

ORIGINAL PAPER

Tamsulosin plus a new complementary and alternative medicine in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: Results from a retrospective comparative study

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Summary *Background:* We aimed to compare the efficacy of tamsulosin 0.4 mg once a day alone and the combination therapy involving tamsulosin 0.4 mg once a day plus the complementary and alternative medicine consisting of vitamins (C and D), herbal products (*Cucurbita maxima*, *Capsicum annum*, *Polygonum capsicatum*) and amino acid L-Glutamine bid in patients with lower urinary tract symptoms related to benign prostatic hyperplasia (LUTS/BPH). *Methods:* We performed a retrospective matched paired comparison. The clinical records of LUTS/BPH patients who underwent medical therapy with tamsulosin 0.4 mg/day plus the complementary and alternative medicine consisting of vitamins (C and D), herbal products (*Cucurbita maxima*, *Capsicum annum*, *Polygonum capsicatum*) and amino acid L-Glutamine bid between January 2019 to September 2019 were reviewed (Group 1). These patients were compared in a 1:1 fashion with LUTS/BPH patients who underwent therapy with tamsulosin 0.4 mg/day alone (Group 2). Total, storage, voiding and Quality of Life (QoL) international prostate symptom (IPSS) score, as well as overactive bladder (OAB)-v8 score and treatment-related adverse events recorded at 40 days follow-up in both groups were compared.

Results: At 40 days follow-up mean total, storage, voiding and QoL IPSS sub-scores as well as OAB-v8 score significantly improved in both groups. Intergroup comparison showed statistically significant lower mean total IPSS score (11.6 vs 12.4, $p = 0.04$) mean storage IPSS sub-score (6.5 vs 7.5, $p = 0.01$), and mean OAB v8 score (16.7 vs 18.8, $p = 0.03$) in patients in the Group 1.

Conclusions: The combination of tamsulosin 0.4 mg/die plus the complementary and alternative medicine consisting of vitamins (C and D), herbal products (*Cucurbita maxima*, *Capsicum annum*, *Polygonum capsicatum*) and amino acid L-Glutamine bid provides statistically significant advantages in terms of storage LUTS improvements in patients with LUTS/BPH compared to tamsulosin 0.4 mg/day alone.

These findings are preliminary and further prospective studies on a greater number of patients are needed to confirm it.

KEY WORDS: Benign prostatic hyperplasia; Combination therapy; Lower urinary tract symptoms; Phytotherapy.

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INTRODUCTION

Lower urinary tract symptoms related to benign prostatic hyperplasia (LUTS/BPH) represent a common complaint in

everyday urological practice and their prevalence increases with ageing (1-3). In the EPIC study, Riboli *et al.* reported an incidence of storage and voiding LUTS of about 51% and 26% of men evaluated, respectively (3). Interestingly, approximately 18% of men reported the coexistence of storage and voiding symptoms (4, 5). The European Association of Urology (EAU) guidelines strongly recommend α 1-adrenoceptor antagonists as first-line therapeutic option in patients with moderate to severe symptoms as they significantly improve urinary symptoms and maximum urinary flow (Q_{max}) (6). In men with moderate-to-severe LUTS who mainly have bladder storage symptoms EAU Guidelines strongly recommend muscarinic receptor antagonists (strong recommendation) or beta-3 agonists (weak recommendation) (7). However, a number of concerns have been reported with the prescription of these drugs. Antimuscarinics might theoretically decrease bladder strength, thus increasing post-void residual volume (PVR) urine and causing urinary retention. Moreover, not all antimuscarinics have been evaluated in elderly men, and long-term studies on their efficacy in men of any age with LUTS are not yet available. Furthermore, antimuscarinics are contraindicated in patients with angle-closure glaucoma, gastrointestinal obstruction, paralytic ileus, myasthenia gravis, severe heart disease (8, 9). On the other hand, mirabegron has been evaluated mainly in female patients (8, 9). In recent years the prescription of phytotherapeutic compounds in patients with LUTS/BPH has gained growing interest (10). These agents represent a heterogeneous group and may contain differing concentrations of active ingredients. The complementary and alternative medicine *Kubiker* (*Naturmed*, Italy), consisting of vitamins (C and D), herbal products (*Cucurbita maxima*, *Capsicum annum*, *Polygonum capsicatum*) and amino acid L-Glutamine, has been proposed in the treatment of overactive bladder syndrome (OAB) (11). We aimed to compare the efficacy of the combination therapy involving tamsulosin 0.4 mg once a day plus *Kubiker* bid and therapy with tamsulosin 0.4 mg alone in patients with LUTS/BPH.

MATERIALS AND METHODS

We performed a retrospective comparative study. The clinical records of LUTS/BPH patients who underwent

No conflict of interest declared.

medical therapy with tamsulosin 0.4 mg/day plus *Kubiker* bid between January 2019 to September 2019 were reviewed (Group 1). These patients were compared in a 1:1 fashion with LUTS/BPH patients who underwent therapy with tamsulosin 0.4 mg/day alone (Group 2). The followings were considered exclusion criteria: post-void residual volume (PVR) > 150 ml, prostate specific antigen (PSA) > 10 ng/ml, concomitant therapy with 5-alpha reductase inhibitors and/or phosphodiesterase type 5 inhibitors and/or muscarinic receptor antagonists or beta-3 agonists, presence of neurological disorders, previous pelvic surgery, diabetes, urinary tract infections, history of acute urinary retention. The matched-pair comparison was based on the following criteria: PSA, prostate volume (PV), Q_{max} , PVR, total international prostate symptom score (IPSS), and 8-item *overactive bladder questionnaire* - 8 (OAB-v8) score. Total, storage, voiding and *Quality of Life* (QoL) IPSS scores, as well as OAB-v8 score and treatment-related adverse events recorded at 40 days follow-up in both groups were compared. Descriptive data of continuous variables were expressed as mean \pm standard deviation (SD) and compared using the Student's t tests. The analyses were considered significant for a p-value < 0.05. All statistical analyses were performed with SPSS version 16.0 software.

The study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Verbal informed consent was obtained from subjects.

RESULTS

Overall, 36 eligible patients who underwent medical therapy with tamsulosin 0.4 mg/day plus *Kubiker* were identified and compared to 36 patients who underwent therapy with tamsulosin 0.4 mg/day alone. Baseline patients' characteristics in both groups are reported in Table 1. At 40 days follow-up mean total, storage, voiding and QoL IPSS sub-scores significantly improved in both groups (Table 2). Similarly, a statistically significant improvement in terms of OAB v8 score and Q_{max} was observed in both groups (Table 2).

Intergroup comparison showed statistically significant lower mean total IPSS score, mean storage IPSS sub-score,

Table 1.
Baseline patients' characteristics in both groups.

	Group 1 (n = 36)	Group 2 (n = 36)	p
Age, years, mean (SD)	65.3 (9.6)	63.4 (8.5)	0.32
Prostate volume, mL, mean (SD)	44.1 (24.4)	46.1 (22.7)	0.73
PSA, ng/mL, mean (SD)	2.9 (0.8)	3.2 (0.4)	0.91
PVR, mL, mean (SD)	37.0 (11.2)	39.0 (10.8)	0.26
Q_{max} , mL/sec, mean (SD)	11.2 (0.7)	12.5 (0.8)	0.18
IPSS total, mean (SD)	17.9 (0.9)	18.0 (0.8)	0.59
IPSS voiding, mean (SD)	8.5 (2.2)	9.1 (1.3)	0.15
IPSS storage, mean (SD)	9.3 (2.0)	8.8 (1.2)	0.18
IPSS QoL, mean (SD)	2.9 (0.3)	3.2 (0.4)	0.23
OAB v8, mean (SD)	19.6 (0.8)	20.1 (0.9)	0.29

IPSS: International Prostate Symptom Score; QoL: Quality of Life; OAB v8: 8-item overactive bladder questionnaire; PSA: Prostate Specific Antigen; PVR: Post-void residual volume; Q_{max} : maximum urinary flow; SD: Standard Deviation.

Table 2.
IPSS and OAB v8 scores in both groups at 40-day follow-up.

	Group 1 (n = 36)	Group 2 (n = 36)	p
IPSS total, mean (SD)	11.6 (1.7) *	12.4 (1.5) *	0.04
IPSS voiding, mean (SD)	5.1 (2.1)	4.8 (1.1)	0.58
IPSS storage, mean (SD)	6.5 (1.9) *	7.5 (1.6) *	0.01
IPSS QoL, mean (SD)	2.1 (0.8)	2.4 (0.8)	0.20
OAB v8, mean (SD)	16.7 (0.5) *	18.8 (0.8) *	0.03
Q_{max} mL/sec, mean (SD)	13.6 (0.8)	14.1 (0.7)	0.20
PVR, mL, mean (SD)	28.0 (10.2)	32.0 (8.8)	0.42

IPSS: International Prostate Symptom Score; OAB v8: 8-item overactive bladder questionnaire; PVR: Post-void residual volume; Q_{max} : maximum urinary flow; QoL: Quality of Life; SD: Standard Deviation.
*: p < 0.05 with respect to baseline.

and mean OAB v8 scores in patients in the Group 1. Not statistically significant differences in terms of voiding IPSS sub-score, Q_{max} and PVR emerged from intergroup analysis. Not clinically significant treatment-related adverse events were recorded in both groups.

DISCUSSION

Benign prostatic obstruction has been reported to cause morpho-functional alterations involving the detrusor muscle. Clinically, these alterations can impair bladder contractility and cause detrusor overactivity, decreasing bladder compliance, and onset of storage LUTS characterized by an altered bladder sensation, increased daytime frequency, nocturia, urgency and urgency incontinence (121). Experimental models have shown that bladder outlet obstruction causes detrusor smooth muscle cells hypertrophy and hyperplasia as well as extracellular matrix alterations that may lead, over time, to detrusor overactivity and, later, to reduced bladder contractility (13-15). As reported in the EpiLUTS study, 45.7% of the 14,139 men evaluated had storage LUTS (16). α 1-blockers act by inhibiting the effect of endogenously released noradrenaline on smooth muscle cells in the prostate thus reducing prostate tone and bladder outlet obstruction (17). These drugs can reduce both storage and voiding LUTS and are considered the first-line drug treatment for male LUTS due to their good efficacy, and low rate and severity of adverse events. LUTS/BPH patients with mainly bladder storage symptoms represent a difficult to treat subset of patients. Indeed, therapy with α 1-blockers may be suboptimal. On the other hand, both muscarinic receptor antagonists and beta-3 agonists should be prescribed with cautions and adherence to treatments with these drugs is often inadequate. Herbal treatments are an increasingly popular alternative for treating storage LUTS (18). To the best of our knowledge, we compared, for the first time, the clinical efficacy of the combination of tamsulosin 0.4 mg/day plus *Kubiker* and tamsulosin 0.4 mg/day alone in patients with LUTS/BPH. We found that the combination therapy provided statistically significant advantages in terms of storage LUTS as demonstrated by lower IPSS storage sub-scores as well as lower OAB-v8 score. A number of evidences exist about the potential beneficial effects provided by the compounds contained in the food supple-

ment *Kubiker*. *Cucurbita maxima*, contained in pumpkin seeds, has been reported to provide benefits in both pre-clinical and clinical models of lower urinary tract dysfunction (19-25). Pre-clinical studies have shown that pumpkin seeds have antioxidant and inflammatory properties and inhibit lipid peroxidation (20). Pumpkin seeds administered to rats affected by overactive bladder (OAB) syndrome showed to cause an increase of the production of nitric oxide (NO) via the NO/arginine pathway (22). Independently of the acetylcholin/adrenaline system, this pathway generated the relaxation of the bladder detrusor muscle (23). Pumpkin seeds were also shown to modulate prostate growth. *Abdel Rahman et al.* found that rats fed with high amounts of pumpkin seeds in the diet had smaller prostate sizes as compared to untreated rats (24). Furthermore, *Tsai and co-workers* showed that rats receiving subcutaneous testosterone to induce an increase in prostate size and subsequently treated with pumpkin seeds for 14 days, presented a smaller prostate gland compared to the control group treated only with prazosin (25). *Nishimura et al.* observed that the administration of pumpkin seed extract for 12 weeks significantly reduced the symptoms of OAB with no side effects (19). *Polygonum capsicatum* has a strong antioxidant activity, which has been observed *in vitro* (26). Capsaicin is the first vanilloid investigated for therapeutic purposes and evidence exists demonstrating its efficacy in the treatment of LUTS (11). The capsaicin has been used for the treatment of OAB syndrome due to its ability to desensitize the transient receptor potential vanilloid 1 receptor (27). Evidence exists demonstrating that vitamin C from food and beverages can modulate voiding symptoms (11). However, the knowledge of the exact mechanism of action deserves further investigations. Vitamin D is essential for the proper functioning of the pelvic floor. It has been widely reported that a vitamin deficiency can predispose patients to a high risk of developing LUTS and incontinence (28, 29). To date, the role of glutamine in patients with LUTS is widely under-investigated and deserves careful investigations. Overall, although preliminary, results from the present study have relevant clinical implications and pose the basis for further investigations. The combination of α 1-adrenoceptor antagonists and phytotherapeutic agents containing a mixture of compounds that can interfere with the pathophysiology of bladder dysfunction at multiple levels like *Kubiker* may represent a strategy to discuss in patients with prevalent storage LUTS/BPH for which therapy with α 1-adrenoceptor antagonists alone is suboptimal and medical treatments with muscarinic receptor antagonists or beta-3 agonists are not recommended or not tolerated. The main limits of the present study are the retrospective design, the small sample size, and the short follow-up. Moreover, the specific role of the various components of *Kubiker* could not be assessed. Therefore, results from the present study should be considered preliminary and further studied are needed to confirm the efficacy and safety of the combination of tamsulosin and the food supplement *Kubiker* in LUTS/BPH patients and to identify the subset of patients that can benefit most from this approach.

The role of *Kubiker* in women with storage LUTS represents a further area of interest (11, 30).

CONCLUSIONS

The combination of tamsulosin 0.4mg/die plus *Kubiker* bid provides statistically significant advantages in terms of storage LUTS improvements in patients with LUTS/BPH compared to tamsulosin 0.4 mg/day alone. These findings are preliminary and further prospective studies on a greater number of patients are needed to confirm it.

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