Collaboration of Japanese Kampo Medicine and Modern Biomedicine

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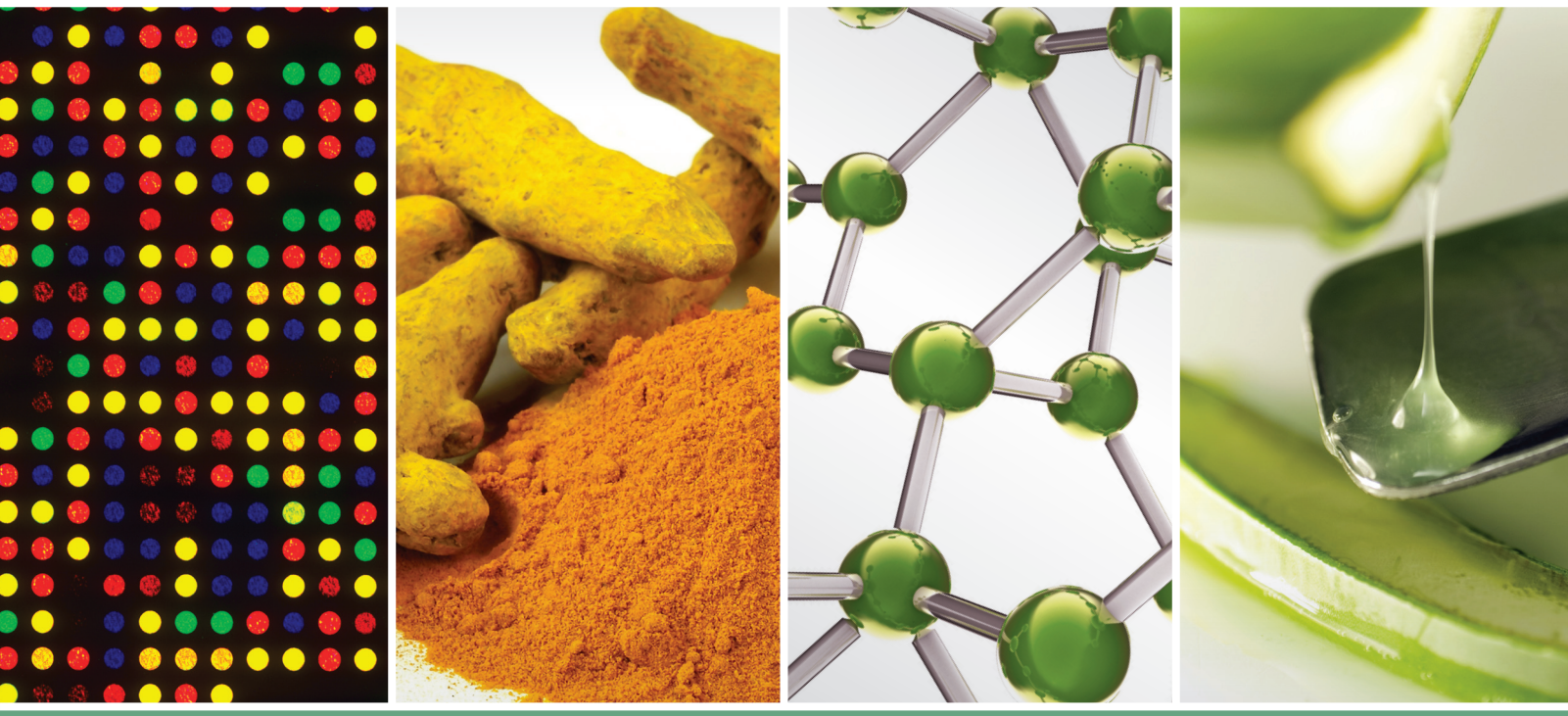

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Editorial Board

Contents

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Editorial

Collaboration of Japanese Kampo Medicine and Modern Biomedicine

Kenji Watanabe,[1] Gregory A. Plotnikoff,[2] Takeshi Sakiyama,[3] and Heidrun Reissenweber-Hewel[4]

[1] *Faculty of Environment and Information Studies, Keio University, Fujisawa, Kanagawa 252-0882, Japan*
[2] *Penny George Institute for Health and Healing, Allina Health, Minneapolis, MN 55407, USA*
[3] *Ishikawa Clinic, Hacchobori, Chuo, Tokyo 104-0032, Japan*
[4] *Technical University of Munich and Private Clinic for Japanese Medicine, Gräefelfing, 82166 Munich, Germany*

Correspondence should be addressed to Kenji Watanabe; watanabekenji@a6.keio.jp

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Worldwide, health care systems are increasingly highlighting the importance of traditional medicines. The World Health Organization (WHO) plans to introduce traditional medicine into the international classification of diseases (ICD) for the first time since it started in 1900. Kampo medicine is a traditional Asian medical system that is unique in many ways. Kampo was transferred from the ancient Han Chinese dynasty and uniquely developed in Japan, especially during the Edo period (1603–1867). The theoretical understanding and the use of the abdominal examination "Fukushin" to assess the patient's constitutional state are particular to Kampo.

After the Meiji restoration in 1867, Japan's new government accepted only Western medicine from Europe and founded one medical licensure system. The result was suppression of acquired wisdom and insights with marginalization of practitioners until 1976. At that time, the Japanese Medical Association promoted its coverage by Japan's National Health Insurance program by physicians who were trained in Western medicine. And now, all of Japan's 80 medical schools teach Kampo medicine. As a result, roughly 90% of physicians use Kampo medicine in their daily practice. This is a very unique model of integration of traditional medicine and modern biomedicine. To better understand the promise of this integration, this special issue features Kampo medicine in the context of modern biomedicine.

Many provocative articles are included in this special issue. To begin, K. Katayama et al. address the current situation of Kampo use in the National Health Care program. The authors analyzed 67,113,579 health care claim records and found that only 1.34% represented Kampo prescriptions. This suggests that a very small portion of conventional practice includes Kampo treatment even though many physicians use Kampo. H. Okamoto et al. present us with a case series of patients with refractory glossodynia. Among 39 patients, 69.2% of patients reported a beneficial effect. This is one of the examples in which Kampo treatment is effective even for the difficult cases in the Western biomedicine. K. Ogawa et al. show the usefulness of daiobotanpito for the treatment of acute diverticulitis. Y. Tanaka and T. Sakiyama report the case series of the usefulness of the Kampo treatment for pediatric emotional and behavioral disorders which were also refractory to the modern biomedicine. M. A. Bahar et al. reported that goshajinkigan prevents paclitaxel induced peripheral neuropathy without interfering with the anticancer action of paclitaxel in the basic research. Kampo medicines are often used for the purpose of the reduction of the side effects of chemotherapy for malignancies. K. Watanabe et al. report the potentially preventive effect of diabetic complications. Goshajinkigan is often used for the neuropathy from diabetes mellitus. Additionally, this Kampo medicine may be beneficial for the blood glucose control. K. Katayama et al. report a computer-based diagnostic way of Kampo patient patterns termed "Sho." This represents a promising blend of modern technology for a new world of traditional medicine in the future. Y.-C. P. Arai et al. reported about Fukushin, Kampo's

unique diagnostic procedure. Certain Fukushin findings are related to the anxiety-depression levels. T. Namiki et al. report that cytosine-adenine (CA) repeat polymorphism of the estrogen receptor β gene can be the predictive biomarker of the effectiveness of Kampo medicine for the treatment of the climacteric syndrome. T. Yoshino et al. and H. Tokunaga et al. describe *hie* (cold sensation) and *hiesho* (cold disorder). Hie and hiesho are very important concepts in Kampo treatment. T. Yoshino et al. characterized hie and hiesho. H. Tokunaga et al. characterized the differences of male hie, female hie with menstruation, and female hie after menopause by data mining method. To conclude, S. Yakubo et al. summarize the history and pattern diagnosis of Kampo medicine.

Together, these articles represent the promise and challenges present in the scientific understanding of Japan's herbal medicine tradition. We hope these articles help the readers to understand and appreciate the potential power of Kampo medicine outside of Japan. We invite you to explore Kampo.

Kenji Watanabe
Gregory A. Plotnikoff
Takeshi Sakiyama
Heidrun Reissenweber-Hewel

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Research Article

Long-Term Effects of Goshajinkigan in Prevention of Diabetic Complications: A Randomized Open-Labeled Clinical Trial

K. Watanabe,[1] A. Shimada,[2] K. Miyaki,[3] A. Hirakata,[4] K. Matsuoka,[2] K. Omae,[5] and I. Takei[6]

[1] *Center for Kampo Medicine, Faculty of Environment and Information Study, Keio University School of Medicine, 5322 Endo, Fujisawa, Kanagawa 252-0882, Japan*
[2] *Division of Internal Medicine, Saiseikai Central Hospital, 1-14-17 Mita, Minato-ku, Tokyo 108-0073, Japan*
[3] *Department of Clinical Research and Informatics, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan*
[4] *Department of Ophthalmology, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan*
[5] *Department of Preventive Medicine and Public Health, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan*
[6] *Tokyo Dental College, Ichikawa General Hospital, 5-11-13 Sugano, Ichikawa, Chiba 272-8513, Japan*

Correspondence should be addressed to K. Watanabe; watanabekenji@a6.keio.jp

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Objective. This clinical trial was designed to investigate whether goshajinkigan reduces the onset of diabetic complications or not. *Materials and Methods*. A total of 332 type 2 diabetic mellitus patients were registered from 9 clinical centers from March 2000 to August 2007. Patients were randomly assigned to take goshajinkigan extract powder, 2.5 grams for 3 times a day or no kampo therapy, additionally to the regular treatment. The primary endpoints were the onset of macrovascular diseases or progression of nephropathy or retinopathy. Statistical analysis was performed by the intention-to-treat method. *Results*. After 5 years of observation, 116 patients were submitted to analysis. Among them, no macrovascular events were observed in both groups. Although 43 participants had upstaging of retinopathy or nephropathy in total, there was no significant difference between goshajinkigan group and control group. Deterioration of ankle reflex was suppressed in goshajinkigan group. Also glycated hemoglobin, and fasting plasma glucose were decreased in the goshajinkigan group. *Conclusion*. Although the power of analysis was too low to demonstrate any effects of goshajinkigan on the progression of macrovascular diseases, retinopathy or nephropathy, goshajinkigan may be beneficial for diabetic neuropathy and glycemic control.

1. Introduction

Diabetes mellitus has become a big problem all over the world. Also in Japan, the number of patients with diabetes mellitus has steadily increased on an annual basis. In 1998, the Ministry of Health and Welfare estimated that there were 6.9 million diabetics in Japan. Afterwards, this estimate was increased to 7.4 million and 8.9 million in 2002 and 2007, respectively [1]. According to the Diabetes Atlas (the International Diabetes Federation) published in 2011, the number of patients with diabetes living in Japan was 10.7 million [2].

Several studies have shown that the progression of diabetic microvascular complications, such as retinopathy, nephropathy, and neuropathy, can be inhibited by a good glycemic control [3–5]. However, several recent large scale randomized clinical trials have shown that glycemic control alone was not sufficient to prevent the progression of macrovascular complications, such as cerebral and myocardial infarction [5–9]. Furthermore, in terms of arteriosclerosis and microcirculation disorders, elderly individuals often have a number of risk factors for cardiovascular events, including hypertension and dyslipidemia [9]. However, protective effects of antihypertensive therapy and lipid control

have been found to have limited effects for preventing macrovascular complications. Hence, an improvement in lifestyle is required, such as smoking cessation and weight control. Given the above, preventing the progression of complications only by glycemic control in the elderly is difficult, and new treatment methods are needed [10].

Clinical conditions similar to diabetes were treated with the administration of hachimijiogan in the Jingui Yaolue, a Chinese classic written approximately 1,800 years ago. Goshajinkigan, a kampo product, contains 10 herbal ingredients adding two herbs, that is, Achyranthis radix and Plantaginis semen, to hachimijiogan and is applied to patients with lumbago, edema of the lower legs, dysuria, and so forth. In an animal model of diabetes, goshajinkigan showed inhibition of weight gain, inhibitory effects on blood glucose, suppression of microalbuminuria [11], preventative effects on hypertriglyceridemia [12], inhibition of platelet aggregation [13], and elevation of the pain threshold [14, 15], all of which appeared to be effective in preventing further complications from diabetes. To date, however, no report has been published on the preventive effects of goshajinkigan for diabetic complications, with the exception of neuropathy and corneal disorders [16]. As such, a large study is needed for investigating whether kampo is effective in preventing the progression of diabetic complications.

This trial was specifically designed to determine whether a kampo formulation of goshajinkigan would reduce the rate of cardiovascular events, microvascular complications, and laboratory abnormalities, as compared with a control group without this kampo formulation in middle-aged and older people with type 2 diabetes mellitus and additional cardiovascular risk factors. Here, we report the effects of the kampo formulation on the primary composite outcome of major cardiovascular events and microvascular complications in middle-aged and older people with type 2 diabetes mellitus.

2. Methods

2.1. Eligibility and Study Design. This multicenter clinical study was conducted in 9 clinical centers in Japan. We recruited outpatients of type 2 diabetes mellitus of age between 40 and 75 years from March 2000 to August 2007. In order to investigate the progression of diabetic complications, glycated hemoglobin level of ≥6.5% was selected in the inclusion criteria. Exclusion criteria were a past macrovascular events, like cereberal stroke, myocardial infarction, angina pectoris, foot gangrene, or atherosclerotic obstruction. Other exclusion criteria were nephropathy with macroalbuminuria or with a serum creatinine levels of 1 mg/dL or more and proliferative and preproliferative retinopathy. Additional exclusion criteria which were related to goshajinkigan pattern were a body mass index of ≥30 kg/m^2, 2 or more digestive system symptoms (e.g., gastrointestinal weakness, anorexia, nausea, and diarrhea), and 3 or more symptoms or activities indicative of sensitivity to heat, including a preference for dressing lightly, sweating upwards from the neck, a tendency to drink cold water, a flushed face, congestion of the eyeballs, and a high body temperature (not less than 36.7°C).

2.2. Intervention. All 116 patients were randomly assigned to the goshajinkigan group or control group. Randomization was accomplished by a study controller, and allocations were provided in sealed envelopes. Because of the long-term clinical study, we anticipated that the dropout rate is high in goshajinkigan group and allocation to goshajinkigan group was planned to be double of control group. The trial was open once patients were randomized. Only the readers of the fundus photographs were blinded. No placebo treatments were given.

As a background treatment, all participants received nutrition and physical activity counseling every year upon entering the study. Nutrition counseling included a recommendation that the caloric intake should not exceed the number of calories derived from multiplying the estimated body weight (kg) by a factor of 25. Current smokers and drinkers received smoking and drinking cessation counseling. All participants received glucose-lowering therapy, the same as the one before entering the study, as well as lipid-lowering therapy and/or blood pressure-lowering therapy. No restrictions were made regarding the choice of medications, with the exception that no kampo formula other than goshajinkigan could be used. The targeted glycated hemoglobin was lower than 6.9% (National Glycohemoglobin Standardization Program); targeted blood pressure was lower than 130/85; targeted body mass index was lower than 22.0 kg/m^2; targeted total cholesterol was lower than 220 mg/dL; targeted high-density lipoprotein was higher than 40 mg/dL, according to the Japanese Diabetes Society Guide of 1999 for the treatment of diabetes, the Japanese Society of Hypertension Guidelines of 2000 for the management of hypertension, and the Japan Atherosclerosis Society Guidelines of 1997 for the diagnosis and treatment of hyperlipidemia.

Patients received instructional materials and behavioral counseling regarding diabetes care and were provided with goshajinkigan. Therapeutic regimens were individualized at the discretion of the investigators and patients on the basis of study-group assignments and response to therapy. The adverse effects of therapy were carefully audited both locally and centrally to ensure the safety of the patients.

2.3. Goshajinkigan. Patients in the goshajinkigan treatment group received 2.5 g of goshajinkigan extract (TJ-107; Tsumura Co., Tokyo, Japan) preprandially which included 4.5 g of the compound extracts of 10 herbal medicines: *Rehmanniae radix* (5g), *Achyranthis radix* (3g), Corni fructus (3g), *Dioscoreae rhizoma* (3g), Hoelen (3g), *Plantaginis semen* (3g), *Alismatis rhizoma* (3g), *Moutan cortex* (3g), *Cinnamomi cortex* (1g) and heat-processed *Aconiti* radix (1g). The extract product Goshajinkigan (TJ-107, Tsumura goshajinkigan extract granules) is a standardized spray-dried water extract, which includes magnesium stearate, lactose, and fructose fatty acid esters as diluents. The manufacturing process meets all requirements of the Japanese and international GMP guidelines.

2.4. Primary and Secondary Outcomes. The prespecified primary endpoints were the first occurrence of nonfatal myocardial infarction or nonfatal stroke or worsening of diabetic

nephropathy (DN) or retinopathy (DR). The progression of DN was evaluated by the new onset of renal failure by dialysis or an increase in the amount of urinary protein. The urinary protein was calculated by dividing the morning urinary albumin by the urinary creatinine not related to any acute intercurrent illness. The amount of urinary protein was divided into 3 stages: <30 mg/gCr, 30–300 mg/gCr, and >300 mg/gCr.

The progression of DR was evaluated by standardized eye examinations conducted by ophthalmologists or optometrists, along with fundus photography of 4 standard stereoscopic fields at baseline and every year. The photographs were gathered at the Fundus Photograph Reading Center, located at the University of Kyorin (Mitaka, Tokyo), and were graded by trained personnel masked to the treatment assignments of the participants. The presence of capillary aneurysms, retinal bleeding, hard exudate, ring-like hard exudate, soft exudate, intraretinal microvascular abnormalities, venous abnormalities, and new blood vessels was evaluated. The DR stage was divided into 8 steps from normal to proliferative (3 classifications each pertained to the simple and preproliferative steps).

The study investigators also measured the effect of the intervention on body weight, blood pressure, fasting blood glucose, glycated hemoglobin, serum insulin (c-peptide reactivity in the insulin user), total cholesterol, triglyceride, high-density lipoprotein, serum creatinine, urea nitrogen, and DN as secondary outcomes. DN was evaluated by using two-way analysis of variance. The grade of the ankle reflex was classified into 3 steps: normal, decreased, and absent. Moreover, the results of the questionnaire on 10 subjective symptoms were evaluated by 4 steps, and 4 of these 10 symptoms were also evaluated with a visual analogue scale (graded from 0 to 100). The questionnaire included lightheadedness, abnormal sweating, occurrence of constipation and diarrhea, impotence, abnormal feeling like pater stuck to the soles, uncomfortable heat sensation of hands and feet, pain of hands and feet, abnormal sensation of hands and feet, cold sensation of hands and feet, and muscle cramp.

2.5. Safety Analyses. For monitoring side effects, aspartate aminotransferase, alanine aminotransferase, serum creatinine, urea nitrogen, uric acid, urinary blood, glucose, and ketone were investigated every 6 months. When critical side effects were suspected because of goshajinkigan, the treatment was stopped immediately, and suitable treatment was performed. Concomitantly, a report was promptly made to the research center.

2.6. Sample Size. We aimed to recruit 1000 cases for the goshajinkigan group and 500 for the control group. The sample size was calculated for an event rate of 6% per year, an effect of 20%, an alpha error of 5%, and a power level of 80%.

2.7. Statistical Analyses. All statistical analyses were conducted at the coordinating center with the use of SAS software, version 9.1 (SAS Institute). Baseline characteristics were compared in the 2 study groups with the use of chi-square tests and two-sample t-tests. At each assessment visit, glycated hemoglobin levels and fasting plasma glucose levels were summarized with the use of medians and interquartile ranges. Exposure to glucose-lowering drugs was summarized according to the study group as the number of patients who received a prescription for a medication. Analysis of the primary outcome was performed with the use of the log-rank method according to the intention-to-treat principle, and the occurrences of this outcome in the 2 study groups were compared with the use of hazard ratios and 95% confidence intervals. Kaplan-Meier estimates were used to obtain the proportion of patients who had an event during follow-up. Analyses of the secondary outcomes were performed with the use of log-rank methods, two-sample Wilcoxon's test, and Fisher's exact test. We report here all nominal P values, unadjusted for the multiplicity associated with the various tests performed for this study or the monitoring of the primary and mortality endpoints by the data and safety monitoring committee.

3. Results

3.1. Participants Registration, Allocation, Follow-Up, and Analysis. A total of 332 patients were registered for this clinical trial (Figure 1), among which 162 patients were excluded because they were out of criteria. The main reason of the exclusion was the retinopathy. Even though, in the regular ophthalmological check, these patients matched the inclusion criteria, fundus photography revealed that these patients did not match the inclusion criteria. Another reason was out of goshajinkigan pattern. This was relatively difficult for the physician who contributed to this study. As a result, 170 patients were allocated to goshajinkigan (GJG) group (n = 100) to control group (n = 49).

3.2. Baseline Characteristics of Study Groups. A total of 116 patients were submitted for analysis of this study. Table 1 shows the baseline characteristics of two groups. Age, sex distribution, and duration of diabetes were similar in the 2 study groups. Smoking habits were also similar. Blood chemistry profile was also similar in the 2 groups. The mean duration of follow-up was 28 months for the goshajinkigan group and 15 months for the control group.

3.3. Primary Outcomes. No macrovascular events, like myocardial infarction, angina pectoris, or cerebrovascular diseases, occurred in either group. None of the patients had macrovascular events. A total of 43 participants had a progression of stages in either nephropathy or retinopathy: 40.2% in the goshajinkigan group and 39.1% in the control group (Figure 2). In terms of nephropathy, 25 participants had nephropathy at the end of this study: 27.2% in goshajinkigan group and 18.7% in control group (P = 0.244) (Figure 3). In terms of retinopathy, a total of 25 participants had nephropathy at the end of this study: 17.9% in goshajinkigan group and 20.0% in control group (P = 0.816) (Figure 4).

3.4. Secondary Outcomes. The progression of the grade of the ankle reflex was significantly more frequent in the control

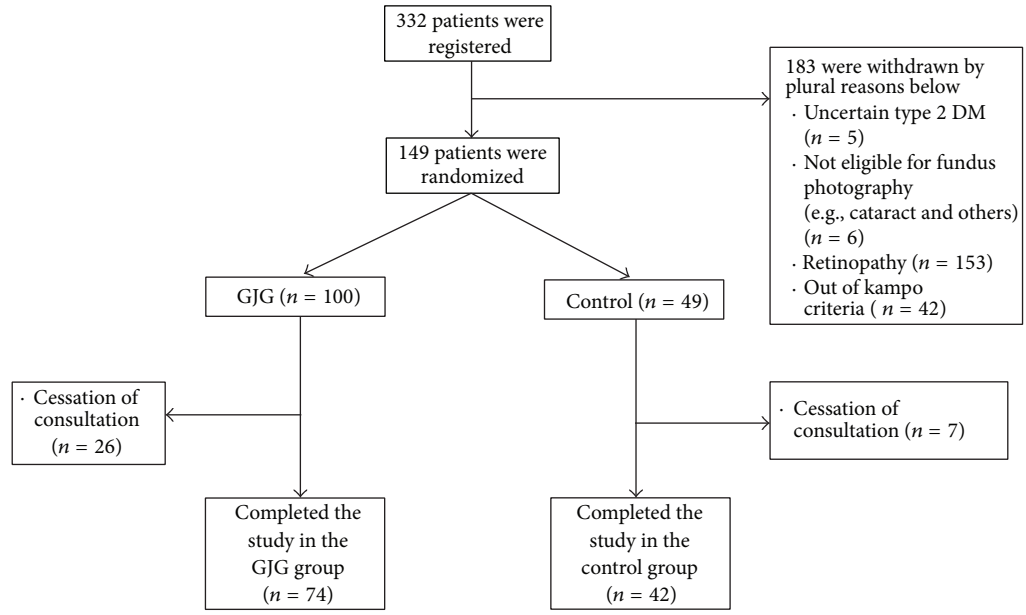

Figure 1: Enrollment, randomization, and follow-up of study participants. A total of 116 men and women were randomly assigned to either the goshajinkigan group or the control group. The trial was stopped when the national funding stopped, although significantly more volunteers were to be included in the trial.

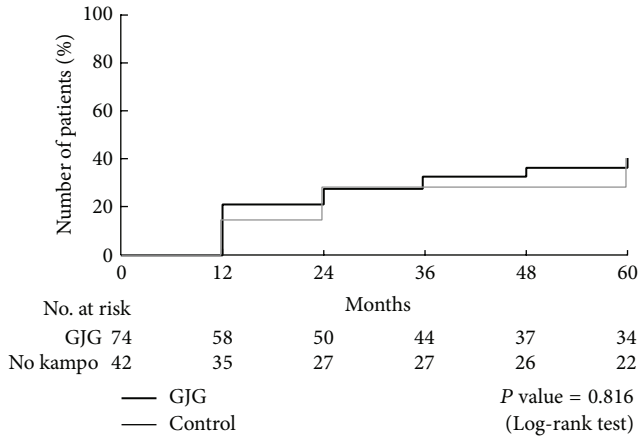

Figure 2: Primary endpoint. A total of 43 participants had a microvascular event and no macrovascular events: 40.2% in the goshajinkigan group and 39.1% in the control group ($P = 0.816$). The mean duration of follow-up was 28 months for the goshajinkigan group and 15 months for the control.

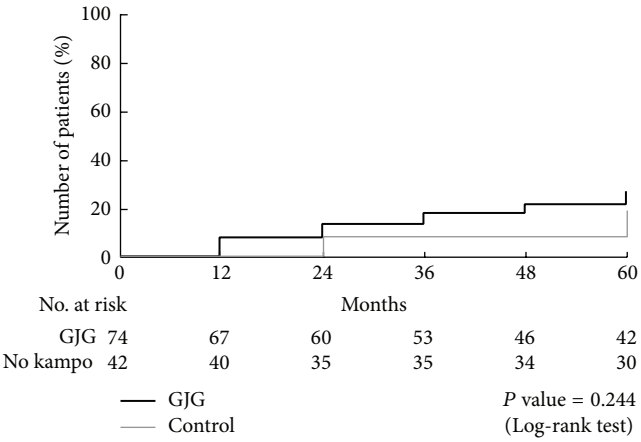

Figure 3: Progression of nephropathy. A total of 25 participants had nephropathy at the end of this study: 27.2% in goshajinkigan group and 18.7% in control group ($P = 0.244$).

group. The hazard ratio was calculated as 0.436 (95% CI: 0.198–0.962), and the P value was 0.040 as determined by the log-rank test (Figure 5).

Stable median levels of glycated hemoglobin of 7.8% (interquartile range, 6.4–11.5) and 7.9% (interquartile range, 6.7–13.5) were maintained in the goshajinkigan and control groups, respectively, throughout the follow-up period. According to an exploratory examination, the glycated hemoglobin of the goshajinkigan group decreased significantly in the 60th month as compared to the control group (Figure 6). Fasting plasma glucose also decreased significantly beginning at the 36th month relative to baseline (Figure 7), while no significant changes were observed in the control group. No significant differences were observed in terms of insulin doses or oral antidiabetic medications.

Most patients had no subjective symptoms through the trial period. An analysis of only the patients who had a change in subjective symptoms was performed, in addition to an analysis of the entire set of patients. For the patients who experienced a change in symptoms, the occurrence of constipation and diarrhea was significantly improved in the goshajinkigan group. For the entire set of patients, no significant changes occurred for any of the issues addressed in the questionnaire. There was no dropout because of the side effects of goshajinkigan.

Table 1: Baseline characteristics of study groups.

	Goshajinkigan group (n = 74)	Control group (n = 42)
Age (y)	59.4 ± 7.8	60.9 ± 7.4
Female sex (%)	41.9	40.0
Duration of diabetes (y)	12 ± 6.8	10.9 ± 6.1
Weight (kg)	60.2 ± 12.2	57.2 ± 11
Body mass index	23 ± 4.1	22.1 ± 3.1
Cigarette-smoking status (%)		
Current	31.1	31.0
Former	17.6	14.3
Never	48.6	50.0
Unknown	2.7	4.8
Complications (%)		
None	45.9	38.0
Hypertension	23.0	21.4
Dyslipidemia	21.6	21.4
Atrial fibrillation	2.7	2.4
Other	31.1	38.1
Unknown	1.4	2.4
Blood pressure (mmHg)		
Systolic	131.6 ± 16.1	132.1 ± 19.4
Diastolic	78.5 ± 11.5	76.8 ± 10.2
Glycated hemoglobin (%)		
Mean	7.7 ± 1.0	7.7 ± 1.1
Fasting serum glucose (mg/dL)	170.5 ± 45.3	164.7 ± 38.5
Cholesterol (mg/dL)		
Total	205.9 ± 32.8	208.4 ± 36.7
High-density lipoprotein	54.7 ± 12.0	55.2 ± 12.6
Serum triglyceride (mg/dL)	124.9 ± 88.0	103.6 ± 42.3
Medications (%)		
Insulin	17.6	16.7
Metformin	18.9	21.4
Any sulfonylurea	58.1	52.4
Any other oral hypoglycemic agents	39.2	28.6

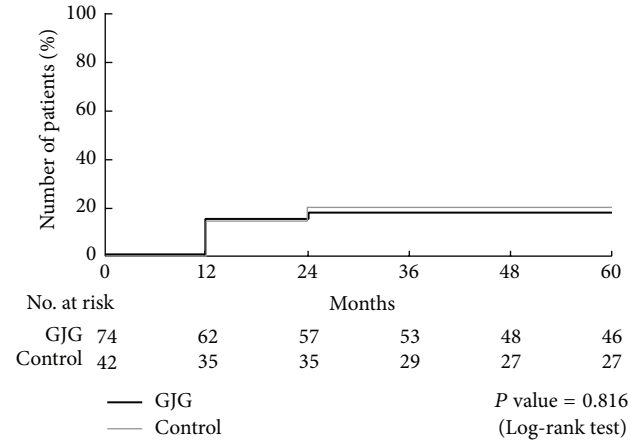

Figure 4: Progression of retinopathy. A total of 25 participants had retinopathy at the end of this study: 17.9% in goshajinkigan group and 20.0% in control group (P = 0.816).

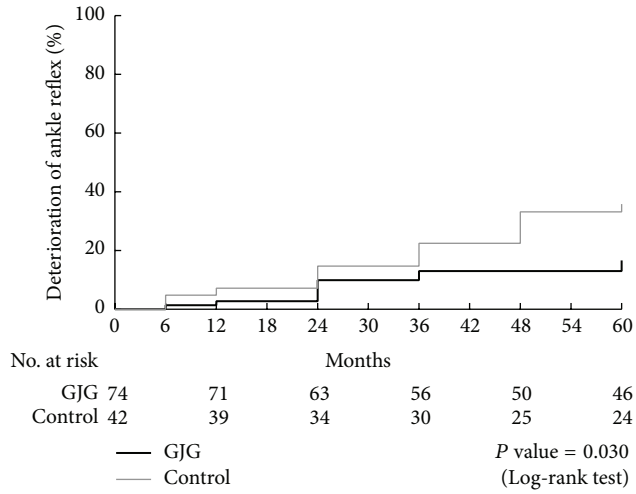

Figure 5: Progression of neuropathy (%). Progression of the ankle reflex was significantly decreased in the goshajinkigan group compared with the control group. The hazard ratio was calculated as 0.436 (95% CI: 0.198–0.962), and the P value was 0.030 as determined by the log-rank test.

Other outcomes, including body mass index and laboratory test results, showed no significant differences.

4. Discussion

Goshajinkigan extract (TJ-107) is a pharmaceutical drug covered by national health insurance program. The indications include pain in low extremities, back pain, numbness, blurred vision, dysuria, pollakiuria, and edema. It is mainly used for the senile problems. Goshajinkigan is a medicine for kidney function deficiency in terms of traditional medicine. Kidney function deficiency means a loss in congenital energy. With aging, this function is deteriorated. In this case, kidney function is not the organ kidney function. Kidney keeps one's congenital energy and, with aging, this function is deteriorated. Goshajinkigan is the derivative of hachimijiogan and two additional herbs, Achyranthis Radix and Plantaginis Semen, are added.

There are studies to show either hachimijiogan or goshajinkigan is effective for diabetic complications. Yokozawa et al. investigated that hachimijiogan had a protective effect against the diabetic nephropathy in the animal models [17–19]. They speculated that the mechanism of hachimijiogan is the protection of the formation of advanced glycation end-product by Corni Fructus which is one of the ingredients of hachimijiogan [20] or suppression of oxidative stress [21].

For retinopathy, Cameron-Schaefer et al. showed the protective effect of goshajinkigan against the diabetic retinopathy [22]. They showed that lipid peroxidation was enhanced by

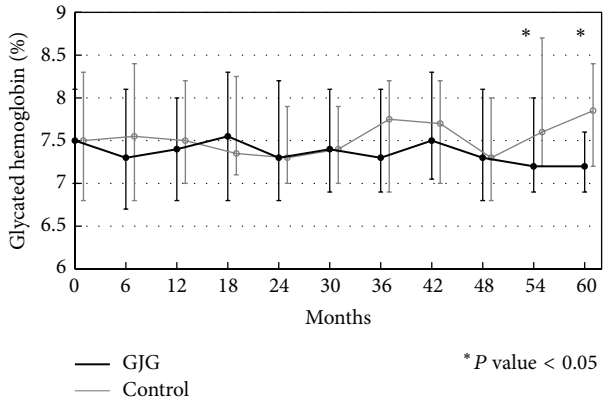

Figure 6: Glycated hemoglobin (%). Glycated hemoglobin was significantly decreased in the goshajinkigan group compared with the control group (no kampo treatment) at the 54th and 60th months.

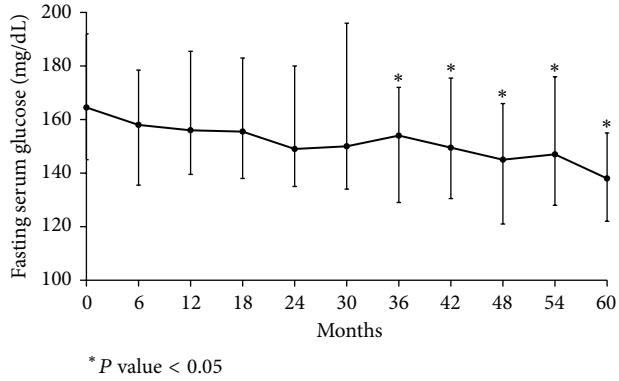

Figure 7: Fasting serum glucose (mg/dL). Fasting serum glucose was significantly decreased in the goshajinkigan group compared with the baseline value at the 36th, 42nd, 48th, 54th, and 60th months.

streptozotocin-induced hyperglycemia and that goshajinkigan prevented lipid peroxidation. They showed that soluble guanylate cyclase activation is a key mechanism to decrease the lipid peroxidation.

Although it has not been shown that goshajinkigan prevented diabetic macroangiopathy, Suzuki et al. evaluated the effects of goshajinkigan on platelet aggregation in streptozotocin-induced diabetic rats. They concluded that goshajinkigan could improve platelet aggregation in diabetes through increased production of nitric oxide via bradykinin B2-receptors and muscarinic acetylcholine receptors [13].

This clinical trial was designed based on these publications. However, we found a difference between animal models and complex clinical trials. The chosen endpoint, macroangiopathy, might have been inappropriate for clinical setting in such a short period. Whilst changes of microangiopathy might not be visible anatomically on fundus photography, goshajinkigan might influence the metabolism in the retina and thus have effects on a functional level—an effect which cannot easily be studied in humans in vivo. There had been no cases of macrovascular events. And there were no differences in the progression of retinopathy and nephropathy. Because the progression of retinopathy and nephropathy takes time, we enrolled the elder type 2 diabetes patients with moderate hyperglycemia. However, 5 years follow-up time is long for patients and the final number for the analysis was only 116 cases. The power was very low compared to the original calculation. So we could not conclude any definite effects of goshajinkigan on preventing macrovascular events such as myocardial infarction or stroke, nor could we state effects on diabetic nephropathy. Recently, some surrogate markers of macroangiopathy were proposed, like flow mediated dilation, ankle brachial pressure index, or pulse wave velocity. These are covered by the Japanese national health insurance and could be in consideration as surrogate markers.

On the other hand, our results support a beneficial effect of goshajinkigan on diabetic neuropathy, which we chose as secondary endpoint. There have been a lot of manuscripts showing that goshajinkigan had a beneficial effect on diabetic neuropathy in the animal model [21] or in the clinical settings [23, 24].

The mechanism of action of goshajinkigan on diabetic neuropathy was speculated partially by the inhibition of the aldose reductase [25, 26].

Moreover, recently, goshajinkigan has been reported to relieve the peripheral neuropathy due to oxaliplatin in patients with advanced or recurrent colorectal cancer that were receiving FOLFOX therapy [27]. The author speculated that the mechanism of goshajinkigan was the promotion of the release of dynorphin and nitric oxide production. This may be explained by the varying modes of action of the different ingredient of goshajinkigan.

Our data has also shown that goshajinkigan has some beneficial effect on serum glucose and glycated hemoglobin. When we have compared the medications in two groups, the patients in the control group had more progressed medications in 5 years (nonmedication to medication or medication to insulin). Body mass index was similar at the beginning of this study, but in 5 years, GJG group kept BMI and the control group lost weight. These two facts support that GJG reduces the serum glucose compared to the control group. Because the difference of the blood serum glucose or glycated hemoglobin was observed only in the late years, we assumed that GJG itself does not affect the insulin secretion itself. An improvement of insulin resistance may be involved to decrease the blood glucose level. This speculation was supported by the previous studies [28, 29].

In large RCTs such as the Action to Control Cardiovascular Risk in Diabetes trial and the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial [30, 31], hypoglycemia has been noted as one of the reasons that strict glycemic control showed no benefit in lowering the incidence and mortality of macroangiopathy. If goshajinkigan can control blood glucose without any risk of hypoglycemia, patients can receive it safely over the long term. Even though the primary endpoints were not met, our data support a positive effect of goshajinkigan on diabetic neuropathy. It furthermore might positively affect glucose metabolism in the long term. Further studies are necessary

with the focus on diabetic microangiopathy and especially neuropathy.

Conflict of Interests

Center for Kampo Medicine, Keio University, was financially supported by Tsumura & Company. Dr. Watanabe received honorariums from Tsumura & Company for speaking engagements. The other authors report no conflict of interests or need for any disclosure.

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Research Article

Clinical Data Mining Related to the Japanese Kampo Concept "*Hie*" (Oversensitivity to Coldness) in Men and Pre- and Postmenopausal Women

H. Tokunaga,[1] K. Munakata,[2] K. Katayama,[3] R. Yamaguchi,[3] S. Imoto,[3] S. Miyano,[3] and K. Watanabe[1,2]

[1] *Center for Kampo Medicine, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan*
[2] *Faculty of Environment and Information Study, Keio University, 532 Endo, Fujisawa, Kanagawa 252-0882, Japan*
[3] *Laboratory of DNA Information Analysis, Human Genome Center, Institute of Medical Science, University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan*

Correspondence should be addressed to K. Watanabe; watanabekenji@a6.keio.jp

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"*Hie*" is a subjective oversensitivity to cold and a condition experienced in 60% of Japanese citizens. The condition of *hie* has not been documented in Western medicine. However, in Kampo medicine, *hie* is an important target of treatment, because it has been considered one of the sources of all kinds of diseases. This study aimed to clarify the symptoms and findings associated with *hie* and contribute to increased precision in *hie* diagnosis. During 2005-2006, data from interviews of 1691 patients during their initial visit to the Kampo Clinic of Keio University Hospital were analyzed using a classification and regression tree (CART) analysis, a data mining technique. Symptoms and findings characteristic of each group are follows as, postmenopausal women: fatigability, absence of lower abdominal pain, and absence of hot flashes of feet: women with menstruation: leg swelling, knee pain, and abdominal pain; men: insomnia, leg weakness, and absence of excess saliva. From the perspective of Kampo medicine the result suggested that the feature of *hie* condition in postmenopausal women, women with menstruation, and men is statistically different.

1. Introduction

"*Hie*" is a condition that interferes with daily life because a person experiences pain in the entire body or in some parts of the body due to a feeling of cold at temperatures that are not normally considered cold by most people [1]. *Hie* is experienced by about 60% of Japanese people [2, 3]. Most people complaining of oversensitivity to cold temperatures are women. Approximately 45% of these women were within the age range of 15–39 years, whereas 49.6% were within the age range of 40–64.5 years [4]. In addition, men's oversensitivity to cold temperatures has been studied recently and was shown to have approximately one-sixth the frequency of the *hie* experienced by women [5].

Kampo medicine practitioners refer to *hie* as a physical condition in which the hands, the legs, and the lower back rapidly become cold because of poor blood circulation. In general, *hie* is believed to occur because of an abnormality or bias in the balance between heat production/transport and heat dissipation. Peripheral circulatory failure associated with autonomic imbalance is believed to be one of the major causes of *hie*, mainly attributable to stress and an irregular lifestyle. In addition, circulatory insufficiency is likely to occur because of anemia, hypotension, and poor muscular development. People with large amounts of subcutaneous fat are cut off from the temperature in the outside world and are likely to develop peripheral circulatory failure; in other words, such people are likely to develop *hie*. In addition, people with less muscle mass produce less heat and are likely to develop oversensitivity to cold temperatures. A number of other causes of cold oversensitivity have been identified, including decreased levels of estrogen and progesterone. In addition, external factors such as tight underwear, shoes, and socks are likely to cause a circulatory deficit; furthermore, intense

temperature differences inside and outside of rooms because of air conditioner usage are likely to cause hypofunctioning of the autonomic nervous system, leading to *hie* [6].

Conversely, symptomatic oversensitivity to cold temperatures is present in Buerger's disease, Raynaud's phenomenon [7, 8], collagenosis, diabetic peripheral neuropathy [9], arteriosclerosis obliterans due to peripheral arterial circulatory insufficiency, and venous circulatory insufficiency, such as in thrombophlebitis, varicose veins, and venous thrombosis, as well as leprosy [10] and reflex sympathetic dystrophy (RSD) [11]. *Hie* is one of the symptoms of hypothyroidism.

Additionally, Western medicine has shown some of the causes of symptomatic *hie*. However, the term *hie* does not exist in Western medicine. Western medicine is currently the mainstream approach for treatment in Japan; in the absence of underlying disease, *hie* is perceived as constitutional. For some people, *hie* is a part of daily life, but most physicians considered it as a condition that does not require active treatment because no objective diagnostic method has yet been established [5].

However, Kampo physicians have regarded *hie* as an important target of medical treatment.

In Kampo medicine, the concept of disease prevention is very strong. An early deviance of the patient's condition should be treated before an obvious pathology has been developed. *hie* is considered as one of such early deviances.

For the treatment of *hie* as a disease entity, prescriptions covered by the health insurance include *shimotsu-to*, *keishi-bukuryogan*, *goshakusan*, and *kami-shoyosan* [12]. This study aimed to educate nonspecialized physicians in Kampo medicine on the importance of treating *hie* and to increase awareness of the utility of Kampo medicine in such treatments.

Therefore, at the Kampo Clinic of Keio University Hospital, the determined therapeutic efficacy and relationship between the symptoms and Kampo medicine-based diagnostic "evidence" were analyzed using the following techniques: data mining based on patients' subjective medical information, Kampo medical diagnoses determined by the physicians, and prescription information. In addition, a system providing support for Kampo medical diagnosis and treatment has been developed for establishing guidelines for general physicians' use, in order to administer Kampo treatment appropriately and for the widespread use of Kampo medicine-based treatment. In this study, the symptoms and findings associated with *hie* were determined on the basis of accumulated patient data during their initial visit and were analyzed for elaborating the diagnosis of *hie*.

2. Materials and Methods

The study was conducted on 1691 patients (482 men and 1209 women) whose initial visit at the Kampo Clinic of Keio University Hospital occurred between April 2005 and March 2007. Findings and symptoms associated with oversensitivity to cold temperatures were analyzed using the data mining software, Clementine 12.2 (IBM), on the basis of 137 items including body mass index (BMI); blood pressure; Kampo medical findings (e.g., tongue, pulse, and abdominal examination); and subjective symptoms.

The patients who met any one of the following criteria were considered as *hie* patients: those whose entire body or part of the body displayed symptoms of *hie* and those who were at least "sensitive to cold" or who "easily develop frostbites." Patients with data deficiencies and those younger than 15 years old were excluded. Patients with atopic dermatitis were excluded because of their particular pathological background. A decision tree analysis (classification and regression tree: CART) was performed separately on the female and male *hie* patients (female: 464/744; men: 102/276; total: 566/1020), using the same software, and the factors related to *hie* were extracted.

In the CART algorithm, we focus on the data of a single variable and divide the patients into two exclusive groups, where the patients in one group have the values that are greater than the cutoff and the values of the patients in the other group are smaller. The variable used for patients' division is selected so that *hie* or non-*hie* patients are more enriched in each of the obtained patient groups than the group before division. We started with the all patients and applied the CART algorithm that generated a tree structure of patients' division, called decision tree, with the variables used. The tree structure can be regarded as a sequential classification of patients and we investigate the sequence of the used variables from a medical viewpoint.

We treated real numerical data such as BMI and blood pressure as categorical variables as much as we possibly could to improve their interpretability, according to the standards of academic societies. The standards are summarized as follows.

(i) BMI: the patients' BMI were classified into 3 categories on the basis of the standard criteria of the Japan Society for the Study of Obesity: thin (less than 18.5), standard (18.5 or higher but less than 25), and obese (25 or higher).

(ii) Blood pressure: on the basis of the standard criteria of the Japanese Society of Hypertension, the patients were classified into 4 blood pressure categories: optimal, normal, high-normal, and high. In addition, although the academic society has no clear standard criteria stating that *hie* is often encountered in families with hypotension, patients with a systolic blood pressure of less than 100 mmHg were classified into 1 category designated as having "hypotension." The patients' blood pressure was classified into 5 categories.

(iii) Frequency of urination: on the basis of the standard criteria of respective academic societies, the frequency of urination was classified into 2 categories. A frequency of more than 8 times per day was considered as "frequent daytime urination" (International Continence Society), whereas a urine frequency of once or more per night was considered as "nocturia" (Neurogenic Bladder Society).

Table 1: Demographic background of patients (Av. ± SD).

	Total (n = 1020)	Postmenopause (n = 235)	Menstruating (n = 509)	Male (n = 276)
Age (years)	47.3 ± 17.1	62.4 ± 9.8	36.1 ± 9.6	52.1 ± 18.3
Height (cm)	159.8 ± 7.8	154.2 ± 5.7	158.9 ± 5.6	168.1 ± 6.2
Weight (kg)	55.0 ± 11.0	51.3 ± 9.4	52.6 ± 8.7	64.5 ± 11.1
Body mass index (kg/m^2)	21.5 ± 3.5	21.6 ± 3.6	20.9 ± 3.3	22.8 ± 3.4
Systolic blood pressure (mmHg)	116.9 ± 19.1	126.3 ± 18.7	109.0 ± 15.7	122.9 ± 19.1
Diastolic blood pressure (mmHg)	71.3 ± 13.3	74.8 ± 12.7	67.2 ± 11.7	76.7 ± 14.1
Percentage of *hie* symptom (%)	59.0	60.0	72.0	37.0
Percentage of frequent urination (%)	32.0	35.7	33.0	24.0
Percentage of constipation (%)	7.8	5.5	11.4	4.7

Table 2: Selected Kampo terms (ICD11Beta).

Kampo terms	ICD terms	Description
Kyo	Deficiency pattern	A pattern characterized by fatigue or weakness; at the onset of febrile condition, characterized by cold sensitivity and tendency to sweat, floating weak pulse; in case of nonfebrile condition, characterized by weak pulse, weak abdominal wall. It may be explained by weak response to pathogens.
Jitsu	Excess pattern	A pattern characterized by (at the onset of febrile condition) severe chills with no sweating, strong pulse; in case of nonfebrile condition, strong pulse, strong abdominal wall. It may be explained by strong response to pathogens.
Oketsu	Blood stasis patterns	A pattern characterized by various menstrual disorders such as amenorrhea, dysmenorrhea, and menopausal syndrome; lower abdominal fullness, varicose veins, hemorrhoids, and mood swings. It may be explained by impaired peripheral blood circulation or obstruction of venous return.
Suidoku	Fluid disturbance patterns	A pattern characterized by fluid retention or dehydration in the digestive tract, body tissues, or cavities. It may be explained by abnormal distribution of body fluids and an imbalance in fluids and electrolytes.
Kikyo	Qi deficiency pattern	A pattern characterized by decreased vitality, fatigue, weakness, and appetite loss. It may be explained by deficiency of energy, such as exhausted state, which is almost always accompanied by deficiency of the upper abdominal region.
Kiutsu/Kitai	Qi stagnation pattern	A pattern characterized by feeling of obstruction at the level of throat, feeling of ear tube obstruction, abdominal distension due to intestinal gas retention, depressive state, and intractable pain. It may be explained by functional discommunication leading to gas retention in bowels, mental depression, or other manifestations.
Geshou no kyo	Deficiency in lower energizer pattern	A pattern characterized by dysfunctions of the urogenital system. It may be explained by weakness in the lower part of the body.

(iv) Frequency of stools: although the academic society has no clear-cut standard criteria for this parameter, a stool frequency of once every 3 days or longer was considered as "constipation."

Furthermore, subjective symptoms found in the women and men were analyzed. In women, *hie* is easy to occur due to decreasing blood levels of estrogen, progesterone [13]. According to the National Livelihood Survey in Japan 1998 by the Ministry of Health and Welfare, women also become aware of *hie* hands and feet, increased rapidly from around the time of postmenopause over the age of 55. Therefore, we thought that the properties of *hie* are different in the presence or absence of menstruation. After the overall analysis was performed, the findings in postmenopausal female patients and in women who menstruated were compared (Table 1). The analysis procedure was as follows.

(1) A two-branch decision tree was constructed using CART to classify the data on the basis of the existence or absence of *hie*.

(2) Based on each decision tree, we performed a knowledge extraction on the following items:

(A) significance test of the presence or absence of *hie* in each population after divergence;

(B) Kampo-based interpretation of each branch (Table 2);

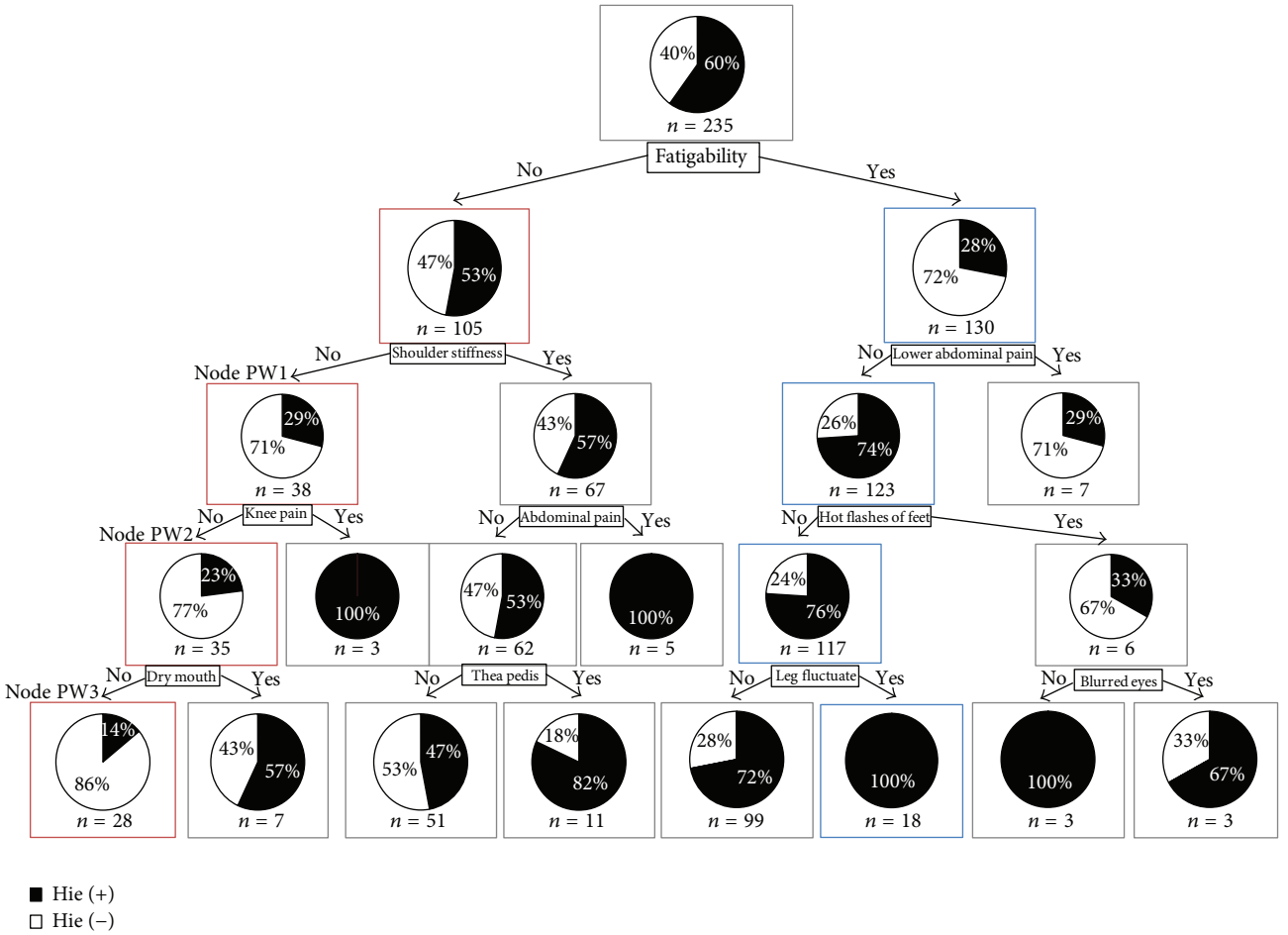

Figure 1: CART of postmenopausal women by *hie* related symptoms and findings. The root node of Figure 1 indicates that there were 235 total observations ($n = 235$), and the black part of the pie chart means 60% of "*n*," who have had an episode of *hie* (hie(+)). And the white part of the pie chart means 40% of "*n*," who have not had an episode of *hie* (hie(−)). Each node below the root node has the same meaning.

(C) test of the significance of biases in the findings of each population after divergence.

(3) Comparison of findings.

CART is a data mining method that allows the classification and regression of samples with multiple, measurable features. Our study method utilized the presence or absence of *hie* as a patient information label and used the patient interview data as feature variables to repeatedly divide the patient population into 2 exclusive groups based on the patient population size (i.e., large or small, if the feature value was a continuous variable); assignment to a specific category (if the feature variable was a categorical variable, e.g., blood pressure); and rate of *hie* (e.g., high and low rates). This method allowed for statistical learning based on multiple feature variables, as well as the generation of a decision tree. Significant differences in (2) (A) and (2) (C) were examined using Fisher's exact test to compare the original population (or "base population," namely, the population at the highest level, which was the root node of the decision tree) and the populations after the division. We call this type of analysis subanalysis.

3. Results

3.1. Postmenopausal Women. First, a decision tree pertaining to the postmenopausal women group was constructed using CART (Figure 1). Fisher's exact test was performed to detect populations (nodes) with significantly larger (or smaller) numbers of patients with *hie*, as compared to that of the base population (node 0). Originally, 60% of the patients in the base population presented with *hie*.

3.1.1. Group of Patients with Significantly More Hie. The result showed that a path formed a population with significantly more *hie* on the right side of the decision tree than on the left side; in Figure 1, the variables surrounded by blue boxes are included in this path. This path included patients who had the following characteristics: fatigability (+), lower abdominal pain (−), hot flashes of feet (−), and leg fluctuate (−); all patients in the resulting group had *hie*.

3.1.2. Group of Patients with Significantly Less Hie. On the other hand, in Figure 1, on the left side of the decision tree, a path with red-boxed variables gathers a population with a

significantly less rate of *hie*. The patients selected by this path had the following characteristics: fatigability (−), shoulder stiffness (−), knee pain (−), and dry mouth (−); only 14% of the patients in the resulting group had *hie*.

Next, the significance of the bias in the findings from the nodes with significant differences in *hie* was examined using Fisher's exact test. None of the nodes in the path with a significantly more rate of *hie* showed any finding of bias. Conversely, in the path with significantly less *hie*, we found several findings.

(i) In the node PW1, the number of patients whose excess of pulse are greater than those with deficiency of pulse (excess > deficiency), while in the base population we found that patients with deficiency of pulse are greater than those with excess of pulse (deficiency > excess).

(ii) In the nodes PW1 and PW2, the tenderness points of blood stasis were found to be 13.6% and 11.4% which were approximately 18% and 20% lower than that of the result found in the base population (31.5%), respectively.

(iii) In the node PW3, the number of patients whose humidity of tongue is dry is almost equal to those with normal humidity of tongue and is greater than those with wet (dry = normal > wet), while in the base population we found that patients with normal humidity of tongue are greater than those with dry and dry is much greater than wet (normal > dry ≫ wet).

(iv) In the node PW3, the number of patients whose size of tongue are normal is greater than those with enlarge size of tongue and enlarge is greater than thin (normal > enlarge > thin). On the other hand, in the base population we found that patients with normal size of tongue are much greater than enlarge size of tongue and enlarge is greater than thin (normal ≫ enlarge > thin).

(v) In the node PW3, the tenderness point of blood stasis was found to be 10.7%, which was 20% less than that of the result found in the base population.

We summarized the results of subanalysis in Table 3.

3.2. Women with Menstruation. Second, decision tree pertaining to the women with menstruation was constructed (Figure 2). Paths with significantly more (or less) rates of *hie* were searched through comparison with the base population (node 0) using Fisher's exact test. Originally, 72% of the patients in the base population presented with *hie*. Although we described 2 paths with significantly less rates of *hie*, they were counted as one single path because most of their nodes were common to both.

3.2.1. Group of Patients with Significantly More Hie. In Figure 2, on the right side of the decision tree, we found 2 paths indicated by the blue-boxed variables. These paths comprised a population with significantly more rates of *hie*. The patients selected by one path had leg swelling (+), and 85% of the patients in the resulting group had *hie*. The other path had leg swelling (−) and knee pain (+), and all patients in the resulting group had *hie*.

Table 3: Summary of subanalysis: findings and P value.

		Findings	P value
Node	PW1	Tenderness point of blood stasis	0.080
		Excess of pulse	0.094
	PW2	Tenderness point of blood stasis	0.065
	PW3	Tenderness point of blood stasis	0.075
		Humidity of tongue	0.097
		Size of tongue	0.044
	W1	BMI < 18.5	0.084
	W2	Blood pressure	0.016
	W3	Excess of abdominal strength	0.062
	W4	Epigastric tightness and resistance	0.064
	M1	Abnormal complexion	0.012
	M2	Floating pulse	0.013
	M3	Floating pulse	0.023
	M4	Floating pulse	0.023
		Epigastric stiffness	0.013

3.2.2. Group of Patients with Significantly Less Hie. In Figure 2, on the left side of the decision tree, we found a path indicated by the connections of red-boxed nodes (more strictly there are 2 paths, but almost all nodes are shared and we consider the connection of red-boxed nodes as one path). The patients in the terminal nodes (nodes W3 and W4) had leg swelling (−), knee pain (−), abdominal pain (−), and sneezing (−) or (+) and this path formed a population with significantly less rates of *hie* (63% of the patients in the node W3 had *hie* and 44% of the patients in the node W4 had *hie*).

The bias of the findings in each node was examined using Fisher's exact test. In the nodes with a significantly more *hie* rate, we found the following.

(i) From BMI of the patients in the node W1, the percentage of the patients with thin body types was significantly more than that in the base population ($P = 0.084$).

(ii) In the node W2, there are no patients with hypotension or normal blood pressure, while in the base population they are approximately 22% for hypotension and 10% for normal blood pressure. Also, in the base population, while the number of patients with high blood pressure is greater than that of the patients with high-normal, in the node W2 they are switched.

In the path with less rates of *hie*, namely, in terms of abdominal strength, the following group was determined.

(i) In the node W3, excess of abdominal strength accounted for 2.7% of the cases, which was weakly significantly less than that of the observed result of 4.9% in the base population ($P = 0.062$).

(ii) In the node W4, the presence of epigastric tightness and resistance accounted for 0%, which was weakly significantly less than that of the observed result of 9.6% in the base population ($P = 0.064$).

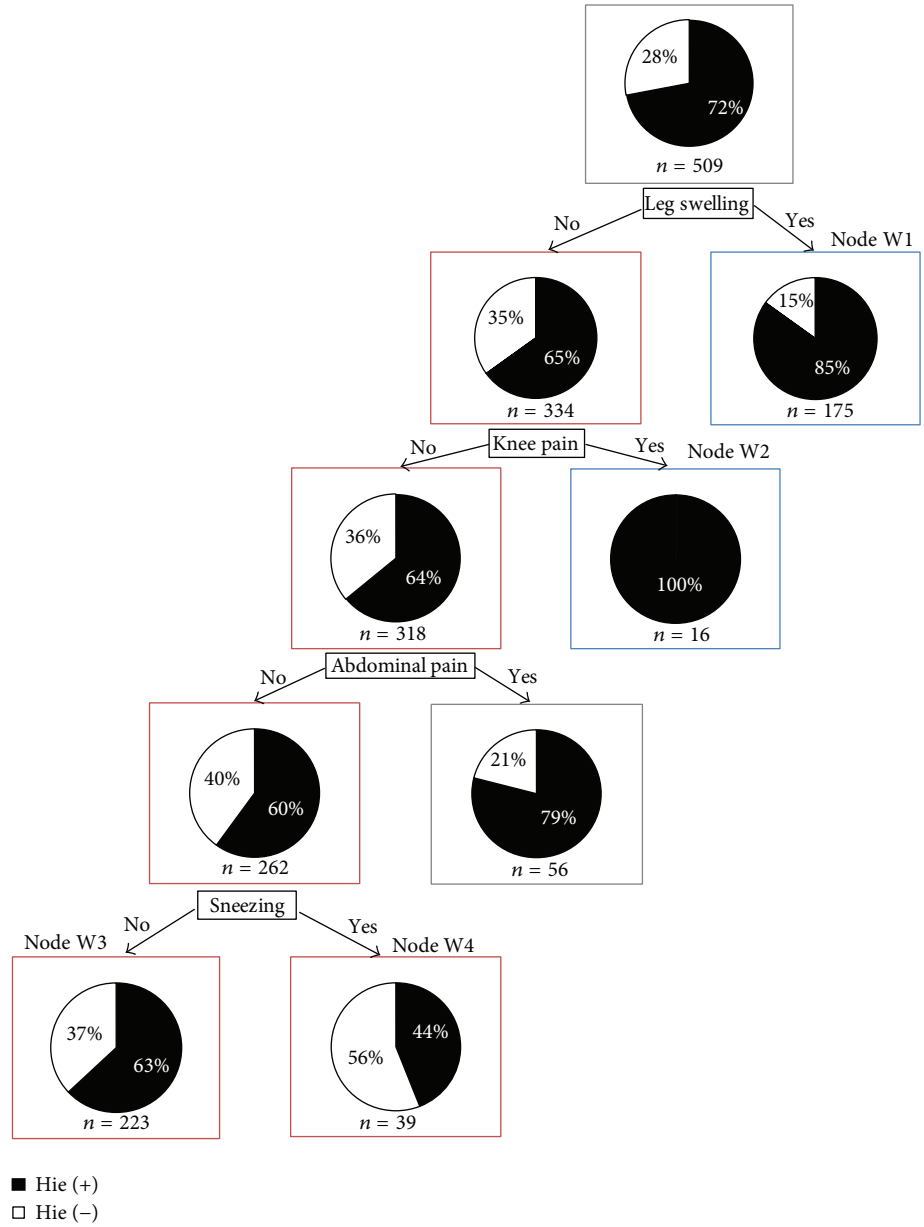

Figure 2: CART of women with menstruation by *hie* related symptoms and findings. The root node of Figure 2 indicates that there were 509 total observations ($n = 509$), and the black part of the pie chart means 72% of "*n*," who have had an episode of *hie* (hie(+)). And the white part of the pie chart means 28% of "*n*," who have not had an episode of *hie* (hie(−)). Each node below the root node has the same meaning.

3.3. Men. Finally, a decision tree pertaining to *hie* in men was constructed (Figure 3). Paths that had significant differences in *hie* were searched using Fisher's exact test and by comparing this with the base population (node 0). The findings showed 2 paths with significantly more *hie* rates and one path with significantly less *hie* rates.

3.3.1. Group of Patients with Significantly More Hie. In Figure 3, on the right side of the decision tree, we found 2 paths indicated by the connection of blue-boxed nodes. These paths formed a population with significantly more rates of *hie*. All patients in the terminal node of the 1st path, which is characterized by insomnia (+), leg weakness (+), and excess saliva (−), had *hie* and in the terminal node of the 2nd path, with insomnia (+), leg weakness (−), oversensitivity to heat (+), and neck stiffness (+), 92% of the patients had *hie*.

3.3.2. Group of Patients with Significantly Less Hie. In Figure 3, on the left side of the decision tree, we found a path indicated by the red-boxed nodes. This path formed a population with significantly less rates of *hie*. The patients in the terminal node of this path had insomnia (−), shoulder pain (−), postnasal drip (−), and abdominal pain (−), and only 11% of patients in the terminal node had *hie*.

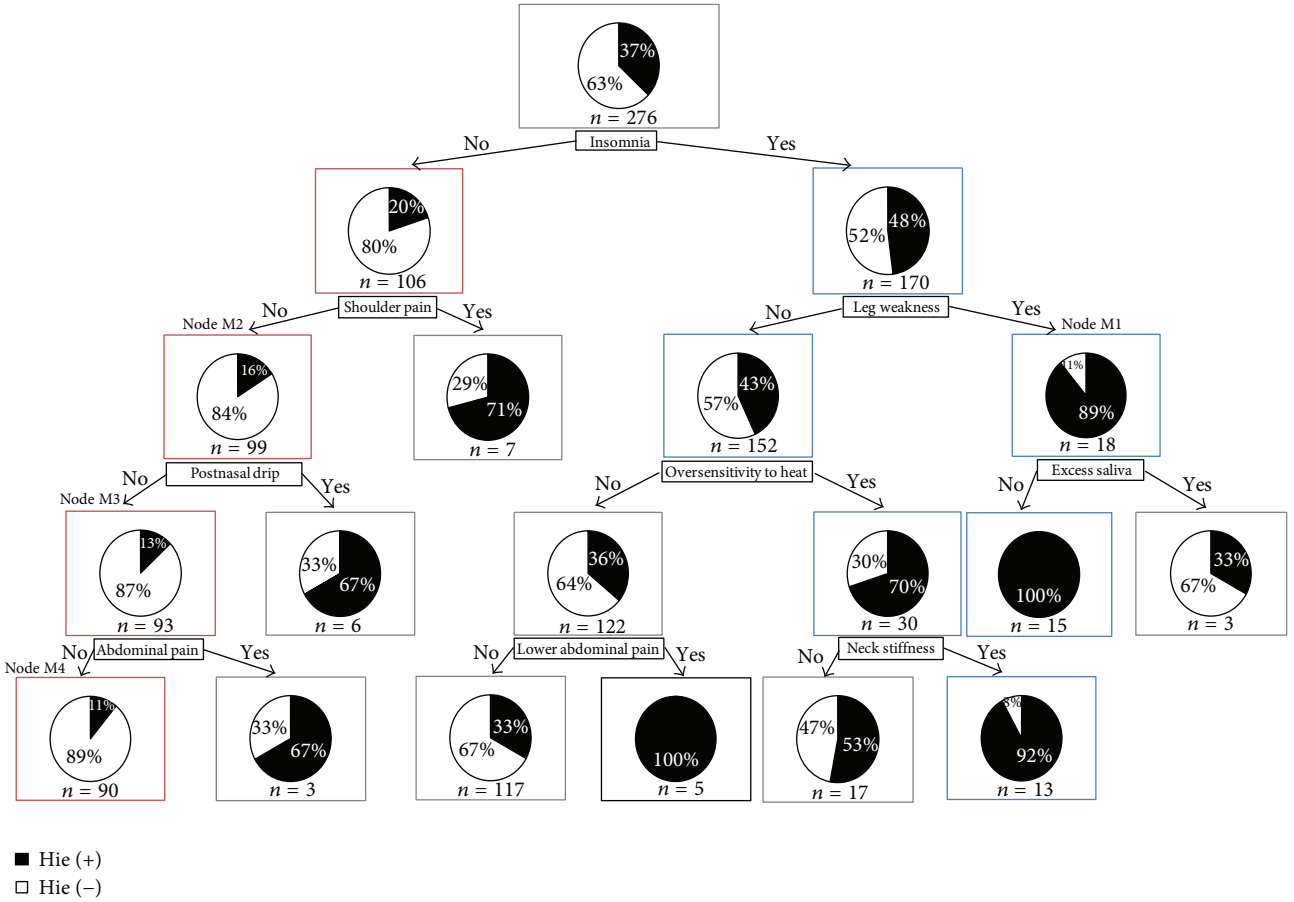

FIGURE 3: CART of men by *hie* related symptoms and findings. The root node of Figure 3 indicates that there were 276 total observations ($n = 276$), and the black part of the pie chart means 37% of "*n*," who have had an episode of *hie* (hie(+)). And the white part of the pie chart means 63% of "*n*," who have not had an episode of *hie* (hie(−)). Each node below the root node has the same meaning.

Next, bias in the findings in each node was examined using Fisher's exact test. The results can be summarized as follows.

(i) In the 1st path described above, in which the rates of *hie* were high, namely, in the node M1, abnormal complexion accounted for 46.2% of the cases, which was significantly more than that of the observed result of 15.2% in the base population ($P = 0.012$).

(ii) The findings in the 2nd path showed no significant bias.

(iii) In the path with less *hie* shown by the red-boxed nodes, we found the following about pulse depth. In the nodes M2, M3, and M4, a floating pulse in these groups accounted for 0%, which was significantly less than that of the observed result of 11.6% in the base population ($P = 0.013$ for node M2, $P = 0.023$ for node M3, and $P = 0.023$ for node M4).

(iv) In the node M4, the presence of epigastric stiffness accounted for 0%, which was significantly less than that of the observed result of 0.72% in the base population ($P = 0.013$).

4. Discussions

In the past, treatment with Kampo medicine was performed based on experience; however, today, medical treatments are based on data. Nevertheless, *hie* has not yet been studied in a large number of patients.

Previous studies on *hie* have focused on comparing single variables that may have influenced the development of subjective symptoms among healthy subjects and diagnosed patients [14]. This current study serves as the first effort to analyze *hie* in a large number of patients using multivariate data mining and statistical analysis methods and to highlight its properties on the basis of strongly related symptoms and their combinations. The results of this study suggested that the symptoms strongly related to *hie* were different among the groups of postmenopausal women, women with menstruation, and men and that the percentages of *hie* were different depending on the symptom combinations. By interpreting these symptoms from the perspective of Kampo medicine, common and differing traits for *hie* in each group were elucidated.

With respect to the findings pertaining to the postmenopausal women with *hie*, from the Kampo medicine

perspective, the previously mentioned results suggested that the blood stasis pattern and the Qi deficiency pattern were important in the presence or absence of *hie* after menopause.

From the perspective of Kampo medicine, the above-mentioned results pertaining to the presence or absence of *hie* in women with a normal menstrual cycle suggested that a blood stasis and water retention pattern played an important role in the development of the *hie* condition. In the nodes with a large number of patients with *hie*, the findings were characterized by the unexpected fact that both hypotension and normal blood pressure accounted for 0%, despite the initial expectation for a high percentage.

As for the summary of the findings pertaining to male patients with *hie*, the results suggest that from the perspective of Kampo medicine a Qi stagnation pattern, a deficiency of lower energizer pattern, and a blood stasis pattern influenced the development of the *hie* condition.

Interestingly, "oversensitivity to heat (+)" was included despite the fact that the node was comprised of a large number of patients with *hie*. *Hie* in this node could probably be attributable to autonomic imbalance.

From this rationale, it became clear that *hie* and a blood stasis pattern are both concepts of Kampo medicine and are closely related. Most prescriptions used to cure *hie* actually treat a blood stasis pattern as well. Moreover, *hie* is closely related to the peripheral circulation disorder. From the viewpoint of the peripheral circulatory failure, the pathology of *hie* is estimated to be related to the following: a decrease in cardiac output, functional and organic changes in the vessel wall [15], and changes in blood fluidity [16, 17], as well as changes in platelet function, coagulation, and fibrinolysis [18]. From the viewpoint of Western medicine, attempts to clarify the factors involved in a blood stasis pattern have been made.

At our Kampo clinic, our actual experience has shown marked differences between women who menstruate and postmenopausal women, as well as between men and women. Thus, our results statistically confirm what Kampo doctors had already collected during their long clinical experience with respect to the concept *hie*. The differences in the *hie* characteristics in each group can be considered to be influenced by differences in the hormonal environment and age-related changes and gender, as well as other factors.

Our research group will conduct further studies using a larger number of patients, include symptoms other than *hie*, and involve a time-course analysis of the efficacy of the prescribed treatment. We hope this study will contribute to creating more transparency and evidence in the field of traditional Japanese Kampo medicine.

5. Conclusion

By using the method of data mining, our study helped to statistically clarify that the characteristics of the concept *hie* are different among postmenopausal women, menstruating women, and men. Thus, the findings suggested from experience could be confirmed. The results from this study may also support physicians in selecting the appropriate Kampo prescription.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Pattern Classification in Kampo Medicine

S. Yakubo,[1] M. Ito,[1] Y. Ueda,[1] H. Okamoto,[1] Y. Kimura,[1] Y. Amano,[1] T. Togo,[1] H. Adachi,[1] T. Mitsuma,[1] and K. Watanabe[1,2]

[1] *Committee for Terminology and Classification, Japan Society for Oriental Medicine, 1-9-18 Kaigan, Minato-ku, Tokya 105-0022, Japan*
[2] *Center for Kampo Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan*

Correspondence should be addressed to K. Watanabe; watanabekenji@a6.keio.jp

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Pattern classification is very unique in traditional medicine. Kampo medical patterns have transformed over time during Japan's history. In the 17th to 18th centuries, Japanese doctors advocated elimination of the Ming medical theory and followed the basic concepts put forth by Shang Han Lun and Jin Gui Yao Lue in the later Han dynasty (25–220 AD). The physician Todo Yoshimasu (1702–1773) emphasized that an appropriate treatment could be administered if a set of patterns could be identified. This principle is still referred to as "matching of pattern and formula" and is the basic concept underlying Kampo medicine today. In 1868, the Meiji restoration occurred, and the new government changed its policies to follow that of the European countries, adopting only Western medicine. Physicians trained in Western medicine played an important role in the revival of Kampo medicine, modernizing Kampo patterns to avoid confusion with Western biomedical terminology. In order to understand the Japanese version of traditional disorders and patterns, background information on the history of Kampo and its role in the current health care system in Japan is important. In this paper we overviewed the formation of Kampo patterns.

1. Introduction

The globalization of health care has not left traditional medicine behind. The World Health Organization (WHO) took the initiative for globalization of traditional medicine by founding the Division of Traditional Medicine in 1972 [1]. In 1978, the Alma-Ata Declaration on Primary Health Care called on countries and governments to include the practice of traditional medicine in their primary health care approach [2]. Thirty years later, traditional medicine is widely available, affordable, and commonly used in many parts of the world.

WHO is presently updating its International Classification of Diseases from the 10th (ICD-10) to 11th edition (ICD-11) [3, 4] and plans to incorporate traditional medicine into this new version. International experts from China, Korea, Japan, Australia, the US, and the EU are involved in this project. The ICD-11 alpha version was released in 2011, and the beta version was released in May 2012, with a version also available on the web [5].

The ICD-11 beta version contains 2 sections on traditional medicine: "traditional disorders" and "patterns" (zheng in Chinese). China and Korea referred to their own national standards to develop these sections. China used the 1995 classification and codes of traditional disorders and patterns of traditional Chinese medicine (GB95) as a national standard. The third edition of the Korean Classification of Diseases of Oriental Medicine (KCDOM3) was incorporated into the Korean modification of ICD-10 (KCD-6) in 2010. KCD-6 was groundbreaking because it was the first publication in which Western biomedicine and traditional medicine shared a common platform in terms of medical statistics.

For Japan's contribution to this edition, the Committee for Terminology and Classification of the Japan Society for Oriental Medicine (JSOM) was responsible for organizing the section on Kampo classification. Kampo covers a wide variety of traditional Japanese medicine including acupuncture and moxibustion, existing before Western medicine was introduced to Japan. In contrast to China and Korea, Japan did not have national standards for reference. To understand the Japanese version of traditional disorders and patterns, background information on the history of Kampo and its role in the current health care system in Japan is important.

2. History of Kampo Medicine

Medicines were brought from ancient China to Japan via the Korean peninsula in the 5th or 6th century. While Japanese medicine originally followed the ways of ancient Chinese medicine, Japan adopted Chinese knowledge to suit its own climate and race [6]. Also because not all materials were available, Japan replaced the material to the Japanese herbs and minerals. The first Japanese medical book, "Daidoruijuho," was a collection of Japanese traditional therapies written in 808.

Further modifications of Japanese traditional medicine occurred during the Edo period (1603–1867) [7, 8]. The medicine of Ming-China was introduced at the beginning of this period and spread widely (Gosei school). During this time, Japanese doctors advocated the elimination of Ming Chinese medicine, instead following the basic concepts of Shang Han Lun and Jin Gui Yao Lue introduced during the later Han dynasty (25–220 AD). The physician Todo Yoshimasu promoted his perspective on these classic texts and rejected the theory developed later in China. His approach emphasized that an appropriate treatment could be administered if a set pattern could be identified, a practice still referred to today as "matching of pattern and formula" (Koho school). Later in the Edo period, another school which integrated both Koho style and Gosei style occurred (Setchu school).

Among these three schools, Koho school influenced most the current Kampo practice in Japan.

In the 18th century, European medicine was introduced in Japan. Modern anatomy was first studied in 1754 by Toyo Yamawaki, a famous Kampo doctor who had acquired an anatomy book from Europe. Toyo Yamawaki respected Yoshimasu, who also knew European medicine. Yoshimasu may have tried to reform Kampo medicine to harmonize it with European medicine.

This trend was followed by other doctors like Seishu Hanaoka (1761–1835), who performed the first surgery with general anesthesia in 1804. This event occurred 42 years before William T. G. Morton successfully performed surgery using ether as a general anesthetic. Hanaoka combined Kampo and European medicines, using Kampo mainly for internal medicine and European medicine for surgery.

The Meiji restoration occurred in 1868, and the new government decided to modernize Japan introducing European culture including medicine. With the passing of the 1874 Medical Care Law, the German model was adopted as the national health care system, and all Kampo-related systematic education was stopped. Kampo practitioners were no longer recognized as official medical professionals; for those interested in becoming physicians, the only option available was to study Western medicine and pass a national examination. Thereafter, the practice of Kampo drastically declined.

After difficult years, physicians like Kyushin Yumoto (1876–1941), Keisetsu Otsuka (1900–1980), and Domei Yakazu (1905–2002) played a key role in reviving Kampo medicine. For Kampo medicine to survive, these physicians had to transform it into a more practical form that the new generation of physicians would also find useful. The modern form of Kampo medicine lost much of its theoretical origin, and emphasis was now being placed on proper prescription of Kampo formulas for treating symptoms. These changes made Kampo conceptually easier to understand for the new generation of physicians trained only with Western medicine. Moreover, the "matching of pattern and formula" methodology made the clinical use of Kampo a more appealing form of treatment.

The result of these efforts was that, by 1967, the first 4 Kampo formulas were approved by the government for coverage under the national insurance system.

3. Current Status of Kampo Medicine in Japan

Recent research shows that about 90% of physicians in Japan use Kampo medicines in daily practice, even for cancer patients [9–11]. For women's health, nearly 100% of Japanese obstetrics/gynecology doctors use Kampo medicine [12–14]. Physicians even use Kampo medicine in the university hospital along with high-tech techniques such as organ transplantation or robotic surgery. Physicians often use Kampo medicines along with chemotherapy or radiation therapy for cancer patients. These examples show the magnificent integration of modern Western biomedicine and traditional medicine [15, 16].

Kampo medicine has government-regulated prescription drugs, and now 148 formulas are listed on the Japanese Insurance Program. Kampo practitioners can also use decoctions, selecting several herbs among 243 types covered by the insurance system [17]. In 2001, the Ministry of Education, Culture, Sports, Science and Technology decided to incorporate Kampo medical education into the core curriculum of medical schools. There are 80 medical schools in Japan, all of which now provide Kampo medical education.

4. How the "Kampo Medical Classification" Developed Recently in Japan

The Japan Society for Oriental Medicine (JSOM) was founded in 1950 and is the largest academic association for Kampo medicine. The JSOM Committee for Terminology and Classification decided not to use traditional names for disorders in Kampo classification because many of them overlap with Western biomedical terms. Traditional names for disorders are primarily symptoms, such as "headache" or "watery diarrhea." In contrast, in Western medicine, disease names are based on pathological causes, such as cholera or malaria. Since these diseases have existed for a long time, traditional medicine recognizes these diseases. However, the pathologies of these diseases were unknown when the names were given and so are not reflected in the disease names in traditional medicine. Therefore, it is difficult to map traditional disorder names and biomedical disease names. Sometimes, symptomatic traditional names for disorders are broad and can be mapped to multiple biomedical disease names. Because the restoration of Kampo medicine in Japan was led by physicians, Western

biomedical terms were often used instead of the traditional Kampo terms to avoid confusion.

Organ system patterns are very important in medicine in China and Korea. However, Kampo experts in the Meiji (1868–1912), Taisho (1912–1925), and Showa (1926–1989) eras chose not to use organ systems to avoid overlap with biomedical terms. As a result, Kampo medicine is sometimes criticized because of the relative lack of terms to describe patients' conditions. The pathogenesis rather than host reaction is most important in Western biomedicine. In contrast, the host's reaction to the pathogen is the most important factor in traditional medicine. In this regard, Kampo medicine has been developed in harmony with Western biomedicine.

5. Kampo Medicine Patterns

Kampo patterns were reconstructed logically according to the ICD principles, which are both jointly exhaustive and mutually exclusive. Several parameters are used for determining Kampo patterns: yin-yang, deficiency-excess, cold-heat, 6 stages of acute febrile diseases, and qi-blood-fluid [18]. Of these, yin-yang, deficiency-excess, cold-heat, and interior-exterior belong to the 8 principles used in Chinese medicine. In China, each component is used in combination with the others to define the pattern, such as "liver yin deficiency pattern," and is not usually used independently. Among 8 principles, yin-yang is a polysemic word. Sometimes it is used for the sensible temperature in Japan. Under international harmonization, yin-yang is usually a high-level concept of deficiency-excess, cold-heat, and interior-exterior. To avoid confusion, we decided not to use yin-yang for the sensible temperature.

Kampo patterns are determined for all patients according to the flow charts shown in Table 1 and Figure 1. Patient conditions are divided into 2 groups: acute febrile infectious conditions and chronic conditions (Figure 1). A 6-stage pattern, based on Shang Han Lun, is used for describing acute febrile infectious diseases like influenza. Qi-blood-fluid patterns are mainly used for describing chronic diseases.

One issue raised regarding Kampo patterns concerns the "between deficiency and excess" pattern. The deficiency and excess pattern is usually based on the strength of the pathogen. However, in Japan, deficiency and excess patterns are primarily based on the patient's condition. The ancient textbook of Huangdi Neijing (Former Han dynasty; 220 AD to 8 AD) explains that "when the foreign pathogen is strong, it is called as excess, and when body energy is weakened, it is called as deficiency." The problem with this statement is that deficiency is defined by the strength of foreign pathogens, and deficiency is defined by the energy of the host. Many traditional medical terms are polysemic, mainly due to their long history. However, the deficiency-excess terms are originally polysemic; this has created much confusion.

In Japan, deficiency-excess was originally determined by the strength of the foreign pathogen in the case of acute febrile infectious diseases and by the strength of the body energy in the case of chronic diseases. Additionally, Kampo medicine

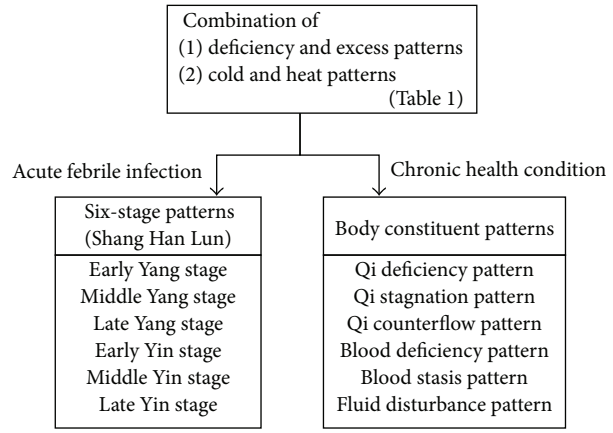

Figure 1: Diagnostic flow used in Kampo medicine. All patients are assigned a specific category as described in Table 1 and then divided into 2 groups according to whether they have acute febrile infectious disease or chronic disease. For acute febrile disease, the 6 stages of Shang Han Lun are very important. For chronic diseases, the host body constituent patterns are very important.

was used extensively for acute febrile infectious diseases before antibiotics were developed, where the strength of the foreign pathogen was very important. Since the development of antibiotics, Kampo medicine has been used more often for chronic diseases, in which the strength of the body energy is more important. In the modern version of Kampo, the host condition is assigned a high value, while the foreign pathogen is addressed by Western biomedicine. Therefore, the host energy is of greater importance. The need thus arose for the option to designate the body energy level as "neutral" rather than just "deficient" or "excessive." This issue was raised by Tokaku Wada (1743–1803), a physician in the Edo period [19]. His clinical wisdom was described in "Dosui Sagen" which was published in 1805. In this book, "between deficiency and excess" was described in the type of edema. This idea is thought to have influenced Kazuo Tatsuno (1905–1976) [20, 21] and other physicians in the Showa era. For example, a patient with impaired glucose tolerance appears normal according to the older Kampo designations, even though Kampo medicine is indicated for this condition. In such cases, the "neutral" designation enables acknowledgment of a condition that lies between deficiency and excess.

6. Formula Pattern

The formula pattern is also very unique in Kampo medicine. While traditional Chinese medicine (TCM) prescriptions are individualized at the herbal level, Kampo medicine is individualized at the formula level. This practice may have started during the Edo period, as usage of different amounts of herbs was described in a book by Kaibara in 1712 [22]. According to this book, the amount of each herb used in Japan was 1/5 to 1/3 that used in China. Kaibara explained that one of the reasons for this practice was the difficulty in importing herbs from China. Even though alternative herbs available in Japan were used, some had to be imported from

Table 1: Combinations of deficiency-excess and cold-heat patterns.

Components	Cold	Heat	Between cold and heat	Tangled cold and heat
Deficiency	Cold, deficiency	Heat, deficiency	Between cold and heat, deficiency	Tangled cold and heat, deficiency
Excess	Cold, excess	Heat, excess	Between cold and heat, excess	Tangled cold and heat, excess
Between deficiency and excess	Cold, between deficiency and excess	Heat, between deficiency and excess	Between cold and heat, between deficiency and excess	Tangled cold and heat, between deficiency and excess

Regardless of acute or chronic health conditions, all patients are classified into 1 of these 12 combinations. Very limited combinations are used for acute diseases. Between deficiency and excess; neutral in "deficiency and excess"; between cold and heat; neutral in "cold and heat"; tangled cold and heat; mixture "cold and heat," for example, cold foot and hot flush on face.

China. These differences in the amounts of herbs used are still prevalent. This may explain why Kampo medicine is individualized at the formula level. During the Edo period, doctors carefully studied the roles of formulas and decided the characteristics of each formula. This practice led to Yoshimasu's idea of "matching of pattern and formula."

Physicians continue to follow this principle today. Clinical trials have been conducted using the same Kampo formula used previously for a specific disease, determining the appropriate Kampo formula based on host patterns. "Matching of pattern and formula" has thus been shown to be a sophisticated approach.

By 1967, the first 4 Kampo formulas were approved by the government for coverage under the national insurance system, and 148 are now listed.

The acceptance of Kampo formulas into the national health insurance system marked the start of the exponential growth of Japan's market in Kampo medicines. Between 1976 and 1992, the sales of Kampo medicine grew more than 10-fold in Japan (Japan Kampo Medicine Manufacturers Association, 2007) [23].

With such a rapid increase in the number of Kampo drug products sold, the government and pharmaceutical industry needed to ensure that high standards were maintained. In 1987, the government established the Good Manufacturing Practice (GMP) law to ensure safety in manufacturing processes, including the production of Kampo formulas. The stringent manufacturing process for Kampo medicine has increased the legitimacy of this modality, as people can now expect uniformity and high quality from the different formulas. This facilitates "matching of pattern and formula," because if the formulas are not stable, it is very difficult to consistently match pattern to formula.

7. Future Challenges

Even though all 80 medical schools in Japan have incorporated Kampo medical courses into their curricula, the number of such courses is very small compared to that of Western biomedicine courses. Postgraduate and continuous Kampo medical education have not been established. Statistics indicate that Kampo formulas are used in daily practice by 90% of physicians, which represents over 260,000 physicians. However, the number of Kampo experts certified by the JSOM is only 2150. This great discrepancy means that most physicians use Kampo formulas based on Western biomedical disease diagnoses without deep consideration of patterns. Further education is necessary for the users of Kampo formulas.

Another concern for the future is the coding rule used for the qi-blood-fluid pattern. Deficiency, excess, and between deficiency and excess are mutually exclusive. Likewise, cold-heat and the 6 stages are mutually exclusive in the same category. However, several abnormalities in qi-blood-fluid may exist in 1 patient. We conducted a small clinical trial without establishing any coding rules. Some doctors provided only 1 code for the qi-blood-fluid pattern, while others provided 4 codes. For more accurate statistics, coding rules should be developed and training in coding should be imparted.

In terms of international comparisons, Kampo patterns are too simple compared to TCM and traditional Korean medicine (TKM). Organ system patterns are particularly lacking in Japan. However, in ICD-11, all the patterns will be presented on the common platform of Western biomedicine. Some organ system patterns can be linked to Western biomedicine disease codes, even though they do not map one-to-one. ICD 11 has terminology that is novel to ICD. This allows ontology software precisely describe the content of each term and links the different codes to each other. The next stage of ICTM development will be field testing. We expect that the international field test will allow for international comparisons.

8. Conclusion

Kampo patterns are rather unique compared to Chinese or Korean patterns. There are 2 explanations for this difference. First, Kampo medicine was separated from the theory of the Ming dynasty and then reestablished based on Shang Han Lun theory during the Edo period. Second, Kampo medicine is used in combination with Western biomedicine by licensed doctors in Japan. Kampo terminology was redeveloped in order to avoid confusion with Western biomedicine.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgment

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Research Article

Analysis of Questionnaire for Traditional Medicine and Development of Decision Support System

Kotoe Katayama,[1] Rui Yamaguchi,[1] Seiya Imoto,[1] Kenji Watanabe,[2,3] and Satoru Miyano[1]

[1] *Human Genome Center, Institute of Medical Science, University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan*
[2] *Center for Kampo Medicine, Keio University School of Medicine, 35 Shinano-machi, Shinjuku-ku, Tokyo 160-8582, Japan*
[3] *Faculty of Environment and Information Study, Keio University, 5322 Endo, Fujisawa, Kanagawa 252-0882, Japan*

Correspondence should be addressed to Satoru Miyano; miyano@ims.u-tokyo.ac.jp

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Kampo medicine is the Japanese adaptation of traditional medicine. In Kampo medicine, "medical interview" plays an important role. "Medical interview" in Japanese traditional medicine includes not only chief complaint but also a questionnaire that asked about the patient's lifestyle and subjective symptoms. The diagnosis by Kampo is called "Sho" and determined by completely different view from Western medicine. Specialists gather all available information and decide "Sho." And this is the reason why non-Kampo specialists without technical knowledge have difficulties to use traditional medicine. We analyzed "medical interview" data to establish an indicator for non-Kampo specialist without technical knowledge to perform suitable traditional medicine. We predicted "Sho" by using random forests algorithm which is powerful algorithm for classification. First, we use all the 2830 first-visit patients' data. The discriminant ratio of training data was perfect but that of test data is only 67.0%. Second, to achieve high prediction power for practical use, we did data cleaning, and discriminant ratio of test data was 72.4%. Third, we added body mass index (BMI) data to "medical interview" data and discriminant ratio of test data is 91.2%. Originally, deficiency and excess category means that patient is strongly built or poorly built. We notice that the most important variable for classification is BMI.

1. Introduction

Interest in traditional medicine has increased nowadays. People in many countries look to traditional medicine to maintain their health or cure their disease. The WHO Western Pacific Regional Office (WHO WPRO) published "WHO International Standard Terminologies on Traditional Medicine (TM) in the Western Pacific Region (WHO ISTT)" in 2007 and linked the modern and traditional medicines together. The World Health Organization (WHO) suggests the integration of traditional medicine into the next edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-11) [1–4].

Kampo medicine—the Japanese adaptation of traditional medicine—was developed uniquely. Since 1967, the Japanese government has included Kampo medicine in the national medical system. In 2013, a total of 149 Kampo drugs are approved as prescription drugs and covered by the public insurance. Uniqueness of Kampo medicine is in that it has been a traditional medicine integrated into a public health care system in conjunction with modern medicine, while traditional medicines in other countries, for example, China and Korea, are often separated from modern medicine [5–9].

In Japanese traditional medicine, there are some types of examinations: "medical interview," tongue diagnosis, audioolfactory assessment, abdominal diagnosis, palpation, and so on. Kampo specialists consider all the various factors together. In particular, "medical interview" plays an important role. "Medical interview" includes not only chief complaint but also a questionnaire that asked about the patient's lifestyle and subjective symptoms which are seemingly unrelated to chief complaint. Specialists will gather all available information and decide "Sho" and traditional herbal medicine. The diagnosis by Kampo is called "Sho" and determined by completely different view from Western medicine. The diagnosis by Kampo is described by combination of

categories such as deficiency and excess, cold and heat, Qi, blood, and fluid. Each category has some patterns of "Sho." In deficiency and excess category, there are five "Sho:" deficiency pattern, slightly deficiency pattern, between-deficiency-and-excess pattern, slightly excess pattern, and excess pattern. Also, in cold and heat category, there are three patterns of "Sho": cold pattern, between cold and hot pattern, and hot pattern. And in Qi, Blood, and Fluid categories, there are 6 patterns of "Sho": Qi-deficiency pattern, Qi-counterflow pattern, Qi-depression pattern, blood-deficiency pattern, Oketsu pattern, and fluid-disturbance pattern [10]. When the patient is cold in Western diagnosis, the diagnosis by Kampo is, for example, deficiency pattern, between cold and hot pattern, or Qi-counterflow. The same "Sho" does not always describe the same Western diagnosis. Even if the patient has the same Western diagnosis, "Sho" is different among patients. In order to determine herbal medicine or "Sho," technical knowledge and experience are required. For non-Kampo specialist, it is hard to connect result of "medical interview" and "Sho".

In this paper, we focus on deficiency and excess category. If the repairing responses shown by the patient against his/her disease condition are strong or fully active, the patient is said to be in excess pattern, while, if they are weak or hollow, they are said to be in deficiency pattern [10]. Moreover deficiency and excess category means that patient is strongly built or poorly built. We analyze "medical interview" data to establish an indicator for non-Kampo specialist without technical knowledge to perform suitable traditional medicine.

2. Subjects and Methods

Since 2006, Center of Kampo Medicine, Keio University School of Medicine, has collected data about patients' "medical interview," "Sho," Western disease name (ICD-10 code), and prescribed herbal medicine. From April 2006 till December 2011, we collected 16805 records which include return to clinic records, and the number of first-visit patients that we analyzed was 2830. All registered patients provided written informed consent. Patients enter "medical interview" information via touch panel operation. "Medical interview" has 362 items, ranges in content from physical sign to food preference, and is important for Kampo diagnosis. We use patients' 128 subjective symptoms. There are two types of questions, yes-no (24 items) questions and Visual Analogue Scale (VAS) questions (104 items). The Visual Analogue Scale (VAS) has been developed to allow the measurement of individual's responses to physical stimuli, such as heat. The VAS is a method that can be readily understood by most people to measure a characteristic or attitude that cannot be directly measured. It was originally used in the field of psychometrics, and nowadays it is widely used to assess changes in patient health status with treatment. A VAS consists of a line on a page with clearly defined end points and normally a clearly identified scale between the two end points. For guidance, the phrases "no pain" and "worst imaginable pain" are placed at both sides of the line, respectively. Minimum values 0 of the VAS means "no pain" and maximum values 100 means "worst imaginable pain." In this paper, we use normalized VAS. To get normalized VAS, we divided VAS by each patients' maximum VAS value [11].

We predict "Sho" by using 2830 first-visit patients' "medical interview" data. In this paper, we focus on deficiency and excess category as a target and adopt random forests algorithm. In deficiency and excess category, there are five "Sho": deficiency pattern (437 patients), slightly deficiency pattern (395 patients), Between-deficiency-and-excess pattern (1500 patients), slightly excess pattern (268 patients), and excess pattern (230 patients). These data were diagnosed by Doctors of Center of Kampo Medicine, Keio University School of Medicine, who are Kampo specialist.

Random forests algorithm was proposed by Breiman [12, 13] and is an algorithm for classification that uses an ensemble of classification trees. Random forests algorithm has performance in classification tasks, comparable to support vector machines. It is unexcelled in accuracy among current algorithms, can handle thousands of input variables without variable deletion, and gives estimates of which variables are important in the classification. The overview of random forests algorithm is as follows: random forests algorithm grows many classification trees. To classify a new object from an input vector, put the input vector down each of the trees in the forest. Each tree gives a classification, and we say that the tree "votes" for that class. The forest chooses the classification having the most votes. We set training and test data that has labels consistent with that type of classification. All statistical analyses were conducted using R software, version 2.15.2 (The R Foundation for Statistical Computing; October 26, 2012), on Mac OS X10.7.5 powered by 3.2 GHz Quad-Core Intel Xeon.

3. Results

3.1. 2830 First-Visit Patients' Profiling. The mean age was 46.7 ± 18.6 years. With regard to sex, there were 814 men and 2016 women.

3.2. All Data. We selected randomly 200 patients as a training data (each 100 patients from deficiency pattern and excess pattern). And others are test data. The discriminant ratio of training data was perfect but that of test data is 67.0% (Table 1). In Figure 1, points are patients' prediction probabilities. The closer value of 1 means that the patient is deficiency pattern and the closer value of 0 means excess pattern. If above 0.5, we estimate that he is deficiency pattern. If below 0.5, he is excess pattern.

3.3. After Data Cleaning. To get prediction power enough for practical use, we try to do data cleaning. From 2830 first-visit patients, we choose patients who answered more than 20 items of "medical interview." The number of target first-visit patients is 2540: deficiency pattern (400 patients), slightly deficiency pattern (364 patients), Between-deficiency-and-excess pattern (1335 patients), slightly excess pattern (239 patients), and excess pattern (202 patients). We selected

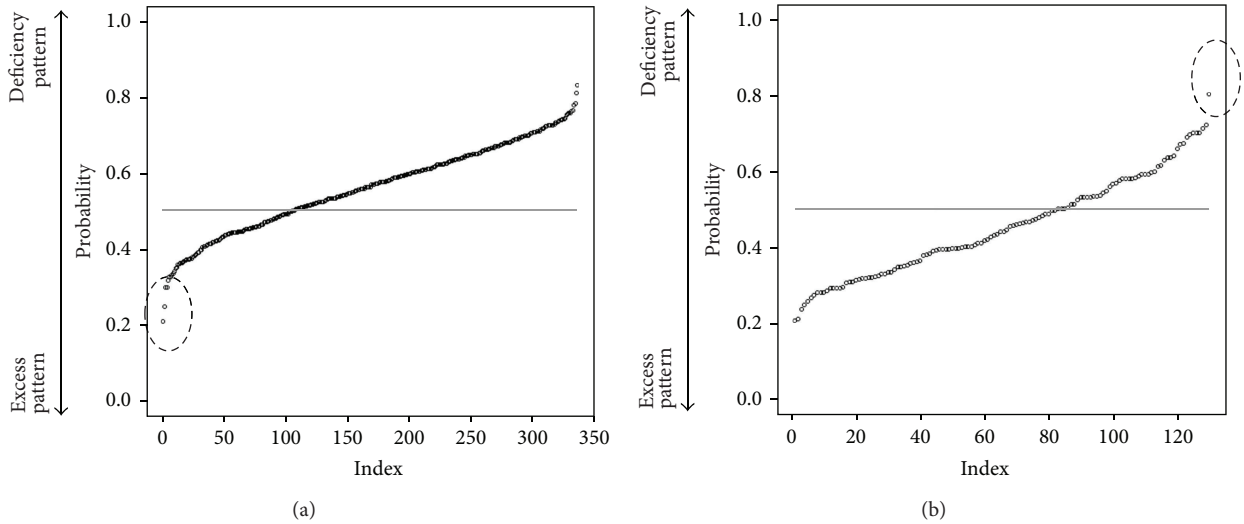

Figure 1: Each patient's prediction probability of test data. (a) label is deficiency pattern (b) label is exess pattern. (a) plotted probability of deficiency pattern test patients data (point means each patient) and the closer value of 1 means that the patient is of deficiency pattern and the closer value of 0 means excess pattern. So if each point is above horizon line = 0.5, the point is classified into deficiency pattern. (b) plotted probability of excess pattern test patients' data (point means each patient) and the closer value of 1 means that the patient is of deficiency pattern and the closer value of 0 means excess pattern. So if each point is below horizon line = 0.5, the point classified is into excess pattern. We can notice some outlier predictions in circles. They answered few "medical interviews".

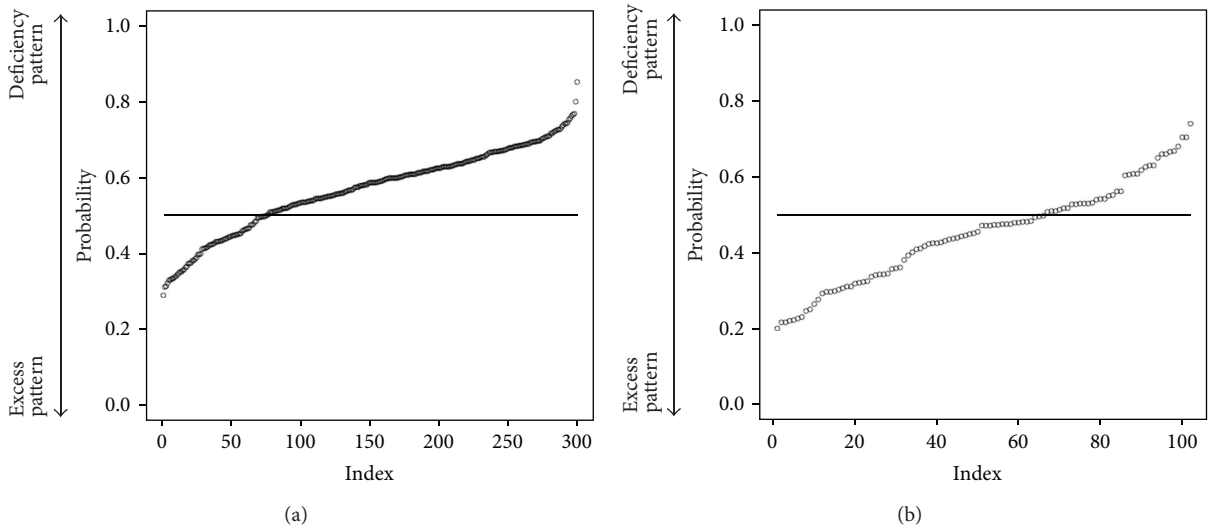

Figure 2: Each patient's prediction probability of test data answered more than 20 items of "medical interview". (a) plotted probability of deficiency pattern patients' data (point means each patient) and the closer value of 1 means that the patient is of deficiency pattern and the closer value of 0 means excess pattern. So if each point is above horizon line = 0.5, the point is classified into deficiency pattern. (b) plotted probability of excess pattern patients' data (point means each patient) and the closer value of 1 means that the patient is of deficiency pattern and the closer value of 0 means excess pattern. So if each point is below horizon line = 0.5, the point is classified into excess pattern. We notice that there are no outlier predictions.

randomly 200 patients as a training data (each 100 patients from deficiency pattern and excess pattern). And others are test data. The discriminant ratio of training data was also perfect and that of test data is 72.4% (Table 2). In Figure 2, points are patients' prediction probabilities. We tried to use Slightly Deficiency pattern and Slightly Excess pattern data as test data. Discriminant ratio was 63.8% (Table 3). Important variables in this classification are in Figure 3.

3.4. Predict of "Sho" with Body Mass Index. We added body mass index (BMI) data to "medical interview" data. Center of Kampo Medicine, Keio University School of Medicine,

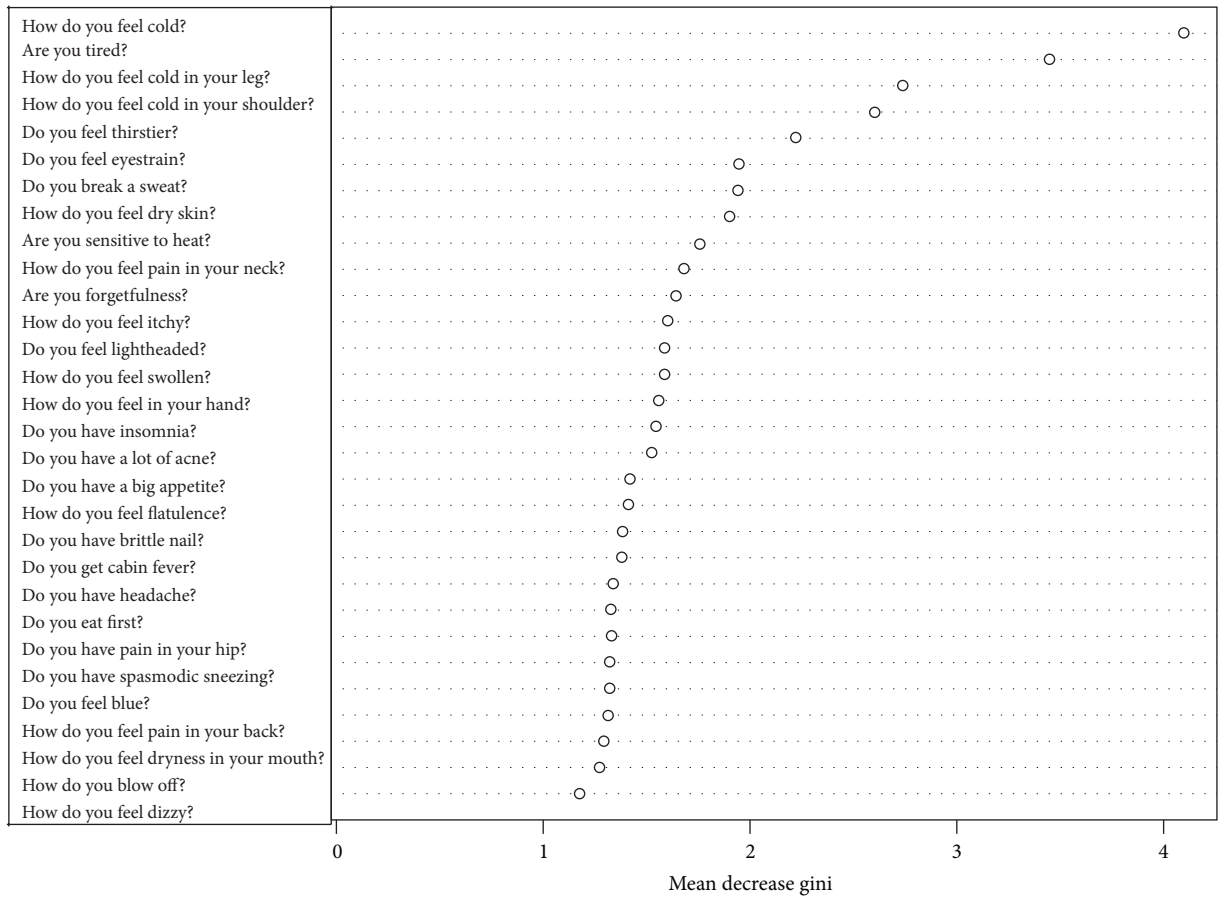

Figure 3: Top 30 important variables answered more than 20 items of "medical interview". Higher value of mean decrease gini means that the item makes a sizable contribution to predict the "Sho."

Table 1: All data results of test data.

	Deficiency pattern	Excess pattern	Discriminant ratio
Predict			
Deficiency pattern	231	48	67.00%
Excess pattern	106	82	
Total	337	130	

Table 2: After data cleaning result of test data.

	Deficiency pattern	Excess pattern	Discriminant ratio
Predict			
Deficiency pattern	225	36	72.40%
Excess pattern	75	66	
Total	300	102	

Table 3: After data cleaning result of slightly deficiency pattern and slightly excess pattern of test data.

	Slightly Deficiency pattern	Slightly Excess pattern	Discriminant ratio
Predict			
Deficiency pattern	244	92	63.80%
Excess pattern	120	147	
Total	364	239	

Table 4: Predict with BMI result of test data.

	Deficiency pattern	Excess pattern	Discriminant ratio
Predict			
Deficiency pattern	51	2	91.20%
Excess pattern	4	15	
Total	55	17	

Table 5: Predict with BMI result of slightly deficiency pattern and slightly excess pattern of test data.

	Slightly deficiency pattern	Slightly excess pattern	Discriminant ratio
Predict			
Deficiency pattern	21	3	85.10%
Excess pattern	7	36	
Total	28	39	

has patients' BMI data of 2011. The number of target first-visit patients is 402: Deficiency pattern (75 patients), Slightly deficiency pattern (28 patients), Between-deficiency-and-excess (223 patients), Slightly excess pattern (39 patients), and Excess pattern (37 patients). We selected randomly 40 patients as a training data (each 20 patients from deficiency pattern and excess pattern). And others are test data. The discriminant ratio of training data was perfect and that of test data is 91.2% (Table 4). In Figure 4, points are patients' prediction probabilities. We try to use slightly deficiency pattern and slightly excess pattern data as test data. Discriminant ratio was 85.1% (Table 5). In Figure 5, points are patients' prediction probabilities. Important variables in this classification are in Figure 6. The most important variable is BMI.

4. Discussion

We predicted "Sho" by using random forests algorithm which is a powerful algorithm for classification. First, we used all the 2830 first-visit patients' data. The discriminant ratio of training data was perfect but that of test data is only 67.0%. In Figures 1(a) and 1(b), we can notice some outliers in red circles. It was problem of data itself. Some people answer few "medical interview questions". This data is meaningless, and prediction failed. So we did data cleaning to get prediction enough for practical use. We choose patients who answered more than 20 items. In this situation, the discriminant ratio of training data was also perfect and that of test data is 72.4% (Table 2). It was slightly better than first situation. And we notice that there are no outlier predictions in Figure 2. However, it was not an acceptable result. Originally, deficiency and excess category means that patient is strongly built or poor built and our "medical interview" did not include such indicator. In Figure 3, there are no items by which we can determine someone's appearance. Our "medical interview" questionnaire did not take patient's appearance into account, so this prediction with random forests did not work well. If we had chosen another statistical strategy, we would obtain almost the same results, because our questionnaire lacks appropriate questions that ask about body appearance. The relationships among deficiency, excess categories, and BMI are in Figure 7; however, it is not, linear relationship. If we use only BMI for classification, discriminant ratio was just 62.0%.

To cover the shortcomings of our questionnaire, we added BMI data to "medical interview" data. BMI is a simple index of weight-for-height that is commonly used to classify underweight, overweight, and obesity in adults. It is defined as the weight in kilograms divided by the square of the height in meters. The discriminant ratio of test data was 91.2%. We notice that patients' prediction probabilities are higher in Figure 4(a) and lower in Figure 4(b). It provided better discriminant ratio than the others. From Figure 3, we notice that the most important variable for classification is BMI. To get better classification, we have to know what is the feature of the target and check the data. In our result, BMI contributed to predict the "Sho" highest level than the other; however, by only using BMI prediction is flimsy. When non-Kampo specialists try to diagnose Deficiency and Excess category, they should first pay attention to patients' BMI. After that, non-Kampo specialists should ask some questions in medical examination. The questions also have higher contribution to predicting the "Sho": Do you break a sweat? How do you feel cold? Do you feel blue? How do you feel pain in your neck? Are you sensitive to heat? How do you feel numbness in your leg? Are you tired? Do you have a big appetite? How do you feel pain in your shoulder? These questions indicate that a patient seems to be of deficiency pattern if the answer is yes. Of course there are many kinds of "medical interviews"; we think that the smaller number of questions is good for non-Kampo specialists, and it is enough for practical use.

5. Conclusion

In Japanese traditional medicine, Kampo, "medical interview" plays an important role. "Medical interview" is a questionnaire that asked about the patient's lifestyle and subjective symptoms. The diagnosis by Kampo is called "Sho" and determined by completely different view from Western medicine. And this is the reason why non-Kampo specialists without technical knowledge have difficulties to use traditional medicine. In addition, the diagnosis by Kampo

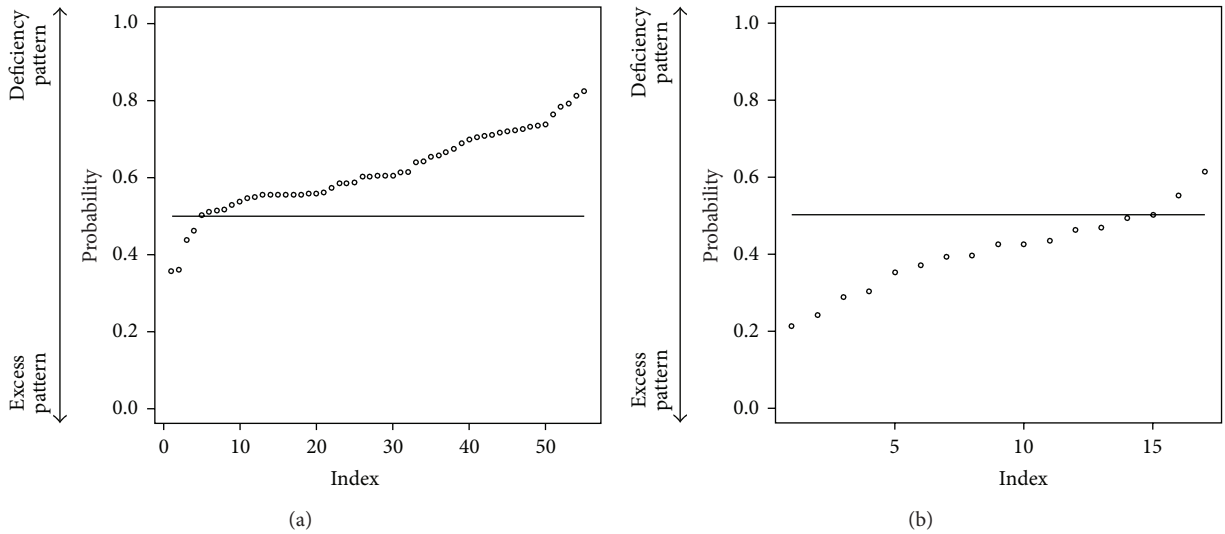

Figure 4: Each patient's prediction probability of test data. Predict with BMI. (a) label is deficiency pattern. (b) label is excess pattern. (a) plotted probability of deficiency pattern test patients' data (point means each patient) and the closer value of 1 means that the patient is of deficiency pattern and the closer value of 0 means excess pattern. So if each point is above horizon line = 0.5, the point is classified into deficiency pattern. (b) plotted probability of excess pattern test patients' data (point means each patient) and the closer value of 1 means the patient is of deficiency pattern and the closer value of 0 means excess pattern. So if each point is below horizon line = 0.5, the point is classified into excess pattern.

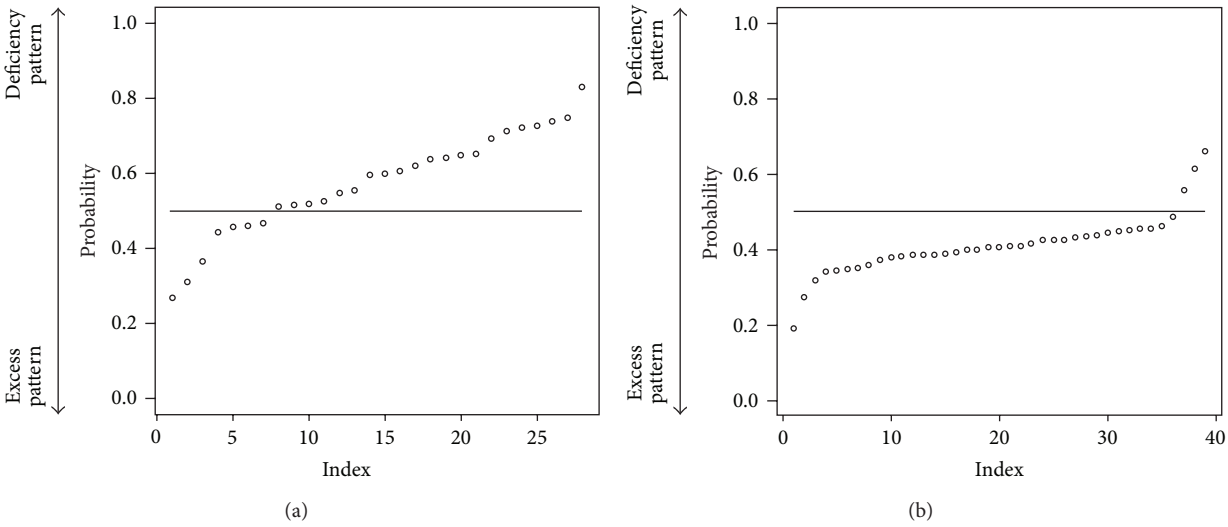

Figure 5: Each patient's prediction probability of test data. Predict with BMI. (a) label is slightly deficiency pattern. (b) label is slightly excess pattern. (a) plotted probability of slightly deficiency pattern test patients' data (point means each patient) and the closer value of 1 means that the patient is of deficiency pattern and the closer value of 0 means excess pattern. So if each point is above horizon line = 0.5, the point is classified into deficiency pattern. (b) plotted probability of slightly excess pattern test patients' data (point means each patient) and the closer value of 1 means that the patient is of deficiency pattern and the closer value of 0 means excess pattern. So if each point is below horizon line = 0.5, the point is classified into excess pattern. The patients' prediction probabilities are higher in Figure 5(a) and lower in Figure 5(b).

that is called "Sho" is problem of increasing complexity because "Sho" is used in combination. We predicted "Sho" by using random forests algorithm which is powerful algorithm for classification. In our result, BMI is of higher contribution; however, if we only use BMI to predict "Sho" in deficiency and excess category, the discriminant ratio was 62.0%. To get higher-accuracy prediction, we should use both BMI and "medical interviewv" It is applied to non-Kampo specialists as well, so they try to use BMI and some "medical interview" which has higher contribution.

In this research, prediction of Deficiency and Excess category is enough for practical use if we added body mass index (BMI) data to "medical interview" data. Other categories are remained and are our future targets.

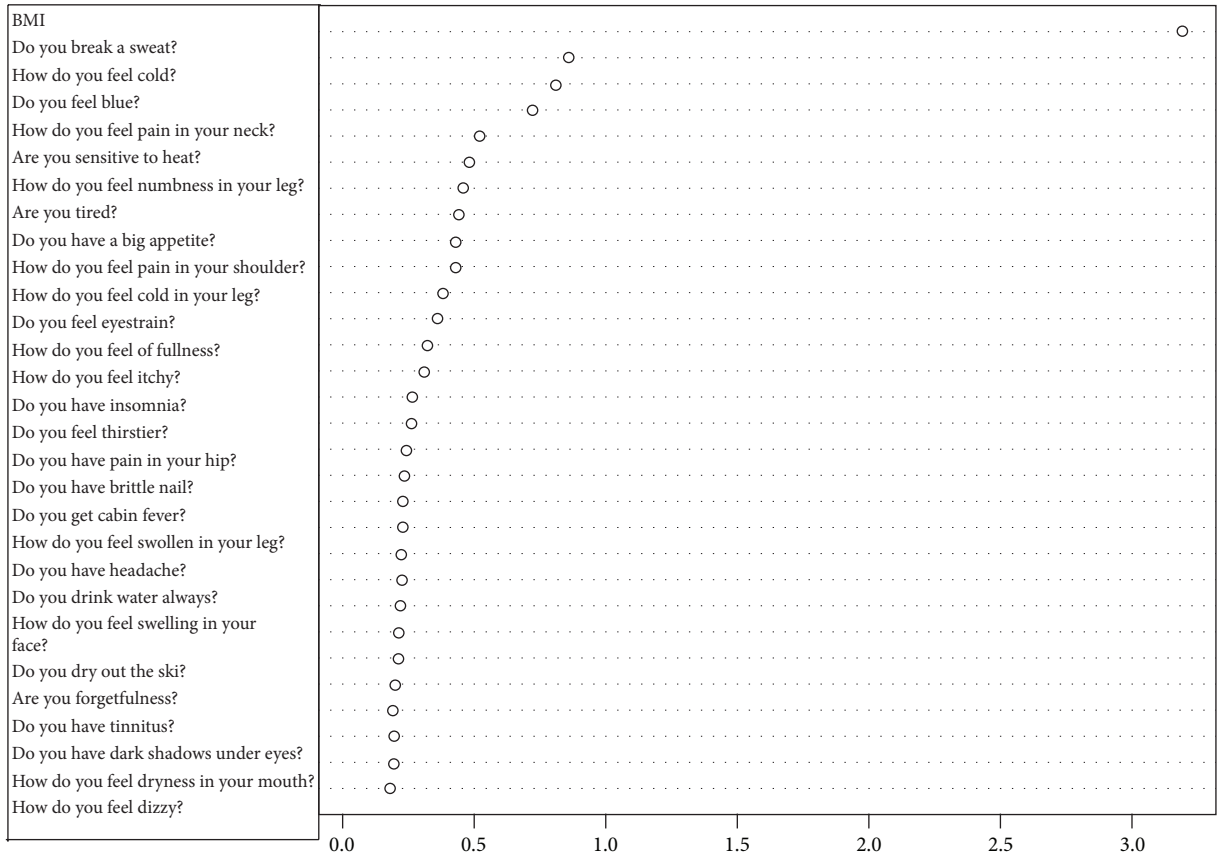

Figure 6: Top 30 important variables. Predict with BMI. Higher value of mean decrease gini means that the item makes a sizable contribution to predict the "Sho." We notice that the most important variable is BMI.

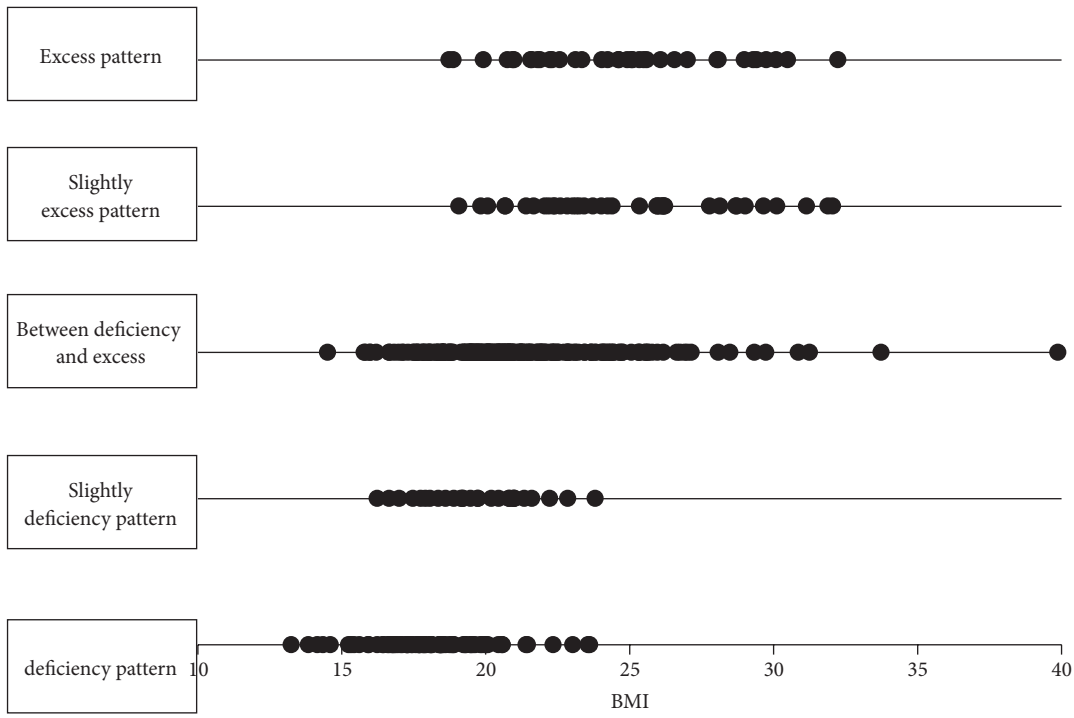

Figure 7: Relationship between BMI and deficiency and excess category. This is not a linear relationship, so it is hard to describe the relationship with BMI and deficiency and excess category by linear approximation.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Identification of a Predictive Biomarker for the Beneficial Effect of Keishibukuryogan, a Kampo (Japanese Traditional) Medicine, on Patients with Climacteric Syndrome

Takao Namiki,[1] Hiromi Sato,[2] Yukari Matsumoto,[2] Haruka Kakikura,[2] Koichi Ueno,[2,3] Atsushi Chino,[4] Hideki Okamoto,[1] Akito Hisanaga,[1] Akiyo Kaneko,[1] Toshiaki Kita,[1] Maki Kihara,[5] Makio Shozu,[5] and Katsutoshi Terasawa[4]

[1] *Department of Japanese-Oriental (Kampo) Medicine, Graduate School of Medicine, Chiba University, Chiba 260-8670, Japan*
[2] *Department of Geriatric Pharmacology and Therapeutics, Graduate School of Pharmaceutical Sciences, Chiba University, Chiba 260-8670, Japan*
[3] *Center for Preventive Medical Science, Chiba University, Chiba 260-0856, Japan*
[4] *Chiba Chuo Medical Hospital, Chiba 264-0017, Japan*
[5] *Department of Reproductive Medicine, Graduate School of Medicine, Chiba University, Chiba 260-8670, Japan*

Correspondence should be addressed to Takao Namiki; tnamiki@faculty.chiba-u.jp

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Keishibukuryogan (KBG; *Guizhi-Fuling-Wan* in Chinese) is one of the Kampo (Japanese traditional) medicines used to treat patients with climacteric syndrome. KBG can be used by patients who cannot undergo hormone replacement therapy due to a history of breast cancer. We evaluated whether cytosine-adenine (CA) repeat polymorphism of the estrogen receptor β gene can be a predictor of the beneficial effect of KBG on climacteric syndrome. We also investigated the relationship between CA repeat polymorphism, the patients' profiles, and the therapeutic effect. We found that CA was an SS, SL, or LL genotype according to the number of repeats. We studied 39 consecutive patients with climacteric disorders who took KBG for 12 weeks. The diagnosis of climacteric disorders was made on the basis of the Kupperman index. KBG significantly improved the patients' climacteric symptoms (i.e., vasomotor symptoms in the patients with the LL genotype and melancholia in the patients with the SL genotype). No relationship between the patients' profiles and CA repeat polymorphism was recognized. CA repeat polymorphism could thus be a potential biomarker to predict the efficacy of KBG in climacteric syndrome, and its use will help to reduce the cost of treating this syndrome by focusing the administration of KBG on those most likely to benefit from it.

1. Introduction

Climacteric syndrome, which is caused by a decrease of the estrogen level during menopause, often severely impairs a woman's quality of life [1, 2]. Many climacteric women suffer from vasomotor symptoms, mood disorders, vaginal dryness, headache, shoulder stiffness, and other problems. Hormone replacement therapy (HRT) is one of the most effective treatments for climacteric symptoms, especially for vasomotor symptoms, mood problems, and vaginal dryness. In recent years, however, epidemiological studies have reported adverse reactions to HRT such as an increase in the risks for stroke, deep vein thrombosis, dementia, and breast cancer [3–6]. In Japan, the use of Kampo medications (Japanese herbal medicine) is one alternative for controlling these symptoms in women who reject HRT or who cannot receive HRT due to a history of breast cancer [7].

Keishibukuryogan (KBG; *Guizhi-Fuling-Wan* in Chinese) is a Kampo medicine that has been effective in patients with climacteric syndrome. KBG consists of five crude drugs: cinnamon bark (*Cinnamomum cassia* Blume), peony root (*Peonia lactiflora* Palls), peach kernel (*Prunus persica* Batsch),

poria sclerotium (*Poria cocos* Wolf), and moutan bark (*Peonia suffruticosa* Andrews). However, at present, the clinical evidence of KBG's efficacy is still limited because there have been few large-scale clinical trials. In addition, in a recent randomized study in the United States, patients with hot flashes did not show improvement as a result of KBG treatment, suggesting that the inclusion criteria of patients in clinical trials are important in showing the efficacy of Kampo medicine [8].

In 1996, the estrogen receptor (ER) β gene was identified in an animal study [9]. Five isoforms of ERβ were subsequently confirmed in human ovarian tissue [10]. ERβ expression has also been observed in all types of granulose cells of the follicle [11], and polymorphisms of the ERβ gene are associated with abnormal ovulation [12]. The ERβ gene is suggested to play an important role in ovarian function. A retrospective study by our group revealed that the cytosine-adenine (CA) repeat polymorphism of the ERβ gene is correlated with climacteric symptoms [13]. In the present prospective study, therefore, we aimed to clarify the association between the CA repeat polymorphism of the ERβ gene and the therapeutic effects of KBG on women with climacteric symptoms. We evaluated whether the contribution of the CA repeat polymorphism of the ERβ gene has a role in the effectiveness of KBG in women with climacteric syndrome.

2. Subjects and Methods

2.1. Subjects. The subjects were 39 consecutive females over 40 years old with climacteric symptoms at Chiba University Hospital and Chiba University's Kashiwanoha Clinic. Of these, 18 subjects were postmenopausal and the others were not yet menopausal. Menopause was diagnosed when the patient had not had a period in the past 12 months. The inclusion criterion of climacteric syndrome was a Kupperman index (KI) score over 20. The KI represents the total score of 11 components including vasomotor symptoms (hot flashes), paresthesia, insomnia, nervousness, melancholia, vertigo, concentration disorders, arthralgia or myalgia, headache, palpitations, and formication (a sensation of insects crawling over the skin). We simultaneously defined menopause via blood measurement as a follicle-stimulating hormone (FSH) level $\geq$40 mIU/mL, as an estradiol (E_2) level $\leq$20 pg/mL, or as an anti-Müllerian hormone (AMH) of <14.3 pmol/L as a reference of ovarian reserve. We excluded patients with physical diseases such as thyroid disease via blood examinations and psychiatric diseases such as depression via Self-rating Depression Scale (SDS) questionnaires.

2.2. Study Objective and Design. We investigated (1) the relationship between the CA repeat polymorphism and the KI before treatment with KBG and (2) the efficacy of KBG by comparing the total or component scores of the KI before and after treatment with KBG.

All patients took KBG extract granules at a dose of 2.5 grams (TJ-25, Tsumura Co., Tokyo) three times a day for 12 weeks. During the study, the patients came to our outpatient clinic every 4 weeks, and they underwent blood tests at the first visit and the final visit after the 12 week treatment was completed. The cessation or any change in the KBG treatment for any reason (including at the request of the patient) was considered dropping out of the study.

We explained the objectives of the study to each patient by asking her to fill out questionnaires (including Kupperman index, menstrual cycle, preset symptoms, and past history questionnaires) and obtained written informed consent from all patients. The study questionnaires were completed by patient interviewers.

We analyzed the correlation of each component of the KI with the detailed climacteric symptoms. We examined all patients for the CA repeat of the ERβ gene. The number of CA repeats was classified into two categories: $\leq$21, defined as short (S), and >21, defined as long (L). We defined the three genotypes involving combinations of alleles as SS, SL, and LL.

This study was approved by the ethics committees of the Graduate School of Medicine, Chiba University, the Graduate School of Pharmaceutical Sciences, Chiba University, and the Chiba University Environment Field Science Center. In addition, as genetic information and personal medical information are critical to personal privacy, we managed all data very carefully with a stand-alone personal computer.

2.3. Analysis of CA Polymorphisms of the ERβ Gene. Genomic DNA was extracted from human peripheral blood leukocytes using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. Polymerase chain reaction (PCR) was performed in 75 μL of reaction mixture with the following components: 150 ng of human genomic DNA, oligonucleotide primers designed to amplify polymorphic CA repeats in intron 6 of the human ERβ gene (forward: 5′-CAA TTC CCA ATT CTA AGC CT-3′ and reverse: 5′-ATT CTT CTT TAG GCC AGG CA-3′) at 0.4 μM, dNTP mixture (TaKaRa Bio, Otsu, Japan) at 200 μM, 7.5 μL of 10× reaction buffer (containing 15 mM $MgSO_4$) (Transgenomic, Omaha, NE), and 2.5 U of optimase polymerase (Transgenomic). The reactions were brought to a total volume of 75 μL by adding MilliQ water.

The amplification profiles were as follows: 35 cycles of denaturing at 94°C for 30 sec, annealing at 60°C for 30 sec, and extension at 72°C for 30 sec. The PCR products were purified with the QIAquick PCR Purification Kit (Qiagen) and used in the following analysis.

We conducted the analysis of the CA repeat polymorphisms by dye-terminator cycle sequencing using the Dye Terminator Cycle Sequencing Quick Start Kit (Beckman Coulter, Fullerton, CA) and the CEQ2000 DNA Analysis System (Beckman Coulter) according to the manufacturer's protocols.

2.4. Statistical Analysis. The statistical analysis was carried out as follows. The comparison of dispersibility between generations was done using the Bartlett test. Multiple comparisons were done using the Tukey-Kramer test in the case of equal dispersion or by the Steel-Dwass test in the case of nondispersion. The comparison of healthy subjects and

Table 1: Clinical characteristics of the post- and premenopause patients.

	All	Postmenopause	Premenopause	P
	$n = 34$	$n = 17$	$n = 17$	
Age	49.5 ± 4.69	51.2 ± 5.45	47.7 ± 3.02	0.028*
Height (cm)	156.8 ± 3.46	155.6 ± 3.44	158.1 ± 3.09	0.033*
Body weight (kg)	52.7 ± 6.67	53.7 ± 7.49	51.7 ± 5.78	0.394
BMI (kg/cm^2)	21.5 ± 3.22	22.3 ± 3.75	20.7 ± 2.44	0.278
Age of menarche	12.5 ± 1.13	12.2 ± 0.81	12.8 ± 1.35	0.121
SDS	46.2 ± 8.51	45.2 ± 9.15	47.2 ± 7.98	0.502
Hysterectomized	2	2	0	
Ratio of menopause (%) (delited hysterectomized)	44.1	88.2	0	

Data are mean ± SD. BMI: body mass index, SDS: self-rating depression scale. The P values (post versus pre) were obtained by Student's t-test or Mann-Whitney test. *$P < 0.05$.

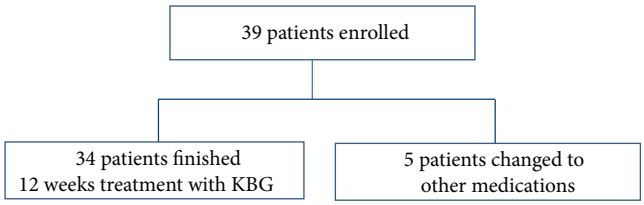

Figure 1: Flow chart of patients enrolled in the study.

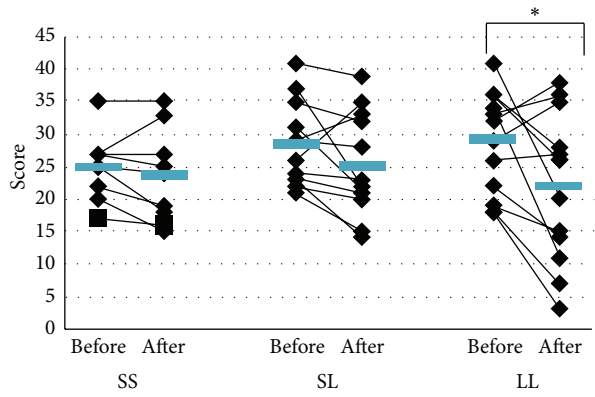

Figure 2: Changes in the subjects' Kupperman index (KI) from before KBG treatment to after the treatment were compared with each of the three genotypes of the CA repeat polymorphism of the ERβ gene. Transverse bars indicate averages. P values (before versus after) were obtained by paired t-test. *$P < 0.05$.

patients with climacteric disorders exhibiting dispersibility was done by F-test and analyzed using Student's t-test in the case of equal dispersion or Welch's t-test in the case of nondispersion. The coefficient of correlation was obtained by Pearson's correlation test using PASW Statistics 18. The sensitivity, specificity, and the distribution of frequencies were calculated using cross-tabulation with PASW Statistics 18. StatLight 1997 software (Yukms, Tokyo) was used for the statistical analyses. P values < 0.05 were accepted as significant in all analyses.

3. Results

3.1. Characteristics of the Subjects Enrolled in This Study. Five of the 39 subjects dropped out; the remaining 34 patients with climacteric symptoms all took the KBG for 12-weeks (Figure 1). The postmenopause and premenopause groups were each 17 subjects. There were no significant differences between these groups except in age and height (Table 1). The past histories of 11 subjects showed myoma uterus or endometriosis. Two subjects had the history of hysterectomized. No serious adverse reaction to KBG was observed.

3.2. Relationship between Subjects' Profiles and CA Genotype. We classified the 34 patients into three genotypes: 9 patients as SS, 12 as SL, and 13 as LL. We compared the patients' total KI scores before treatment according to the CA genotype, and we found no significant differences in the patients' profiles among the genotypes (Table 2). There were no significant differences among the three genotype groups except for the FSH level in the LL genotype (Table 3). The high FSH and low E_2 levels indicated that those subjects were in perimenopause.

3.3. Correlation between KBG's Clinical Efficacy and CA Genotypes. To examine the effectiveness of KBG in patients with climacteric symptoms, we compared the changes in the patients' KI before and after treatment in each CA genotype. Regarding the total KI score, a significant improvement was observed only in the LL group (Figure 2). Likewise, we evaluated the improvement in the 11 climacteric symptoms included in the KI. The patients with the LL genotype showed significant improvement in climacteric KI components such as vasomotor symptoms, and patients with the SL genotype showed a significant beneficial effect on melancholia following the KBG treatment (Table 4).

Table 2: Clinical characteristics of 34 patients who finished the KBG treatment, classified by their CA repeat polymorphism of the ERβ gene.

	SS $n = 9$	SL $n = 12$	LL $n = 13$	P
Age	50.1 ± 2.37	51.2 ± 5.29	47.5 ± 4.86	0.100
Height (cm)	157.1 ± 3.78	155.6 ± 3.22	157.7 ± 3.39	0.502
Body weight (kg)	54.0 ± 8.26	53.3 ± 6.26	51.2 ± 6.07	0.913
BMI (kg/cm^2)	22.0 ± 4.18	22.1 ± 3.21	20.6 ± 2.43	0.747
Age of menarche	12.6 ± 1.33	12.3 ± 1.07	12.5 ± 1.13	0.901
SDS	46.8 ± 10.29	46.0 ± 9.05	45.9 ± 7.30	0.971
KI	25.0 ± 5.12	28.4 ± 6.49	29.2 ± 7.85	0.341
Hysterectomized	0	1	1	
Ratio of menopause (%) (delited hysterectomized)	33.3	66.7	30.8	

Data are mean ± SD. S: short allele, L: long allele, SDS: self-rating depression scale, and KI: Kupperman index. P values (SS versus SL versus LL) were obtained by Kruskal-Wallis test or 1-way ANOVA.

Table 3: The patients' hormone levels before and after treatment compared by CA repeat polymorphism of the ERβ gene.

	SS $n = 9$	SL $n = 12$	LL $n = 13$	P
E_2(pg/mL)				
Before	69.2 ± 103.9	65.2 ± 89.5	104.6 ± 142.8	0.305
After	59.0 ± 97.3	32.0 ± 41.6	78.3 ± 100.9	0.235
FSH (mIU/mL)				
Before	49.0 ± 29.0	53.4 ± 27.2	24.1 ± 29.3	0.044$^{\#}$
After	39.1 ± 21.7	55.1 ± 29.5	25.5 ± 26.7	0.051
AMH (pmol/L)				
Before	1.33 ± 1.03	1.12 ± 1.22	6.46 ± 7.53	0.095
After	1.11 ± 1.22	0.90 ± 0.48	4.42 ± 4.83	0.107

Data are mean ± SD. S: short allele, L: long allele. P values (SS versus SL versus LL) were obtained by Kruskal-Wallis test or 1-way ANOVA. $^{\#}P < 0.05$.

4. Discussion

We determined the CA repeat polymorphism of the ERβ gene in 34 climacteric patients and investigated the relationships of the CA genotypes with the patients' backgrounds and the therapeutic effects of KBG. The results suggested that KBG was effective in climacteric patients who had either the LL or SL genotype. The serum estrogen levels in the LL genotype patients, which were higher than those in the other two genotype groups, might partially explain the efficacy of KGB; although the KI values in the LL group were higher than those in the SS group.

The use of KBG for patients with climacteric syndrome can be very beneficial because KBG has no contraindications except in patients with an allergy to KBG. Because KBG has no direct effect on increasing estrogen levels, it can also be used for patients with climacteric syndrome who have a history of breast or ovarian cancer, both of which are contraindications for HRT.

In ERs, many genetic polymorphisms including single-nucleotide polymorphisms (SNPs) and a microsatellite polymorphism have been reported. In 1998, Tsukamoto et al. first characterized the CA repeat polymorphism (D14S1026) of the ERβ gene in a Japanese population [14]. A systematic mutation screening subsequently detected five different sequence variants, including two mutations and three polymorphisms [15]. Importantly, in an in vitro functional analysis, the presence of the valine in position 320 showed significantly decreased maximal transcriptional activity [16]. The number of CA repeats ranges from 13 to 30.

The correlation of the CA repeat polymorphism with various diseases has been reported in breast cancer [17], endometrial cancer [18], osteoporosis [19], and Alzheimer's disease [20]. A relationship between the CA repeat polymorphism and the androgen concentration [21] and prolactin levels [22] has also been reported, which strongly suggests that the CA repeat polymorphism is related to the secretion of sexual hormones. The distribution of the number of repeats of CA exhibits racial differences; there is a single peak of the specific CA repeat number in Japan and China [19, 23], while a bimodal distribution has been shown in Caucasians and in India [18, 24]. The racial differences in the distribution of the CA repeat polymorphism may explain why there have been no significant results of clinical trials in the United States.

Table 4: Comparison of Kupperman index components before and after 12 weeks' treatment by genotypes of the CA repeat polymorphism of the ERβ gene.

	SS $n = 9$	SL $n = 12$	LL $n = 13$	P
Vasomotor				
Before	9.78 ± 2.11	10.67 ± 1.97	10.46 ± 2.03	0.583
After	9.33 ± 2.00	10.00 ± 2.70	7.08 ± 4.05*	0.116
Paresthesia				
Before	1.33 ± 1.73	1.33 ± 1.56	2.00 ± 1.83	0.563
After	1.33 ± 1.41	1.33 ± 1.30	1.38 ± 2.06	0.904
Insomnia				
Before	3.11 ± 1.76	2.83 ± 2.17	2.77 ± 2.65	0.933
After	2.44 ± 1.67	2.33 ± 2.23	2.15 ± 2.38	0.884
Nervousness				
Before	3.11 ± 1.76	3.33 ± 1.56	3.69 ± 1.97	0.747
After	3.11 ± 2.26	3.00 ± 1.60	2.92 ± 1.93	0.973
Melancholia				
Before	1.78 ± 0.97	1.92 ± 0.90	1.69 ± 1.18	0.916
After	1.56 ± 0.88	1.25 ± 0.75*	1.38 ± 1.19	0.711
Vertigo				
Before	0.78 ± 0.67	1.00 ± 0.95	0.92 ± 0.86	0.866
After	1.00 ± 0.87	0.83 ± 0.83	0.69 ± 1.03	0.590
Concentration disorders				
Before	1.67 ± 0.87	2.08 ± 0.67	2.23 ± 1.01	0.246
After	1.56 ± 0.88	2.00 ± 0.60	1.92 ± 1.04	0.491
Arthralgia or myalgia				
Before	1.67 ± 0.87	2.00 ± 0.95	2.23 ± 1.01	0.285
After	1.56 ± 0.53	2.00 ± 0.95	1.92 ± 1.04	0.397
Headache				
Before	0.78 ± 0.83	1.75 ± 1.06	1.77 ± 1.17	0.068
After	0.67 ± 0.87	1.42 ± 1.24	1.31 ± 1.11	0.281
Palpitations				
Before	1.00 ± 1.00	0.92 ± 1.00	1.08 ± 1.12	0.947
After	0.89 ± 0.78	0.75 ± 0.62	0.69 ± 0.75	0.808
Formication				
Before	0.00 ± 0.00	0.58 ± 1.00	0.38 ± 0.87	0.177
After	0.11 ± 0.33	0.33 ± 0.49	0.54 ± 0.78	0.322

Data are mean ± SD. P values (SS versus SL versus LL) were obtained by Kruskal-Wallis test. P values (before versus after) were obtained by Signed-Wilcoxon test.* $P < 0.05$.

In our previous study, women with the SS genotype were shown to have an increased risk of perimenopausal symptoms and menopause-related psychological and vasomotor symptoms, and they required HRT to control their severe climacteric symptoms. It has been reported that most patients with the SS genotype show strong vasomotor symptoms, and HRT would likely be used to treat them [13, 25]. ERβ genotypes might relate to the severity of vasomotor symptoms in climacteric syndrome. In the present study, the KBG treatment had no significant effect on vasomotor symptoms in the SS genotype group but it was effective against these symptoms in the LL genotype group. Although our LL patients had high KI scores, vasomotor symptoms were improved in the LL group. This result is related to the "Sho" diagnosis in Kampo medicine ("Sho" diagnosis is diagnostic steps to determine Kampo medicines).

The mechanism of vasomotor symptoms in patients with climacteric syndrome remains unclear. One mechanism that has been reported is the increase of the calcitonin gene-related peptide (CGRP) concentration, which has the effect of microvascular dilation [26], and another is the lowering of blood sex hormone-binding globulin (SHBG) levels due to a decreased blood estradiol concentration [27]. However, it was reported that premenopausal patients with

a relatively short CA repeat of the ERβ gene had higher serum levels of SHBG compared to those with a longer repeat region [21].

Westberg et al. reported that their patients with short CA repeat had higher SBGH levels which might be derived from higher androgen (testosterone) levels, although there was no correlation between E2 levels and genotype [21]. They also checked the relationship between prolactin levels and CA repeats, and they observed a significant difference in prolactin levels: their "SS + SL" group had significantly higher prolactin levels compared to the "LL" group, but there was no such correlation for estradiol and prolactin in any of the subgroups with respect to ERβ [22]. It remains unknown whether ERβ polymorphism has any effect on the SHBG level.

The release of hormones may be affected by the menstrual period. Westberg et al. [21] noted that serum samples are obtained in the follicular phase when the levels of estradiol are relatively low, although doing so is difficult in clinical practice. However, Comings proposed that even though the CA repeat region in the ERβ is situated in a nontranslated region, there are several mechanisms that might explain such a relationship between short repeats in nontranslated regions and gene function, including their potential to form alternative DNA structures (such as Z-DNA) that modulate transcriptional activity [28].

Regarding the mechanism of KBG as a treatment for vasomotor symptoms, it has been reported that the increase in skin temperature is inhibited by the normalization of the high estrogen-independent sensitivity of the CGRP receptor [29, 30]. KBG shows estrogen-like activity [31]. In addition, because KBG shows an agonistic activity for ERβ, KBG has been suggested to act through ERβ [32]. In order to clarify the relationship between CGRP and vasomotor symptoms, measurements of the CGRF level are needed to determine the concentration of CGRF in each genotype. However, it is difficult to detect the peak concentration of CGRP because it occurs during vasomotor symptoms [33, 34].

In the melancholia related to climacteric syndrome, a significant improvement was shown in only the SL genotype patients in the present study. However, the trend in the KI melancholia score before and after KBG treatment was almost the same in all three genotype groups. Kanda et al. reported that Kampo medication can be more effective for the melancholia related to climacteric syndrome than HRT [35]. They reported that melancholia improved in 58% of the patients treated with Kampo medication (KBG was administrated on 25% of the patients) whereas in 33.3% of the patients treated with HRT. Kampo medication might have different effects with HRT on patients with climacteric syndrome.

In Japan, more than 80% of medical doctors prescribe Kampo medicine [7, 36]. Kampo formulae are regulated as prescription pharmaceutical drugs by the Japanese Ministry of Health and have been covered by the national health insurance for about 30 years. By using the theory of Kampo medicine, Kampo specialists analyze a patient's constitution and various complaints and then prescribe various types of Kampo medicine. Making a Kampo diagnosis is relatively difficult for nonspecialist doctors, and thus treating climacteric patients with Kampo medicines is also difficult. Analyzing the CA genotype may therefore help Kampo expert doctors as well as nonexpert doctors to choose an appropriate Kampo prescription.

With these results, we have taken the first step in using the ERβ genotype as a predictive biomarker for the beneficial effects of KBG on patients with climacteric syndrome. A major limitation of our study was its small sample size (n = 39). The sample sizes for each of the three genotypes (SS, SL, and LL) were necessarily even smaller, and this may have affected our ability to determine significant differences between groups. Nevertheless, our study indicates that the ERβ genotype can be expected to eventually be a useful biomarker as a predictor of the efficacy of KBG. Evidence relevant to the CA polymorphism should be collected through larger-scale and more detailed studies.

Conflict of Interests

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Research Article

Statistical Analysis of *Hie* (Cold Sensation) and *Hiesho* (Cold Disorder) in Kampo Clinic

Tetsuhiro Yoshino,[1] Kotoe Katayama,[2] Kaori Munakata,[3] Yuko Horiba,[4] Rui Yamaguchi,[2] Seiya Imoto,[2] Satoru Miyano,[2] and Kenji Watanabe[1,3]

[1] *Center for Kampo Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan*
[2] *Human Genome Center, The Institute of Medical Science, The University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan*
[3] *Faculty of Environmental and Information Study, Keio University, 5322 Endo, Fujisawa, Kanagawa 252-0882, Japan*
[4] *Center for Preventive Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan*

Correspondence should be addressed to Kenji Watanabe; watanabekenji@a6.keio.jp

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A cold sensation (*hie*) is common in Japanese women and is an important treatment target in Kampo medicine. Physicians diagnose patients as having *hiesho* (cold disorder) when *hie* disturbs their daily activity. However, differences between *hie* and *hiesho* in men and women are not well described. *Hie* can be of three types depending on body part where patients feel *hie*. We aimed to clarify the characteristics of patients with *hie* and *hiesho* by analyzing data from new patients seen at the Kampo Clinic at Keio University Hospital between 2008 and 2013. We collected information about patients' subjective symptoms and their severity using visual analogue scales. Of 4,016 new patients, 2,344 complained about *hie* and 524 of those were diagnosed with *hiesho*. *Hie* was most common in legs/feet and combined with hands or lower back, rather than the whole body. Almost 30% of patients with *hie* felt upper body heat symptoms like hot flushes. Cold sensation was stronger in *hiesho* than *non-hiesho* patients. Patients with *hie* had more complaints. Men with *hiesho* had the same distribution of *hie* and had symptoms similar to women. The results of our study may increase awareness of *hiesho* and help doctors treat *hie* and other symptoms.

1. Introduction

In Japan, *hie* (cold sensation) and *hiesho* (cold disorder) are different terms. While *hie* is used to describe the subjective, uncomfortable feeling of coldness, *hiesho* is the diagnosis given by physicians to patients with cold sensations that disturb their daily living. Therefore, the first distinction to make is one between normal and *hie* groups. Those who experience *hie* can further be subdivided into *hiesho* and *non-hiesho* categories (Figure 1).

Hiesho is the most common diagnosis given in Japanese Kampo clinics [1]. In Japanese Kampo medicine, *hiesho* is treated as a unique pathological condition. In contrast, cold sensation is only one of many symptoms asked about in a review of systems in Western medicine. One definition of *hiesho* for diagnosis is an "abnormal, subjective sensitivity to coldness in the lower back, the extremities, other localized regions of the body, or the whole body despite ambient temperatures. It lasts throughout the year for most patients, and disturbs their daily living" [2].

Hie as a subjective symptom is common in Japanese people [1] and is more common in women [3]. However, the epidemiology of this symptom is not clear in Western people. One report comparing Japanese with Brazilians indicated that 57% of Brazilian pregnant women were aware of cold sensations [4]. We think it may be common symptom in other populations as well. In 1987, Kondo and Okamura reported demographic data of 318 Japanese women with *hie* but had no data for men [5]. They reported that *hie* accompanied other uncomfortable symptoms such as shoulder stiffness, constipation, lumbago, fatigue, and hot flushes. In Kampo medicine, treatments not only target *hie*, but also

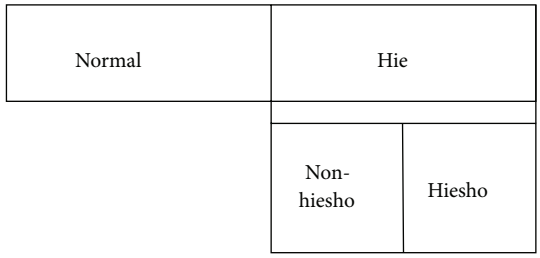

Figure 1: *Hie* and *hiesho*. In Japan *hie* (cold sensation) and *hiesho* (cold disorder) are different terms. While *hie* is the term used to describe the subjective, uncomfortable feeling of coldness, *hiesho* is the diagnosis given by physician to patients with cold sensation disturbing their daily living. Therefore, the first distinction is between normal and *hie* group. The *hie* group is subdivided into *hiesho* and *non-hiesho*.

these accompanied symptoms. Subsequently, there are many Kampo formulas for treating *hiesho*.

Hie has been categorized into three types based on the body part where the symptoms are experienced. We assume different pathophysiology for each type. The first type of *hie* is a general type due to decreased heat production from a loss of muscle volume or decreased basal metabolism. The second type of *hie* is peripheral, due to a disturbance of heat distribution related to decreased peripheral blood flow. The third type of *hie* is upper body heat-lower body coldness with associated vasomotor abnormalities. However, epidemiological information regarding these classifications are unknown.

Keio University first introduced a browser-based questionnaire in 2008 that collects patient's subjective symptoms and changes in symptom severity via visual analogue scales (VAS), life styles, Western and Kampo diagnoses, and prescribed Kampo formulas.

Here, we report results from the analysis of data from male and female patients and attempt to clarify the characteristics associated with *hie* and *hiesho*. We especially focus on classification of *hie* and accompanied symptoms because this information is important for considering the pathophysiology of *hie* and the appropriate Kampo formulas for treating patients with *hiesho*.

2. Methods

2.1. Patient Enrollment. Patients who made their first visit to the Kampo Clinic at Keio University Hospital between May 2008 and March 2013 were included from this study. Exclusion criteria were unwillingness to enter the study and missing data regarding age and/or sex. Patients who answered only about their lifestyle or who were diagnosed as having *hiesho* but did not answer regarding the part of the body where they felt *hie* were excluded. All registered patients provided written informed consent.

2.2. Patient Grouping. In this analysis, we divided patients into three groups: patients with *hie* with a diagnosis of *hiesho* (*hiesho* group), patients with *hie* without a diagnosis of *hiesho* (*non-hiesho* group), and patients without *hie* (Normal group). Our dataset did not include information about how physicians diagnosed patients with *hiesho* (Figure 1).

2.3. Assessment of Subjective Symptoms. We collected information about patients' subjective symptoms using a 128-question binary questionnaire (Table 1). Among these 128 questions, 106 also had VAS when patients answered yes on the binary questionnaire. The VAS was a horizontal line, 100 mm in length, where the left-most side (0 mm) represented no symptoms and right-most side (100 mm) represented the severest symptoms. To normalize within each patient, we divided each patient's VAS by the maximum VAS possible. This is because VAS scores were different from patient to patient. In other words, each patient's original VAS values ranged from 0 to 100 but were transformed to 0 to 1 for easier comparison.

2.4. Between Group Comparisons. We focused on symptoms directory related to *hie* to clarify the differences between the *hiesho* and *non-hiesho* groups. Here, we choose six symptoms from the directory related to *hie*: *hie* of the whole body, *hie* of the hands, *hie* of legs/feet, *hie* of the lower back, cold intolerance, and tendency to get frostbite.

We also analyzed body part combinations where patients felt *hie* and five heat-related symptoms to get epidemiological information regarding *hie* classification. The five heat-related symptoms were as follows: heat intolerance, hot flush, heat sensation of the face, heat sensation of the hands, and heat sensation of legs/feet.

Finally, we focused on accompanying symptoms and compared men and women to clarify differences between these groups.

2.5. Statistical Analysis. All statistical analyses were conducted using R software, version 2.15.2 (The R Foundation for Statistical Computing; October 26, 2012). Characteristics were compared using Wilcoxon's rank sum test, two-sample t-test, and test for equal proportions. We used Wilcoxon's rank sum test to compare the VAS of *hie* because normality did not hold. We used a significant level of 5% for all tests.

3. Results

3.1. Participant Information. Participants included 4,057 registered patients, 41 of whom were excluded because of missing values (one due to missing age, 19 failed to report anything regarding subjective symptoms, and 21 were missing data on the part of the body where they felt *hie* in spite of a diagnosis of *hiesho*). We used data from 4,016 patients in this analysis, including 2,344 patients with *hie*, and 524 of those who were diagnosed as having *hiesho*.

3.2. Age and Sex. We compared age and sex of patients with *hie* with the diagnosis of *hiesho* (*hiesho* group, $n = 524$) and patients with *hie* but no diagnosis of *hiesho* (*non-hiesho* group, $n = 1,820$) to patients without *hie* (Normal group, $n = 1,672$). The mean age was 51.6 ± 1.5 years old for

Table 1: Questionnaire items.

No.	Binary questions	No.	Questions with visual analogue scales	No.	Questions with visual analogue scales
1	Appetite loss	1	Difficulty falling asleep	54	Heat hands
	Good appetite	2	Arousal during sleep	55	Heat legs
2	Slow speed of the meal	3	Early-morning awakening	56	Edema face
	Fast speed of the meal	4	Difficulty urinating	57	Edema hands
3	I dream frequently	5	Urination pain	58	Edema legs
4	Single dose of urine large	6	Urine leakage	59	Headache
	Single dose of urine low	7	Enuresis	60	Sluggishness
5	Hard stool	8	Diarrhea	61	Vertigo
6	Small and round stool	9	Hemorrhoid	62	Lightheadedness
7	Soft stool	10	Anal prolapse	63	Dandruff
8	Hard to stool	11	Bloody stool	64	Hair loss
9	Taking laxatives	12	Depressed mood	65	Decreased visual acuity
10	White nasal discharge	13	Forgetfulness	66	Eyestrain
	Yellow nasal discharge	14	Irritated	67	Blurred vision
11	White sputum	15	Dry skin	68	Bleary eyes
	Yellow sputum	16	Itchy skin	69	Dark circles under eyes
12	Abdominal pain fasting	17	Acne	70	Sneezing
13	Abdominal pain after eating	18	Blot	71	Post nasal drip
14	Abdominal pain at upper	19	Urticaria	72	Stuffy nose
15	Abdominal pain at lower	20	Wart	73	Nosebleed
16	Heavy menstrual flow	21	Athlete's foot	74	Mouth bitter
	Less menstrual flow	22	Brittle nails	75	Saliva comes out
17	Irregular menstruation	23	Get tired easily	76	Throat pain
18	Delivery	24	Easy to sweat	77	Throat jams
19	Spontaneous abortion	25	Night sweats	78	Thirsty
20	Induced abortion	26	Hot flush	79	Dry mouth
21	Abnormal bleeding	27	Heat intolerance	80	Dry lips
22	Pregnancy toxemia	28	Cold intolerance	81	Take water often
		29	Attenuation of sexual desire	82	Tinnitus
		30	Impotence	83	Hearing loss
		31	Neck stiffness	84	Cough
		32	Shoulder stiffness	85	Asthma
		33	Back stiffness	86	Shortness of breath
		34	Lower back stiffness	87	Palpitation
		35	Facial pain	88	Chest pain
		36	Hand pain	89	Burp
		37	Foot pain	90	Heartburn
		38	Shoulder pain	91	Epigastric jamming discomfort
		39	Back pain	92	Nausea
		40	Hip pain	93	Vomiting
		41	Knee pain	94	Motion sickness
		42	Numbness face	95	Stomach fullness
		43	Numbness hands	96	Stomach rumbling
		44	Numbness legs	97	Flatulence
		45	Numbness back	98	Sleepy after eating
		46	Trembling face	99	Abdominal pain
		47	Trembling hands	100	Hand stiffness
		48	Trembling legs	101	Lower extremities weakness
		49	Hie general	102	Legs fluctuate
		50	Hie hands	103	Legs spasms

Table 1: Continued.

No.	Binary questions	No.	Questions with visual analogue scales	No.	Questions with visual analogue scales
		51	Hie legs	104	Frostbite
		52	Hie lower back	105	Menstruation textile
		53	Heat face	106	Menstrual pain

We collected patients' subjective symptoms using a 128-item binary questionnaire. Of these symptoms, 106 corresponded to VAS questions when patients provided an affirmative response.

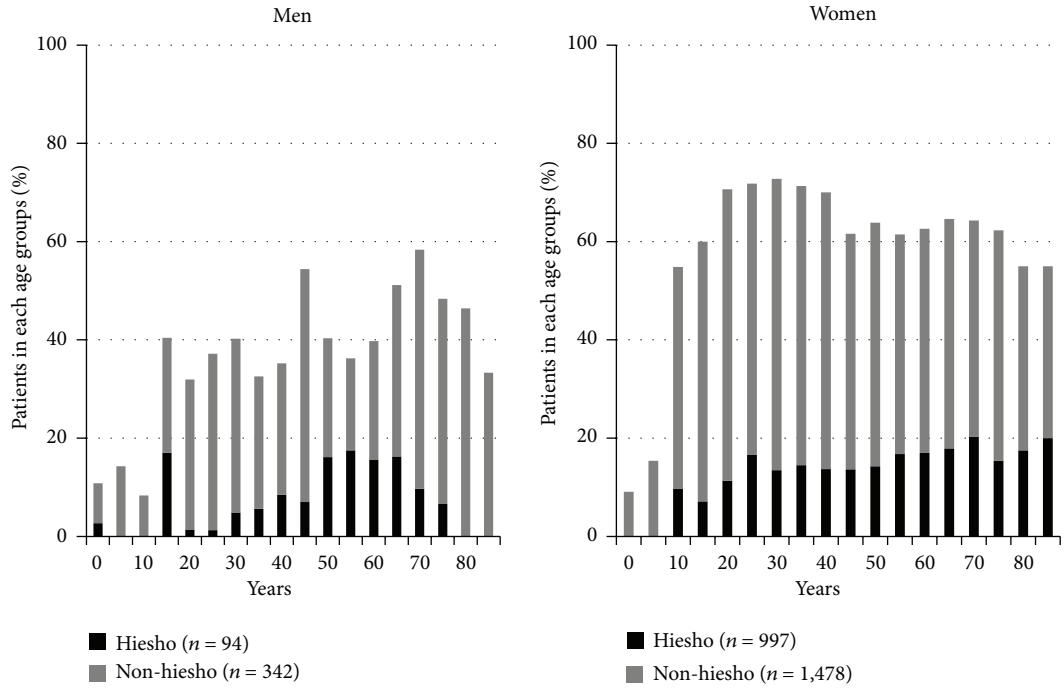

Figure 2: Rate of *non-hiesho* and *hiesho* groups in each age group. *Hie* (cold sensation) and *hiesho* (cold disorder) were uncommon in children, but almost similarly present among young and old patients. We also can see that *hie* and *hiesho* were more common in women.

members of the *hiesho* group, 47.1 ± 0.8 years old for the *non-hiesho* group, and 46.2 ± 1.0 years old for the Normal group. Participant mean age in the *hiesho* group was significantly higher than the *non-hiesho* and Normal groups according to results of a t-test. The number of patients in each group who fell within each age group is shown in Figure 2. *Hie* and *hiesho* were uncommon in children and rates were similar for young and old patients.

With regard to sex, there were 94 men and 430 women (percentage of women: 82.1%) in the *hiesho* group, 342 men and 1,478 women (percentage of women: 81.2%) in the *non-hiesho* group, and 675 men and 997 women (percentage of women: 59.6%) in the Normal group. A test for equal proportions showed significantly more women in both the *hiesho* and *non-hiesho* groups than in the Normal group.

3.3. Differences between Hiesho and Non-Hiesho Groups. We compared the location where *hie* symptoms occurred between the three groups. The frequencies of binary answers for the four parts of the body where patients felt *hie* for *hiesho* and *non-hiesho* groups are as follow: *hie* of the whole body: *hiesho* 40.1%, *non-hiesho* 22.4%; *hie* of the hands: *hiesho* 42.2%, *non-hiesho* 35.1%; *hie* of the legs/feet: *hiesho* 75.6%, *non-hiesho* 77.0%; and *hie* of the lower back: *hiesho* 22.3%, *non-hiesho* 13.8%. Except for legs/feet, the frequencies of *hie* were significantly higher for the *hiesho* group based on results of the test for equal proportions (Figure 3 upper). There were no clear differences seen regarding the distribution of *hie* based on patient age or sex.

The frequencies of binary answers of the other two *hie* related symptoms for all three groups are as follows: cold intolerance: *hiesho* 77.7%, *non-hiesho* 58.0%, and Normal 16.1%; and tendency to get frostbite: *hiesho* 10.7%, *non-hiesho* 6.3%, and Normal 1.5%. The frequencies of binary answers of the two symptoms were significantly higher in the *hiesho* group than the *non-hiesho* group, which were both higher than Normal group as determined by the test for equal proportions. We also compared the differences of VAS scores for *hie* of each body part for members of the *hiesho* and *non-hiesho* groups using Wilcoxon's rank sum test. For every part of the body, *hie* was significantly worse for members of the *hiesho* group (Figure 3 lower). In the same way, VAS values

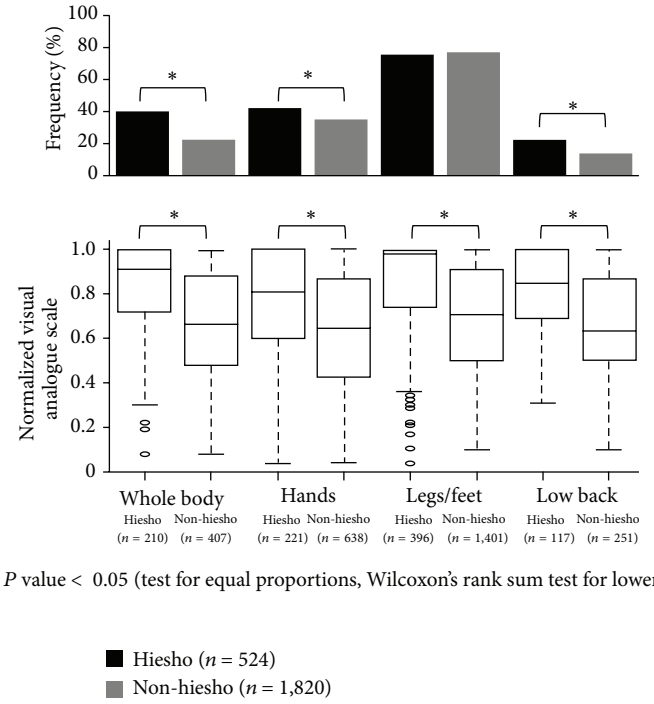

Figure 3: Frequency and severity of *hie* (cold sensation) by affected areas. The frequencies of binary answers of four parts of the body where patients felt *hie* were significantly higher in *hiesho* group except for *hie* of legs/feet as per the test for equal proportions (upper figure). Normalized visual analogue scales of *hie* of each body part of *hiesho* group were compared to *non-hiesho* group by Wilcoxon's rank sum test. *Hie* in every part of the body was significantly worse in *hiesho* group (lower figure).

Table 2: Number of patients with *hie* (cold sensation) as per combination of body parts (%).

	Whole body (n = 617)	Hands (n = 859)	Legs (n = 1,797)	Lower back (n = 368)
Whole body	617 (26.3)			
Hands	172 (7.3)	859 (36.6)		
Legs	265 (11.3)	722 (30.8)	1,797 (76.7)	
Lower back	126 (5.4)	152 (6.5)	286 (12.2)	368 (15.7)

This table shows the combination of body parts where patients with *hie* (n = 2,344, including hiesho and non-hiesho groups) experienced their symptoms. As you can see, 30.8% felt *hie* in both their hands and legs/feet; that is, 84.2% of patients who felt *hie* in their hands also felt *hie* in legs/feet. Similarly, 12.2% felt *hie* in both their lower back and legs/feet; that is, 77.7% of patients who felt *hie* in their lower back also felt *hie* in legs/feet. In contrast, 11.3% of patients felt *hie* throughout their whole body and legs/feet; that is, 43% of patients who felt *hie* throughout whole body also felt *hie* in their legs/feet; this ratio was significantly lower than the former two.

for cold intolerance in the *hiesho* group also were higher than those in the *non-hiesho* group, which were higher than those in the Normal group.

3.4. Body Part Combinations of Hie and Frequencies of Heat-Related Symptoms. We also analyzed body part combinations where patients felt *hie* and frequencies of heat-related symptoms to obtain epidemiological information regarding the classification of *hie*. Regarding body part combination of *hie* symptoms for patients in the *hiesho* and *non-hiesho* group (n = 2,344), 722 patients felt *hie* in both their hands and legs/feet among 859 patients who felt *hie* in their hands; that is, 84.2% of patients who felt *hie* in their hands also felt *hie* in legs/feet. Similarly, among 368 patients who felt *hie* in their lower back, 286 (77.7%) also felt *hie* in their legs/feet. In contrast, among the 617 patients who felt *hie* throughout their whole body, 265 (43.0%) also felt *hie* in their legs/feet and this ratio was significantly lower than the former two as determined by the test for equal proportions (Table 2). We also focused on five heat-related symptoms for the three groups: heat intolerance: *hiesho* 20.2%, *non-hiesho* 24.5%, and Normal 26.4%; hot flushes: *hiesho* 20.2%, *non-hiesho* 18.6%, and Normal 8.6%; heat sensation in the face: *hiesho* 27.1%, *non-hiesho* 29.8%, and Normal 14.8%; heat sensation in the hands: *hiesho* 3.4%, *non-hiesho* 4.6%, and Normal 3.4%; and heat sensation of the legs/feet: *hiesho* 3.6%, *non-hiesho* 2.9%, and Normal 3.9% (Figure 4). We did not separate these groups by sex, as men in the *hiesho* and *non-hiesho* groups had higher frequencies of hot flush or heat sensation of the face the same as women in *hiesho* group or *non-hiesho* group. The frequency of heat intolerance was significantly lower for the *hiesho* group compared to Normal group. In contrast, hot

Table 3: Ten most commonly associated symptoms for patients in the hiesho (cold disorder) group and frequencies in other groups.

	Hiesho (n = 524)	Non-hiesho (n = 1,820)	Normal (n = 1,672)
Mean number of accompanied symptoms ± SD	22.9 ± 1.0	24.5 ± 0.6	15.8 ± 0.5
Common symptoms (women [%]/men [%])			
Shoulder stiffness	338 (78.6)/56 (59.6)	1152 (77.9)/196 (57.3)	633 (63.5)/274 (40.6)
Easily fatigued	306 (71.2)/53 (56.4)	1071 (72.5)/212 (62.0)	562 (56.4)/311 (46.1)
Neck stiffness	283 (65.8)/43 (45.7)	970 (65.6)/168 (49.1)	466 (46.7)/200 (29.6)
Eyestrain	249 (57.9)/35 (37.2)	808 (54.7)/175 (51.2)	425 (42.6)/222 (32.9)
Depressed mood	186 (43.3)/31 (33.0)	721 (48.8)/139 (40.6)	338 (33.9)/183 (27.1)
Constipation	174 (40.5)/26 (27.7)	631 (42.7)/93 (27.2)	339 (34.0)/140 (20.7)
Upper back stiffness	172 (40.0)/25 (26.6)	577 (39.0)/98 (28.7)	240 (24.1)/84 (12.4)
Dry skin	164 (38.1)/27 (28.7)	624 (42.2)/140 (40.9)	334 (33.5)/247 (36.6)
Flatulence	154 (35.8)/35 (37.2)	510 (34.5)/135 (39.5)	247 (24.8)/162 (24.0)
Forgetfulness	145 (33.7)/42 (44.7)	499 (33.8)/124 (36.3)	283 (28.4)/153 (22.7)
Menstrual pain	156 (36.3)/0 (0.0)	580 (39.2)/0 (0.0)	239 (24.0)/0 (0.0)

The mean number of subjective symptoms from 122 symptoms for both hiesho and non-hiesho groups was significantly higher compared to normal group as shown by the t-test. We sorted symptoms by frequency in the hiesho group. The ranking of these symptoms was almost the same between the three groups and by participants' sex. Almost all symptoms were more common in the hiesho and non-hiesho groups compared to the normal group. In women, menstrual pain also was common. Results may be affected by the number of symptoms reported by patients.

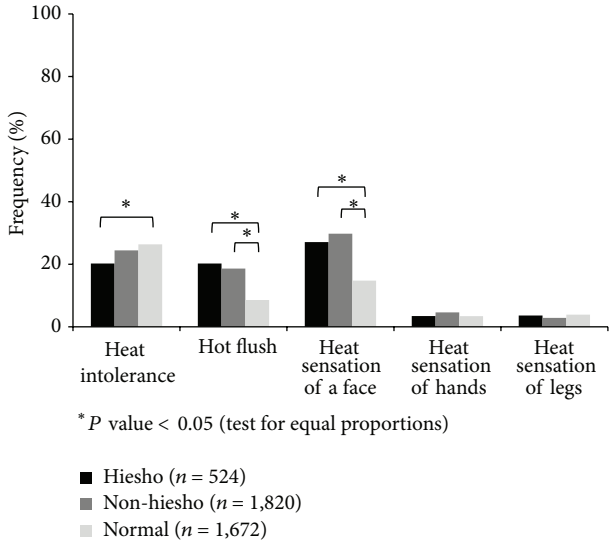

Figure 4: Heat symptoms for *non-hiesho* and *hiesho* groups. The frequencies of binary answers about upper body heat symptoms, such as hot flushes and heat sensation of the face, were significantly common in patients with *hie* (cold sensation). All data were compared using the test for equal proportions.

flush and heat sensation of the face were significantly more frequent for members of the *hiesho* and *non-hiesho* groups compared to the Normal group as indicated by the test for equal proportions.

3.5. Accompanying Symptoms. We also compared accompanying symptoms in members of the three groups. Of 122 symptoms, after removing the 6 *hie* related symptoms, the mean number of subjective symptoms reported was 22.9 ± 1.0 for members of the *hiesho* group, 24.5 ± 0.6 for the *non-hiesho* group, and 15.8 ± 0.5 for the Normal group (Table 3). The mean number of subjective symptoms for both the *hiesho* and *non-hiesho* groups was significantly higher compared to the Normal group as indicated by the t-test. We sorted symptoms by reporting frequency for the *hiesho* group. The top 10 common symptoms were as follows: shoulder stiffness, easily fatigued, neck stiffness, eyestrain, depressed mood, constipation, upper back stiffness, dry skin, flatulence, and forgetfulness. In women, menstrual pain also was common. The ranking of these symptoms was almost the same for members of both sexes and all three groups.

4. Discussion

Kampo physicians diagnose patients as having *hiesho* (cold disorder), when *hie* (cold sensation) and its associated symptoms cause disturbance in daily living. In Japanese Kampo medicine, *hiesho* is treated as a unique pathological condition and there are many Kampo formulas to treat it. When choosing Kampo formulas, the part of the body where *hie* and its accompanied symptoms are felt is important. This is why the present study has focused on the classification of *hie* and its comorbid symptoms.

Fundamental parts of our dataset were consistent with previous reports and supported the generalizability of our data, despite our population being recruited from a Kampo clinic. It has been reported that the subjective symptom of *hie* was common in Japanese people and a diagnosis of *hiesho* was common in Japanese Kampo clinics [1, 6]. Consistent with these past reports, around 60% of patients in our study reported subjective feelings of *hie*, and *hiesho* was one of the most common diagnoses in the Kampo medicine clinic where our study was conducted. It also has been reported that *hie* and *hiesho* are common in women [3], which is

consistent with results of the present study. The frequency of patients in our study who reported experiencing *hie* in their extremities was also consistent with the results of past studies from an obstetrics-and-gynecology clinic in Japan [7] and on working women in Japan [5]. Ushiroyama mentioned that women developed *hie* because of the existence of their pelvic organs, which affected peripheral blood flow to the legs/feet and lower back [7]. Women's pelvic organs develop after puberty and may consume blood flow of lower body. However, according to our research, the legs/feet were the most common parts of the body affected by *hie* for both men and women of all age groups. Thus, explanations regarding the effect of pelvic organs do not help us understand lower body *hie* in men and postmenopausal women.

We found that patients diagnosed as having *hiesho* reported more severe *hie* symptoms. The frequencies of *hie* of the whole body, hands, and lower back as well as reports of cold intolerance and a tendency to get frostbite were higher in the *hiesho* compared to *non-hiesho* group. Furthermore, patients in the *hiesho* group were more likely to have high VAS scores regarding *hie* for any body part and cold intolerance compared to their *non-hiesho* counterparts. There were no other symptoms for which patients in the *hiesho* group had higher VAS scores than those in the *non-hiesho* group. In addition, hypothyroidism was significantly more common in the *hiesho* than *non-hiesho* group (2.5% versus 0.7%); however, most patients in the *hiesho* group did not have organic diseases that might cause *hie* (data not shown). It might be important for us to not only treat *hiesho*, but also to study organic diseases that can cause *hie*, especially in members of the *hiesho* group.

One classification categorizes *hie* into the three as per the areas of the body where people report experiencing it: general, peripheral, and upper body heat-lower body coldness. At the 51st annual meeting of the Japan Society for Oriental Medicine, Kako Watanabe et al. reported the efficacy of the cold-water challenge test to divide *hie* into these three types (not published). They put patients' hands into cold water at 4°C for 30 seconds and measured blood flow recovery. Patients with decreased metabolism complained of whole body *hie* after the cold-water challenge despite normal blood flow recovery, and patients with disturbed peripheral blood flow could not recover blood flow after the cold-water challenge test. In addition, patients with upper body heat-lower body coldness recovered blood flow with fluctuation due to autonomic imbalance. In Kampo theory, the pathophysiology of these three types of *hiesho* has been explained as qi deficiency, blood stagnation, and qi counterflow.

Our results support this classification of *hie*. We observed that many patients who report feeling *hie* in their hands or lower back also felt it in their legs/feet, and these combinations were far more frequent than the combination of whole body and legs/feet. The result supports the first two types of *hie* (general and peripheral). Our results also suggest that the peripheral type might be further subdivided by the type of extremity (e.g., narrowly defined extremity type, which affected hands and legs/feet, and lower body type, which affected the lower back and legs/feet). The general type of *hie* is thought to be related to a loss of heat production from decreased muscle volume and/or basal metabolism, and peripheral *hie* may be due to disturbances in heat distribution due to blood stagnation. We also found that around 20–30% of patients with *hie* felt upper body heat sensations such as hot flushes and heat sensation of the face, and these symptoms were significantly more common in patients with *hie*. This supports the existence of upper body heat-lower body coldness. This type of *hie* may be related to a kind of autonomic imbalance that causes vasomotor disturbances.

We assume representative Western diagnosis for these three types of *hie*. First, one of the organic diseases that causes general *hie* is hypothyroidism. Due to low metabolism, patients complain about feeling cold or cold intolerance, which sometimes may be comorbid with objectively cool peripheral extremities [8]. Based on a randomized crossover trial, thyroxin did not appear effective for patients with normal thyroid function tests and symptoms of hypothyroidism including intolerance to cold [9]. Next, one of the organic diseases that causes peripheral *hie* is peripheral arterial disease due to arteriosclerosis [10]. It is a good adaptation of Western intervention when patients feel acute coldness with resting pain in their foot and toes by critical limb ischemia such as occlusion of an artery where blood flow cannot accommodate basal nutritional needs of the tissues [11]. However, the majority of patients feel chronic cold sensations in their legs/feet without gait disturbances and it is difficult to treat such patients in Western medicine. Finally, one of the organic diseases that causes upper body heat-lower body coldness is perimenopausal disturbance. Hot flushes with lower extremity coldness due to vasomotor disturbance is common for peri- or postmenopausal women [12]. Treatment options are limited for some patients due to side effects of hormone replacement therapy. Kampo medicine may be one treatment option for such patients and we try to apply the appropriate Kampo formulas.

Our data supported that patients with *hie* experienced many uncomfortable symptoms, which may be aggravated by *hie*. It has been reported that women with *hie* and *hiesho* experienced other uncomfortable symptoms such as shoulder stiffness, constipation, lumbago, fatigue, hot flush, headache, and edema in the leg [3, 5]. Our findings support these results for both the sexes; menstrual pain often was found in women with *hie*. Thus, treatment of *hie* may lead to not only its improvement, but also to the improvement of other symptoms. However, the number of symptoms experienced by patients might affect our results, as patients with *hie* reported about 10 more symptoms than those without *hie*. This suggests that patients with *hie* had 1.6–1.8 times more symptoms than patients without *hie*. We also can assume that *hie* is an indicator of patients with many symptoms. Thus, we may obtain more information by segregating patients with *hie* according to their comorbid symptoms.

5. Conclusion

The present study is important because it clarifies some of the epidemiological characteristics of patients with *hie* and *hiesho*. Specifically, we have learned the following. (1) *hiesho*

patients are those who suffer from severe *hie*. (2) Patients with *hie* may be classified roughly into three types. (3) Patients with *hie* experience many comorbid symptoms. (4) Men and women with *hiesho* have almost the same distribution of *hie* and its associated symptoms. Appropriate treatment options for *hiesho* are not available in Western medicine. Therefore, if we are more aware of *hiesho*, we can use Kampo formulas to treat not only the patients' *hie*, but their comorbid symptoms as well.

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Research Article

Prescription of Kampo Drugs in the Japanese Health Care Insurance Program

Kotoe Katayama,[1] Tetsuhiro Yoshino,[2] Kaori Munakata,[2] Rui Yamaguchi,[1] Seiya Imoto,[1] Satoru Miyano,[1] and Kenji Watanabe[2,3]

[1] *Human Genome Center, Institute of Medical Science, University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan*
[2] *Center for Kampo Medicine, Keio University School of Medicine, 35 Shinano-machi, Shinjuku-ku, Tokyo 160-8582, Japan*
[3] *Faculty of Environment and Information Study, Keio University, 5322 Endo, Fujisawa, Kanagawa 252-0882, Japan*

Correspondence should be addressed to Kenji Watanabe; watanabekenji@a6.keio.jp

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Kampo medicine or traditional Japanese medicine has been used under Japan's National Health Insurance scheme for 46 years. Recent research has shown that more than 80% of physicians use Kampo in daily practice. However, the use of Kampo from the patient perspective has received scant attention. To assess the current use of Kampo drugs in the National Health Insurance Program, we analysed a total of 67,113,579 health care claim records, which had been collected by Japan's Ministry of Health, Labour and Welfare in 2009. We found that Kampo drugs were prescribed for 1.34% of all patients. Among these, 92.2% simultaneously received biomedical drugs. *Shakuyakukanzoto* was the most frequently prescribed Kampo drug. The usage of frequently prescribed Kampo drugs differed between the youth and the elderly, males and females, and inpatients and outpatients. Kampo medicine has been employed in a wide variety of conditions, but the prescription rate was highest for disorders associated with pregnancy, childbirth, and the puerperium (4.08%). Although the adoption of Kampo medicine by physicians is large in a variety of diseases, the prescription rate of Kampo drugs is very limited.

1. Introduction

Interest in traditional medicine has increased globally in recent years. The World Health Organization (WHO) recommends that physicians use traditional medicine for care and treatment and encourages the integration of traditional medicine into the next edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-11) [1–4].

Kampo medicine (Japanese traditional medicine) became integrated into the Japanese health care system—the National Health Insurance Program—46 years ago alongside modern medicine, and the program has covered all citizens since 1961.

Because there is only one type of medical license in Japan, physicians prescribe both Kampo medicine and western biomedicine. At present, 148 Kampo extracts are approved as prescription drugs. Currently, 80–90% of physicians use Kampo drugs in daily practice [5–9], but most use a very limited number of Kampo drugs. In that sense, the number of patients receiving prescriptions for Kampo drugs is unknown. Similarly, their joint use with biomedical drugs has not received the appropriate amount of attention. In this study, therefore, we examine Kampo drug prescription within the Japanese national health care system.

2. Material and Method

The Ministry of Health, Labour and Welfare (MHLW) of Japan collects health care claims data annually. The MHLW conducts an annual survey in order to assess the medical status of treatments, diseases and injuries, and drug administration; obtain basic data for the management of medical insurance; and report on the use of drugs under the health insurance system managed by the Japan Health Insurance Association, society-managed employment-based

Table 1: Numbers of institutions and detailed statements reviewed in the surveillance study.

	Number of medical institutions	Number of detailed statements		
		Total	General medical care	Medical care system for the elderly in the later stages of life
Medical institutions	11,133	359,489	221,272	138,217
Hospitals	1,409	115,447	78,299	37,148
Clinics	9,724	244,042	142,973	101,069
Dental care institutions	1,004	28,391	18,175	10,216
Pharmacies	4,816	77,121	47,037	30,084

Table 2: Distributions of the usage of Kampo drugs for sex, patient type, and age.

Drug	Total[1]	Sex[2]		Patient		Age									
		Male	Female	Inpatient	Outpatient	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–98
All	67,095,008	42.81%	57.19%	2.88%	97.12%	9.05%	4.70%	5.28%	7.86%	7.82%	11.19%	18.58%	21.75%	11.82%	1.95%
Kampo	898,797	33.09%	66.91%	7.01%	92.99%	1.57%	1.76%	6.89%	9.80%	10.69%	9.85%	17.55%	23.81%	15.49%	2.59%

[1]Kampo drugs were perscribed for $100(89,897/67,095,0081) = 1.34\%$ patients of the total number of prescription.
[2]For male, Kampo drugs were prescribed for $100((89,897 \times 0.3309)/(67,095,008 \times 0.4281)) = 1.04\%$ patients. For female $100((89,897 \times 0.6691)/(67,095,008 \times 0.5719)) = 1.57\%$.

health insurance schemes, the national health insurance scheme, and the medical care system for the elderly in later stages of life. We elucidate the usage of Kampo drugs by examining MHLW's records from 2009.

We assessed detailed statements selected from a stratified random two-stage sampling process; insurance-covered medical care institutions and pharmacies formed the primary sampling unit; and detailed statements were the secondary sampling unit (Table 1). We analysed the retrieved data for age, sex, diagnostic name, use of drugs (designation and dosage), and the number of prescriptions dispensed to inpatients and outpatients.

3. Results

The MHLW approves of three categories of Kampo drugs for reimbursement under the National Health Insurance Program. These include Kampo formulation extracts (extracts based on Kampo preparation formulae), crude drugs (including powdered crude drugs), and crude drug preparations. Of the 382 categories of approved drugs covered by public health insurance, they are the 28th (0.80%), 177th (0.05%), and 238th (0.02%) most-prescribed categories, respectively (numbers in parentheses indicate the quantity of Kampo drugs as a percentage of the total number of retrieved and prescribed drugs). In the following analyses, only drugs of the first category—the Kampo formulation extracts, which are largely provided as granules or powders of extracts from multiple crude drugs—were included. Hereafter, we will refer to Kampo formulation extracts as *Kampo extracts*.

Table 2 shows descriptive statistics for the usage of Kampo drugs in patients' sex, type, and age. Kampo drugs accounted for 1.34% of the total number of prescriptions (1.04% and 1.57% for male and female patients, resp.), with Kampo prescription being more frequent in female patients. As with other drugs, Kampo drugs were more frequently prescribed for outpatients (92.99%) than for inpatients (7.01%); this, however, was not the case for all Kampo extracts. Details are provided in a later section. We also found that Kampo drugs were prescribed more frequently than other drugs for young (under 20 years old) and elderly (older than 70 years old) patients.

We also assessed the joint use of Kampo extracts and biomedical drugs and found that 92.2% of patients who had been prescribed Kampo extracts were coadministered biomedical drugs during single consultations. The large percentage of patients undergoing combinatorial treatment reflects the uniqueness of the Japan's medical license and health care system, according to which physicians are allowed to prescribe both Kampo extracts and biomedical drugs. Statistics for diseases where Kampo extracts were prescribed as treatment are available in Table 3 and based on ICD-10 categories.

As shown in Table 4, the disease class "XV: pregnancy, childbirth, and the puerperium" contained the highest percentage (4.05% of the total number of patients in the class) of patients who were prescribed Kampo extracts; this may be because Kampo extracts are known to have fewer and relatively milder effects than biomedical drugs in pregnant and postpartum women. The next most frequent disease categories were "XIV: diseases of the genitourinary system" (3.08%) and "XI: diseases of the digestive system" (2.94%). Kampo extracts are, therefore, frequently prescribed to women and patients with digestive diseases. They were rarely used for diseases of the eye and adnexa (category VII; 0.09%) and congenital malformations, deformations, and chromosomal abnormalities (category XVII; 0.21%). None of the patients categorized into "XVI: certain conditions originating in the perinatal period" received prescriptions for Kampo extracts.

Table 3: Disease classification based on the International Classification of Diseases (ICD) 10th revision for 2008.

Category	Description
I	Certain infectious and parasitic diseases
II	Neoplasms
III	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
IV	Endocrine, nutritional, and metabolic diseases
V	Mental and behavioural disorders
VI	Diseases of the nervous system
VII	Diseases of the eye and adnexa
VIII	Diseases of the ear and mastoid process
IX	Diseases of the circulatory system
X	Diseases of the respiratory system
XI	Diseases of the digestive system
XII	Diseases of the skin and subcutaneous tissue
XIII	Diseases of the musculoskeletal system and connective tissue
XIV	Diseases of the genitourinary system
XV	Pregnancy, childbirth, and the puerperium
XVI	Certain conditions originating in the perinatal period
XVII	Congenital malformations, deformations, and chromosomal abnormalities
XVIII	Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified
XIX	Injury, poisoning, and certain other consequences of external causes

http://apps.who.int/classifications/icd10/browse/2008/en.

Table 4: Ratios of Kampo extract use per ICD-10 category.

ICD-10 category	Fraction of patients prescribed Kampo drugs per ICD-10 category		Fraction of patients per ICD-10 category		Ratio of patients prescribed Kampo drugs to total number of patients
I	37,458	(4.17%)	2,698,197	(4.02%)	1.39%
II	34,688	(3.86%)	2,811,687	(4.19%)	1.23%
III	2,933	(0.33%)	243,543	(0.36%)	1.20%
IV	81,481	(9.06%)	6,020,386	(8.97%)	1.35%
V	50,770	(5.65%)	3,171,006	(4.72%)	1.60%
VI	23,817	(2.65%)	1,752,559	(2.61%)	1.36%
VII	5,836	(0.65%)	6,865,056	(10.23%)	0.09%
VIII	3,671	(0.41%)	1,142,209	(1.70%)	0.32%
IX	189,799	(21.11%)	13,456,856	(20.05%)	1.41%
X	117,320	(13.05%)	8,920,202	(13.29%)	1.32%
XI	110,688	(12.31%)	3,761,886	(5.61%)	2.94%
XII	36,727	(4.08%)	4,178,405	(6.23%)	0.88%
XIII	101,762	(11.32%)	6,336,119	(9.44%)	1.61%
XIV	72,101	(8.02%)	2,344,046	(3.49%)	3.08%
XV	10,501	(1.17%)	259,084	(0.39%)	4.05%
XVI	0	(0.00%)	55,404	(0.08%)	0.00%
XVII	336	(0.04%)	161,658	(0.24%)	0.21%
XVIII	7,459	(0.83%)	777,263	(1.16%)	0.96%
XIX	11,835	(1.32%)	2,158,013	(3.22%)	0.55%
Total	899,182	(100.00%)	67,113,579	(100.00%)	1.34%

Table 5 shows the top ten most-prescribed Kampo extracts. *Kakkonto, tokishakuyakusan*, and *shoseiryuto* were prescribed for younger patients. *Shakuyakukanzoto*, *daikenchuto*, and *goshajinkigan,* meanwhile, were prescribed for elderly patients. *Daikenchuto* and *goshajinkigan* were more often prescribed for males than for females; *tokishakuyakusan* and *bofutsushosan*, in turn, were mostly prescribed for female patients. As with other traditional medicines, Kampo medicine is generally used as primary care for outpatients. Nevertheless, *daikenchuto* was more frequently administered to inpatients than outpatients.

The most prescribed Kampo drug was *shakuyakukanzoto*, which is widely used in musculoskeletal disorders such as muscle cramps and lumbago or associated conditions, such as dysmenorrhea. *Shakuyakukanzoto* acts on not only skeletal [10] but also smooth muscles [11].

Some Kampo extracts were specifically used for certain diseases; *bakumondoto*, for instance, was most frequently prescribed for bronchitis or bronchial asthma. Other Kampo extracts were applied to a wide variety of disease categories: *hochuekkito*, for instance, is prescribed for diseases of the circulatory system (category IX), digestive diseases (category XI), and conditions affecting the genitourinary system (category XIV), among others. Many Kampo extracts are coadministered with biomedical drugs. *Kakkonto* was prescribed with gargles and troches (13.23%), compresses containing anti-inflammatory chemicals (15.32%), or antipyretics (5.75% (acetaminophen)). *Goshajinkigan* was often used with anticancer drugs (20.24%).

4. Discussion

The Japanese health care system is unique in that Japan is the only country where traditional medicine is fully integrated alongside with modern medicine in daily practice. Currently, Japanese physicians, all trained in western medical schools, employ both biomedicine and traditional Japanese Kampo medicine in the clinic and university hospitals [5]. Kampo medicine, which originated in ancient China, had been Japan's primary health care system for over 1,500 years prior to the Meiji Restoration (1868–1912). In 1874, the government approved the Medical Care Law, which called for the adoption of the German model of health care and only legitimized western medical licenses. Early-twentieth-century physicians, however, continued to work towards reinstating Kampo as an official part of Japan's health care system.

In 1967, the first four Kampo extracts were approved for reimbursement under the National Health Insurance system. At the time of publication, this number has increased to 148 Kampo formulation extracts, 241 crude drugs, and 5 crude drug preparations. The present study examined only Kampo extracts because most Kampo drugs are prescribed in this form. The government also established the Good Manufacturing Practice (GMP) law in 1987 to ensure that all Kampo products are of uniformly high quality. The pharmaceutical industry, too, focused on Kampo medicine, engaging in research and development of high quality Kampo extracts. During the 52-year history of National Health Insurance in Japan, traditional medicine was also covered; as a result, both medicines coexist in one system [5].

However, the current status of traditional medicine's integration was largely unknown despite the MHLW's systematically collecting data on more than 60 million health care claims every year. We have analysed the use of Kampo medicine on the basis of these data.

We found that 1.34% of all patients were prescribed Kampo drugs. This appears small when contrasted with the fact that 70–80% of Japanese physicians prescribe Kampo drugs in their daily practice [5–9]. How can we explain this gap? Even though most physicians use Kampo drugs in daily practice, the proportion of patients who receive prescriptions for Kampo drugs is very small. Most physicians use only biomedicine and occasionally add Kampo drugs. Although we can speculate that the indications of Kampo drugs are very limited, Table 4 shows that all types of diseases are covered by Kampo treatment.

In Japan, most physicians are educated to be specialists. The Japanese government considers this to be problematic in an ageing society like Japan's. Elderly patients have multiple complaints at once, and general physicians are in demand in Japan. Our results show that indications of Kampo drugs are limited to one physician according to that physician's specialty, perhaps due to a western biomedical diagnosis. This is not in accordance with traditional use of Kampo drugs: Kampo medicine is a system similar to general medicine.

Until 2001, very few medical schools taught Kampo medicine. Most of physicians had not been educated in either general or Kampo medicine. In 2001, the Ministry of Education, Science, and Technology set new guidelines that incorporated Kampo education into the core curriculum of Japanese medical schools. Additionally, medical society features more and more the importance of general medicine. This may lead to a change in physicians' attitudes in the near future.

In the present study, we found that the use of Kampo extracts is relatively common in women with category XV health conditions. This may explain that why female patients are prescribed Kampo more frequently than are male patients; menopausal syndromes [12–15] and premenstrual syndrome are good indications of Kampo medicine and exclusively affect women.

The most frequently prescribed Kampo extract was *shakuyakukanzoto*, which is indicated for muscle cramp, lumbago, and abdominal pain. This drug is used as a muscle relaxant. Because it is so effective, many physicians use it as an alternative to analgesics. This Kampo extract is composed of 6 grams of peony root and 6 grams of liquorice root. Liquorice root contains glycyrrhizin and may cause pseudoaldosteronism, which can be very severe in rhabdomyolysis. Interestingly, liquorice root is included in 70% of the aforementioned 148 Kampo extracts. Physicians sometimes combine Kampo extracts, which increases the risk of pseudoaldosteronism [16]. To avoid this, proper education and drug information are necessary.

The use of Kampo has been modernized with western biomedicine. For example, the most commonly used Kampo

Table 5: The ten most-frequently used Kampo extracts and their use rates according to age, sex, hospitalization, and ICD-10 categories.

Rank	1 Shakuyakukanzoto extracts	2 Kakkonto extracts	3 Daikenchuto extracts	4 Hochuekkito extracts	5 Shoseiryuto extracts	6 Tokishakuyakusan extracts	7 Rikkunshito extracts	8 Bofutsushosan extracts	9 Bakumondoto extracts	10 Goshajinkigan extracts
Total	79,580	72,224	45,090	37,058	31,625	27,941	26,513	25,784	24,545	23,253
Age[1]	71.73	54.84	70.16	62.36	53.83	48.40	63.11	56.42	55.86	72.65
Male	31.61%	31.13%	52.30%	34.50%	34.41%	1.66%	33.67%	8.90%	32.09%	47.68%
Female	68.39%	68.87%	47.70%	65.50%	65.59%	98.34%	66.33%	91.10%	67.91%	52.32%
Inpatients	4.63%	2.47%	38.59%	7.50%	3.69%	4.14%	12.26%	3.45%	3.67%	7.79%
Outpatients	95.37%	97.53%	61.41%	92.50%	96.31%	95.86%	87.74%	96.55%	96.33%	92.21%
I	1.34%	3.08%	2.29%	1.40%	1.15%	7.89%	2.26%	0.33%	0.02%	3.32%
II	3.84%	0.80%	17.00%	5.49%	1.58%	2.05%	5.28%	0.04%	1.12%	20.24%
III	0%	0.07%	0.14%	0%	0.07%	0.05%	0%	0%	0.24%	0%
IV	10.54%	6.33%	3.31%	8.88%	3.11%	14.41%	6.05%	15.44%	6.25%	10.08%
V	1.12%	2.23%	12.95%	9.05%	2.94%	1.90%	8.18%	6.36%	0.00%	1.86%
VI	0.46%	4.13%	6.18%	4.52%	0.40%	5.38%	6.48%	1.65%	2.63%	3.17%
VII	0%	0.35%	0%	1.40%	1.93%	0%	0%	0.00%	1.31%	2.15%
VIII	0%	0.14%	0%	0%	0%	0%	0%	0.00%	0.00%	10.15%
IX	27.88%	26.58%	17.48%	23.89%	16.94%	11.53%	16.28%	33.05%	9.61%	13.64%
X	3.68%	26.66%	5.40%	5.96%	27.42%	1.88%	10.69%	0.13%	59.15%	4.29%
XI	5.34%	8.31%	25.70%	11.38%	24.53%	8.05%	32.60%	8.44%	5.36%	4.04%
XII	1.19%	0.58%	0.82%	7.73%	1.22%	1.35%	0.04%	15.38%	0%	0.08%
XIII	34.89%	13.38%	1.61%	7.16%	5.57%	8.68%	6.79%	13.83%	6.66%	19.39%
XIV	5.32%	4.97%	1.10%	10.47%	10.54%	30.71%	3.91%	3.63%	4.47%	6.46%
XV	0.04%	2.07%	0.48%	0.15%	1.21%	4.97%	0.06%	0.00%	2.62%	0%
XVI	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
XVII	0%	0%	0.03%	0%	0%	0%	0.92%	0%	0%	0%
XVIII	1.07%	0.01%	2.17%	0%	0.64%	0.68%	0.45%	0.78%	0%	0.65%
XIX	3.28%	0.32%	3.34%	2.51%	0.74%	0.47%	0.02%	0.95%	0.56%	0.47%

[1]Age: the average age of the patients who were prescribed the indicated Kampo drug.

drug for digestive diseases was *daikenchuto*. In *Jinkui Yaolue*, an ancient textbook of the second century, *daikenchuto,* was indicated for abdominal pain caused by the cold. Currently in Japan, *daikenchuto* is used for prevention of postsurgical ileus. Yasunaga et al. also showed that *daikenchuto* improved postoperative ileus requiring long-tube decompression [17]. Because the mechanism of action is well understood [18–20], many surgeons use *daikenchuto* routinely after operation; some hospitals have even adopted *daikenchuto* into their established clinical course. This is why *daikenchuto* is used more frequently in hospital settings than other Kampo extracts, which are generally used for outpatients in primary care settings.

Our data shows that 92.2% of patients prescribed Kampo extracts used them in combination with biomedical drugs. *Goshajinkigan* is one such Kampo extract that is often prescribed with anticancer drugs. It is frequently used to reduce numbness of the extremities, an adverse effect of anticancer drugs [21].

Another example is *kakkonto*, which is mainly prescribed for the treatment of the common cold. It was coadministered with gargles and troches. We also found that it was prescribed with antipyretics at a considerably high rate. In the view of Kampo medicine, such a combination is not ideal: one of the main effects of *kakkonto* is to raise the body temperature in order to eliminate high-temperature-sensitive viruses. If antipyretics are used in combination with *kakkonto*, the effect of *kakkonto* will be masked. It is possible that such misuse occurs because physicians ignored Kampo medicine theory and prescribed it in the light of westernized biomedicine.

There are only 2,420 board-certified Kampo doctors among the 280,000 licensed physicians of Japan. Historically, Kampo treatment was advised based on the patient's total body pattern. For effective Kampo treatment, drugs must be used in their traditional way. Additionally, although many physicians demand clinical evidence of Kampo medicine, most of the Kampo clinical studies have been performed based on western diagnoses [22].

Therefore, in order to prescribe Kampo extracts properly and avoid their misuse, education and clinical evidence based on traditional use of Kampo medicine should be established. In order to do so, standardized Kampo diagnosis is necessary. The WHO sets out to create an international classification of traditional medicine, and plans to incorporate it into the ICD-11 revision [2–4]. Mutual communication between traditional medicine and biomedicine specialists will thereupon be promoted and become more visible internationally. It is necessary to extend Kampo education in medical schools and to set up systematic continuous Kampo education after graduation. The safety and effectiveness of Kampo treatments are of utmost importance. Knowledge of Kampo diagnosis and proper use of Kampo drugs are, therefore, essential. This will ensure that future generations of Japanese physicians are able to truly integrate Kampo medicine into their practice.

5. Conclusion

We shed light on the prescription rate of Kampo drugs in Japan, analysing 67,113,579 health care claims records collected by the Ministry of Health, Labour and Welfare. The rate of Kampo prescription is still very low compared to the high rates of physicians' use of Kampo drugs. This gap may be caused by the Kampo drugs that were not used based on Kampo medicine theory, but by western biomedical diagnosis. Kampo drugs are more effective when they are used in the proper Kampo way, and proper education in this regard may be necessary.

Acknowledgments

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Research Article

A Valid Approach in Refractory Glossodynia: A Single-Institution 5-Year Experience Treating with Japanese Traditional Herbal (Kampo) Medicine

Hideki Okamoto, Atsushi Chino, Yoshiro Hirasaki, Keigo Ueda, Masaki Raimura, and Takao Namiki

Japanese-Oriental (Kampo) Medicine, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-Ku, Chiba 260-8670, Japan

Correspondence should be addressed to Hideki Okamoto; bon@sa2.so-net.ne.jp

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Glossodynia is often refractory to conventional medicine, and there is only limited evidence to guide clinicians in its management. Patients with refractory glossodynia are often introduced to Japanese traditional herbal (Kampo) medicine experts under such circumstances because Kampo medicine has become known in Japan to be effective in treating a wide variety of symptoms refractory to conventional medicine. Herein, we report our single-institution 5-year experience treating patients with Kampo medicine for primary glossodynia that was refractory to conventional medicine. We found that 69.2% of patients reported a beneficial effect of Kampo medicine on glossodynia, and the average onset of improvement was 8.0 ± 7.7 weeks after starting Kampo treatment. The top two frequently used Kampo medicines for glossodynia were seinetsuhokito and mibakuekkito among high responders who showed a decrease of severity by 50% or more. The top four most overlapped herbs among effective Kampo medicines for glossodynia were Glycyrrhiza Root, Ginseng Root, Hoelen, and Atractylodes (lancea) Rhizome, which compose an essential Kampo prescription called shikunshito. Although more research is required to further clarify the effectiveness of Kampo medicine, it has valid efficacy even in cases of glossodynia that remain incurable by conventional treatments.

1. Introduction

Primary glossodynia, also known as glossopyrosis (burning tongue) or glossalgia (tongue pain), is characterized by chronic oral dysaesthesia in the setting of no identifiable clinical lesions, laboratory abnormalities, or causative systemic disease. Glossodynia is regarded as a type of burning mouth syndrome (BMS) that is often refractory to conventional medicine, and there is only limited evidence to guide clinicians in the management of patients with BMS. It is recommended that the treatment be tailored to each patient and that it be administered in a multidisciplinary facility [1]. The difficulty of treating BMS may result in BMS patients being unfavorably associated with a specific pattern of personality disorder comorbidity [2].

The Headache Classification Subcommittee of the International Headache Society defines BMS as "an intraoral burning sensation for which no medical or dental cause can be found" (Headache Classification Committee of the International Headache Society, 2004), and the International Association for the Study of Pain defines it as "a pain of at least 4–6 months duration located on the tongue or other mucosal membranes in the absence of clinical or laboratory findings." Thus, BMS has been defined principally by the quality or location of the pain, and the diagnosis of BMS depends on the exclusion of a detectable organic basis for the complaint. A wide variety of pathogenic conditions therefore must be included such as local irritation; various mucocutaneous diseases; nutritional, metabolic, or endocrine disorders; xerostomia; and dysgeusia [3]. Kampo medicine, Japanese traditional herbal medicine, which originated in China, treats BMS based on Kampo-specific diagnostics, regardless of the pathogenesis determined on the basis of conventional medicine.

The Japanese Ministry of Health, Labor, and Welfare has approved more than 210 Kampo prescriptions for clinical use in the same way that conventional medicines are

prescribed. More than 80% of conventional medical doctors use Kampo medicine in their clinical practice, and most Kampo prescriptions are prescribed as freeze-dried extract granules. Freeze-dried Kampo-extract granules are manufactured by several pharmaceutical companies, and more than 140 Kampo prescriptions composed of those herbal extract granules are available for clinical use. Recently, Kampo medicine has received renewed attention because it provides a valid approach to treating symptoms refractory to conventional medicine and has become integrated with conventional medicine under the control of the Japanese Ministry of Health, Labor, and Welfare [4, 5].

We here focus on glossodynia, excluding pain in the other mucosal membranes, because the tongue is supposed to show the heart's condition in the five parenchymatous viscera theory in Kampo medicine, whereas the other parts of the mouth are not. There are some reports showing the effectiveness of alternative medicine for glossodynia, but no systematized medication with a high rate of effectiveness has been reported until now. Herein, we report our single-institution 5-year experience treating glossodynia with Kampo medicine.

2. Methods

This is a retrospective study of BMS patients over 5 years, when our outpatient clinic was established in November 2005 to October 2010. Fifty-nine BMS patients were listed by searching our outpatient database using the keywords tongue, mouth, glossodynia, glossitis, and BMS. Twenty patients were excluded: 12 patients who felt pain not on their tongues but on the oral mucous membrane or lips, 3 who felt numbness or an abnormal sensation on the tongue rather than pain, 1 who could not take the medication at all because his respiratory status grew worse due to lung cancer, 1 whose glossitis-like symptom was not a chief complaint but a secondary symptom and no longer was mentioned after the first consultation, and 3 who did not come back after the first consultation, including one who died a few days after the first consultation due to an accident. Consequently, 39 out of 59 BMS patients were diagnosed as suffering from primary glossodynia and appropriate for further investigation. All 39 patients had been diagnosed with primary glossodynia by a specialist such as a dentist and/or otorhinolaryngologist and, before consulting us, had already tried more than one of the conventional solutions such as NSAIDs; vitamin B complex; antidepressants including amoxapine, amitriptyline, paroxetine, and sertraline; anticonvulsants including gabapentin and clonazepam; antianxiety medicines; antipsychotics; pregabalin; and topical steroids, all of which had no effect or failed to have a sufficient effect. Most of the 39 patients stopped the conventional medications according to their own judgment before starting Kampo treatment, and, among the rest of the patients, those medications were not changed during the Kampo treatment.

The 11-Point Numerical Rating Scale for Pain Intensity (NRSI) is a verbally administered scale that measures pain intensity ("how much pain do you feel right now?") and is broadly used for the assessment of a wide variety of painful diseases. However, glossodynia patients often describe their pain mixed with unpleasantness, taste hypersensitivity, or other elusive sensations. Those symptoms, in addition, are prone to change into each other in a short while even during the treatment, which makes it difficult for patients to describe the improvement of symptoms merely in terms of comparing "pain" before and after the treatment. Therefore, all doctors defined the score 10 as corresponding to the severity of glossodynia before the start of the Kampo treatment and asked the patients to describe on a scale of 0–10 the severity of the symptoms remaining after the Kampo treatment, including unpleasantness, taste hypersensitivity, or other elusive sensations. In other words, a score of 10 meant that there was no change, a score of 5 meant that 50% of the severity of the symptoms due to glossodynia remained, and score of 0 meant that all symptoms caused by glossodynia were gone.

Patients were regularly followed up on nearly every 4 weeks during the treatment. A Kampo prescription was regarded as effective when the patient's glossodynia remained improved for 2 or more consecutive consultations after each Kampo medication was started, and the score at the last consultation was utilized, whether a patient suddenly stopped attending the consultations by choice, changed his chief complaint and sought improvement for other symptoms rather than for glossodynia, or was still under treatment at the time.

Each Kampo medicine was prescribed as a decoction or as freeze-dried Kampo-extract granules according to each Kampo doctor's decision and/or each patient's preference. Decoction medicine was handmade at each patient's home following our clinic's protocol in which one day's herb mixture, dispensed at a pharmacy, was put in 600 mL of boiling water, was then boiled down to about 300 mL after 30~40 minutes, and this 300 mL was divided into 2 or 3 parts to be drunk 2 or 3 times throughout the day after the herbal residues were removed. The composition and herb doses for each decoction medicine are fixed by our school, whereas the extract granule medicines are manufactured, and the composition and herb doses of each extract granule medicine are fixed by pharmaceutical companies. The composition and herb doses of the 6 most effective Kampo prescriptions for glossodynia are described in Table 1.

Data are expressed as n (%) or mean ± standard deviation (SD) in Tables 2 and 3. The following statistical tests were applied as appropriate: unpaired Student's t-test and chi-squared test with Fisher's exact test. A two-tailed $P < 0.05$ significance level was selected for all analyses. Microsoft Excel 2010 software was used for the computation of all statistical analyses.

This study received approval from the Human Research Ethics Committee of Chiba University Graduate School of Medicine (Identification no.: 1368).

3. Results

Reflecting that the use of complementary and alternative medicine (CAM) is most prevalent among women [6], 32 patients out of 39 (82.1%) were females, as most of our

Table 1: Composition and herb doses of the 6 most effective Kampo prescriptions for glossodynia.

Seinetsuhokito
Ginseng Root (3), Angelica Root (3), Peony Root (3), Ophiopogon Tuber (3), Atractylodes Rhizome (3.5), Hoelen (3.5), Cimicifuga Rhizome (1), Schisandra Fruit (1), Scrophularia Buergeriana Root (1), and Glycyrrhiza Root (1)
Mibakuekkito
Astragalus Root (4), Glycyrrhiza Root (1.5), Jujube Fruit (2), Ginseng Root (4), Atractylodes Rhizome (4), Ginger Rhizome (1), Angelica Root (3), Citrus Unshiu Peel (2), Cimicifuga Rhizome (0.5), Bupleurum Root (2), Schisandra Fruit (2), and Ophiopogon Tuber (5)
Kamishoyosan
Bupleurum Root (3), Peony Root (3), Atractylodes Lancea Rhizome (3), Angelica Root (3), Hoelen (3), Gardenia Fruit (2), Moutan Bark (2), Glycyrrhiza Root (1.5), Ginger Rhizome (1), and Mentha Herb (1)
Orento
Pinellia Tuber (6), Coptis Rhizome (3), Glycyrrhiza Root (3), Cinnamon Bark (3), Jujube Fruit (3), Ginseng Root (3), and Ginger Rhizome (3)
Bukuryoingohangekobokuto
Pinellia Tuber (6), Hoelen (5), Atractylodes Lancea Rhizome (4), Magnolia Bark (3), Citrus Unshiu Peel (3), Ginseng Root (3), Perilla Herb (2), Immature Orange (1.5), and Ginger Rhizome (1)
Ji'inshihoto
Cyprus Rhizome (3), Bupleurum Root (3), Peony Root (3), Anemarrhena Rhizome (3), Citrus Unshiu Peel (3), Angelica Root (3), Ophiopogon Tuber (3), Atractylodes Rhizome (3), Hoelen (3), Glycyrrhiza Root (1), Mentha Herb (1), Lycium Bark (3), and Fritillary Bulb (2)

Seinetsuhokito and mibakuekkito are decoction medicines, and kamishoyosan, orento, bukuryoingohangekobokuto, and ji'inshihoto are extract-granule medicines. The numbers in the round brackets show the one-day dose of each herb (grams).

Table 2: Patient demographic characteristics.

	Total (n = 39)	Female (n = 32)	Male (n = 7)	P value (Female versus male)
Age (years)	65 ± 9	64.3 ± 8.8	70 ± 6.7	NS[#]
No improvement (nonresponders)	12 (30.8%)	9 (28.1%)	3 (42.9%)	NS[*]
Decreased scores ≦ 2	27 (69.2%)	23 (71.9%)	4 (57.1%)	NS[*]
Average residual scores	4.6 ± 4.2	4.6 ± 4.1	4.8 ± 4.9	NS[#]
Average onset of improvement (weeks)	8.0 ± 7.7	8.4 ± 8.3	5.8 ± 3.5	NS[#]
Decreased scores ≦ 5 (high responders)	23 (59.0%)	19 (59.4%)	4 (57.1%)	NS[*]

Data are presented as n (%) or mean ± SD.
[#]t-test, [*]chi-squared test.
NS: no significance.

Table 3: Comparison between nonresponders and high responders.

	Nonresponders (n = 12)	High responders (n = 23)	P value
Age (years)	65.8 ± 7.6	64.8 ± 9.7	NS[#]
Female/male	9 (75%)/3 (25%)	19 (82.6%)/4 (17.4%)	NS[*]
Rate of decoction	5 (41.7%)	9 (39.1%)	NS[*]

Data are presented as n (%) or mean ± SD.
[#]t-test, [*]chi-squared test.
NS: no significance.

outpatients are, and there was no significant difference in age, average residual scores, or average onset of improvement between genders (see Table 2). The average duration of suffering from glossodynia was 107.2±138.4 weeks, and the average duration of time spent on the conventional medication was 59.6 ± 88.1 weeks until the first consultation among all 39 patients (expressed as means ± standard deviation, resp.) (not shown in Tables).

Twelve (30.8%) patients had no improvement (nonresponders), 27 (69.2%) patients had their severity of glossodynia lowered by 20% or more, and 23 (59.0%) patients showed a reduction of severity by half or more (high responders) out of a total of 39 patients. The average scores were decreased to 4.6 ± 4.2 from 10, and the average onset of improvement was 8.0 ± 7.7 weeks after starting Kampo treatment. The average latency to gain the max efficacy of Kampo treatment could not be calculated because 14 out of 39 patients were still in recovery as of March 1st, 2011. Those 14 patients' efficacy rates, gender difference, and average residual scores showed no significant change compared to the other patients (data not shown).

Table 3 shows the comparison data between 12 nonresponders and 23 high responders whose scores decreased by 5 or more. There were no significant differences between the nonresponders and high responders in age, female/male ratio, and the rate of decoction. Not enough supplementary information was provided in clinical charts to compare nonresponders with high responders in mental aspects. The average drop-out time among the 12 nonresponders was 14.0 ± 15.9 weeks after starting Kampo treatment (data not shown), which is reasonable considering that the average onset of improvement was 8.0 ± 7.7 weeks after starting Kampo treatment (see Table 2). Five out of the 12 nonresponders, however, dropped out of Kampo treatment after their second consultation, which may have been too early to evaluate Kampo's effectiveness.

All Kampo prescriptions were chosen based on Kampo diagnoses made by Kampo experts. Figure 1 shows the effective Kampo prescriptions in 23 high responders. Seinetsuhokito and mibakuekkito, both of which are decoction medicines used empirically for glossodynia in our school, were likely to be used more often than other medicines. However, all in all, a wide variety of Kampo prescriptions turned out to be effective for glossodynia, and there was no pattern among the effective Kampo prescriptions. Therefore, all herbs used in the 23 high responders were listed, and Figure 2 shows the 10 herbs that overlapped most among effective Kampo prescriptions. The most overlapped herb turned out to be Glycyrrhiza Root, also known as Licorice, which was used in 21 out of the 23 high responding patients. In addition, the top 4 most overlapped herbs, Glycyrrhiza Root, Ginseng Root (Panax Ginseng), Hoelen (Poria cocos Wolf), and Atractylodes (lancea) Rhizome, compose an essential Kampo prescription called "shikunshito", a basic Kampo prescription from which many Kampo prescriptions derive. Shikunshito is prescribed to improve not only weakened gastrointestinal function but also hypofunction accompanied by decreased physical and mental strength such as in generalized fatigability [5].

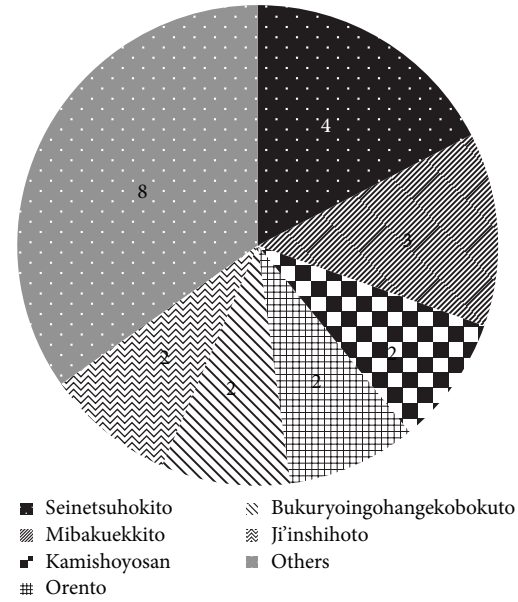

Figure 1: Effective Kampo prescriptions. The numbers show the patients per each Kampo prescription. Others: the combination of bakumondoto and daikenchuto, the combination of shosaikotokakikyosekko and tokakujokito, saikokeishikankyoto, bukuryoin, keihito, the combination of hachimigan and tokakujokito, kanzoshashinto, seishinrenshiin.

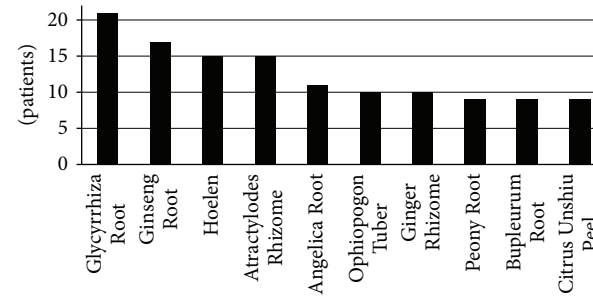

Figure 2: Ten herbs that overlapped most among effective Kampo prescriptions for glossodynia.

4. Discussion

Conventional medical doctors introduce patients to Kampo experts when the Kampo medicines prescribed by them are not effective enough or when conventional medicine cannot improve patients' symptoms [7]. Quality control of the herbs used in Kampo has been established for both extract granules and decoctions, and the safety and reliability of Kampo have been well-established through the strict monitoring of side effects under the control of the Japanese Ministry of Health, Labor, and Welfare in the same way as conventional medicines are used [8]. In addition, the clinical efficacy of some Kampo medicines, especially daikenchuto and yokukansan, has been demonstrated in many clinical trials done by conventional medical doctors using the standard methods of conventional medicine [7, 9–11]. Our group has recently reported on other Kampo medicines which are

remarkably effective in many cases refractory to conventional medicine [12–16]. The reliability and effectiveness of Kampo medicine thus promotes its integration with conventional medicine in Japan.

In our study, all patients had already tried one or more conventional treatments for glossodynia for a long time (59.6 ± 88.1 weeks on average, as described previously in Section 3) and showed no improvement, and they were consequently introduced to us or consulted us by themselves. After being treated with Kampo medicine, 69.2% of them exhibited a decrease in the severity of glossodynia of 20% or more, and 59.0% of them showed a reduction of severity by half or more, which demonstrates that Kampo medicine should be a valid alternative approach to refractory glossodynia. Compared to conventional treatments such as clonazepam [17], chlordiazepoxide [18], pregabalin [19], and SSRIs [20, 21], the effective rate of Kampo medicine for glossodynia could be superior, because we treated only refractory glossodynia cases that had already tried conventional medicine. However, it might be meaningless to compare the efficacy rate between conventional treatment and Kampo medicine because Kampo medicine can still function as a valid alternative approach for patients whose glossodynia remains incurable even after all conventional treatments have been tried.

Glossodynia has female predominance (female-to-male ratio of 3 : 1 to 7 : 1) [22], and we found that female glossodynia patients may need more time until the onset of improvement than male patients (see Table 2). Although this result must be confirmed in a larger population, this tendency may be because glossodynia is often caused by a long history over which vital energy deficiency and blood deficiency are developed, and women tend to have a more serious and longer history of such deficiencies after menopause than men.

There was no significant difference in the rate of decoction between nonresponders and high responders, although Kampo decoction medicines are often expected to work with more effectiveness than extract granule medicines (see Table 3). In other words, the effectiveness of extract granule prescriptions is equal to that of decoction medicines as long as the choice of prescription is appropriate to each case based on Kampo diagnosis. More than 60% of high responders, in fact, were successfully treated with extract granule prescriptions (see Table 3). Whether in the form of extract granules or decoction, Kampo medicine employs a much smaller amount (1/2~1/10) of herbs than other Asian traditional herbal medicines while realizing the high quality and efficacy of the treatment (see Table 1). This characteristic of Kampo medicine contributes greatly to the protection of rare plants.

Seinetsuhokito was used most frequently among effective prescriptions (see Figure 1), which was consistent with the previous report written in Japanese that the first choice for glossodynia is seinetsuhokito in Kampo medicine [23]. Kamishoyosan, one of the third most frequently used prescriptions in our current study, is used most frequently for glossodynia in another report written in Japanese [24]. All in all, however, there was almost no pattern among effective Kampo prescriptions, which implies that it may be difficult for non-Kampo experts to choose an appropriate Kampo medicine for each glossodynia patient. This is not surprising because Kampo prescriptions by nature are chosen based on Kampo-specific diagnosis regardless of conventional diagnosis, which means that different Kampo prescriptions are effective as long as each patient has a tailored Kampo diagnosis even if patients have the same conventional diagnosis. However, we tried to find any common tendency in Kampo philosophy among glossodynia patients and found that 10 herbs, which overlapped most among effective prescriptions for glossodynia in our current study, indicate a certain solution for glossodynia (see Figure 2).

Glycyrrhiza Root, the herb that overlapped most among the effective treatments, is thought to harmonize the effects of the other constituent herbs without diminishing their characteristics, and it is contained by more than 70% of Kampo prescriptions [5]. The frequency of its use in our study (21 out of 23 patients) was clearly higher than 70%, suggesting that Glycyrrhiza Root alone has some ameliorating efficacy in glossodynia. Accumulating studies have revealed that Glycyrrhiza has an anti-inflammatory effect [25] and, interestingly, a randomized, double-blind, placebo-controlled trial shows that a patch containing extract of Glycyrrhiza Root is significantly effective in treating recurrent aphthous ulcers [26], which also strongly indicates that Glycyrrhiza Root alone can be effective for an inflammatory symptom appearing inside the mouth.

Ginseng Root was the second most overlapped herb among effective prescriptions for glossodynia in our current study (see Figure 2). Ginseng Root is one of the most well-known herbs in the world and ranks as a frequently used herbal remedy in Europe [27]. The therapeutic efficacy of Ginseng Root in painful diseases such as fibromyalgia [28] is still controversial, although Ginseng Root was lately revealed to moderate the immune response in a systematic review [29] and to potentially have anti-inflammatory and analgesic effects in several animal studies [30, 31]. Both Hoelen and Atractylodes Rhizome were the third most overlapped herb among effective prescriptions for glossodynia (see Figure 2). Hoelen has been traditionally used for promoting urination and reducing edema in clinical practice, and actually recent researches show that Hoelen has renoprotective effects by modulating water balance [32, 33]. Atractylodes Rhizome not only has a diuretic effect similar to Hoelen by suppressing water reabsorption in the kidney [34] but also a randomized pilot study showed that Atractylenolide I, extracted from Atractylodes Rhizome, improves appetite and performance status in gastric cancer cachexia patients [35].

Generally, it is regarded as meaningless to list the overlapping herbs used by high responders and to assert an individual herb's function, because Kampo prescriptions are thought to exert their effectiveness as a function of the herb combination. However, our most important finding in our current study is that the top 4 overlapping herbs form a specific Kampo prescription, called "shikunshito". Shikunshito is one of the most well-known and basic Kampo prescriptions and is used to improve deficiencies of vital energy ("Ki" in Kampo medicine and "Qi" in Chinese) and deficiencies of digestive function in Kampo medicine [5, 36].

In fact, an old Japanese medical book "Kohouyakugi" written in 1894 by Sohaku Asada, a famous Kampo doctor, reported that Ginseng Root, Hoelen, and Atractylodes Rhizome exert a common efficacy in recovering the gastrointestinal function, although each herb also has many other differing therapeutic effects. This common ameliorating effect of Ginseng Root, Hoelen, and Atractylodes Rhizome on the gastrointestinal function, when taken together with other differing therapeutic efficacies of Glycyrrhiza Root, Ginseng Root, Hoelen, and Atractylodes Rhizome, reenergizes patients with a declined physical and mental status, which is the core therapeutic efficacy of shikunshito. A different group reported 5 cases that were successfully treated with Kampo medicine, and shikunshito-containing prescriptions were used in 3 out of the 5 cases [37], and, in our current study, in fact, 17 out of 23 high responders took prescriptions including 3 or more herbs which compose shikunshito.

Although our current study suggests that shikunshito has a key role, a single shikunshito prescription may not improve glossodynia on its own. The other overlapping herbs should be concomitantly effective for glossodynia because they also play important roles, according to Kampo philosophy. Ginger Rhizome is usually decocted with shikunshito and improves the digestive system; a finding that is supported by accumulating reports showing its effectiveness for chemotherapy-induced, pregnancy-induced, and postoperative nausea and vomiting [38, 39]. Angelica Root has several subspecies, and one of them, Angelica sinensis (dong quai in Chinese), which is the most well-known Angelica used also in other CAMs, is thought to treat female menstrual ailments, nourish blood, and invigorate vital energy in Chinese medicine [40]. Angelica sinensis, as a matter of fact, is proven to increase sexual activity and influence fertility in animal models, although human studies could not support this finding [41]. Japanese Angelica, which is used in Kampo medicine, has a reputation for its safety and quality control [42] and is thought to have a similar function to Angelica sinensis, although its pharmacological mechanism is not scientifically elucidated in detail yet. Ophiopogon Tuber is thought to have an anti-inflammatory effect and to treat dry cough and dry mouth, tongue, and throat by nourishing and moistening the lungs and the bowels [40]; a finding that is supported by the reports that Ophiopogon has anti-inflammation activity [43] and has a beneficial effect on a mouse model for Sjogren's syndrome [44] and on an epithelial injury model for studies of mucociliary transport [45]. Peony Root is often concurrently used with Angelica Root and improves blood deficiency, dissipates blood stagnation, and relieves pain [5, 36, 40]. Shakuyakukanzoto, a Kampo prescription consisting of Glycyrrhiza Root and Peony Root, has been well-known among primary care doctors in Japan for having an immediate relieving effect on muscle cramps [5, 36], which has been proven by several open-labeled trials in hemodialysis patients [46, 47]. Shakuyakukanzoto also has a significant suppressive effect on duodenal spasms during endoscopic retrograde cholangiopancreatography [48]. Taken together, the combination of Glycyrrhiza Root and Peony Root seems to have an antispasmodic pain-relieving effect on both skeletal and smooth muscle. In addition, Paeoniflorin, one of the main ingredients in Peony extract, has a protective effect on its own on gastric mucosal injury [49]. Bupleurum Root is an important herb in Kampo medicine, and it forms a "Bupleurum" prescription category that is used for specific pathological conditions such as alternating chills and fever, fullness and a choking feeling in the chest and hypochondriac region, and stress-induced imbalance [5, 36]. Accumulating reports have revealed that Bupleurum has immunomodulatory, antiinflammatory, antiviral, and anti-ulcer activities [50] as well as an antidepressant-like effect in animal depression models [51, 52]. Citrus Unshiu Peel has a releasing action for Ki regurgitation, whereas Bupleurum Root has an obstruction-removing action for Ki when there is obstruction [5], which means that both have ameliorating effects on mental imbalance. In summary, glossodynia is a complicated pathological state caused not only by sustained vital energy deficiency and/or blood deficiency but also by mental imbalance from the viewpoint of Kampo philosophy. Kampo medicine for glossodynia, therefore, should be carefully chosen among prescriptions including shikunshito by considering which deficiency or imbalance is most necessary to improve depending on the case. In addition, it would be intriguing to make a new antiglossodynia Kampo prescription consisting of these top 10 overlapping herbs.

5. Conclusions

We have herein reported our single-institution 5-year experience treating refractory glossodynia with Kampo medicine. Kampo treatment had beneficial effects on 69.2% of refractory glossodynia patients, and the top 4 overlapping herbs used to treat the responders are the components of a well-known Kampo prescription, shikunshito. Thus, Kampo medicine showed valid efficacy, even in cases in which glossodynia remained incurable after conventional treatments were tried. Although more research is required to further clarify the effectiveness of Kampo medicine, these findings confirm that Kampo medicine is a promising alternative for treating refractory glossodynia.

Conflict of Interests

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The authors declare that they have no financial conflict of interests.

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Research Article

Herbal Medicine Goshajinkigan Prevents Paclitaxel-Induced Mechanical Allodynia without Impairing Antitumor Activity of Paclitaxel

Muh. Akbar Bahar,[1] Tsugunobu Andoh,[1] Keisuke Ogura,[2] Yoshihiro Hayakawa,[2] Ikuo Saiki,[2] and Yasushi Kuraishi[1]

[1] *Department of Applied Pharmacology, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Toyama 930-0194, Japan*
[2] *Division of Pathogenic Biochemistry, Institute of Natural Medicine, University of Toyama, Toyama 930-0194, Japan*

Correspondence should be addressed to Yasushi Kuraishi; kuraisiy@pha.u-toyama.ac.jp

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Chemotherapy-induced peripheral neuropathy is a major dose-limiting side effect of commonly used chemotherapeutic agents. However, there are no effective strategies to treat the neuropathy. We examined whether Goshajinkigan, a herbal medicine, would prevent paclitaxel-induced allodynia without affecting the anticancer action in mice. Murine breast cancer 4T1 cells were inoculated into the mammary fat pad. Paclitaxel (10 and 20 mg/kg, intraperitoneal, alternate day from day 7 postinoculation) inhibited the tumor growth, and Goshajinkigan (1 g/kg, oral, daily from day 2 postinoculation) did not affect the antitumor action of paclitaxel. Mechanical allodynia developed in the inoculated region due to tumor growth and in the hind paw due to paclitaxel-induced neuropathy. Paclitaxel-induced allodynia was markedly prevented by Goshajinkigan, although tumor-associated allodynia was not inhibited by Goshajinkigan. These results suggest that Goshajinkigan prevents paclitaxel-induced peripheral neuropathy without interfering with the anti-cancer action of paclitaxel.

1. Introduction

Pain in cancer patients is due to the tumor itself or due to the cancer treatment including chemotherapy [1]. The incidence of pain is 58% to 69% in patients with terminal cancer and 44% to 73% in patients receiving chemotherapeutic agents [2]. The high prevalence of debilitating pain explains the lack of effective therapies, and cancer-related pain is still a severe clinical problem. Experimentally, pain can enhance the growth and metastasis of tumor [3, 4]. Therefore, pain relief is very important for both improving the quality of life and cancer treatment.

Paclitaxel is an antimicrotubule agent, which is widely indicated to treat solid neoplasms such as ovarian, breast, and lung cancer [5, 6]. Nevertheless, the use of paclitaxel is confined by its main side effect sensory neuropathy that is characterized by cold allodynia, mechanical allodynia, spontaneous pain, shooting and burning pain, tingling, and numbness, with a stocking and glove distribution [7]. These symptoms are the most common causes for the termination or dose reduction of the treatment, potentially leading to cancer progression [8]. Moreover, the cessation of therapy occasionally does not alleviate these disabling side effects and become persistent for months or years [9]. The incidence of paclitaxel-induced peripheral neuropathy is ranging from 59% to 78% [10].

Prevention is the most recommended way to treat chemotherapy-induced neuropathy. The prerequisites of ideal prophylaxis agents are potent, have no significant side effects, and are not undermining antitumor effect of the chemotherapeutic agents [11, 12]. Several medications and vitamins have been preclinically and clinically tested for their

efficacy in preventing chemotherapy-induced peripheral neuropathy, but the conflicting results have been reported [8, 13–15].

Goshajinkigan is a traditional medicine which is composed of *Rehmanniae radix*, *Achyranthis radix*, *Corni fructus*, *Dioscoreae rhizome*, *Plantaginis semen*, *Alismatis* r*hizome*, *Hoelen*, *Moutan cortex*, *Cinnamoni cortex,* and *Aconiti Calefactum tuber*. Goshajinkigan has ability to inhibit oxaliplatin-induced pain without weakening the antitumor activity of oxaliplatin [12, 16]. In clinical setting, Goshajinkigan has been shown to attenuate the progression of peripheral neuropathy induced by docetaxel in breast cancer patients and by paclitaxel/carboplatin in ovarian or endometrial cancer patients [17, 18]. However, there are only a few reports on its effects on paclitaxel-induced mechanical allodynia in animals [19] and no reports on the effects on malignancy-induced pain and the antitumor action of paclitaxel. Therefore, in this present study, we investigated the effects of Goshajinkigan using the mice bearing breast cancer.

2. Materials and Methods

2.1. Animals. Female BALB/c mice (Japan SLC Ltd., Shizuoka, Japan), 6 weeks of age at the start of experiments, were used. They were housed 6 per cage under controlled temperature (21–23°C) and humidity (45%–65%). The room was lighted from 7:00 am to 7:00 pm and during the behavioral test. Food and water were available *ad libitum*. The study was approved by the Committee for Animal Experiments at the University of Toyama.

2.2. Tumor Inoculation. Breast cancer 4T1 cells, a mammary tumor cell line derived from BALB/c mouse, were cultured in Roswell Park Memorial Institute 1640 medium containing 10% fetal bovine serum at 37°C and in a humidified atmosphere of 5% CO_2. The 4T1 cells (5×10^4 cells/20 μL) or the culture medium were inoculated into the right abdominal mammary fat pad of the mice.

2.3. Drugs. Paclitaxel was purchased from Sigma (St. Louis, MO, USA) and dissolved in saline containing 10% v/v Cremophor EL (Sigma) and 10% v/v ethanol. Paclitaxel or the vehicle was injected intraperitoneally (i.p.) every other day from day 7 after tumor cell inoculation. In preliminary experiments, paclitaxel at doses of 10 and 20 mg/kg significantly inhibited tumor growth, the lower dose of 5 mg/kg did not produce a significant inhibition, and the higher dose of 40 mg/kg induced severe weight loss. Therefore, the doses of 10 and 20 mg/kg were selected. Goshajinkigan extract granules were obtained from Tsumura & Co. Ltd. (Tokyo, Japan). Goshajinkigan was dissolved in tap water and administered orally every day from day 2 after tumor cells inoculation. The dose (1 g/kg) of Goshajinkigan was selected from our preliminary experiments and the published literature on the effect of Goshajinkigan on oxaliplatin-induced sensory neuropathy [12].

2.4. Evaluation of Body Weight, Tumor Volume, and Tumor Weight. The body weight was measured every day using an electronic balance. The tumor size was measured every day from day 8 postinoculation by using a caliper square; the longest diameter (a) and the width (b) were measured, and tumor volume was calculated by using the formula tumor volume (mm^3) = $(a \times b^2) \div 2$ [20]. The weight of tumor was determined after mice being sacrificed on day 26 by taking out the tumor.

2.5. Behavioral Test. Mechanical allodynia was evaluated by stimulating the tumor-bearing region and the hind paw on the opposite side using a fine von Frey filament with a bending force of 0.69 mN (innocuous stimulation) [21, 22]. Responses of the tumor-bearing region to the stimulus were ranked as follows: 0, no response; 1, lifting of the hind paw; and 2, head motion toward the stimulation filament or flinching. Responses of the hind paw to the stimulus were ranked as follows: 0, no response; 1, lifting of the hind paw; and 2, flinching or licking of the hind paw. A stimulation of the same intensity was applied six times to the tumor-bearing region and the hind paw at intervals of several seconds, and the average of six values was used as the pain-related score and presented as percentage. The evaluation of mechanical allodynia was carried out before drug administration.

2.6. Statistical Analysis. Data are presented as mean ± standard error of the mean (SEM). Time-course data were analyzed with two-way repeated measures analysis of variance (ANOVA). Statistical significance between groups was analyzed using one-way ANOVA and post hoc Holm-Sidak multiple comparisons. $P < 0.05$ was considered significant. The statistical analyses were performed using SigmaPlot graphing and statistical software (version 11; Systat Software, Inc., Chicago, IL, USA).

3. Results

3.1. Effects of Paclitaxel and Goshajinkigan on the Volume and Weight of Tumor. An inoculation of 4T1 cells into the mammary fat pad of mice increased time dependently the nodule of tumor, which could be measured from day 8 postinoculation (Figure 1). Paclitaxel (10 and 20 mg/kg) inhibited the increase of tumor volume in a dose dependent manner (Figure 1(b)). When Goshajinkigan (1 g/kg) was administered daily, paclitaxel (10 and 20 mg/kg) similarly inhibited the increase of tumor volume (Figure 1(c)). On day 26 post inoculation, tumor masses were isolated from mice and weighed. Paclitaxel (10 and 20 mg/kg) reduced dose dependently tumor weight with significant inhibition at a dose of 20 mg/kg (Figure 2). In mice given repeated Goshajinkigan (1 g/kg) administration, paclitaxel also produced a dose dependent inhibition of tumor weight with significant inhibition at a dose of 20 mg/kg (Figure 2).

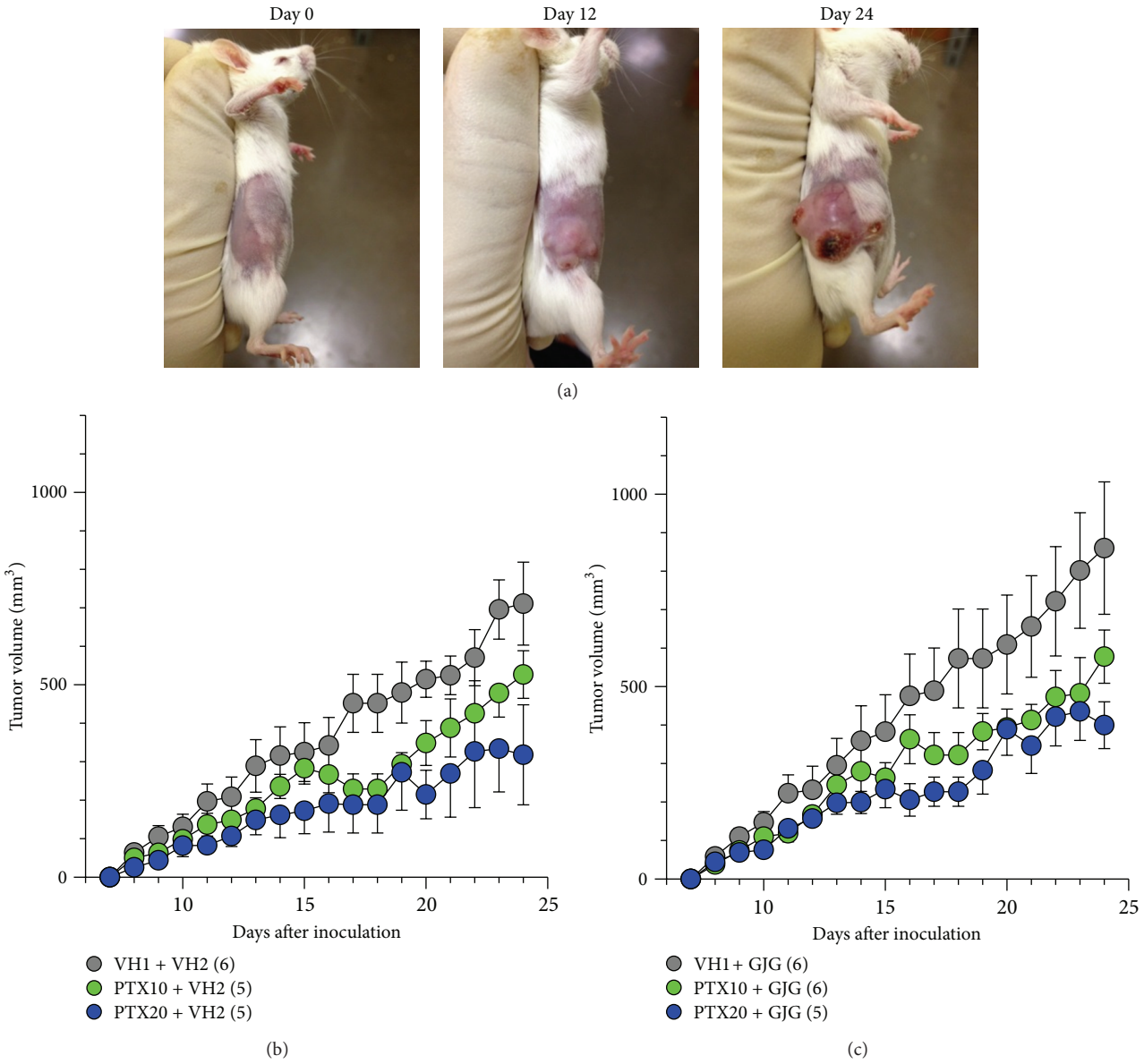

Figure 1: Effects of paclitaxel (PTX) and Goshajinkigan (GJG) on the growth of 4T1 cells in mice. The 4T1 cells were inoculated into the right abdominal mammary fat pad on day 0. (a) Typical example of tumor growth in the mouse breast. ((b), (c)) Time-course of the effects of PTX on the tumor growth (b) with or (c) without GJG administration. PTX (10 and 20 mg/kg) and vehicle (VH1) were injected intraperitoneally every other day from day 7 after tumor cell inoculation. GJG (1 g/kg) and vehicle (VH2) were administered orally every day from day 2 after tumor cell inoculation. Values represent the means ± SEM. Figures in parentheses indicate the number of animals. (b) Interaction between PTX treatment and time, $F_{34,221} = 2.624$, $P < 0.001$ (two-way repeated measures ANOVA). (c) Interaction between PTX treatment and time, $F_{34,238} = 2.262$, $P < 0.001$ (two-way repeated measures ANOVA).

3.2. Effects of Paclitaxel and Goshajinkigan on Body Weight and Survival. The inoculation of 4T1 cells alone was not lethal to mice at least during the experimental period (Table 1). However, unexpectedly, one mouse died in each group treated with paclitaxel (10 and 20 mg/kg) alone on day 17 or 18 after the 4T1 cell inoculation (Table 1). In contrast, in the groups treated with Goshajinkigan (1 g/kg), one mouse died on day 19 postinoculation (on day 12 after the start of 20 mg/kg paclitaxel administration), and no mice died after administration of 10 mg/kg paclitaxel (Table 1).

The administration of paclitaxel (10 mg/kg) alone did not decrease body weight during the observation period as compared with vehicle control, but the higher dose of 20 mg/kg significantly decreased body weight from day 14 postinoculation. Figure 3 shows body weight on day 24 postinoculation; the administration of paclitaxel (10 and 20 mg/kg) caused a dose dependent decrease in body weight. In contrast, in the groups treated with Goshajinkigan (1 g/kg), paclitaxel (10 and 20 mg/kg) did not significantly decrease

Table 1: The number of survival mice.

		Days after inoculation											
		0	1	2	16	17	18	19	20	21	22	23	24
		The number of mice survived											
VH1	VH2	6	6	6	6	6	6	6	6	6	6	6	6
PTX (10)	VH2	6	6	6	6	6	5	5	5	5	5	5	5
PTX (20)	VH2	6	6	6	6	5	5	5	5	5	5	5	5
VH1	GJG	6	6	6	6	6	6	6	6	6	6	6	6
PTX (10)	GJG	6	6	6	6	6	6	6	6	6	6	6	6
PTX (20)	GJG	6	6	6	6	6	6	5	5	5	5	5	5

PTX: paclitaxel; VH1: vehicle for PTX; GJG: Goshajinkigan; VH2: vehicle for GJG.
Figures in parentheses indicate the dose (mg/kg) of PTX.
Administration schedules for PTX and GJG are shown in Figure 1.

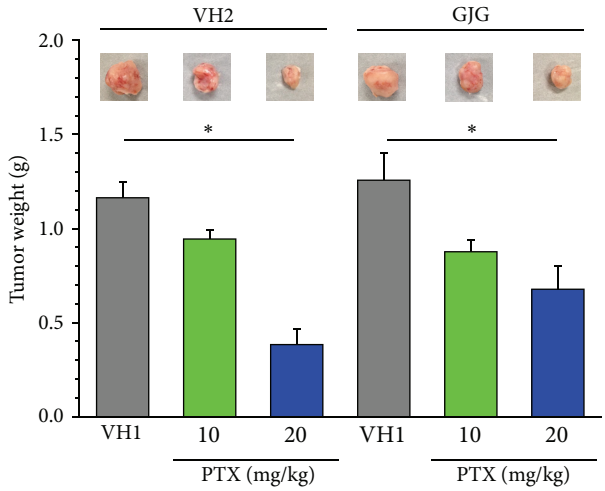

Figure 2: Effects of paclitaxel (PTX) and Goshajinkigan (GJG) on tumor weight in mice with breast cancer. Tumor masses were isolated from mice shown in Figure 1 on day 26 after the 4T1 cell inoculation. The photographs show typical examples of tumor mass isolated. PTX (10 and 20 mg/kg) and vehicle (VH1) were injected intraperitoneally. GJG (1 g/kg) and vehicle (VH2) were administered orally. Values represent the means ± SEM for three to six animals. $^{*}P < 0.05$ (Holm-Sidak multiple comparisons).

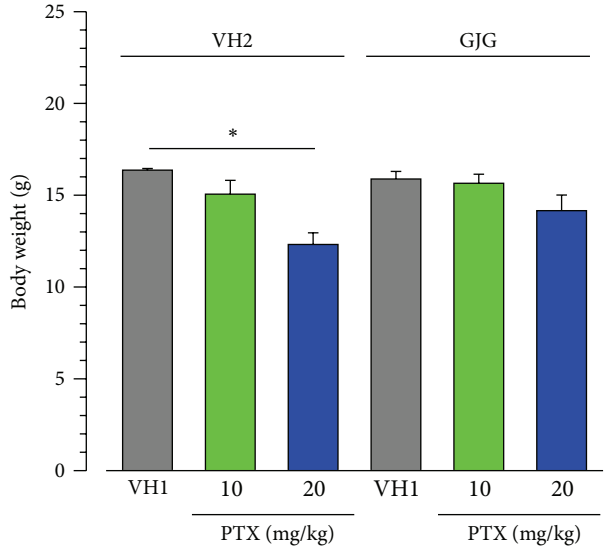

Figure 3: Effects of paclitaxel (PTX) and Goshajinkigan (GJG) on body weight in mice with breast cancer. The data were obtained from mice shown in Figure 1 on day 24 after the 4T1 cell inoculation. PTX (10 and 20 mg/kg) and vehicle (VH1) were injected intraperitoneally. GJG (1 g/kg) and vehicle (VH2) were administered orally. Values represent the means ± SEM for five to six animals. $^{*}P < 0.05$ (Holm-Sidak multiple comparisons).

body weight during the observation period; Figure 3 shows body weight on day 24 postinoculation.

3.3. Effects of Paclitaxel and Goshajinkigan on Allodynia in the Hind Paw. Since paclitaxel causes peripheral neuropathy, especially allodynia and dysesthesia that often occur in a "glove and stocking" distribution, we evaluated paclitaxel-induced allodynia in the hind paw in mice (Figure 4(a)). Breast cancer 4T1 cells were inoculated into the right abdominal mammary fat pad, and it is possible that pain-related responses of the ipsilateral hind paw are affected by the tumor. Therefore, we evaluated allodynia in the contralateral (left) hind paw in mice with breast cancer. Mechanical allodynia in the hind paw developed from 2 days after the start of paclitaxel (10 and 20 mg/kg) administration, although dose dependency was not obvious (Figure 4(b)). In contrast, in the groups that were given daily administration of Goshajinkigan (1 g/kg), paclitaxel (10 and 20 mg/kg) did not induce allodynia in mice with breast cancer (Figure 4(c)).

3.4. Effects of Paclitaxel and Goshajinkigan on Mechanical Allodynia in the Tumor Region. Mechanical allodynia was evaluated in the region of breast cancer 4T1 cell inoculation (Figure 5(a)). Mechanical allodynia developed from day 8 postinoculation and rapidly increased to reach maximum on day 10 (Figure 5(b)). Maximal allodynia was kept at least during the observation period (day 24 postinoculation). The repeated administration of paclitaxel (10 and 20 mg/kg), Goshajinkigan (1 g/kg), or both did not affect the mechanical allodynia (Figures 5(b) and 5(c)).

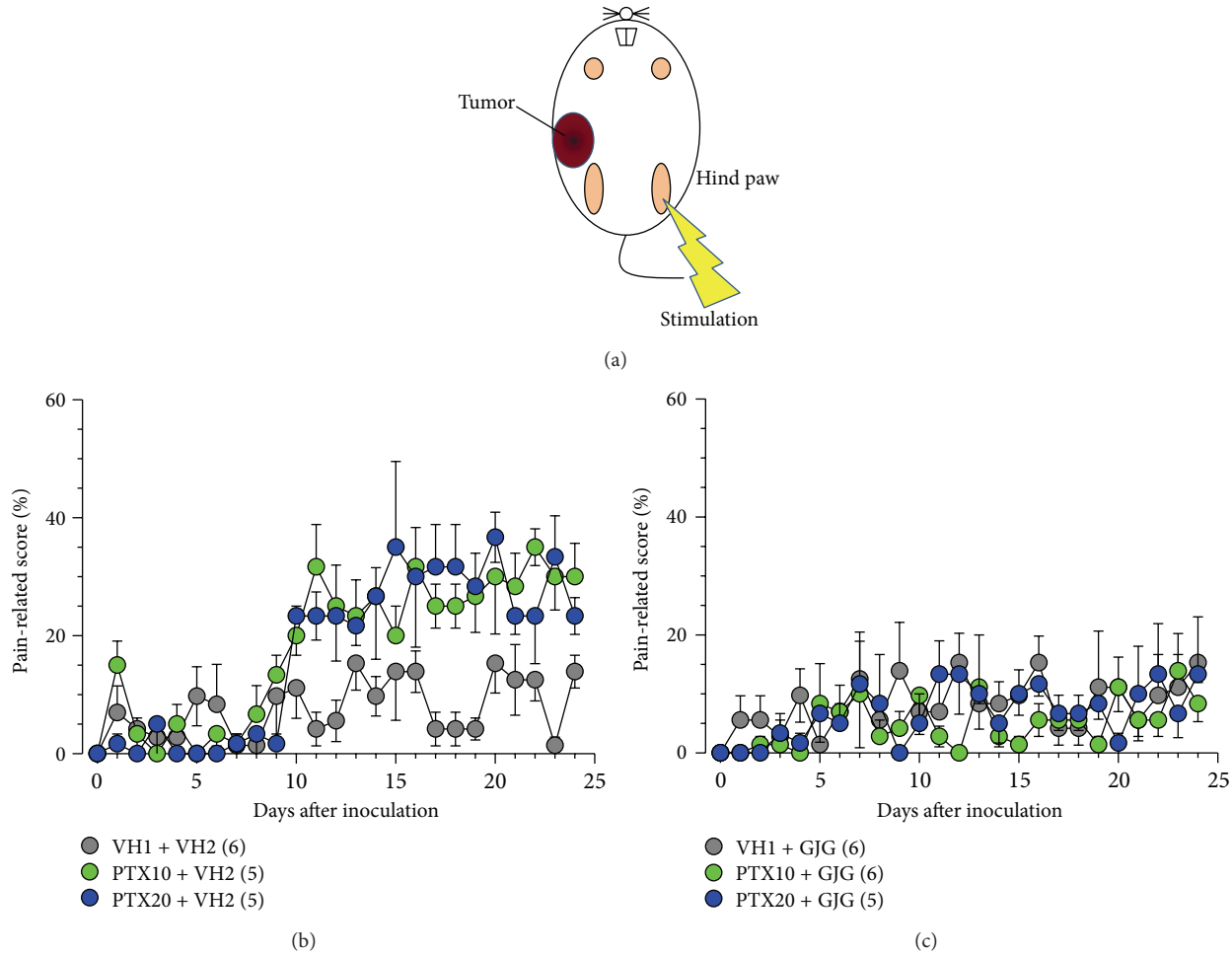

Figure 4: Paclitaxel- (PTX-) induced mechanical allodynia with or without Goshajinkigan (GJG) administration in mice with breast cancer. PTX (10 and 20 mg/kg) and vehicle (VH1) were injected intraperitoneally, and GJG (1 g/kg) and vehicle (VH2) were administered orally, as described in Figure 1 legend. The evaluation of pain-related responses using a von Frey filament was performed before drug administration every day. (a) The site of allodynia evaluation. ((b), (c)) Time-course of allodynia induced by PTX administration (b) with or (c) without GJG administration. Values represent the means ± SEM. Figures in parentheses indicate the number of animals. (b) Main effect of PTX treatment, $F_{2,312} = 8.922$, $P = 0.004$; interaction between PTX treatment and time, $F_{48,312} = 2.505$, $P < 0.001$ (two-way repeated measures ANOVA).

4. Discussion

An inoculation of 4T1 cells into the mammary fat pad increased time dependently the nodule of tumor in the inoculated site in mice. Although not completely, repeated treatment with paclitaxel (10 and 20 mg/kg) significantly inhibited an increase in the tumor volume and the weight of tumor at the end of experiments. Goshajinkigan did not affect the antitumor activity of paclitaxel in mice. Goshajinkigan has also been shown not to interrupt the antitumor action of oxaliplatin on colon cancer cells [12, 16]. Thus, Goshajinkigan may not affect antitumor activity of chemotherapeutic agents.

An inoculation of 4T1 cells induced mechanical allodynia in the tumor-bearing site in mice; allodynia became apparent around day 7 postinoculation and thereafter rapidly increased for several days. Similar time-courses in tumor growth and allodynia in the tumor site were observed after melanoma cell inoculation into the hind paw in mice [21]. Although paclitaxel significantly inhibited the tumor growth, it did not affect the onset and increase of allodynia in the tumor-bearing site. Therefore, this allodynia might not be due to the increase of the tumor volume. In this context, tumor cells have been shown to release algogenic substances [23, 24]. However, it is unknown whether breast cancer cells release algogenic substances [25].

Paclitaxel induces mechanical allodynia in human [7] and in rodents [26]. Although the mechanisms are not completely understood, paclitaxel produces nerve damage by disrupting the action of microtubules necessary for axonal transport [27, 28]. Single administration of paclitaxel induces mechanical allodynia, and the effect peaks 14 days after administration and then gradually decreases [22]. In this study, repeated administration of paclitaxel elicited long-lasting allodynia in the hind paw that did not bear tumor. Repeated administration of chemotherapeutic agents may produce long-lasting

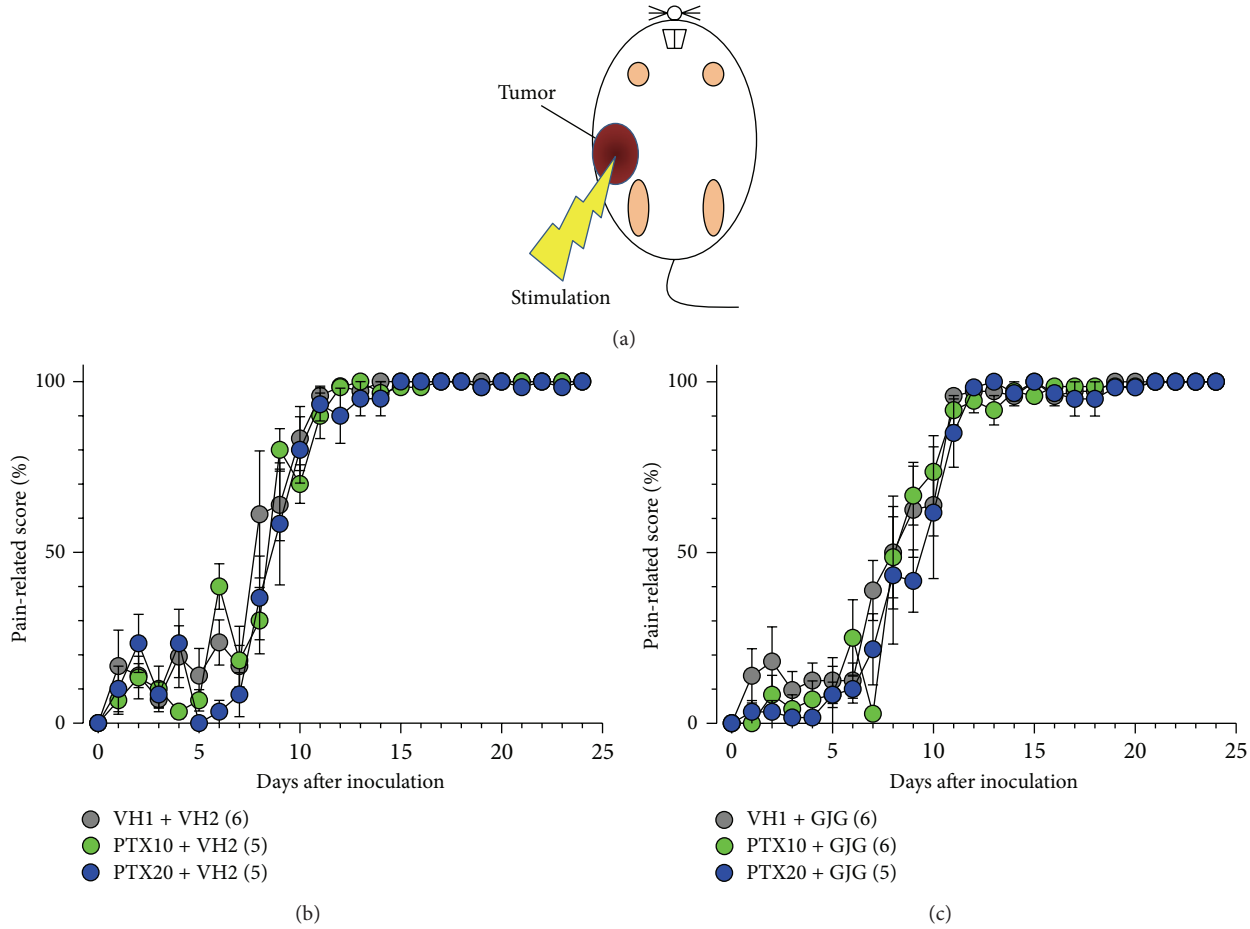

Figure 5: Effects of paclitaxel (PTX) and Goshajinkigan (GJG) on tumor-induced mechanical allodynia in mice with breast cancer. PTX (10 and 20 mg/kg) and vehicle (VH1) were injected intraperitoneally, and GJG (1 g/kg) and vehicle (VH2) were administered orally, as described in Figure 1 legend. The evaluation of pain-related responses using a von Frey filament was performed before drug administration every day. (a) The site of allodynia evaluation. ((b), (c)) Time-course of allodynia induced by tumor with or without PTX and GJG administration. Values represent the means ± SEM. Figures in parentheses indicate the number of animals.

allodynia [26]. Repeated administration of Goshajinkigan markedly prevented paclitaxel-induced mechanical allodynia. The mechanisms of antiallodynic activity of Goshajinkigan are still unknown. There are two conflicting reports that paclitaxel induces axonal degeneration in the sciatic nerve [29] or not [30]. However, Goshajinkigan does not prevent the oxaliplatin-induced axonal degeneration in the rat sciatic nerve, although it inhibits oxaliplatin-induced allodynia [12]. Thus, an antiallodynic activity of Goshajinkigan may not be due to the prevention of axonal degeneration, if any, after paclitaxel administration. Single paclitaxel administration gradually reduces peripheral blood flow, and the prevention of the decrease of the blood flow with limaprost alfadex, an analogue of prostaglandin E1, attenuates paclitaxel-induced mechanical allodynia [22], suggesting the involvement of the decrease of peripheral blood flow in the paclitaxel-induced mechanical allodynia. Goshajinkigan has been shown to increase blood flow and to increase nitric oxide production by activating of NO synthase [31]. Thus, it is conceivable that the improvement of peripheral blood flow is involved in antiallodynic activity of Goshajinkigan. Paclitaxel-induced mechanical allodynia is mediated by reactive oxygen species [32]. The components of Goshajinkigan have antioxidant properties [33, 34]. Thus, it is also conceivable that antioxidant action of Goshajinkigan is involved in the inhibition of paclitaxel-induced allodynia.

5. Conclusion

Goshajinkigan prevented paclitaxel-induced allodynia without affecting the antitumor activity of paclitaxel. Thus, Goshajinkigan may be useful in the prevention of paclitaxel-induced peripheral neuropathy.

Conflict of Interests

The authors state that they have no conflict of interests.

Acknowledgment

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Research Article

Potential Usefulness of the Kampo Medicine *Yokukansan*, Containing *Uncaria* Hook, for Paediatric Emotional and Behavioural Disorders: A Case Series

Yoshiyuki Tanaka[1] and Takeshi Sakiyama[2]

[1] *Comfo Garden Clinic, 3-2 Kawada-cho, Shinjyuku-ku, Tokyo 162-0054, Japan*
[2] *Terutane Yamada Memorial Shibuya Clinic, 2-10-7 Dougenzaka, Shibuya-ku, Tokyo 150-0043, Japan*

Correspondence should be addressed to Yoshiyuki Tanaka; yoshiyuki_tanaka_md@yahoo.co.jp

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Background. Paediatric emotional and behavioural disorders (EBD) are relatively common diseases. Although nonpharmacologic and pharmacologic treatments are utilized in these cases, it is sometimes difficult to manage the symptoms of EBD. Historically, *Uncaria* hook has been used for treating nighttime crying and convulsions in children. Recent clinical studies have demonstrated that the Kampo medicine *Yokukansan* (YKS), which contains *Uncaria* hook, is efficacious for behaviour disorders in Alzheimer's disease patients. Herein, we investigated the clinical efficacy and safety of YKS in a series of cases with paediatric EBD. *Patients and Methods*. We retrospectively reviewed all paediatric patients who sought Japanese Kampo therapy at our outpatient clinics between April 1, 2012, and April 30, 2013; we selected patients who were diagnosed with paediatric EBD and were treated with YKS. *Results*. After screening all candidates, 3 patients were eligible for this analysis. Their average age was 11.6 years (range 10–13 years). All 3 patients responded very well to YKS within 1 month. No drug-related adverse events were observed during the course of YKS treatment. *Conclusion*. *Yokukansan* may be efficacious for paediatric EBD. We believe these results warrant further evaluation of the clinical efficacy and safety of *Yokukansan* for paediatric EBD in a carefully designed, double-blind, randomized clinical study.

1. Introduction

Paediatric emotional and behavioural disorders (EBD) are relatively common diseases. Although there is no clear definition of EBD, attention deficit hyperactivity disorder (ADHD), conduct disorder, and autism are considered to be included in EBD. For example, the incidence of physician-diagnosed ADHD in children aged 5 to 11 years in Southern California was 3.1% in 2010 [1]. In fact, a relationship exists between ADHD and schoolteachers' input, as, in many cases, it is a teacher, not a physician, who diagnoses a student with ADHD. Once diagnosed, nonpharmacologic treatments, such as behavioural modification, and pharmacologic treatments, such as administration of stimulants, are commonly used as standard therapies.

Uncaria hook (UH) is the hook or the hook-bearing stem of *Uncaria rhynchophylla* Miquel, *Uncaria sinensis* Haviland, or *Uncaria macrophylla* Wallich (*Rubiaceae*). This drug has been empirically used for a long time to treat hypertension-related symptoms, such as headache and dizziness, and central nervous system related symptoms, such as seizure and epilepsy. The quality of UH used for therapeutic purposes is strictly defined by the Japanese Pharmacopoeia (JP) [2]. The JP specifies the details regarding UH, in particular, its identification, loss upon drying, total ash, extract content, and assays, including the methods, operating conditions, and system suitability. According to these regulations, UH must contain not less than 0.03% of total alkaloids (rhynchophylline and hirsutine), as calculated on a dried basis. The major indole alkaloids that comprise UH include rhynchophylline, isorhynchophylline, corynoxeine, isocorynoxeine, hirsuteine, hirsutine, and geissoschizine methyl and have been demonstrated to possess vasodilative effects [3, 4]. Geissoschizine methyl ether is a potent serotonin-1A receptor agonist [5–7] and may play an important role in the therapeutic efficacy of UH for various physiological and neurological

disorders. In Japan, one of the most popular Kampo formulas containing UH is *Yokukansan* (YKS). YKS consists of 7 ingredients, namely, *Atractylodis lanceae rhizoma, Poria, Cnidii rhizoma, Radix Angelicae, Radix Bupleuri, Radix Glycrrhizae*, and *Uncaria* hook. Several clinical studies have been conducted regarding the behavioural and psychological symptoms of dementia (BPSD) in patients with dementia [8–11]. A systematic review of these studies showed the beneficial effects of YKS on the Neuropsychiatric Inventory (NPI) and Activity of Daily Living (ADL) scores in patients with dementia [12]. Therefore, many Japanese physicians are now commonly using YKS together with Western medicines such as donepezil and memantine for the treatment of dementia. The first description of YKS is considered to be in the classical Chinese paediatric textbook entitled *Bao-Ying-She-Yao*, written in the 16th century, and YKS was introduced in this textbook for paediatric convulsions, nighttime crying, and insomnia. Some Japanese paediatricians empirically use YKS for paediatric EBD and believe that it may be efficacious for that condition. Hence, we retrospectively investigated a series of patients with paediatric EBD who were treated with YKS.

2. Patients and Methods

2.1. Patients. All paediatric patients who visited our clinics between April 1, 2012, and April 30, 2013, were screened and selected based on following criteria: (a) the diagnosis met the criteria of EBD in ICD-10; (b) the patient continuously used YKS; and (c) the patients were under 18 years of age. Any patient who took Western drugs with YKS was excluded from this investigation. The diagnoses were reevaluated based on information from their mothers and their schoolteachers.

2.2. Evaluation of Efficacy and Safety. We identified 3 patients (2 ADHD cases, ICD-10 F90, and 1 school nonattendance case who had physical symptoms derived from emotional and behaviour factors, ICD-10 F54 and ICD-10 F98) who were consecutively treated with YKS. We assessed the treatment outcomes and safety based on periodic feedback from the patients' mothers and schoolteachers.

2.3. Dose and Regimen. All 3 patients were administered ethical YKS manufactured by Tsumura (TJ-54, Tsumura & Co, Tokyo, Japan), with a starting dose of 5 g per day and a maximum dose of 7.5 g per day. *Shokenchuto* or *ogikenchuto* was also administered with YKS to all 3 patients, as the sweet taste of either kenchuto could increase patient compliance with YKS but would not affect the treatment of paediatric EBD.

3. Results

Only three patients met the criteria during the observation period. The patients' average age was 11.6 years (range, 10–13 years). All 3 patients responded very well to YKS, and the average duration between the YKS prescription start date and the response onset was 16.3 days (range 14–21 days).

Patient 1 was a 13-year-old boy who used to have psychogenic fever. After entering junior high school, he often complained of various symptoms such as abdominal pain and fever prior to going to school. Six months before visiting our clinic, he could not attend any classes. We believed his psychological factors were affecting his physical condition and that his symptoms met the criteria of ICD-10 F54; psychological and behavioural factors that are associated with disorders or diseases are classified elsewhere and are also categorized into ICD-10 F98, other behavioural and emotional disorders, with onset usually occurring in childhood and adolescence. At his first visit to our clinic, he was irritable and restless. Upon physical examination, the patient was thin and had a dark-purplish skin colour around his eyes, a red-purplish tongue, and dilated sublingual veins. His pulse was weak, and he was hypersensitive to touch and had abdominal muscle contractions, as well as subcostal stiffness in his abdomen. YKS and *ogikenchuto* were prescribed. Twenty-one days after starting Kampo treatment, he was able to attend classes 3 days a week; on the 96th day, he had an almost normal school life. The YKS administration was terminated on the 114th day due to the patient's will. No YKS-related adverse reactions were observed throughout the treatment course.

Patient 2 was a 10-year-old boy who was diagnosed with ADHD around the time he entered elementary school. His excessive activity and lack of persistence in cognitively involved activities led to the patient having difficulty attending school, even in a special class. His symptoms met the criteria of ICD-10 F90, hyperkinetic disorder. Although he tried to use stimulants, he discontinued the agents because of drug-induced diarrhoea. His mother brought him to our clinic for Kampo treatment. At his first visit to our clinic, he looked thin and was restless. A rose-pink tongue and dilated sublingual veins were observed. His pulse was weak, and he had hypersensitivity to touch and abdominal muscle contraction, as well as subcostal stiffness in his abdomen. YKS and *shokenchuto* were prescribed. Forty days after beginning YKS, the frequency of his excessive activity was found to have reduced; 57 days later, his behavioural problems had almost disappeared. The patient was still receiving YKS at the time of writing this report. No YKS-related adverse reactions had been observed throughout the treatment course.

Patient 3 was a 12-year-old boy who had excessive activity, lack of persistence in cognitively involved activities, restlessness, and impulsiveness. His behavioural abnormality has been gradually increasing throughout elementary school. Six months prior to visiting our clinic, his teacher recommended that he receive medical intervention to continue school. All his behavioural abnormalities met the criteria of ICD-10 F90, hyperkinetic disorder. His mother wanted him to try the Kampo treatment prior to starting standard therapy, so she brought him to our clinic. At his first visit to our clinic, he was talkative and restless but had normal stature. His pulse was weak. Mild abdominal muscle contraction and subcostal stiffness in his abdomen were observed. YKS and *shokenchuto* were prescribed. Forty days after beginning YKS, the frequency of his excessive activity had reduced; 119 days later, his behavioural problems had almost resolved. The patient was still receiving YKS at the time of writing this report. No YKS-related adverse reaction had been observed throughout his treatment course.

4. Discussion

EBD represent a broad category that is commonly used in educational settings for children and adolescents to group a range of more specific perceived difficulties. Both the general definitions and the concrete diagnosis of EBD may be controversial, as the observed behaviour may depend on many factors. ICD-10 elaborates on the diagnostic criteria for EBD. Patients 2 and 3 met the criteria of EBD in ICD-10. However, the first patient's diagnosis might be considered controversial as to whether his symptoms met the criteria of EBD in ICD-10. He did not have any hyperactivity but did have some anxiety while attending school, and his physical problems appeared to be related to his behavioural and emotional factors. Therefore, we categorized him as having EBD and included him in this investigation.

Based on our literature search, we could not find any predesigned clinical study that included a randomized controlled study with YKS for paediatric EBD. Recently, Miyaoka et al. reported the efficacy and safety of YKS in pervasive developmental disorders and Asperger's disorder by conducting a 12-week prospective, open-label study with 40 subjects aged 8 to 40 years [13]. Interestingly, as this report demonstrated that 36 out of the 40 patients responded to YKS during only a 12-week observation [8], it may be understandable that all of our cases also responded to YKS and showed responses within 1 month. Thus, from a clinical viewpoint, a 1- or 2-month observation period may be enough to judge if a patient may respond to YKS. Moreover, a relatively short observation period may be sufficient to demonstrate the efficacy of YKS if a randomized controlled trial were to be designed.

In Japan, during the 18th century, Dr. Tokaku Wada discovered that YKS was widely applicable for emotional disorders, not only in the paediatric population but also in the adult population. Based on the clinical experiences reported in Japan over the last 300 years, to date, some clinical manifestations have been targeted by Kampo specialists for a YKS prescription. These manifestations are as follows: (a) feeling of anger, irritability, or both; (b) abdominal rectus muscle contraction; (c) pulsation in the upper abdomen; and (d) subcostal stiffness. All of our cases had abdominal rectus muscle contraction and subcostal stiffness. In Japanese Kampo medicine, this set of manifestations is called *sho*, and a Kampo specialist utilizes *sho* to select a particular formulation. However, the process of incorporating *sho* into a study design for a randomized controlled trial would be a significant issue in establishing scientific evidence for the therapeutic efficacy of YKS.

The pharmacological mechanisms of YKS for EBD are still unknown. However, recent basic research showed that YKS acts agonistically on serotonin-1A (5-HT_{1A}) or serotonin-2A (5-HT_{2A}) receptors, dopamine 2 receptors, or both [14]. Furthermore, an in vitro binding study demonstrated that geissoschizine methyl ether, an alkaloid in *Uncaria* hook and a galencial constituent of YKS, binds agonistically to the 5-HT_{1A} and dopamine 2 (D_2) receptors [15]. Because ADHD has been associated with low levels of dopamine and norepinephrine, an increase in the synaptic concentrations of both norepinephrine and dopamine is a key step for the treatment of ADHD, and the dopamine signal can be significantly enhanced with an agonist or a partial agonist of the 5-HT_{1A} autoreceptors [16–19]. Therefore, the therapeutic efficacy and pharmacological mechanism of YKS might involve an increase in the synaptic concentrations of norepinephrine and dopamine.

5. Conclusion

This study provides quite limited evidence for the potential usefulness of YKS due to the limited number of patients. However, considering the excellent safety profile and potential therapeutic benefit of YKS, further investigation, including a carefully designed randomized controlled trial, would be valuable for the treatment of EBD.

Conflict of Interests

All authors declare that there is no conflict of interests for this study.

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Research Article

Effectiveness of Traditional Japanese Herbal (Kampo) Medicine, Daiobotanpito, in Combination with Antibiotic Therapy in the Treatment of Acute Diverticulitis: A Preliminary Study

Keiko Ogawa,[1] Koji Nishijima,[2] Fumio Futagami,[2] Takashi Nakamura,[2] and Genichi Nishimura[2]

[1] *Clinic of Japanese-Oriental (Kampo) Medicine, Department of Otorhinolaryngology & Head and Neck Surgery, Kanazawa University Hospital, 13-1 Takaramachi, Kanazawa, Ishikawa 920-8641, Japan*
[2] *Department of Surgery, Japanese Red Cross Kanazawa Hospital, Mima 2-251, Kanazawa 921-8162, Japan*

Correspondence should be addressed to Keiko Ogawa; ikkandoo@gmail.com

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In traditional Japanese herbal (Kampo) medicine, daiobotanpito (DBT) or Da Huang Mu Dan Tang in Chinese has been used in medical treatment of acute diverticulitis for many years based on the experience. Our aim was to investigate whether the treatment of acute diverticulitis can be treated with intravenous antibiotics plus orally administrated DBT than intravenous antibiotics alone. A retrospective nonrandomized open-label trial was established to compare patients with acute diverticulitis who received oral DBT associated with intravenous antibiotics with those who received intravenous antibiotic alone. We included 34 patients, eleven patients in group 1 with DBT and 23 patients in group 2 without DBT. Both groups were comparable in patient demographics and clinical characteristics. There was a significantly better outcome in the group treated with DBT than in the group without DBT when comparing duration of fever, abdominal pain, and antibiotics administration. A trend toward a day shorter mean hospital stay and fasting was seen in group 1, although this did not reach statistical significance. In conclusion, most patients with acute diverticulitis can be managed safely with oral DBT. Although randomized, double-blind study must be done, we could show the possibility to use daiobotanpito as an additional option in treating acute diverticulitis.

1. Introduction

The prevalence of diverticular disease is estimated to range between 20% and 60% in the general population [1, 2]. The most frequent complication of diverticular disease is acute diverticulitis. Although 75% of patients with diverticulosis remain symptom-free during their lifetime, the prevalence of patients that require medical or surgical treatment has increased 16% in the last 20 years, consequently increasing morbidity [3–5].

According to the guideline of the American Society of Colon and Rectal Surgeons [6], the initial treatment of uncomplicated colonic acute diverticulitis is bowel rest and broad-spectrum antibiotics. Patients who do not respond to medical therapy should be considered for surgery depending on the clinical situation. Selected abscess detected on abdominal ultrasound may be drained percutaneously. Elective resection is recommended after two well-documented attacks, depending on age, medical fitness of the patient, and severity of the attack. Complicated diverticulitis is diverticulitis associated with obstruction, stricture, fistula, or abscess. In cases of perforated diverticulitis, after a careful selection of patients, the technique of choice should be resection with primary anastomosis.

The unique role played by traditional Japanese herbal (Kampo) medicine is gradually attracting worldwide attention. In Kampo medicine, daiobotanpito (DBT; Da-Huang-Mu-Dan-Tang) is used in relatively strong patients with Yang

excess in the interior layers of the body with signs of local Qi congestion and blood stasis (Oketsu). Traditionally, it has thus been used for abscesses of the intestine, such as diverticulitis or appendicitis. From the view of Kampo medicine, DBT drains heat, breaks up blood stasis, disperses clumping, and reduces swelling. It is especially used in relatively strong patients with abdominal distention and constipation. Daiobotanpito consists of five crude drugs: *Rhei Rhizoma*, *Natrium sulfuricum*, *Moutan Cortex*, *Persicae Semen*, and *Benincasae Semen*. For example, *Rhei Radix et Rhizoma* and *Moutan Cortex* drain heat and dispel blood stasis. They are attributed to heat and constraint that allows the formation of toxins which secondarily leads to the formation of pus. The appropriate strategy of Kampo medicine is to discharge the toxin, eliminate the phlegm, clear the heat, and open the restraint [7].

As described above, surgery should be performed in patients who do not respond to medical therapy in difficult or complicated clinical situation. DBT may be an alternative or supportive therapy in acute diverticulitis to avoid surgical treatment. Even though DBT is traditionally used for diverticulitis, no clinical reports or trials have been published in the English literature.

The authors hypothesize that additional oral DBT is superior to the standard therapy in acute diverticulitis. This paper aims to investigate the effectiveness of the treatment of acute colonic diverticulitis with Kampo medicine, DBT.

2. Patients and Methods

2.1. Patients. Between April and November 2012, standard treatment was offered to 34 patients who were diagnosed to have acute diverticulitis by surgeons in the Japanese Red Cross Kanazawa Hospital.

Diagnosis was based on the image of computed tomography (CT), diverticula-like structure in accordance with tenderness or abdominal pain, a thickening of colon wall, signs of inflammation of the pericolonic fat, the tissue density, and vascular involvement. Pericolonic abscess, free air or extravasation, and accumulation of fluid were also noticed to predict prognosis. The standard treatment for acute uncomplicated diverticulitis is bowel rest (fasting), intravenous fluids, and intravenous antibiotics. Antibiotics were continued until CRP becomes negative.

Eleven of 34 patients agreed to add Kampo treatment, DBT. We used daiobotanpito extract which consists of five crude drugs in fixed proportions: *Rhei Rhizoma* (2.0 g), *Natrium sulfuricum* (1.8 g), *Moutan Cortex* (4.0 g), *Persicae Semen* (4.0 g), and *Benincasae Semen* (6.0 g), in 7.5 g of extract. We excluded 4 patients who received an operation from the last analysis. Therefore, we evaluated ten patients treated with DBT and 20 patients treated with only antibiotics. We checked the patients' background (age, sex, and location, etc.) (Table 1) to demonstrate that both groups were almost homogenous. Although there were significant differences in number of episodes of diverticulitis and previous diverticulitis, there was no significant difference in other factors.

Table 1: Characteristic of patients.

	Group 1 ($n = 11$)	Group 2 ($n = 23$)	P value
Age (mean)	25–77 (43.5)	25–79 (45.8)	0.34[a]
Sex (male/female)	1/10	5/18	0.365[b]
CRP	6.18	6.49	0.451[a]
WBC	10740	11408	0.266[a]
Previous diverticulitis	4 (36.3%)	1 (4.3%)	0.0137[b]
Number episodes of diverticulitis	0.45 (0–3)	0.043 (0-1)	0.00494[a]
Lesion (right/left)	9/2	19/4	0.955[b]
Operation	1 (9.1%)	3 (13.0%)	0.827[b]
BMI	21.6	23.3	0.082[b]

[a]Student's t-test.
[b]Fisher's exact test.

2.2. Study Design. An open-label nonrandomized retrospective controlled trial was designed to investigate the efficacy of the standard therapy versus the standard therapy plus DBT for acute diverticulitis. The study protocol was designed in accordance with the ethical principles in the Declaration of Helsinki and regional regulations.

No restrictions were imposed on the standard treatments for acute diverticulitis or any other disease, while DBT was administered. If the clinical evolution was right, a regular diet was initiated, and the patient was discharged and was controlled as an outpatient a week later.

There were two treatment groups. (1) "DBT group" (group 1) patients began antibiotics and DBT administration within 24 h after admission when their symptoms improved and CRP became negative. After obtaining informed consent, DBT extract (Tsumura, Tokyo, Japan) at 2.5 g was administered three times a day, 7.5 g per day. (2) The "Without DBT group" (group 2) patients only received antibiotics intravenously.

Clinical improvement was defined as pain decrease, absence of abdominal pain or tenderness, absence of fever, and negative CRP.

The endpoint of the study was duration of fever, abdominal pain, antibiotics administration, days of initiation of regular diet, and days of hospital stay.

2.3. Statistical Analysis. The data were analyzed using Excel; 2010. Analysis was restricted to patients with diverticulitis. Continuous variables were analyzed with Student's t-test examining the endpoints febrile days, days with abdominal pain, days of hospital stay, days of antibiotic administration, and days to initiation of regular diet. A P value of less than 0.05 was considered statistically significant.

3. Results

Of the 34 patients, four were excluded because of the operation. Clinical data were thus investigated for 31 patients, 10 from group 1 and 20 from group 2. There were no adverse effects of DBT in group 1.

Both groups were comparable in patient demographics and clinical characteristics. Considering all the patients, 5 (14.7%) had suffered previous episodes of diverticulitis (mean of episodes 1.4). Data on both groups are shown in Table 1. Temperature on admission was below 38°C in 20 patients (58.8%).

In all cases, CT scan showed bowel wall thickness with different degrees of pericolic fat infiltration and the presence of diverticula. The two groups were comparable with respect to age, sex, previous diagnosis of diverticulosis, previous episodes of diverticulitis, duration of symptoms before admission, and CRP/WBC at admission (Table 1).

All patients in group 1 except two were discharged before day 9 of admission, and all patients in group 2 were discharged before day 15. Data of clinical evolution of both groups are shown in Table 2.

There was a significantly better outcome in the groups treated with DBT than in the group without DBT when comparing for duration of fever, abdominal pain, and antibiotics administration. A trend toward a day shorter mean hospital stay and fasting was seen in group 1, although this did not reach statistical significance.

There was no adverse effect with antibiotics and DBT in both groups. There was complete resolution of symptoms in both groups.

Table 2: Clinical evolution during admission.

Days	Group 1 ($n = 10$)	Group 2 ($n = 20$)	P
Start of oral diet	5.1	6.1	0.055
Antibiotic therapy	5.1	7.0	<0.05
Hospital stay	7.6	9.0	0.061
Abdominal pain	4.8	5.8	<0.05
Febrile	2.3	3.4	<0.05

4. Discussion

The main reason that led us to propose this study was the necessity to prove the real effect of DBT in acute diverticulitis.

In this study, we showed the significantly better differences in the groups treated with DBT combined with antibiotics than in the group without DBT when comparing for duration of fever, abdominal pain, antibiotics administration, and days of initiation of regular diet. A trend toward a day shorter mean hospital stay and fasting was seen in group 1, although this did not reach statistical significance. Although there were more patients with episodes of recurrent diverticulitis in group 1 than in group 2, there were some advantages in the standard therapy plus DBT, which may improve patients' quality of life (QOL). Operation might be prevented, even in cases with recurrent diverticulitis. This also implies an economical advantage.

Diverticula can occur at any sites in the colon; however, due to the thickened consistency of the stools, diverticulitis mostly occurs in the sigmoid colon. The standard treatment for acute uncomplicated diverticulitis has been bowel rest (fasting), intravenous fluids, and intravenous antibiotics. Case-by-case therapy is initiated by the attending surgeon, so there was a diversity of the antibiotics such as ceftriaxone, flomoxef, sulbactam, cefmetazole, and doripenem, used for patients in this study. This is caused by variability in the use of antibiotics in clinical practice among centers in the management of acute diverticulitis particularly relating to the selection of antibiotic. Additionally, while there are a lot of trials focused on surgical treatment, there are very few studies dedicated to medical treatment of acute diverticulitis. A review of the published data confirmed the impression that there is no standardization in the medical treatment of uncomplicated acute diverticulitis [8]. In the next research, randomization and unified antibiotic regimen would be necessary to investigate the effect of DBT. Treatment with DBT is perhaps to be considered as an effective option for the treatment of acute uncomplicated colonic diverticulitis. Also the findings indicate that this treatment may be suitable both for first occurrence and, importantly, for recurrent occurrences of the disease although we could not find clinical report even from the Japanese literature.

In Kampo medicine, internal abscesses generally mean abscesses of the lungs and intestines. Similar to external abscesses, they are attributed to heat and constraint that allows the formation of toxins. This secondarily leads to the formation of pus. The appropriate strategy is to discharge the toxin, eliminate the phlegm, clear the heat, and open the constraint. If there is also clumping of heat with stasis and stagnation, herbs such as *Rhei Radix et Rhizoma* (Da Huang 大黄) and *Moutan Cortex* (Mu Dan Pi 牡丹皮) can be added to drain heat and dispel stasis [7]. In this concept, DBT is one of the most suitable formulas for treatment of acute diverticulitis.

DBT might have preventive effects on the recurrence of diverticulitis, although prognosis of patients was not investigated in this study.

Most herbal medicines are orally administrated, and most components of these medicines are inevitably brought into contact with the intestinal microflora in the alimentary tract. Some are transformed by the intestinal bacteria before their absorption from the gastrointestinal tract [9]. Although administration of intravenous antibiotics may influence the intestinal microflora and the effect of DBT might be changed compared with classical therapy, this study showed the possibility to use both intravenous antibiotics and DBT at the same time.

Daiokanzoto (DKT), a Kampo medicine that includes the combination of two crude drugs, rhubarb and glycyrrhizae, is clinically effective for constipation. The combination of two crude drugs, rhubarb and glycyrrhize radix, are also contained in DBT. Matusi et al. showed the influence of glycyrrhizae radix and antibiotics on the purgative action of sennoside A of rhubarb from DKT in mice [10]. The purgative actions of rhubarb and sennoside A were significantly intensified when glycyrrhizae radix was coadministered orally to mice. On the other hand, the purgative action of sennoside A was significantly reduced by the preadministration of minocycline (tetracyclin antibiotics), whereas that of DKT was not affected. Other crude drugs such as glycyrrhizae radix may have the ability to recover the action of other drugs

suppressed by antibiotics via an unknown mechanism. This is the advantage of complexity of Kampo medicine.

DBT consists of five crude drugs: *Rhei Rhizoma*, *Natrium sulfuricum, Moutan Cortex, Persicae Semen,* and *Benincasae Semen*. Of these, *Rhei Rhizoma* or *rhubarb* are one of the most important traditional herbal medicines widely used in Kampo and traditional Chinese medicines for thousands of years, especially as a purgative. It might prevent bowel retention, overgrowth of toxic bacteria in patients with acute diverticulitis, and result in resolution of acute inflammation.

Studies on other functions of rhubarb in modern medical research both in clinical and basic science settings have revealed that rhubarb has multiple effects including defervescence, anti-inflammatory actions, and especially expelling a variety of harmful materials such as endogenous as well as exogenous toxins from the bowel and the body.

It is shown that rhubarb protects against acute lung injury induced by LPS and that rhubarb administration improves respiratory function of the body. Its effect is related to the regulation of the production of nitric oxide as well as phospholipase A and platelet-activating factor activities [11]. These effects may be related to the improvement of inflammation in diverticulitis.

As for *Moutan Cortex (MC)*, the root cortex of *Paeonia suffruticosa*, is a herbal medicine widely used as an analgesic, an antispasmodic, and an anti-inflammatory agent. *Moutan Cortex* is reported to inhibit the secretions of interleukin- (IL-) 8, a major mediator of acute neutrophil-mediated inflammation, and macrophage chemoattractant protein- (MCP-) 1, a potent mediator of chronic macrophage-mediated inflammation in human monocytic U937 cells [12]. Recently, MC was shown to protect against sepsis induced by lipopolysaccharide/D-galactosamine [13]. The known chemical components of MC include paeonol, paeonoside, paeonolide, paeoniflorin, benzoylpaeoniflorin, oxypaeoniflorin, benzoyloxypaeoniflorin, and apiopaeonoside.

MC inhibited the LPS/r lFN-γ-induced expression of inducible nitric oxide synthase (iNOS) and TNF-α release. The LPS/r lFN-γ-induced activation of NF-κB was almost completely blocked by MC [13].

Persicae Semen or *Prunus persica* is also well known as a traditional medicine in Japan, China, and other Asian countries. They are frequently used as an ingredient in a variety of Kampo and Chinese medicine formula, particularly those used to treat women's diseases. The chemical constituents of the herb include the cyanogenic glycosides, amygdalin, and prunasin as major components, along with glycerides, sterols, and emulsion. Amygdalin is also abundant in the seeds of bitter almond and apricots of the *Prunus* genus and other rosaceous plants. *Persicae Semen* have antiedema, antiwrithing, and anti-inflammation activities.

Each of these crude drugs has some anti-inflammatory effects, and the combination of these crude drugs may produce the synergy of Kampo medicine.

5. Conclusion

Most patients with acute diverticulitis could be managed safely with intravenous antibiotics plus oral DBT. Although randomized, double-blind study must be done, the patients benefit from the use of DBT as an additional option in the treatment of acute diverticulitis. Prognosis has to be investigated in the next study.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Research Article

Kampo Diagnostic Procedure, *Fuku shin*, Could Be a Useful Diagnostic Tool for Psychopathological Patients Suffering from Chronic Pain

Young-Chang P. Arai, Makoto Nishihara, Shinsuke Inoue, and Izumi Makino

Multidisciplinary Pain Center, Aichi Medical University, 21 Karimata Nagakutecho, Aichigun, Aichi 480-1195, Japan

Correspondence should be addressed to Young-Chang P. Arai; arainon@aichi-med-u.ac.jp

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Kampo, or traditional Japanese herbal medicine, has been used for clinical practice in Japan. The most appropriate *Kampo formula* should be chosen for each individual based on specific diagnostic procedures. *Fuku shin*, the abdominal exam, is one of the most important diagnostic procedures. There are several *Fukusho*s (abdominal conformations). Depression and anxiety have been shown to be related to *Shin ka hi koh*, epigastric obstructive hardness, and neuroses have an association with *Kyoh kyoh ku man*, hypochondriac distress. The aim of our study was to compare *Fukusho*s at each level of depression and anxiety symptoms and to assess the associations between occurrence and pain catastrophizing. Two hundred and twenty-nine patients were assigned to high-, moderate-, or low-level anxiety-depression groups based on the hospital anxiety and depression scale and were investigated for occurrence of major *Fukusho*s. Moreover, the associations between occurrence and the pain catastrophizing scale (PCS) were analyzed. The moderate and high anxiety-depression groups showed a higher occurrence of *Shin ka hi koh* [low, 29%; moderate, 51%; high, 67%] ($P < 0.0001$). In contrast, the relationship between the occurrence of *Kyoh kyoh ku man* and the PCS showed a significant albeit small correlation ($r_s = 0.1296$, $n = 229$, $P = 0.0491$).

1. Introduction

Kampo, or traditional Japanese herbal medicine based on traditional Chinese herbal medicine, has been used for the treatment of chronic pain in Japan [1–3]. Traditional Chinese medicine and *Kampo* developed a characteristic system [1–3]. There are essentially three dichotomies and three substance concepts in the system. The three dichotomies are Yin-You (ying-yang), Kyo-Jitsu, and Netsu-Kan. In English, they could be translated as positive-negative, hollow-full, and hot-cold, respectively. The three substance categories are Ki (Qi), Ketsu and Sui. Ki (Qi) is energy fundamental to living things. In contrast to the Ki (Qi) concept, Ketsu, and Sui are material and much closer to the usual concepts of blood and body fluids, respectively. In *Kampo*, the healthy state of human beings means a well-balanced or undeviated condition of the three dichotomies and the three substance concepts. Disease due to deviation or imbalance is assessed by four specific diagnostic procedures. According to *Kampo theory*, the most appropriate *Kampo formula* should be chosen for each individual based on four diagnostic procedures [1–4]. *Fuku shin*, the abdominal exam, is unique to Japan and is one of the most important approaches of the four diagnostic procedures in *Kampo* [2, 3, 5]. There are several *Fukusho*s (abdominal conformations) when administering *Fuku shin*. There are four major *Fukusho*s: *Shin ka hi koh*, epigastric obstructive hardness; *Kyoh kyoh ku man*, hypochondriac distress and fullness; *Ri kyuh*, inside spasm (rectus muscle tension); *Sho fuku koh man*, lower-abdomen hardness and fullness [2, 3]. In *Kampo*, depression and anxiety have been shown to be related to *Shin ka hi koh*, epigastric obstructive hardness, and neuroses have an association with *Kyoh kyoh ku man*, hypochondriac distress [2, 3].

Recent studies have shown the role of psychological variables on patients' pain experience and quality of life. Catastrophizing, anxiety, and depression are major factors

[6]. However, one of the important issues for clinicians is the choice of screening tool. The hospital anxiety and depression scale (HADS) has been used in a number of studies [6]. The HADS was designed to assess two separate dimensions of anxiety and depression. The HADS consists of 14 items; the anxiety (HADS-A) and depression (HADS-D) subscales each include 7 items [6, 7]. A 4-point response scale (from 0 representing absence of symptoms to 3 representing maximum symptoms) is used, with possible scores for each subscale ranging from 0 to 21. Moreover, catastrophizing has been assessed by the pain catastrophizing scale (PCS) [8–10]. The PCS is a 13-item scale that assesses three types of negative thinking styles related to pain. Subjects are asked to reflect on past painful experiences and indicate on a 5-point scale ranging from 0 ("not at all") to 4 ("always") the degree to which they experienced each of the 13 thoughts or feelings when in pain [8–10].

We hypothesized that *Shin ka hi koh*, epigastric obstructive hardness, and *Kyoh kyoh ku man*, hypochondriac distress, are signs of psychiatric comorbidity. We thus compared the occurrence of four major *Fukusho*s at each level of depression and anxiety symptoms to assess the associations between occurrence and level of depression-anxiety symptoms or pain catastrophizing.

2. Methods

Retrospective analysis from April 2011 to November 2012 was performed on 842 patients suffering from chronic pain who visited the pain center of Aichi Medical University Hospital. All patients were referred from other hospitals to the pain center. Patients who underwent *Kampo diagnosis* for *Kampo formula* were included.

The HADS and the PCS are routinely administered to all patients on admission to the pain center. The existing translation of the Japanese version of HADS and PCS [7, 11] is used in our daily clinical practice. The HADS, the PCS, and the abdominal exam records of *Kampo diagnosis* from April 2011 to November 2012 were extracted from medical records for the present study, after receiving approval from the Ethics Committee of Aichi Medical University. Consequently, 229 subjects were included in the present study.

In the abdominal exam records, we focused on and investigated the occurrence of only four major *Fukusho*s out of a wider group of documented abdominal findings: *Shin ka hi koh*, epigastric obstructive hardness; *Kyoh kyoh ku man*, hypochondriac distress and fullness; *Ri kyuh*, inside spasm (rectus muscle tension); *Sho fuku koh man*, lower-abdomen hardness and fullness [2, 3].

Shin ka hi koh, epigastric obstructive hardness: patients report that their epigastrium feels "stuffed," and upon palpation by the physician, tightness and resistance are detected.

Kyoh kyoh ku man, hypochondriac distress: there is a feeling of fullness in the hypochondrium, as well as distress and pain. It can be verified objectively as resistance and pressure pain.

Ri kyuh, inside spasm (rectus muscle tension): upon palpation by the physician, a spasm is detected, which feels like a sudden jerk or contraction beneath the surface of the abdomen.

Sho fuku koh man, lower-abdomen hardness and fullness: the lower abdomen is inflated and shows resistance as well.

The patients were assigned to high-, moderate-, or low-level anxiety-depression groups based on the subscales of the HADS [12, 13]. To be in the high group, scores had to be high on both the depression and anxiety subscales (i.e., at least 9 on each, HADS total score ≥18). To be in the low group, scores had to be low on both subscales (total score ≤12), and the moderate group included all others not meeting high or low criteria.

Values are numbers or median [range]. Patient's characteristics were compared using one-way ANOVA followed by Tukey's test or chi-square test. The occurrence of each *Fukusho* was analyzed using chi-square test. Associations between the occurrence of each *Fukusho* and the level of depression-anxiety symptoms or pain catastrophizing were analyzed using Spearman's rank correlation coefficient (r_s). A P value of < 0.05 was considered significant.

Table 1: Patient's characteristics.

	Low	Moderate	High	P
Sex (M/F)	20/50	18/62	24/55	0.5070
Age (years)	61 [15–86]	53 [13–86]	49 [23–86]	0.5301
Weight (kg)	52 [34–82]	52.5 [32–82]	51 [38–92]	0.2581

Values are numbers or median [range]. There were no significant differences.

3. Results

Patient's characteristics are presented in Table 1. Seventy of the patients were in the low psychopathology group, 80 in the moderate psychopathology group, and 79 in the high psychopathology group. There were no significant differences between the patients' characteristics among the three groups. The occurrence of *Shin ka hi koh* was higher in the moderate and high anxiety-depression groups than in the low anxiety-depression group [low, 29%; moderate, 51%; high, 67%] ($P < 0.0001$) (Table 2). There were no significant differences in the occurrence of *Kyoh kyoh ku man, Ri kyuh*, and *Sho fuku koh man* among the three groups. Moreover, the relationship between the occurrence of *Shin ka hi koh* and level of depression and anxiety symptoms showed a significant and positive albeit small correlation ($r_s = 0.3086$, $n = 229$, $P < 0.0001$). In contrast, the relationship between the occurrence of *Kyoh kyoh ku man* and the PCS showed a significant and positive albeit small correlation ($r_s = 0.1296$, $n = 229$, $P = 0.0491$) (Table 3).

4. Discussion

The main findings of the present study are that while the moderate and high anxiety-depression groups showed a higher occurrence of *Shin ka hi koh*, epigastric obstructive hardness, the relationship between the occurrence of *Kyoh kyoh ku man* and the pain catastrophizing scale (PCS) showed a significant and positive albeit small correlation, based on

Table 2: Occurrence of each abdominal conformation.

	Low	Moderate	High	P
Shin ka hi koh (+/−)	20/50 (29%)	41/39 (51%)*	53/26 (67%)*	<0.0001
Kyoh kyoh ku man (+/−)	20/50 (29%)	27/53 (34%)	26/53 (33%)	0.3764
Ri kyuh (+/−)	22/48 (31%)	17/63 (21%)	34/45 (29%)	0.0921
Sho fuku koh man (+/−)	41/29 (59%)	37/43 (46%)	42/37 (53%)	0.7934

Values are numbers. *Significantly different from low group.

Table 3: Associations between the occurrence of each abdominal conformation and the pain catastrophizing scale (Spearman's rank correlation coefficient (r_s)).

	Shin ka hi koh	*Kyoh kyoh ku man*	*Ri kyuh*	*Sho fuku koh man*
r_s	0.09387	0.1296	0.06221	0.02733
P	0.1568	**0.0491**	0.3487	0.6807

one type of *Kampo diagnosis*, *Fuku shin* (the abdominal exam).

Recent studies have shown the role of psychological variables on patients' pain experiences and quality of life. Catastrophizing, anxiety, and depression are major factors [6]. The HADS was originally designed to assess two separate dimensions of anxiety and depression [6, 7]. As a brief screening tool, the HADS scale has increased in popularity. A review article concludes that the HADS performs well in screening for cases of anxiety disorders and depression in patients from nonpsychiatric hospital clinics [14]. Catastrophizing has been assessed by PCS [8–10]. Pain catastrophizing is an exaggerated, negative focus on pain and related to various indices of psychological distress. However, we have to keep in mind that such tests are by no means sophisticated or rigorous enough to establish anything other than a relatively superficial psychiatric diagnosis. We thus need further studies.

There are the four diagnostic procedures that make up what is called in *Kampo* the four exams by which *Kampo formula* is prescribed for each individual [1–4]. One is called *Setsu shin*, the tactile exam, which consists of *Fuku shin*, the abdominal exam, and *Myaku shin*, the pulse exam. In *Kampo*, sensations from the outside rule the pulse and internal damages govern the abdomen [1, 2]. This means that diagnosis of exogenous agent-induced disease such as acute febrile disease depends on the pulse, while the progress of chronic illness is taken to be endogenously induced and the diagnosis should be made in accordance with abdominal signs. That is, chronic illness is induced by mental factors to such an extent and an abdominal sign could indicate psychiatric illness.

Fuku shin is the component of examination based on *Kampo* abdominal palpation. Physicians have the patient lie on his or her back with both legs extended. The physicians stand on the side of the patients, examine with the hands, and stroke from the chest to the abdomen to determine whether the abdominal wall is thick or thin and to sense the abdominal wall condition [2, 3]. *Fuku shin* contributes to the classification of pathology on a theoretical level, and furthermore it is first and foremost a practical, treatment-oriented diagnosis method.

When *Fukusho*, *Shin ka hi koh* (epigastric obstructive hardness), is present, the most commonly used recipes are specific *Kampo formulas*, *Hangekohbokutoh*, and *Kohsosan*. When *Kyoh kyoh ku man* (hypochondriac distress and fullness) is present, we prescribe *Shosaikotoh*, *Daisaikotoh*, and *Kamishoyousan*. These formulas can treat psychiatric illness [1–3]. In fact, when these *Fukusho*s were present, we prescribed these formulas for the patients. Furthermore, the present study showed that moderate and high anxiety-depression patients had *Shin ka hi koh* and there was a significant association between the occurrence of *Kyoh kyoh ku man* and the PCS. We thus postulate that *Fuku shin*, the abdominal exam, could be a diagnostic tool for psychiatric illness.

In conclusion, moderate and high anxiety-depression patients displayed a higher occurrence of the abdominal sign, *Shin ka hi koh* (epigastric obstructive hardness), and there was a significant association between the occurrence of *Kyoh kyoh ku man* and PCS.

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