

원 저

## A Preliminary Study on the Inhibitory Effect of *Chunghyul-dan* on Stroke Recurrence in Patients with Small Vessel Disease

Ki-ho Cho, Nam-gue Jee, Woo-sang Jung, Seong-uk Park,  
Sang-kwan Moon, Chang-nam Ko, Young-suk Kim, and Hyung-sup Bae

Department of Cardiovascular & Neurologic Diseases(Stroke Center)  
College of Oriental Medicine, Kyung-Hee University

**Background:** *Chunghyul-dan* is a combinatorial herbal medicine; previous studies reported it had therapeutic effects for microangiopathy, a major part in the progression of small vessel disease, as well as having anti-hypertensive, anti-hyperlipidemic, anti-apoptotic, anti-oxidative, and anti-inflammatory activities. Therefore, we examined the inhibitory effect of *Chunghyul-dan* on stroke recurrence in patients with small vessel disease.

**Methods:** We prescribed *Chunghyul-dan* at 600 mg a day to patients with small vessel disease, and monitored stroke recurrence, drug compliances, and adverse effect for 1 year. We then performed follow-up brain MRI to find new vascular lesions after 1 year of *Chunghyul-dan* medication. For the subjects lost to follow-up, we assessed their prognosis after 1 year by telephone.

**Results:** There were 73 subjects treated with *Chunghyul-dan* for 1 year; new vascular events were found in 3. Of the 85 subjects lost to follow-up, fifty four could be contacted, and eight of them had stroke recurrence. One year of *Chunghyul-dan* medication reduced the odds ratio of stroke recurrence by 75% compared to the subjects lost to follow-up and the rate increased to 88%, when adjusted for other relevant risk factors for stroke occurrence. These reductions were much higher than those of aspirin and other kinds of conventional anti-platelets. There was no adverse effect in any of the study subjects.

**Conclusions:** We suggest *Chunghyul-dan* could be useful for inhibition of stroke recurrence. Further study with a randomized controlled trial is needed to confirm this suggestion.

**Key Words:** Stroke recurrence, small vessel disease, *Chunghyul-dan*

### Introduction

For thousands of years, herbs have been used to treat and prevent stroke in Asia. In spite of their actual effectiveness, much of them have not yet been fully understood or appreciated by western biomedicine. However, considering that their mechanism and applications have appeared with increasing frequency in literature of basic and clinical science, we believe that some kinds of herbal formulas have inhibitory effects on stroke occurrence. *Chunghyul-dan* is one of them. It is a combinatorial drug consisting of *Scutellariae Radix*, *Coptidis Rhizoma*, *Phellodendri Cortex*,

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· 교신저자 : Woo-sang Jung, Oriental Medical Doctor, Ph.D.  
Assistant professor, Department of Cardiovascular and Neurologic Diseases (Stroke Center), Hospital of Oriental Medicine, Kyung Hee Medical Center, 1 Hoegi-dong, Dongdaemun-gu, Seoul, South Korea  
(Tel : 02-958-9289, Fax : 02-958-9132,  
E-mail : WSJung@khu.ac.kr)

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*Gardeniae Fructus*, and *Rhei Rhizoma*. Previous studies revealed that *Chunghyul-dan* inhibited HMG-CoA reductase<sup>1)</sup>, and had anti-apoptotic<sup>2)</sup>, anti-oxidative<sup>1)</sup>, anti-inflammatory<sup>3)</sup>, and anti-hypertensive activity<sup>4)</sup>. These effects might be helpful for reducing the risk of microangiopathy, which is believed to be a major factor in the progress of small vessel disease, which essentially refers to blockage of very small vessels in the brain. Therefore, we intended to examine the possibility of *Chunghyul-dan* as a preventive medicine for small vessel disease.

## Methods

### 1. Subjects

The study population was composed of 158 subjects with small vessel disease, who had been treated with *Chunghyul-dan* from March 1, 2002 to July 1, 2003 in our department at Kyung Hee Medical Center. The diagnosis of small vessel disease was made from the Classification of Cerebrovascular Diseases III<sup>5)</sup> (see Appendix 1). Diagnosis of hypertension, diabetes mellitus, and hyperlipidemia was assigned for subjects already receiving treatment or when the World Health Organization diagnostic criteria were fulfilled at

the time of enrollment. Relevant information on past medical history and smoking habits was obtained from all subjects. Informed consensus was obtained from the study subjects after a full explanation of this study.

### 2. Materials

*Chunghyul-dan* is a capsulated 80% ethanol extract(300 mg per one capsule) of *Scutellariae Radix*, *Coptidis Rhizoma*, *Phellodendri Cortex*, *Gardeniae Fructus*, and *Rhei Rhizoma*(Table 1). Each herbal medicine was extracted with 80% ethanol in boiling water for 2 hours. These extracts were filtered and evaporated in a rotary vacuum evaporator and then finally lyophilized with a freezing dryer. To standardize the quality of *Chunghyul-dan*, berberine in *Coptidis Rhizoma* and *Phellodendri Cortex*, baicalin in *Scutellariae Radix*, geniposide in *Gardeniae Fructus*, and sennoside A in *Rhei Rhizoma* were quantitatively assayed according to the previous methods<sup>6)</sup>.

### 3. Procedures

We prescribed 600 mg(2 capsules) *Chunghyul-dan* a day to patients with small vessel disease, and monitored their drug compliance, adverse effect, and stroke recurrence every two months. Stroke

Table 1. Composition of *Chunghyul-dan*

Constitute herbs	Scientific name	Weight (g)
<i>Scutellariae Radix</i>	<i>Scutellaria baicalensis</i> GEORGI from Korea	0.28
<i>Coptidis Rhizoma</i>	<i>Coptis japonica</i> MAKINO from Korea	0.28
<i>Phellodendri Cortex</i>	<i>Phellodendron Amurense</i> RUPRECHT from Korea	0.28
<i>Gardeniae Fructus</i>	<i>Gardenia jasminoides</i> ELLIS from Korea	0.28
<i>Rhei Rhizoma</i>	<i>Rheum palmatum</i> L. from Korea	0.07
Total		1.2

1 capsule(300 mg) of *Chunghyul-dan* was extracted from the above 1.2g of raw materials.

recurrence was defined when new clinical syndrome characterized by rapidly developing clinical symptoms and signs of focal and at times global loss of brain function was accompanied with evidence of new cerebral infarction in the clinically relevant area of the brain from a brain imaging study. After 1 year of *Chunghyul-dan* medication, we performed follow-up brain MRI to find new lesions, comparing it with the image taken 1 year before. We tried to contact the subjects lost to follow-up by telephone to assess their prognosis after 1 year. Information was obtained from the subject him(her)self or his(her) family.

### 3. Statistical analysis

To estimate the magnitude of the association between stroke recurrence and *Chunghyul-dan* medication, we used odds ratio(OR) and 95% confidence intervals(CI). For the crude analysis of baseline characteristics, we used independent t-test for age, and chi-square test for categorical variables. For the multivariate analysis, we used

logistic regression to adjust for possible confounders - i.e., age, sex, anti-platelets medication, current smoking, prior stroke, hypertension, diabetes mellitus, and hyperlipidemia. Also, logistic regression models were used to estimate the OR of *Chunghyul-dan* medication for stroke recurrence. The analysis was performed using SPSS for Windows, version 10.0(SPSS Inc., Chicago, Illinois, USA).

## Results

There were 73 subjects treated with *Chunghyul-dan* for 1 year with follow-up brain MRI performed. Seventy(95.9%) of them had no stroke recurrence(Table 2 and Fig 1 to 6), but three subjects(4.1%) had new vascular lesion in the brain(Fig 7). One 73-year-old male felt right side weakness after 3 months of *Chunghyul-dan* medication, but he ignored it because the symptom was mild and disappeared in a few days. He did not report it until the follow-up brain MRI

Table 2. Subjects' Demographic Data

	One year of <i>Chunghyul-dan</i> medication	Lost to follow-up	P*
No. of subjects	73	54	
Sex (male : female)	36 : 37	27 : 27	> 0.05
Age, yr	63.9 ± 8.9	63.8 ± 9.0	> 0.05
Medical history(%)			
Prior stroke	9 (12.3)	9 (16.7)	> 0.05
Hypertension	51 (69.9)	33 (61.1)	> 0.05
Diabetes mellitus	23 (31.5)	6 (11.1)	0.007
Hyperlipidemia	10 (13.7)	9 (16.7)	> 0.05
Current smoker(%)	23 (31.5)	22 (40.7)	> 0.05
Medication periods, m	18.3 ± 6.5	3.1 ± 2.6	
Anti-platelets medication	15 (20.5)	22 (40.7)	0.013
No. of stroke recurrence(%)	3 (4.1)	8 (14.8)	0.034

\* : P-values were calculated by independent t-test for age, and Chi-square test for categorical variables.

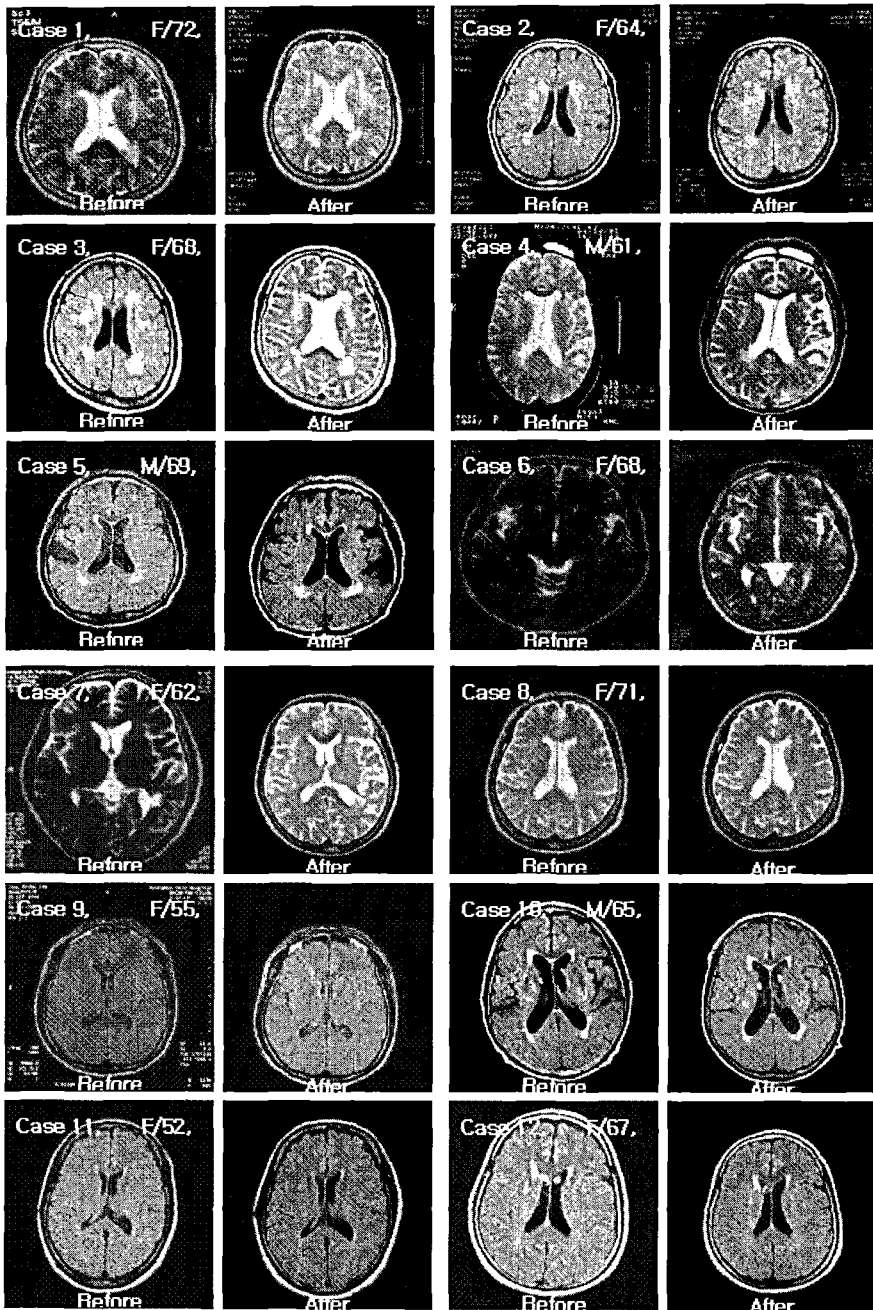


Fig. 1. Brain MRI before and after 1 year of *Chunghyul-dan* medication in Cases 1 to 12

revealed a new lesion at the right parietal lobe. A 69-year-old female had no newly developed

neurologic deficits, but a new ischemic infarction at the left occipitoparietal lobe was found in the

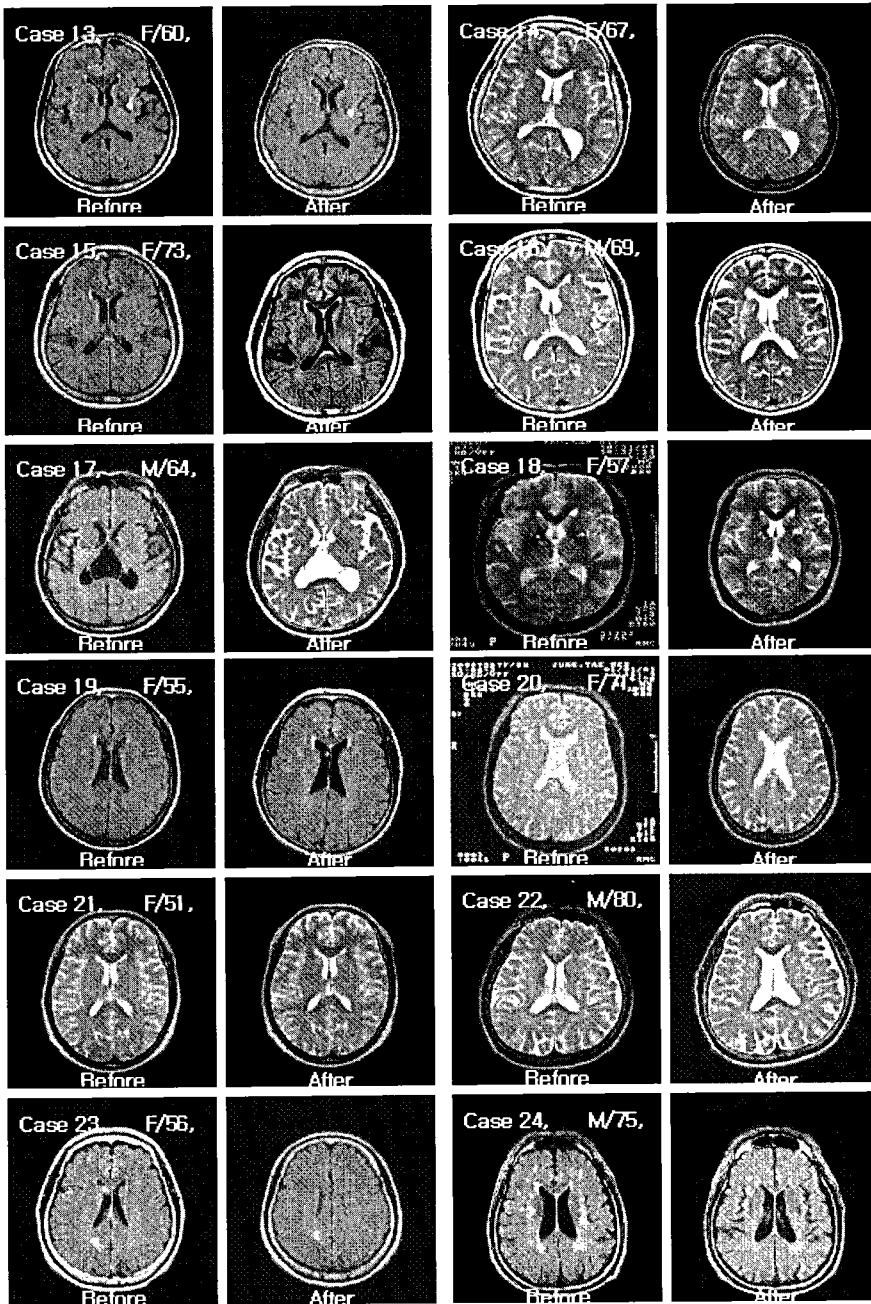


Fig. 2. Brain MRI before and after 1 year of *Chunghyul-dan* medication in Cases 13 to 24

follow-up brain MRI. A 71-year-old male was in an advanced stage of left side weakness after 353

days of *Chunghyul-dan* medication, and follow-up brain MRI showed there was acute to subacute

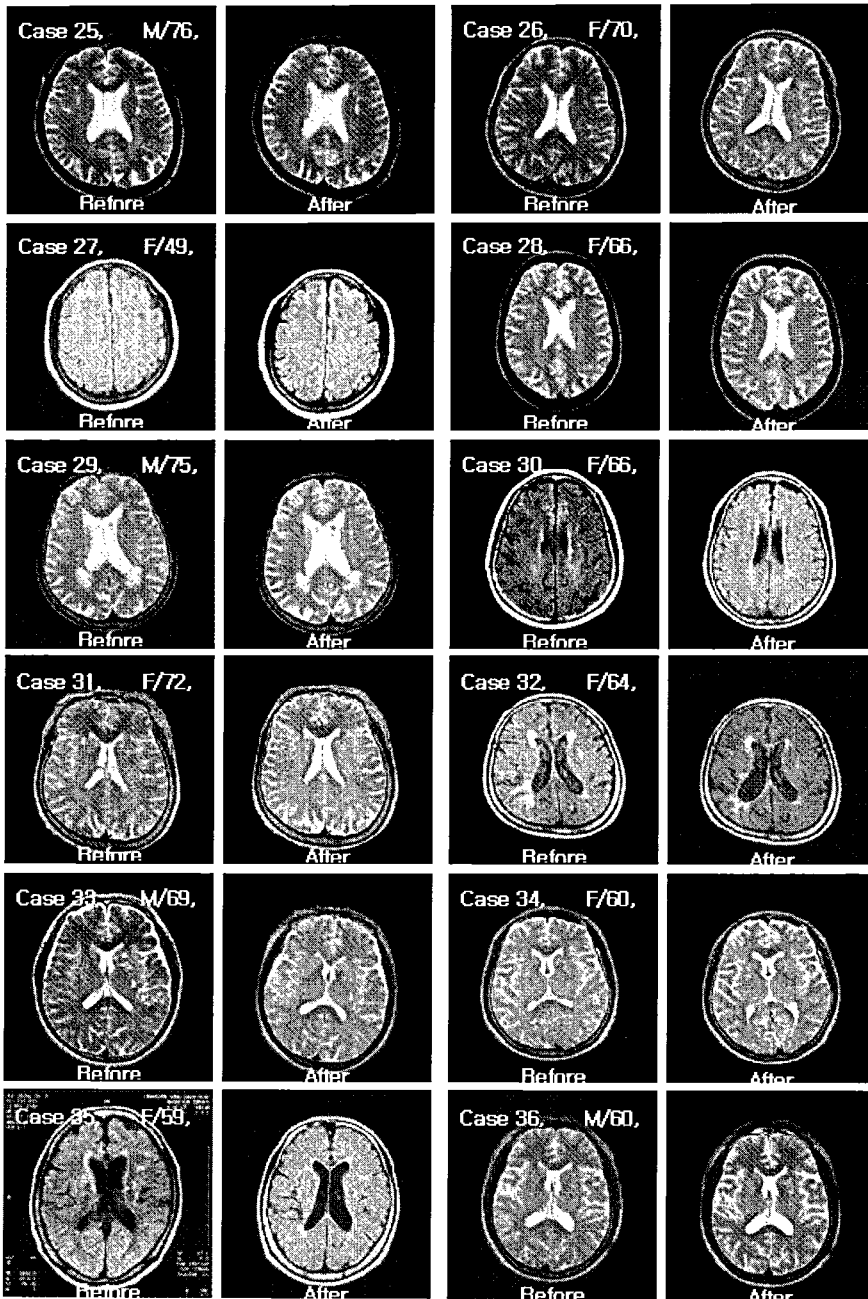


Fig. 3. Brain MRI before and after 1 year of *Chunghyul-dan* medication in Cases 25 to 36

focal infarction at right basal ganglia with diffusion abnormality(Fig. 7).

There were 85 subjects lost to follow-up before 1 year of *Chunghyul-dan* medication. Of them,

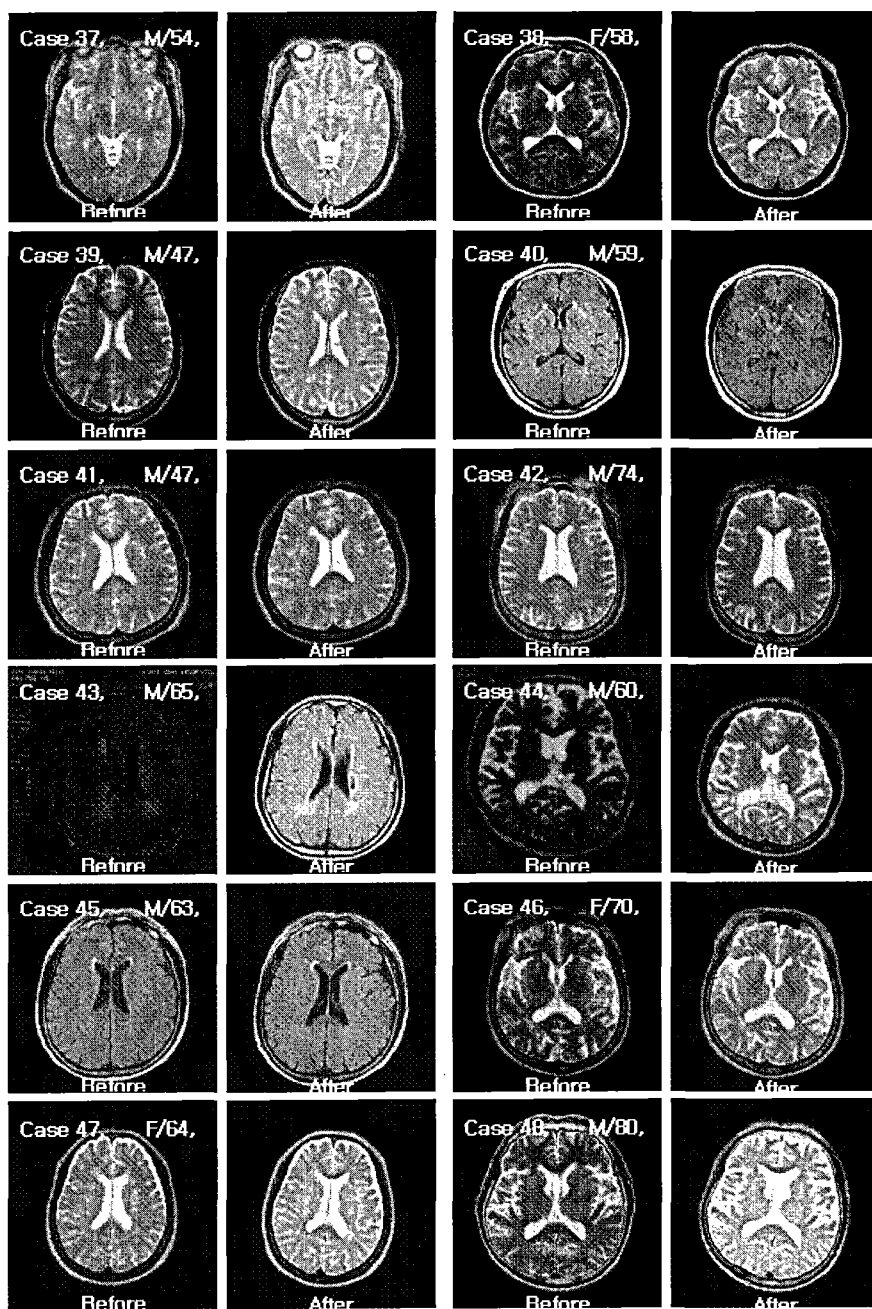


Fig. 4. Brain MRI before and after 1 year of *Chunghyul-dan* medication in Cases 37 to 48

we included 54 in the final analysis, because we could not get in contact with the remaining 31.

The demographic data are shown in Table 2.

As noted, no adverse effect was reported in

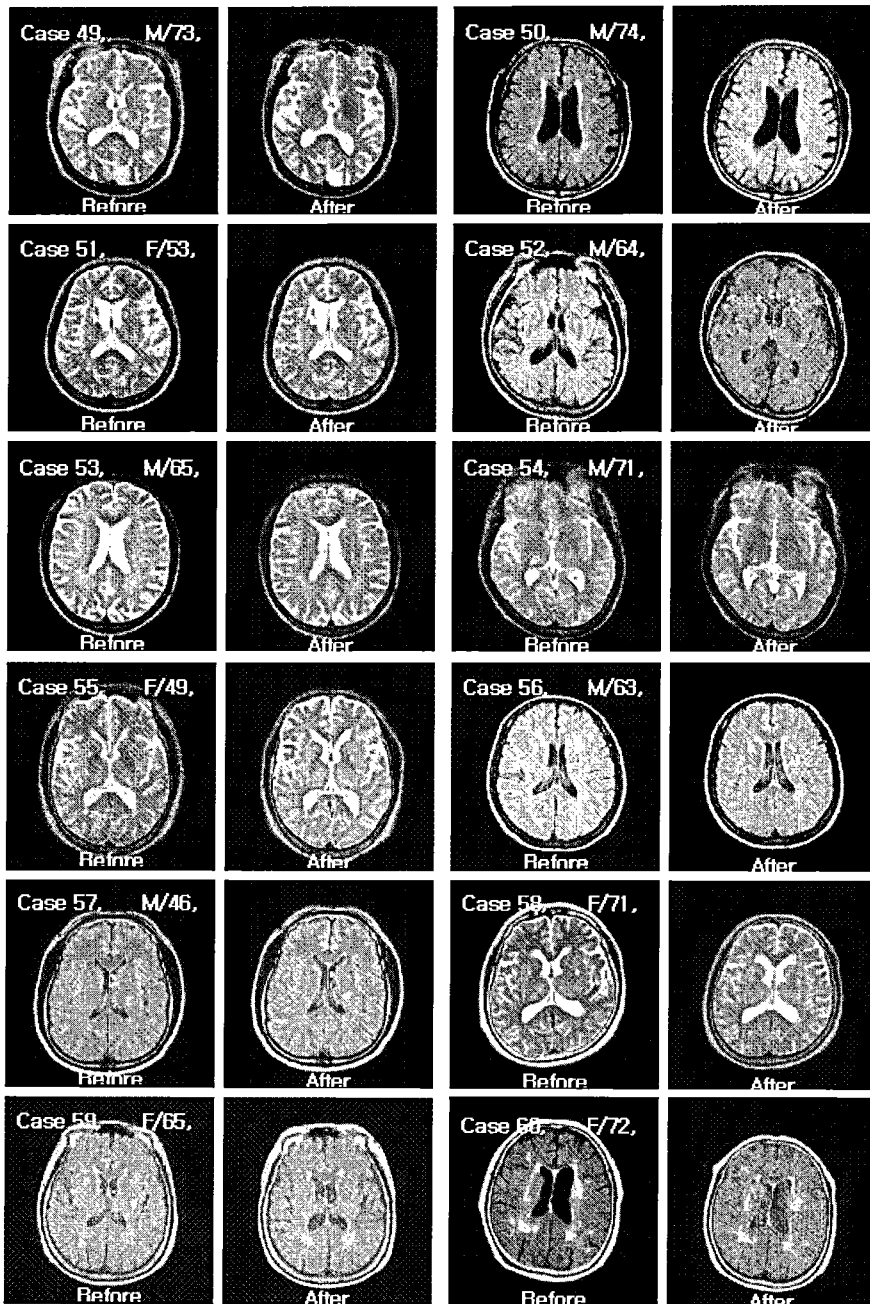


Fig. 5. Brain MRI before and after 1 year of *Chunghyul-dan* medication in Cases 49 to 60

those lost to follow-up. Eight subjects had stroke recurrence, which had been confirmed by medical

examination including brain imaging study at other hospitals. One of them expired due to fatal



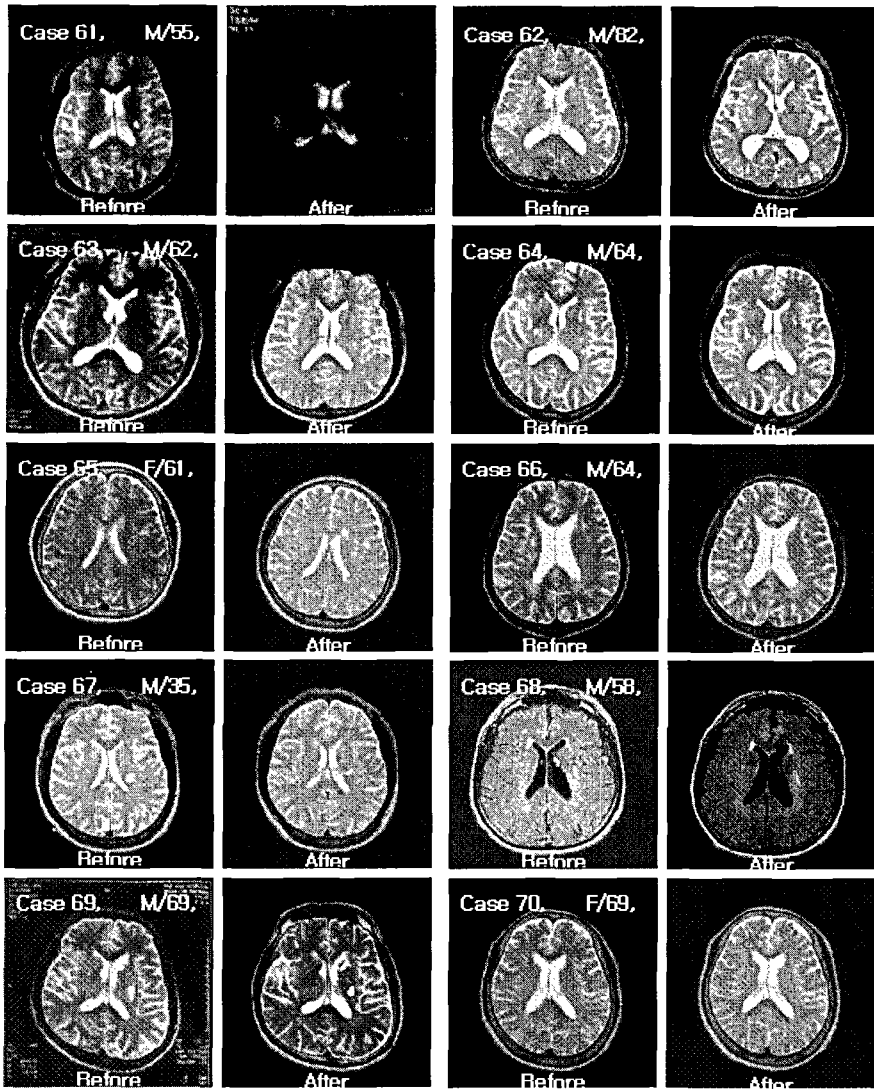


Fig. 6. Brain MRI before and after 1 year of *Chunghyul-dan* medication in Cases 61 to 70. The above figures(Fig. 1 to Fig 6) show no new vascular lesions after 1 year of *Chunghyul-dan* medication compared to the old images.

re-attack of stroke(Table 3).

Table 4 showed that the OR of *Chunghyul-dan* medication for stroke recurrence was 0.25 times that of the lost to follow-up, and decreased to 0.12 when adjusted for other relevant risk factors for stroke occurrence.

### Discussion

In this study, although the *Chunghyul-dan*-treated subjects had more diabetes mellitus( $p=0.007$ ) and less anti-platelets medication( $p=0.013$ ), their rate of stroke recurrence was lower than that of the subjects lost to follow-up(4.1% vs. 14.8%,

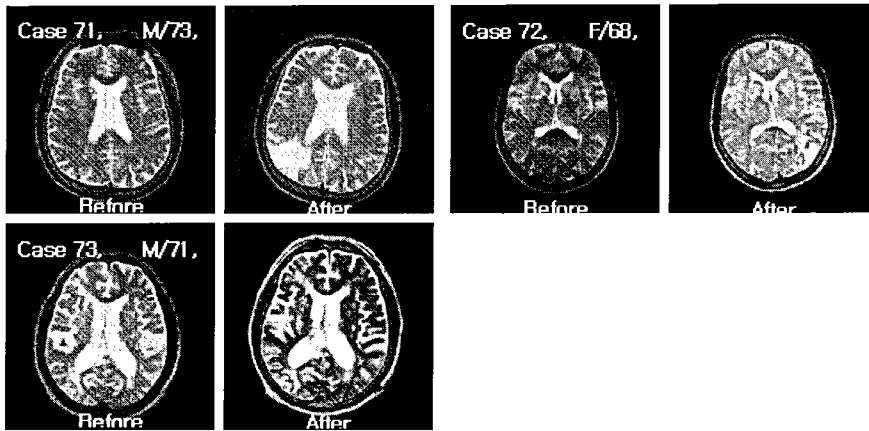


Fig. 7. Brain MRI before and after 1 year of *Chunghyul-dan* medication in Cases 71 to 73. New vascular events were found in these three cases: Case 71 had a new lesion at the right parietal lobe; Case 72 had a new ischemic infarction at the left occipitoparietal lobe; and Case 73 had acute to subacute focal infarction at the right basal ganglia.

$p=0.034$  in Table 2). Furthermore, it was lower than 12~13%, the risk of stroke recurrence at 1 year<sup>7-9)</sup>.

Anti-platelet agents are widely used for secondary prevention of vascular events in patients with ischemic stroke or TIA, but there is a high

Table 3. Results of the Questionnaire on the Subjects Lost to Follow-up

	No. of cases (%)
Over the past year, why did you stop <i>Chunghyul-dan</i> medication?	
Because of its adverse effect.	0
Because it was more expensive than aspirin.	5 (9.3)
Because my home is too far from your hospital.	20 (37.0)
Because I was introduced to other clinics by my friends or family.	7 (13.0)
I had no special reason.	22 (40.7)
Which treatment did you take after stopping <i>Chunghyul-dan</i> medication?	
Anti-platelets	22 (40.7)
Herbal medicine (intermittently)	2 (3.7)
None	30 (55.6)
Did you have stroke recurrence confirmed by a medical examination in other hospitals?	
Yes	8* (14.8)
No	46 (85.2)

\* : One of them had expired due to fatal stroke recurrence, so the answer was obtained from his family.

Table 4. Relative Risk for Stroke Recurrence

	Lost to follow-up	One year of <i>Chunghyul-dan</i> medication
Crude OR (95% CI)	1.00	0.25 (0.06 to 0.98)
Model 1	1.00	0.22 (0.05 to 0.92)
Model 2	1.00	0.19 (0.04 to 0.79)
Model 3	1.00	0.12 (0.02 to 0.74)

Model 1 was the adjusted OR (95% CI) for age + sex; model 2, for age + sex + anti-platelets medication; and model 3, for age + sex + anti-platelets medication + current smoking + prior stroke + hypertension + diabetes mellitus + hyperlipidemia. All  $p < 0.05$ :  $p$ -values derived from multiple logistic regressions.

incidence of side effects including hemorrhagic tendency, headache, gastrointestinal disturbance, neutropenia, purpura, etc<sup>10</sup>). Previous studies reported that the inhibitory rate of aspirin on stroke recurrence was 15% to 20%<sup>11-15</sup>), dipyridamole 15% to 40%<sup>13,16</sup>), and ticlopidine 20% to 25%<sup>17,18</sup>). We calculated the inhibitory rate of *Chunghyul-dan* on stroke recurrence by using multiple logistic regressions. One year of *Chunghyul-dan* medication reduced the odds ratio of stroke recurrence by 75% compared to the subjects lost to follow-up, of whom, 40.7% were taking anti-platelet agents. The inhibitory rate increased to 88%, when adjusted for other relevant risk factors for stroke occurrence. These reductions were much higher than that of aspirin and other kinds of conventional anti-platelets.

These results might be explained by various biochemical effects of *Chunghyul-dan* on micro-angiopathy, which is closely related with cell cycle progression, hypertension, hyperlipidemia, vascular inflammation, and oxidative damage. A previous study showed therapeutic effects of *Chunghyul-dan* on rats with hypercholesterolemia induced by high cholesterol diet, or Triton WR-1339<sup>19</sup>). A further in vitro study suggested the underlying mechanisms by showing that *Chunghyul-dan* inhibits HMG-CoA reductase and pancreatic lipase<sup>1</sup>). The other in vitro and in vivo study reported that *Chunghyul-dan* was exhibited to work as an anti-apoptotic agent, a cell cycle progressive agent and a cell-migration inducing agent<sup>2</sup>). Also, *Chunghyul-dan* showed anti-oxidative activity by scavenging free radicals<sup>1</sup>), and anti-inflammatory activity<sup>3</sup>). Some clinical studies showed its anti-hypertensive effect on stage I hypertensive patients with stroke by using 24

hour ambulatory blood pressure monitor<sup>4</sup>), and serum lipid lowering-effect after 4 weeks of medication<sup>20</sup>).

As noted, no adverse effect required the subjects to stop *Chunghyul-dan* medication. These findings are in accordance with the previous study, which assessed the clinical safety of *Chunghyul-dan* based on 656 subjects<sup>21</sup>).

We confess that we can hardly draw a concrete conclusion from this study, because it is not a randomized controlled trial. However, considering that the inhibitory rate of *Chunghyul-dan* on stroke recurrence was much higher than that of the conventional agents, we suggest *Chunghyul-dan* may be useful for inhibition of stroke recurrence.

## Appendix

Criteria for Small Vessel Disease(either condition a, b, or c is true).

Condition a : Brain images show a deep infarction (1.5cm) in its maximal diameter that is appropriate to a clinical classical lacunar syndrome.

Condition b : Brain images show no lesion to explain the clinical syndrome, and the clinical presentation is one(including the following) classically associated with a small deep infarct. *Pur-motor hemiplegia* : Hemiparesis or hemiplegia involving the face, arm, and leg equally or arm and leg equally, without other neurological findings. Although mild sensory symptoms can be present, there is no sensory loss on examination that is related to the infarct. *Pure sensory stroke* : Isolated sensory loss or disturbance involving the entire hemiface and hemibody or the hemibody alone. There may be incidental motor weakness from

another cause. *Ataxia-hemiparesis*: Hemiparesis with ipsilateral ataxia. Paresis more commonly crural. *Dysarthria-clumsy hand syndrome*: Dysarthria with a clumsy hand. Facial weakness is possible. *Hemiballismus, hemiathetosis, or hemidystonia*: Must be of acute onset. *Sensorimotor stroke*: Weakness and sensory loss involving face, arm, and leg equally, without other neurological findings.

Condition c: CT scan shows a deep infarct (<1.5cm) in its maximal diameter that is appropriate to the clinical syndrome, but the syndrome is not one of the classical syndromes for lacunar stroke.

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