

EFFECTS OF HERBAL MEDICINE DAIKENCHUTO ON PATIENTS OF REFRACTORY OVERACTIVE BLADDER OR LOWER URINARY TRACT SYMPTOMS WITH CONSTIPATION OR HYPERSENSITIVITY TO COLD

Hypothesis / aims of study

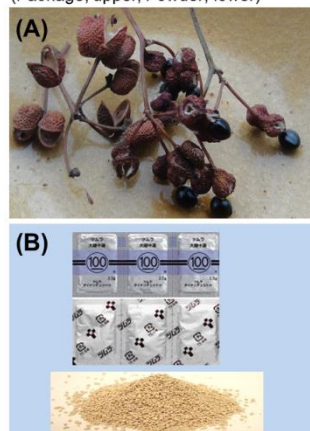
Daikenchuto (DKT, Tsumura Co., Ltd., Tokyo, Japan), a pharmaceutical-grade traditional Japanese (Kampo) medicine, has been widely used for the treatment of various gastrointestinal disorders including postoperative ileus and has been integrated into the modern medical care system in Japan as a prescription drug. The results of a clinical study have clearly indicated that DKT accelerates intestinal transit in healthy humans without severe adverse events including diarrhea (1). DKT consists of processed ginger rhizome, ginseng, Japanese pepper (zanthoxylum fruit), and as an additive maltose powder (Figure 1). Ginger rhizome, including ginger tea, can be taken to prevent common cold in winter season by keeping body hot in Japanese tradition. Indeed, DKT has effect to make human feel hot and can be also taken for treatment of hypersensitivity to cold (HC) in Japan.

On the other hand, colorectum and urinary bladder are closely related to each other in human and animals. In animal in vivo and vitro experiments, bladder-to-colorectum and colorectum-to-bladder reflexes were shown in healthy rats and pathological animal model. Furthermore, previous clinical studies showed that constipation alter bladder sensation. Taken together, conditions of colorectum and bladder tightly influence each other and management of colorectal condition may be important for overactive bladder (OAB) patients (2). In that sense, traditional anticholinergic therapies are limited in their effectiveness because constipation is one of the main side effects of anticholinergic drugs.

In general, environmental cold stress can elicit increases in urinary urgency and frequency, especially in elder people. The previous study showed that in men who were acclimatized to the Antarctic environment, exposure to cold for long durations caused increased excretion of urinary epinephrine, norepinephrine, and salivary cortisol, all of which were associated with significant changes in heart rate and blood pressure (3). Then, HC may be influence on lower urinary tract disorder too.

Taken all together, we hypothesize that constipation and HC can be indirect therapeutic targets for lower urinary tract symptom (LUTS)/OAB, and DKT may have a therapeutic role on LUTS/OAB patients in the way of treatment for bowel disorder or HC. The aim of this study is to assess the clinical effects of DKT on refractory LUTS/OAB patients with constipation or HC.

Figure 1 (A) Gross appearance of Japanese pepper (zanthoxylum fruit) **(B)** Gross appearance of Daikenchuto (Package; upper, Powder; lower)



The presented photos of DKT were taken from DKT drug information (Tsumura Co., Ltd.).

Table I. Characteristics of patients in this study

Patient		
Sex	Male	15
	Female	5
Age (y.o.)		77.4 ± 8.2
Prostate volume (gram)		29.0 ± 18.7
Medicated period (day)		35.9 ± 11.0
Distribution of patients		
	N for subjective analysis	N for objective analysis
All	20	11
HC with/without Constipation	17	10
Constipation with/without HC	14	6
HC with Constipation	11	5
Pretreatment for LUTS /OAB		
Alpha-blocker	16	
Anticholinergics agent	5	
5-alpha-reductase-inhibitor	2	
Anticholinesterase agent	2	
Cathartic drug	3	

HC; hypersensitivity to cold, LUTS; lower urinary tract symptom

Study design, materials and methods

In this study, refractory LUTS/OAB patients with constipation or HC were retrospectively enrolled. Among the patients receiving conventional medication for LUTS/OAB, DKT was additionally administered for treatment of constipation or HC. DKT was taken at dose of 5.0 g orally as a solution three times daily immediately before meals for one month. The study population is shown in Table I. Subjectively, total IPSS, IPSS subscore (voiding, storage, and post-voiding symptom score), QOL score, and OABSS were analysed comparing before and after the administration of DKT in all of patients. Objectively, voided volume, Qmax, Qave, and residual volume were assessed before and after the administration of DKT, using a flowmeter and ultrasound, respectively. The effects on constipation and HC were also evaluated according to self-description. All of the obtained data was evaluated classifying the enrolled patients into 3 groups; HC with/without constipation, constipation with/without HC, and HC with constipation. The HC and constipation were evaluated according to self-description. All data were indicated as the mean ± SEM, and $p < 0.05$ was considered to indicate significant difference. The changes from the baseline in total IPSS scores, IPSS subscores, QOL scores, and OABSS were analyzed, using a paired t-test. And the values of voided volume, Qmax, Qave, and residual urine were also compared using a paired t-test.

Results

There were no significant differences of age, prostate volume, medication period, and baseline value of subjective and objective parameters among the groups. The results of this study were shown in Table II and III. Of the 14 patients complaining of

constipation, 8 (61.5 %) returned to normal defecation after the treatment. Of the 17 patients complaining of HC, 11 (61.1%) improved to HC after the treatment. Seventeen (85.0 %) patients received some beneficial outcome including micturition, defecation, or HC in the overall patients. Of 5 patients with improvement of constipation and HC after DKT administration, IPSS and OABSS were improved (mean decrease of IPSS; -4.8, mean decrease of OABSS; -3.4, respectively). Severe adverse events were not revealed in this study.

Table II Subjective values after Daikenchuto administration

	N	Mean \pm SD	p value
IPSS			
Total			
All	20	-1.55 \pm 4.72	N.S.
HC with/without Constipation	17	-1.76 \pm 5.09	N.S.
Constipation with/without HC	14	-2.43 \pm 4.50	< 0.05
HC with Constipation	11	-2.73 \pm 4.96	< 0.05
Voiding symptom score			
All	20	0.10 \pm 3.73	N.S.
HC with/without Constipation	17	0.71 \pm 3.65	N.S.
Constipation with/without HC	14	-1.00 \pm 3.42	N.S.
HC with Constipation	11	-0.36 \pm 3.50	N.S.
Storage symptom score			
All	20	-1.50 \pm 2.54	< 0.05
HC with/without Constipation	17	-1.41 \pm 2.29	< 0.05
Constipation with/without HC	14	-1.71 \pm 2.79	< 0.05
HC with Constipation	11	-1.64 \pm 2.50	< 0.05
Post-voiding symptom score			
All	20	-0.45 \pm 1.67	N.S.
HC with/without Constipation	17	-0.76 \pm 1.39	N.S.
Constipation with/without HC	14	-0.29 \pm 1.49	< 0.05
HC with Constipation	11	-0.73 \pm 0.90	< 0.01
QOL			
All	20	-0.35 \pm 1.39	N.S.
HC with/without Constipation	17	-0.24 \pm 1.35	N.S.
Constipation with/without HC	14	-0.29 \pm 1.44	N.S.
HC with Constipation	11	-0.18 \pm 1.33	N.S.
OABSS			
All	20	-1.10 \pm 1.39	N.S.
HC with/without Constipation	17	-1.35 \pm 1.35	< 0.05
Constipation with/without HC	14	-1.71 \pm 1.44	< 0.05
HC with Constipation	11	-1.91 \pm 1.33	< 0.05

HC; hypersensitivity to cold

Table III Objective values before and after Daikenchuto administration

	N	Mean \pm S.D.		p value
		before	after	
Voided Volume (ml)				
All	11	143.15 \pm 77.84	150.69 \pm 66.12	N.S.
HC with/without Constipation	10	131.20 \pm 81.97	149.66 \pm 55.78	N.S.
Constipation with/without HC	6	130.82 \pm 101.63	166.42 \pm 73.38	N.S.
HC with Constipation	5	104.98 \pm 69.18	133.50 \pm 41.53	N.S.
Qmax (ml/sec)				
All	11	9.15 \pm 4.12	10.01 \pm 4.82	N.S.
HC with/without Constipation	10	8.99 \pm 4.31	10.31 \pm 4.97	N.S.
Constipation with/without HC	6	6.95 \pm 1.50	8.95 \pm 2.12	< 0.05
HC with Constipation	5	6.86 \pm 1.66	9.28 \pm 2.20	< 0.05
Qave (ml/sec)				
All	11	5.75 \pm 2.46	6.27 \pm 3.25	N.S.
HC with/without Constipation	10	5.65 \pm 2.56	6.35 \pm 3.42	N.S.
Constipation with/without HC	6	4.65 \pm 1.47	5.38 \pm 2.02	< 0.05
HC with Constipation	5	4.86 \pm 1.54	5.90 \pm 1.77	< 0.05
Residual urine (ml)				
All	11	41.92 \pm 29.60	29.36 \pm 31.31	N.S.
HC with/without Constipation	10	41.01 \pm 31.04	26.40 \pm 31.34	N.S.
Constipation with/without HC	6	53.50 \pm 31.33	27.50 \pm 34.94	< 0.05
HC with Constipation	5	56.00 \pm 34.35	26.00 \pm 38.85	< 0.05

HC; hypersensitivity to cold

Interpretation of results

The results of this study indicated that DKT improved symptoms, especially storage symptom, and objective findings in the refractory LUTS/OAB patients with constipation or HC. DKT may affect lower urinary tract as a consequence of improvement of constipation or HC.

Concluding message

DKT can be an effective add-on therapeutic option in management for refractory LUTS/OAB patients with constipation or HC.

References

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Disclosures

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