Original Article
ISSN (Online): 2350-0530
ISSN (Print): 2394-3629

International Journal of Research - GRANTHAALAYAH
February 2023 11(2), 78–86

CLINICAL SIGNIFICANCE OF THE TRADITIONAL JAPANESE MEDICINE, KEISHIKA-SHAKUYAKU-TO, IN ABDOMINAL SPASTIC PAIN

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Received 28 January 2023
Accepted 27 February 2023
Published 03 March 2023

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DOI
10.29121/granthaalayah.v11.i2.2023.5020

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ABSTRACT

Primary goal: To assess the usefulness of Kampo for the outpatient treatment of abdominal spastic pain.
Research Design: Retrospective study
Methodology: A total of 85 patients with symptoms of abdominal spasmodic pain and diarrhea of unknown cause, including the patients with contraindications for anticholinergic drugs, were included in the study. The patient was administered oral Keishika-Shakuyaku-to (TJ-60: 7.5 g/day) to treat spastic pain and diarrhea. The degree of improvement in pain was evaluated using a numerical rating scale at the start of treatment and 3 months later and used as an indicator of continuation.
Main outcomes and Results: Therapeutic effects were seen in 77.6% (66/85) of the included patients with the level of pain decreasing by over 50% 3 months after the first treatment. Additionally, no side effects from oral administration or adverse events leading to drug discontinuation were observed.
Conclusions: Kampo, Keishika-Shakuyaku-to was found to reduce abdominal pain and diarrhea of unknown cause and could be used safely without causing significant side effects even in patients with contraindications for anticholinergic drugs.

Keywords: Abdominal Spastic Pain, Antispasmodic Drug, Keishika-Shakuyaku-To

1. INTRODUCTION

Even in the age of modern medical science, people often suffer from abdominal pain of unknown etiology. Since ancient times, abdominal spastic pain has occurred under various occasions and interfered with daily human life, posing a common problem for humankind. Many situations in life lead to mental and physical tension; thus, spasm pain-like symptoms affect people from childhood to old age. Although abdominal pain may occur from organic causes such as intestinal inflammation,

spasm pain, which is a functional pain, is thought to occur more likely because of modern societal stress. Since abdominal spasm pain may be accompanied by frequent diarrhea and abdominal pain, it may be difficult to distinguish it from irritable bowel syndrome, but it is presumed that there are many symptomatic people regardless of sex or age.

Anticholinergic drugs such as scopolamine butylbromide cannot be used in patients with underlying diseases, even if used for acute pain, to avoid suppression of the parasympathetic nerves. Additionally, continued use of anticholinergic drugs is met with hesitation when it is frequent or in cases of chronic pain. In contrast, even though the Chinese herbal medicine Keishika-Shakuyaku-to is contraindicated for a few diseases, it is expected to be effective with a single use and is useful for controlling abdominal pain in daily life.

We present our clinical experience on the usefulness of Kampo in the outpatient department for the treatment of abdominal spasm pain, especially in patients with glaucoma, prostate hypertrophy, serious heart disease, and a history of ileus.

2. METHODS AND MATERIALS

2.1. PATIENTS

The study included 85 patients who were admitted to the Department of Surgery II, Tokyo Women's Medical University School of Medicine, and the Department of General Medicine, Dokkyo University School of Medicine, Saitama Medical Center, Outpatients Department between July 2013, and December 2018, with symptoms requiring oral therapy. The patients were administered Keishika-Shakuyaku-to according to concurrent diseases and effect required. The average age of the patients was 59.9 years, of which 44 were male (mean age 63, range 25–86 years) and 41 were female (mean age 57, range 24–80 years).

2.2. DRUGS

Keishika-Shakuyaku-to (TJ-60) Extract Granules for Ethical Use (Tsumura and Co., Product number TJ-60) (7.5 g), contained 3.75 g of a dried extract obtained from mixed crude herbs in the following ratio: JP Peony Root, 6.0 g; JP Cinnamon Bark, 4.0 g; JP Jujube, 4.0 g; JP Glycyrrhiza, 2.0 g; and JP Ginger, 1.0 g. The drug has been approved for medicinal use by the Japanese Ministry of Health and Welfare.

2.3. SAMPLE PREPARATIONS

A granule of TJ-60 (1.0 g) was extracted with methanol (20 mL) under ultrasonication for 30 min, and was centrifuged at 3000 rpm for 5 min. The supernatant was filtrated with a membrane filter (0.45 μm) and then submitted for high-performance liquid chromatography (HPLC) analysis (30 μL).

2.4. THREE DIMENSIONAL (3D)-HPLC ANALYSIS

The HPLC apparatus consisted of a Shimadzu LC 10A (analysis system software: CLASS-M10A ver. 1.64, Tokyo, Japan) equipped with a multiple wavelength detector (UV 200 –400 nm) (Shimadzu SPD-M10AVP, diode array detector) and an auto injector (Shimadzu CTO-10AC). HPLC conditions were described as follows: column, ODS (TSK-GEL 80TS, 250×4.6 mm i.d., TOSOH, Tokyo, Japan); eluent (A) 0.05 M AcONH4 (pH 3.6) and (B) 100% CH3CN. A linear gradient of 90% A and 10% B

changing over 60 min to 0% A and 100% B was used (100% B was continued for 20 min), with temperature, 40°C, and flow rate, 1.0 mL/min Figure 1.

Figure 1

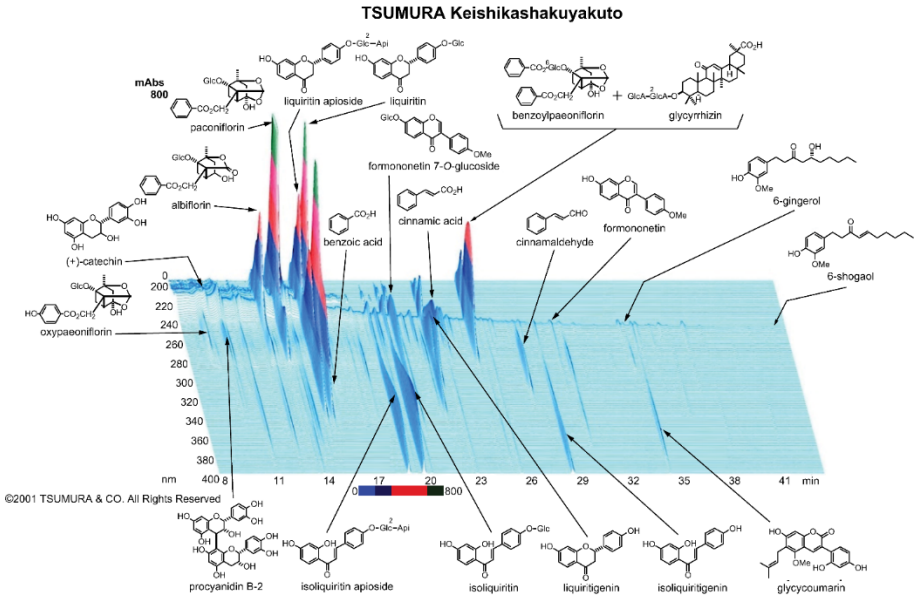

Figure 1 The Three-Dimensional High-Performance Liquid Chromatography Profile Pattern of TJ-60

2.5. COMPONENT ATTRIBUTION METHOD

Standard compounds that were isolated, purified, and identified (via Mass spectrometry (MS), Infrared Spectrophotometer (IR), and Nuclear Magnetic Resonance (NMR)) from botanical raw materials in Keishika-Shakuyaku-to were analyzed under the same conditions, and data from the UV spectrum and column retention time were used to create a chromatogram library. By using the peak-detector (an auxiliary function of HPLC) of the library, the degree of coincidence and spectral homogeneity of the peaks were evaluated.

2.6. ANALYSIS

We collated the presenting symptoms and clinical findings, as well as any concurrent diseases, from the outpatient database. As far as possible, we followed the patients' progress and outcomes.

3. RESULTS

The number and proportion of patients with concurrent diseases that influenced the selection of Kampo for antispasmodic purposes are shown in Figure 2. These included glaucoma (n=6), prostate hypertrophy (n=7), cardiovascular disease (n=9), ileus history (n=3), bronchial asthma (n=5), colonic diverticulum discovered during examination (n=8), and no particularly dexterous disease in the background (n=47) Figure 2.

Figure 2

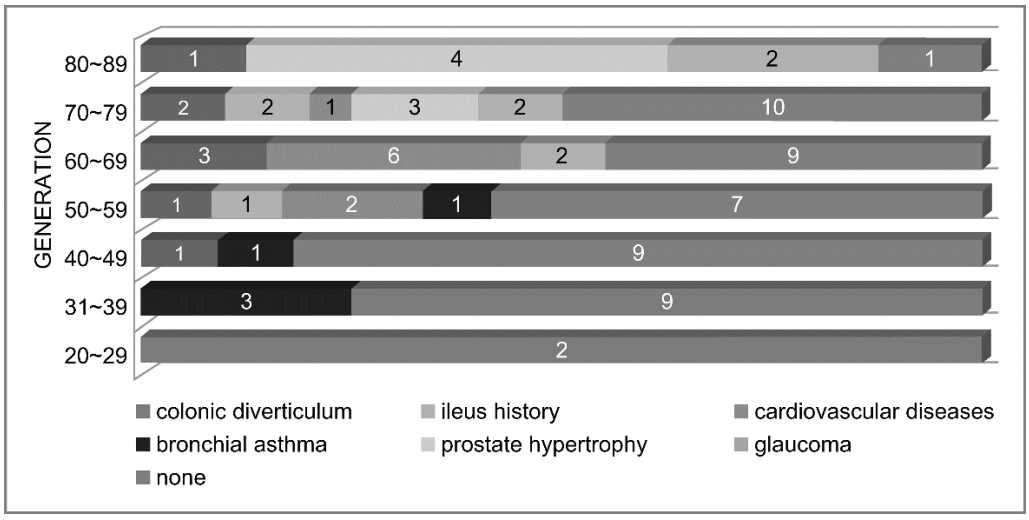

Figure 2 Number and Age Group of Patients with Underlying Diseases

The effect of antispasmodic Kampo preparations, including its administration in patients with underlying diseases for which anticholinergic drugs are contraindicated, are shown in Table 1. It was found that 77.6% (66/85) of the cases showed a therapeutic effect, with the level of pain decreasing by over 50% three months after administration of the test drug. Comparing the effective group and the ineffective group, the mean age was almost the same at 59.3 and 60.0 years, respectively, and the percentage of people with underlying diseases that contraindicated anticholinergic drugs was 41.7% (5/12) and 45.2% (33/73), showing no significant difference. In terms of duration of oral administration, 66.6% (8/12) of patients in the ineffective group were administered with the drug for less than 6 months, two cases for less than 1 year; and no cases for 5 years. In contrast, the drug was administered for less than 6 months (19.2%; 14/73) in the effective group, and patients tended to self-adjust and continue the oral medication for 1 to 4 years, depending on the degree of pain. This includes an example of internal use as needed for pain. Regarding safety, there were no adverse events such as side effects of oral administration or hypokalemia leading to discontinuation of drug administration.

Table 1

Table 1 Effects of Keishika-Shakuyaku-To on Patients with Abdominal Spastic Pain

No.	Age	Sex	Underlying condition	Dose of Keishika-Shakuyaku-to (g/day)	Primary Pain Level (NRS)	After 3M Pain Level (NRS)	Duration of administation	Side Effect	Judgement
1	64	F	None	7.5	6	3	for 1~4 yrs	none	Effective
2	62	F	None	7.5	5	2	less than 6 mo.	none	Effective
3	83	M	Prostate hypertrophy	7.5	5	2	for 1~4 yrs	none	Effective
4	72	M	Cardiovascular diseases	7.5	5	5	for 1~4 yrs	none	Ineffective
5	32	F	None	7.5	5	4	less than 6 mo.	none	Ineffective

6	32	M	Bronchial asthma	7.5	4	1	less than 1 yr	none	Effective
7	66	F	Glaucoma	7.5	6	3	for 5 yrs	none	Effective
8	42	F	Colonic diverticulum	7.5	6	3	less than 1 yr	none	Effective
9	40	M	None	7.5	7	2	for 5 yrs	none	Effective
10	38	F	None	7.5	6	3	for 1~4 yrs	none	Effective
11	73	F	None	7.5	4	1	for 1~4 yrs	none	Effective
12	80	F	Colonic diverticulum	5.0	6	6	less than 6 mo.	none	Ineffective
13	63	F	None	7.5	5	2	for 1~4 yrs	none	Effective
14	36	F	None	7.5	4	4	less than 6 mo.	none	Ineffective
15	68	M	None	7.5	5	2	for 1~4 yrs	none	Effective
16	61	F	None	7.5	6	3	for 1~4 yrs	none	Effective
17	52	F	None	7.5	6	2	for 1~4 yrs	none	Effective
18	63	M	Glaucoma	7.5	4	1	for 1~4 yrs	none	Effective
19	77	F	None	5.0	4	2	for 1~4 yrs	none	Effective
20	50	M	Colonic diverticulum	7.5	6	2	less than 6 mo.	none	Effective
21	42	M	Bronchial asthma	7.5	6	5	less than 6 mo.	none	Ineffective
22	65	F	None	7.5	5	5	less than 6 mo.	none	Ineffective
23	69	M	Cardiovascular diseases	7.5	4	2	less than 6 mo.	none	Effective
24	65	M	None	7.5	5	1	less than 1 yr	none	Effective
25	81	M	None	7.5	6	2	for 1~4 yrs	none	Effective
26	78	M	None	7.5	5	5	less than 6 mo.	none	Ineffective
27	62	F	Cardiovascular diseases	7.5	4	1	less than 6 mo.	none	Effective
28	58	M	None	7.5	6	3	for 1~4 yrs	none	Effective
29	81	M	Glaucoma	7.5	6	5	less than 1 yr	none	Ineffective
30	66	M	None	7.5	6	3	for 1~4 yrs	none	Effective
31	41	F	None	7.5	6	3	less than 6 mo.	none	Effective
32	79	F	None	7.5	4	1	less than 1 yr	none	Effective
33	81	M	Prostate hypertrophy	7.5	5	2	for 1~4 yrs	none	Effective
34	76	F	Glaucoma	5.0	5	2	for 1~4 yrs	none	Effective
35	36	M	None	7.5	6	5	less than 6 mo.	none	Ineffective
36	51	M	None	7.5	5	2	for 1~4 yrs	none	Effective
37	57	F	None	7.5	5	3	for 5 yrs	none	Effective
38	50	M	None	7.5	6	3	less than 6 mo.	none	Effective
39	25	M	None	7.5	6	3	for 1~4 yrs	none	Effective
40	49	M	None	7.5	5	3	for 1~4 yrs	none	Effective
41	83	M	Prostate hypertrophy	7.5	4	1	for 1~4 yrs	none	Effective
42	66	M	Cardiovascular diseases	7.5	5	2	less than 6 mo.	none	Effective
43	45	F	None	7.5	7	4	for 1~4 yrs	none	Effective
44	36	F	Bronchial asthma	7.5	4	1	for 1~4 yrs	none	Effective
45	63	M	Colonic diverticulum	7.5	7	3	for 5 yrs	none	Effective
46	42	F	None	7.5	5	2	for 1~4 yrs	none	Effective

47	48	F	None	7.5	6	3	for 1~4 yrs	none	Effective
48	51	F	None	7.5	7	3	for 1~4 yrs	none	Effective
49	52	F	Ileus history	7.5	8	3	for 5 yrs	none	Effective
50	37	M	Bronchial asthma	7.5	4	2	for 1~4 yrs	none	Effective
51	67	F	Cardiovascular diseases	5.0	7	4	for 5 yrs	none	Effective
52	47	F	None	7.5	6	2	for 1~4 yrs	none	Effective
53	34	F	None	7.5	7	3	for 1~4 yrs	none	Effective
54	74	M	None	7.5	4	4	less than 6 mo.	none	Ineffective
55	67	F	None	7.5	5	3	for 5 yrs	none	Effective
56	24	F	None	7.5	5	1	for 1~4 yrs	none	Effective
57	57	M	Cardiovascular diseases	7.5	5	1	less than 6 mo.	none	Effective
58	55	F	None	7.5	6	2	for 1~4 yrs	none	Effective
59	78	F	None	5.0	4	2	for 1~4 yrs	none	Effective
60	73	M	Ileus history	7.5	5	1	less than 6 mo.	none	Effective
61	86	M	Glaucoma	5.0	3	1	for 1~4 yrs	none	Effective
62	85	M	Prostate hypertrophy	7.5	7	6	less than 1 yr	none	Ineffective
63	76	M	Prostate hypertrophy	7.5	4	2	less than 6 mo.	none	Effective
64	49	F	None	7.5	7	4	for 1~4 yrs	none	Effective
65	66	M	Cardiovascular diseases	7.5	4	1	less than 1 yr	none	Effective
66	73	M	None	7.5	4	2	less than 1 yr	none	Effective
67	71	F	Colonic diverticulum	7.5	6	2	for 1~4 yrs	none	Effective
68	30	M	None	7.5	4	4	for 1~4 yrs	none	Ineffective
69	72	F	Glaucoma	7.5	6	2	less than 6 mo.	none	Effective
70	74	M	None	7.5	5	2	for 1~4 yrs	none	Effective
71	77	M	Prostate hypertrophy	7.5	4	2	for 1~4 yrs	none	Effective
72	63	M	Colonic diverticulum	7.5	5	1	less than 6 mo.	none	Effective
73	55	F	Bronchial asthma	7.5	5	2	for 1~4 yrs	none	Effective
74	78	M	Ileus history	7.5	6	3	less than 1 yr	none	Effective
75	43	F	None	7.5	6	2	for 1~4 yrs	none	Effective
76	37	M	None	7.5	6	2	for 1~4 yrs	none	Effective
77	72	F	None	7.5	5	2	for 1~4 yrs	none	Effective
78	78	M	Prostate hypertrophy	7.5	3	0	less than 6 mo.	none	Effective
79	65	F	Cardiovascular diseases	7.5	5	2	for 1~4 yrs	none	Effective
80	32	M	None	5.0	5	2	for 1~4 yrs	none	Effective
81	58	F	Cardiovascular diseases	7.5	5	2	for 1~4 yrs	none	Effective
82	71	M	None	7.5	4	1	for 1~4 yrs	none	Effective
83	68	M	Colonic diverticulum	7.5	7	4	less than 1 yr	none	Effective
84	73	F	Colonic diverticulum	7.5	7	3	less than 6 mo.	none	Effective
85	76	M	None	7.5	5	1	for 1~4 yrs	none	Effective

4. DISCUSSION

Hypersensitive movements of the human bowel tract are likely to occur due to organic factors, such as after various interstitial inflammations, in women during menstruation, or functionally accompanied by mental tension. Based on the experience of repeated medical examinations comparing the results of bowel examinations with abdominal symptoms, in cases where diverticulum occurs frequently in the bowel tract, clinical symptoms of spasm pain are often treated as abdominal pain of unknown cause and referred Bielefeldt et al. (2009), Binder (2009), Lakhan and Kirchgessner (2010), Sanders et al. (2010), Juckett and Trivedi (2011), Spencer et al. (2012), Gallego et al. (2010).

Furthermore, the modern environment predisposes people to abdominal symptoms including abdominal pain and diarrhea due to the influence of multiple stress factors in society. There are many situations in daily life that involve mental and physical tension, and people do not always go to the hospital for these factors.

Additionally, anticholinergic drugs such as scopolamine butylbromide are often given to patients with abdominal pain who have few significant findings on abdominal diagnostic imaging or endoscopic examination in cases where patients seek medical assistance. The mechanism of action of these anticholinergic drugs is to suppress the parasympathetic nerve by inhibiting the binding of acetylcholine to the receptor Yoshihiko and Noriyoshi (2012). The following reports have been made regarding the effect of suppressing intestinal peristalsis: 1) TJ-60 affects the contractile activity of circular smooth muscle from the distal colon of rats, 2) TJ-60 (both 1 mg/ml) inhibits spontaneous contractions of circumferentially cut preparations of intact mucosa, 3) TJ-60 has minor effects on contractile responses (phasic contractions and off-contractions) evoked by transmural nerve stimulation and increased basal tone, and 4) TJ-60 likely inhibits spontaneous contractions of the distal colon of rats through the production of nitric oxide (NO). Activation of small conductance calcium-activated potassium (SK) channels seems to be involved in the inhibitory effects of TJ-60 Yoshihiko and Noriyoshi (2012).

As a result, the excessive contraction of smooth muscle caused by the excitement of the parasympathetic nerve is suppressed, leading to the suppression of excessive spasm of the gastrointestinal tract and pain. The main side effects of anticholinergics include dry mouth, accommodation dysregulation, palpitations, hot flushes, and dizziness. Furthermore, when the underlying disease is angle-closure glaucoma, sympathetic nerve suppression increases and mydriasis occurs, urinary dysfunction worsens in prostatic hypertrophy, and heart rate increases due to sympathetic nerve enhancement in severe heart disease. Additionally, administration of anticholinergics is contraindicated due to the risk of stress on the heart and there is a tendency for symptoms to recur in patients with a history of paralytic ileus. In recent years, the number of people suffering from diseases associated with age has increased, and as a result the number of people suffering from cardiovascular diseases (e.g., heart disease), glaucoma, and benign prostatic hyperplasia is remarkably high.

As an alternative for anticholinergic drugs, Kampo preparations can be considered as a treatment option for abdominal spasm pain Yoshihiko and Hikaru (2010). Keishika-Shakuyaku-to suppresses spontaneous contraction while maintaining the peristaltic movement of the gastrointestinal tract, and its

component, peony, has antidepressant effects through central nervous system action and anti-stress action. We used the Keishika-Shakuyaku-to (TJ-60) for the purpose of antispasmodic in abdominal spasm pain cases, including patients contraindicated for anticholinergic drugs because the antispasmodic effect of Kampo preparations is effective. As a result, improvement effects on abdominal pain and diarrhea were observed in cases without a specific organic cause, and in some cases, it was possible to shift from regular oral administration to oral administration as needed. Notably, TJ-60 could be used safely without serious side effects even in patients contraindicated for anticholinergic drugs Chey et al. (2011).

In general, there are few contraindications for administration of Chinese herbal preparations. However, it should be noted that hypokalemia may occur when taking Keishika-shakuyaku-to; thus a blood electrolyte test, which is easy to conduct even during the course of use, is often performed in the clinical department related to the underlying disease, to ensure that there are few obvious contraindications for its administration. Thus, improvement therapy by oral administration of Kampo preparations for abdominal spasm pain, especially introduction of Kampo preparations having antispasmodic action in anticholinergic contraindicated cases, can be considered useful.

5. CONCLUSION

We assessed the usefulness of oral treatment with Kampo oral treatment, a Japanese traditional medicine, for abdominal spastic pain and found the following:

1) Approximately, 77.6% (66/85) of the cases experienced a >50% decrease in the level of pain three months after starting treatment.
2) Kampo improved abdominal pain and diarrhea symptoms in cases with unknown etiology and could be used safely without serious side effects even in patients contraindicated for anticholinergic drugs.
3) With regards to safety, no adverse events or incidents of hypokalemia warranting discontinuation of the use Kampo were observed.

CONFLICT OF INTERESTS

None.

ACKNOWLEDGMENTS

We would like to thank Editage (www.editage.com) for English language editing.

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