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Short communication

Clinical efficacy and tolerability of Gosha-jinki-gan, a Japanese traditional herbal medicine, for nocturia

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ABSTRACT

We evaluated the efficacy and tolerability of Gosha-jinki-gan (GJG; 濟生腎氣丸 jì shēng shèn qì wán) in 30 cases of nocturia (夜尿 yè niào) unresponsive to α1-blockers or antimuscarinic drugs. All patients received GJG extract powder (2.5 g) three times a day for 12 weeks as an add-on therapy to α1-blockers or antimuscarinic drugs. Subjective outcomes assessed by the International Prostate Symptom Score—quality of life, and the benign prostatic hyperplasia impact index and objective outcomes assessed by urinary frequency and the urine production rate at night showed significant improvement after treatment. Moreover, other objective outcomes assessed by maximum flow rates, postvoid residual, serum human atrial natriuretic peptide levels, and urinary 8-hydroxy-2′-deoxyguanosine levels did not change. Adverse events were observed in 10% of cases; however, these events were mild. GJG appears to be a safe and effective potential therapeutic alternative for patients with nocturia unresponsive to α1-blockers or antimuscarinic drugs. Further clinical investigations are required to elucidate the precise pathophysiologic mechanisms of GJG in nocturia.
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1. Introduction

Bothersome nocturia (夜尿 yè niào) reduces quality of life (QOL) and can lead to embarrassment, social anxiety, and poor self-esteem.[1] It is frequently associated with daytime drowsiness, inability to concentrate, and decreased motivation to perform activities.[2] All these consequences are potential risks for depression.[3]

Nocturnal polyuria (NP) is an important cause of nocturia, and about 70% of outpatients with nocturia have NP.[4] Although the detailed mechanism of NP has yet to be elucidated fully, low serum arginine–vasopressin levels during the night and high serum human atrial natriuretic peptide (hANP) levels can cause this condition.[5]

Although prebedtime vasopressin treatment is widely applied to reduce nocturnal urine volume, adverse effects of hyponatremia are not uncommon.[6] Other options for NP are the application of loop diuretics during the daytime and a Japanese traditional blended herbal medicine, Gosha-jinki-gan (GJG; 濟生腎氣丸 jì shēng shèn qì wán).[7]

GJG has been used widely and empirically in Japan to treat patients with lower urinary tract symptoms. Since this herbal drug can be purchased over the counter, it is used as a traditional medicine for nocturia. However, to the best of our knowledge, there is little evidence on the efficacy of this drug for nocturia treatment.[8]

In this study, we attempted to evaluate the efficacy and safety of GJG as an add-on therapy for elderly patients with nocturia resistant to α1-blockers or antimuscarinic drugs. We evaluated patients based on their International Prostate Symptom Score (IPSS), IPSS-QOL, benign prostatic hyperplasia impact index (BII), uroflowmetry results, frequency–volume chart (FVC), serum hANP levels, and urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels.

2. Materials and methods

2.1. Safety analysis

Prior to commencing the study, we obtained approval from the Institutional Review Board. We obtained written informed consent from all the participants after thoroughly explaining the efficacy of GJG and its possible adverse reactions such as hypersensitivity, liver

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dysfunction, epigastric discomfort, and accelerated heart palpitations. For monitoring side effects, levels of aspartate aminotransferase, alanine aminotransferase, serum creatinine, urea nitrogen, uric acid, urinary blood, glucose, and ketone were investigated prior to and after treatment.

2.2. *Gosha-jinki-gan* (GJG; 濟生腎氣丸 jì shēng shèn qì wán)

GJG (TJ-107; Tsumura Co., Tokyo, Japan) is the extract product, which included 4.5 g of the compound extracts of 10 herbal medicines: Rehmanniae Radix (地黃 dì huáng) (5 g), Achyranthis Radix (牛膝 niú xī) (3 g), Corni Fructus (山茱萸 shān zhū yú) (3 g), Dioscoreae Rhizoma (山藥 shān yào) (3 g), Hoelen (Poria Cocos; 茯苓 fú ling) (3 g), Plantaginis Semen (車前子 chē qián zǐ) (3 g), Alismatis Rhizoma (澤瀉 zé xiè) (3 g), Moutan Cortex (牡丹皮 mǔ dān pí) (3 g), Cinnamoni Cortex (桂皮 guì pí) (1 g), and heat-processed Processi Aconiti Radix (附子 fù zǐ) (1 g). It is a standardized spray-dried water extract, which includes 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 consulted our hospital with lower urinary tract symptoms between June 2013 and May 2014 were candidates for enrollment. Inclusion criteria were as follows: (1) age ≥ 65 years; (2) ≥ 2 voids per night despite treatment with α1-blockers or antimuscarinic drugs for at least 4 weeks; (3) total IPSS ≥ 8; and (4) IPSS-QOL ≥ 3. Patients with neurogenic bladder, urethral stricture, and active urinary tract infection possibly affecting voiding functions were excluded. All patients were administered GJG 2.5 g preprandially for 12 weeks as an add-on therapy to α1-blockers or antimuscarinic drugs. Prior to and after treatment, FVC (3 consecutive days), IPSS, IPSS-QOL, BII, uroflowmetry, hANP, and urinary 8-OHdG levels were examined. We then used the FVC data to calculate the void frequency and voided volume over 24 continuous hours. The NP index was calculated by dividing nocturnal urine volume by the total urine volume per day, and hours of undisturbed sleep was defined as the duration between going to bed and the first nocturnal void. The nocturnal bladder capacity index was also calculated.[9] Polyuria was defined as producing >40 mL/kg urine over a 24-hour period, and NP was defined as an NP index score of >0.33.[10] As a marker of oxidative stress, we evaluated urinary 8-OHdG levels using an ICR-001 device (Techno Medica, Yokohama, Japan) according to the manufacturer's recommendations.

2.4. Statistical analysis

Data are reported as mean ± standard deviation and analyzed using SPSS software, version 12.0 (IBM, Chicago, IL, USA). Wilcoxon's signed rank test was used to evaluate the effect of treatment, and $p < 0.05$ was considered significant.

3. Results

3.1. Effect of GJG

A total of 30 patients were included in this study. Table 1 shows the baseline characteristics. The mean patient age ± standard deviation was 75.5 ± 5.1 years. Nocturnal frequency, urine volume, and NP index were 4.4 ± 1.3 mL, 951 ± 504 mL and 0.45 ± 0.14 mL, respectively. FVC scores revealed NP in 25 patients (83.3%), decreased nocturnal bladder capacity in eight patients (26.7%), and both NP and decreased nocturnal bladder capacity in five patients (16.7%). A summary of the effects of GJG on voiding functions is listed in Table 2. Subjective outcomes assessed by total IPSS, IPSS-QOL, and BII significantly decreased after treatment. Both voiding symptoms (intermittency, straining, weak stream, and incomplete emptying) and storage symptoms (urgency, micturition frequency, and nocturia (夜尿 yè niào)) improved after treatment (6.4 ± 4.4 vs. 4.3 ± 3.2, $p = 0.011$ and 8.1 ± 2.9 vs. 6.1 ± 2.0, $p = 0.002$, respectively). Maximum flow rates and voided volume from the baseline did not change significantly after treatment—from 10.7 ± 10.0 to 10.3 ± 8.2, $p = 0.800$, and from 108 ± 73 to 113 ± 68, $p = 0.812$, respectively. No significant change in postvoid residual was observed after treatment (26 ± 26 to 24 ± 23, $p = 0.735$). Objective outcomes, which included the number of nocturnal voids and the urine production rate at night, were significantly decreased, from 4.4 ± 1.3 to 3.5 ± 1.9, $p = 0.008$ and from 0.45 ± 0.14 to 0.39 ± 0.16, $p = 0.009$, respectively. However, other objective parameters, such as hours of undisturbed sleep, hANP, and urine 8-OHdG levels, remained unchanged.

Table 1
Baseline patient characteristics.

Age (y)	75.5 ± 5.1
Sex	24/6
Urinary frequency	
24 h	12.1 ± 2.9
Nocturnal	4.4 ± 1.3
Urine volume	
24 h (mL)	2088 ± 741
Nocturnal (mL)	951 ± 504
NPI	0.45 ± 0.14
HUS (min)	126 ± 58
24 h polyuria (>40 mL/kg)	5 (16.7%)
NP (NPI > 0.33)	25 (83.3%)
Decreased NBC	8 (26.7%)
NP + decreased NBC	5 (16.7%)

HUS = hours of undisturbed sleep; NBC = nocturnal bladder capacity; NP = nocturnal polyuria; NPI = nocturnal polyuria index.

Table 2
Effects of Gosha-jinki-gan on various voiding parameters.

	Baseline	After 12 wk	p^*
IPSS			
Total	14.5 ± 6.2	10.4 ± 3.9	<0.001
Voiding symptoms	6.4 ± 4.6	4.3 ± 3.2	0.011
Storage symptoms	8.1 ± 2.9	6.1 ± 2.0	0.002
QOL	4.2 ± 1.2	3.3 ± 1.5	0.007
BII	6.3 ± 4.1	5.0 ± 3.4	0.024
UFM			
Q_{max} (mL/s)	10.7 ± 10.0	10.3 ± 8.2	0.800
Voided volume (mL)	108 ± 73	113 ± 68	0.812
Residual volume (mL)	26 ± 26	24 ± 23	0.735
FVC			
nocturia (夜尿 yè niào)	4.4 ± 1.3	3.5 ± 1.9	0.008
HUS (min)	126 ± 58	168 ± 88	0.058
NUV (mL)	951 ± 504	833 ± 496	0.087
NPI	0.45 ± 0.14	0.39 ± 0.16	0.009
hANP (pg/mL)	30.7 ± 22.3	30.9 ± 22.1	0.930
8-OHdG (ng/mLCRE)	16.9 ± 10.5	14.8 ± 6.5	0.221

BII = benign prostatic hyperplasia impact index; FVC = frequency–volume chart; hANP = human atrial natriuretic peptide; HUS = hours of undisturbed sleep; IPSS = International Prostate Symptom Score; NUV = nocturnal urine volume; NPI = nocturnal polyuria index; QOL = quality of life; UFM = uroflowmetry; 8-OHdG = 8-hydroxy-2′-deoxyguanosine.
Wilcoxon's signed rank test.
* Two data samples are matched if they come from repeated observations of the same subject. Using the Wilcoxon's signed rank test, we can decide whether the corresponding data population distributions are identical without assuming them to follow the normal distribution.

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