EFFECT OF CHINESE HERBAL MEDICINE ON OVERACTIVE BLADDER

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Gosha-jinki-gan (GJG), a traditional Chinese medicine, is known to be potentially effective for urinary disturbance. For the clinical evaluation of Gosha-jinki-gan, we administered GJG for 6 weeks to elderly male patients with overactive bladder (OAB) and assessed its efficacy and tolerability. In this study, 30 male patients with over 6 months of OAB symptoms had received 2.5 g GJG mixture × 3/day. After 6 weeks of treatment, the efficacy, safety, and tolerability were assessed. We evaluated International Prostate Symptom Score (I-PSS), Overactive Bladder Symptom Score (OABSS), quality of life (QOL), maximal urinary flow rate (Qmax), average urinary flow rate (Qave), incidence of urinary incontinence, and post-void residual before and after treatment. We observed significant improvements in I-PSS (15.2 ± 1.0 vs. 12.0 ± 0.9, $p < 0.0001$), OABSS (7.5 ± 0.6 vs. 4.9 ± 0.5, $p < 0.0001$), and QOL score (4.4 ± 1.0 vs. 3.3 ± 1.1, $p < 0.0001$, Wilcoxon rank sum test). GJG was significantly effective in improving urgency, micturition frequency, nocturia, and urinary incontinence ($p < 0.05$). However, Qmax, Qave, and post void residual did not significantly change. Mild adverse effects were observed in 3 cases. The symptoms were diarrhea, nausea, and urinary frequency. These data suggest that *Gosha-jinki-gan* may be a new potential therapeutic agent for OAB without deterioration of voiding function in men with benign prostatic obstruction (BPO).

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Key words : Overactive bladder, Phytotherapy, Chinese herbal medicine, *Goshajinkigan*

INTRODUCTION

Overactive bladder (OAB) is a condition characterized by urinary urgency, with or without urge incontinence, usually associated with frequency and nocturia, and is known to significantly deteriorate one's quality of life[1]. Recent figures from the National Overactive Bladder Evaluation (NOBLE) program show that the overall prevalence of OAB is 16.5% in the United States-representing more than 34 million men and women[2,3]. Another study indicated that the prevalence of OAB in Japan may be similar : in a survey of 10,096 Japanese men and women aged 40 years or older, the prevalence of OAB was 12.4%[4]. The prevalence rates for OAB wet and dry were 6.4 and 6.0%, respectively.

Antimuscarinic drug therapy, in conjunction with behavioral therapy such as bladder retraining, remains the first line management of patients with OAB. While currently available antimuscarinic agents have proven their efficacy, the drugs are associated with bothersome antimuscarinic side effects of dry mouth, constipation, somnolence, or blurred vision. The development of new antimuscarinic drugs such as tolterodine, darifenacin, and solifenacin has improved the tolerance due to reduced adverse side effects, but in some OAB patients, especially with bladder outlet obstruction, these drugs are still contraindicated due to the risk of acute urinary retention.

Chinese herbal medicines are becoming more and more popular around the world, and are actually being used widely in China, Japan, and South Korea for treatment of various diseases. *Gosha-jinki-gan* (GJG), a traditional Chinese medicine, has been effective for patients with lower urinary tract symptoms (LUTS) with less frequent adverse effects compared with antichorinergics. Several clinical studies have reported that GJG improved the QOL in patients with storage symptoms[5,6]. Tokunaga et al. administered GJG in patients with urinary disturbance and reported that it significantly decreased the micturition frequency, although voiding symptoms did not improve[7]. A recent study suggested that activated spinal kappa-opioid receptors inhibited bladder motility and were associated with the anti-pollakisuria effects of GJG[8]. However, the potential clinical role and the safety of GJG have not been explored extensively.

For the clinical evaluation of *Gosha-jinki-gan*, we prescribed GJG mixture for 6 weeks to male patients with OAB. To assess the effect of GJG on OAB symptoms, we evaluated the International Prostate Symptom Score (I-PSS), Overactive Bladder Symptom Score (OABSS), Quality of life (QOL) index, incidence of urinary incontinence per day, uroflowmetry, and postvoid residual.

METHODS

1) Study design and patient selection

The study was approved by the Ethical Committee of our institutinal ethics board for clinical study and all

patients provided informed consent. Thirty men with a mean age of 65.7 years (range, 40–85 years) who presented to the outpatient clinic complaining of irritative bladder symptoms were enrolled in the current study. All patients were subjected to a diagnostic work-up of medical history I-PSS, OABSS and QOL index, physical examination (including digital rectal examination [DRE]), blood biochemistry (including PSA), urinalysis, and urine culture. The I-PSS was also divided into the storage symptom scores (frequency, nocturia, and urgency) and the voiding symptom scores (incomplete emptying, reducing stream, straining, and intermittency). Transabdominal ultrasonic estimation of prostate volume was also performed. The gland volume was estimated from anteroposterior, transverse and sagittal dimensions, assuming an ellipsoid prostate.

The inclusion criteria were: (i) one or more episode (s) of urinary urgency/day; (ii) a score of three or more points on the OABSS; and (iii) two or more points on the storage symptom scores of I-PSS. Patients suspected of prostate cancer based on digital rectal examination and serum prostate-specific antigen (PSA) level, were excluded from the study. Patients with any complications possibly affect the voiding function, such as neurogenic bladder, severe diabetes, urethral stricture, active urinary tract infection, and cerebrovascular diseases were excluded. Patients with any history of medical or surgical therapeutic intervention for their urinary symptoms were also excluded. Patients having post void residual of 100 ml or greater were excluded in the current study.

All patients received 2.5 g GJG mixture × 3/day. After 6 weeks of treatment, the efficacy, safety and tolerability were assessed. I-PSS, OABSS, QOL index, and incidence of urinary incontinence per day were recorded, and uroflowmetric study was also performed. Adverse effects were recorded.

2) Statistical analysis

Using the Wilcoxon rank sum test, several parameters before and after treatment of GJG was examined. The statistical analysis of OABSS, IPSS, QOL index, storage and voiding symptom scores, and incidence of urinary incontinence per day were calculated by the Wilcoxon rank sum test. P values <0.05 were considered statistically significant.

Table 1. Storage symptoms and uroflowmetry palameters at baseline and 6 week after treatment

	Baseline	After 6 weeks	p Value[a]
No. pts		30	
I-PSS	15.2±1.0	12.0±0.9	0.0001
Voiding sympotm score	7.5±0.6	6.6±0.6	0.0097
Storage sympotm score	7.8±0.5	5.4±0.4	0.0001
OABSS	7.5±0.6	4.9±0.5	0.0001
QOL index	4.4±0.2	3.3±0.2	0.0001
Daytime frequency	3.1±0.3	2.2±0.2	0.0001
Urgency	2.4±0.3	1.4±0.3	0.0006
Noctuira	2.3±0.2	1.8±0.2	0.0045
Incontinence	0.8±0.3	0.3±0.1	0.0269
Qmax (ml/sec)	16.3±1.4	15.1±1.3	0.1328
Residual Volume (ml)	28.1±4.9	27.3±5.8	0.8911
Prostate volume (ml)	30.7±1.7	31.4±2.4	0.8121

[a] The statistical significance of the differences in the analyses was calculated using the Wilcoxon rank sum test.

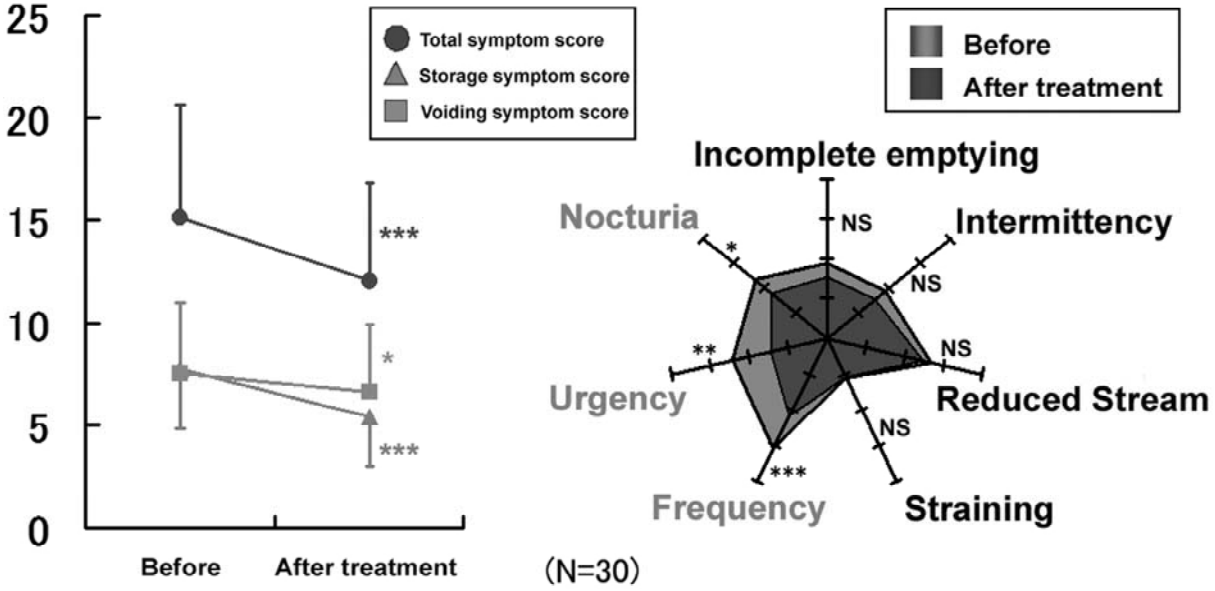

Fig. 1. Effect of GJG on storage and voiding symptom scores of the International Prostate Symptom Score (I-PSS). Both storage and voiding symptom scores improved (7.8±0.5 to 5.0±0.4, $p<0.0001$ and 7.5±0.6 to 6.6±0.6, $p=0.0097$, Wilcoxon rank-sum test, respectively). The Gosha-jinki-gan was significantly ($p<0.01$) effective for improving urgency, micturition frequency, and nocturia. In contrast, GJG was not significantly effective for the voiding symptoms (intermittency, straining, weak stream, and incomplete emptying).

RESULTS

1) Effect of Gosha-jinkigan on OAB

A total of 30 men were included in the current study. The mean patient age±SD was 65.7±8.0 years. The mean prostate volume was 30.7±9.3 mL (range 13.4–57.4 mL). I-PSS, OABSS, and QOL index were 15.2±1.0, 7.5±0.6, and 4.4±1.0, respectively. The mean baseline PSA was 1.95 ng/mL. Table 1 showed the effect of GJG on I-PSS, OABSS, and QOL index of OAB patients. Total I-PSS, OABSS, and QOL score significantly decreased after treatment with GJG ($p < 0.0001$). Both the total storage and voiding symptom scores improved after treatment (7.8±0.5 vs. 5.0±0.4, $p < 0.0001$ and 7.5±0.6 vs. 6.6±0.6, $p = 0.0097$, respectively, Fig. 1). GJG was also significantly ($p < 0.01$) effective for improving each storage symptoms (urgency, micturition frequency, and nocturia). GJG did not significantly affect the voiding symptoms (intermittency, straining, weak stream, and incomplete emptying). Maximum and average flow rates from baseline were not significantly changed after treatment with GJG, 16.3±1.4 to 15.1±1.3, $p = 0.1328$ and 7.3±0.7 to 6.9±0.6, $p = 0.2754$, respectively. No significant change in post void residual was observed after treatment (28.1±4.9 to 27.3±5.8, $p = 0.8911$). Invidence of urinary incontinence per day significantly decreased after treatment with GJG (0.8±0.3 to 0.3±0.1, $p = 0.0269$). Eight wet OAB patients became pad-free after treatment of GJG. The *Gosha-jinki-gan* was also effective for wet OAB.

2) Safety and tolerability

The adverse reactions occurred in only three men (10%) treated with GJG and all such cases were of mild severity (Table 2). The symptoms were nausea, diarrhea and worsening of daytime frequency. The two men, who had gastrointestinal symptoms after medication, responded to dose reduction or withdrawal from treatment. The worsening of daytime frequency occurred in one BOO patient who had voiding difficulty, and was then switched to alpha-blockade. Dry mouth did not occur.

DISCUSSION

This study is the first reported trial to evaluate the effect of *Gosha-jinkigan* on overactive bladder. In this trial, we did not compare GJG with placebo control or other drugs like anti-cholinergics, and therefore it might not reflect the exact efficacy of GJG. However, the dramatic changes observed only in irritative symptoms suggested that GJG may be potentially effective for urinary storage symptoms without a troublesome anticholinergic adverse effect. Furthermore, the present study demonstrated that GJG did not worsen uroflowmetric parameters in patients with OAB, unlike typical anticholinergic drugs.

Table 2. Adverse effect of Gosha-jinki-gan

Toxicity	Grade CTC	
Diarrhea	1	Responded to dose reduction
Nausea	1	Responded to withdrawal
Frequency	1	Shift to α-blockade

The effective management of OAB depends on a through evaluation followed by identification and treatment of all likely causes and contributing factors[11]. The symptoms of OAB often have several etiologies, and effective treatment often requires a multimodal approach involving both nonpharmacologic and pharmacologic interventions. Pharmacotherapy is generally based on blocking bladder muscarinic receptor activity using anticholinergic drugs[12]. However, the antimuscarinic agents are generally difficult to be administered to men with bladder outlet obstruction, due to the theoretical concern that inhibition of detrusor contractility may exacerbate voiding difficulties. Recently, some studies have actually proved favorable for antimuscarinic therapy in regards to safety and tolerability[13,19,20], but such therapy would still be difficult in clinical OAB management due to several side effects. The most commonly reported adverse effect associated with anitimuscarinic drugs is dry mouth. Dyspepsia, constipation, abdominal pain, and flatulence were reported by 1% to 10% of patients who received antimuscarinic drugs[14]. In addition, antimuscarinic drugs are contraindicated in patients with angle-closure glaucoma and must be used with caution in patients with GI obstructive disorders.

What therapy could we select for OAB symptoms if anti-cholinergic agents were contraindicated, especially in elderly patients with BPO ? Some men with BPH are given the option of herbal remedies for their symptoms, including saw palmetto and stinging nettle roots, rather than medication or surgery[15]. Many herbal agents might not necessarily be more effective than standard pharmacologic therapy of alpha-blockade for BPH. A recent study reported that although saw palmetto is used by over 2 million men in the United States for the treatment of benign prostatic hyperplasia, it did not improve symptoms[16]. They are most likely used in a less enthusiastic way when physicians are left with no other choice for therapy However, the advantage of herbal therapy are mild action to elderly patients, and the adverse effects are of mild or moderate severity. In general, for elderly patients, important considerations include tolerability, absence of interactions to other drugs, and the availability of a range of dosages to tailor treatment to individual patients. The present study showed that GJG has the advantage of causing few side effects. Only three patients had minor adverse symptoms of nausea, diarrhea, and urinary frequency, and all of them responded to dose reduction or withdrawal from therapy. No patient reported serious adverse effects. Therefore, GJG can be safely administered to elderly patients who may have complications.

Gosha-jinkigan is composed of 10 crude drugs in fixed

proportions : *Rehamanniae* radix (5.0 g), *Achyranthis* radix (3.0 g), *Cori* frunctus (3.0 g), *Moutan* cortex (3.0 g), *Alismatis* rhizoma (3.0 g), *Dioscoreae* rhizoma (3.0 g), *Plantanginis* semen (3.0 g) *Hoelen* (3.0 g), processed *Aconitii* tuber(1.0 g), and *Cinnamomi* corte (1.0 g). The drug was prepared as aspray-dried powder from a hot-water extract (yield 16.1%, Tsumura & Co, Tokyo). Previous reports demonstrated in dogs that GJG decreases the amplitude of distension-induced rhythmic bladder contractions while decreasing its frequency[9,10]. Recent evidence indicated that the descending monoaminergic systems inhibit bladder motility[21,22]. Goto et al. suggested that both noradrenergic and serotonergic mechanisms play important roles in the inhibitory effects of GJG on the micturtion reflex[8]. The action of processed Aconiti tuber, one of the crude drug components of *Gosha-jinki-gan*, stimulates spinal k-opioid receptors via dynorphin release and subsequently activates the decending inhibitory system. These findings are consistent with our clinical study of GJG. The present study clearly demonstrated that GJG was effective for improving storage symptoms, while GJG had little influence on voiding function. Thus, GJG can improve troublesome OAB symptoms of BPH men without deterioration of voiding.

CONCLUSIONS

Gosha-jinki-gan may be potentially useful for treating OAB by exerting its inhibitory effect on the micturition reflex. Current study indicated that GJG is associated with few adverse effects. The safety profile of GJG is quite useful with treatment in elderly patients. Further clinical investigation and referral are required to elucidate the precise mechanism of GJG in OAB pathophysiology.

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和文抄録

過活動膀胱に対する牛車腎気丸の作用

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頻尿，尿意切迫などを主症状とする過活動膀胱に対して以前より西洋薬とともに漢方薬も排尿障害に広く使われており，なかでも牛車腎気丸は過活動膀胱に対する基礎的研究が報告され始め，その臨床的応用が期待できる漢方薬である．われわれは頻尿，尿意切迫などを主症状とする過活動膀胱の男性患者30人に牛車腎気丸を6週間投与し，国際前立腺症状スコア，QOLスコア，尿失禁回数，最大尿流率，残尿量を測定した．

その結果，牛車腎気丸は頻尿，夜間頻尿，切迫性尿失禁などの蓄尿症状に有効であった．一方，排出症状スコア，最大尿流率，残尿量について有意差はなかった．

牛車腎気丸は頻尿，夜間頻尿，切迫性尿失禁などの過活動膀胱の症状を改善する可能性があり，高齢者や抗コリン薬非適応症例の治療薬として期待できる．

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