Efficacy of Keishibukuryogan, a Traditional Japanese Herbal Medicine, in Treating Cold Sensation and Numbness After Stroke: Clinical Improvement and Skin Temperature Normalization in 22 Stroke Patients

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Abstract

Cold sensation and numbness have been reported as post-stroke sensory sequelae attributable to distal axonopathy, which is caused by chronic ischemia of diseased limbs resulting from dysfunction of vaso-motor regulatory systems. Keishibukuryogan is a traditional herbal medicine used to treat symptoms of peripheral ischemia such as cold extremities. This study investigated clinical improvement and skin temperature in peripheral ischemia patients to determine the efficacy of keishibukuryogan in alleviating post-stroke cold sensation and numbness. Twenty-two stroke patients with cold sensation and/or numbness were enrolled in this study. Subjective cold sensation and numbness, evaluated using the visual analogue scale, were found in 21 and 31 limbs, respectively. The skin temperature of diseased and healthy limbs was recorded. We observed all patients for 4 weeks and 17 patients for 8 weeks after administration of keishibukuryogan. The skin temperature of diseased limbs was significantly higher than baseline at 4 weeks and 8 weeks, whereas that of healthy limbs did not change significantly. Cold sensation and numbness were significantly improved at 4 weeks and 8 weeks compared to baseline. Keishibukuryogan administration resulted in warming of diseased limbs and improved cold sensation and numbness, probably by increasing peripheral blood flow.

Key words: herbal medicine, keishibukuryogan, stroke, cold sensation, numbness

Introduction

Cold sensation and numbness are common sensory sequelae of strokes and may be caused by involvement of the spino-thalamic tract, medial lemniscal tract, and spino-recticulo-thalamic tract in sensory disturbances. On the other hand, damage to the central autonomic network may also cause vaso-motor regulatory system dysfunction, resulting in chronic ischemia and actual coldness, not merely perceived coldness, in diseased limbs, in turn causing distal axonopathy of the nerve fibers, leading to chronic cold sensation and numbness. Our interviews of stroke patients with these sequelae had similar findings: Cold weather was a provoking factor, and the symptoms sometimes improved in warm weather or after a hot bath. Therefore, improving the peripheral blood flow in diseased limbs may ameliorate post-stroke cold sensation and numbness aggravated by distal axonopathy.

Oriental medicine uses herbal complexes to treat the symptoms of peripheral ischemia, such as cold extremities. Keishibukuryogan, a traditional herbal medicine approved as an ethical medicine by the Ministry of Health, Labour and Welfare of Japan, has often been used to treat peripheral coldness and/or ischemia in Japan. The present study investigated the efficacy of keishibukuryogan for alleviating cold sensation and numbness in stroke patients by measuring clinical improvement and skin temperature.

Subjects and Methods

Stroke patients meeting the following conditions were enrolled after giving informed consent: subjective complaints of cold sensation and/or numbness,
including sensation of tingling and squeezing, in diseased limbs; lower skin temperature of a diseased limb than of the contralateral limb; and palpable pulse of the radial or dorsalis pedis arteries without laterality.

This study examined 32 diseased limbs of 22 outpatients, 13 men and 9 women aged 26 to 75 years (mean 59 years). The time since the stroke onset was 3 to 42 months (mean 17 months) in the 19 patients with confirmed onset dates. More than 2 years had passed since the stroke onset in two patients and more than 15 years in one patient. Ten cases were caused by cerebral infarction and 12 by intracerebral hemorrhage, in the cerebral cortex in 3 cases, basal ganglia in 7 cases, internal capsule in 1 case, thalamus in 9 cases, pons in 1 case, and medullary cortex in 1 case. Subjective cold sensation and numbness were found in 21 and 31 limbs, respectively. All patients were observed for 4 weeks and 17 patients for 8 weeks after keishibukuryogan administration. Five patients withdrew 8 weeks later.

Keishibukuryogan (Kracie Pharmaceutical, Tokyo) was prescribed with doses ranging from 2.0 to 6.0 g/day. The patients continued their current use of the following medicines: antihypertensive drugs in 15 cases, antiplatelet drugs in 9 cases, antiepileptic drugs in 4 cases, and antidepressant drugs in 5 cases. There was no change of prescription during this study.

The severity of the cold sensation and numbness was evaluated according to the visual analogue scale (VAS) at baseline before, and at 4 and 8 weeks after administration of keishibukuryogan. VAS is a psychometric response scale used in questionnaires. Patients specify the severity of subjective symptoms by indicating a position along a continuous 10-cm line with the scale in centimeters and millimeters. Blood pressure, heart rate, axillary temperature, and skin temperature were also recorded after the patient lay on the back for 20 minutes while barehanded and barefoot. Blood pressure was measured using a mercury sphygmomanometer, and heart rate was measured by 60-second radial pulse count. Axillary temperature, instead of deep body temperature, was measured with an electrothermometer (C202; Terumo, Tokyo). Skin temperature, the indicator of peripheral blood flow in this study, was recorded with a thermocouple thermometer (PTC–201; Unique Medical, Tokyo). Room temperature during the examination was recorded with the same thermometer. The daily mean temperature on examination day in the city of Tsukuba, which has the nearest meteorological station to our hospital, was obtained because cold sensation and numbness may improve or worsen due to seasonal temperature change. We obtained the official daily mean temperatures recorded by the Japan Meteorological Agency through the Internet.

Statistical analysis was performed with StatMate III software (ATMS, Tokyo). Differences between the baseline and 4 or 8 weeks later were compared using the Wilcoxon signed-rank test. All reported p values are two-sided. P values less than 0.05 were considered statistically significant.

### Results

The results of this study, except for the VAS findings, are summarized in Table 1. There were no significant differences in daily mean temperature, body temperature, heart rate, or diastolic blood pressure during the 8-week period. However, systolic blood pressure decreased significantly by 6 mmHg on average at 8 weeks compared to the baseline. Room temperature was also significantly lower at 4 weeks. The skin temperature of the healthy limbs was similar at 4 weeks and 8 weeks. On the other hand, the

**Table 1 Changes in clinical factors**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 Weeks</th>
<th>8 Weeks</th>
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</thead>
<tbody>
<tr>
<td>Daily mean temperature (°C)</td>
<td>11.4 ± 1.53</td>
<td>10.6 ± 1.72</td>
<td>11.9 ± 1.92</td>
</tr>
<tr>
<td>Axillary temperature (°C)</td>
<td>36.5 ± 0.09</td>
<td>36.5 ± 0.08</td>
<td>36.5 ± 0.1</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>65 ± 2.9</td>
<td>66 ± 2.4</td>
<td>63 ± 2.9</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>128 ± 3.3</td>
<td>136 ± 3.7</td>
<td>122 ± 4.5*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>77 ± 2.2</td>
<td>82 ± 2.6</td>
<td>74 ± 4</td>
</tr>
<tr>
<td>Room temperature (°C)</td>
<td>24 ± 0.2</td>
<td>23.5 ± 0.19*</td>
<td>24.1 ± 0.31</td>
</tr>
<tr>
<td>Skin temperature of healthy limbs (°C)</td>
<td>30.6 ± 0.4</td>
<td>30.6 ± 0.46</td>
<td>30.4 ± 0.59</td>
</tr>
<tr>
<td>Skin temperature of diseased limbs (°C)</td>
<td>29.2 ± 0.46</td>
<td>29.8 ± 0.5*</td>
<td>29.8 ± 0.63*</td>
</tr>
<tr>
<td>Laterality (diseased – healthy) of skin temperature (°C)</td>
<td>−1.5 ± 0.18</td>
<td>−0.9 ± 0.25*</td>
<td>−0.57 ± 0.26*</td>
</tr>
</tbody>
</table>

Values are means ± standard error of the mean. Comparison of variables at baseline and at 4 weeks or 8 weeks used the Wilcoxon signed-rank test, "p < 0.05.
Herbal Medicine Improves Sensory Sequelae

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Skin temperature of the diseased limbs was significantly higher at 4 and 8 weeks compared to the baseline. Consequently, the laterality of skin temperature was significantly reduced at 4 and 8 weeks.

The VAS findings are shown in Figs. 1 and 2. Cold sensation was improved significantly at 4 weeks, by 2.5 points, and at 8 weeks, by 3.6 points on average compared to the baseline. Numbness was also improved significantly at 4 weeks, by 1.5 points, and at 8 weeks, by 3.0 points on average.

Discussion

The present study showed that keishibukuryogan administration normalized the skin temperature of cold diseased limbs and improved cold sensation and/or numbness at 4 and 8 weeks. The skin temperature of the diseased limbs was significantly higher at 4 and 8 weeks compared to the baseline, whereas the skin temperature of the healthy limbs, the axilla-

ry temperature, and the room temperature had no upward trend during the 8 weeks. Changes in daily mean temperature did not influence the improvement of cold sensation and numbness, because the daily mean temperature showed no statistically significant trend throughout the 8 weeks.

Keishibukuryogan consists of five herbal components: cassia bark, peach kernel, tree peony bark, peony root, and tuckahoe. Keishibukuryogan is reported to improve blood circulation by increasing blood velocity, erythrocyte deformability, and arterial diameter, and decreasing blood viscosity, platelet aggregation, erythrocyte aggregation, and hematocrit. Effects of the individual components have also been reported. Cassia bark, tree peony bark, and peony root all increase activated partial thromboplastin time. Cassia bark and peony root increase arterial diameter. Cassia bark, peach kernel, tree peony bark, and peony root inhibit platelet aggregation. None of the herbal compounds affect prothrombin time. Peach kernel and tuckahoe activate, and cassia bark, tree peony bark, and peony root inhibit the fibrinolytic system. It is unclear whether keishibukuryogan activates or inhibits the fibrinolytic system, but no thrombotic or hemorrhagic complications occurred in our patients.

Some specific medicinal molecules have been identified. Paeonol and paeoniflorin, which are included in both tree peony bark and peony root, inhibit platelet aggregation and blood coagulation. Triolein in peach kernel inhibits blood coagulation. Cinnamaldehyde in cassia bark is an endothelium-dependent vasodilator. Cinnamic acid in cassia bark is an endothelium-dependent vasodilator. Paeoniflorin, paeonidanin, and galloylgucose in peony root are endothelium-dependent vasodilators. Improving blood flow results in improved peripheral nerve conduction velocity in diabetic neuropathy, in which reduced nerve blood flow is involved.

Skin temperature and peripheral nerve conduction velocity are reported to have a positive correlation. Therefore, the pharmacological action of keishibukuryogan probably increased peripheral blood flow and raised the skin temperature of the diseased limbs, resulting in improving axonopathy in the diseased limbs, although peripheral blood flow and nerve conduction velocity were not measured in this study. This speculation can explain the rise in the skin temperature of diseased limbs as well as the improvement in cold sensation and/or numbness. On the other hand, the temperature of healthy limbs did not rise probably because the homeostatic function remained intact. Low-temperature sauna
bathing (LTSB) improves numbness in cerebral palsy patients by increasing peripheral blood flow.\textsuperscript{11)} We agree that increasing peripheral blood flow improves numbness. However, the long-term benefit of LTSB is unclear because the post-LTSB measurements were recorded at a single time point, which was approximately 30 minutes after LTSB.

Antiepileptic drugs such as gabapentin with gamma-aminobutyric acid-ergic activity, and lamotrigine with antiglutamatergic activity, as well as antidepressant drugs such as amitriptyline with norepinephrine reuptake inhibitory activity, are reportedly efficacious in ameliorating central post-stroke pain, which is a known post-stroke sensory sequela.\textsuperscript{2,23)} The present study of the pharmacological activities of keishibukuryogan found that improving peripheral blood flow of diseased limbs is the main mechanism of keishibukuryogan. Diseased limbs occurring as a result of brain lesions may be colder or warmer than healthy limbs due to dysfunction in the vasomotor regulatory systems.\textsuperscript{2,5,22,33)} In this study, we focused on cold diseased limbs.

The major limitation of this study is the small number of patients selected to determine the efficacy of keishibukuryogan, and the fact that the study was not randomized. A randomized controlled trial using a large series of cases is required to confirm these preliminary uncontrolled results, before keishibukuryogan can be indicated for the treatment of post-stroke sensory sequelae. Further investigation of peripheral blood flow, sympathetic flow response, such as the cold stress test, and nerve conduction velocity in the extremities is necessary to determine the efficacy of keishibukuryogan or its main components for these symptoms. However, the present detailed description of medical therapy for post-stroke cold sensation and numbness does demonstrate the apparent efficacy of keishibukuryogan.

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Commentary

This interesting paper describes the efficacy of keishibukuryogan in treating cold sensation and numbness after stroke. Keishibukuryogan consists of five herbal components: cassia bark, peach kernel, tree peony bark, peony root, and tuckahoe. Effects of the individual components have been reported. Although peripheral blood flow, nerve conduction velocity, and other indicator were not measured, the pharmacological action of keishibukuryogan probably increased peripheral blood flow and raised the skin temperature of diseased limbs. As the authors also pointed out, the major limitation of this study is the small number of patients (22 out-patients) selected to determine the efficacy of keishibukuryogan, and also this study was not randomized. A randomized control trial with a large series of cases is required to confirm these preliminary results. Thus, further investigation including peripheral blood flow and another quantitative parameters is required to determine the efficacy of keishibukuryogan for post-stroke cold sensation and numbness. I look forward to the next report of a larger number of cases with quantitative...
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This is a clinically informative paper indicating the efficacy of keishibukuryogan, a kampo product, for the treatment of cold sensation and numbness after stroke. To date only a small number of papers on the effect of kampo formulations (traditional Japanese herbal medicines) have published in international scientific journals, but the number is gradually increasing. Over the last few years, the Food and Drug Administration (U.S.A.) has begun shifting its focus to traditional Japanese herbal medicines with high quality and standardized ingredients from Chinese ones.1) The initiative in collecting evidence-based information on kampo products should be taken in Japan.

The authors in this article stated from their analyses of 22 patients with stroke that administration of keishibukuryogan resulted in improvement of skin temperature, cold sensation and numbness of diseased limbs presumably by increased peripheral blood flow. These results suggest the efficacy of keishibukuryogan for such clinical symptoms after stroke, though further investigation such as peripheral blood flow measurement and analysis of larger number of patients is required to determine its mechanism as the authors refer.

Reference


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