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Short communication

Clinical efficacy and tolerability of two Japanese traditional herbal medicines, Hachimi-jio-gan and Gosha-jinki-gan, for lower urinary tract symptoms with cold sensitivity

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ABSTRACT

We evaluated the efficacy and tolerability of Hachimi-jio-gan (HJG; 八味地黃丸 bā wèi dì huáng wán) and Gosha-jinki-gan (GJG; 濟生腎氣丸 jì shēng shèn qì wán), two traditional Japanese medicines, in 60 patients with lower urinary tract symptoms (LUTS) having cold sensitivity unresponsive to α1-blockers or antimuscarinic drugs. All patients received a mixture of HJG or GJG for 12 weeks in addition to α1-blockers or antimuscarinic drugs as add-on therapy. International Prostate Symptom Score, International Prostate Symptom Score–Quality of Life, Benign Prostatic Hyperplasia Impact Index, and the number of nocturnal voids were statistically much improved. However, there was no change in maximal urinary flow rate and post-void residual urine. Urinary 8-hydroxy-2-deoxyguanosine was statistically greatly improved from baseline after treatment in the HJG group compared to the GJG group. Adverse reactions were observed in 8.3% of patients, but all reactions were mild. Both HJG and GJG mixtures can serve as safe and effective potential therapeutic alternatives in patients with LUTS and cold sensitivity unresponsive to α1-blockers or antimuscarinic drugs. Additionally, HJG mixture was found to have antioxidative activity, and therefore further long-term clinical investigations are needed to examine its anti-aging effects in addition to its effect on urinary symptoms.

1. Introduction

The incidence of lower urinary tract symptoms (LUTS) gradually increases with age, greatly affecting quality of life (QOL).[1] Treatment options for LUTS range from behavioral modification, such as bladder training, to medical treatment. Antimuscarinic agents and α1-blockers are the most frequently prescribed drug options, but in Japan, complex formulations of Japanese traditional herbal medicines have been widely used and empirically evaluated in patients with LUTS and cold sensitivity.[2] Recent animal studies have revealed that Hachimi-jio-gan (HJG; 八味地黃丸 bā wèi dì huáng wán) and Gosha-jinki-gan (GJG; 濟生腎氣丸 jì shēng shèn qì wán) increased bladder capacity and decreased frequency of distension-induced bladder contractions via the spinal kappa-opioid receptor.[3] Previous clinical studies have demonstrated the efficacy of HJG and GJG, frequently in conjunction with antimuscarinic agents or α1-blockers, for treating LUTS.[4]

Although LUTS has various symptoms, we have focused on cold sensitivity, a key indication in Japanese traditional herbal medicine. In the present study, we attempted to determine the efficacy and safety of HJG and GJG as an add-on therapy for patients with LUTS and cold sensitivity, unresponsive to α1-blockers or antimuscarinic drugs by using the International Prostate Symptom Score (IPSS), IPSS-Quality of Life (IPSS-QOL), Benign Prostatic Hyperplasia Impact Index (BII), uroflowmetry (UFM), frequency volume chart (FVC), and urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG).

2. Materials and methods

2.1. Safety analysis

Before commencing the study, we obtained approval from our institution's ethical review board and obtained written informed

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consent from all participants after thoroughly explaining the efficacy and possible adverse reactions of HJG (八味地黃丸 bā wèi dì huáng wán) and GJG (濟生腎氣丸 jì shēng shèn qì wán) mixture.

2.2. Hachimi-jio-gan and Gosha-jinki-gan

HJG (TJ-7; Tsumura Co., Tokyo, Japan) is the extract product which included 4.0 g of the compound extracts of 8 herbal medicines: Rehmanniae radix (地黃 dì huáng) (6.0 g), Corni fructus (山茱萸 shān zhū yú) (3.0 g), Dioscoreae rhizoma (山藥 shān yào) (3.0 g), Hoelen (茯苓 fú ling) (3.0 g), Alismatis rhizoma (澤瀉 zé xiè) (3.0 g), Moutan cortex (牡丹皮 mǔ dān pí) (2.5 g), Cinnamoni cortex (桂皮 guì pí) (1.0 g) and heat-proscessed Aconiti radix (附子 fù zǐ) (0.5 g). On the other hand, GJG (TJ-107; Tsumura Co., Tokyo, Japan) includes 4.5 g of the compound extracts of 10 herbal medicines: Rehmanniae radix (5.0 g), Achyranthis radix (牛膝 niú xī) (3.0 g), Corni fructus (3.0 g), Dioscoreae rhizoma (3.0 g), Hoelen (3.0 g), Plantaginis semen (車前子 chē qián zǐ) (3.0 g), Alismatis rhizoma (3.0 g), Moutan cortex (3.0 g), Cinnamoni cortex (1.0 g) and heat-proscessed Aconiti radix (1.0 g). They are standaedized spray-dried water extracts, which include magnesium stearate, lactose and fructose fatty acid esters as diluents. The manufacturing process meets all requirements of the Japanese and international GMP guidelines.

2.3. Eligibility and study design

Patients who visited our hospital with LUTS for consultation between November 2012 and May 2014 were considered for enrollment. The inclusion criteria were as follows: age 60 years or older; IPSS total score of 8 or more points despite treatment with α1-blockers or antimuscarinic drugs for at least 4 weeks; IPSS-QOL score of 3 or more points; subjective complaints such as cold hands and/or legs even in a warm environment. Patients with any complications possibly affect the voiding function, such as neurogenic bladder, urethral stricture, and active urinary tract infection, were excluded.

The study was designed as an open, non-randomized, two-armed study comparing two Japanese traditional herbal medicines for treating LUTS. All patients received 7.5 g/day HJG or GJG mixture for 12 weeks as add-on therapy to α1-blockers or antimuscarinic drugs. Blood cell count, standard chemistry panel, and urinalysis were assessed routinely at the initial examination. IPSS, IPSS-QOL, BII, 3-day FVC and UFM were examined before and after administration. We evaluated urinary 8-OHdG levels as a marker of oxidative stress using an ICR-001 device (The selling agency of ICR-001 device is Selista Inc, Tokyo) according to the manufacturer's recommendations.

2.4. Statistical analysis

Data are reported as mean ± SD. Data were analyzed using SPSS software, version 12.0 (IBM, Chicago, IL). To evaluate the treatment effect between before and after mediation, Wilcoxon's signed-rank test was used to Tables 1 and 4. The other hand, Student's t-test was used to Tables 2 and 3. $P < 0.05$ was considered significant.

3. Results

3.1. Effect of HJG (八味地黃丸 bā wèi dì huáng wán) and GJG (濟生腎氣丸 jì shēng shèn qì wán)

Clinical characteristics of the 60 patients are shown in Table 1. Thirty patients (23 men and 7 women, aged 68–80 years, mean 74.7 ± 6.2) received HJG mixture and 30 (24 men and 6 women,

Table 1
Clinical characteristics of the 60 patients.

	HJG	GJG	P value[#]
Age (years)	74.7 ± 6.2	75.5 ± 5.1	0.142
Sex (M/F)	23/7	24/6	
IPSS Total score	13.4 ± 5.2	14.5 ± 6.2	0.182
Storage score	6.4 ± 2.3	8.1 ± 2.9	0.014
Voiding score	7.0 ± 4.1	6.4 ± 4.6	0.974
QOL	3.4 ± 1.4	4.2 ± 1.2	0.028
BII	4.4 ± 2.6	6.3 ± 4.1	0.055
UFM PVR (ml)	36.1 ± 35.2	26.1 ± 26.7	0.362
Qmax (ml/s)	10.9 ± 5.6	10.7 ± 10.1	0.793
Nocturnal voids (times)	2.8 ± 1.0	4.4 ± 1.3	<0.001
8-OHdG (ng/ml creatinine)	17.2 ± 5.8	16.9 ± 10.7	0.725

HJG = Hachimi-jio-gan.
GJG = Gosha-jinki-gan.
IPSS = International Prostate Symptom Score.
QOL = quality of life.
BII = benign prostatic hyperplasia impact index.
UFM = uroflowmetry.
PVR = post-void residual urine.
Qmax = maximum flow rate.
8-OHdG = 8-hydroxy-2′-deoxyguanosine.
[#]Wilcoxon's signed rank test ($p < 0.05$ was considered significant).

Table 2
Effects of HJG on LUTS resistant to α1 blockers and antimuscarinic drugs.

	Baseline	After 12 weeks	P value[#]
IPSS Total score	13.4 ± 5.2	9.7 ± 5.1	<0.001
Storage score	6.4 ± 2.3	4.7 ± 2.3	<0.001
Voiding score	7.0 ± 4.1	4.9 ± 3.4	0.008
QOL	3.4 ± 1.4	2.6 ± 1.3	0.014
BII	4.4 ± 2.6	2.9 ± 1.9	0.021
UFM PRV (ml)	36.1 ± 35.2	37.2 ± 29.4	0.935
Qmax (ml/s)	10.9 ± 5.6	9.8 ± 4.6	0.361
Nocturnal voids (times)	2.8 ± 1.0	2.2 ± 1.1	0.005
8-OHdG (ng/ml creatinine)	17.2 ± 5.8	12.3 ± 4.1	0.001

HJG = Hachimi-Jio-gan.
LUTS = lower urinary tract symptoms.
IPSS = International Prostate Symptom Score.
QOL = quality of life.
BII = benign prostatic hyperplasia impact index.
PVR = post-void residual urine.
Qmax = maximum flow rate.
8-OHdG = 8-hydroxy-2′-deoxyguanosine.
[#]Student's t-test ($p < 0.05$ was considered significant).

Table 3
Effects of GJG on LUTS resistant to α1 blockers and antimuscarinic drugs.

	Baseline	After 12 W	P Value[#]
IPSS Total score	14.5 ± 6.2	10.4 ± 3.9	<0.001
Storage score	8.1 ± 2.9	6.1 ± 2.0	0.003
Voiding score	6.4 ± 4.6	4.3 ± 3.2	0.012
QOL	4.2 ± 1.2	3.3 ± 1.5	0.007
BII	6.3 ± 4.1	5.0 ± 3.4	0.024
UFM PVR(ml)	26.1 ± 26.7	24.2 ± 23.4	0.821
Qmax (ml/s)	10.7 ± 10.0	10.3 ± 8.2	0.802
Nocturnal voids (times)	4.4 ± 1.3	3.5 ± 1.9	0.008
8-OHdG (ng/ml creatinine)	16.9 ± 10.5	14.8 ± 6.5	0.241

GJG = Gosha-jinki-gan.
IPSS = International Prostate Symptom Score.
QOL = quality of life.
BII = benign prostatic hyperplasia impact index.
UFM = uroflowmetry.
PVR = post-void residual urine.
Qmax = maximum flow rate.
8-OHdG = 8-hydroxy-2′-deoxyguanosine.
[#]Student's t-test ($p < 0.05$ was considered significant).

Table 4
Change from baseline after 12 weeks of treatment with HJG or GJG.

	HJG	GJG	P Value[#]
IPSS Total score	−2.6 ± 3.8	−4.3 ± 4.3	0.113
Storage score	−1.1 ± 1.7	−2.1 ± 2.5	0.151
Voiding score	−1.5 ± 3.3	−2.2 ± 2.9	0.305
QOL	−0.8 ± 1.4	−0.9 ± 1.6	0.805
BII	−1.6 ± 3.0	−1.4 ± 3.1	0.909
UFM PVR (ml)	0.5 ± 44	−1.4 ± 31	0.892
Qmax (ml/s)	−1.0 ± 5.3	−0.3 ± 7.0	0.703
Nocturnal voids (times)	−0.6 ± 0.9	−0.8 ± 1.16	0.388
8-OHdG (ng/ml creatinine)	−5.7 ± 5.4	−0.9 ± 5.1	0.017

HJG = Hachimi-jio-gan.
GJG = Gosha-jinki-gan.
IPSS=International Prostate Symptom Score.
QOL = quality of life.
BII = benign prostatic hyperplasia impact index.
UFM = uroflowmetry.
PVR = post-void residual urine.
Qmax = maximum flow rate.
8-OHdG = 8-hydroxy-2′-deoxyguanosine.
[#]Wilcoxon's signed rank test ($p < 0.05$ was considered significant).

aged 67–80 years, mean 75.5 ± 5.1) received GJG mixture. Total IPSS score, BII, post-void residual urine (PVR), maximal urinary flow rate (Qmax), and urinary 8-OHdG did not significantly differ between the HJG and GJG groups. However, IPSS storage subscore, QOL and nocturnal voids were significantly greater in the GJG group.

Results of treatment with HJG are shown in Table 2. Significantly improved subjective outcomes were IPSS total and subscore, QOL, and BII, and significantly improved objective outcomes were fewer nocturnal voids and lower urinary 8-OHdG. Other objective parameters such as Qmax and PVR did not improve. In the GJG group (Table 3), significantly improved subjective outcomes were IPSS total and subscore, QOL, and BII. Although the number of nocturnal voids decreased significantly, other objective parameters, namely, Qmax, PVR, and urinary 8-OHdG did not improve.

Table 4 presents the change from baseline after treatment. No statistical significant differences were found between the HJG and GJG groups in terms of total IPSS score, IPSS subscore, QOL, BII, PVR, Qmax, or number of nocturnal voids. However, there was a significantly larger decrease in urinary 8-OHdG in the HJG group (−5.7 ± 5.4) than in the GJG group (−0.9 ± 5.1) ($P = 0.017$).

3.2. Safety and tolerability

Adverse reactions of HJG were observed in 2 men (6.7%). The symptoms were gastric discomfort and nausea. On the other hand, the adverse reactions of GJG were observed in 2 men and 1 woman (10%). The symptoms were gastric discomfort in 2 patients and nausea in one, and all such cases were of mild sevirity (grade 1) and were followed up closely without therapy. No patients discontinued the treatment due to these adverse evevnts.

4. Discussion

HJG (八味地黃丸 bā wèi dì huáng wán) and its modified prescription GJG (濟生腎氣丸 jì shēng shèn qì wán) are prescribed to patients with edema in the lower extremities and LUTS with cold sensitivity. The way by which HJG and GJG treat LUTS have remained unclear, but resent basic research has gradually clarified these mechanisms.[5–9] Gotoh et al.[3] reported that the effects on LUTS are associated with inhibition of the micturation reflex and reduction of bladder sensation via spinal kappa-opioid receptors.[7] Among the ingredients contained in these medicines, Aconiti Rhizhoma (附子 fù zǐ) from *Aconitum carmichaelii* may be mainly responsible for the antinociceptive effect.[9] In addition to the effect of Aconiti Rhizhoma, Kupelian et al. hypothesized that other ingredients, such as Alismatis Rhizoma (澤瀉 zé xiè) from *Alisma orientale* and Poria (茯苓 fú ling) from *Poria cocos*, could be effective for decreasing nocturnal urine production and thereby regulating the distribution of fluid in the body.[10] In the present study, we selected patients with LUTS unresponsive to both α1-blockers and antimuscarinic drugs. We had a tendency of prescribing GJG for patients with more edematous extremities, so that it is suggested that IPSS storage subscore, QOL and nocturnal voids were significantly greater in the GJG group.

Some people have experience of "cool hands and/or legs (四肢冰冷 sì zhī bīng lěng)" even in a warm environment, without clinically evident cardiovascular disease.[11] These sensations are an indication of cold sensitivity, an important concept in oriental medicine. By comparing the cold stress rat model to control rats, Imamura et al. reported that cold stress-induced detrusor overactivity is mediated through a resiniferatoxin-sensitive C-fiber sensory nerve pathway.[12] In a separate study, Imamura et al. showed that HJG-treated rats tended to have higher skin temperature during low-temperature exposure and that their cold stress-induced detrusor overactivity associated with increased micturition frequency and decreased micturition volume was inhibited.[13] In this study, we didn't evaluate the relevance of LUTS and cold sensitivity by continuous skin surface temperature measurement. However, our findings in of improved subjective and objective outcomes for LUTS are support these previous findings in the cold rat model.

Oxidative stress is reported to result in pathophysiological conditions of the urinary bladder via damage to the urothelium and sensitization of bladder afferent signaling.[14] Previous studies have shown that oxidative stress mediates capsaicin-sensitive C-fibers to induce bladder hyperactivity.[15] Therefore, the elimination of oxidative stress might ameliorate pathophysiological conditions in the urinary bladder and be a possible therapy for LUTS unresponsive to α1-blockers or antimuscarinic drugs.[16,17] In the present study, we found anti-oxidative effects of HJG but not GJG. The GJG formula is a modification of HJG formed by addition of Achyranthis Radix (牛膝 niú xī) from *Achyranthes fauriei* and Plantaginis Semen (車前子 chē qián zǐ) from *Plantago asiatica*, yet there was no anti-oxidative effect as indicated by production of 8-OHdG. The reason for this is not clear from the present study, but recent studies have revealed that Chinese medicinal herbs (CMHs; 中草藥 zhōng cǎo yào)indicate anti-oxidative effects to a living body by biological response modifier (BRM).[18] Adding two herbal agents (Achyranthis Radix and Plantaginis Semen) to HJG, BRM of HJG might be influenced to the anti-oxidative effects. Although anticholinergic agents are presently most commonly used in the treatment of overactive bladder, the anti-oxidant properties of HJG could have a therapeutic role in the treatment of bladder hyperactivity.

The major drawbacks of this study are small number of patients, lack of a placebo-controlled group, and lack urodynamic study data. The possibility of a placebo effect may be high in LUTS, which has a strong placebo component. Therefore, it remains unclear whether HJG and GJG may be potential therapeutic alternatives in elderly patients with LUTS and cold sensitivity unresponsive to α1-blockers or antimuscarinic drugs. A future prospective evaluation is necessary.

5. Conclusions

The HJG (八味地黃丸 bā wèi dì huáng wán) and GJG (濟生腎氣丸 jì shēng shèn qì wán) Japanese herbal formulations might have the potential to provide additional therapeutic effects in treating cold stress–exacerbated LUTS resistant to α1-blockers or antimuscarinic

drugs. However, further clinical investigations are required to elucidate their precise mechanisms.

Conflict of interest

None.

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