A placebo-controlled study: Phellodendron Bawei tablets combined with standard management can improve storage symptoms, sleep quality, and medication compliance in patients with benign prostatic hyperplasia compared to placebo with standard management

1. Research purpose and significance:

the purpose of this prospective study was to analyze whether the combination of standard therapeutic drugs (α1-receptor blockers + 5α reductase inhibitors) and Phellodendron Bawei tablets confers greater advantages than do placebo with standard management in improving LUTs, sleep quality, sexual function, and Medication Adherence Questionnaire (MAQ) score in patients with BPH.

2. Research status

Benign prostatic hyperplasia (BPH) is a common micturition disorder in middle-aged and older adult males, and it is one of the most common urology-related diseases worldwide. The prevalence of clinical BPH in males over 50 years is 50–75%. It has a negative impact on the quality of life in many areas, resulting in disordered sleep, sexual dysfunction, and reduced sexual satisfaction, along with lower urinary tract symptoms (LUTs).

Recently, an increasing number of published articles have reported that BPH may be an immune-mediated disease, and persistent inflammation is the key factor for its development and progression. Guidelines strongly recommend the use of α1-receptor blockers combined with 5α reductase inhibitors for treating patients with BPH with moderate-to-severe LUTs and risk of progression, but neither of these drugs provides anti-inflammatory or anti-infective effects. Non-steroidal anti-inflammatory drugs (NSAIDs), commonly used in clinical practice, can be highly toxic, with their side effects mainly being gastrointestinal inflammation, upper gastrointestinal ulcers, and even perforation and bleeding, and additional side effects being related to the kidneys, central nervous system, hematological system, respiratory system, skin, and liver. The use of NSAIDs is also a risk factor for BPH. Although antibiotics can effectively control recurrent urinary tract infections due to BPH, long-term use of antibiotics results in many side effects, such as the alteration of the intestinal flora and increased abundance of drug-resistant bacteria, with renal insufficiency also often arising in older adult patients. Therefore, identifying effective and low-toxicity anti-inflammatory drugs that

can replace NSAIDs and antibiotics may be an important means to strengthening treatment compliance, reducing recurrence rate, and improving the quality of life for patients with BPH.

In recent years, more plant extracts and proprietary Chinese medicines have been used in the treatment of BPH and related LUTs to obtain a good therapeutic effect. The Phellodendron Bawei tablet is a proprietary Chinese medicine,.and its main components are Cortex Phellodendri, pine-soot ink, Fructus Gardeniae, Radix Glycyrrhiza, Flos Carthami, Fructus Piperis Longi, Pulvis Billis Bovis, and Resina Liquidambaris,with anti-inflammatory and anti-infective effects. Its main component, Cortex Phellodendri, contains berberine, palmatine, phellodendrine, and obacunone, which may exert a synergistic anti-infectious effect by downregulating the messenger RNA (mRNA) expression of tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and cyclooxygenase-2 (COX-2). Other ingredients, such as Radix Glycyrrhizae and Flos Carthami, are used as components of Chinese medicines for insomnia. And there are no reports of serious adverse events of Phellodendron Bawei tablet. However, thus far, there has been no report concerning the effects of Phellodendron Bawei tablets on the improvement of LUTs and sleep quality in patients with BPH.

3. Research content and research methods

Patients

This study is a prospective, double-blind, single-center, 6-month clinical trial in patients with BPH. This study followed the ethical principles of the Declaration of Helsinki and the Guidelines for Good Clinical Practice. The protocol was approved by the Medical Ethics Committee of Xiangya Hospital of Central South University (approval No. 201703545). All subjects provided written, informed consent before registration. Patients aged 45–75 years diagnosed with BPH in the outpatient clinic of Xiangya Hospital from September 2019 to July 2020 were enrolled and randomly divided into control and experimental groups using a random number method, with 60 patients in each group.

Inclusion criteria were as follows: 45–75 years of age; a history of BPH/LUTs for more than 6 months, moderate-to-severe LUTs [International Prostate Symptom Score (IPSS) ≥8], maximum urine flow rate (Qmax) of <15 mL/s, and prostate volume (PV) of >30 mL. Patients with prostate cancer, urethral stricture, and urinary tract infection, as well

as those with previous urethral surgery, absolute indications for surgery, and drug allergies, were excluded.

Treatment

The standard management (SM) group was treated with tamsulosin 0.2 g once a day (qd) + finasteride 5 mg qd + placebo [5 tablets, three times a day (tid)], while the experimental group (Phellodendron Bawei tablets + SM) was treated with tamsulosin 0.2 g qd + finasteride 5 mg qd + Phellodendron Bawei tablets (5 tablets, tid). It was difficult to distinguish between the placebo and Phellodendron Bawei tablets in appearance. The observation period was 6 months, and the indicators were as follows: (I) Clinical indicators including body mass index (BMI), blood prostate-specific antigen (PSA), PV, and Qmax; (II) LUTs, including IPSS, IPSS voiding subscore (IPSS-V), IPSS storage subscore (IPSS-S), and IPSS quality of life (IPSS-QOL) score; (III) sexual function score according to International Index of Erectile Function (IIEF-5) score (13) (5–7 points for severe sexual dysfunction, 8–11 points for moderate sexual dysfunction, 12–21 points for mild sexual dysfunction, and 22–25 points for normal erectile function) (13); (IV) sleep status score according to the Athens Insomnia Scale (AIS) (14) (0–3 points for no sleep disorder, 4–6 points for suspected insomnia, and 7 points or more for insomnia) (14); (V) MAQ (a total score of 8 points: 0 points for low compliance, 1–2 points for medium compliance, and 3 points for low compliance) (15). (VI) Observe for adverse drug reactions.

Statistical analysis

All statistical analyses were carried out using SPSS 22.0 (IBM Corp., Armonk, NY, USA) software. We have analyzed whether parameters were normally distributed using Shapiro-Wilk test, $\alpha=0.05$. According to Shapiro-Wilk test age, PSA, BMI, IPSS, IPSS-S, IPSS-V, IIEF-5 are normally distributed, while TPV, Qmax, QoL, AIS and MAQ are not. Normally distributed continuous variables are expressed as the mean ± standard deviation, and non-normally distributed continuous variables are expressed as median [inter quartile range (IQR)]. The student's t-test and Mann-Whitney U test were used to compare the clinical indicators before and after medication, as well as the clinical data between the two groups. All tests were 2-sided, and a P-value of <0.05 was considered a statistically significant difference. We performed a per-protocol analysis (PP analysis). For continuous primary and secondary outcome variables, the Markov chain Monte Carlo multiple imputation method was used to impute missing data using 10 iterations.

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