Chinese Journal of Integrative Medicine
Available online at link.springer.com/journal/11655
Journal homepage: www.cjim.cn/zxyjhen/zxyjhen/ch/index.aspx
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Original Article

Efficacy and Safety of Guihuang Formula in Treating Type Ⅲ Prostatitis Patients with Dampness-Heat and Blood Stasis Syndrome: A Randomized Controlled Trial*

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ABSTRACT **Objective**: To observe the efficacy and safety of Guihuang Formula (GHF) in treating patients with type Ⅲ prostatitis and Chinese medicine syndrome of dampness-heat and blood stasis. **Methods**: Sixty-six type Ⅲ prostatitis patients with dampness-heat and blood stasis syndrome were randomly divided into the treatment group (GHF) and the control group (tamsulosin) using a random number table, with 33 cases each group. The treatment group received GHF twice a day, and the control group received tamsulosin 0.2 mg once daily before bedtime. Patients in both groups received treatment for 6 weeks and was followed up for 2 weeks. The outcomes included the National Institute of Health Chronic Prostatitis Symptom Index (NIH-CPSI) score, Chinese Medicine Symptoms Score (CMSS), expressed prostatic secretions (EPS) and adverse events (AEs). **Results**: After treatment, the NIH-CPSI total score and domain scores of pain discomfort, urination and quality of life decreased significantly from the baseline in both groups (P<0.05). The CMSS score decreased in both groups (P<0.05). The white blood cell (WBC) count decreased and lecithin body count increased in both groups (P<0.05). GHF showed a more obvious advantage in reducing the pain discomfort and quality of life domain scores of NIH-CPSI, reducing the CMSS score, increasing the improvement rate of the WBC and lecithin body counts, compared with the control group (P<0.05). There were no significant differences in decreasing urination domain score of NIH-CPSI between two groups (P>0.05). In addition, no serious AEs were observed. **Conclusion**: GHF is effective in treating type Ⅲ prostatitis patients with dampness-heat and blood stasis syndrome without serious AEs. (Registration No. ChiCTR1900026966)

KEYWORDS type Ⅲ prostatitis, dampness-heat and blood stasis syndrome, Guihuang Formula, Chinese medicine, randomized controlled trial

Type Ⅲ prostatitis by National Institute of Health category, also known as chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), is one of the most common urinary system diseases in young and middle-aged men.[1] It severely affects patients' physical and mental fitness and quality of life (QOL), with long-term, multisite, refractory voiding dysfunction and chronic pain or discomfort located in the pelvic area.[2,3] The incidence of type Ⅲ prostatitis is rising as human lifestyles change.[4]

The etiology of type Ⅲ prostatitis has not been completely elucidated until now. Generally, the occurrence of type Ⅲ prostatitis is considered to be associated with infection by pathogenic microorganisms, oxidative stress response, and psychological factors.[5] Alpha-blockers and/or antibiotics are the first-line drugs for chronic prostatitis, however, although they can relieve patients' symptoms to some extent, they have limited effects and unsatisfactory patient outcomes for chronic prostatitis patients.[6,7] Overall, there are limited treatment options.

Chinese medicine (CM) has been used in the treatment of type Ⅲ prostatitis and could markedly improve patients' clinical symptoms and QOL by

*Supported by the National Natural Science Foundation of China (No. 82104880), Scientific and Technological Innovation Project of China Academy of Chinese Medical Sciences (No. CI2021A02208) and the Nursery Project of Xiyuan Hospital of China Academy of Chinese Medical Sciences (No. 2019XYMP-23)

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DOI: https://doi.org/10.1007/s11655-022-3467-1

Chin J Integr Med 2022 Oct;28(10):879-884

acting on multiple targets.[8] Previous studies showed that CM can bring good outcomes of symptom improvement,[4,7,8] so there is an urgent need to evaluate CM interventions for type Ⅲ prostatitis. Guihuang Formula (归黄方, GHF) is a traditional CM formula, which is capable of clearing away heat and dampness, removing blood stasis in the theory of CM. At present, GHF had shown good therapeutic effects in type Ⅲ prostatitis, but the clinical use of GHF is still depending on empirical treatment.[7] Further evaluation of the clinical benefit and safety of GHF is warranted. Here, we conducted a randomized controlled trial (RCT) to explore the efficacy and safety of GHF in treating patients with type Ⅲ prostatitis and CM syndrome of dampness-heat and blood stasis.

METHODS

Diagnostic Criteria

The diagnosis of prostatitis was based on the 2019 Guidelines for the diagnosis and treatment of urological and andrological diseases in China,[9] and the diagnostic criteria were as follows: (1) lower urinary tract symptoms: frequent urination, urgency, dysuria, and incomplete emptying; (2) pain or discomfort symptoms: pain or discomfort symptoms mostly in the pelvic region, which can also be observed in the penis, urethra, perineum, perianal, pubic, or lumbosacral area; and (3) bacterial culture: the "two-cup method" was used to examine midstream urine of premassage and postmassage, and bacterial cultures were negative; (4) expressed prostatic secretions (EPS) examinations: white blood cells (WBCs) ⩾10/HP (ⅢA), WBCs <10/HP (ⅢB), lecithin body decreased or disappeared.

Dampness-heat and blood stasis syndrome was defined according to the "Expert consensus on the diagnosis and treatment of chronic prostatitis with integrated traditional Chinese and Western medicine"[8] and was defined when the patients had primary symptoms and at least one of the secondary symptoms combined with the corresponding tongue and pulse. (1) Primary symptoms include voiding symptoms and pain symptoms; voiding symptoms include frequent urination, burning astringent pain, and endless residue; and pain symptoms occur in the perineum or lower abdomen or inguinal region; (2) secondary symptoms consist of yellow urine, dry mouth, and wet scrotum; (3) tongue and pulse: red tongue with ecchymosis, yellow greasy moss, and slippery string pulse.

Inclusion, Exclusion and Drop-Out Criteria

Patients who met the following inclusion criteria were included: (1) Western medicine diagnostic criteria of type Ⅲ prostatitis and dampness-heat and blood stasis syndrome differentiation standard of CM mentioned above; (2) age of 18–50 years old; (3) disease duration more than 3 months; and (4) provided a signed consent form.

The exclusion criteria were as follows: (1) patients with urinary tract infection, benign prostatic hyperplasia, varicocele, urinary tumor and other urinary system diseases; (2) patients with severe cardiovascular and cerebrovascular diseases, severe renal and/or hepatic injury, severe mental disorders, hematological disease, and other serious complications; (3) patients who were allergic to any drug used in the study; and (4) patients who participated in other clinical trials within 3 months.

Drop-out criteria included: (1) subjects with poor compliance and self-exit during treatment; (2) patients received other therapies or self-change therapy during the experiment; and (3) patients with severe adverse events (AEs) or complications.

Patients

Sample size was estimated based on previous literature, and the formula for clearing away heat and depriving dampness of CM could produce an approximately 3-point reduction in the National Institute of Health Chronic Prostatitis Symptom Index (NIH-CPSI).[10] We calculated that 30 subjects per group were required to achieve 80% power at 5% two-sided type Ⅰ error. As the lost-to follow-up rate was anticipated to be 10%, a total of 66 subjects from 2 groups were required.

Sixty-six patients were recruited from the Department of Andrology, Xiyuan Hospital, China Academy of Chinese Medical Sciences between September 2019 and February 2021. The baseline assessment of the eligible patients was completed a week before the treatment. The patients were randomly assigned to treatment or control groups at a ratio of 1:1 using a computer-generated random number table by SAS software version 9.2. This trial was approved by the Medical Ethics Committee of Xiyuan Hospital, China Academy of

Chinese Medical Sciences (No. 2019XLA019-3) and registered at the Chinese Clinical Trial Registry (No. ChiCTR1900026966).

Treatment

Patients in the treatment group received GHF granules, consisting of *Angelicae Sinensis Radix* 12 g, *Phellodendri Chinensis Cortex* 12 g, *Lonicerae Japonicae Flos* 15 g, *Curcumae Longae Rhizoma* 10 g, *Olibanum* 5 g, *Myrrha* 5 g, *Angelicae Dahuricae Radix* 10 g, *Plantaginis Herba* 15 g, *Herba Hedyoti Diffusae* 15 g, *Citri Reticulatae Pericarpium* 10 g, prepared by Department of Pharmacology, Xiyuan Hospital, 1 package each time, twice a day.[11] Meanwhile, patients in the control group were administered tamsulosin (Zhejiang Hailisheng Pharmaceutical Co., Ltd., batch No. H20020623, 0.2 mg), 1 capsule before bedtime.[12] The intervention time in both groups lasted for 6 weeks and was followed up for 2 weeks. The investigator recorded at 0, 2, 4, 6 and 8 weeks.

Outcome Measures

The primary outcomes were the change in the NIH-CPSI before and after treatment, and the total score, pain discomfort (4 items, 0–21 points), urination (2 items, 0–10 points) and QOL (3 items, 0–12 points) were evaluated.[13] The secondary outcomes were Chinese Medicine Symptoms Score (CMSS, Appendix 1) and EPS before and after treatment.[8,14] For CMSS, the primary symptoms were scored as 0 (none), 2 (light), 4 (medium) and 6 (severe), and the secondary symptoms were scored as 0 (none), 1 (light), 2 (medium) and 3 (severe). The EPS examination included detection of WBC and lecithin body levels.[15] The criteria for the improvement, stability and deterioration of WBC examination were defined as follows: improved, decrease of "+"; stable, no change; deteriorated, an increase of "+". The criteria of lecithin evaluation were quite the opposite.

To evaluate the safety of GHF, routine blood and urine tests, liver and kidney function tests, and electrocardiographs were performed before and after treatment during the trial.

Statistical Analysis

All of the statistical analyses were performed using SPSS software (version 25.0, Chicago, IL, USA), and graphs were generated with GraphPad Prism software version 8.0 (San Diego, CA, USA). Continuous variables are presented as mean ± standard deviation ($\bar{x} \pm s$) and were analyzed with an unpaired *t*-test for two group comparisons and a paired *t* test for comparison of two paired groups when the data distribution was assumed to be normal. The Mann-Whitney *U* test was used for unpaired groups, and the Wilcoxon signed rank test was used for the two paired groups when the data did not meet the assumptions of normality. Dichotomous variables are shown as percentages and were evaluated using χ^2 or Fisher's exact test when appropriate. A *P* value less than 0.05 was considered statistically significant.

RESULTS

Participants and Baseline Characteristics

Sixty-six subjects were enrolled, and 58 subjects completed the 8-week study, as shown in Figure 1. Five patients dropped out in the trial, and all of whom could not continue to take medicine due to the epidemic situation of COVID-19. Three patients were excluded due to taking other drugs at the same time during enrollment. A total of 58 cases were included and performed via a per-protocol set (PPS) analysis. There were no significant differences in patient demographics or other baseline data between groups (*P*>0.05, Table 1).

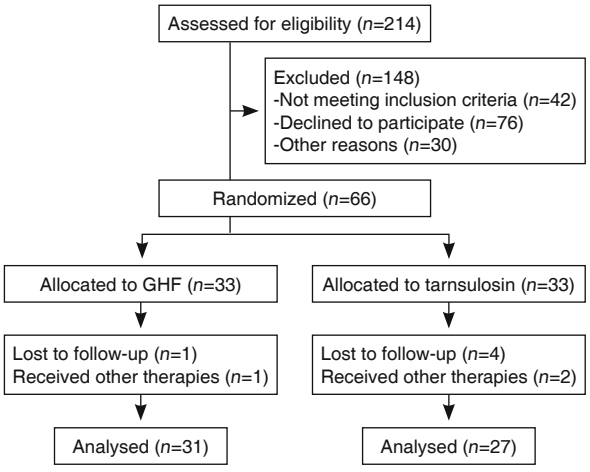

Figure 1. Flow Diagram of Guihuang Formula for Type Ⅲ Prostatitis Patients with Damp-Heat and Blood Stasis Syndrome

Comparison of NIH-CPSI Score between Groups

As shown in Figure 2 and Appendix 2, the NIH-CPSI total and domain scores in both groups were significantly reduced compared with baseline (*P*<0.05). The treatment group had a larger reduction in NIH-CPSI total score and domain scores, including pain discomfort and QOL, from the second week (*P*<0.05). There were no significant differences in urination domain score

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Table 1. Comparison of Baseline Characteristics of Patients between Groups

Characteristic	Treatment group (*n*=31)	Control group (*n*=27)
Age (Year, $\bar{x}\pm s$)	31.56±5.42	32.27±4.18
Symptom duration (Month, $\bar{x}\pm s$)	28.47±7.12	26.44±8.19
Type of prostatitis [Case (%)]		
ⅢA	17 (54.84)	15 (55.56)
ⅢB	14 (45.16)	12 (44.44)
Mean NIH-CPSI (Score, $\bar{x}\pm s$)	28.62±8.61	26.74±7.72
Pain discomfort	11.72±3.91	12.11±3.73
Urination	5.62±2.43	5.13±2.22
QOL	11.37±4.31	9.58±3.61
CMSS (Score, $\bar{x}\pm s$)	19.03±1.54	19.48±1.34
WBC [Case (%)]		
In normal range	14 (45.16)	12 (44.44)
Beyond normal range	17 (54.84)	15 (55.56)
Lecithin body [Case (%)]		
In normal range	10 (32.26)	12 (44.44)
Beyond normal range	21 (67.74)	15 (55.56)

between the two groups at week 4, 6 or 8 (*P*>0.05).

Comparison of CMSS

As shown in Figure 3 and Appendix 3, CMSS in the two groups were significantly reduced compared with baseline (*P*<0.05), and CMSS in the treatment group was significantly lower than the control group (*P*<0.05).

EPS Examination

As shown in Figure 4 and Appendix 4, after the intervention, the WBC count was reduced and lecithin body levels were improved in both groups compared with baseline (*P*<0.05). The treatment group had higher improvement rate of WBC and lecithin body levels than the control group (*P*<0.05).

AEs

Three patients in the treatment group had slight gastrointestinal discomfort, and the symptoms disappeared after taking the drug after meal. Two

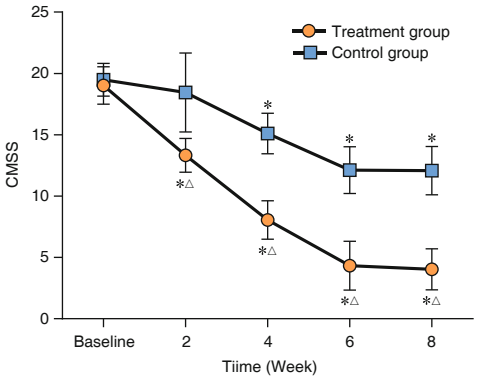

Figure 3. Comparison of CMSS between Groups ($\bar{x}\pm s$)
Notes: **P*<0.05 *vs*. baseline; *△P*<0.05 *vs*. control group

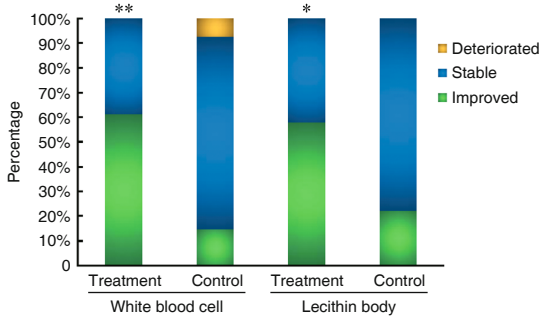

Figure 4. Comparison of WBC and Lecithin Body Count Changes between Groups
Notes: **P*<0.05, ***P*<0.01 *vs*. control group

cases in the control group experienced transient hypotension, and the symptoms disappeared when patients slept immediately after taking the drug. No abnormalities were detected in the laboratory examination. No serious AEs occurred in either group.

DISCUSSION

Although advancements in medical treatment are rapidly developing, there is still a long way to go in the prevention and treatment of prostatitis.[2] Type Ⅲ prostatitis is a disease caused by nonisolated factors that may lead to pain or discomfort in the groin area, pelvic pain, irritable urination and sexual dysfunction.[3,16] Tamsulosin, which is typical for alpha-blocker drugs, is the first-line drug for chronic prostatitis; it can relieve urination symptoms to some extent, but

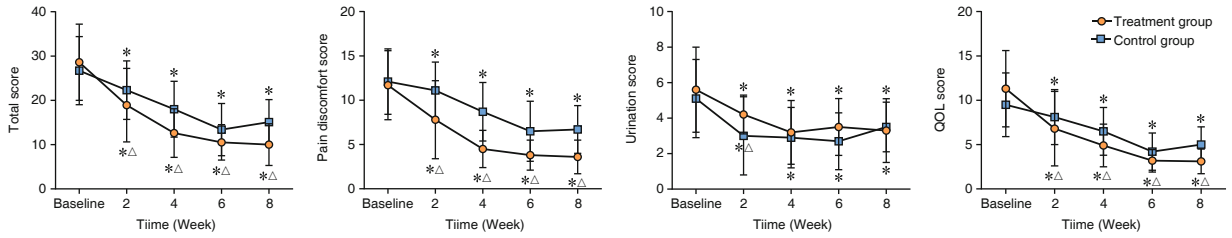

Figure 2. Comparison of NIH-CPSI Score between Groups ($\bar{x}\pm s$)
Notes: **P*<0.05 *vs*. baseline; *△P*<0.05 *vs*. control group

unfortunately, it has limited effects and unsatisfactory outcomes in either infection control or pain relief.[17]

CM provides unique advantages for the treatment of prostatitis, and the fundamental cause of prostatitis lies in dampness-heat and blood stasis syndrome.[8] According to sore-ulcer-resolving theory, GHF is derived from the CM classical formula Xianfang Huoming Drink (仙方活命饮, XHD), which was recorded in the CM monograph *Notes and Commentary on Effective Prescriptions for Women* (Jiaozhu Furen Liangfang) during the Ming Dynasty of ancient China. XHD had been used to treat sores and carbuncles for hundreds of years, and showed inhibitory effects on the production of pro-inflammatory cytokines and inflammatory proliferation.[18] XHD also could significantly improve the symptoms of patients with type Ⅲ prostatitis.[19] As an experience formula in the treatment of type Ⅲ prostatitis, GHF has been used in Xiyuan Hospital, China Academy of Chinese Medical Sciences for decades and has shown obvious advantages in treating type Ⅲ prostatitis.[11] Modern pharmacological studies have indicated that GHF decreases the prostate index, attenuates histological damage in the prostate, downregulates the proinflammatory cytokines interleukin-6, cyclooxygenase-2, tumor necrosis factor-α, and monocyte chemoattractant protein-1 and enhances antioxidant capacity. The characteristics of multiple components, multiple targets, multiple pathways, and multiple action mechanisms of GHF were elucidated and confirmed using network pharmacology and molecular docking. We confirmed that GHF inhibits the progression of type Ⅲ prostatitis via downregulation of the PI3K/Akt/NF-κB signaling pathway, which was uncovered by further experimental validation.[20]

The study is an RCT to evaluate the efficacy and safety of a GHF compared to tamsulosin. The pilot study demonstrated that GHF significantly reduced pain or discomfort in the pelvic area of patients with type Ⅲ prostatitis. After treatment, the NIH-CPSI score and CMSS in both groups were significantly reduced compared with baseline (P<0.05). The WBC count decreased and lecithin body count increased in both groups. The results showed that there were no significant differences in alleviating voiding symptoms between GHF and tamsulosin, and they can equally improve the urination symptoms of patients. However, GHF shows a more obvious advantage in relieving pain or discomfort symptoms, reducing the CMSS, improving QOL, decreasing the WBC level and increasing lecithin body rates. Caution is still needed because there were 3 cases of gastrointestinal AEs during the application of GHF, and these AEs need to be investigated further in a large sample study.

In conclusion, the study provides evidence on Guihuang Formula as an effective and safe intervention for the treatment of type Ⅲ prostatitis. The results confirmed that promoting the development of CM, giving full play to the advantages of the characteristics of CM, further improving the ability of CM in the prevention and treatment of type Ⅲ prostatitis remains of great significance.

Conflict of Interest

There is no conflict of interest.

Author Contributions

Gao QH and Guo J contributed to research implementation, experiment supervision, and fund managers. Liu SJ contributed to the writing of the paper and experimental design. Zeng Y and Zhao M contributed to the data analysis. Liu SJ, Deng YJ, ZY, Guo J, and Gao QH participated in the experiments.

Electronic Supplementary Material: Supplementary material (Appendices 1–4) is available in the online version of this article at https://doi.org/10.1007/s11655-022-3467-1.

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(Accepted November 17, 2021; First Online April 13, 2022)
Edited by YUAN Lin