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# A well-controlled study of Choto-san and placebo in the treatment of vascular dementia

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## Abstract

A multi-center, well-controlled study was carried out to evaluate the efficacy of Choto-san extract (7.5 g/day) in comparison with a placebo, each given three times a day for 12 weeks to patients suffering from vascular dementia. Sixty patients, 9 males and 51 females, with a mean age of 78.9 years, were enrolled and analyzed, and 57 completed the study. Choto-san was superior to the placebo with statistical significance in global improvement rating, utility rating, global improvement rating of subjective symptoms, global improvement rating of psychiatric symptoms and global improvement rating of disturbance in daily living activities. However, neurological symptoms were not improved by the treatment with Choto-san. Such symptoms as dizziness or vertigo, shoulder stiffness, palpitation, decline in interest in television or books, lack of facial expression, disorientation and disturbance of excretion were significantly improved by Choto-san compared to the placebo at one or more evaluation points. Furthermore, in the Choto-san group, the mean revised version of Hasegawa's dementia scales for all evaluation points at 4, 8 and 12 weeks were higher, with statistical significance, than that at the beginning of the study. These results suggest that Choto-san is effective in the treatment of vascular dementia.

**Key words** Choto-san, vascular dementia, well-controlled study, placebo.

**Abbreviations** ALT, alanine aminotransaminase ; AST, aspartate aminotransferase ; Choto-san (Diao-Teng-San), 釣藤散 ; DSM-III-R, Diagnostic and statistical manual of mental disorder (Third edition-revised) ; HDS-R, Revised version of Hasegawa's dementia scale ; 5-HT, 5-hydroxytryptamine.

## Introduction

Together with the prolongation of the average life span, the accompanying cerebrovascular disorders and dementia have become social problems, and effective therapy for vascular dementia has been anticipated.

Traditionally in Oriental medicine, Choto-san has been administered to relatively aged patients with physical weakness and such subjective symptoms as headache, dizziness, vertigo, tinnitus, shoulder stiffness and so forth. In recent years, clinical studies that revealed the efficacy of Choto-san on tinnitus,[1] vertigo and dizziness[2] and so on, have been carried out in Japan. Many of these symptoms are thought to originate from disorders in the cerebrovascular system. Furthermore, Yamamoto[3] reported that Choto-san was effective in the treatment of dementia of Alzheimer type.

We therefore believed that Choto-san might have the capability of improving vascular dementia and the accompanying symptoms. So, for the purpose of evaluating the efficacy of Choto-san on vascular

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dementia objectively, we set out to perform a well-controlled, Choto-san versus placebo, study.

## Patients and Methods

*Patient selection* : Patients diagnosed as vascular dementia were selected according to the following criteria :

1) Patients were defined according to the criteria of DSM-III-R,[4] their Carlo Loeb modified ischemic scores[5] were 5 points or more, and their general condition was stable.

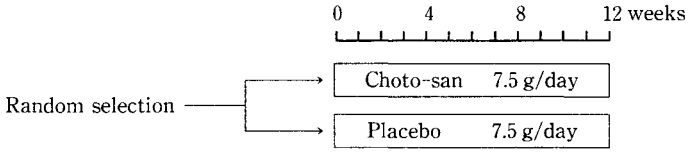
2) One month or more had passed since the last stroke such as cerebral infarction, cerebral bleeding, subarachnoidal bleeding, *etc.*

3) Patients with dementia of Alzheimer type, severe dementia, complicated by other severe diseases, and judged to be inappropriate for this study by the investigators, were excluded from entry into this trial.

Informed consent was obtained from the patients and/or their families prior to enrolment in this trial.

*Methods* :

1) Study protocol (Fig. 1) : This study was designed by the controller (Dr. Takaori, President of Shimane Medical University), and was planned as a multi-center, placebo-well-controlled, inter-patient trial. Patients were randomly selected to be administered either Choto-san extract (TJ-47, Tsumura & Co., 7.5 g/day) or matched placebo after meals three times a day for 12 weeks. The placebo used in this study was made by Tsumura & Co., consisted of lactose, dextrin, maltose, cellulose, hydroxypropyl cellulose, magnesium stearate, colorants and flavors, and could not be distinguished from the active drug in form, color tone and taste by a number of examiners before this trial. Moreover, it was guaranteed by the controller that discrimination between the active drug and the placebo used in this study was impossible. During the trial, no other major new medication was




| | | | | |
|---|---|---|---|---|
| Patient Characteristics | ○ | | | |
| Brain computed tomography | ○ | | | |
| Global severity rating | ○ | ○ | ○ | ○ |
| Global improvement rating | | ○ | ○ | ○ |
| Overall safety rating | | | | ○ |
| Utility rating | | | | ○ |
| Global severity rating of subjective symptoms | ○ | ○ | ○ | ○ |
| Global improvement rating of subjective symptoms | | ○ | ○ | ○ |
| Global severity rating of neurological symptoms | ○ | ○ | ○ | ○ |
| Global improvement rating of neurological symptoms | | ○ | ○ | ○ |
| Global severity rating of psychiatric symptoms | ○ | ○ | ○ | ○ |
| Global improvement rating of psychiatric symptoms | | ○ | ○ | ○ |
| Global severity rating of disturbance in daily living activities | ○ | ○ | ○ | ○ |
| Global improvement rating of disturbance in daily living activities | | ○ | ○ | ○ |
| Severity rating of each symptom | ○ | ○ | ○ | ○ |
| Improvement rating of each symptom | | ○ | ○ | ○ |
| Revised version of Hasegawa's dementia scale | ○ | ○ | ○ | ○ |
| Laboratory tests | ○ | △ | △ | ○ |

○ : assessed necessarily, △ : assessed as much as possible

Fig. 1 Study protocol.

Table I Symptoms evaluated in the study.

| Subjective symptoms | Psychiatric symptoms |
|---|---|
| Heaviness of head | Spontaneity |
| Headache | Expression of intentions |
| Dizziness or vertigo | Interest in television or books |
| Shoulder stiffness | Interest in housework or rehabilitation |
| Palpitation | Conversation |
| Distress feeling of chest | Global spontaneity |
| Feeling of hot flushes | Emotion |
| Tinnitus | Lack of facial expression |
| Numbness of limbs | Bad humor |
| Coldness of limbs | Depressed mood |
| General malaise | Emotional incontinence |
| Appetite loss | Anxiety |
| | Global emotion |
| Neurological symptoms | Intellectual ability |
| | Disorientation |
| Aphasia | Disturbance in short-term memory |
| Dysarthria | Disturbance in long-term memory |
| Motor disturbance | Decline in simple arithmetic ability |
| Tremor | Global intellectual ability |
| Rigidity | Abnormal behavior |
| Sensory disturbance | Hyperkinesia or wandering |
| Urinary incontinence | Restlessness or excitement |
| | Nocturnal delirium |
| Disturbance in activities of daily living | Global abnormal behavior |
| | Sleep disturbance |
| | Hallucination or delusion |
| Sitting | |
| Standing | |
| Walking | |
| Washing face and hands | |
| Putting on and taking off clothes | |
| Having meals regularly | |
| Excretion | |
| Bathing | |

allowed.

Patient characteristics were assessed and brain computed tomography was done before entry. Global severity rating, the global severity ratings of subjective symptoms, neurological symptoms, psychiatric symptoms and disturbance in daily living activities, as well as the severity rating of each symptom were evaluated by the investigators at the beginning, and after 4, 8 and 12 weeks of medication by means of a 5-point rating scale (0=no symptom, 1=very slightly affected, 2=slightly affected, 3=moderately affected, 4=severely affected). The respective symptoms evaluated are described in Table I. Global improvement rating, the global improvement ratings of subjective symptoms, neurological symptoms, psychiatric symptoms and disturbance in daily living activities, as well as the improvement rating of each symptom were evaluated after 4, 8 and 12 weeks of medication by means of a 6-point rating scale (I=remarkable improvement, II=moderate improvement, III=slight improvement, IV=unchanged, V=aggravation, VI=no symptom both at the beginning and at the point of evaluation). Furthermore, the overall safety and utility ratings were also evaluated at the end of the study. HDS-R [6] was assessed by the investigators at the beginning, and after 4, 8 and 12 weeks of medication. In addition, routine laboratory tests were performed at the beginning and the end of the study.

2) Trial period : August 1992 to March 1993.

3) Statistical analysis : Mann-Whitney U test, Chi-square test and Student's $t$-test were used for the statistical analyses, and $p<0.05$ was considered significant.

## Results

*Patients*

The total enrolment consisted of 60 subjects, 9 males and 51 females, and the mean age (±S.D.) was 78.9±7.6. The Choto-san group consisted of 32 cases and the placebo group 28 cases. Administration was completed for 57 cases, 31 in the Choto-san group and 26 in the placebo group. The discontinuing patients were 1 in the Choto-san group, who was affected by adverse effects, and 2 in the placebo group who both declined medication during the course of the trial.

*Patient characteristics* (Table II)

There was no statistical difference between the Choto-san and placebo groups in terms of sex, age, duration of dementia, in- or out-patient, causal disease of dementia, complications, rehabilitation, concomitant drugs and results of the brain computed tomography.

*Overall safety rating* (Table III)

There was no statistical significance between the Choto-san and placebo groups in terms of overall safety rating.

One Choto-san case (3.1 %) suffered from adverse effects and medication was stopped. With the discontinuation of medication, the elevated levels AST and ALT returned to normal. Another Choto-san case suffered a slight decrease in the serum potassium level, but medication was continued. In all the other cases, there were no negative changes in laboratory data that could be attributed to the administration of

Table II Patient characteristics.

| | | | Choto-san | Placebo | Total | |
|---|---|---|---|---|---|---|
| Sex | Male | | 6 | 3 | 9 | N.S.[a] |
| | Female | | 26 | 25 | 51 | |
| Age (years, mean±S.D.) | | | 80.3±5.5 | 77.3±9.2 | 78.9±7.6 | N.S.[b] |
| Duration of dementia (months, mean±S.D.) | | | 41.6±33.2 | 54.6±61.4 | 47.5±48.6 | N.S.[b] |
| In- or Out-patient | Inpatient | | 4 | 5 | 9 | N.S.[a] |
| | Outpatient | | 25 | 21 | 46 | |
| | Inpatient ↔ Outpatient | | 3 | 2 | 5 | |
| Causal disease of dementia | Cerebral infarction | | 32 | 27 | 59 | N.S.[a] |
| | Cerebral bleeding | | 0 | 0 | 0 | |
| | Subarachnoidal hemorrhage | | 0 | 1 | 1 | |
| Complication | None | | 4 | 5 | 9 | N.S.[a] |
| | Hypertension | | 18 | 15 | 33 | |
| | Ischemic heart disease | | 5 | 8 | 13 | |
| | Diabetes mellitus | | 2 | 1 | 3 | |
| | Parkinson syndrome | | 2 | 1 | 3 | |
| | Liver disease | | 1 | 1 | 2 | |
| | Renal disease | | 0 | 1 | 1 | |
| | Others | | 12 | 9 | 21 | |
| Rehabilitation | Doing | | 11 | 10 | 21 | N.S.[a] |
| | Not doing | | 21 | 18 | 39 | |
| Concomitant drugs | Cerebral circulation improver | | 4 | 3 | 7 | N.S.[a] |
| | Cerebral metabolic activator | | 3 | 2 | 5 | |
| Low density area of brain computed tomogram | Number | Single | 7 | 11 | 18 | N.S.[a] |
| | | Multiple | 25 | 17 | 42 | |
| | Focal lesions | Anterior cerebral artery | 4 | 5 | 9 | N.S.[a] |
| | | Middle cerebral artery | 31 | 25 | 56 | |
| | | Posterior cerbral artery | 5 | 2 | 7 | |
| | | Vertebro-basilar artery | 1 | 1 | 2 | |

a : Chi-square test, b : U test, N. S. : not significant

Choto-san or placebo by the investigators.

*Global improvement rating* (Table IV)

Choto-san was superior to placebo with statistical significance in the global improvement rating for each evaluating point at 4 weeks ($p<0.05$), 8 weeks ($p<0.01$) and 12 weeks ($p<0.01$).

*Utility rating* (Table V)

Choto-san was superior to placebo in the utility rating with statistical significance ($p<0.01$).

*Subjective symptoms*

(1) Global improvement rating of subjective symptoms (Table VI)

Choto-san was superior to placebo with statistical significance in the global improvement rating of subjective symptoms for each evaluating point at 4 weeks ($p<0.05$), 8 weeks ($p<0.01$) and 12 weeks ($p<0.01$).

(2) Improvement rating of each subjective symptom

Table III Overall safety rating.

| | No adverse effect | Slight adverse effect with continuing medication | Adverse effect with reducing medication | Adverse effect with discontinuing medication | U test |
|---|---|---|---|---|---|
| Choto-san (n=32) | 30 (93.8) | 1 (3.1) | 0 (0.0) | 1 (3.1) | N.S. |
| Placebo (n=28) | 28 ( 100) | 0 (0.0) | 0 (0.0) | 0 (0.0) | |

( ) : percent, N.S. : not significant

Table IV Global improvement rating.

| | | Remarkable improvement | Moderate improvement | Slight improvement | Unchanged | Aggravation | U test |
|---|---|---|---|---|---|---|---|
| 4 weeks | Choto-san (n=31) | 0 ( 0.0) | 2 ( 6.5) | 9 (29.0) | 20 (64.5) | 0 ( 0.0) | $p<0.05$ |
| | Placebo (n=26) | 0 ( 0.0) | 0 ( 0.0) | 4 (15.4) | 19 (73.1) | 3 (11.5) | |
| 8 weeks | Choto-san (n=31) | 0 ( 0.0) | 4 (12.9) | 15 (48.4) | 11 (35.5) | 1 ( 3.2) | $p<0.01$ |
| | Placebo (n=26) | 0 ( 0.0) | 0 ( 0.0) | 5 (19.2) | 18 (69.2) | 3 (11.5) | |
| 12 weeks | Choto-san (n=31) | 0 ( 0.0) | 8 (25.8) | 14 (45.2) | 8 (25.8) | 1 ( 3.2) | $p<0.01$ |
| | Placebo (n=26) | 0 ( 0.0) | 2 ( 7.7) | 4 (15.4) | 15 (57.7) | 5 (19.2) | |

( ) : percent

Table V Utility rating.

| | Very useful | Useful | Slightly useful | Useless | Harmful | U test |
|---|---|---|---|---|---|---|
| Choto-san (n=32) | 2 ( 6.3) | 12 (37.5) | 11 (34.4) | 6 (18.8) | 1 ( 3.1) | $p<0.01$ |
| Placebo (n=28) | 0 ( 0.0) | 2 ( 7.1) | 5 (17.9) | 17 (60.7) | 4 (14.3) | |

( ) : percent

Table VI Global improvement rating of subjective symptoms.

| | | Remarkable improvement | Moderate improvement | Slight improvement | Unchanged | Aggravation | U test |
|---|---|---|---|---|---|---|---|
| 4 weeks | Choto-san (n=30) | 0 ( 0.0) | 1 ( 3.3) | 12 (40.0) | 14 (40.0) | 3 (10.0) | $p<0.05$ |
| | Placebo (n=24) | 0 ( 0.0) | 0 ( 0.0) | 4 (16.7) | 16 (66.7) | 4 (16.7) | |
| 8 weeks | Choto-san (n=29) | 0 ( 0.0) | 3 (10.3) | 14 (48.3) | 10 (34.5) | 2 ( 6.9) | $p<0.01$ |
| | Placebo (n=24) | 0 ( 0.0) | 0 ( 0.0) | 5 (20.8) | 11 (45.8) | 8 (33.3) | |
| 12 weeks | Choto-san (n=29) | 0 ( 0.0) | 5 (17.2) | 11 (37.9) | 9 (31.0) | 4 (13.8) | $p<0.01$ |
| | Placebo (n=24) | 0 ( 0.0) | 0 ( 0.0) | 5 (20.8) | 9 (37.5) | 10 (41.7) | |

( ) : percent

Choto-san was superior to placebo with statistical significance in the improvement rating of such subjective symptoms as dizziness or vertigo at 4 weeks ($p < 0.05$), shoulder stiffness at 4 weeks ($p < 0.05$) and 12 weeks ($p < 0.05$), and palpitation at 12 weeks ($p < 0.05$). Furthermore, for the improvement rating of such subjective symptoms as dizziness or vertigo at 4 weeks, feeling of hot flushes at 12 weeks, and general malaise at 8 and 12 weeks, Choto-san tended to be superior to placebo with no statistical significance, with their significant levels being less than 0.1.

*Neurological symptoms*

(1) Global improvement rating of neurological symptoms (Table VII)

There was no statistical significance between the Choto-san and placebo groups in the global improvement rating of neurological symptoms at any of the evaluation points.

(2) Improvement rating of each neurological symptom

Choto-san was inferior to placebo with statistical significance in the improvement rating of urinary incontinence at 8 weeks ($p < 0.05$) and 12 weeks ($p < 0.05$).

*Psychiatric symptoms*

(1) Global improvement rating of psychiatric symptoms (Table VIII )

Choto-san was superior to placebo with statistical significance in the global improvement rating of psychiatric symptoms at 4 weeks ($p < 0.05$), 8 weeks ($p < 0.01$) and 12 weeks ($p < 0.01$).

(2) Improvement rating of each psychiatric symptom

Choto-san was superior to the placebo with statistical significance in the improvement rating of such psychiatric symptoms as decline in interest in television or books at 8 weeks ($p < 0.05$) and 12 weeks ($p < 0.05$), lack of facial expression at 12 weeks ($p < 0.05$) and disorientation at 4 weeks ($p < 0.05$). Furthermore, in the improvement rating of such psychiatric symptoms as a decline in the expression of intentions at 12 weeks, decline in interest in housework or rehabilitation at 4 weeks, lack of facial expression at 4 weeks, bad humor at 8 weeks, anxiety

Table VII Global improvement rating of neurological symptoms.

| | | Remarkable improvement | Moderate improvement | Slight improvement | Unchanged | Aggravation | U test |
|---|---|---|---|---|---|---|---|
| 4 weeks | Choto-san (n=20) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 20 ( 100) | 0 ( 0.0) | N.S. |
| | Placebo (n=16) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 6.3) | 15 (93.8) | 0 ( 0.0) | |
| 8 weeks | Choto-san (n=20) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 5.0) | 18 (90.0) | 1 ( 5.0) | N.S. |
| | Placebo (n=16) | 0 ( 0.0) | 0 ( 0.0) | 2 (12.5) | 14 (87.5) | 0 ( 0.0) | |
| 12 weeks | Choto-san (n=21) | 0 ( 0.0) | 0 ( 0.0) | 3 (14.3) | 16 (76.2) | 2 ( 9.5) | N.S. |
| | Placebo (n=16) | 0 ( 0.0) | 0 ( 0.0) | 4 (25.0) | 12 (75.0) | 0 ( 0.0) | |

( ) : percent, N. S.: not significant

Table VIII Global improvement rating of psychiatric symptoms.

| | | Remarkable improvement | Moderate improvement | Slight improvement | Unchanged | Aggravation | U test |
|---|---|---|---|---|---|---|---|
| 4 weeks | Choto-san (n=31) | 0 ( 0.0) | 3 ( 9.7) | 10 (32.3) | 17 (54.8) | 1 ( 3.2) | $p<0.05$ |
| | Placebo (n=25) | 0 ( 0.0) | 0 ( 0.0) | 4 (16.0) | 17 (68.0) | 4 (16.0) | |
| 8 weeks | Choto-san (n=31) | 0 ( 0.0) | 1 ( 3.2) | 17 (54.8) | 10 (32.3) | 3 ( 9.7) | $p<0.01$ |
| | Placebo (n=25) | 0 ( 0.0) | 0 ( 0.0) | 3 (12.0) | 15 (60.0) | 7 (28.0) | |
| 12 weeks | Choto-san (n=31) | 0 ( 0.0) | 2 ( 6.5) | 16 (51.6) | 10 (32.3) | 3 ( 9.7) | $p<0.01$ |
| | Placebo (n=25) | 0 ( 0.0) | 1 ( 4.0) | 5 (20.0) | 10 (40.0) | 9 (36.0) | |

( ) : percent

Table IX Global improvement rating of disturbance in daily living activities.

| | | Remarkable improvement | Moderate improvement | Slight improvement | Unchanged | Aggravation | U test |
|---|---|---|---|---|---|---|---|
| 4 weeks | Choto-san (n=24) | 0 ( 0.0) | 0 ( 0.0) | 4 (16.7) | 19 (79.2) | 1 ( 4.2) | $p<0.05$ |
| | Placebo (n=17) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 14 (82.4) | 3 (17.6) | |
| 8 weeks | Choto-san (n=24) | 0 ( 0.0) | 1 ( 4.2) | 6 (25.0) | 15 (62.5) | 2 ( 8.3) | N.S. |
| | Placebo (n=17) | 0 ( 0.0) | 0 ( 0.0) | 2 (11.8) | 11 (64.7) | 4 (23.5) | |
| 12 weeks | Choto-san (n=24) | 0 ( 0.0) | 1 ( 4.2) | 8 (33.3) | 14 (58.3) | 1 ( 4.2) | $p<0.05$ |
| | Placebo (n=16) | 0 ( 0.0) | 0 ( 0.0) | 3 (18.8) | 8 (50.0) | 5 (31.3) | |

( ) : percent, N.S. : not significant

Table X Revised version of Hasegawa's dementia scale.

| | Beginning point | U test | 4 weeks | T test | U test | 8 weeks | T test | U test | 12 weeks | T test | U test |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Choto-san (n=31) | 15.34±3.76 | N.S. | 16.65±4.43 | $p<0.05$ | N.S. | 17.94±4.79 | $p<0.01$ | N.S. | 19.39±5.71 | $p<0.01$ | N.S. |
| Placebo (n=26) | 14.89±3.84 | | 16.42±5.25 | N.S. | | 15.81±5.82 | N. S. | | 16.50±5.97 | N. S. | |

(Mean±S. D.) T test : Vs. coresponding beginning point, N. S.: not significant

at 4 weeks, disorientation at 12 weeks, disturbance in long-term memory at 8 weeks, restlessness or excitement at 12 weeks, nocturnal delirium at 12 weeks and global abnormal behaviors at 12 weeks, Choto-san tended to be superior to the placebo with no statistical significance, and with their significant levels being less than 0.1.

*Disturbance in the daily living activities*

(1) Global improvement rating of disturbance in the daily living activities (Table IX)

Choto-san was superior to placebo with statistical significance in the global improvement rating of disturbance in daily living activities at each evaluating point at 4 weeks ($p<0.05$) and 12 weeks ($p<0.05$).

(2) Improvement rating of each disturbance in the daily living activities

Choto-san was superior to the placebo with statistical significance in the improvement rating in the disturbance of excretion at 4 weeks ($p<0.05$). Furthermore, in the improvement rating of having meals regularly at 4 weeks, Choto-san tended to be superior to the placebo with no statistical significance, with the significant level being less than 0.1,

*Revised version of Hasegawa's dementia scale* (Table X)

In the Choto-san group, the mean HDS-Rs of all evaluation points at 4 weeks ($p<0.05$), 8 weeks ($p<0.01$) and 12 weeks ($p<0.01$) were higher than those at the beginning of this study with statistical significance. On the other hand, in the placebo group, there was no statistical significance between the mean HDS-R at the beginning and those at all the evaluation points at 4, 8 or 12 weeks. Between the mean HDS-Rs of the Choto-san and placebo groups, there was no statistical significance at any of the evaluation points of 4, 8 or 12 weeks.

## Discussion

Dementia is mainly classified into two types, dementia of the Alzheimer type and vascular dementia. Many efforts have been made for the development of drugs in the treatment of dementia, including cerebral metabolic activators. However, in general, it is recognized that the treatment of dementia is very difficult. The reason for this is that dementia of the Alzheimer type is a degenerative and progressive disease, and vascular dementia is also thought to be a

naturally progressive disease brought about by the recurrence of cerebrovascular accidents and aging. However, if progression of vascular dementia would stop and any accompanying symptoms would improve, this would be of much benefit to the patients of vascular dementia.

In Japan, the clinical efficacy of Choto-san has been reported for such symptoms as headache, dizziness,[2] vertigo,[2] tinnitus,[1] shoulder stiffness and so on mainly accompanied by cerebrovascular sclerosis, cerebrovascular disorders and hypertension in relatively elderly patients. Furthermore, the effectiveness of Choto-san on dementia of the Alzheimer type has also been reported.[3] For the purpose of objectively evaluating the efficacy of Choto-san on vascular dementia and accompanying symptoms, we planned a well-placebo-controlled study of Choto-san.

There have been few clinical studies on the efficacy of Kampo medicines in comparison with a placebo.[7] One of the reasons for this is the difficulty in making placebos that have a similar color tone, smell and taste as the active Kampo medicines. In our case, it was confirmed by plural examiners and the controller that active drug could not be distinguished from the placebo used in this study.

In this trial, Choto-san was found to be superior to the placebo with statistical significance in the global improvement rating, utility rating, global improvement rating of subjective symptoms, global improvement rating of psychiatric symptoms and global improvement rating of disturbance of daily living activities. Furthermore, in the Choto-san group, HDS-Rs at all of the evaluation points at 4, 8 and 12 weeks were significantly higher than at the beginning. These results suggest that Choto-san is effective in the treatment of vascular dementia. However, in this study, there was no difference in the global improvement rating of neurological symptoms between the Choto-san and placebo groups, indicating that this agent is not effective in the treatment of fixed neurological symptoms.

The reason for the superiority of the placebo over Choto-san in the improvement rating of urinary incontinence in this study is unclear, but in the Choto-san group the number of cases with aggravated urinary incontinence was only one, so at least this medicine does not cause the progression of urinary incontinence. As for improvement rating of such subjective symptoms as dizziness or vertigo, shoulder stiffness, palpitation, feeling of hot flushes and general malaise at any of the evaluating points, Choto-san was statistically favorable or at least showed a superior tendency, with their levels of significance being less than 0.1. This result suggests that these subjective symptoms of vascular dementia patients are relatively easily improved by the administration of Choto-san. In addition, Choto-san outperformed the placebo for some psychiatric symptoms and the disturbance in daily living activities, so this Kampo medication can also be expected to positively influence spontaneous behavior, emotion, intellectual faculty, abnormal behavior and the quality of daily living.

It was reported that the use of Choto-san decreased blood pressure in patients with essential hypertension,[8] and decreased blood pressure and hypertensive lesions of stroke-prone spontaneously hypertensive rats.[9] However, in our present study, there was no case in the Choto-san group whose blood pressure was judged to have decreased due to the medication, and there was no statistical significance in either systolic or diastolic blood pressure between the beginning and the end point of the trial in the Choto-san group. So, at least in this study, the clinical efficacy of Choto-san on vascular dementia was not due to a hypotensive effect of Choto-san, but rather to other factors.

Choto-san is a Kampo formulation composed of 11 herbs, those are Chotoko (釣藤鈎), Uncariae Uncis Cum Ramulus, *Uncaria rhynchophylla* MIQUEL or *sinensis* OLIVER, Chimpi (陳皮), Aurantii Nobilis Pericarpium, *Citrus unshiu* MARKOVICH, Hange (半夏), Pinelliae Tuber, *Pinellia ternata* BREITENBACH, Bakumondo (麦門冬), Ophiopgonis Tuber, *Ophiopogon japonicus* KER-GAWLER, Bukuryo (茯苓), Hoelen, *Poria cocos* WOLF, Ninjin (人参) Ginseng Radix, *Panax ginseng* C. A. MEYER, Kikka (菊花), Chrysanthemi Flos, *Chrysanthemum morifolium* RAMATULLE or indicum LINNÉ, Bofu (防風), Saposhnikoviae Radix, *Saposhnikovia divaricata* SCHISCHKIN, Kanzo (甘草), Glycyrrhizae Radix, *Glycyrrhiza uralensis* FISCHER or *Glycyrrhiza glabra* LINNNÉ, Sekko (石膏), Gypsum Fibrosum, $CaSO_4 \cdot 2H_2O$ and Shokyo (生姜), Zingiber-

is Rhizoma, *Zingiber officinale* ROSCOE.

Among these herbs, Chotoko is recognized as the most important, and its pharmacological function has already been investigated. It was demonstrated that the extract of Chotoko and its fraction possess hypotensive activity,[10,11] and the principle of Chotoko has the action of a calcium antagonist.[12] Concerning the central nervous system, it was revealed that the alkaloids obtained from Chotoko were partial agonists for 5-HT receptors in rats,[13] and Chotoko extract had an activating effect on the dopaminergic system and an inhibitory effect on lipid peroxidation in iron-induced acute epileptic rats.[14] As to the other herbs comprising Choto-san besides Chotoko, it is known that Ninjin has many effects, such as an activating effect on the central nervous system by brain monoamine-related substances in mice,[15] anti-fatigue effect on exhaustive exercise in mice,[16] anti-thrombic effect in experimental models of disseminated intravascular coagulation in rats,[17] and so on. Furthermore, Kanzo has an anti-platelet action[18] and possible regulation of cellular senescence.[19] In total, then, clinical effects of Choto-san on vascular dementia in this study are thought to be due to these and other unknown effects of the respective herbs that comprise Choto-san. Further pharmacological investigations on the efficacy of Choto-san are anticipated.

From the results of this trial, it was suggested that Choto-san has a favorable effect on vascular dementia. For an investigation of the efficacy of Choto-san on vascular dementia based on more objective criteria, we are now planning a double-blind, placebo-controlled study.

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## 和文抄録

釣藤散の脳血管性痴呆に対する臨床効果を検討する目的で，多施設におけるプラセボを対照とした封筒法による比較試験を行なった。解析対象は60例で，釣藤散エキス顆粒またはプラセボを1日7.5g分3，12週間投与し，4週毎に各調査項目を評価した。その結果，釣藤散はプラセボに比べて，全般改善度，有用度，自覚症状全般改善度，精神症候全般改善度，日常生活動作障害全般改善度において有意に優れていた。また，めまい，肩こり，動悸，テレビや本に対する興味，表情の乏しさ，見当識障害，用便の障害の改善において，釣藤散がプラセボに比べて有意に優れている評価時点がみられた。さらに，釣藤散群の群内比較において，改訂長谷川式簡易知能評価スケールが，開始時に比べてすべての評価時点において有意に改善した。以上の成績は，脳血管痴呆に対する釣藤散の有用性を示唆するものと考えられた。

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