The effects of a Chinese herbal medicine (VGHBP0) on patients with benign prostatic hyperplasia: A pilot study

Hsin-Fu Yeh, Tsai-Feng Li, Cheng-Hung Tsai, Pei-Wen Wu, Yi-Hsiu Huang, William J. Huang, Fang-Pey Chen, Ta-Peng Wu

Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; Institute of Traditional Medicine, National Yang-Ming University, Taipei, Taiwan, ROC; Center for Traditional Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; Department of Urology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC; School of Chinese Medicine, China Medical University, Taichung, Taiwan, ROC; Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

Abstract

Background: The current Western medicine treatment options for benign prostatic hyperplasia (BPH) have various degrees of documented effectiveness. However, the uses of these interventions are limited to specific patient populations or have certain side effects that interfere with patient quality of life. This study evaluated the clinical effects of a Chinese herbal medicine (CHM) on patients with BPH.

Methods: This was a single-arm pilot study. Twenty BPH patients were enrolled, and they were required to take the investigated CHM three times a day for 8 weeks, along with their Western medicine. Patients returned to clinics as scheduled and completing international prostate symptoms scores (IPSS), aging male symptoms score, international index of erectile function, and body constitution questionnaire of traditional Chinese medicine. Uroflowmetry and sonography were also applied to evaluate the changes in urinary velocity and post-voiding residual urine volume from the baseline to the end of the study.

Results: The mean IPSS total score was significantly decreased by 2.5 points after 8 weeks of treatment with the CHM (from 17.5 to 15.0, p = 0.03). The mean IPSS voiding subscore was decreased by 1.7 points (from 10.1 to 8.4, p = 0.02), and the mean incomplete emptying subscore was decreased by 0.8 points (from 2.9 to 2.1, p = 0.02), with both decreases being statistically significant. A descending trend in the post-voiding residual urine volume was also observed (from 52.9 to 30.8 mL, p = 0.07).

Conclusion: This trial indicated that the add-on CHM treatment (VGHBP0) might be a potential treatment for improving the lower urinary tract symptoms of BPH patients.

Keywords: Body Constitution; Medicine, Chinese traditional; Prostatic hyperplasia

1. INTRODUCTION

Benign prostatic hyperplasia (BPH) is a very common problem among middle-aged and older males. According to statistics, the incidence of BPH in males >50 years old is around 40%, while it is >90% among males >80 years old. When the enlarged prostate places pressure on the urethra or on the wall of the urinary bladder, patients often develop lower urinary tract symptoms (LUTS), such as hesitancy, diminished and weak stream, intermittency, the sensation of incomplete emptying, terminal dribbling, frequency, nocturia, urgency, and dysuria, among others. The quality of life of patients suffering from LUTS is affected, while erectile dysfunction has also been shown to be highly related to LUTS. The treatment options for BPH offered by Western medicine include medication (i.e. alpha-1 receptor blockers) and surgery (i.e. transurethral resection of the prostate), but these treatments may come with a risk of developing ejaculatory problems or erectile dysfunction. Therefore, some BPH patients seek alternative or auxiliary treatments.

The first-line treatments for BPH consist of alpha-blockers, including doxazosin and tamsulosin, which can relieve the pressure on the smooth muscle of the prostate and bladder neck and decrease the resistance of the urethra, to improve the voiding symptoms. However, these medications are categorized as neurogenic drugs, and they are not capable of reducing the total size of the prostate. Another category of medications is 5-alpha reductase inhibitors, including finasteride and dutasteride. By inhibiting 5-alpha reductase, they can reduce the production of dihydrotestosterone, which is believed to be the primary stimulus of prostate hyperplasia.
The effects of complementary and alternative medicine (CAM) on patients with BPH have always been controversial. Moreover, the clinical efficacy of Chinese herbal medicine (CHM) has not been sufficiently demonstrated by evidence-based clinical trials. Although there are a variety of CHM-based auxiliary and alternative treatment methods for patients with BPH, the targets of related studies have mostly consisted of single herbs or extracts, while the effects of CHM powders have yet to be sufficiently investigated. Therefore, we developed a CHM powder formula (VGHBPH0) based on the CHMs most commonly prescribed for patients with BPH in Taiwan (unpublished data), as well as the opinions of numerous experienced traditional Chinese medicine (TCM) physicians and relevant studies published in renowned journals, for investigation in this study. In other words, the CHM formula prescribed and investigated in this pilot clinical trial was developed on the basis of rigorous research.

### 2. METHODS

#### 2.1. Study design

We selected 20 patients with BPH who were treated in the Department of Urology of Taipei Veterans General Hospital and met our inclusion criteria. These patients signed the informed consent, agreeing to undergo the additional CHM treatment along with their formal western medication treatment, and were then enrolled in our patient-oriented pilot study.

#### 2.2. Study population

We assessed the eligibility of all the patients who volunteered for this pilot study, each of whom had been diagnosed by a urologist with pure BPH and had been using first-line Western medications such as α1-blockers or 5-α reductase inhibitors regularly for >3 months. The exclusion criteria were as follows: (1) simultaneous use of Chinese herbs or auxiliary treatments, such as other healthy foods or acupuncture, in the preceding month; (2) sexually transmitted diseases, such as syphilis, gonorrhea, or other healthy foods or acupuncture, in the preceding month; (3) previous trauma or operation history that induced muscle or neck fibrosis, interstitial cystitis, or urethral stricture; (5) other urinary tract infections; (6) diseases that caused renal function impairments, such as upper urinary tract obstruction, or hydrenephrosis; and (7) inability to sign the informed consent or communicate with our researchers.

#### 2.3. Study interventions

The patients took the CHM powder as prescribed an hour after their conventional Western medication (GMP)-compliant by the Food and Drug Administration (FDA) of the Ministry of Health and Welfare of Taiwan. The ingredients of the CHM powder formula prescribed and investigated in this pilot clinical trial was developed on the basis of rigorous research.

#### 2.4. Study outcomes

The primary outcomes were the significant decreases in the mean IPSS and AMS after the CHM treatment. The secondary outcomes were an escalation in the mean urine flow rate and a decline in the mean PVR volume after the CHM treatment. The tertiary outcomes were the alteration of the mean BCQ score and an obvious increase in the mean IIEF after the CHM treatment.

#### 2.5. Sample size and statistical analysis

The results of this study were analyzed using SPSS software, version 12.0. The data for the patients from before and after the treatment were mainly analyzed by Wilcoxon signed-rank test, except for the changes in the physique as measured by the BCQ, which were analyzed with McNemar’s test. A p value of <0.05 was considered statistically significant.

### 3. RESULTS

A total of 20 patients were screened and fully met the eligibility criteria. However, one patient did not return to our clinic.
after receiving his first CHM prescription, while another patient dropped out of the trial due to feelings of exhaustion after taking the CHM for 4 weeks. The date on which the first patient included in the study was registered was April 26, 2018, and the date on which the final patient’s data had been fully collected was November 12, 2018. The mean age of the study patients was 70.2 ± 9.6 years (Table 2). Harnalidge (tamsulosin) was the formal Western medication used most commonly in combination with the CHM (Table 3).

According to the BCQ results, 9 of the 19 patients who took the CHM (47.4%) had the Yang-deficient physique before taking the CHM, and that number increased to 10 out of 19 (52.6%) after the patients received the CHM treatment (p = 1.00). With respect to the Ying-deficient physique, there were 14 patients (73.7%) who had it before the CHM treatment and 12 (63.2%) who had it after the treatment (p = 0.63). For the phlegm and water retention physique, there were seven patients (36.8%) who had it before the CHM treatment and six (31.6%) who had it after the treatment (p = 1.00) (Table 4). Among the 44 BCQ items, item number 26 was “I have symptoms of excessive thirst, dry mouth, and chapped lips,” and the average score for this item before the CHM treatment was 2, while the post-CHM average score was 1.63, meaning that there was a significant difference between the pre- and post-CHM scores (p = 0.01).

There were no significant differences in the UFR test results before and after the CHM treatment (Table 5). However, the sonogram measurements of the PVR volume indicated a decrease after the patients received the CHM treatment. The average pre-CHM PVR volume of the patients was 52.9 ± 48.7 mL, while the average post-CHM volume was 30.8 ± 40.1 mL. In addition, the number of patients whose PVR volume exceeded 50 mL decreased from eight to three, showing a trend of overall improvement. Meanwhile, the p values for these differences were 0.07 and 0.06, respectively (Table 6). Overall, the patients exhibited a significant improvement in terms of the IPSS. The mean pre-CHM total score was 17.5 ± 5.3, while the mean post-CHM total score was 15.0 ± 6.8, for a significant decrease of 2.5 points (p = 0.03). With respect to specific questions from the IPSS questionnaire, the mean pre-CHM score for the incomplete emptying symptom was 2.9 ± 1.3, while the mean post-CHM score for the incomplete emptying symptom was 2.1 ± 1.2, for a significant decrease of 0.8 points (p = 0.02). The mean pre-CHM sum of the voiding symptom subscores was 10.1 ± 3.6, and the mean post-CHM sum of the voiding symptom subscores was 8.4 ± 4.2, for a significant decrease of 1.7 points (p = 0.02).

For the AMS scale, there were no significant changes in the scores for the individual scale items except for question number 12, which requires a self-evaluation of the “feeling that you

### Table 2

**Descriptive statistics of baseline characteristics (n = 20)**

| Age, yo | 70.20 ± 9.57 |
| Height, cm | 164.61 ± 4.49 |
| Weight, kg | 63.70 ± 6.98 |
| BMI, kg/m² | 23.6 ± 2.14 |
| Prostate volume, cm³ | 42.48 ± 18.88 |
| PSA level, ng/mL | 4.81 ± 2.73 |

BMI = body mass index; PSA = prostate specific antigen.

### Table 3

**Western medications used for the combination therapy at baseline (n = 20)**

| Drug names and dosage | No. of people (n) | Ratio, % |
|-----------------------|-------------------|----------|
| α₁-adrenergic antagonists |                  |          |
| Harnalidge (tamsulosin) 0.4 mg | 9 | 45 |
| Doxaben (doxazosin) 4 mg | 3 | 15 |
| Dophilin (doxazosin) 2 mg | 5 | 25 |
| Unif (silodosin) 4 mg | 2 | 10 |
| Telowasin (terazosin) 2 mg | 1 | 5 |
| 5α-reductase inhibitors |                  |          |
| Proscar (finasteride) 5 mg | 1 | 5 |
| Avodart (dutasteride) 0.5 mg | 1 | 5 |
| Cholinergic agents |                  |          |
| Wecoli (bethanechol) 25 mg | 1 | 5 |
| Others |                  |          |
| Minixin (desmopressin) 0.1 mg | 1 | 5 |
| Rowaprazin (pipoxolan) 10 mg | 3 | 15 |

### Table 4

**The physiques of the patients before and after taking the CHM formula**

| No. of patients | Taking CHM |  |  |  |
|-----------------|------------|---|---|---|
| n | Before | After |
| n (%) | n (%) | p |
| Yang deficiency physique | 19 | 9 (47.37) | 10 (52.63) | 1.00 |
| Ying deficiency physique | 19 | 14 (73.68) | 12 (63.16) | 0.63 |
| Phlegm and water retention physique | 19 | 7 (36.84) | 6 (31.58) | 1.00 |

### Table 5

**The uroflowmetry test results of the patients before and after taking the CHM formula**

| Urine flow-rate | Before | After |
|-----------------|--------|-------|
| Volume, mL | 17 | 179.00 ± 108.94 | 173.59 ± 93.15 | 0.74 |
| Flow time, s | 17 | 37.41 ± 15.29 | 37.18 ± 18.89 | 0.69 |
| Void time, s | 17 | 43.52 ± 21.58 | 41.89 ± 22.72 | 0.52 |
| \(Q_{\text{max}}\), mL/s | 17 | 4.69 ± 2.12 | 4.81 ± 1.92 | 0.91 |
| \(Q_{\text{mean}}\), mL/s | 17 | 9.99 ± 4.54 | 9.61 ± 4.09 | 0.57 |
| \(T_{Q_{\text{max}}}\), s | 17 | 12.20 ± 12.68 | 10.89 ± 9.680 | 0.93 |

Wilcoxon signed-rank test.

### Table 6

**The post-void residual urine volume test results of the patients before and after taking the CHM formula**

| PVR volume, mL | Before | After |
|----------------|--------|-------|
| n | Mean ± SD | Mean ± SD | p |
| 18 | 52.94 ± 48.66 | 30.83 ± 40.06 | 0.07 |

Wilcoxon signed-rank test.

CHM = Chinese herbal medicine; PVR = post-void residual urine.

*McNemar's test.
After to be safer, milder, cheaper, and to cause fewer side effects than prevalent therapies for BPH and have generally been considered tries, meanwhile, CHMs and CAMs have been among the more can improve LUTS in patients with BPH. However, Cereale Secale Pygeum africanum and there is also strong evidence that α is capable of inhibiting the activity of 5-reductase without any side effects of sexual dysfunction. Meanwhile, Palmetto Saw palmetto has commonly been used in treating patients with BPH.

4. DISCUSSION

CAM has commonly been used in treating patients with BPH. In South American Indian culture, Saw palmetto has long been used to treat diseases of the urinary system such as cystitis, urethritis, and prostatitis. Many studies have shown that saw palmetto is capable of inhibiting the activity of 5α-reductase without any side effects of sexual dysfunction. Meanwhile, there is also strong evidence that Pygeum africanum and Secale cereale can improve LUTS in patients with BPH. However, many retrospective studies have criticized the theory that such CAMs can be used to improve LUTS, arguing that the numbers of patients who participated in the clinical trials indicating positive effects of CAMs were insufficient and that the processes used in such trials were not rigorous enough. In Asian countries, meanwhile, CHMs and CAMs have been among the more prevalent therapies for BPH and have generally been considered to be safer, milder, cheaper, and to cause fewer side effects than competing Western medicines. The theories of TCM are mostly about the adjustment of the whole body and mind, with TCM therapies being aimed at providing improved health in a natural and comprehensible way. CHM is one branch of TCM, and as such, the topic of using CHMs as treatments against urinary tract diseases in men has drawn considerable attention and discussion throughout the world in recent years.

In ancient China, the term “benign prostatic hyperplasia” did not exist; rather, people used the term “Long Bi” to refer to symptoms such as difficulty in urinating and urinary retention. Related theories can be traced back to The Yellow Emperor’s Classic of Internal Medicine, and the symptoms included in the concept of “Long Bi” were approximately similar to the symptoms of BPH, such as anuria, urinary retention, voiding difficulties, and so forth.

| Table 7 | The IPSS results of the patients before and after taking the CHM formula |
|---------|-------------------------------------------------|
|         | Before                                | After                                | p       |
| N       | Mean ± SD                             | Mean ± SD                             |         |
| IPSS questions |
| Incomplete emptying | 19 | 2.89 ± 1.29 | 2.11 ± 1.15 | 0.02* |
| Frequency | 19 | 3.16 ± 1.17 | 2.63 ± 1.16 | 0.06 |
| Intermittency | 19 | 2.74 ± 1.24 | 2.26 ± 1.19 | 0.09 |
| Urgency | 19 | 2.16 ± 1.26 | 2.11 ± 1.52 | 0.90 |
| Weak stream | 19 | 2.89 ± 1.20 | 2.47 ± 1.22 | 0.07 |
| Straining | 19 | 1.53 ± 1.39 | 1.58 ± 1.35 | 0.72 |
| Nocturia | 19 | 2.11 ± 1.05 | 1.84 ± 1.07 | 0.19 |
| Total IPSS score | 19 | 17.47 ± 5.25 | 15.00 ± 6.77 | 0.03* |
| Sum of four voiding symptoms | 19 | 10.08 ± 3.63 | 8.42 ± 4.19 | 0.02* |
| Sum of three storage symptoms | 19 | 7.42 ± 2.65 | 6.58 ± 3.02 | 0.15 |
| IPSS V/S ratio | 19 | 1.48 ± 0.64 | 1.34 ± 0.56 | 0.22 |

Wilcoxon signed-rank test.

IPSS = International Prostate Symptom Score; CHM = Chinese herbal medicine; V/S ratio = voiding/storage scores ratio.

*p < 0.05.

have passed your peak,” with the response value ranging from 1 to 5. For this item, the mean pre-CHM score was 2.7, while the mean post-CHM score was 2.1, for a significant decrease of 0.6 (p = 0.02). As for the IIEF, we were not able to perform any analysis of the IIEF results due to the fact that more than half of the patients in the study (11 patients) reported engaging in no sexual activities at this point in their lives.

**Table 7**

The IPSS results of the patients before and after taking the CHM formula

| IPSS questions       | N  | Mean ± SD Before | Mean ± SD After | p       |
|----------------------|----|------------------|-----------------|---------|
| Incomplete emptying  | 19 | 2.89 ± 1.29      | 2.11 ± 1.15     | 0.02*   |
| Frequency            | 19 | 3.16 ± 1.17      | 2.63 ± 1.16     | 0.06    |
| Intermittency        | 19 | 2.74 ± 1.24      | 2.26 ± 1.19     | 0.09    |
| Urgency              | 19 | 2.16 ± 1.26      | 2.11 ± 1.52     | 0.90    |
| Weak stream          | 19 | 2.89 ± 1.20      | 2.47 ± 1.22     | 0.07    |
| Straining            | 19 | 1.53 ± 1.39      | 1.58 ± 1.35     | 0.72    |
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Wilcoxon signed-rank test.

IPSS = International Prostate Symptom Score; CHM = Chinese herbal medicine; V/S ratio = voiding/storage scores ratio.

*p < 0.05.

Ji-Sheng-Shen-Qi-Wan and Sang-Piao-Xiao-San were the CHM formulae most commonly used to treat BPH. Moreover, the most commonly used CHM single herbs were Yi Zhi Ren (Fructus Alpiniae Oxyphyllae), Fu Pen Zi (Fructus Rubi), Che Qian Zi (Semem Plantaginis), and Wu Yao (Radix Linderae). The specific CHM formula used in this pilot study was based on those commonly used herbs, as well as the recommendations of experienced TCM physicians. Ji-Sheng-Shen-Qi-Wan (Kidney Qi Pill) was first prescribed by Yong-He Yen in AD 1253. This formula was modified from Jin-Gui-Shen-Qi-Wan in the classical Chinese text Jin Gui Yao Lue (Essential Prescriptions from the Golden Cabinet) written ca. AD 210 by Zhong-Jing Zhang. Ji-Sheng-Shen-Qi-Wan was composed of 10 herbs (Table 3) and is said to warm the kidney Yang, tonify the kidney Qi, aid in water transformation, promote urination, and reduce edema. According to a previous statistical analysis, the most common physique among BPH patients was Kidney Qi deficiency, and Ji-Sheng-Shen-Qi-Wan was the most popular formula for treating kidney Qi deficiency among the various CHM formulae. Moreover, there have been several clinical studies on the use of Ji-Sheng-Shen-Qi-Wan for improving LUTS in BPH published in China and Japan, and the safety of the formula has been confirmed.

In addition to Ji-Sheng-Shen-Qi-Wan, Sang-Piao-Xiao-San (Mantis Formula), which was first prescribed by Tsong-Shi Ko in AD 1116 and is composed of eight herbs, was a formula that was commonly prescribed by TCM physicians for patients with BPH in Taiwan (Table 3). According to TCM theory, this formula was intended to regulate the heart and kidneys. In modern times, meanwhile, there have been only a few studies on the application of Sang-Piao-Xiao-San for nocturnal enuresis and interstitial cystitis.

As for single herbs, both Yi Zhi Ren (Fructus Alpiniae Oxyphyllae) and Wu Yao (Radix Linderae) were the main components of Suo-Quan-Wan (Pills for Enuresis), which were first prescribed by Chi-Ming Chen in AD 1237. On the basis of TCM theory, these two herbs were commonly combined for use as urine astringent and for warming the kidneys and were also commonly prescribed by TCM physicians for BPH. Meanwhile, recent studies have reported on the quantitative analysis of their major constituents and the resulting improvement of renal function. Fu Pen Zi (Fructus Rubi) was among the commonly prescribed single herbs for BPH patients in Taiwan. It is believed to tonify and stabilize kidney Qi and has been widely used for urinary incontinence and frequency. Meanwhile, Dan Shen (Radix Salviae Miltiorrhizae) has been used, according to TCM theory, to invigorate the blood and dispel blood stasis, and there have been a lot of reports on this herb in regard to its characteristic effects against cardiovascular disease, its anti-inflammatory and antioxidant effects, and its chemosensitization effects. In TCM theory, chronic disease is often blamed for blood stasis, and among the CHMs, Dan Shen was the most commonly used herb for dispelling blood stasis.

Yin Yang Huo (Herba Epimedii) was used, according to TCM theory, to strengthen kidney Yang, increase the libido, and treat impotence. These indications were first stated in Shen Nong Ben Cao Jing (Shen-Nong’s Root and Herbal Classic) ca. AD 200. Recent pharmaceutical research studies, meanwhile, have mainly focused on icariin, the main extract ingredient of Yin Yang Huo, which possesses anti-cancer, anti-oxidant, and neuro-protective effects. Moreover, Yin Yang Huo is also believed, according to TCM theory, to elicit penile erection. As a consequence, we chose to include this herb in our prescription formula not only due to its potential anti-oxidant effects for improving BPH, but also because it might improve the accompanying symptoms of sexual dysfunction related to BPH, thereby further improving patient quality of life. Finally, we also chose to include small amounts of Huang Bo (Cortex Phellodendri)
and Zhi Mu (Rhizoma Anemarrhennae) in our formula, with both included for the purposes of clearing heat and purging kidney fire, according to TCM theory. The combination of Huang Bo, Zhi Mu, and Rou Gui (Cortex Cinnamomi) was first used in Zhi-Shen-wan (Pills for Nourishment of Kidney), which were first prescribed by Dong-Yuan Lee and discussed in a treatise published in AD 1276. The main indication of Zhi-Shen-wan was dysuria, and there have been a few researches of Zhi-Shen-wan to improve BPH in recent years.7

After the combined therapy consisting of the investigated CHM formula and various Western medicines, the patients with BPH showed significant improvement in terms of their LUTS, especially with respect to their voiding and incomplete emptying symptoms. The patients also experienced improvements in other symptoms affecting their quality of life, such as dry mouth, residual urine sensations, and excessive thirst. Further rigorous double-blinded clinical trials should be implemented in the future to further confirm and clarify the effects of the CHM formula.

In conclusion, this trial indicated that the add-on CHM formula (VGHBPH0) consisting of Ji-Sheng-Shen-Qi-Wan, Sang-Piao-Xiao-San, Wu Yao, Yi Zhi Ren, Dan Shen, Yin Yang Huo, Fu Pen Zi, Huang Bo, and Zhi Mu might be a potential treatment to improve the lower urinary tract symptoms of BPH patients.

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