Effect of Gui-zhi-fu-ling-wan on Hot Flashes in Young Patients: A Retrospective Case Series

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Abstract
Hot flashes are one of the main problems in postmenopausal patients. Hormone replacement therapy is the standard treatment for this vasomotor symptom, but long-term estrogen treatment can produce serious adverse effects such as higher risks of cardiovascular disease and breast cancer. For this reason, hormone replacement therapy may not be advisable for young patients. Gui-zhi-fu-ling-wan is an herbal decoction for hot flashes used in traditional Chinese medicine. We have extensive experience treating hot flashes in young women; this preliminary case series evaluates the effectiveness of Gui-zhi-fu-ling-wan for alleviating hot flashes in young patients. In this retrospective case series, we reviewed the medical records of outpatients who visited the Department of Cardiovascular and Neurologic Disease, Kyung Hee Oriental Medical Center for hot flashes from October 1, 2003 to October 1, 2008. Of the 60 cases, 37 met the inclusion criteria. Mean improvement in symptoms, as assessed using the visual analog scale, was 40.4±28.5%; 51.3% of patients experienced a 50% improvement. According to the secondary analysis, the results of differential diagnosis of cold and hot syndrome and blood stasis syndrome did not affect scores. Only 2.7% of the patients reported adverse events. Our findings suggest that Gui-zhi-fu-ling-wan improves hot flashes in young patients in a relatively safe manner. However, rigorous clinical studies are needed to confirm these results.

1. Introduction
Hot flashes are associated with menopause or hormonal changes that accompany certain treatments, such as androgen deprivation therapy for prostate cancer and estrogen antagonist therapy after breast cancer surgery [1–4]. Although the prevalence of hot flashes is unknown, many young patients who experience hot flashes but have no significant medical disorders are seen in clinical practice. Hormone replacement therapy, which is the standard treatment for hot flashes, carries a substantial risk of cardiovascular disease and breast cancer [5]. Thus, nonhormonal alternatives, including lifestyle modification, exercise, acupuncture, and herbal remedies (e.g., phytoestrogen and herbal treatments) are widely used. Considerable clinical evidence for these interventions has been recently assessed [6–10]. Gui-zhi-fu-ling-wan (GFW) is an herbal formula consisting of five herbs. GFW has been widely used to...
treat hot flashes in Korea, China and Japan. Previous studies have reported that GFW improves the hot flashes of menopausal women [11], possibly by increasing calcitonin gene-related peptide (CGRP) activity. GFW inhibited CGRP-induced elevation of skin temperature without restoring serum estrogen in rats that had undergone ovariectomies [12]. In this study, we evaluated the effectiveness of GFW for treating hot flashes in young patients.

2. Methods and Methods

2.1. Inclusion criteria

We reviewed the medical records of outpatients who visited the clinic of a traditional Korean medical doctor in the Department of Cardiovascular and Neurologic Disease (Stroke Center), Kyung Hee Oriental Medical Center, Seoul, Korea, for hot flashes from October 1, 2003 to October 1, 2008. Inclusion criteria were as follows: frequent temporal sensations of heat for at least 1 month; age between 18 and 55 years old; no serious medical diseases with symptoms that included hot flashes (e.g., prostate cancer, breast cancer); and no medications or treatments for hot flashes. The sex of the patient was not a criterion for study inclusion.

2.2. Exclusion criteria

We excluded patients who were in menopause, had serious diseases, or had undergone medical procedures such as surgery on sex organs, which could induce hormonal changes. Patients whose medical records were incomplete were also excluded.

2.3. Administration of GFW

The patients were prescribed dry GFW extract powder (5.0−7.5 g/day; Tsumura & Co. Ltd., Japan) according to the severity of symptoms, taking into account conditions such as digestive function and body strength. Each 7.5 g GFW contained 1.75 g extract mixture composed of equal amounts of Cinnamomum cortex, Paeoniae radix, Moutan cortex, Hoelen, and Persicae semen [12]. The remaining 5.75 g consisted of light anhydrous silicic acid, stearic acid, magnesium, and lactose hydrate used as excipients. GFW extract was administered orally two or three times a day.

2.4. Evaluation and outcome variables

The medication’s effectiveness was estimated from changes in the number and severity of hot flashes compared with baseline. Patients evaluated their experiences using a 100-mm visual analog scale (VAS). Cure rate was also evaluated. Results were classified into five groups: remarkably effective (RE, VAS score improvement >75), more than effective (ME, VAS score improvement of 50–75), effective (EF, VAS score improvement of 25–50), not effective (NE, VAS score improvement <25), or aggravating (AG, no improvement or worsening of VAS score). Responders were defined as the patients whose VAS scores improved by more than 50%. Safety was assessed by the type and frequency of adverse events, which were classified as none, mild, or severe.

To determine the relationship between hot flashes and blood stasis syndrome, the blood stasis score was determined according to Terasawa’s “Oketsu” scoring system (Table 1) [13]. During the physician’s four examinations, cold syndrome and hot syndrome were also diagnosed.

2.5. Statistical analysis

SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The Mann-Whitney U test was used for comparisons between men and women, hot and cold syndrome groups, and blood stasis syndrome (BSS) and non-blood stasis syndrome.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Diagnostic criteria for blood stasis syndrome [12]</th>
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<tbody>
<tr>
<td>Symptom</td>
<td>Score</td>
</tr>
<tr>
<td>Dark-rimmed eyes</td>
<td>10</td>
</tr>
<tr>
<td>Areas of dark pigmentation on face</td>
<td>2</td>
</tr>
<tr>
<td>Rough skin</td>
<td>2</td>
</tr>
<tr>
<td>Livid lips</td>
<td>2</td>
</tr>
<tr>
<td>Livid gingiva</td>
<td>10</td>
</tr>
<tr>
<td>Livid tongue</td>
<td>10</td>
</tr>
<tr>
<td>Telangiectasis/spider veins</td>
<td>5</td>
</tr>
<tr>
<td>Subcutaneous hemorrhage</td>
<td>2</td>
</tr>
<tr>
<td>Palmar erythema</td>
<td>2</td>
</tr>
<tr>
<td>Resistance and tenderness on pressure of the left paraumbilical region</td>
<td>5</td>
</tr>
<tr>
<td>Resistance and tenderness on pressure of the right paraumbilical region</td>
<td>10</td>
</tr>
<tr>
<td>Resistance and tenderness on pressure of the umbilical region</td>
<td>5</td>
</tr>
<tr>
<td>Resistance and/or tenderness on pressure of the ileocecal region</td>
<td>5</td>
</tr>
<tr>
<td>Resistance and/or tenderness on pressure of the sigmoidal region</td>
<td>5</td>
</tr>
<tr>
<td>Resistance and/or tenderness on pressure of the subcostal region</td>
<td>5</td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>10</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>10</td>
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</tbody>
</table>

Total score >20 indicates blood stasis syndrome.
Guizhi-fu-ling-wan for hot flashes in young patients

(NBSS) groups, because these data were not normally distributed. Correlation analysis was used to examine the relationship between VAS improvement and other factors (age, number of visits, total medication days, and duration of hot flashes).

3. Results

3.1. Patient characteristics

We reviewed the medical records of 60 patients; 23 patients were excluded because of inadequate medical records. Thirty-seven patients were included in the analysis. The mean age was 32.3±10.3 years (mean±SD), and the duration of hot flashes was 7.2±6.4 years. Twenty-two patients were women, and 15 were men. Most of the patients were white-collar workers, two patients were soldiers, and three were unemployed.

There were several accompanying symptoms: sweating (n=4), cold hands and feet (n=4), sleep disturbance (n=3), and other (n=4). On average, patients visited the clinic 3.4±1.5 times and took GFW for 128±103.2 days.

3.2. Effectiveness assessment

Mean VAS score improvement was 40.4±28.5; 19 (51.3%) of the patients were classified as responders (Table 2). There was no difference between men and women in terms of effectiveness (Mann-Whitney U test, z=−0.670, p=0.503). The total number of days of herbal formula use was positively correlated with its effectiveness (Spearman’s r=0.452, p=0.005), but the total visiting days, duration of symptoms, and age showed little or no correlation with the change in VAS score (Spearman’s r=0.279, −0.180, and −0.064, respectively; p=0.095, 0.317, and 0.695, respectively).

3.3. Comparison of effectiveness between cold syndrome group and hot syndrome group

Twelve patients received a diagnosis of cold syndrome, and 12 patients received a diagnosis of hot syndrome. This diagnosis did not influence VAS score improvement (Mann-Whitney U test, z=−0.602, p=0.547).

3.4. Comparison of effectiveness between blood stasis syndrome group and non-blood stasis syndrome group

We compared VAS score improvement between the BSS group (n=5) and the NBSS group (n=4) and detected no statistical difference between the groups (z=−0.809, p=0.418).

3.5. Safety assessment

Adverse events were reported in two patients (5.4%). In one case, treatment was terminated immediately because of itching and edema. The other patient reported a mild adverse event of dyspepsia and constipation.

4. Discussion

Hormonal changes such as those that occur during menopause are considered to be the main causes of hot flashes. Alternative therapy has been shown to be useful in treating hot flashes [6]. In traditional Chinese medicine, GFW is generally used for hot flashes. Previous studies have reported the effectiveness of GFW for treating hot flashes, but most focused on menopausal patients. In the present study we evaluated GFW for treating hot flashes in young patients who have no serious medical problems.

We found GFW to be effective in 81% of patients (Table 1). Moreover, about 51% of patients were responders. Patients who took GFW for more than 100 days experienced better relief of symptoms; however, patient age or duration of symptoms did not correlate with VAS score improvement. Traditional Chinese medicine recognizes numerous syndromes that exhibit various symptoms. Hot syndrome or cold syndrome was diagnosed based on the patient’s symptoms; however, the diagnosis of hot or cold syndrome did not influence VAS score improvement in this study. GFW is usually prescribed for patients who have BSS; however, no significant difference was detected in the improvement of VAS scores between the BSS and NBSS groups. This result may be due in part to the exclusion of patients whose medical records (n=28) did not contain sufficient information to diagnose BSS.

The physical mechanism of GFW’s effect on hot flashes is uncertain. However, GFW regulates the elevation of skin temperature induced by CGRP without estrogen activation [14,15]. The mechanism by which GFW treats hot flashes is not related to

Table 2 Assessment of Gui-zhi-fu-ling-wan treatment

<table>
<thead>
<tr>
<th>Cases (n)</th>
<th>Effectiveness, n (%)</th>
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<tbody>
<tr>
<td></td>
<td>RE</td>
</tr>
<tr>
<td>37</td>
<td>9 (24)</td>
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</tbody>
</table>

RE=remarkably effective; ME=more than effective; EF=effective; NE=not effective; AG=aggravating.
estrogen; therefore, adverse effects associated with estrogen can be avoided when treating hot flashes with GFW.

GFW is one of the treatments for blood stasis established by Zhang Zhongjing. Originally, it was used to activate the blood and eliminate masses for women who had aggregation–accumulation conditions [16]. In this context, GFW might be used to treat hot flashes in young patients. Such hot flashes were thought to typically originate in the stagnation of qi and blood in cases of liver qi depression and liver–spleen disharmony.

Itching and edema, which were reported by one patient, could be explained by P. radix, an herbal component of GFW, which may induce hepatotoxicity and elicit a hypersensitivity reaction [17,18]. Dyspepsia may be related to the inhibitory action of P. radix on gastric acid [19]. However, no severe adverse events and only a small number of minor adverse events were reported in this study. Therefore, GFW was shown to be relatively safe in this small preliminary study.

The putative relationship between physical activity and hot flashes is controversial [7,20]. Heavy physical activity induces vasodilatation and makes hot flashes more intense. However, in our study most of the patients were white-collar workers. Stress from mental exertion can induce qi stagnation, which may account for hot flashes experienced by white-collar workers [21].

Seventeen patients were not included in this study, because they visited the doctor only once. In a follow-up telephone interview, two replied that GFW did not work for them. This retrospective case study has many limitations. First, this study did not include a control group, and only a small number of cases were used for the analysis; therefore, the effects of GFW for treating hot flashes cannot be precisely determined from these data. Second, this study has methodological flaws, such as the absence of objective outcomes and the lack of a consistent endpoint. We depended primarily on assessments of medical history and determined symptom improvement using subjective self-reporting by patients without hormonal evaluation. Different endpoints for assessing hot flashes in each patient preclude the use of these findings for obtaining conclusive evidence of the effects of GFW. Nevertheless, case studies or case series have value, because they provide the rationale for clinical trials. Despite its limitations, this study provides some basic knowledge regarding the clinical effectiveness of GFW in young patients. Rigorous clinical trials are needed to evaluate the effectiveness of herbal treatments including GFW for treating hot flashes in young patients.

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References