




Responder Analysis of Daikenchuto Treatment for Constipation in Poststroke Patients: A Subanalysis of a Randomized Control Trial

Ryutaro Arita, MD¹ , Takehiro Numata, MD, PhD¹,
 Shin Takayama, MD, PhD^{1,2}, Taku Obara, PhD²,
 Akiko Kikuchi, MD, PhD^{1,2}, Minoru Ohsawa, MD, PhD^{1,2},
 Akifumi Suzuki, PhD¹, Takashi Yokota, LLB¹, Mizue Kusaba, PhD¹,
 Nobuo Yaegashi, MD, PhD², and Tadashi Ishii, MD, PhD^{1,2}

Abstract

A traditional Japanese medicine, daikenchuto (DKT), is used for treating abdominal bloating and pain with coldness. In modern medicine, it is used to treat postoperative intestinal dysfunction and ileus. We previously showed the effective improvement in functional constipation with DKT in poststroke patients. However, response prediction for the treatment has not been elucidated. We investigated the data from the prior trial (UMIN000007393) to predict the DKT treatment response. We assessed the efficacy of DKT for chronic constipation in poststroke patients. Neurogenic bowel dysfunction score (NBDS) and the Gastrointestinal Symptom Rating Scale–constipation subscale (GSRs-C) score were newly analyzed comparing the pre- and post-intervention data after intake of 15 g of DKT extract granule daily for 4 weeks. Single and multiple regression analyses were performed to examine the correlations between the changes in NBDS, GSRs-C score, patient characteristics, clinical symptom score, gas volume in the gut, and serum calcitonin gene-related peptide level. The total NBDS and GSRs-C score were significantly reduced after DKT administration. The total NBDS, GSRs-C score, and gas volume score at baseline were significantly correlated with the change in these scores. Higher NBDS and GSRs-C scores and more gas volume in the gut may be possible predictors of response to DKT when treating constipation.

Keywords

traditional Japanese medicine, daikenchuto, constipation

Received April 25, 2019. Accepted for publication October 28, 2019.

Functional constipation in the elderly is one of the problems of the aging society of Japan. Over 1 million patients have cerebrovascular disease in Japan,¹ and approximately half of them have constipation.² The Japanese clinical practice guideline for functional constipation recommends laxatives or stimulant purgatives to improve symptoms.³ However, other clinical practice guidelines for medical treatment and its safety in the elderly do not recommend the prolonged use of laxatives. This is due to the risk of tolerance and the potential for abuse. Recommendations suggest the use of traditional Japanese (Kampo) medicine for the treatment of constipation.⁴

A Kampo medicine, daikenchuto (DKT), has been focused on as a treatment for gut motility issues,⁵ to promote microcirculation,⁶⁻⁸ and for its anti-inflammatory effect.⁹

Meta-analyses have shown the efficacy of DKT for improving intestinal dysfunction after abdominal surgery¹⁰ and for relieving the postoperative ileus in patients undergoing surgery for gastrointestinal cancer.¹¹ Currently, DKT is widely prescribed for abdominal surgeries in Japan.

¹ Tohoku University Hospital, Sendai, Miyagi, Japan

² Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan

Corresponding Author:

Shin Takayama, MD, PhD, Department of Kampo Medicine, Tohoku University Hospital, 1-1 Seiryō-machi, Aoba Ward, Sendai 980-8574, Miyagi, Japan.
 Email: takayama@med.tohoku.ac.jp



A few studies have shown that DKT is effective for constipation in adult, pediatric, and pregnant patients, as well as patients with Parkinson's disease.¹²⁻¹⁵ Our prior randomized controlled trial¹⁶ performed in 2014 reported that addition of DKT to the conventional laxative treatment can significantly improve constipation in poststroke patients based on a Constipation Scoring System (CSS)¹⁷ and gas volume in the gut compared with conventional treatment alone. One problem prescribing Kampo medicine is the selection of likely responders to the treatment. However, predictions of patient characteristics with the best DKT response were not given in the previous studies. Here, we investigated the correlation of the efficacy of DKT treatment for functional constipation in poststroke patients and patient characteristics to predict the response of patients to the DKT treatment.

Methods

The data analyzed in this study were collected from the previous randomized control trial.¹¹

Subjects

This study included both male and female patients aged older than 20 years with functional constipation who were diagnosed using Rome III criteria¹⁸ and who remained stable over a 6-month period from the onset of stroke (including cerebral hemorrhage, cerebral infarction, and subarachnoid hemorrhage). Patients received nutrition orally, or through a nasogastric, or gastrostomy tube. The subjects were recruited from National Hospital Organization Yonezawa Hospital, Ishinomaki Rehabilitation Hospital, National Hachinohe Hospital, Hikarigaoka Spellman Hospital, Miyagi Rifu Ekisaikai Hospital, and Wakuya Medical and Welfare Center from September 2012 to December 2013.

Exclusion criteria encompassed patients who were diagnosed with, or were at risk for the following: intestinal adhesion following abdominal surgery, inflammatory bowel diseases, malignant gastrointestinal diseases, hypoxic encephalopathy or myelopathy, history of interstitial pneumonia, liver and/or kidney dysfunction, severe diabetes (HbA1c $\geq 9\%$); cancer, and neurodegenerative disorders.

Study Protocol

The study protocol was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review boards of the research facilities and hospitals. Written informed consent was obtained from all the patients or their families. The data that support the findings of this study are openly available in the University hospital Medical Information Network data center at <https://www.umin.ac.jp/ctr/index.htm> (reference number UMIN00007393).

Patients were randomly assigned to the DKT treatment group or the control group. The control group underwent conventional treatment for constipation, such as laxative administration, enemas, and dis-impaction. The DKT treatment group additionally received 5.0 g of DKT extract granules for ethical use (Tsumura & Co, Tokyo, Japan) 3 times a day before meals for 4 weeks in addition to the conventional treatment. The total daily dosage of 15 g of DKT extract granules contains a dried herbal extract mixture in the following proportions: 3.0 g of JP ginseng, 5.0 g of JP processed ginger, 2.0 g of JP

Zanthoxylum fruit, and 10.0 g of JP koi. The Japanese Ministry of Health, Labor and Welfare has approved DKT for the treatment of abdominal cold feeling and pain accompanied by abdominal flatulence.¹⁹ The quality of this formulation (without koi) is registered in the Japanese Pharmacopoeia 17th Edition.²⁰ Each clinical constipation and gastrointestinal symptom was scored using the CSS (0-26 points), score without "Time" subscale, (when the symptom could not be accurately assessed), neurogenic bowel dysfunction score (NBDS, 0-47 points), and Gastrointestinal Symptom Rating Scale-Constipation Subscale (GSRs-C, 1-7 points), this was an average of items 10, 13, and 15.^{17,21,22} These scores are presented in the Supplemental Material. The higher scores indicate greater severity of the constipation or gastrointestinal symptoms. Fasting abdominal X-rays and blood samples were taken before and after the 4-week trial. Gas volume score (GVS) was calculated as a percentage of abdominal gas area, divided by abdominal square area, on abdominal radiographs with Koide's method²³ by using ImageJ²⁴ (0% to 100%). Plasma calcitonin gene-related peptide (CGRP) level was measured using SRL Inc, Tokyo, Japan.

Statistical Analysis

Baseline intergroup comparisons were conducted using Student's *t* tests for continuous variables and chi-square tests for categorical variables. Comparison between the DKT treatment and control groups at pre- and postintervention was performed using a 2-way analysis of variance (ANOVA). Comparisons of the CSS, NBDS, and GSRs-C total scores between pre- and postintervention of DKT were performed using a paired *t* test. Comparison of the NBDS and GSRs subscale scores were performed using Wilcoxon signed rank test. Linear and multiple regression analyses were performed with respect to CSS, NBDS, GSRs-C total score, and GVS as target variables, with age, sex, body mass index (BMI), and each score at baseline. Statistical significance was set at .05. Statistical analysis was performed using R software (version 2.5.2, The R Foundation for Statistical Computing Platform).

Results

Participant Characteristics at the Baseline

Thirty-four patients participated in the study, with 17 participants each assigned to the DKT treatment group and control group. Demographic characteristics of the participants and CSS, NBDS, GSRs-C, GVS, and serum CGRP levels at baseline are shown in Table 1.¹⁶ There was no significant difference in patient characteristics between the 2 groups.

Intergroup and Intragroup Comparison Analyses

Significant differences between the 2 groups were seen in the NBDS and GSRs-C total scores (2-way ANOVA, $P < .001$ and $P < .001$, respectively). In the DKT treatment group, the NBDS and GSRs-C scores were significantly improved at postintervention (NBDS, from 16.2 ± 8.3 to 11.2 ± 6.6 , $P < .001$; GSRs-C, from 3.5 ± 1.1 to 2.4 ± 0.9 , $P < .001$). These scores did not improve significantly in the control group (NBDS, from 18.7 ± 6.7 to 18.8 ± 6.7 , $P = .85$; GSRs-C, from 3.6 ± 1.5 to 3.7 ± 1.5 , $P = 1$; Figure 1). The subscale scores for the frequency of defecation (item 1) and time spent in defecation

Table 1. Characteristics of Study Patients in the Conventional Treatment With DKT and Conventional Treatment Alone Groups.^a

	DKT Treatment Group, Mean ± SD	Control Group, Mean ± SD	P
Total n (females n)	17 (9)	17 (8)	.73
Age, y	77.5 ± 11.9	78.7 ± 12.1	.78
Height, cm	156.3 ± 12.1	154.1 ± 9.3	.56
Body weight, kg	48.4 ± 10.2	48.3 ± 9.4	.98
Body mass index	19.9 ± 4.1	20.3 ± 3.8	.72
Diagnoses, n			.31
Brain infarction	10	14	
Cerebral hemorrhage	4	2	
Subarachnoid hemorrhage	3	1	
Illness duration, y	7.8 ± 6.1	4.8 ± 4.2	.15
CSS, ^b points	8.0 ± 3.1	8.1 ± 3.7	.96
NBDS, points	16.3 ± 8.3	18.7 ± 6.7	.35
GSRs-C, points	3.5 ± 1.1	3.6 ± 1.5	.84
CGRP, pg/mL	302 ± 207 ^c	262 ± 170	.54
GVS, %	16.3 ± 6.7	14.3 ± 7.1 ^d	.43

Abbreviations: DKT, daikenchuto; CSS, Constipation Scoring System; NBDS, Neurogenic Bowel Dysfunction Score; GSRs-C, Gastrointestinal Symptom Rating Scale–Constipation Subscale; CGRP, calcitonin gene-related peptide; GVS, gas volume score.

^aData are referred from Numata et al,¹⁶ with new additions of NBDS and GSRs Scores.

^bCSS: not including Q5.

^cCGRP: 1 missing value in the treatment group.

^dGVS: 1 missing value in the control group.

(item 2) on the NBDS were significantly reduced after intervention ($P = .02$ and $P < .01$, respectively).

As for CSS and GVS, we previously reported that significant differences were observed between the 2 groups (2-way ANOVA, $P < .01$ and $P = .03$, respectively). In the DKT treatment group, significant improvement was observed in the CSS score from 8.0 ± 3.1 to 6.0 ± 3.1 points ($P < .001$), and in the GVS from $16.3\% \pm 6.7\%$ to $9.9\% \pm 6.0\%$ ($P = .001$). In the control group, there were no significant improvement in the CSS score from 8.1 ± 3.7 to 8.2 ± 3.7 ($P = .33$), and in the GVS from $14.3\% \pm 7.1\%$ to $13.4\% \pm 8.0\%$ ($P = .61$).¹⁶

Linear and Multiple Regression Analyses

Linear regression analysis in the DKT treatment group revealed a significant correlation between the total scores of NBDS at baseline and the change in scores from pre- to postintervention, $R^2 = 0.37$, $F(1, 15) = 8.8$, $P = .009$; this was also true for GSRs-C, $R^2 = 0.43$, $F(1, 15) = 11.17$, $P = .004$ and GVS, $R^2 = 0.37$, $F(1, 15) = 8.7$, $P = .01$ (Figure 2). No significant correlations were observed between measured scores (NBDS, GSRs-C score, and GVS) and the baseline data of sex, age, and BMI. In the control group, no significant correlation was observed between the scores measured at baseline and the change in scores: NBDS, $R^2 = 0.001$, $F(1, 15) = 0.028$, $P = .87$; GSRs-C, $R^2 = 0.003$, $F(1, 15) = 0.005$, $P = .77$; GVS, $R^2 =$

0.12 , $F(1, 13) = 1.77$, $P = .22$, or baseline characteristics of the patients.

Multiple regression analysis revealed that NBDS scores at baseline predicted the change in NBDS ($\beta = 0.35$, $P = .028$) in the DKT treatment group; this was also true for GSRs-C ($\beta = 0.56$, $P = .015$), and a similar tendency was shown as for GVS ($\beta = 0.50$, $P = .06$; Table 2). No significant correlation was observed between the measured scores (NBDS, GSRs-C score, and GVS) and sex, age, and BMI.

One extraordinarily high value of CGRP >2000 pg/mL was noted in 1 participant in the DKT treatment group; this was excluded from the analysis. In linear and multiple regression analyses, no significant correlation was observed for either CGRP levels in the DKT treatment group or any score in the control group.

Safety

No adverse effect was observed in both groups.

Discussion

In this study, we found that DKT with conventional treatment decreased NBDS and GSRs total score, and that the initial NBDS, GSRs-C total score, and GVS were correlated with the degrees of their improvement in poststroke patients treated with DKT. This indicates that scores of these measurements at baseline can be used as predictors of the effectiveness of DKT treatment. In other words, DKT may be more effective for patients with moderate-to-severe constipation or with large amounts of intestinal gas, regardless of conventional treatment.

DKT can alleviate constipation in the chronic stage of stroke, despite the insufficient effect of conventional treatment on constipation. In this study, NBDS and GSRs-C score, particularly the subscale scores for constipation, were significantly reduced in the DKT treatment group. Constipation significantly impairs health-related quality of life (QOL).²⁵ NBDS is a symptom-based scale for neurogenic bowel dysfunction, which is correlated with QOL.²¹ GSRs-C is subjective assessment scales of QOL focusing on constipation.²² Accordingly, DKT could improve not only the symptoms of constipation but also QOL in patients with constipation.

DKT would be effective for prolonged constipation in the chronic stage after the onset of stroke, because the average illness duration after the onset of stroke was over 7 years ago in the DKT treatment group. The incidence of constipation is more frequent in the rehabilitation stage than in the acute stage of stroke.² Constipation involves nursing care, and many of the patients are administered laxatives. Prolonged use of laxatives is not recommended due to their risk of dependency.⁴ Continually increasing amounts of laxatives may be needed to produce a bowel movement. In Japan, magnesium oxide is often used for the treatment of chronic constipation. Recent research revealed magnesium oxide dosage and concomitant use of stimulant laxatives are significantly associated with high serum magnesium concentration.²⁶ DKT may hence have a

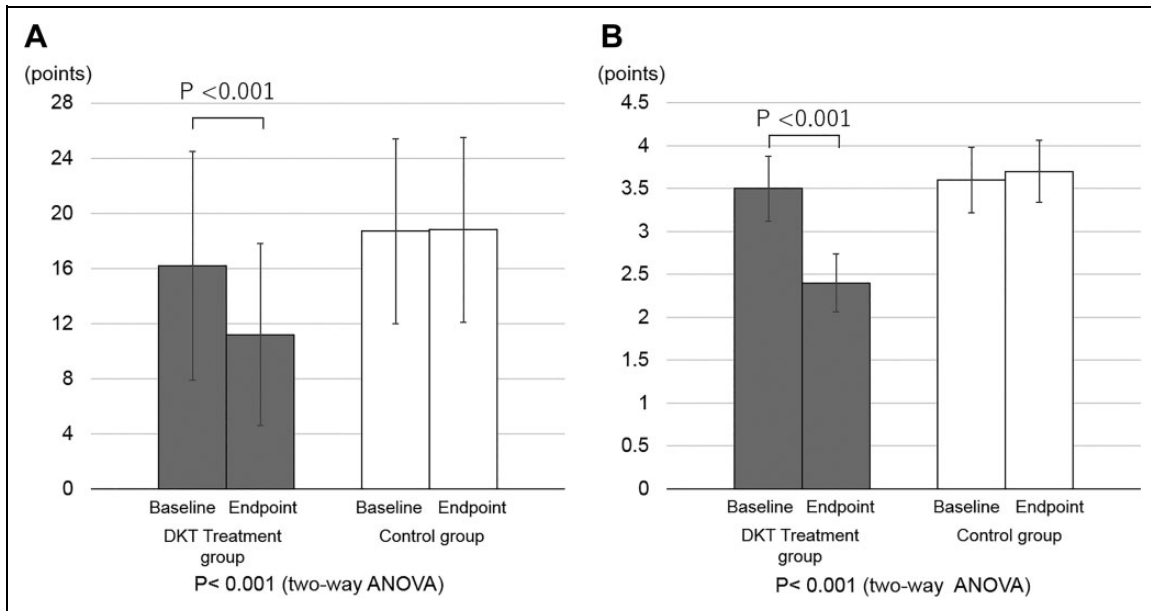


Figure 1. Changes in NBDS and GRS-C at the baseline and over 4 weeks of treatment. (A) Changes in the NBDS. Two-way analysis of variance (ANOVA) showed significant difference between the 2 groups ($P < .001$). In the DKT treatment group, The NBDS was significantly decreased from 16.2 ± 8.3 to 11.2 ± 6.6 points ($P < .001$), and in the control group, it changed from 18.7 ± 6.7 to 18.8 ± 6.7 points with no statistical significance. (B) Changes in the GRS-C. Two-way ANOVA showed significant difference between the 2 groups ($P < .001$). In the DKT treatment group, The GRS-C was significantly decreased from 3.5 ± 1.1 to 2.4 ± 0.9 points ($P < .001$), and in the control group, it changed from 3.6 ± 1.5 to 3.7 ± 1.5 points with no statistical significance. NBDS, Neurogenic Bowel Dysfunction Score; GRS-C, the Constipation subscale of Gastrointestinal Symptom Rating Scale; DKT, daikenchuto.

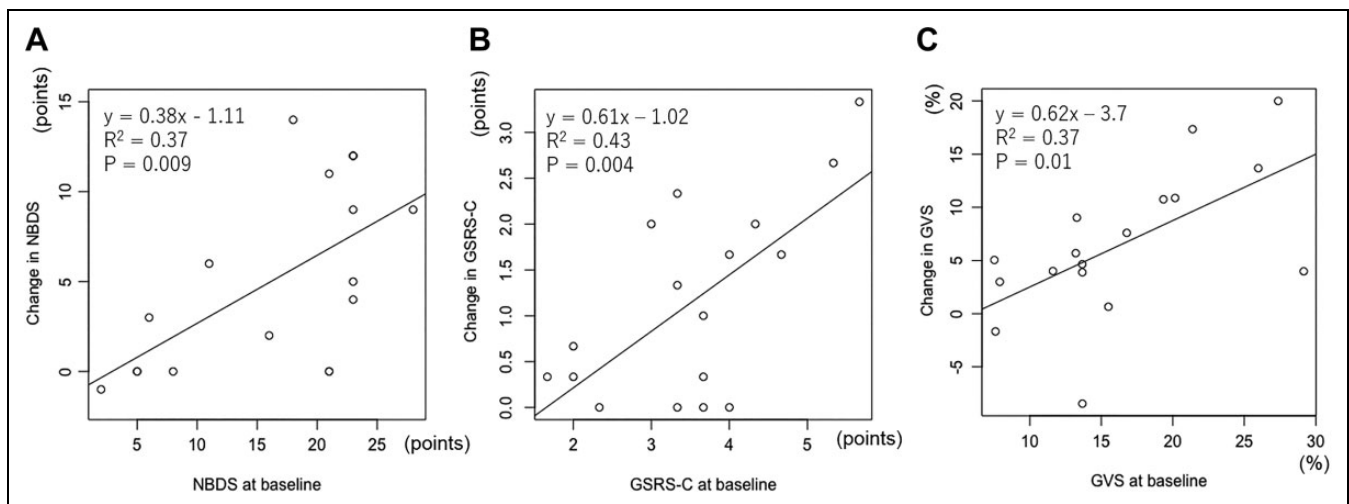


Figure 2. Correlation of the change in the NBDS, GRS-C, and GVS with their baseline values in the DKT treatment group. (A) Linear regression analysis showed significant correlation between the change in the NBDS and its baseline values: $R^2 = 0.37$, $F(1, 15) = 8.8$, $P = .009$. (B) Linear regression analysis showed significant correlation between the change in the GRS-C and its baseline values: $R^2 = 0.43$, $F(1, 15) = 11.17$, $P = .004$. (C) Linear regression analysis showed significant correlation between the change in the GVS and its baseline values: $R^2 = 0.37$, $F(1, 15) = 8.7$, $P = .01$. NBDS, Neurogenic Bowel Dysfunction Score; GRS-C, Gastrointestinal Symptom Rating Scale–Constipation Subscale; GVS, gas volume score; DKT, daikenchuto.

therapeutic effect and may reduce the dose of conventional laxatives in poststroke patients.

Poststroke patients have an increased risk for arteriosclerosis and often experience abdominal pain accompanied by a cold sensation in the abdomen (associated with low abdominal

blood perfusion). DKT has been proved to increase the intestinal blood flow. DKT activates transient receptor potential cation channel subfamily V1 and A1, which promote the secretion of CGRP and adrenomedullin, respectively.⁶⁻⁸ These peptides dilate the intestinal vessels and increase microcirculation.

Table 2. Multiple Regression Analysis of Variables Affecting NBDS, GSRS, and GVS in DKT Treatment Group.

	β	SE	t	P	Partial R ²
NBDS; multiple R ² = 0.44, adjusted R ² = 0.25					
(Intercept)	2.28	4.89	0.47	.65	
NBDS at baseline	0.35	0.14	2.51	.03*	0.34
Sex	-2.01	2.36	-0.85	.41	0.06
Age (≥ 80 y)	-1.24	2.43	-0.51	.62	0.02
Obesity (BMI ≥ 20 kg/m ²)	1.91	2.28	0.84	.42	0.06
GSRS-C; multiple R ² = 0.49, adjusted R ² = 0.32					
(Intercept)	-0.12	1.13	-0.10	.92	
GSRS-C at baseline	0.57	0.20	2.82	.02*	0.40
Sex	-0.56	0.45	-1.23	.24	0.11
Age (≥ 80 y)	0.14	0.48	0.30	.77	0.01
Obesity (BMI ≥ 20 kg/m ²)	0.04	0.45	0.10	.92	<0.001
GVS; multiple R ² = 0.47, adjusted R ² = 0.30					
(Intercept)	0.004	0.06	0.06	.95	
GVS at baseline	0.50	0.24	2.08	.06	0.26
Sex	0.01	0.03	0.47	.65	0.02
Age (≥ 80 y)	-0.05	0.03	-1.40	.19	0.14
Obesity (BMI ≥ 20 kg/m ²)	-0.02	0.03	-0.60	.56	0.03

Abbreviations: SE, standard error; DKT, daikenchuto; NBDS, Neurogenic Bowel Dysfunction Score; GSRS-C, Gastrointestinal Symptom Rating Scale—Constipation Subscale; GVS, gas volume score; BMI, body mass index.

*P < .05.

In a clinical study, DKT significantly increased blood flow in the superior mesenteric artery²⁷ and portal blood flow in the early treatment phase after oral administration²⁸ and significantly increased plasma CGRP levels in healthy subjects.²⁹ No significant difference was shown in the plasma CGRP level, potentially because of high variation in the CGRP levels; these results are identical to those of our previous study.

Recent studies have demonstrated that DKT altered the gut microbiota in rodents. Hasebe et al³⁰ reported that dietary administration of DKT increased several bacteria genera, including members of *Clostridia* and *Lactococcus lactis*. Metabolism of ginsenoside Rb1, which is a component of ginseng, was enhanced after administration of DKT. DKT changed mouse microbiota in a time- sex- and dose-dependent manner.³¹ Similar changes in the microbiota of the human gut may occur and may influence the clinical effectiveness of DKT. In this study, no significant correlation between sex and measured scores was observed. Further clinical studies, including gut microbiota and analysis of the administration of DKT, will be required in order to reveal the correlation between the change in microbiota and its' clinical effectiveness.

Our results correspond with the traditional concept of DKT treatment. A classical Chinese book *Jin Gui Yao Lue* introduced the application of DKT as suitable for patients with abdominal bloating and pain with coldness. These symptoms are partly caused by large amounts of intestinal gas, which can be evaluated by abdominal radiography. The effects of DKT treatment on GVS in this study support the traditional application of DKT.

There were some limitations in this study. This study used a small sample size limited to hospitalized patients. In addition, abdominal coldness, which is a symptom suitable for administration of DKT, was not measured using objective parameters, as these are not available. Finally, the placebo effect of oral administration cannot be overlooked. A randomized double-blind comparative study using a placebo would be ideal and would eliminate the placebo effect; however, it is difficult to produce a placebo without bioactivity that has a smell and flavor like DKT. Accordingly, the present study did not use a placebo control but rather compared conventional treatment.

Conclusion

Severe constipation and higher gas volume in the gut may be a possible predictor of response to the treatment of constipation with DKT in poststroke patients.

Acknowledgments

The authors sincerely appreciate the individuals who participated in the trial throughout the entire study as well as their families. They are grateful to the staff at National Yonezawa Hospital, Ishinomaki Rehabilitation Hospital, Miyagi Rifu Ekisaikai Hospital, Hikarigaoka Spellman Hospital, National Hachinohe Hospital, and Wakuya Medical and Welfare Center for their help with data collection. We would like to thank Editage (www.editage.com) for English language editing.

Author Contributions

ST and TN planned this study. TN performed data acquisition. TO and RA performed data analysis. RA, TO, and ST wrote the manuscript. AK, MO, AS, TY, MK, and TY gave suggestions for the manuscript. NY and TI acquired the permission of the institutional review board in Tohoku University School of Medicine.


Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: ST, AK, MO, and TI belong to the Department of Kampo and Integrative Medicine at Tohoku University School of Medicine. The department received a grant from Tsumura, a Japanese manufacturer of Kampo medicine; however, the grant was used as per Tohoku University rules. Potential conflicts of interests were addressed by the Tohoku University Benefit Reciprocity Committee and were managed appropriately. The other authors have no additional conflicts of interest to declare.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The present study was conducted using a Grant-in-Aid for Scientific Research (Academic Research Grant No. 23590867).

ORCID iD

Ryutaro Arita, MD  <https://orcid.org/0000-0003-4676-7242>

Supplemental material

Supplemental material for this article is available online.

Ethical Approval

The study protocol was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Boards of Tohoku University Hospital and the 6 collaborating hospitals. Written informed consent was obtained from all the patients or their families.

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