JOURNAL OF THE
ANUS, RECTUM AND COLON
dx.doi.org/10.23922/jarc.2019-012
http://journal-arc.jp

ORIGINAL RESEARCH ARTICLE

Clinical efficacy of Japanese herbal medicine daikenchuto in the management of fecal incontinence: A single-center, observational study

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Abstract:

Objectives: The purpose of this study was to investigate whether the symptoms of fecal incontinence (FI) or anal sphincter dysfunction are improved by daikenchuto (DKT). Methods: This is a retrospective observational study that analyzes the effects of DKT. The study was conducted at Kunimoto Hospital. Patients who visited the hospital from January 2012 to December 2016 due to symptoms of FI with a certain degree of chronic constipation and who took DKT were enrolled. The drug to be evaluated was "Tsumura Daikenchuto Extract Granules for Ethical Use (TJ-100)" manufactured by Tsumura & Co., Tokyo, Japan. The primary outcome measures were changes in the scores of the Cleveland Clinic Incontinence Score (CCIS) and Constipation Scoring System (CSS) before and after the administration of DKT. Results: A total of 157 patients were enrolled. On the CCIS, "leakage of solid stool," "leakage of liquid stool," "pad use," and "total score" were significantly improved. On the contrary, on the CSS, the score of "type of assistance" was significantly improved after the administration of DKT, but no significant difference was found in the total score. On the Bristol Stool Form Scale, the administration of DKT showed a tendency to normalize stool consistency. Maximum resting anal pressure and maximum squeeze anal pressure significantly increased after the administration of DKT. No side effects caused by DKT were observed during the study. Conclusions: DKT appears to be a safe and useful agent for the management of FI in patients with defecation disorders and internal anal sphincter dysfunction.

Keywords:

daikenchuto, fecal incontinence, chronic constipation, resting anal pressure, stool form scale

J Anus Rectum Colon 2019; 3(4): 160-166

Introduction

Daikenchuto (DKT) is a traditional Japanese medicine (Kampo), originally described in a Chinese classic article (*Jin Gui Yao Lue*) and independently developed in Japan. It is a botanical drug made from ginseng, processed ginger, and Japanese pepper, with maltose. "Tsumura Daikenchuto Extract Granules for Ethical Use (TJ-100)" (Tsumura & Co., Tokyo, Japan) is a granule preparation of DKT for easy administration, and it is approved and sold as a prescription drug in Japan. DKT is indicated for the relief of abdominal cold feeling and pain accompanied by abdominal bloating, and it is widely used as a medical drug for improving various abdominal symptoms. DKT has pharmacological actions, including increasing intestinal motility[1)] and blood flow[2)] and an anti-inflammatory effect[3)]. In addition, DKT can improve postoperative ileus in various clinical studies conducted in Japan. Various clinical trials of DKT have been conducted in the USA under an Investigational New Drug application[4)]. DKT has been shown to lower the gastrointestinal sensation threshold in patients with chronic constipation (CC) and increase anal pressure (internal anal sphincter

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Received: April 15, 2019, Accepted: August 6, 2019

(IAS) elevating function)[5].

At Kunimoto Hospital, DKT has been used for the treatment of fecal incontinence (FI) symptoms. FI is defined as "recurrent uncontrolled passage of fecal material in an individual with a developmental age of at least 4 years" in Rome IV[6], and this symptom greatly reduces the patient's quality of life. The prevalence of FI in Japan is reported to be approximately 6%-8%; thus, it is not a rare disease. The most common cause of this disease is anal sphincter injuries due to parturition[7]. However, in a recent survey in Japan, where the decline in birthrate and aging are progressing, the functional decline of the IAS associated with aging was the most common cause[8]. In elderly people, including men, many FI cases are also caused by CC, fecal impaction, and incomplete rectal emptying during defecation[9].

The IAS consists of a thickened area of the circular smooth muscle layer of the rectum and is primarily responsible for maintaining anal resting continence. Although IAS function is often damaged in anorectal surgery, vaginal delivery, pelvic radiation therapy, and aging, the effective treatments for IAS dysfunction are lacking. The components contained in DKT, namely, hydroxy-α-sanshool and hydroxy-β-sanshool, contract smooth muscle cells[1]. In addition, previous clinical report has suggested that DKT may increase resting anal pressure[5]. Thus, DKT may also act on the smooth muscle of the IAS muscle and the gastrointestinal tract.

We have observed the efficacy of DKT for patients with CC and FI in our routine clinical practice. Accordingly, we retrospectively investigated whether the FI symptoms or anal sphincter dysfunction were improved by DKT.

Methods

Study Design

This was a retrospective, observational study that analyzes the effects of DKT on FI with a certain degree of CC symptoms with reference to the medical records of patients who visited our hospital. This study was performed with respect to the Declaration of Helsinki, and it complied with the study protocol and "Ethical Guidelines for Medical and Health Research Involving Human Subjects". This study was approved by the Institutional Review Board of the Maebashi Hirosegawa Clinic, and the study was registered with Japan's University Hospital Medical Information Network (UMIN000031475).

Study Participants

Patients who visited the hospital from January 2012 to December 2016 due to FI as the major complaint and were treated with DKT were included as study participants. Patients with organic disorders of the rectoanal region, such as rectal prolapse, abscess, and tumor, or who used treatment other than DKT were excluded.

As this is a retrospective observational research using existing data collected by the hospital, the written consent was not obtained from the patients in advance. Therefore, the contents of the research were posted in the hospital to inform the subjects, providing the opportunity to refuse the usage of their data in the research.

Anorectal Manometry

All patients underwent comprehensive anorectal physiology tests with the rectum unprepared. Anorectal manometry (ARM) was performed using a 5-mm-diameter, one-channel, solid-state catheter with a microtip transducer ARM system. The lubricated catheter was introduced into the rectum, with the patient in the left lateral position and hips flexed to 90°. The maximal resting pressure (MRP) was recorded using a rapid pull-through technique and defined as the highest recorded resting pressure. Subsequently, the maximal squeeze pressure (MSP), defined as the highest recorded pressure above the baseline (zero) at any level of the anal canal during maximum squeeze effort by the patient, was measured. Then, each patient's internal and external anal sphincters were scanned by endoanal ultrasound (EAUS) with a 7-MHz rotating endoprobe scanner.

Variables

The following variables recorded in the medical record in the routine practice and that can be extracted from the medical record were collected: background characteristics of the patients (age, sex, height, body weight, obstetrical history, medical history, concomitant medicine, and classification of FI), Cleveland Clinic Incontinence Score (CCIS)[10], Constipation Scoring System (CSS)[11], Bristol Stool Form Scale (BSFS)[12], MRP, and MSP.

Medication

The drug to be evaluated was "Tsumura Daikenchuto Extract Granules for Ethical Use (TJ-100)" manufactured by Tsumura & Co., Tokyo, Japan. This drug was a medicinal granule preparation mixed with extract powder as the drug substance from three botanical raw materials and additives, such as maltose and lactose. The extract powder was produced by the following process: botanical raw materials, including *Zanthoxylum* fruit, processed ginger, and ginseng, were mixed at a ratio of 3:2:5, extracted with hot water, and then dried by a spray drying system. The usual daily dose of this drug is 7.5 g.

Endpoints

The endpoints were changes in the total score and each domain score of the CCIS and CSS and changes in MRP, MSP and BSFS before and after the administration of DKT.

Table 1. Patients' Baseline Characteristics.

Patients	Total 157
Sex	
Male	40 (25.5)
Female	117 (74.5)
Age, y	
Mean (range)	73.6 (32-93)
< 65	29 (18.5)
65-80	83 (52.9)
> 80	45 (28.7)
Body mass index, kg/m^2	
Mean	22.5
< 20	25 (15.9)
20-25	84 (53.5)
> 25	26 (16.6)
Unknown	22 (14.0)
Vaginal delivery	
0	12 (10.3)
1-2	67 (57.3)
≥ 3	30 (25.6)
Unknown	8 (6.8)
Type of fecal incontinence	
PI	86 (54.8)
UI	8 (5.1)
PUI	63 (40.1)
Bristol stool scale	
1, 2 (lumpy and hard)	41 (26.1)
3-5 (normal)	94 (59.9)
6, 7 (mushy and watery)	22 (14.0)

Values in parentheses are percentages unless otherwise indicated.
PI: passive incontinence, UI: urge incontinence.
PUI: passive and urge incontinence.

Table 2. Potential Underlying Causes of Fecal Incontinence in 40 Males and 117 Females.

	No. of patients
Anal sphincter injury due to vaginal delivery	42
Internal anal sphincter degeneration	26
Idiopathic	25
Spinal cord disorders	18
Chronic constipation	11
Diabetic mellitus	10
Central nervous system disorders	6
Rectal prolapse	4
Anal sphincter injury due to anal surgery	4
Others	11

Statistics

Summary statistics were calculated using values before and 1 month after the administration of DKT described in the medical record. Score values were considered continuous variables. Values before and after the administration were compared by the one-sample Wilcoxon test, and a p-value < 0.05 indicated significance. Data completion for missing values was not performed.

Table 3. Patients' History, Comorbid Disease, and Medications.

History and comorbid disease	
Hypertension	63
Mental disease	49
Hyperlipidemia	42
Diabetes	30
Anal surgery	28
Hysterectomy	19
Back injury/surgery	11
Brain disease	8
Concomitant medication	
Sleeping pills	51
Laxatives	45
Antacids	44
Antiplatelet drugs/anticoagulants	34
Vasodilators	32
Antihistamines	24
Urological agents	21
Diuretics	17
Antiarrhythmic drugs	16

Results

Participants

A total of 157 patients who fulfilled the appropriate criteria within the study period were enrolled. Their mean age was 73.6 years old, and female patients accounted for 75%.

The type of FI was passive incontinence in 86 cases, urge incontinence in 8 cases, and passive and urge incontinence in 63 cases (Table 1).

The potential underlying causes of FI based on the questionnaires and the results of the ARM and EAUS are shown in Table 2.

Table 3 shows the medical history of the patients and the concomitant medications with DKT. Of the subjects of this study, 45 had already used laxatives.

Incontinence symptoms

The results of the CCIS are shown in Table 4. Of the individual factors, "leakage of solid stool," "leakage of liquid stools," and "pad use" were significantly improved after the administration of DKT (each $p < 0.001$, $p < 0.001$, $p = 0.0177$). The total score of all eight factors was also significantly improved (10.4 ± 4.5 before the administration, 8.4 ± 5.4 after the administration; $p < 0.001$).

Constipation symptoms

The results of the CSS are shown in Table 5. Of the individual factors, "type of assistance" was significantly improved after the administration of DKT (p = 0.0366), but in the total score of all eight factors, no significant difference was observed (5.5 ± 4.0 before the administration, 5.0 ± 4.1 after the administration; p = 0.1337).

Table 4. Changes in the Cleveland Clinic Incontinence Score before and after the Treatment (n = 149).

Symptoms	Baseline value	After 1 month	P-value
Solid	1.5 ± 1.5	0.9 ± 1.4	< 0.001
Liquid	2.5 ± 1.4	1.7 ± 1.6	< 0.001
Gas	2.3 ± 1.7	2.3 ± 1.7	0.8544
Pad use	2.7 ± 1.6	2.4 ± 1.8	0.0177
Lifestyle alteration	1.4 ± 1.8	1.2 ± 1.7	0.2749
Total CCIS	10.4 ± 4.5	8.4 ± 5.4	< 0.001

Data are presented as means ± SD. CCIS, Cleveland Clinic Incontinence Score.
Statistical testing performed using the Wilcoxon rank sum test.

Stool Consistency

The histogram of BSFS scores before and after the administration of DKT is shown in Figure 1. Scores 1 and 2 indicate that the hard stool markedly decreased, and score 4 means that the normal stool increased. The administration of DKT showed a tendency to normalize stool consistency (Figure 1).

Anal Pressure

The results for changes in the anal pressure are shown in Table 6. The maximum resting pressure significantly increased from 28.3 ± 12.6 mmHg to 33.6 ± 15.2 mmHg with the administration of DKT (p < 0.001). Similarly, the maximum squeeze pressure significantly increased after the ad-

Table 5. Change in the Constipation Scoring System before and after the Treatment (n = 147).

Symptoms	Baseline value	After 1 month	P-value
Frequency of bowel movements	0.3 ± 0.7	0.2 ± 0.5	0.0996
Painful evacuation effort	0.8 ± 1.2	0.6 ± 1.1	0.4076
Incomplete evacuation	1.7 ± 1.4	1.6 ± 1.3	0.2904
Abdominal pain	0.4 ± 0.8	0.4 ± 0.9	0.5234
Minutes in lavatory per attempt	0.4 ± 0.8	0.5 ± 0.8	0.3196
Type of assistance	0.5 ± 0.8	0.4 ± 0.6	0.0366
Unsuccessful attempts for evacuation	0.5 ± 0.6	0.4 ± 0.7	0.4724
Duration of constipation	0.9 ± 1.2	0.9 ± 1.2	0.8818
Total CSS score	5.5 ± 4.0	5.0 ± 4.1	0.1337

Data are presented as means ± SD. CSS, constipation scoring system.
Statistical testing performed using the Wilcoxon rank sum test.

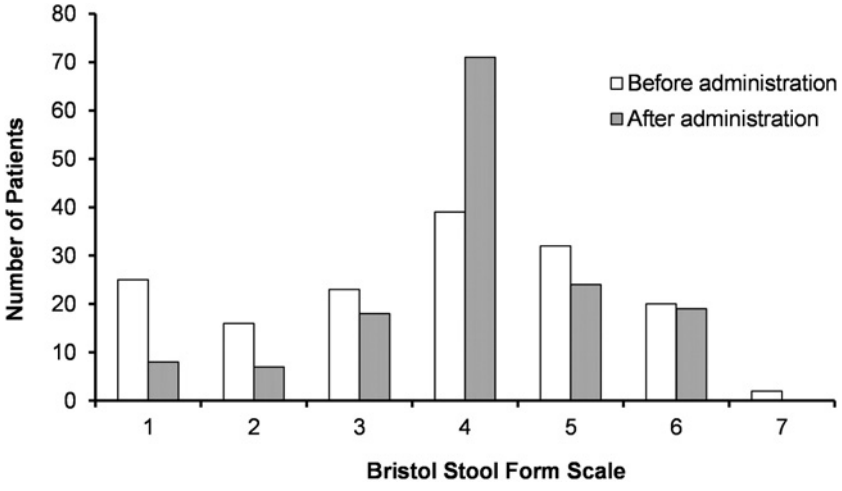

Figure 1. Changes in the Bristol Stool Form Scales before and after the treatment.

Table 6. Change in the Manometric Data before and after Treatment (n = 141).

Symptoms	Baseline value	After 1 month	P-value
MRP (mmHg)	28.3 ± 12.6	33.6 ± 15.2	< 0.001
MSP (mmHg)	134.8 ± 68.4	153.0 ± 76.6	< 0.001

Data are expressed as means ± SD. MRP, maximal resting pressure. MSP, maximal squeeze pressure.
Statistical testing performed using the Wilcoxon rank sum test.

ministration of DKT ($p < 0.001$).

Safety

No side effects caused by DKT were observed during the study period.

Discussion

This is the first comprehensive clinical study on the efficacy of DKT in patients with complaints of FI with a certain degree of CC. The present study shows that DKT can be an effective intervention for FI treatment, and the efficacy results were objectively demonstrated by two measures, CCIS and anal pressure.

Nonsurgical therapy is usually the first choice of treatment for reducing symptoms of FI. Antidiarrheal agents, such as loperamide hydrochloride or diphenoxylate/atropine sulfate, can produce modest improvements in the symptoms of FI and remain the mainstays of drug treatment[13]. Loperamide hydrochloride can slow bowel motility and increase fluid absorption. Moreover, loperamide hydrochloride increases resting anal sphincter pressure[14]. Although it is useful, particularly in patients with diarrhea and urge-related FI, its use in other types of incontinence is often associated with unsatisfactory outcomes.

Although FI is commonly exacerbated by liquid stool or diarrhea, constipation and incomplete evacuation of stool may also be involved in the pathogenesis of FI. The occurrence of leakage after defecation indicates weakness of resting anal sphincter tone or problems with incomplete rectal emptying during defecation[15]. The presence of incomplete evacuation is considered an independent risk factor of FI[16]. Fecal impaction is also an important cause of FI, particularly in older people and persons living in nursing homes. In patients whose underlying cause is constipation, antidiarrheal agents, such as loperamide hydrochloride, can worsen the constipation. By contrast, DKT reportedly improves constipation; therefore, it can be administered to a broader patient population irrespective of the etiology of FI.

Several studies evaluating the effect of DKT on functional constipation have been reported so far, and many reports have shown efficacy in such cases. Sakakibara et al. reported that colonic transit time was significantly reduced by administering DKT to 10 male patients with intractable constipation with Parkinsonian syndrome[17]. Iwai et al. reported the administration of DKT to 10 children with intractable constipation; their rectoanal sensation threshold decreased and rectal reservoir function improved[18]. In addition, Numata et al. reported significant improvement of the CSS and a significant reduction of intestinal gas volume after administration of DKT for patients with constipation and sequelae of cerebrovascular disorders[19]. Moreover, in the present study, a tendency to improve difficulty in defecation was observed with the administration of DKT.

On the contrary, Iturrino et al. reported that after administering DKT to 45 female patients with functional constipation, no significant change was observed in stool frequency and consistency and in the small intestinal and colonic transit[5]. However, the patients in their study were obese with a mean BMI of 25.8 kg/m^2 and a mean age of 43.6 years; thus, the patient background is largely different from the study of Numata et al. (mean age: 77.5 years old; mean BMI: 19.8 kg/m^2)[19] and the current study (mean age: 73.6 years old; mean BMI: 22.5 kg/m^2). Furthermore, because the patients in the study of Numata et al. had sequelae of cerebrovascular disorders[19], a large difference in the patient population exists, such as a strong suggestion of reduced digestive function due to reduction of intestinal blood flow accompanying arteriosclerosis.

In a study of 45 females with functional constipation, 28-day DKT treatment was associated with a trend for a lower rectal sensation threshold and higher MRP compared with the placebo group[5]. The present investigation of anal pressure also indicated that MRP improved with DKT treatment. Although the MRP increases after the administration of DKT, the average value is still below the normal value. Therefore, controlling FI by only increasing resting anal pressure may be difficult. DKT appears to normalize stool consistency and improve rectal sensation, and these effects may collectively work to reduce the symptoms of incontinence.

DKT has been administered from ancient times on the premise of the patient's general condition named "Sho," the Kampo diagnostic criteria, not of the diagnosis or disease name of Western medicine. "Sho" is a criteria showing the general condition of the patients, such as weakness or tenacity. As DKT has a history to be used for patients with a weak condition, administration with consideration of the physical condition of the patients may lead to efficacy improvement.

The reported incidence of adverse effects associated with DKT, such as gastrointestinal discomfort and liver dysfunction, was 2.0%[20]. In the present study, no adverse effects were observed during the 1-month treatment period. Therefore, the treatment is generally considered safe and time

tested.

The limitations of this study include its open observational design, absence of a control group, short observation period, and inclusion of only Japanese patients.

In conclusion, DKT appears to be a safe and useful agent for the management of FI in patients with IAS dysfunction. Further prospective, double-blinded, randomized, controlled studies are required in the future to confirm the efficacy of DKT.

Conflicts of Interest

This study was done in collaboration with Tsumura & Co., T. Abe received a research funding from Tsumura & Co.

Author/Coauthor Contributions

T. Abe: Substantially contributed to the conception and design, acquisition, analysis, maintaining a database, and interpretation of data; critically drafted and revised the article for important intellectual content; and gave final approval of the version to be published.

M. Kunimoto: Substantially contributed to the conception and design, supplying patients, analysis, and interpretation of data; critically drafted and revised the article for important intellectual content; and gave final approval of the version to be published.

Y. Hachiro: Substantially contributed to the conception and design, acquisition, obtaining follow-up data and analysis; critically drafted and revised the article for important intellectual content; and gave final approval of the version to be published.

K. Ohara: Substantially contributed to the acquisition of data; critically drafted and revised the article for important intellectual content; and gave final approval of the version to be published.

M. Murakami: Substantially contributed to the acquisition of data; critically drafted and revised the article for important intellectual content; providing criticism of a manuscript; and gave final approval of the version to be published.

Information of the Institutional Review Board (IRB)

Name of the IRB: IRB of the Maebashi Hirosegawa Clinic

Approval code: 20180124-3

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