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UROLOGY – ORIGINAL PAPER

Randomized crossover comparison of tamsulosin and alfuzosin in patients with urinary disturbances caused by benign prostatic hyperplasia

Erkan Karadağ · Sedat Öner · Yasemin U. Budak · Özcan Atahan

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Abstract
Purpose The aim of this study was to compare the efficacy and safety of alfuzosin (Alf) and tamsulosin (Tam) in patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).
Materials and methods One hundred men with benign prostatic hyperplasia (BPH) who were admitted to our urology department with lower urinary tract symptoms (LUTS) were enrolled in this randomized cross-over study. At enrollment, detailed medical history was recorded, and International Prostate Symptom Score (IPSS), digital rectal examination, urinary ultrasound, prostate specific antigen (PSA) level, and uroflowmetry were determined. BPH patients with IPSS greater than 8 and maximum urinary flow rate (Q_{max}) lower than 15 ml/s were randomly divided into a Alf-Tam group (Alf for 8 weeks, followed by Tam for 8 weeks) or a Tam-Alf group (Tam for 8 weeks, followed by Alf for 8 weeks). There was no withdrawal period (washout) when switching drugs.
Results In the first treatment period, each drug significantly improved IPSS and Q_{max}. In both the Alf-Tam and Tam-Alf groups, cross-over was effective in improving IPSS and Q_{max}. Alf and Tam significantly lowered IPSS and significantly increased Q_{max} from baseline ($P < 0.001$). Neither drug affected serum PSA levels.
Conclusions Tam and Alf, which were used during different time frames in the same individuals, are associated with similarly favorable outcomes. When one alpha-blocker does not provide a desired effect in the treatment of BPH, switching to another alpha-blocker seems to be beneficial.

Keywords Benign prostate hyperplasia · Alpha-blocker treatment · Alfuzosin · Tamsulosin

E. Karadağ · S. Öner · Ö. Atahan
Urology Department, Yüksek İhtisas Education and Research Hospital, Bursa, Turkey

Y. U. Budak (✉)
Clinical Laboratory Department, Sevket Yilmaz Education and Research Hospital, 16016 Yildirim, Bursa, Turkey
e-mail: yaseminbudak2000@yahoo.com

Introduction

Benign prostatic hyperplasia (BPH) is the most common medical condition in aging men and has a particularly high prevalence in those aged 40–79 years. Benign prostatic hyperplasia (BPH) is a major cause for lower urinary tract symptoms (LUTS) and is responsible for LUTS in 13% of 40–49-year-old men and in 28% of men older than 70 years [1].

Extensive research has indicated that BPH results from dynamic and static processes. In this model, the dynamic component of bladder outlet obstruction

(BOO) is mediated by tension of prostate smooth muscle via alpha-adrenoceptors; the static component of BOO is mediated by anatomic obstruction that results from enlargement of the prostate, which is regulated by androgens [2]. Thus, there are BPH therapies that target the static components and the dynamic components of this disease [3]. In particular, BPH can be treated by drug therapy or by surgery [3]. Drug therapy has become the first-line therapy for BPH because surgery can lead to operative and postoperative complications, such as retrograde ejaculation, incontinence, and impotence.

Currently, alpha-adrenergic receptor blockers (alpha-blockers) and/or 5-alpha-reductase inhibitors (5-ARIs) are used for the medical treatment of BPH [3]. Selective alpha 1-adrenergic antagonists relax the smooth muscle of the prostate and bladder neck without affecting the detrusor muscle of the bladder wall, thus decreasing the resistance to urine flow without compromising bladder contractility. There have been numerous studies of the safety and efficacy of alfuzosin (Alf) and tamsulosin (Tam), both of which are alpha-blockers, in patients with symptomatic BPH [4–8]. The results indicate that these agents have similar effects in improving symptom scores and Q_{max} of patients with BPH [9–11].

Alpha-blockers are the most widely used agents in the treatment of LUTS in males, and clinicians may switch between specific alpha-blockers when one drug does not yield the desired effect. However, there are insufficient data on the treatment outcomes with different alpha-blockers within the same patient. In the present study, we assessed the efficacy of Tam and Alf in BPH patients, and the effects of switching between these drugs in patients who did not benefit from the first alpha-blocker.

Materials and methods

BPH patients who were admitted to our urology department (Bursa Yuksek Ihtisas Research and Education Hospital) were enrolled in this prospective, randomized, cross-over trial that compared changing from Tam to Alf (Tam-Alf) *vs* changing from Alf to Tam (Alf-Tam). BPH diagnosis was made clinically according to AUA guidelines [12]. All enrolled patients ($n = 100$) were given thorough explanations of both modes of treatment and provided informed consent prior to randomization. All patients were recently diagnosed clinically with BPH, had peak urinary flow rate (Q_{max}) less than 15 ml/s, and had International Prostate Symptom Score (IPSS) of at least 8. Patients were excluded if they had a history of prostate carcinoma, history of bladder tumor, previous prostate surgery, urethral stenosis, total prostate specific antigen (tPSA) more than 4 ng/ml, stone in the urinary system, BPH with an indication of surgery, diabetes mellitus, or if they had previously used alpha-blockers and/or 5 α-reductase inhibitors.

Patients were randomized to two groups: The Tam-Alf group ($n = 50$) was given Tam HCl (0.4 mg *qd*) for 8 weeks, and then switched to Alf HCl (10 mg *qd*) for 8 weeks; the Alf-Tam group ($n = 50$) was given Alf HCl (10 mg *qd*) for 8 weeks and then switched to Tam HCl (0.4 mg *qd*) for 8 weeks. Patients were evaluated at the beginning of the study, at the time of the cross-over (8 weeks), and at the end of the treatment (16 weeks) by the same doctor.

At the initial evaluation, patients were given detailed clinical evaluations, including a complete history, physical examination, urinalysis, urine culture, and digital rectal examination (DRE). In addition, the following parameters were measured: CBC (complete blood count); serum glucose, urea, creatinine (Cr), aspartate transaminase (AST), alanine transaminase (ALT), and tPSA levels; prostate volume (by transrectal ultrasonography, TRUS); uroflowmetry; and post-void residual (PVR) urine volume. The IPSS and Quality of life questionnaire (QoL) were also evaluated. Blood urea nitrogen (BUN), SCr, tPSA, uroflowmetry, IPSS, QoL, and PVR were evaluated at the two follow-up visits. Treatment efficacy was measured as a change in IPSS and Q_{max}.

The Wilcoxon signed rank test was used for statistical analysis of IPSS and QoL, and the *t*-test was used for analysis of average flow rate and voided urine volume. A one-sample Kolmogorov–Smirnov test was used to determine the distribution of variables. A *P*-value less than 0.05 was considered statistically significant.

Results

At the onset of this study, there were no significant differences between the Tam-Alf group and Alf-Tam group in age, tPSA, IPSS, and Q_{max} (Table 1).

Table 1 Baseline characteristics of patients treated with Tam for 8 weeks and then with Alf for 8 weeks (Tam-Alf) and of patients treated with Alf for 8 weeks and then with Tam for 8 weeks (Alf-Tam)

	Tam-Alf ($n = 50$)	Alf-Tam ($n = 50$)	P
Age (years)	60.6 ± 6.8	62.3 ± 7.0	0.805
Q_{max}	11.32 ± 2.02	11.48 ± 2.16	0.091
IPSSo	11.42 ± 4.34	11.32 ± 4.14	0.293
IPSSi	7.66 ± 3.09	7.76 ± 3.17	0.743
IPSSt	19.08 ± 5.70	19.08 ± 5.72	0.264
PSA (ng/ml)	1.4 ± 1.1	1.6 ± 1.2	0.088

Q_{max} maximum flow rate of urination, *IPSSo* obstructive symptom score, *IPSSi* irritative symptom score, *IPSSt* total symptom score. Values show mean ± SD

In the Tam-Alf group (Table 2), there were overall improvements in IPSS and Q_{max} at week 8. In addition, 21 patients (42%) had significant improvements in Q_{max} and IPSS, 20 patients (40%) had significant improvement in one of these parameters, and 9 patients (18%) had no significant changes in either parameter at week 8. Analysis of IPSS and Q_{max} in the Tam-Alf group at week 8 (before cross-over) and week 16 (8 weeks after cross-over) indicated that 29 patients (58%) appeared to benefit from the change in treatment.

In the Alf-Tam group (Table 3), there were overall improvements in IPSS and Q_{max} at week 8. In addition, 26 patients (52%) had significant improvements in Q_{max} and IPSS, 22 patients (44%) had an improvement in one of these parameters, and 2 patients (4%) had no changes in either parameter at week 8. Analysis of IPSS and Q_{max} in the Alf-Tam group at week 8 (before cross-over) and week 16 (8 weeks after cross-over) indicated that 32 patients (64%) appeared to benefit from the change in treatment.

Interestingly, for both groups, Q_{max} at the time of cross-over (week-8) was significantly higher than before treatment and remained significantly higher at week 16 (8 weeks after cross-over) (Tables 2, 3). Similar significant differences ($P < 0.001$) were obtained when the total IPSSt, IPSSi, IPSSo, QoL scores were compared (Tables 2, 3).

For both treatment groups, QoL at the time of cross-over (week 8) was significantly lower than before treatment and remained significantly lower at week 16 (Alf-Tam: QoL = 4.86 ± 1.16 at initiation, QoL = 1.60 ± 1.58 at the end point; Tam-Alf: QoL = 4.86 ± 1 at initiation, QoL = 1.74 ± 1.71 at the end point).

In the Tam-Alf group, there were no differences in voided urine volume at initiation, at week 8, and at week 16. However, in the Alf-Tam group, there was a significant increase in voided urine volume at week 8, and this was sustained at week 16 (Tables 2, 3). For both groups, mean PSA was unaffected by treatment (data not shown).

When we compared the 8-week and 16-week data for the Alf-Tam group, the IPSSo, IPSSi, and IPSSt scores decreased significantly on going from weeks 8 to 16 ($P = 0.001$, $P = 0.003$, $P < 0.000$; respectively) (Table 3). Similarly, in the Tam-Alf group, the IPSSo, IPSSi and IPSSt scores were significantly lower at week 16 compared to week 8 (Table 2) ($P = 0.003$, $P = 0.006$ $P = 0.002$; respectively). Q_{max}, Qol, and voided urine volume did not differ significantly between weeks 8 and 16 in either treatment group.

Finally, we assessed adverse effects in both groups (Table 4). Retrograde ejaculation and insomnia occurred in patients during the 8 weeks of Tam treatment, and retrograde ejaculation, hypotension, dizziness, insomnia, head ache, and dry-mouth

Table 2 Changes in Q_{max}, IPSSo, IPSSi, IPSSt, QoL, and voided urine volume in the Tam-Alf group

Tam-Alf	Initiation	Week-8	P (baseline vs. week-8)	Week-16	P (baseline vs. week-16)	P (week 8 vs. week-16)
Q_{max}	11.32 ± 2.02	13.78 ± 3.64	<0.001	14.44 ± 4.55	<0.001	0.126
IPSSo	11.42 ± 4.34	6.30 ± 4.70	<0.001	5.34 ± 4.80	<0.001	0.003
IPSSi	7.66 ± 3.09	4.28 ± 3.33	<0.001	3.56 ± 3.46	<0.001	0.006
IPSSt	19.08 ± 5.70	10.52 ± 7.08	<0.001	8.90 ± 7.24	<0.001	0.002
QoL	4.68 ± 1.21	1.66 ± 1.49	<0.001	1.60 ± 1.58	<0.001	0.443
Voided urine V	248.22 ± 100.67	268.40 ± 114.64	0.140	269.36 ± 93.94	0.061	0.635

Table 3 Changes in Q_{max}, IPSSo, IPSSi, IPSSt, QoL, and voided urine volume in the Alf-Tam group

Alf-Tam	Initiation	Week 8	*P* (baseline vs. week 8)	Week 16	*P* (baseline vs. week 16)	*P* (week 6 vs. week 16)
Q_{max}	11.48 ± 2.16	14.12 ± 4.00	<0.001	14.84 ± 4.17	<0.001	0.182
IPSSo	11.32 ± 4.14	4.96 ± 3.49	<0.001	3.92 ± 3.61	<0.001	0.001
IPSSi	7.76 ± 3.17	3.30 ± 2.47	<0.001	2.88 ± 2.60	<0.001	0.003
IPSSt	19.08 ± 5.72	8.26 ± 5.24	<0.001	6.80 ± 5.57	<0.001	<0.001
QoL	4.86 ± 1.16	1.78 ± 1.54	<0.001	1.74 ± 1.71	<0.001	0.346
Voided urine V	234.78 ± 90.18	270.66 ± 114.14	0.01	273.76 ± 111.508	0.002	0.406

Table 4 Adverse effects in the Alf-Tam and Tam-Alf groups

	Adverse effects occurring during Tam treatment ($n = 100$)	Adverse effects occurring during Alf treatment ($n = 100$)
Retrograde ejaculation	14	3
Hypotension	0	2
Dizziness	0	1
Insomnia	1	1
Headache	0	1
Dry mouth	0	1
Total	15	9

occurred in patients during the 8 weeks of Alf treatment.

A total of 14 patients in the Tam-Alf group and 11 patients in the Alf-Tam group were given prostate surgery due to failure of drug therapy.

Discussion

Alpha-adrenergic blockers are the main treatment option for patients with BPH who present with LUTS. Previous studies indicated that treatment with alpha-blockers resulted in 15–30% improvement of total symptom score and Q_{max} within 8–12 weeks [9, 13, 14]. Although all alpha-blocking compounds have similar efficacy in the treatment of LUTS, newer agents, such as Alf and Tam, tend to yield better results in patients with prostate and bladder problems. Tam and Alf are both are alpha-adrenergic blockers, but they have different molecular properties. In particular, Alf is non-subtype selective, and blocks all three α_1-adrenergic receptor subtypes. In contrast, Tam blocks α_{1A}- and α_{1D}-adrenergic receptors with 10-fold greater affinity than α_{1B}-adrenergic receptor and is considered α_1-adrenergic-receptor-subtype selective [15].

Numerous previous studies have investigated differences in efficacy attributable to pharmacological differences in affinity for adrenoceptor subtypes [2, 7, 11], and other studies have compared the effects of Alf and Tam [10, 16]. Our study is unique in that we assessed the effectiveness of switching alpha-blockers in the same individuals. We defined patients as responders or non-responders based on improvement in IPSSt and Q_{max} of at least 20% [9, 17]. Our results are similar to those of previously reported results, in that we found a 42% success rate in the Tam-Alf group and a 44% success rate in Alf-Tam group at week 8 [9, 13, 14]. In the Tam-Alf group, 8 of the 29 patients who did not respond to Tam by week 8, responded to Alf by week 16. In the Alf-Tam group, our response rate at week 8 was 47% and the response rate at week 16 was 61%.

Kirby et al. [18] compared the effects of doxazosin and Tam on IPSSt and Q_{max} in patients with BPH. Each drug significantly relieved LUTS and increased Q_{max} from baseline. In a previous cross-over study, Ikemoto et al. [19] administered the alpha-adrenoceptor antagonists Tam and naftopidil (Naf) to 96 patients with BPH for 8-week periods. For both the Naf-to-Tam and Tam-to-Naf groups, cross-over was effective when the initial drug was judged both subjectively and objectively to have been ineffective. Compliance was acceptable for both drugs.

In the present study, both treatment groups showed improvement in Q_{max} from baseline, and this continued after the cross-over, particularly in the Alf-Tam group. We also evaluated IPSS, IPSSo, IPSSi, IPSSt, all of which were substantially improved with each drug by week 8, and changing drugs seemed to result

in further improvement by week 16. However, it is possible that the total duration of drug use (16 vs. 8 weeks), and not the changing of drugs, was responsible for this additional improvement.

Previous studies have shown that α_1-blockers, such as doxazosin and terazosin, induce apoptosis of prostate stromal smooth muscle and epithelial cells without affecting cellular proliferation, and that these changes were correlated with abatement of symptoms [20, 21]. However, no systematic studies have tested this hypothesis, although there is evidence that α_1-blockers do not affect serum PSA [21, 22]. Because 4 months of treatment (as in the present study) may not be long enough to induce changes in prostate volume, additional long-term studies are required to determine the effect of α_1-blockers on prostate volume.

In our study, Tam and Alf were both well tolerated, and the treatment-emergent adverse events did not lead to any patient withdrawal. Alf did not cause any sexual dysfunction, while Tam, as reported in several previous studies, caused retrograde ejaculation in 14% of patients [23, 24]. Recent clinical findings have suggested that alpha-blockers cause retrograde ejaculation owing to their effect on semen formation and/or transport rather than their effect on urethral smooth muscle relaxation [25].

In conclusion, we found that Tam and Alf were equally effective in the treatment of BPH. However, our results indicate that if a BPH patient does not respond to one alpha-blocker, then switching to a different alpha-blocker may provide benefit for 25–27.5% of patients. Thus, we suggest that if one alpha-blocker is unsuccessful in the treatment of BPH, treatment with a second alpha-blocker should be considered, especially when surgery is not a suitable option.

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