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ORIGINAL ARTICLE

경두개 도플러초음파 박동성지수와 대뇌백질 고강도신호 병변과의 관련성

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Relationship Between Transcranial Doppler Pulsatility Index and Cerebral White Matter Hyperintensities

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ABSTRACT

Background: The Effect of Cilostazol in Acute Lacunar Infarction Based on Pulsatility Index of the Transcranial Doppler (ECLIPse) study showed a significant decrease in the transcranial Doppler (TCD) pulsatility index (PI) with cilostazol treatment at 90 days after acute lacunar infarction. The aim of the present study was to perform a subgroup analysis of the ECLIPse study in order to explore the relationship between TCD PI and cerebral white matter hyperintensities (WMH) volume in acute lacunar infarction. **Methods**: For this subgroup analysis, WMH volume was measured for those subjects for whom fluid-attenuated inversion recovery (FLAIR) images were available using semi-automated computerized software. **Results**: Of the 203 patients in eight hospitals in the ECLIPse study, 130 participants from six hospitals were included in this subgroup analysis. The mean WMH volume was 11.57 cm3 (0.13 to 68.45, median 4.86) and the mean MCA PI was 0.95 (0.62 to 1.50). The WMH volume was strongly correlated with age (r=0.388, p<0.001) and mMCA PI (r=0.178, p=0.043). Multiple linear regression analysis revealed that age (p<0.001, β coefficient=0.384) was significantly associated with WMH volume. **Conclusions**: Though multiple linear regression analysis revealed that only age was significantly associated with WMH volume, our findings indicate that TCD PIs are elevated when small vessel disease (SVD) is present. These parameters may be a useful physiologic index of the presence and severity of SVD. Further clinical trials focusing on WMH volume and clinical outcomes are required to assess the TCD as a screening tool for SVD.
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Key Words: Lacunar infarcts, Pulsatility index, White matter hyperintensities

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INTRODUCTION

The Effect of Cilostazol in Acute Lacunar Infarction Based on Pulsatility Index of Transcranial Doppler (ECLIPse) study was a clinical trial that evaluated the differences between the efficacy of cilostazol and a placebo in reducing the pulsatility index (PI) in patients with acute lacunar infarction using serial transcranial Doppler (TCD) examination. The main finding of the ECLIPse study was a significant decrease in TCD PIs with cilostazol treatment from the baseline to 90 days after acute lacunar infarction, as compared to treatment with a placebo.[1]

Previous studies have suggested that white matter hyperintensities (WMH) are closely associated with cerebral arterial pulsatility.[2,3] Elevated TCD PIs correlate well with WMH severity and are an independent predictor of small vessel disease (SVD).[2-6] The middle cerebral artery (MCA) pulsatility was the strongest physiological correlate of WMH, and was independent of age.[2] The aim of the present study was to perform a subgroup analysis of the ECLIPse study in order to explore the relationship between TCD PI and cerebral WMH volume in acute lacunar infarction.

METHODS

The design and results of the ECLIPse study have been published previously.[1] In brief, the study was a multicenter, randomized, double-blind, placebo-controlled study conducted at multiple trial sites in Korea. Patients were eligible for the trial if they had experienced their first lacunar infarction within the preceding seven days and were 45 years of age or older. Lacunar infarction was classified according the Trial of ORG 10172 in the Acute Stroke Treatment (TOAST) classification system, and the criteria were strictly applied.[7] A total of 203 patients were consecutively enrolled from eight tertiary-care hospitals over two years. A baseline TCD was performed within 10 days of symptom onset. The TCD was followed up at 14 and 90 days after starting the study medications. The primary outcome was a change in the PIs for the MCA and basilar artery (BA) at 14 and 90 days from the baseline TCD study. TCD examinations were performed according to the respective standardized manual of operations.[1] Doppler signals from the main stem of MCA were obtained transtemporally with a traditional 2-MHz transducer at depths of 56, 58, and 60 mm. The mean, systolic, and diastolic flow velocities were measured. Gosling and King's PI was determined as the difference between the peak systolic and end-diastolic velocities divided by the mean flow velocity in each artery.[8] If TCD data were not available for both MCAs due to a poor temporal acoustic window on one side, the single value was used for analysis. In this study, 18 patients (13.8%) had a poor temporal acoustic window on one side.

For this subgroup analysis, patients with brain MRI scans performed on a 1.5-T scanner with axial T1-weighed, T2-weighed, and fluid-attenuated inversion recovery (FLAIR) images, were enrolled. WMH volumes were measured when FLAIR images were available using semi-automated computerized software (Xelis, Infinitt, Korea). A single trained neurologist (T.J.S.) blinded to the study measured the WMH volumes. WMH volumes were checked twice, and the mean value was entered for statistical analysis. Intraclass correlation was excellent (0.93; 95% confidence interval, 0.83-0.97).

All patients provided written informed consent. The study protocol was approved by the institutional review boards of each of the participating hospitals.

Statistical analysis

Data are expressed as means (standard deviations) or numbers (percentages). Categorical data were examined by χ^2 analysis. The Mann–Whitney *U* test was used to compare the non-normally distributed data, and Student's *t*-test was used to compare normally distributed data. Pearson's correlation coefficients were calculated to evaluate the correlations between WMH volume and TCD PI. Univariate relationships between continuous variables were assessed by linear regression. Multivariate linear regression models were used to analyze the association of significant univariate variables. Two-sided null hypotheses of no difference were rejected at $p<0.05$. SPSS version 20.0 for Windows was used for statistical analysis.

RESULTS

Of the 203 patients in eight hospitals in the ECLIPse study, 130 participants from six hospitals were entered for this subgroup analysis. Table 1 showed the baseline characteristics of the enrolled patients. Their mean age was 64.7 years and 20.8% were women. Among the enrolled patients, 54.6% had a history of hypertension, 31.5% of diabetes, 13.1% of dyslipidemia, and 33.1% were current smokers. The mean WMH

Table 1. Baseline characteristics of patients by treatment

Variables	Control (n=67)	Cilostazol (n=63)	*p*-value
Age, yr	65.0 (9.99)	64.43 (9.97)	0.732
Female	14 (20.9)	13 (20.6)	0.971
Hypertension	36 (53.7)	35 (55.6)	0.862
Diabetes mellitus	20 (29.9)	21 (33.3)	0.709
Hypercholesterolemia	8 (11.9)	9 (14.3)	0.797
Coronary artery disease	0 (0)	0 (0)	
Smoking within the past month	21 (31.3)	22 (34.9)	0.789
Systolic blood pressure, mmHg	137.2 (16.68)	138.7 (21.79)	0.668
Diastolic blood pressure, mmHg	83.4 (10.73)	84.1 (9.59)	0.692
Fasting glucose, mg/dL	120.9 (37.15)	122.0 (49.03)	0.894
Total cholesterol, mg/dL	184.6 (34.53)	185.5 (32.84)	0.868
LDL-cholesterol, mg/dL	118.6 (29.60)	117.2 (27.35)	0.518
HDL-cholesterol, mg/dL	44.0 (10.27)	42.9 (8.54)	0.774
Triglyceride, mg/dL	148.8 (80.15)	167.8 (105.37)	0.252
WMH volume, cm^3	11.73 (15.69)	11.41 (16.27)	0.912
mMCA PI	0.96 (0.17)	0.95 (0.18)	0.815
PI change from baseline to 14 day	0.08 (0.10)	0.09 (0.11)	0.456
PI change from baseline to 90 day	0.07 (0.11)	0.13 (0.12)	0.020[a]
NIHSS score at randomization, median (range)	2 (0-7)	2 (0-6)	0.583
mRS at randomization, median (range)	1 (0-4)	1 (0-3)	0.363
Time to randomization, day	5.6 (2.7)	5.3 (2.1)	0.499

Data are presented as means (standard deviations) or numbers (%) unless otherwise indicated (i.e., baseline scale score).
LDL; low-density lipoprotein, HDL; high-density lipoprotein, WMH; white matter hyperintensities, mMCA; mean middle cerebral artery, PI; pulsatility index, NIHSS; National Institutes of Health stroke scale, mRS; modified Rankin scale.
[a]Significant *p*.

volume was 11.57 cm^3 (0.13 to 68.45 cm^3, median 4.86) and the mean MCA (mMCA) PI at baseline was 0.95 (0.62 to 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). All baseline characteristics were well balanced across the two groups, and there were no significant differences in these characteristics except in the changes of PI from the baseline to the 90-day point (p=0.02; Table 1).

The WMH volume was strongly correlated with age (r= 0.388, p<0.001) and mMCA PI (r=0.178, p=0.043) (Table 2). While there were no significant correlations between WMH volume and the changes in PIs, a trend of inverse correlation was observed between the WMH volume and the changes in PIs from the baseline to the 90-day point (r=–0.126, p=0.229). Multiple linear regression analysis revealed that age (p<0.001, β coefficient=0.384) was significantly associated with WMH volume. Total WMH volume was categorized into quartiles for subgroup analysis. Univariate comparison between those with and without severe WMH (ie, 4th quartile) showed that age (p<0.001) and mMCA PI (p=0.023) were associated with severe WMH. However, multiple linear regression analysis revealed that only age (p=0.01, β coefficient=0.280) was significantly associated with severe WMH volume.

DISCUSSION

In this study, we explored the relationship between TCD PI and WMH volume. Our study showed that WMH volume was associated with age and TCD PI in patients with acute lacunar infarction. These findings supported the hypothesis that the TCD PI reflects the degree of downstream resistance in the cerebral circulation and that these measures are elevated when WMH is present.[5]

Cerebral SVD is usually used to describe a syndrome of

Table 2. Pearson's Correlation of WMH volume with vascular risk factors

Variables	WMH volume (n=130)	
	r	*p*-value
Age	0.388	<0.001[a]
Systolic blood pressure	0.101	0.252
Diastolic blood pressure	0.002	0.985
Hypertension	0.161	0.067
Diabetes mellitus	0.019	0.828
Hypercholesterolemia	0.051	0.567
Smoking within the past month	0.086	0.332
Fasting glucose	-0.109	0.239
Total cholesterol	0.018	0.842
LDL-cholesterol	0.015	0.869
HDL-cholesterol	0.049	0.582
Triglyceride	-0.034	0.702
mMCA PI at baseline	0.178	0.043[a]
PI change from baseline to 14-day	0.117	0.240
PI change from baseline to 90-day	-0.126	0.229

WMH, white matter hyperintensities; LDL, low-density lipoprotein; HDL, high-density lipoprotein; mMCA, mean middle cerebral artery; PI, pulsatility index.
[a]Significant *p*.

Table 3. Multiple linear regression analysis to predict WMH volume from vascular risk factors

	Unstandardized coefficients		Standardized coefficients	*p*-value
	B	SE	β	
Age	0.614	0.150	0.384	0.002[a]
mMCA PI	0.863	8.740	0.009	0.921

WMH; white matter hyperintensities, SE; standard error, mMCA; mean middle cerebral artery, PI; pulsatility index.
[a]Significant *p*.

clinical, cognitive, neuroimaging, and neuropathological findings thought to arise from diseases affecting the small arteries, arterioles, venules, and capillaries of the brain.[9,10] The main imaging features of SVD include acute lacunar infarcts or hemorrhages, WMH, visible perivascular spaces, cerebral microbleeds (CMB), and brain atrophy.[9,11] Of these, WMH are common in older individuals. These lesions are also known as leukoaraiosis, white matter lesions, leukoencephalopathy, and white matter disease.[12] WMHs are more common and more extensive in patients with acute lacunar infarctions than in patients with other stroke subtypes, and are associated with lacunes, perivascular spaces, CMB, and brain atrophy.[11,13,14] Although it is strongly associated with cerebrovascular disease and vascular risk factors, the pathogenesis of WMH is not well understood and might be multifactorial.[15,16]

The PI is designed to measure vascular resistance. This index becomes elevated with old age, diabetes mellitus, hypertension, intracranial hyper tension, vascular dementia, and SVD.[17] The major factors influencing PI are the flow velocity in the cerebral vessels and blood viscosity. PI is also influenced by physiological factors, such as age, the partial pressures of oxygen and carbon dioxide, and arterial pressure.[18] WMH volume is strongly associated with the TCD PIs of the MCA.[2,3,5] WMH is closely related with cerebral arterial pulsatility, which is strongly dependent on aortic pulsatility and large artery stiffness.[2] Arterial stiffening results in increased aortic pulsatility, and its transmission to the cerebral circulation may play a pathophysiological role in the development of WMH.[2] Age exerts the marked influence on PI. The PI was increasing with age but alterations in PI are the reflection of multifactorial, pleiotropic events occurring in the cardio and cerebral vascular system of elderly individuals.[19] Stiffening of the intracranial vessels and reduced cardiac output may be important factors for increased PI.[20] While multiple linear regression analysis showed that only age was significantly associated with WMH volume in our study, it might be related to advanced age of the subjects (median age 68.2 years) since WMH are common in older individuals.

Our study has limitations. In the ECLIPse study, patients with acute first-ever lacunar infarction and 45 years of age or older were enrolled for the study, limiting the generalizability to other stroke types. The sample size for this subgroup analysis was not decided on the basis of subgroup analysis. So the limitation of our study is mainly related to lower power and generalizability. Also, 19% of patients had no temporal windows. These limitations should be considered when interpreting our data.

In conclusion, this study showed that WMH volume was associated with age and TCD PI in patients with acute lacunar infarction. Though multiple linear regression analysis revealed that only age was significantly associated with WMH volume, our findings indicate that TCD PIs are elevated when small vessel disease (SVD) is present. These parameters may be a useful physiologic index of the presence and severity of SVD.

Further clinical trials focusing on WMH volume and clinical outcomes are required to assess the TCD as a screening tool for SVD.

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