

Effects of a Traditional Japanese Medicine Goshajinkigan, Tokishigyakukagoshuyushokyoto on the Warm and Cold Sense Threshold and Peripheral Blood Flow

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Abstract

The purpose of this study was to investigate the effects of a traditional Japanese medicine Goshajinkigan (TJ-107) and Tokishigyakukagoshuyushokyoto (TJ-38) on warm sense threshold, cold sense threshold and the peripheral blood flow. 31 healthy volunteers (control group: 9 people, TJ-107 group: 12 people, TJ-38 group: 10 people) were examined. Drugs administered 2.5 g a dose. Analysis was before and after 1 hour dosage. The warm and cold sense threshold in the thenar of the non-handedness site of these subjects was measured using a thermostimulator (Intercross-200, Intercross Co., Tokyo, Japan). The peripheral blood flow in the finger of the non-handedness site of these subjects was measured using a full-field laser perfusion imager (FLPI, Moor Instruments Ltd., England). Control: The vehicle had no significant effect on the warm sense threshold, cold sense threshold and the peripheral blood flow. TJ-107: The warm sense threshold and cold sense threshold were significantly decreased, and the reaction latency of cold sense was significantly shortening. The peripheral blood flow was significantly increased second and third finger at 115.6%, 119.3%, respectively. TJ-38: The cold sense threshold and the reaction latency of cold sense were significantly increased. The peripheral blood flow was significantly increased second and third finger with 114.3%, 112.8%, respectively. These results suggest that TJ-107 and TJ-38 have effects on the changed warm sense threshold, cold sense threshold and increased peripheral blood flow.

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Keywords

A Traditional Japanese Medicine; Goshajinkigan; Tokishigyakukagoshuyushokyoto; The Warm and Cold Sense Threshold; Peripheral Blood Flow

1. Introduction

Recently, as a method for objectively evaluating has been reported a novel method of assessing thermal sensation that involves heat flux measurement, for allodynia and hyperesthesia of patients with neuropathic pain and the warm and cool susceptibility [1]-[5]. Heat flux is the heat-flow rate per unit area (W/m^2) between 2 materials at different temperature. Heat flux measurement has many advantages. It is not affected by the skin temperature of the subjects. It enables the accurate evaluation of thermal sensation in a short period of time and separate measurement of warm and cold sense threshold [1] [4]. The latter was impossible with conventional methods that used temperature itself as an index. Physiologically, warm sensation is transmitted by C fibers and cold is transmitted by $A\delta$ and C-fiber [6] [7]. This method enables separate measurements of warm and cold sense thresholds. There study shows that heat flux is a precise indicator of thermal threshold and that heat-flux measurement is a clinically useful quantitative sensation test.

Goshajinkigan (TJ-107) and tokishigyakukagoshuyushokyoto (TJ-38), a traditional Japanese medicine referred to as a “*kampo* medicine” has been approved by the Ministry of Health, Labor, and Welfare of Japan. TJ-107 has approved it as a remedy for leg pain, low back pain, numbness, blurred vision in old patients, pruritus, dysuria, frequent urination and edema. TJ-107 is generally applied for kidney-related disorders along with ageing [8]. Recently, TJ-107 has been shown to prevent the oxaliplatin-induced peripheral neuropathy in clinical studies [9]-[11]. TJ-38 has approved it as a remedy for chilblain, headache, lower abdominal pain and low back pain. Recently, TJ-38 has been shown to prevent the cold syndrome and dizziness with feelings of coldness [12] [13].

In the present study, we evaluated for the effects of TJ-107 and TJ-38 on the on warm and cold sense threshold and the peripheral blood flow.

2. Materials and Methods

2.1. Subjects

The subjects were 31 healthy volunteers obtained consent by a purpose of this study. In the control group, 9 people (3 males, 6 females, age; 35.6 ± 8.2 years old), TJ-107 group assumed 12 people (6 males, 6 females, age: 38.1 ± 11.3 years old), TJ-38 group assumed 10 people (5 males, 5 females, age: 37.1 ± 12.5 years old). All subjects provided informed consent for participation.

2.2. Drugs

Goshajinkigan (TJ-107) and Tokishigyakukagoshuyushokyoto (TJ-38) were manufactured and provided by Tsumura & Co. Ltd. (Tokyo, Japan). TJ-107 was composed of ten dried medicinal herbs, 5 g of *Rehmannia radix* (*Rehmannia glutinosa* Liboschitz); 3 g each of *Achyranthis radix* (*Achyranthes bidentata* Blume), *Corni fructus* (*Cornus of fi cinalis* Sieb. et Zucc), *Dioscoreae rhizoma* (*Dioscorea batatas* Decaisne), *Plantaginis semen* (*Plantago asiatica*), *Alismatis rhizoma* (*Alisma orientale* Juzep), *Hoelen* (*Poria cocos* Wolf), and *Moutan cortex* (*Paeonia suf fruticosa* Andrews); and 1 g each of *Cinnamomi cortex* (*Cinnamomum cassia* Blume) and *Aconiti tuber* (*Aconitum carmichaelii* Debeaux).

Tokishigyakukagoshuyushokyoto (TJ-38) was composed of nine dried medical herbs, 5 g of *zizyphi fructus* (*Zizyphus jujuba* Miller var. *inermis* Rehder): 3 g each of *Cinnamomi Cortex* (*Cinnamomum cassia* Blume), *Paeoniae Radix* (*Paeonia lactiflora* Pallas), *Angelica Radix* (*Angelica acutiloba* Kitagawa) and *Akebiae Caulis* (*Akebia quinata* Decaisne): 2 g each of *Glycyrrhizae Radix* (*Glycyrrhiza uralensis* Fischer), *Evodiac Fructus* (*Evodia rutaecarpa* Bentham) and *Asiasari Radix* (*Asiasarum sieboldi* Maekawa): and 1 g of *Zingiberis Rhizoma* (*Zingiber officinale* ROSCE).

Drugs were orally administered 2.5 g a dose with water. The control group was administered only water.

2.3. Measurements of Warm and Cold Sensation Thresholds

The warm and cold sense thresholds were measured on thenar of the non-handedness side, using a thermal stimulator that was controlled by prove of Peltier element and a push-button switch (Intercross-200, Intercross Co., Tokyo, Japan) (Figure 1) [1]-[5]. The surface area of the probe in contact with the skin was 25×25 mm. The probe consisted of a heat flux sensor, a peripheral temperature sensor and a thermode. A stimulus temperature was increased or decreased with a constant rate of change starting from an adaptation temperature. The speed of warming and cooling of the probe was set at $0.1^\circ\text{C}/\text{sec}$ until the subject felt a warm or cold sensation. All subjects were instructed to push the switch when they felt 'slightly warm' or 'slightly cold' from their thermal neutral state. We measured the warm sense threshold (W/m^2) and cold sense threshold (W/m^2) was calculated by integrating each heat flux until the subjects felt warm or cold respectively. The reaction latency was time until a felt warm sensation or cold sensation. The experiments were performed with the subjects sitting position in an air-conditioned (temperature 22°C - 26°C , humidity 45% - 55%) room. At the beginning of each session, subjects were given 30 min. to adapt to the room temperature. All tests were conducted by the same investigator to ensure consistency. The measurement was performed 60 min after the drug administration.

2.4. Measurements of Peripheral Blood Flow

The peripheral blood flow measured the blood flow of the finger (the second, three or four fingers) of the non-handedness side using a full-field laser perfusion imager (Moor FLPI, Moor Instruments, Essex, UK) [14] [15]. The measurement was performed 60 min after the drug administration. We analyzed mean blood flow of one minute and showed the increase and decrease of the blood flow after the medication for 100 with the blood flow before the medication.

2.5. Statistical Analysis

All the data are presented as means \pm SD. The data were analyzed by the Wilcoxon test. P values of <0.05 were defined as statistically significant.

3. Results

3.1. Warm Sensation Thresholds and Cold Sensation Thresholds

The control group did not change in the warm and cold sense thresholds, skin temperature and reaction latency (Figure 2).

TJ-107 group was significantly decreased the warm and cold sense thresholds, the warm sense varied from $647.9 \pm 398.0 \text{ W}/\text{m}^2$ to $444.3 \pm 283.5 \text{ W}/\text{m}^2$, the cool sense varied from $846.5 \pm 339.7 \text{ W}/\text{m}^2$ to $595.3 \pm 282.8 \text{ W}/\text{m}^2$ (Figure 3(a)). TJ-107 was significantly shortened reaction latency of cold sense shortened from 24.0 ± 15.2 sec. to 19.1 ± 15.2 sec. the reaction latency of warm sense shortened from 30.4 ± 11.7 sec. to 21.9 ± 13.9 sec. (Figure 3(b)). The skin temperature was not show cold and warm sense respectively (Figure 3(c)).

TJ-38 group was significantly increased a cold sense thresholds from $633.9 \pm 246.2 \text{ W}/\text{m}^2$ to $753.3 \pm 397.2 \text{ W}/\text{m}^2$, the warm sense threshold was increased from $537.2 \pm 282.2 \text{ W}/\text{m}^2$ to $702.4 \pm 627.5 \text{ W}/\text{m}^2$ (Figure 4(a)).



Figure 1. (a) The thermostimulator (Intercross-200, Intercross Co., Tokyo, Japan) comprising a probe, a push-button switch and thermocontroller; (b) Region measurement, on thenar of the non-handedness side.

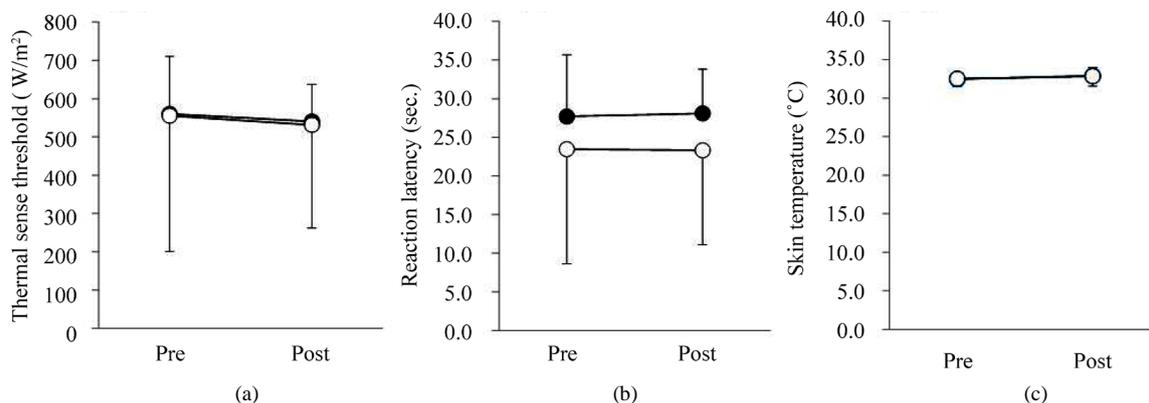


Figure 2. Effect of vehicle on warm and cold sense threshold. (a) Thermal threshold; (b) Reaction latency; (c) Skin temperature (Mean \pm S.D. n = 9).

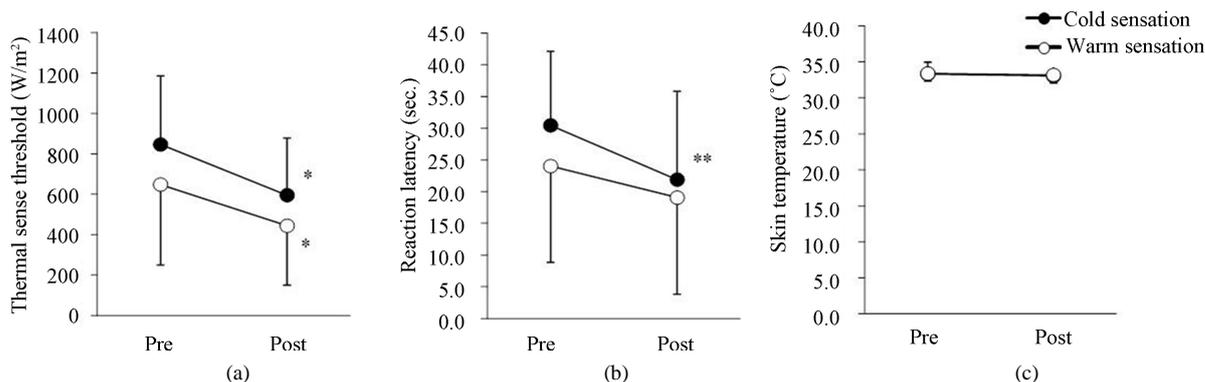


Figure 3. Effect of Goshajinkigan (TJ-107) on warm and cold sense threshold. (a) Thermal threshold, (b) Reaction latency, (c) Skin temperature. (Mean \pm S.D. n = 12, *: $P < 0.05$, **: $P < 0.01$ vs. Pre.).

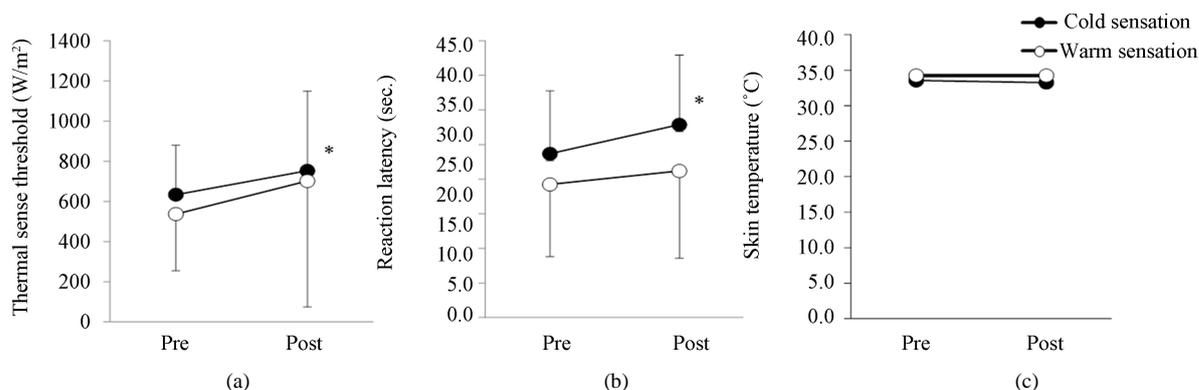


Figure 4. Effect of Tokishigyakukagoshuyushokyo (TJ-38) on warm and cold sense threshold. (a) Thermal threshold, (b) Reaction latency, (c) Skin temperature. (Mean \pm S.D. n = 10, *: $P < 0.05$ vs. Pre.).

TJ-38 was significantly prolonged reaction latency of cold sense from 23.7 ± 9.1 sec. to 27.9 ± 10.1 sec., the reaction latency of warm sense prolonged from 19.3 ± 10.4 sec. to 21.2 ± 12.6 sec. (Figure 4(b)). The skin temperature was not show cold and warm sense respectively (Figure 4(c)).

3.2. The Peripheral Blood Flow

The control group did not change in the peripheral blood flow (Figure 5(a)).

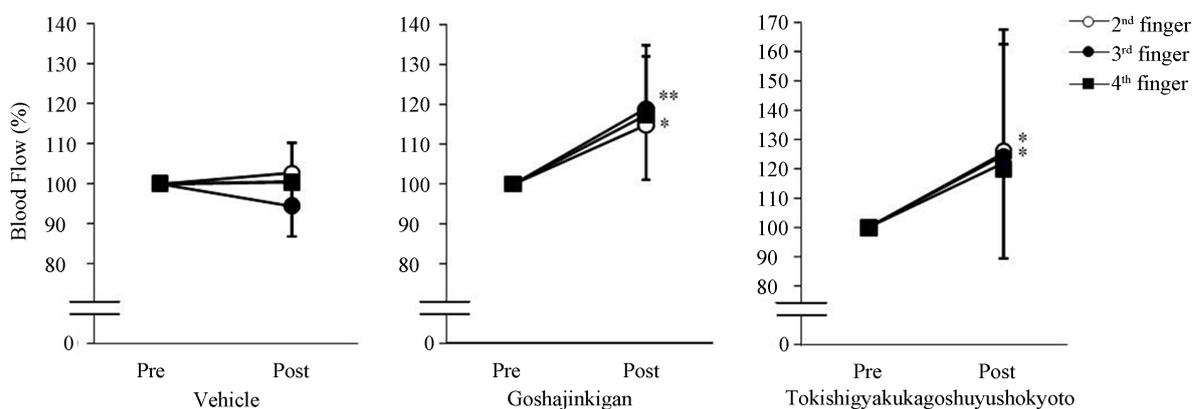


Figure 5. Effects of vehicle, Goshajinkigan (TJ-107) and Tokishigyakukagoshuyushokiyoto (TJ-38) on peripheral blood flow. (Mean \pm S.D. *: $P < 0.05$, **: $P < 0.01$ vs. Pre.).

TJ-107 group was significantly increased the peripheral blood flow of second and third finger at 115.6%, 119.3%, respectively (Figure 5(b)).

TJ-38 group was significantly increased the peripheral blood flow of second and third finger at 114.3%, 112.8%, respectively (Figure 5(c)).

4. Discussion

The results of the present study demonstrate that TJ-107 and TJ-38 have effects on the changed warm sense threshold, cold sense threshold and increased peripheral blood flow. Physiologically, warm sensation is transmitted by small unmyelinated fibers (C-fiber) and cold sensation is transmitted by small myelinated fiber ($A\delta$) and C-fiber [6] [7]. Therefore, it is inferred that C-fiber function has influence on warm sensation and to same degree in cold sensation. Also, it is inferred that $A\delta$ -fibers function has influence on cold sensation. To measure warm and cold sense threshold is to study the function of C-fiber and $A\delta$ -fibers, respectively.

TJ-107 is a traditional Japanese medicine (kampo) which is *Rehmanniae radix*, *Achyranthis radix*, *Corni fructus*, *Dioscoreae rhizoma*, *Plantaginis semen*, *Alismatis rhizoma*, *Hoelen*, *Moutan cortex*, *Cinnamomi cortex* and *Aconiti tuber*. TJ-107 has been widely used to treat symptoms like leg pain, low back pain, numbness, peripheral neuropathy, dropsy and cold sensation. Recently, efficacy for the symptom on the neuropathy, increased of blood flow as a result of increased nitric oxide (NO) production, platelet aggregation inhibitory effect and produced a concentration dependent vasodilatation in rat aorta [16] [17]. Moreover, TJ-107 has been shown to prevent the oxaliplatin-induced peripheral neuropathy such as numbness and cold hyperalgesia [9]-[11]. In the present study, it is shown that TJ-107 was significantly decreased the warm and cold sense thresholds, significantly shortened the reaction latency of cold sense and shortened the reaction latency of warm sense. These results suggest that TJ-107 was sensitive of the sensory in affecting on $A\delta$ -fiber and C-fiber. Also, TJ-107 was significantly increased peripheral blood flow. The present result was consistent with previous reports.

TJ-38 is a traditional Japanese medicine (kampo) which is *zizyphi fructus*, *Cinnamomi Cortex*, *Paeoniae Radix*, *Angelica Radix*, *Akebiae Caulis*, *Glycyrrhizae Radix*, *Evodiace Fructus*, *Asiasari Radix*, *Zingiberis Rhizoma*. TJ-38 has been widely used to treat symptoms such as low back pain, chilblains, headaches, lower abdominal pains with feeling of coldness and Raynaud's symptom. The results of the present study shown that TJ-38 was significantly increased a cold sense thresholds, significantly prolonged reaction latency and significantly increased peripheral blood flow.

Feeling of cold or a chilly sensation is called “Hie-sho” in Japanese, meaning cold syndrome. Patients with chilly sensation predominantly experience a sensation of being cold in the extremities when healthy people do not. The factors responsible for chilly sensation are assumed to be poor peripheral blood flow and impaired metabolism. Peripheral blood circulation is influenced by the activation of the sympathetic nervous system through the stimulation on α -adrenoceptors of vascular smooth muscle cells of the small artery. Therefore, the activity of sympathetic neurons may be important for chilly sensation [18]. These results suggest that TJ-38 was insensitive of the sensory in affecting on $A\delta$ -fiber and C-fiber. Moreover, these findings suggest that TJ-38 may be useful for the treatment of chilly sensation.

In this study, we evaluated for the effects of a traditional Japanese medicine (kampo) on the on warm and cold sense threshold using thermostimulator. The thermal threshold measurement has many advantages. It is not affected by the skin temperature of the subjects. It enables the accurate evaluation of thermal sensation in a short period of time and separate measurement of warm and cold sense threshold. The latter was impossible with conventional methods that used temperature itself as an index [1] [4]. Therefore, it is important to establish a new method for allodynia, hyperesthesia of patients with neuropathic pain and the warm and cool susceptibility.

In conclusion, the present results suggest that TJ-107 and TJ-38 has effects on the warm and cold sensation.

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