# Effect of Keishi-bukuryo-gan on asymptomatic cerebral infarction for short term

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## Abstract

The efficacy of Keishi-bukuryo-gan in patients suffering from asymptomatic cerebral infarction was studied. 142 patients, 32 males and 110 females, with a mean age of 68.9 years, were enrolled and analyzed, and 139 completed the study. They were given Keishi-bukuryo-gan extract (7.5g/day) three times a day for 12 weeks. In comparison to the beginning of the study, Keishi-bukuryo-gan showed improvement with statistical significance in the mean revised version of Hasegawa's dementia scale, Apathy scale and Self-rating depression scale. The number of patients with subjective symptoms as headdullness, headache and dizziness decreased by the treatment with Keishi-bukuryo-gan, and diastolic blood pressure was decreased with statistical significance as compared to the beginning of the study. These results suggest that Keishi-bukuryo-gan is effective against dysfunction of acknowledgment, emotional disorder and subjective symptoms with asymptomatic cerebral infarction.

**Key words** asymptomatic cerebral infarction, Keishi-bukuryo-gan, the revised version of Hasegawa's dementia scale, Apathy scale, Self-rating depression scale.

**Abbreviation** Keishi-bukuryo-gan (Gui-Zhi-Fu-Ling-Wan), 桂枝茯苓丸.

## Introduction

Asymptomatic cerebral infarction is diagnosed as small cerebral infarctions by magnetic resonance imaging (MRI) and computed tomography (CT) without neurological symptoms. It was recently reported that cerebral stroke and vascular dementia are related to asymptomatic cerebral infarction.[1)] Asymptomatic cerebral infarction was reported to be characterized by the mental symptoms of the lowering of the function of acknowledgment[2)] and the state of depression.[3)] Non-specific symptoms of asymptomatic cerebral infarction are headache, headdullness and dizziness.[4)] It is suggested that the origin of asymptomatic cerebral infarction is decreasing cerebral circulation by aging, and hypertension.[1,5)] In terms of prevention by western medicine, anti-coagulant therapy was not able to suppress its advance,[6)] and only the control of blood pressure to prevent cerebral infarction by hypertension is available.[7)]

Keishi-bukuryo-gan (Gui-Zhi-Fu-Ling-Wan) is a Kampo formula that possesses the effect of improving the microcirculation.[8)] Clinically, it was reported that it had good hemorheological and anti-coagulative effects.[9)] Keishi-bukuryo-gan was also demonstrated to have an antioxidant effect[10)] and a hypotensive effect in spontane-

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ously hypertensive rat.[11] Taken together then, it is suggested that Keishi-bukuryo-gan has a salutary effect on asymptomatic cerebral infarction. In the present study we examined the effect of Keishi-bukuryo-gan on asymptomatic cerebral infarction in terms of mental symptoms, subjective symptoms and blood pressure.

## Patients

*Patient selection:*

1) Patients, who were neurologically normal, were diagnosed as asymptomatic cerebral infarction based on high-intensity lesions greater than 3 mm in size on T2-weighted images that coincided with low-intensity lesions on T1-weighted images on MRI.

2) Patients with 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. Furthermore we excluded the patients whose condition are extreme excess or deficiency. Informed consent was obtained from the patients prior to enrollment according to our institutional guidelines.

## Methods

1) Study protocol (Figure 1): Patients were administered Keishi-bukuryo-gan extract (TJ-25, Tsumura & Co., 7.5 g/day) between meals three times a day for 12 weeks. A Keishi-bukuryo-gan extract granule of 7.5g contains 1.75g of the extracts of 5 kinds of dried medical herbs mixed in the following ratio: Cinnamomi Cortex (3.0g, bark of *Cinnamomum cassia* BLUME), Paeoniae Radix (3.0g, root of *Paeonia lactiflora* PALLAS), Persicae Semen (3.0g, seed of *Prunus persica* BATSCH), Hoelen (3.0g, fungus of *Poria cocos* WOLF) and Moutan Radicis Cortex (3.0g, root bark of *Paeonia suffruticosa* ANDREWS). During the trial, no other major new medication was allowed.

Patient characteristics were assessed before entry. The revised version of Hasegawa's dementia scale (HDS-R),[12] Apathy scale,[13] and Self-rating depression scale (SDS)[14] were assessed by the investigators at the beginning, and at 4,8 and 12 weeks of medication. Subjective symptoms (heaviness of head, headache, dizziness or vertigo, shoulder stiffness, palpitation, distress feeling of chest, feeling of hot flushes, tinnitus, numbness of limbs, coldness of limbs, general malaise, appetite loss) and their global severity ratings were evaluated by the investigators at the beginning, and at 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 global improvement ratings of the subjective symptoms were evaluated at 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. In addition, blood pressure measurement and routine laboratory tests were performed at the beginning and the end of the study.

2) Trial period: June 1997 to May 2000.

3) Statistical analysis: Data are shown as mean ±S.D. Two-way repeated-measures ANOVA and Student's *t*-test were used for the statistical analysis, and $p<0.05$ was considered significant.

## Results

*Patients*

The total enrollment consisted of 142 subjects, 32 males and 110 females, and the mean age (±S.D.) was 68.9±8.1. The protocol was completed for 139 cases.

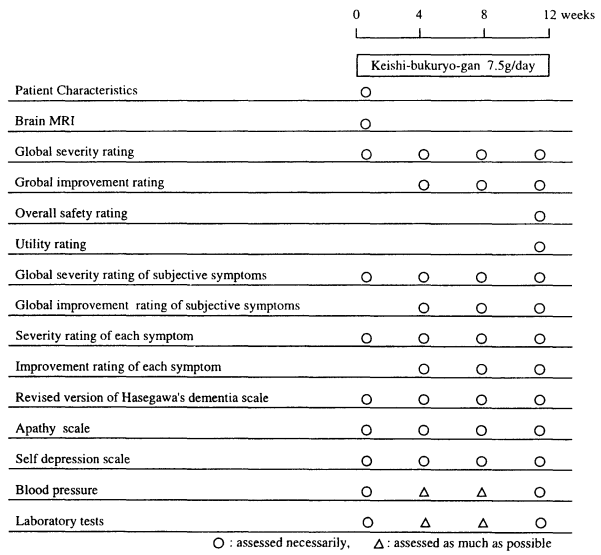


Fig. 1 Study protocol.

*Patient characteristics*

Their complications were 71 cases of hypertension, 10 cases of diabetes mellitus, 27 cases of hyperlipidemia, and 8 cases of ischemic heart decease. On brain MRI, there were 29 cases with one lacunar infarction, and 113 cases had two or more. Periventricular hyperintensity was absent or very mild in 81 cases, mild in 41 cases, intermediate in 16 cases, and severe in 4 cases.

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

The mean HDS-R of all evaluation points at 4 weeks (26.1±4.5, $p<0.01$), 8 weeks (26.6±4.4, $p<0.01$) and 12 weeks (27.3±4.0, $p<0.01$) were higher, with statistical significance, than those at the beginning (25.5± 4.2) of this study.

*Apathy scale* (Table I)

The mean apathy scale of all evaluation points at 4 weeks (12.0±7.3, $p<0.01$), 8 weeks (11.5±7.7, $p<0.01$) and 12 weeks (11.7±8.5, $p<0.01$) were lower, with statistical significance, than those at the beginning (13.1± 7.1) of this study.

*Self-rating depression scale* (Table I)

The mean SDS of all evaluation points at 4 weeks (37.0±10.9, $p<0.01$), 8 weeks (35.5±10.7, $p<0.01$) and 12 weeks (35.5±11.1, $p<0.01$) were lower, with statistical significance, than those at the beginning (38.4± 10.1) of this study.

*Subjective symptoms*

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

After 12 weeks, global improvement ratings of subjective symptoms were 1 case (1%) of remarkable improvement, 10 cases (7%) of moderate improvement, 57 cases (41%) of slight improvement, 61 cases (44%) of unchanged, and 10 cases (7%) of aggravation.

2) Improvement rating of each subjective symptom

The respective subjective symptoms at the beginning were 78 cases (56%) of heaviness of head, 79 cases (57%) of headache, 60 cases (43%) of dizziness or vertigo, 102 cases (73%) of shoulder stiffness, 59 cases (42%) of palpitation, 44 cases (32%) of distress feeling of chest, 57 cases (41%) of feeling of hot flushes, 59 cases (42%) of tinnitus, 82 cases (59%) of numbness of limbs, 81 cases (58%) of coldness of limbs, 88 cases (63%) of general malaise, and 26 cases (19%) of appetite loss.

Those who improved, with slight improvement or more, at 12 weeks were 40 cases (51%) of heaviness of head, 48 cases (61%) of headache, 36 cases (60%) of dizziness or vertigo, 54 cases (53%) of shoulder stiffness, 36 cases (61%) of palpitation, 27 cases (61%) of distress feeling of chest, 31 cases (54%) of feeling of hot flushes, 31 cases (53%) of tinnitus, 40 cases (49%) of

Table I. Revised version of Hasegawa's dementia scale (HDS-R), Apathy scale, Seif-rating depression scale (SDS) and Blood pressure

| | Beginning point | 4 weeks | 8 weeks | 12 weeks |
|---|---|---|---|---|
| HDS-R | 25.5± 4.2 | 26.1± 4.5** | 26.6± 4.4** | 27.3± 4.0** |
| Apathy scale | 13.1± 7.1 | 12.0± 7.3** | 11.5± 7.7** | 11.7± 8.5** |
| SDS | 38.4±10.1 | 37.0±10.9* | 35.5±10.7** | 35.5±11.1** |
| Systolic blood pressure (mmHg) | 140.0±15.9 | — | — | 137.8±16.5 |
| Diastolic blood pressure (mmHg) | 82.1±11.5 | — | — | 80.0±11.4* |

(Mean±S.D.) *$p<0.05$ vs. coresponding beginning points. **$p<0.01$ vs. coresponding beginning points.

Table II. Global improvement rating of subjective symptoms

| | Remarkable improvement | Moderate improvement | Slight improvement | Unchanged | Aggravation |
|---|---|---|---|---|---|
| 4 weeks | 0 (0) | 5 (4) | 33 (24) | 92 (60) | 9 (7) |
| 8 weeks | 0 (0) | 5 (4) | 53 (38) | 70 (50) | 11 (8) |
| 12 weeks | 1 (1) | 10 (7) | 57 (41) | 61 (44) | 10 (7) |

( ): percent

Table III. Global improvement rating

| | Remarkable improvement | Moderate improvement | Slight improvement | Unchanged | Aggravation |
|---|---|---|---|---|---|
| 4 weeks | 3 (2) | 2 ( 1) | 45 (32) | 87 (63) | 2 (1) |
| 8 weeks | 2 (1) | 6 ( 4) | 56 (40) | 72 (52) | 3 (2) |
| 12 weeks | 12 (9) | 18 (13) | 45 (32) | 61 (44) | 3 (2) |

( ): percent

numbness of limbs, 47 cases (58%) of coldness of limbs, 42 cases (48%) of general malaise, and 18 cases (69%) of appetite loss.

*Blood pressure* (Table I)

The mean systolic blood pressure was 140.0±15.9 mmHg at the beginning, and 137.8±16.5mmHg at 12 weeks ($p$=0.1348). Diastolic blood pressure decreased significantly from 82.1±11.5mmHg at the beginning to 80.0±11.4mmHg at 12 weeks ($p$<0.05).

*Global improvement rating* (Table III)

At 12 weeks, global improvement ratings showed 12 cases (9%) with remarkable improvement, 18 cases (13%) with moderate improvement, 45 cases (32%) with slight improvement, 61 cases (44%) unchanged, and 3 cases (2%) with aggravation.

*Overall safety rating*

Overall safety ratings, which were judged by adverse effects and laboratory data, showed 133 cases (94%) with no adverse effects, 6 cases (4%) with slight adverse effects with continuing medication, and 3 cases (2%) with adverse effects and cessation of medication. These latter 3 cases suffered from diarrhea, palpitation, and itching, respectively, and their medication was stopped within 4 weeks.

*Utility rating*

The utility ratings were evaluated by physicians who considered all the data, and 9 cases (6%) were judged as very useful, 30 cases (21%) as useful, 47 cases (33%) as slightly useful, 53 cases (37%) as useless, and 3 cases (2%) as harmful.

## Discussion

The clinical presentations of asymptomatic cerebral infarction were reported to be dysfunction of acknowledgment,[2] emotional disorder,[4] and non-specific symptoms as headdullness and vertigo *etc.*.[3] As for the dysfunction of acknowledgment, it is important to gain an understanding of how asymptomatic cerebral infarction advances to dementia. In order to achieve this, long-term studies utilizing large groups of patients with asymptomatic cerebral infarction will need to be carried out. There have as yet been no such mass studies. As matters stand now, there have only been a few reports regarding cases with multiple cerebral infarction and failing intellectual function,[15] and that leukoarainosis is related to intellectual function.[16] At the outset of the present study, it was not certain whether HDS-R was lower in patients with asymptomatic cerebral infarction compared with healthy controls. But by 12 weeks of the administration of Keishi-bukuryo-gan, HDS-R had improved significantly compared to before its administration. Thus, the possibility of Keishi-bukuryo-gan exerting a favorable effect on intellectual function was suggested. As for emotional disorders, it has been suggested that asymptomatic cerebral infarction is related to the tendency toward depression.[4] In our study, 50 of 139 cases were judged as apathetically positive by the Apathy scale. Then, at 12 weeks of Keishi-bukuryo-gan, the positive patients had decreased to 41, and the mean value of the Apathy scale had decreased significantly. 61 of 139 patients were judged to be suffering from depression according to SDS. At 12 weeks of Keishi-bukuryo-gan administration, the positive group had decreased to 49 cases. The mean value of SDS had also significantly decreased.

Under subjective symptoms, there were many patients with neck stiffness and general fatigue. Further, those complaining of headdullness, headache and dizziness, the reported original symptoms of asymptomatic cerebral infarction, were about 50% of the total patients. The patients showing slight improvement or better in global improvement rating of subjective symptoms after the administration of Keishi-bukuryo-gan were 49%. The cases experiencing improvement of headdullness and headache were even more numerous.

One of the causes of asymptomatic cerebral infarction was reported to be a decrease in cerebral circula-

tion.[17] In this study, the evaluation of cerebral circulation was not performed. However, diastolic blood pressure was decreased significantly, suggesting that Keishi-bukuryo-gan had a dilatation effect on the systemic vessels. In addition, as this Kampo formula was also reported to have a favorable hemoreological effect,[8,9] it is suggested that these effects of Keishi-bukuryo-gan had a positive influence on the cerebral circulation.

Finally, it is clear that studies with comparison to control groups as well as long-term studies will be required to confirm the protective effects of Keishi-bukuryo-gan against cerebral attack and vascular dementia.

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## 和文抄録

無症候性脳梗塞患者に対する桂枝茯苓丸の効果を検討した。142例（男性32例，女性110例，平均年齢68.9才）を対象とし，副作用のため内服を中止した3例を除く139例に対して，桂枝茯苓丸エキス1日量7.5gを12週間投与した。投与開始時と比較して，改訂長谷川式簡易知能評価スケール，Apathyスケール（やる気スケール），SDS（うつ状態スケール）は有意に改善した。また，頭重感，頭痛，めまいの自覚症状も桂枝茯苓丸の投与により改善し，拡張期血圧は投与前に比べ有意に低下した。これらの結果から，桂枝茯苓丸が無症候性脳梗塞に伴う認知機能の低下，精神症状や自覚症状の悪化に対して有効である可能性が示唆された。

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