Original Article

Efficacy of Kampo Formula Tokishigyakukagoshuyushokkyoto for Cold Syndrome Evaluated with a Novel Clinical Method using a Patient-based Questionnaire Database

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患者自身による自覚症状の評価システムを用いた 冷え症に対する当帰四逆加呉茱萸生薑湯の有効性について

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Abstract

Objectives : Persistent coldness is a common complaint for which Kampo, traditional Japanese herbal medicine, is often tried, because there is no definition or objective measure of subjective coldness in Western medicine. The aim of this study was to evaluate the efficacy of a common Kampo agent, tokishigyakukagoshuyushokkyoto, and to identify key symptoms that would predict positive treatment outcomes for coldness.

Design : A retrospective cohort study.

Setting : 181 patients who complained of coldness without any organic abnormalities self-surveyed their health using a Kampo questionnaire database system on their first visit. Another 28 patients were assigned to verify the discriminatory predictability of treatment efficacy.

Interventions : Patients were treated with extract product, 7.5 grams a day for a month.

Outcome measures : Treatment efficacy as a binary response.

Results : Frequency and severity scales (0 to 4) for coldness decreased from 3.2 ± 0.7 to 2.1 ± 0.1 ($p < 0.01$) and from 3.1 ± 0.7 to 2.2 ± 0.9 ($p < 0.01$), respectively. Improvements in both frequency and severity of coldness were observed in 74.0% of patients. The status of tenderness in the iliac region, without upset stomach or depression, was obtained as an appropriate model for the prediction of treatment effect, and its discriminatory predictability was calculated as 84.4%. The predictive accuracy of the model was validated with 82.1% for the 28 new patients.

Conclusions : Coldness susceptible to tokishigyakukagoshuyushokkyoto was very frequently accompanied by tenderness in iliac region, without upset stomach or depression.

Key words : cold syndrome/coldness, tokishigyakukagoshuyushokkyoto, tenderness in the iliac region, upset stomach, depression

要旨

目的：当帰四逆加呉茱萸生薑湯が有効な冷え症のタイプを検討した。

研究デザイン：後ろ向きコホート研究。

対象：冷え症患者181名を対象とし、初診時に自覚症状をデータベースに登録した。さらに、外的妥当性を新規28名で評価した。

介入：エキス顆粒7.5 g/日服用1ヵ月後に評価。

評価項目：治療効果の有無。

結果：冷えは74%の患者で改善し、頻度および程度（0－4）は各々 3.2 ± 0.7 から 2.1 ± 0.1 ($p < 0.01$)、 3.1 ± 0.7 から 2.2 ± 0.9 ($p < 0.01$)に減少した。治療効果予測の最適モデルとして、胃もたれおよび抑うつを伴わない腸骨窩圧痛の有無が選ばれ、判別予測率は84.4%であった。このモデルを別の28名の患者で検証したところ、予

測精度は82.1%であった。

結論：胃もたれや抑うつ感がみられず、腹診にて腸骨窩圧痛が認められる冷えの患者で、当帰四逆加呉茱萸生姜湯が有効である可能性が示唆された。

キーワード：冷え症、当帰四逆加呉茱萸生姜湯、腸骨窩圧痛、胃もたれ、抑うつ

Introduction

We often encounter patients complaining of persistent and intolerable “coldness” (chilly sensation) in their bodies, fingertips and toes in a heated room in winter, or in an air-conditioned room even in summer. This unusual feeling of coldness, which is more often observed in women than in men, is called “hi-e-sho” (cold syndrome) in Japanese¹⁾. Cold syndrome has been believed to exist in many traditional medical theories in Korea, Iran, Greece, Arabia, Rome, India, etc²⁾³⁾. However, there is no definition of subjective coldness in Western medicine, and therefore it is not even recognized as a symptom or disease to be treated.

The lack of an objective outcome measure has prevented Kampo from being accepted as a global standard and an alternative for medical practitioners in the West. We have developed a computer-aided Kampo database referred to as Tokyo Women’s Medical University Oriental Medicine Research Active Support System (TOMRASS), which accumulates patient-based evaluations covering a wide range of complaints, symptoms, and conditions^{4)~6)}.

We applied the TOMRASS database in order to evaluate the efficacy of a common Kampo agent, tokishigyakukagoshuyushokyoto in patients with cold syndrome. We believe this approach may provide a new paradigm that will allow Kampo medicine to be integrated into Western medicine.

Subjects and methods

Patient eligibility

Subjects were 181 Japanese patients attending Tokyo Women’s Medical University Institute of Oriental Medicine (9 males and 172 females, mean age 43 years, age range 17-79 years) who complained of coldness without any apparent organic abnormalities at their first medical examination between September 2006 and September 2010. They were diagnosed as exhibiting eligible Sho, which can be translated into English as symptoms, signs, evidence or constitution, to be treated with the granulated extract product of tokishigyakukagoshuyushokyoto (Kracie Holdings, Ltd., Tokyo or Tsumura & Co., Tokyo), 7.5 grams a day for a month.

The aim of logistic regression is to correctly pre-

dict an outcome for individual cases without Kampo diagnosis. To verify the predictability using a model for the efficacy of treatment of coldness with tokishigyakukagoshuyushokyoto, additional 28 patients with coldness in the extremities at their first visit between October 2010 and April 2011 (one male and 27 females, mean age 42 years, age range 25-75 years) were selected for assessing an external validity. Sho was not taken into account for these new-comer patients. The Ethics Committee of Tokyo Women’s Medical University School of Medicine approved all procedures, and informed consent was obtained from every patient.

Evaluated items in TOMRASS database

Patients were self-surveyed about their health using the Kampo questionnaire at their first visit and at every reexamination on a touchscreen computer without intervention by medical staff. After the patients had completed the questionnaire, medical doctors reviewed the completed questionnaire during a medical examination. The Kampo questionnaire was prepared with reference to the classical literature and guidelines of recognition through the basic Kampo concepts; the three major substances of life (qi, blood, and fluid), the four essential dichotomies (yin-yang, hypofunction and hyperfunction, heat and cold, superficial and interior), and the five parenchymatous viscera (so-called heart, liver, kidney, spleen, and lung).

Outcome measure

Coldness was quantified by frequency and severity on a scale of 0 to 4. Improvement of coldness was self-evaluated by patients at one month of treatment. To avoid ambiguity of outcome decision, ‘effective’ was defined as a decrease in both frequency and severity, while other cases were regarded as ‘ineffective’.

Items are composed of age, body-mass index, 3 items on the mouth and tongue, an item on sphygmopalpation, 10 items on abdominal signs (**Table 1**), and 40 items on constitution and symptoms including feeling hot/cold (**Table 2**). Assessments of the items other than coldness were categorized as presence or absence.

Statistical Analysis

Paired t test, Chi-square test and Mann-Whitney U test were applied to detect significant associations

Table 1 Details of medical examinations (n=181)

	Effective	Ineffective	p value
General characteristics			
Number of patients	134	47	-
Age, median [range]	43 [17-79]	45 [20-75]	0.88 [†]
Height(cm), mean±SD	159.2±6.3	158.2±10.4	0.57 ^s
Weight (kg)	51.8±7.7	51.5±9.5	0.85 ^s
Body-mass index	20.4±2.6	21.0±7.2	0.41 ^s
Gender			0.052
Male	4	5	
Female	130	42	
Region of coldness (multiple choice)			
Extremities	121	33	0.0017**
Abdomen	41	14	0.92
Back	33	17	0.13
Whole body	24	15	0.062
Femur	1	1	0.45
Pulse signs (exclusive choice)			
Deficiency	51	16	0.73
Excess	1	0	1.0
Signs of the tongue (3 items, multiple choice)			
Teeth-marked tongue	59	32	0.0064**
White fur	83	31	0.73
Sublingual collateral vessels	77	34	0.083
Abdominal signs (10 items, multiple choice)			
Tenderness in iliac region	66	8	<0.0001*
Lack of resistance of lower abdomen	26	16	0.047*
Weakness of abdominal strength	35	17	0.20
Pulsation at pit of stomach	72	19	0.13
Para-umbilical tenderness	71	20	0.24
Subchondrial resistance	62	26	0.31
Excessive strain of abdominal muscles	41	16	0.72
Epigastric resistance	40	15	0.85
Abdominal fluid congestion	16	7	0.61
Recognition of linea alba	11	5	0.57

E: effective, I: ineffective. † Mann-Whitney's U test,

\$ Student's t test, chi-square test for categorical data. * $p < 0.05$, ** $p < 0.01$

between items and effectiveness of the treatment using SPSS Statistics ver.19 (IBM Corp., Armonk, NY, USA). Multiple logistic regression was performed to obtain an appropriate model for the prediction of treatment effect. Predictability was assessed by c-statistic derived from the logistic regression model. Significance was defined at < 0.05 .

Results

Efficacy of tokishigyakukagoshuyushokiyoto

Among 181 patients with cold syndrome, the treatment was effective in 134 patients (74.0%). There was no significant difference in patients' characteristics between the effective and ineffective groups (Table 1). The self-evaluation scales on both

frequency and severity of coldness were improved from 3.2 ± 0.7 to 2.1 ± 0.9 ($p < 0.01$) and from 3.1 ± 0.7 to 2.2 ± 0.9 ($p < 0.01$), respectively. The symptoms frequently accompanying coldness were stiff shoulders (69.1%), general fatigue (63.5%), chilly feeling (51.4%), abdominal fullness (49.2%), eyestrain (48.1%), headache (47.5%), lumbago (46.4%), and listlessness (37.6%).

Seasonal influence on treatment for coldness

Although the patients increased in winter and decreased in summer, the number of effective cases exceeded that of ineffective ones at all times of the year ($p = 0.0020$, Wilcoxon signed rank test). The probability of effectiveness was constant ($75.1 \pm 10.1\%$) without significant correlation to the month

Table 2 Questionnaire for self-surveillance on physical constitution and accompanying symptoms (40 items, multiple answers, n=181)

	Frequency (%)	E	I	P value [£]
Coexistence of coldness and hot flush	32 (17.7)	19	13	0.046*
Appetite loss	13 (7.2)	5	8	0.0054**
Sleepy feeling after meals	57 (31.5)	35	22	0.011*
Upset stomach	44 (24.3)	16	28	<0.0001**
Heartburn	21 (11.6)	7	14	<0.0001**
Diarrhea	23 (12.7)	10	13	0.0014**
Depression	45 (24.9)	25	20	0.0018**
Mood swing	21 (11.6)	9	12	0.0012**
Eyestrain	87 (48.1)	55	32	0.0021**
Stiff shoulders	125 (69.1)	90	35	0.46
General fatigue	115 (63.5)	80	35	0.080
Chilly	93 (51.4)	66	27	0.40
Abdominal fullness	89 (49.2)	62	27	0.24
Headache	86 (47.5)	63	23	0.87
Lumbago	84 (46.4)	59	25	0.31
Listless	68 (37.6)	49	19	0.73
Upset stomach from over-eating	67 (37.0)	46	21	0.22
Paroxysmal sweating	64 (35.4)	46	18	0.72
Constipation	61 (33.7)	48	13	0.37
Dry skin	60 (33.1)	42	18	0.47
Insomnia	59 (32.6)	40	19	0.21
Abdominal pain	53 (29.3)	41	12	0.58
Irritability	43 (23.8)	30	13	0.55
Easily catching cold	43 (23.8)	28	15	0.163
Edema	42 (23.2)	29	13	0.43
Cramp in legs	40 (22.2)	27	13	0.31
Vertigo	39 (21.5)	33	6	0.10
Difficulty in waking up	37 (20.4)	23	14	0.091
Chilblain	36 (19.9)	30	6	0.20
Neuralgia	32 (17.7)	21	11	0.27
Angry outburst	31 (17.1)	21	10	0.38
Hot flush	27 (14.9)	16	11	0.093
Pollakiuria	25 (13.8)	18	7	0.81
Hot feeling	24 (13.3)	17	7	0.80
Unpleasant wind	21 (11.6)	12	9	0.069
Fullness of the chest	20 (11.0)	13	7	0.42
Palpitation	20 (11.0)	12	8	0.17
Cold intolerance	15 (8.3)	10	5	0.54
Belch	14 (7.7)	9	5	0.36
Stuck feeling in throat	6 (3.3)	3	3	0.18

E: effective, I: ineffective, £ chi-square test. * $p < 0.05$, ** $p < 0.01$

of first visit ($r = -0.008$, $p = 0.79$, Pearson's correlations).

Univariate analysis

The positively correlated variables were coldness in extremities and tenderness in iliac region, while the negatively correlated variables were teeth-marked tongue, lack of resistance of lower abdominal region, coexistence of coldness and hot flushes, appetite loss, sleepy feeling after meals, upset stomach, heartburn, diarrhea, depression, mood swings and eyestrain (Tables 1 and 2).

Discriminatory predictability of the efficacy of treatment

Logistic regression analysis chose tenderness in iliac region (x_1), upset stomach (x_2) and depression (x_3) to maximize the predictive accuracy of the model (Table 3). The discriminatory predictability of the efficacy of treatment was calculated as 84.4% (Table 3).

Prospective verification of model adaptation

A simple administration for the newcomer 28 patients without the complex Kampo diagnosis demonstrated that the sensitivity and specificity of the

Table 3 Significant items in multiple logistic regression analysis and predictive accuracy of the model (n=181)

Item	Coefficient	Odds ratio	95% CI of odds	P value
Tenderness in iliac region (x_1)	1.76	5.8	2.15–15.6	<0.0001
Upset stomach (x_2)	-2.35	0.096	0.040–0.226	<0.0001
Depression (x_3)	-1.26	0.28	0.116–0.691	0.0055

Result of treatment	Predicted efficacy [§] of subjects (n=181)			Predicted efficacy [§] of new patients [†] (n=28)		
	Effective	Ineffective	Correct	Effective	Ineffective	Correct
Effective	126	9	93.3%	20	0	100.0%
Ineffective	19	27	58.7%	5	3	37.5%
Correct	86.9%	75.5%	-	80.0%	100.0%	-
Predictive accuracy	84.4%			82.1%		

§ The probability of effectiveness, $P(x) = 1 / \{1 + \exp(-y)\}$ where $y = 1.65 + 1.76x_1 - 2.35x_2 - 1.26x_3$. $P(x)$ above 0.5 is taken as effective. † The patients on their first visit between October 2010 and April 2011 who were independent of the subjects enrolled in to make the logistic regression model.

model were 100.0% and 37.5%, respectively, and the predictive accuracy was 82.1% (Table 3).

Discussion

Kampo medicine, based on traditional Chinese herbal medicine, has been the backbone of Japanese medicine for four hundred years, and has its own system of disease cognition and its own healing philosophy, which have their roots in the Japanese way of thinking. Though Kampo is currently not the mainstream of medical treatment in Japan, which is based on Western medicine, ordinary Japanese people still give it a degree of credence, and Kampo formulae are covered by the National Health Insurance System (NHIS) in Japan. Therefore, it is important to examine the effect of Kampo medicine on disease entities understood in the framework of modern Western medicine⁷⁾.

50-60% of patients visiting general gynecological clinics have reported complaints of coldness in Japan^{8)~10)}, and 40% and over of Chinese in good health have experienced coldness in extremities¹¹⁾. Miyazaki recently reported that this complaint worsened the health-related quality of life with a correlation to mental components in the short form health survey¹²⁾. Increased sensitivity of the body to cold, associated with low thyroid function and activation of sympathetic nerves in the extremities, are involved, though the mechanism remains unclear⁹⁾¹³⁾¹⁴⁾.

Tokishigyakukagoshuyushokyoto is decoction of 9 herbs: Angelicae Radix, Evodiae Fructus, Paeoniae Radix, Zizyphi Fructus, Cinnamoni Cortex, Asiasari Radix, Akebiae Aculis, Zingiberis Rhizoma, and Glycyrrhizae Radix. The pharmaceutical-grade granulated extract products are covered by NHIS as

high-quality, well-standardized, government-regulated versions of Kampo botanicals. They are usually given for hypofunctional constitution with yin-syndrome, headache and unusual coldness of the extremities¹⁵⁾.

The computer-aided analysis of the patient-based database indicated that the effectiveness of the treatment could be predicted with the predictive accuracy and positive predictive value of 82.1% and 80.0% in 28 new patients, respectively, by the status of only three items among dozens of accompanying symptoms at the first visit even though Sho, the traditional and complicated Kampo's cognition, was not taken into account.

A holistic view based on the diverse peripheral symptoms and physical constitutions accompanying the chief complaint are very important for Kampo's cognitive paradigm to restore the balance between mental and physical activities. Placebo-controlled trials do not reflect the usual use of Kampo in actual practice. However, the basic concepts, such as ying-yang, qi, five elements, five organs, Sho, etc., seem alien to Western practitioners. Therefore, it is important to establish a new method that would allow Western physicians and scientists to engage with Kampo's system of cognition and philosophy.

In conclusion, cold syndrome susceptible to tokishigyakukagoshuyushokyoto was very frequently accompanied by tenderness in iliac region, without upset stomach or depression. This modern Kampo cognition was obtained by using the computer-aided database of patient-based self-evaluation questionnaires system.

Disclosure Statement

No competing financial interests exist.

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