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Inhibitory Effect of *Chunghyul-dan* on Stroke Recurrence in Small Vessel Disease Patients: A 5-Year Observational Study

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Abstract

We investigated the stroke recurrence rate and the rate of adverse effects induced by an herbal medicine, *Chunghyul-dan*, administered to patients over a 5-year period. We prescribed 600 mg *Chunghyul-dan* a day to patients with small vessel diseases and investigated stroke recurrence, adverse effects, and drug compliance for 5 years. The primary outcome was the prevalence of stroke recurrence (in 3, 4, and 5 years). The secondary outcome was the frequency of adverse effects induced by *Chunghyul-dan*. We recruited 400 patients. Among them, 270, 233, and 195 patients completed 3, 4, and 5 years of follow-up, respectively. Among patients who completed 3, 4, and 5 years of follow-up, cumulative recurrent stroke occurred in 7 (2.6%), 11 (4.7%), and 12 (6.2%) patients. There were no adverse effects. We suggest that *Chunghyul-dan* might be useful for the inhibition of stroke recurrence by reducing microangiography progression. Further study is needed to confirm our hypothesis.

Keywords

Chunghyul-dan, ischemic stroke, small vessel disease, secondary prevention, herbal medicine

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To prevent stroke recurrence, antiplatelet agents have been used worldwide as conventional therapy. However, adverse effects including an increase in hemorrhagic tendency, gastrointestinal disturbance, neutropenia, and purpura are associated with the use of antiplatelet agents.[1] Furthermore, the inhibitory effect of antiplatelet agents is not sufficient (8% to 13%).[2-8] Therefore, we need another strategy for secondary stroke prevention.

Chunghyul-dan is an herbal complex consisting of *Scutellariae Radix*, *Coptidis Rhizoma*, *Phellodendri Cortex*, *Gardeniae Fructus*, and *Rhei Rhizoma*. *Chunghyul-dan* can inhibit 3-hydroxy-3-methylglutaryl (HMG) coenzyme A (CoA) reductase.[9] It also has anti-apoptotic,[10] anti-oxidative,[11] anti-inflammatory,[11] antihypertensive,[12] and antilipidemic effects.[13] We believe that these biochemical effects of *Chunghyul-dan* reduce the progress of microangiopathy, which is a supposedly major factor in the progression of small vessel disease. Therefore, we propose that *Chunghyul-dan* has an inhibitory effect on stroke occurrence induced by small vessel disease. Two previous clinical studies led to the confirmation that the administration of *Chunghyul-dan* for 1 or 2 years inhibits the recurrence of a secondary stroke in silent cerebral infarction patients or small vessel diseases of the brain.[14,15] To expand these results, we investigated the stroke recurrence rate and the rate of adverse effects induced by *Chunghyul-dan*, which was administered to patients over a 5-year period.

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Table 1. Composition of *Chunghyul-dan*.

Constituent Herbs	Binomial Name	Weight (g)
Scutellariae Radix	*Scutellaria baicalensis* Georgi (from Korea)	0.28
Coptidis Rhizoma	*Coptis japonica* Makino (from Korea)	0.28
Phellodendri Cortex	*Phellodendron amurense* Ruprecht (from Korea)	0.28
Gardenia Fructus	*Gardenia jasminodes* Ellis (from Korea)	0.28
Rhei Rhizoma	*Rheum palmatum* L. (from Korea)	0.07
Total		1.2

Methods

We recruited study participants with small vessel diseases from January 1, 2001, to December 31, 2009, in the Stroke Center of Kyung Hee University Korean Medicine Hospital, Seoul, Korea. Small vessel disease was diagnosed using the Classification of Cerebrovascular Disease III[16] (see the appendix). In addition, cases with potential cardioembolic sources or significant proximal arterial stenosis in brain imaging were excluded.

Chunghyul-dan is a capsulated 80% ethanol extract (300 mg per capsule) composed of *Scutellariae Radix*, *Coptidis Rhizoma*, *Phellodendri Cortex*, *Gardeniae Fructus*, and *Rhei Rhizoma* (Table 1). Extraction of each herb was performed with 80% ethanol in boiling water for 2 hours. The extracts were filtered and evaporated in a rotary vacuum evaporator and 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 previous methods.[17]

The study protocol was as follows (Figure 1). We used an observational cohort study design. Details of concomitant diseases such as previous stroke, hypertension, diabetes mellitus, dyslipidemia, and smoking habits were obtained from all patients at the time of enrollment. The diagnoses of hypertension, diabetes mellitus, and dyslipidemia were assigned to patients already receiving medication or when the World Health Organization diagnostic criteria were fulfilled. Every participant confirmed eligible.

We prescribed 600 mg (2 capsules) per day of *Chunghyul-dan* to the patients and monitored their drug compliance, adverse effects, and stroke recurrence every 2 months for a period of 5 years. Data collection was conducted by a single independent researcher every 2 to 3 months, and the following outcomes were evaluated based on these data.

The primary outcome of this study was the prevalence of ischemic stroke recurrence during the follow-up period (36 months, 48 months, and 60 months after consecutive administration of *Chunghyul-dan*). The secondary outcome was the frequency of adverse effects due to the administration of *Chunghyul-dan*. Stroke recurrence was defined as the occurrence of a new clinical syndrome—characterized by rapidly developing clinical symptoms and signs of focal and at times global loss of brain function—accompanied by evidence (from a brain imaging) of new cerebral infarction in the clinically relevant area of the brain. If there is the detection of a new lesion of the brain through brain magnetic resonance imaging without neurological symptoms in medical checkup, we also defined it as asymptomatic ischemic stroke recurrence. When a patient completed 5 years of *Chunghyul-dan* administration and showed lesions with magnetic resonance imaging scan, we performed follow-up brain magnetic resonance imaging to confirm the presence of new lesions by comparing it to the baseline image, which was taken 5 years ago.

Results

We recruited 400 patients with small vessel diseases of the brain. Among them, 270, 233, and 195 patients completed 3, 4, and 5 years of follow-up, respectively. *Chunghyul-dan* was administered for 35.5 $\pm$ 3.2 months (average $\pm$ standard deviation) in 270 subjects who completed 3 years of follow-up. Two hundred thirty-three patients who completed 4 years of follow-up took *Chunghyul-dan* for 47.0 $\pm$ 5.4 months. Furthermore, *Chunghyul-dan* was administered for 58.1 $\pm$ 8.3 months in patients (195 patients) who completed 5 years of follow-up. The other 205 patients did not complete the 5-year follow-up period. We tried to contact them by telephone to assess their prognosis and to investigate the causes of drop out. Information was obtained about 63 patients. Specific causes of drop out are shown in Figure 1.

Among the 270 patients who completed the 3-year follow-up, recurrent stroke occurred in 7 patients. The recurrent rate was estimated as 2.6%. From 3 to 4 years of follow-up, recurrent stroke occurred in 4 of 233 patients. The cumulative recurrent rate of 4 years of follow-up was estimated as 4.7%. After 5 years of follow-up, 12 of 195 patients revealed recurrent stroke. Therefore, the cumulative recurrent rate of 5 years was estimated as 6.2%. The survival curve of survival probability without recurrence is shown in Figure 2.

There were no adverse effects induced by *Chunghyul-dan* administration. Among the patients, 63.3% to 69.2% were coadministered antiplatelet medications such as aspirin or clopidogrel (Table 2). The specific time information on the 12 patients who revealed stroke recurrence is outlined in Figure 1.

Discussion

In the present study, we demonstrated that the 5-year stroke recurrence rate of *Chunghyul-dan*-treated patients (*Chunghyul-dan* mono or *Chunghyul-dan* combined therapy) was 6.2%. There were no adverse effects induced by *Chunghyul-dan* intake.

Although there is no control in this study, to show the superiority of *Chunghyul-dan* over conventional antiplatelet agents, we suggest historical controls, which used antiplatelet agents for the secondary prevention of stroke (Table 3).[2-8] Considering that previous studies reported that the inhibitory rate of aspirin, clopidogrel, dipyridamole, and dual antiplatelet therapies on stroke recurrence was 8.0% to 12.8% during a relatively short period (18-72 months), the recurrence rate of stroke in this study is much lower (6.2%). Although we think that we cannot directly compare the recurrence rate of our study with these studies, we believe that these results indirectly show the superiority of *Chunghyul-dan* on secondary stroke prevention

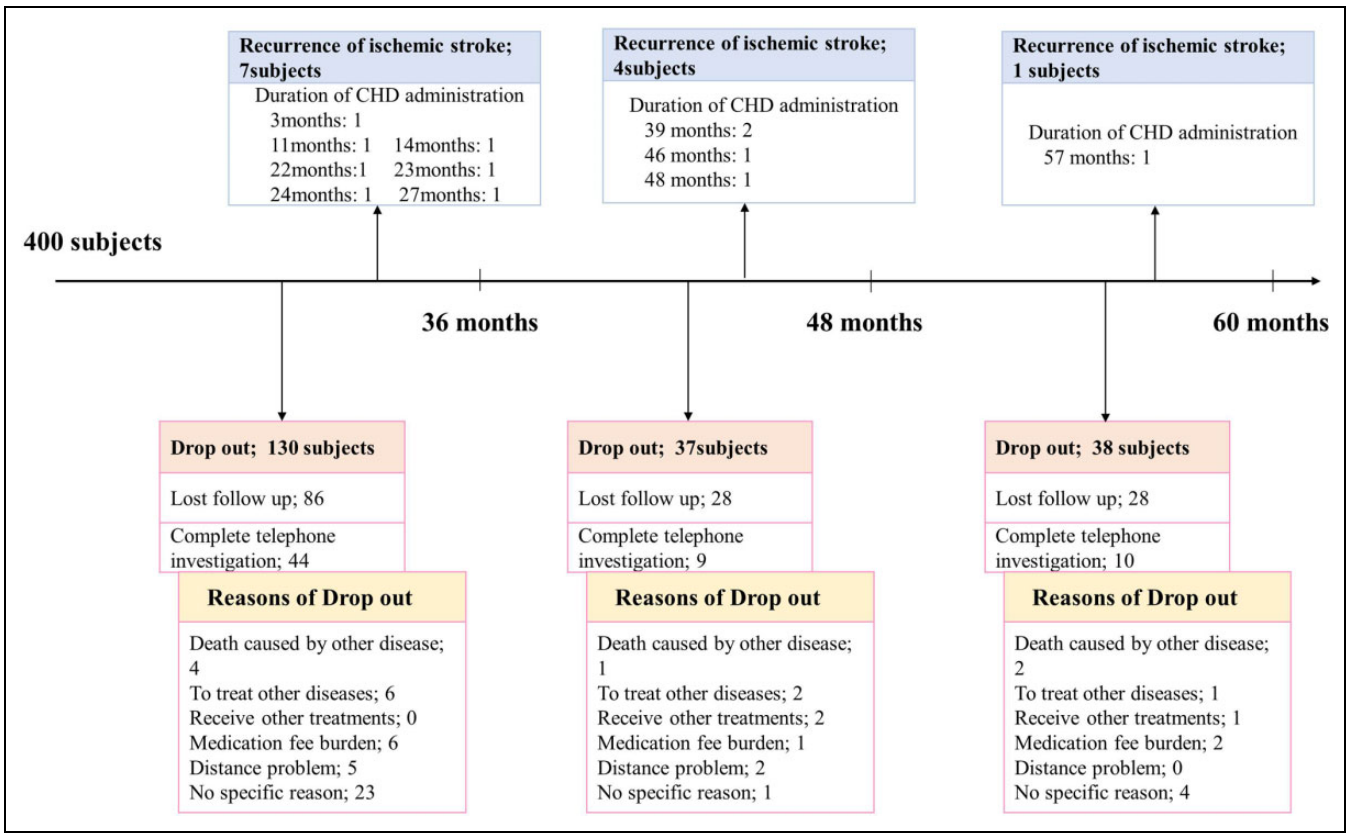

Figure 1. Flow chart.

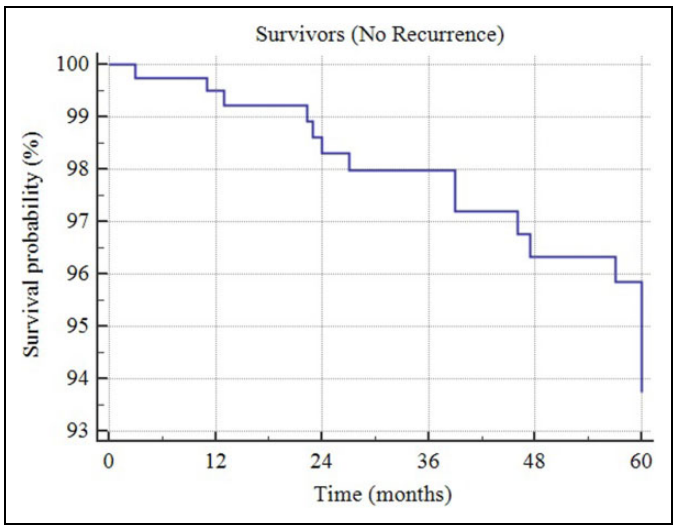

Figure 2. Survival curve of survival probability without ischemic stroke recurrence.

Table 2. Patients' Demographic Data and 5-Year Follow-up Results.

	3-Year Follow-up	4-Year Follow-up	5-Year Follow-up
Number of patients	270	233	195
Gender (male–female)	137:133	119:114	97:98
Age (years), mean (SD)	66.7 (8.5)	66.9 (8.3)	67.1 (8.5)
Concomitant diseases, n (%)			
Previous stroke	101 (37.4)	97 (41.6)	90 (46.2)
Hypertension	191 (70.7)	172 (73.8)	147 (75.4)
Diabetes mellitus	82 (30.4)	71 (30.5)	62 (31.8)
Dyslipidemia	79 (29.3)	79 (33.9)	71 (36.4)
Current smoker, n, (%)	24 (8.9)	21 (9.0)	15 (7.7)
Family history of stroke, n, (%)	82 (30.4)	71 (30.5)	67 (34.4)
Use of combined antiplatelet therapy, n, (%)	171 (63.3)	152 (65.2)	135 (69.2)
Aspirin	128 (47.4)	112 (48.1)	101 (51.8)
Clopidogrel	55 (20.4)	48 (20.6)	40 (20.5)
Period of CHD administration (months), mean (SD)	35.5 (3.2)	47.0 (5.4)	58.1 (8.3)
Cumulative number of stroke recurrence, n, (%)	7 (2.6)	11 (4.7)	12 (6.2)
Number of adverse effect, n, (%)	0	0	0

Abbreviation: CHD, *Chunghyul-dan*.

compared with conventional antiplatelet agents. *Chunghyul-dan* is safe to use. There were no adverse effects induced by *Chunghyul-dan*. These results are in accordance with the previous studies.[14,15]

We assume that the mechanism of the preventive effect of *Chunghyul-dan* in secondary stroke might be based on various biochemical effects on microangiopathy that are closely related to cell cycle progression, hypertension, dyslipidemia, vascular inflammation, and oxidative damage. Previous clinical studies using *Chunghyul-dan* showed that it has anti-hypertensive[12]

Table 3. Prevalence of Ischemic Stroke Recurrence in the Historical Controls in the Previous Studies.[2-8]

Articles	Patients	Interventions and Follow-up Period	Prevalence of Stroke Recurrence, %
ESPS Group (1990)[2]	Previous TIA or stroke	Aspirin 75 mg + dipyridamole 330 mg/day for 24 months	9.1
Farrell et al (1991)[3]	Previous TIA	Aspirin 1200 mg/day for 72 months	12.4
		Aspirin 300 mg/day for 72 months	12.4
The SALT Collaborative Group (1991)[4]	Previous TIA or stroke	Aspirin 75 mg/day for 32 months	12.1
Diener et al (1996)[5]	Previous TIA or stroke	Aspirin 50 mg/day for 24 months	12.5
		Dipyridamole 400 mg/day for 24 months	12.8
		Aspirin 50 mg + dipyridamole 400 mg/day for 24 months	9.5
Matia-Guiu et al (2003)[8]	Previous TIA or stroke	Aspirin 325 mg for 30.1 months	9.6
		Triflusal 600 mg for 30.1 months	9.7
Diener et al (2004)[6]	Previous TIA or stroke	Clopidogrel 75 mg for 18 months	8.0
		Aspirin 75 mg + clopidogrel 75 mg for 18 months	8.0
Shinohara et al (2010)[7]	Previous ischemic stroke	Aspirin 81 mg/day for 29 months	8.9
		Cilostazol 100 mg/day for 29 months	6.1

Abbreviation: transient ischemic attack.

and anti-hyperlipidemic effects.[13] Previous experimental studies including in vivo and in vitro studies also suggested that *Chunghyul-dan* inhibits HMG-CoA reductase and pancreatic lipase[9] and shows anti-oxidative (by scavenging free radicals) and anti-inflammatory activity.[11] Another experimental study also suggested that *Chunghyul-dan* acts as an anti-apoptotic agent, a cell cycle progressive agent, and a cell-migration–inducing agent.[10]

In this study, *Chunghyul-dan* was prescribed at 600 mg (2 capsules) per day. In a previous study that examined the clinical effects of *Chunghyul-dan* on dyslipidemia, we compared the effects of *Chunghyul-dan* 600 mg/day with 1200 mg/day.[18] There was a statistically significant decrease in total cholesterol after 8 weeks at both 600 mg/day and 1200 mg/day, but no significant difference was observed between 600 mg/day and 1200 mg/day. Based on this result, a 600 mg dose was also used in a study that observed the effect of preventing the recurrence of small vessel disease for 2 years.[15] Recently, a study of the prompt effect of *Chunghyul-dan* on cerebral hemodynamics showed that 600 mg was more effective than 1200 mg, once again supporting the 600 mg dose.[19]

The limitations of this study are as follows. First, there was no control group because it was not a randomized controlled trial. Due to lack of concurrent control, we suggest historical controls. However, there are also limitations because historical controls were mostly from non-Asian populations. Furthermore, these historical controls did not focus on small vessel diseases and there are some differences in demographic data between the historical control group and the patients. Second, about 65% of the patients used antiplatelet therapy such as aspirin and clopidogrel. Therefore, it cannot be concluded clearly whether the results of the present study were the effects of *Chunghyul-dan* alone or *Chunghyul-dan* combination. Finally, during a 5-year follow-up period, the patients showed a 50% high dropout rate and poor drug compliance. Because of these limitations, it is difficult to obtain a concrete conclusion about the effect of *Chunghyul-dan* to prevent the recurrence of small vessel disease.

Conclusions

We cannot draw a concrete conclusion from this study because of limitations as mentioned. However, considering that the stroke recurrence rate of subjects to whom *Chunghyul-dan* was administered was much lower than that of the historical control groups, we suggest that *Chunghyul-dan* might be useful in the prevention of ischemic stroke recurrence by reducing microangiography progression. Further study is needed to confirm our hypothesis.

Appendix

Criteria for small vessel disease (either condition A, B, or C is true).

Condition A

Brain images show a deep infarct of 1.5 cm in its maximal diameter that is appropriate to a clinical classical lacunar syndrome.

Condition B

Brain image shows no lesion to explain the clinical syndrome, and the clinical presentation is one (including the following) classically associated with a small deep infarct: (1) Pure 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. (2) 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. (3) Ataxia-hemiparesis: hemiparesis with ipsilateral ataxia. Paresis is more commonly crural. (4) Dysarthria-clumsy hand syndrome: dysarthria with a clumsy hand. Facial weakness is possible. (5) Hemiballismus, hemiathetosis, or hemidystonia; must be of acute onset. (6) Sensorimotor stroke: weakness and sensory loss involving face, arm and leg equally, without other neurological findings.

Condition C

Computed tomography scan shows a deep infarct of <1.5 cm in its maximal diameter that is appropriate to the clinical syndrome, but the syndrome is not one of the classical syndromes for lacunar stroke.

Author Contributions

Study design, writing, data interpretation (Seungwon Kwon, Woo-Sang Jung, and In Kyu Min), data collection (Chul Jin, Joo Young Park), data review and analysis (Hyung Gyu Kim, Young Kwak, and Kyung Wook Kim), data review and literature search (Seong-Uk Park, Sang-Kwan Moon, Jung-Mi Park, Chang-Nam Ko, and Ki-Ho Cho).

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The Institutional Research Board of Kyung Hee University Korean Medicine Hospital approved this study (KOMCIRB-2011-34).

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