The efficacy of combination therapy of tamsulosin and Qianlie Beixi capsule in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia

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Abstract
Objective: We proposed to explore the efficacy and safety of the combination therapy with tamsulosin plus a Chinese herb compound preparation Qianlie Beixi capsule versus tamsulosin monotherapy in treating lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH).

Methods: 120 male patients participated in this research from 2013 to 2015. Patients were r grouped into two: monotherapy group received tamsulosin 0.2mg once every day (60 patients) and the combination therapy group received tamsulosin 0.2mg, once daily plus Qianlie Beixi capsule three times daily (60 patients) for twelve weeks. The main variables to assess efficacy were changed in International Prostatic Symptom Score (IPSS), maximal urinary flow rates (Qmax), Quality of Life (QoL) score as well as nocturia-QoL. The safety parameters include adverse events, results of PSA value, urinalysis, liver function and renal function measurement. At baseline and after twelve weeks of therapy were these parameters assessed.

Results: Both groups had a remarkable reduction in IPSS, QoL and nocturia-QoL scores as well as a rise in Qmax ($p<0.05$). The patients in the combination therapy group had significantly more reduction in IPSS, QoL and nocturia-QoL scores than the monotherapy group ($p<0.05$). All treatments were generally well tolerated. Conclusions: The combination therapy of Qianlie Beixi capsule and tamsulosin may decrease LUTS due to BPH and further increase the quality of life than the monotherapy of tamsulosin with no severe sideeffects.

Keywords: Benign prostatic hyperplasia; Lower urinary tract symptoms; Tamsulosin; Qianlie Beixi Capsule; Quality of life.

Introduction

In elderly men, Benign prostatic hyperplasia (BPH) is the most typical reason for lower urinary tract symptoms (LUTS). LUTS in males with BPH include storage symptoms and voiding symptoms.

At least one LUTS complain was recorded in nearly two-thirds of men. The most common symptom is nocturia and in one-half to two-thirds of the population with BPH accompanying LUTS had severe discomfort and poor quality of life. Poor health condition, sleep disturbance, and unsatisfactory quality of life always occur in patients with nocturia. After adjusting for age, cardiac diseases, diabetes mellitus as well as stroke, nocturia has also had linkage to an increased risk of death.[1]

The fact that voiding symptoms are the most common one does not prevent storage LUTS to have greater effect on quality of life which discomforts the male patients the most. Alpha-adrenergic antagonists alone or together with 5-alpha-reductase inhibitors are always prescribed to patients with LUTS due to BPH. [2] When dealing with BPH, physicians regard alpha-adrenergic antagonists to be the standard of care and tamsulosin is preferred in most clinical settings. However, drugs which focus on the prostate, in many circumstances, do not improve overactive bladder (OAB) symptoms, aswell as might not be the best option for males with storage LUTS.[3]

Up to now, numerous researchers have attempted to create an ideal medication with both high efficacy and low adverse effect for BPH/LUTS with both voiding as well as storage symptoms. In the present research, we report the results of a prospective, randomized trial including 120 BPH patients for evaluating the clinical efficiency of tamsulosin as well as a Chinese herbal medicine Qianlie Beixi capsule combination therapy versus tamsulosin monotherapy for management of symptomatic BPH with accompanying LUTS.

Methods

After receiving approval by the institutional review board of Sir Run Run Shaw Hospital, a prospective, randomized trial was performed on 120 symptomatic patients with LUTS secondary to BPH between May 2013 and May,2015. The inclusion criteria were: age>55 years old, BPH-LUTS for a duration of at least six months of storage symptoms (increased urgency, frequency and nocturia), and/or voiding symptoms (difficulty in initating micturation, sense of incomplete voiding, impaired quality of the stream).

International Prostatic Symptom Score (IPSS)≥13, residual urinary volume≤100ml, maximum urinary flow rate (Q_{max})<15ml/s. Patients with Qmax < 5 ml/s, voided volume < 50 ml, previous lower urinary tract surgery, bladder stone, suspected prostatic carcinoma, urethral stricture, recurrent or active urinary tract infections, neurogenic bladder dysfunctions, history of pelvic irradiation, bladder neck sclerosis, history of continuing medication with 5α-reductase inhibitors and α-adrenergic blockers, were excluded from the study.

Patients were arbitrarily grouped into 2: monotherapy group were given tamsulosin 0.2mg once daily (group A, 60 patients) and the combination therapy group received tamsulosin 0.2mg once daily plus Qianlie Beixi six capsules three times daily (group B, 60 patients) for twelve weeks. All patients were provided with information on the trial, and an informed consent was obtained from each patient.

Assessments: Changes in IPSS, Quality of Life (QoL) score, Qmax, nocturia-QoL were the primary parameters for assessing efficacy. The safety parameters include adverse events, results of PSA value, urinalysis, liver function and renal function measurement. At baseline and after twelve weeks of therapy, these parameters were assessed.

Statistical analysis: Univariate analysis of continuous variables was done utilizing the independent sample t-test with significant statistically difference considered at p<0.05. SPSS statistical software package for Windows 19.0 was used for data analysis.

Results

120 patients who had joined the study had finished the 12-weeks research. The demographics of all the 120 patients in the two groups were presented in Table I. No significant differences (age, prostate volume, IPSS, Qmax, PSA, quality of life as well as residual urine) were noted between the two groups.

After 12 weeks of treatment, mean decrease in IPSS score was 5.2±3.4 and 6.6±4.1 points in groups A and B, correspondingly (p<0.05). The average reduction in Quality of Life score was 1.5±1.4 points in group A as well as 2.2±1.8 points in group B post- treatment (p < 0.05). Both groups had considerable reduction in the IPSS, Qmax as well as QoL scores (p<0.01) compared with baseline. While the two treatment groups were not statistically different in post-treatment Qmax (mean increase 3.9±2.2 vs 4.2±2.5 ml/s) (p>0.05). (Table II)

Table III reveals the difference between baseline and post-treatment nocturia-QoL. For the baseline nocturia-QoL, there was no significant statistically differences. After 12 weeks of treatment, both groups had a obvious improvement in nocturia-QoL (p<0.05). The average score of nocturia-QoL was 3.7±1.2 points in group A as well as 3.1±1.5 points in group B after the treatment (p < 0.05).

Treatments were generally well tolerated. There was no significant statistically differences in the results of PSA value, urinalysis, liver function and renal function measurement between baseline and post-treatment data. There were no severe adverse events in both groups.

Table 1
Patient demographics

	Group A (mean±SD, n=60)	**Group B (mean±SD, n=60)**	**p-value**
Age (years)	68.7±18.9	64.1±20.1	0.199
Prostate volume (ml)	45.6±14.2	42.3±12.7	0.182
IPSS	17.4±4.3	18±5.6	0.512
Qmax (ml/s)	11.7±2.6	10.8±3.2	0.094
PSA (ng/ml)	2.3±1.2	2.8±1.6	0.055
QoL	3.7±1.3	4.0±1.2	0.192
Residual urine (ml)	48.6±30.8	56.3±35.2	0.210

Table 2
Parameter changes from baseline to end of treatment outcomes

	Group A (mean±SD)	**Group B (mean±SD)**	**p-value**
IPSS	-5.2±3.4	-6.6±4.1	0.044
Qmax(ml/s)	3.9±2.2	4.2±2.5	0.487
QoL	-1.5±1.4	-2.2±1.8	0.020

Table 3
Comparison of baseline nocturia-QoL with post-treatment nocturia-QoL

Group		Nocturia-QoL (mean±SD)
Group A	baseline	4.8±1.4
	post- treatment	3.7±1.2*
Group B	baseline	5.0±1.9
	post- treatment	3.1±1.5*,Δ

*p< 0.05, after the treatment in comparison with the baseline; Δp< 0.05, after the treatment group A in comparison with group B

Discussion

In men, over fifty years old, the most commonly diagnosed urological disease is BPH which was related to hyperplasia of the prostate, annoying LUTS as well as bladder outlet obstruction(BOO). Although BPH is a benign condition, it could have obviously troubling effects on patients' QoL. BPH can be the reason for bladder overactivity and reduction of functional bladder capacity, which may lead to storage symptoms e.g., nocturia. Nocturia severely troubles patients with BPH and is regarded one of the utmost annoying symptoms of the disease. The primary objectives of the medical treatment for BPH are to produce rapid, sustained, and safe improvements in the LUTS associated with BPH. So, therapeutic improvement of BPH is always a relevant topic in the area of Urology.

For those patients without absolute indications for surgery to release the bladder outlet obstruction, medicine is the preferred alternative to alleviate the symptoms, improve the living quality, and prevent the development of BPH and the need for surgery. Medical therapies used for BPH include alpha1-adrenergic antagonists, 5α-reductase inhibitors, Chinese herbal medicine and plant extracts. Endogenously released noradrenaline on smooth muscle cells in prostate can be inhibited by alpha1-adrenergic antagonists and such mechanism reduces prostate tone and bladder outlet obstruction. [4] Typical IPSS reduction and Q_{max} improvement prove that alpha1-adrenergic antagonists are capable of alleviating both storage and voiding LUTS. In addition, alpha1-adrenergic antagonists' effect on IPSS reduction and Qmax improvement continue at least four years. [5] Tamsulosin's efficacy and safety for LUTS associated with BPH has already been well explored in a large well-designed, randomized, placebo-controlled trial.[6]

In our study, monotherapy with tamsulosin could significantly improve the Qmax, IPSS and QOL scores, and a reduction in the nocturia-QOL scores. Tamsulosin is a highly selective alpha1A-blocker, which can reduce smooth muscle tone in the prostate. So tamsulosin can rapidly improve the urinary symptoms and flow of BPH patients. However, for men with storage LUTS, alpha1A-blocker might not be the best solution.3 Miwa et al reported that using tamsulosin alone resulted in less nocturia and could be the reason for fewer sleep disturbances.9 Furthermore, in order to get better results, many combination therapy trials launched. In males with LUTS because of BPH, long-term combination treating of dutasteride and tamsulosin was supported by the 4-yr CombAT data.[7]

Although the etiology of BPH remains unclear in several aspects, some possible mechanisms have been put forward in the progression and pathogenesis of BPH.

A major factor in BPH disease progression is chronic inflammation. [8] At histologic examination, inflammatory cells infiltration are found in nearly all surgery-derived BPH specimens. Nickel et al investigated the correlativity of prostatic inflammation, prostate volume as well as seriousness of LUTS. [9] They found patients with higher IPSS scores were associated with much more severe histologic inflammation. Those with prostatic inflammation had greater IPSS than patients with no inflammation and the tissue inflammation grade was heavily associated with the degree of LUTS. The monotherapy of alpha1-adrenergic antagonists has little impact on the tissue inflammation. Because of such an inflammatory pattern, patient outcomes improvement may depend on combined therapies.

The Qianlie Beixi capsule is a compound preparation manufactured by the extracts from the herb of maidenhair, Gryllotalpidae, Spina Gleditsiae, Cowherb Seed and corium erinacei. It has an effect of eliminating dampness and heat, activation of blood circulation to dissipate blood stasis and induction of diuresis for treatment of strangurtia. The components of Qianlie Beixi capsule also have multiple functions such as facilitating microcirculation, anti-infection, anti-bacterial activity, analgesia, detumescence, immunity boost. It can treat the prostatic disease through improving microcirculation, increasing the medicine penetration and patency of the ducts, accelerating the process of removing toxin, relieving tissue inflammation. In China, Qianlie Beixi capsule are widely used in the treatment of prostatitis and unliquefiable semen.

In our study, we investigated the efficacy as well as safety for combining Qianlie Beixi capsule as well as tamsulosin in treating BPH-LUTS through a synergetic effect of traditional Chinese and modern western medicine. The results showed that the combination therapy remarkably improved the Qmax, IPSS, QoL and nocturia-QoL score. Compared with the tamsulocin monotherapy group, the improvements of IPSS, QoL and nocturia-QoL score of the combination therapy group were better which had

statistically significant difference. It should be emphasized that combination therapy had remarkable improvement in nocturia and was significantly superior to tamsulocin monotherapy.

There was no statistical significance in the difference of Qmax between the two groups. We assumed the improvement of Qmax was mainly due to tamsulocin in both groups which could reduce smooth muscle tone and obviously improve urinary flow. The mechanism of Qianlie Beixi capsule may include: (1) it can help to elevate the local drug concentration of tamsulocin via improving microcirculation of the prostate gland; (2) it has an anti-inflammatory effect to alleviate the symptoms as well as decrease the risks of BPH clinical progression via effective drainage of the prostatic ducts; (3) it has an effect on regulating the immune balance which results in immunity improvement and cell repairing.

We are aware of the limitation of the research, which was the lack of Qianlie Beixi capsule or a placebo group, and therefore caution is required to interpret the favorable effect observed in our study.

Conclusion

In conclusion, the combination therapy with tamsulocin and Qianlie Beixi capsule indeed improved IPSS, QoL and nocturia-QoL score, without serious side effects.

We suggest that the combination therapy may be a safe and effective therapy for moderate to severe LUTS because of BPH. However, a long-term follow-up study is required for evaluating the efficacy of this combination therapy.

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