “declined” cognitive change in VCI, which can make comparison and reporting difficult in longitudinal studies.

Conclusions

The results of the present study indicate that although cilostazol did not make a significant difference in cognitive and global status change after ischemic stroke compared with other antiplatelet drugs, it may improve fluency, language and judgment subdomains. These results highlight the need for large-scale, double-blind, long-term studies to clarify the role of cilostazol on cognitive impairment after ischemic stroke.

Abbreviations

AD: Alzheimer’s disease; VaD: Vascular dementia; VCI: Vascular cognitive impairment; Aβ: Amyloid-β; MTA: Medial temporal lobe atrophy; PAOD: Peripheral arterial occlusive disease; MMSE: Mini-mental state examination; CASI: Cognitive Assessment Screening Instrument; CDR-SB: clinical dementia rating sum of boxes

Declarations

Ethics approval and consent to participate

The current study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-E(II)20160075) and all patients provided written informed consent. The funding sources had no involvement in any stage of the study

Consent for publication

Not applicable

Availability of data and materials

The datasets analyses of the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by grants from Kaohsiung Municipal Ta-Tung Hospital (kmtth-105-022). The funding sources had no involvement in any stage of the study.

Authors' contributions

Y-H Y designed the study. Y-H Y and C-H C performed the experiments. L-C H and S-W H analyzed the data and L-C H wrote the manuscript. All authors read and approved the final manuscript.

Acknowledgements

This study was supported by the clinical psychologists and assistant of the Department of Neurology, Kaohsiung Municipal Ta-Tung Hospital and Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung, Taiwan.

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Tables

Table 1. Demographic characteristics of case and control groups

Characteristic	*Case† (N=45)*	*Control‡ (N=45)*	*P-value*
Gender, female	16 (35.6)	9 (20.0)	0.113
Age (year)	72.1±12.6	67.4±10.5	0.059
Education (year)	7.2±4.4	8.3±5.4	0.296
Hypertension	31 (68.69)	34 (75.6)	0.373
Diabetes mellitus	19 (42.2)	16 (35.6)	0.572
PAOD	23 (51.1)	2 (4.4)	<0.001
Total CASI score	69.6±19.8	74.4±22.6	0.302
MMSE	20.3±6.6	21.5±6.8	0.423
CDR			0.998
CDR=0	11 (24.4)	10 (22.2)	
CDR=0.5	26 (57.8)	27 (60.0)	
CDR=1	5 (11.1)	5 (11.1)	
CDR=2	3 (6.7)	3 (6.7)	
CDR-SB	2.7±3.1	2.6±3.3	0.835

†Patients using cilostazol; ‡Patients using aspirin or clopidogrel.

p value for case vs. control group using Student's t test or Chi-squared test.

Data are shown as the mean ± SD for quantitative variables and n (%) for qualitative variables.

PAOD, Peripheral arterial occlusive disease; CASI, Cognitive Assessment Screening Instrument; MMSE, Mini-Mental Status Examination; CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating Sum of Boxes scale.

Table 2. Factors to cognitive and global status change after 6 months follow up by logistic regression.

Factors	*Age*		*Sex (Male/ Female)*		*Education*		*Cilostazol use*	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
ΔCASI	1.03 (0.98-1.07)	0.268	0.59 (0.19-1.78)	0.347	1.11 (0.99-1.24)	0.065	1.40 (0.52-3.74)	0.502
ΔMMSE	1.05 (1.00-1.10)	**0.048**	0.56 (0.19-1.66)	0.297	0.97 (0.87-1.08)	0.578	0.96 (0.36-2.56)	0.938
ΔCDR-SB	1.04 (0.99-1.09)	0.141	1.45 (0.44-4.73)	0.541	0.96 (0.86-1.07)	0.457	1.11 (0.39-3.14)	0.844

ΔCASI = 2nd CASI – 1st CASI; ΔMMSE = 2nd MMSE – 1st MMSE; ΔCDR-SB = 2nd CDR-SB – 1st CDR-SB

ORs are based on comparing odds of decline (ΔCASI <0, ΔMMSE <0, ΔCDR-SB >0) vs. improve (ΔCASI ≥0, ΔMMSE ≥0, ΔCDR-SB ≤0).

OR, Odds Ratio; CI, Confidence Interval; CASI, Cognitive Assessment Screening Instrument; MMSE, Mini-Mental Status Examination; CDR-SB, Clinical Dementia Rating Sum of Boxes scale.

Table 3. Factors to CASI subdomain change after 6 months follow up by logistic regression.

Factors	*Age*			*Sex (male/ female)*			*Education*			*Cilostazol use*		
	OR (95% CI)		P-value	OR (95% CI)		P-value	OR (95% CI)		P-value	OR (95% CI)		P-value
ΔRemote	1.16	(1.04-1.30)	**0.008**	0.06	(0.01-0.67)	**0.021**	1.21	(0.98-1.49)	0.081	2.09	(0.34-12.78)	0.424
ΔOrientation	1.10	(1.04-1.17)	**0.002**	0.43	(0.12-1.56)	0.199	1.10	(0.98-1.25)	0.118	0.61	(0.19-1.94)	0.404
ΔAttention	1.03	(0.98-1.08)	0.229	0.35	(0.12-1.02)	0.054	0.99	(0.88-1.10)	0.795	0.76	(0.28-2.06)	0.587
ΔConcentration	1.04	(0.99-1.09)	0.139	0.55	(0.18-1.72)	0.306	0.95	(0.85-1.07)	0.401	1.13	(0.39-3.26)	0.824
ΔRecent	1.00	(0.96-1.05)	0.878	1.34	(0.43-4.20)	0.615	1.10	(0.98-1.22)	0.106	2.48	(0.90-6.79)	0.078
ΔFluency	1.01	(0.97-1.06)	0.549	1.59	(0.56-4.55)	0.386	0.94	(0.85-1.04)	0.242	0.79	(0.31-2.01)	0.627
ΔLanguage	1.08	(1.02-1.13)	**0.004**	1.17	(0.40-3.45)	0.777	1.02	(0.92-1.13)	0.720	0.46	(0.17-1.24)	0.123
ΔAbstract	0.98	(0.92-1.03)	0.342	0.21	(0.06-0.77)	**0.019**	1.15	(1.00-1.33)	0.045	1.19	(0.39-3.79)	0.771
ΔJudgement	1.01	(0.97-1.06)	0.640	0.60	(0.19-1.97)	0.403	1.10	(0.98-1.23)	0.119	0.96	(0.34-2.72)	0.943
ΔDrawing	1.03	(0.98-1.08)	0.287	0.66	(0.21-2.07)	0.478	0.96	(0.86-1.08)	0.524	1.07	(0.37-3.08)	0.896

ΔCASI subdomain = 2nd CASI subdomain – 1st CASI subdomain.

ORs are based on comparing odds of decline (ΔCASI subdomain <0) vs. improve (ΔCASI subdomain ≥0).

CASI, Cognitive Assessment Screening Instrument; OR, Odds Ratio; CI, Confidence Interval; Remote, Remote memory; Recent, Recent memory; Fluency, Verbal fluency; Abstract, Abstract thinking.

Table 4. Percentage improvement of the cognitive subdomain in cilostazol and control group.

Improvement	*Case*† (%)	*Control*‡ (%)	P-*value*
Remote memory	83.7	95.2	0.084
Orientation	74.4	76.2	0.850
Attention	67.4	69.0	0.874
Concentration	69.8	78.6	0.354
Recent memory	58.1	73.8	0.128
Fluency	**60.5**	57.1	0.756
Language	**58.1**	50.0	0.451
Abstraction	76.7	78.6	0.840
Judgment	**74.4**	73.8	0.949
Drawing	72.1	78.6	0.489

†Patients using cilostazol; ‡Patients using aspirin or clopidogrel.

ΔCASI subdomain = 2nd CASI subdomain – 1st CASI subdomain.

ΔCASI subdomain ≥0 as Improve; Improve (%) = the ratio of improvement of cognitive subdomain in each group.

P-value is the comparison of the case vs. the control group using Chi-squared test.