Fangjihuangqi Tang improved lower urinary tract dysfunction in benign prostatic hyperplasia rats model

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Abstract

OBJECTIVE: To investigated the effect and mechanism of Fangjihuangqi Tang (FHT) on lower urinary tract dysfunction induced by benign prostatic hyperplasia (BPH) in rats.

METHODS: Male rats were randomly divided into seven groups: normal, model, finasteride (0.5 mg/kg), terazosin (0.5 mg/kg), and FHT (10, 5, 2.5 g/kg). Rats were administered testosterone (0.5 mg sc) for 6 weeks after orchiectomy, excluding the normal group. All rats were intragastrically administered assigned drugs for 4 weeks from the third week. Urodynamics were assessed in rats under anesthesia. Serum dihydrotestosterone (DHT) and prostatic acid phosphatase (PAP) were measured. The prostate index (PI), bladder index (BI), and pathological detection were evaluated.

RESULTS: In the model group, the PI, BI, serum DHT, serum PAP, threshold pressure (TP), micturition pressure (MP), and residual urine volume (RV) were significantly higher. Moreover, inter-micturition duration (IMD) was significantly lower and the prostatic and bladder showed obvious pathological changes. The IMD was significantly higher, while BI, TP, MP, and RV were significantly lower and bladder pathological changes were alleviated in the FHT (10, 5 g/kg), finasteride, and terazosin groups. The PI, DHT, and PAP were significantly lower in the finasteride group, but they did not change significantly in the FHT (10, 5, 2.5 g/kg) and terazosin groups.

CONCLUSION: FHT could relieve symptoms of lower urinary tract dysfunction in BPH rats but with no apparent effect on reducing the volume of the enlarged prostate itself.

INTRODUCTION

Lower urinary tract symptoms (LUTS), secondary to benign prostatic hyperplasia (BPH), are a common problem in men and may significantly influence their quality of life. LUTS may occur in up to 30% of men older than 65 years. A population-based cross-sectional survey on LUTS conducted in Austria showed that 64.6% of the male population aged 15-89 may suffer from LUTS.1 The prevalence of LUTS in middle- and old-aged males in China was close to that of Western countries.2 Symptoms of LUTS include voiding (related to the outlet), storage (related to the bladder), or a combina-
tion of both. Notably, 52%-84% of patients have the storage symptom subset of LUTS, which is also termed overactive bladder (OAB) syndrome. OAB might have a greater effect on quality of life compared to that of the voiding symptoms of LUTS in both genders. Results from another study demonstrated that the prevalence of voiding symptoms among Austrian males was 35.5%, but the prevalence of storage symptoms reached as high as 61.6%.

Currently, medical therapy acts as an alternative to surgery in a significant number of LUTS cases with mild-to-moderate symptoms. Phytotherapeutic agents, α1-blockers, and 5α-reductase inhibitors are the three main classes for the treatment of LUTS caused by BPH. A revival of interest in phytotherapeutic agents, both in Europe and North America, is a consequence of patients’ dissatisfaction with the adverse effects of medical alternatives.

Fangjihuangqi Tang (FHT), a classical phytotherapeutic formula from China, was first recorded in Jin Gui Yao Lue, an ancient Chinese medical classic. FHT has been the most popular prescription for treating edema and dysuria in the Traditional Chinese Medical system for more than 1800 years. It contains four herbs: Fangji (Radix Stephaniae Tetrandrae) 12 g, Huangqi (Radix Astragali Mongolici) 15 g, Baizhu (Rhizoma Atractylodis Macrocephalae) 9 g, and Gancao (Radix Glycyrrhizae) 6 g, with the function of improving dysuria and edema. Many studies have demonstrated that FHT could deal with various clinical edemas. The present experiment was conducted to explore if FHT can alleviate BPH in rats, especially in improving the symptoms of lower urinary tract dysfunction.

MATERIALS AND METHODS

Animals

One hundred and five 6-8 week-old male SD rats weighing 150-200 g, supplied by the experimental animals center of Zhengzhou University of China, certificate: SCXK (Yu) 2005-0001, were housed under standard conditions of 22±3°C with 40%-60% humidity under a 12 h light-dark cycle, and were allowed free access to tap water and food. Experimental protocols described in this study were approved by the Ethics Review Committee for Animal Experimentation of Anhui University of Traditional Chinese Medicine and in compliance with the guidelines of laboratory animal care of NIH (NIH publication No. 85-23, revised 1985).

Drugs and reagents

The herbs of FHT were purchased from a local drugstore specializing in herbs (Hefei, China). All plants were authenticated by Prof. Jianli Zhou in the Chinese medicinal plant identification laboratory of Anhui University of Traditional Chinese Medicine (Hefei, China), and a voucher specimen are deposited in our laboratory.

The materials were weighed according to the prescription mentioned above. After water extraction, the solution was condensed to 2 g/mL, and stored at 4°C. The dose of FHT was converted from the original prescription.

Other experimental drugs and reagents were purchased commercially, including finasteride tablets (Guangdong Yishu pharmacy Co. Ltd.; Guangdong, China; batch No. 091018), terazosin hydrochloride tablets (Shanghai Yapei pharmacy Co. Ltd.; Shanghai, China; batch No. 090826), propionate testosterone injection (Shanghai Tongyong pharmacy Co. Ltd.; Shanghai, China; batch No. 090813), serum total acid phosphatase kit (Nanjing Jiancheng biological research institute; Nanjing, China; batch No. 091024), prostatic acid phosphatase kit (Nanjing Jiancheng biological research institute; Nanjing, China; batch No. 090817), and dihydrotestosterone kit (Shanghai Xitang biological technology Co. Ltd.; Shanghai, China; batch No. 090825).

Experimental model of BPH and drug treatment

The rats were divided into seven groups (n=15) according to a randomized block design: normal, model, finasteride (0.5 mg/kg), terazosin (0.5 mg/kg), and FHT (10, 5, 2.5 g/kg). The experiments were carried out according to established methods. Rats were castrated while anaesthetized with chloral hydrate, excluding the normal group, and then they were given penicillin once a day for three days. A week later, the rats were administrated testosterone (0.5 mg sc) once a day for 6 weeks. Each group was intragastrically administered the corresponding drug once a day for 4 weeks, beginning 2 weeks after making the rat model. The normal and model groups were given an equal volume of vehicle.

Determination of urodynamic parameter

The experiments were carried out in accordance with our previously established methods. Briefly, 2 h after final drug administration, urodynamic parameters in at least in four micturition cycles of each rat were recorded by cystometry. Parameters including inter-micturition duration (IMD), threshold pressure (TP), micturition pressure (MP), and residual volume (RV) were recorded.

Measurement of serum dihydrotestosterone (DHT) and prostatic acid phosphatase (PAP)

After the urodynamic parameter measurement, 5 mL blood was taken from rats via the abdominal aorta. Blood was centrifuged (3000 rpm) for 10 min at a low temperature. The separated serum was kept at –20°C. Kits were used to detect the level of DHT, acid phosphatase (ACP), and non-prostatic acid phosphatase (NPAP). Meanwhile, prostatic acid phosphatase (PAP)
was calculated by the formula: PAP = ACP - NPAP.

**PI, BI Determination and pathology examination**

After completing the above examinations, prostates and bladders were isolated from all rats and weighed. Prostate index (PI) was defined as prostate weight/body weight (mg/g). Bladder index (BI) was defined as bladder weight/body weight (mg/g). Afterwards, prostates and bladders were kept in 10% formaldehyde solution and embedded in paraffin. Pathological changes were observed by light microscopy after hematoxylin-eosin (HE) staining.

**Statistical analysis**

Data are expressed as mean ± standard deviation (SD). All analyses were performed using DAS 2.0 statistical software (prepared by the drug clinical research center of Shanghai university of TCM). ANOVA was used in comparisons followed by Tukey’s multiple range tests. \( P < 0.05 \) was considered statistically significant.

**RESULTS**

**General status and behavior observations**

All animals maintained good health throughout the experiments with no significant weight loss. During cystometric measurement, one rat in both the model and terazosin groups died, possibly due to anesthesia intolerance.

**Effects of FHT on urodynamic parameter in BPH rats**

Compared with the normal group, the TP, MP, and RV were significantly higher, while IMD was significantly lower in the model group, indicating that the rats’ emiction function was influenced by BPH. Compared with the model group, the IMD was significantly higher, while TP and MP were significantly lower in the FHT (10, 5 g/kg), finasteride, and terazosin groups. This indicated that FHT could effectively improve frequent micturition and reduce the intravesical pressure in BPH rats. The RV was significantly decreased in FHT (10 g/kg), finasteride and terazosin groups (Table 1).

**Effects of FHT on serum DHT and PAP in BPH rats**

Compared with normal group, the DHT, ACP, and PAP were significantly higher in model group. The above variables were obviously lower in the finasteride group, but they had no significant changes in the FHT group.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Effects of FHT on urodynamic parameters in BPH rats</th>
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<tbody>
<tr>
<td>Group</td>
<td>n</td>
</tr>
<tr>
<td>Normal</td>
<td>15</td>
</tr>
<tr>
<td>Model</td>
<td>14</td>
</tr>
<tr>
<td>Finasteride</td>
<td>15</td>
</tr>
<tr>
<td>Terazosin</td>
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<table>
<thead>
<tr>
<th>Table 2</th>
<th>Effects of FHT on serum DHT and PAP in BPH rats</th>
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<tr>
<td>Group</td>
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<tr>
<td>Normal</td>
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<td>Finasteride</td>
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<td>14</td>
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<tr>
<td>FHT</td>
<td>15</td>
</tr>
</tbody>
</table>

Notes: FHT: Fangjihuangqi Tang; BPH: benign prostatic hyperplasia; IMD: inter-micturition duration; TP: threshold pressure; MP: micturition pressure; RV: residual volume. The dose of FHT was converted from the original prescription. Compared with normal group, \( P < 0.01 \); compared with model group, \*\( P < 0.01 \); \( P < 0.05 \).
(10, 5, 2.5 g/kg) and terazosin groups (Table 2).

**Effects of FHT on PI and BI in BPH rats**

Compared with the normal group, the weight of the prostates and bladders, PI and BI were all significantly higher in the model group. The weight of the prostates and PI were significantly lower in the finasteride group, while the weight of the bladders and BI were significantly lower in the FHT (10 g/kg) and terazosin groups (Table 3).

**Effects of FHT on histopathology of the prostate and bladder in BPH rats**

In the normal group, the prostatic epithelium was composed of simple epithelium, the glandular cavities were regular and flat with little secretion and mesenchyme, and the size and shape of cell nucleuses were consistent. In the model group, the prostates proliferated obviously, the glandular cavities expanded in a zigzag with the drape and incrassated gland extruding, and the prostatic epithelium increased to multiple layers with the secretion and mesenchyme increased obviously. In the finasteride group, the prostatic hyperplasia was obviously alleviated, with thinner epithelium. Meanwhile, there were relatively fewer secretions and mesenchyme in the cavities. The prostate hyperplasia conditions in the FHT (10, 5, 2.5 g/kg) and terazosin groups were similar to the model group (Figure 1).

The detrusor cells of the bladder tended to be long and fusiform, arrayed in parallel, and well-distributed, with little secretion and mesenchyme in the normal group. In the model group, the detrusor cells were irregularly shaped and arrayed disorderedly with the mesenchyme increased obviously. The sizes of the detrusor cells were relatively consistent and well-distributed in the finasteride, terazosin, and FHT (10 g/kg) groups. Though the detrusor cells in the FHT (5, 2.5 g/kg) group were also relatively well-distributed, the mesenchyme had obvious hyperplasia (Figure 2).

**DISCUSSION**

The common etiology of male LUTS is BPH. Similarly, most bladder outflow obstruction is caused by be-

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**Table 3 Effects of FHT on PI and BI in BPH rats**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Dose (g/kg)</th>
<th>PW (mg)</th>
<th>PI (mg/g)</th>
<th>BW (mg)</th>
<th>BI (mg/g)</th>
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<tbody>
<tr>
<td>Normal</td>
<td>15</td>
<td>-</td>
<td>404.41±82.86</td>
<td>1.26±0.32</td>
<td>252.31±39.45</td>
<td>0.79±0.17</td>
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<tr>
<td>Model</td>
<td>14</td>
<td>-</td>
<td>601.51±195.67</td>
<td>1.83±0.51</td>
<td>472.82±134.01</td>
<td>1.44±0.31</td>
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<tr>
<td>Finasteride</td>
<td>15</td>
<td>0.0005</td>
<td>426.52±124.78</td>
<td>1.28±0.29</td>
<td>466.42±137.68</td>
<td>1.40±0.33</td>
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<tr>
<td>Terazosin</td>
<td>14</td>
<td>0.0005</td>
<td>587.47±113.52</td>
<td>1.77±0.33</td>
<td>380.51±98.76</td>
<td>1.14±0.26</td>
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<tr>
<td>FHT</td>
<td>15</td>
<td>10</td>
<td>592.82±193.61</td>
<td>1.78±0.47</td>
<td>387.32±81.31</td>
<td>1.18±0.22</td>
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<tr>
<td></td>
<td>15</td>
<td>5</td>
<td>583.79±144.67</td>
<td>1.73±0.35</td>
<td>469.38±118.71</td>
<td>1.44±0.46</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>2.5</td>
<td>595.31±118.30</td>
<td>1.74±0.40</td>
<td>469.13±124.27</td>
<td>1.38±0.42</td>
</tr>
</tbody>
</table>

Notes: FHT: Fangjihuangqi Tang; PW: prostate weight; PI: prostate index; BW: bladder weight; BI: bladder index. The dose of FHT was converted from the original prescription. Compared with normal group, 'P<0.01; compared with model group, 'P<0.05, 'P<0.01.
Maggi et al compared the increased frequency of micturition was found to be related to increased tone of the prostatic smooth muscle. OAB induced by BOO may either manifest as detrusor overactivity during the filling phase or detrusor underactivity during the voiding phase, or a combination of both. There is evidence that increased strain caused by the obstruction can induce overexpansion of the bladder, which leads to ischemia, anoxia, and overactive bladder. One study indicated that chronic ischemia occurs in the vestibule neck and prostate in older LUTS patients.

Tatemichi et al demonstrated a significantly increased frequency of non-voiding bladder contraction in a rat model of BPH induced by androgen in combination with estrogen. They suggested that estrogen might have a role in stimulating micturition.

Increased frequency of micturition was found to be higher in the combination treatment group compared with the androgen group. Maggi et al compared the urodynamic characteristics of the testosterone-induced BPH rat model to the model developed by urethral ligation in female rats. They reported that high frequency rhythmic contractile activity occurred in the testosterone-treated rat.

In the present study, IMD was significantly decreased while TP, MP, RV, PI, and BI increased in the model group. The levels of serum DHT and PAP were also increased. The glandular epithelium cells were columnar or high columnar pathologically. The cavities expanded obviously with secretion retention and hyperplasia of the mesenchyme in different levels. This indicated that the model rats had hypertrophic prostates, which could lead to lower urinary tract dysfunction. Unlike the 5α-reductase inhibitor finasteride, FHT has no obvious effect on serum DHT and PAP in rats. Therefore, FHT may have no direct inhibitory effect on 5α-reductase in BPH rats.

In conclusion, our findings indicate that FHT may improve lower urinary tract dysfunction in BPH rats by regulating smooth muscles in the bladder and urethra rather than reducing the volume of the enlarged pros-
tate. The exact active ingredients and mechanisms of FHT need to be explored in the future.

REFERENCES


