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A Comparative Study of Efficacy and Adverse Effects Between Alfuzosin and Tamsulosin in the Treatment of Benign Prostatic Hyperplasia

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ABSTRACT

Background & Objective: Before the advent of medical therapy for BPH causing lower urinary tract obstructive symptoms (LUTS), the treatment was primarily a surgical one with higher morbidities and inconsistent outcomes. With the advent of alpha-antagonists, the face of BPH treatment took a new look. Currently majority of the medical managements of BPH includes α-1 adrenoceptor antagonists. Of them tamsulosin and alfuzosin are commonly used with different efficacies and side-effects being claimed. The present study was done to compare the safety and efficacy of tamsulosin and alfuzosin in the treatment LUTS suggestive of BPH.

Patients & Methods: The present prospective randomised clinical trial was conducted at the Department of Urology, Chittagong Medical College Hospital to compare the outcomes of tamsulosin and alfuzosin in the treatment of LUTS suggestive of benign hyperplasia of prostate (BPH). A total of 80 subjects selected for the study were randomly assigned to alfuzosin (n = 40) and tamsulosin (n = 40) groups. Alfuzosin 10 mg and tamsulosin 0.4 mg as once-daily doses were given to the patients of respective groups for consecutive 12 weeks with no initial dose titration. Of the 80 patients, 67 patients - 36 in the alfuzosin and 31 in the tamsulosin groups finally completed the treatment as per protocol. The outcome was evaluated at the end of month 1 and 2 in terms of IPSS, Qmax, PVR and complications encountered.

Result: The mean ages of alfuzosin and tamsulosin groups were 66.5 and 62.3 years respectively. The mean IPSS, Qmax and PVR at baseline were homogeneously distributed between groups ($p = 0.217$, $p = 0.394$, $p = 0.174$). At the endpoint, IPSS and PVR were significantly less in tamsulosin group than those in alfuzosin group ($p = 0.015$ and $p = 0.038$ respectively). The Qmax responded well in both the groups with no significant inter-group difference ($p = 0.453$). The alfuzosin group had a significantly higher postural hypotension, dizziness, asthenia and GI tract upset compared to the tamsulosin group. However, tachycardia, headache and rhinitis were more common in the tamsulosin group than those in the alfuzosin group. At the endpoint alfuzosin group experienced a significant reduction in blood pressure compared to their baseline figures ($p < 0.001$). In the tamsulosin group the diastolic blood pressure decreased slightly in the 1st month of treatment, but they again stabilized during 2nd month of treatment, while systolic blood pressure did not experience any change. Both treatment groups exhibited an improvement of Qmax $\geq$ 3 ml/s from baseline. However, improvement of total symptom score in terms of IPSS $\geq$ 25% from baseline was significantly higher in the alfuzosin group (88.9%) than that in the tamsulosin group (48.9%) ($p < 0.001$).

Conclusion: Tamsulosin is a better than alfuzosin for patients with LUTS suggestive of BPH who are normotensive or hypertensive but well-controlled with conventional antihypertensives.

Key words: *Tamsulosin, alfuzosin, lower urinary tract symptoms & benign prostatic hyperplasia.*

Introduction

Benign prostatic hyperplasia (BPH) is the non malignant enlargement of the prostate gland. Prior to 1980s, the primary treatment of symptomatic BPH was surgical, the morbidities of which were immense and outcomes were always inconsistent. With our increased understanding of the neurologic and hormonal function of the prostate, medical management has become the primary therapy for lower urinary tract symptoms (LUTS).[1]

Of the medical managements, androgen-deprivation therapy (with GnRH agonists, antiandrogens, or 5a-reductase inhibitors) is effective because it reduces the static component of benign prostatic hyperplasia. Among these agents, the 5 α-reductase inhibitors are the most promising because of their low toxicity. Because the prostate gland is an androgen-sensitive organ, androgen deprivation decreases the size of the prostate and the resistance to outflow through the prostatic urethra with consequent improvement in the ability of patients to urinate.[2,3]

Currently alpha-antagonists are the most widely prescribed medical therapy for BPH, encompassing more than 90% of the new prescriptions (Bullock, 2006)[1]. Of them tamsulosin and alfuzosin being commonly used with different efficacies and side-effects reported by different investigators. Buzelin.[4] reported a comparable efficacy between tamsulosin (0.4 mg as once daily dose) and alfuzosin (as thrice daily dose) in the treatment of symptomatic benign hyperplasia of prostate and both treatment were well-tolerated. The main difference between the

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drugs was that tamsulosin had significantly less effect on blood pressure than alfuzosin in patients over 65 years old. On the other hand, alfuzosin being a clinically uroselective alpha-blocker, demonstrated its efficacy and safety (in two large double-blind trials) over placebo in terms of maximum urinary flow rates, BPH symptoms, and quality of life (QOL), with changes in blood pressure or ejaculatory disturbances.[1]

However, the efficacy and safety of the two drugs documented were all the results of placebo-controlled trial[5,6] the comparison of the two drugs in a head-to-head trial is very rare. Recently these drugs are being marketed in our country, though no study has yet been conducted in the context of our population. Urologists are also gradually becoming inclined towards medical treatment of BPH. So prescribing these drugs without any formal study report regarding its efficacy, safety and long-term effect is like throwing stones in the dark. The present study was, therefore, conducted to see which of the two drugs - tamsulosin and alfuzsin - is better (in terms of efficacy and safety) in the treatment of lower urinary tract symptoms (LUTS) caused by benign hyperplasia of prostate (BPH).

Patients & Methods

The present prospective randomised clinical trial was conducted at the Department of Urology, Chittagong Medical College Hospital to compare the efficacy and safety of tamsulosin and alfuzosin in the treatment of LUTS suggestive of benign hyperplasia of prostate (BPH). A total of 80 subjects selected for study were randomly assigned to Alfuzosin (n = 40) and Tamsulosin (n = 40) groups. Men aged > 50 years with a clinical diagnosis of symptomatic BPH or at least 6-months history of lower urinary tract symptoms, an International Prostate Symptom Score (IPSS) of >13 and a peak flow rate (Q_{max}) of 5 - 12 ml/sec for voided volume of >120 ml, and a post voidal residual urine volume (PVR) of >150 ml were included in the study. Patients with concomitant urological diseases, diagnosed or suspected carcinoma of the prostate, hepatic or renal failure, previous bladder neck, prostate or pelvic region surgery, patients with Parkinson's disease, insulin-dependant diabetes, diagnosed or suspected multiple sclerosis, unstable angina or severe heart failure, cerebrovascular disease or CNS disorders were excluded from the study. A history of orthostatic hypotension or syncope on the day '0' (prior to start of treatment), life-threatening previous allergic reactions to α–1-adrenoceptor antagonists, patients previously showing no improvement with treatment with an α-blocker, or patients concomitantly taking drugs like other α-adrenoceptor antagonists, α-adrenoceptor agonists or anticholinergic drugs or calcium anatagonists were also excluded.

Alfuzosin 10 mg and tamsulosin 0.4 mg as once-daily doses were given to the patients of respective groups for consecutive 12 weeks with no initial dose titration. Of the 80 patients, 67 patients - 36 in the alfuzosin and 31 in the tamsulosin groups finally completed the treatment as per protocol and hence were considered as evaluable. The outcome was evaluated at the end of month 1 and 2 in terms of IPSS, Q_{max}, PVR and complications encountered. Data were analysed using Chi-square (χ^2) or Fisher's Exact Test, Student's t-Test, paired sample t-Test and repeated measure ANOV.

Results

All the clinical symptoms, except nocturia, painful urination and obstructive uropathy at baseline were almost identically distributed between groups (table I). Nocturia and obstructive uropathy were significantly higher in the tamsulosin group (83.9% and 16.1% respectively) than those in the alfuzosin group (16.7% and 0% respectively) ($p < 0.001$ and $p = 0.018$), while painful urination was almost invariably present in the alfuzosin group (94.4%) than that in the tamsulosin group (71%) ($p = 0.010$). The mean IPSS, Q_{max} (ml/sec), PVR all were homogeneously distributed between groups ($p = 0.217$, $p = 0.394$, $p = 0.174$). However, systolic and diastolic blood pressures at standing and on lying positions were significantly higher in the alfuzosin group than those in the tamsulosin group ($p < 0.001$) (table -I).

All the outcome variables in alfuzosin group like IPSS, Q_{max} and PVR improved significantly at month 1 from their baseline status. The mean IPSS decreased from 17.3 at baseline to 13.6 at month 1 ($p < 0.001$). The mean Q_{max} increased from 11 ml/sec at baseline to 13.1 ml/sec at month 1 ($p < 0.001$). The PVR reduced from 87.2 ml at baseline to 74.6 ml after month 1. The systolic and diastolic blood pressures also decreased to normal range ($p < 0.001$). Likewise in tamsulosin group, all the outcome variables improved significantly at month 1 from their baseline status. The mean IPSS decreased from 16.9 at baseline to 13.1 at month 1 ($p < 0.001$). The mean Q_{max} increased from 11.2 ml/sec at baseline to 13.3 ml/sec at month 1 ($p < 0.001$). The PVR reduced from 115.8 ml at baseline to 74.8 ml after month 1 ($p < 0.001$). Both the groups responded well wit h respect to outcome measures like IPSS, Q_{max} (ml/sec) PVR with no inter-group difference ($p = 0.249$, $p = 0.144$, $p = 0.942$) (table II).

The evaluation of outcome at month 2 shows that IPSS and PVR were significantly less in tamsulosin group than those in alfuzosin group ($p = 0.015$ and $p = 0.038$ respectively). The Q_{max} responded well in both the

groups and with no significant difference between the groups (14.83 ± 0.38 vs. 14.26 ± 1.24 ml/sec, p = 0.453) (table II). The alfuzosin group had a significantly higher postural hypotension (44.4%), dizziness (100%), asthenia (97.2%) and GI tract upset (77.8%) compared to the tamsulosin group (p < 0.001, p = 0.001, p = 0.007 and p = 0.025) (table I).

However, tachycardia, headache and rhinitis were more common in the tamsulosin group than those in the alfuzosin group (p < 0.001, p = 0.023 and p < 0.001 respectively) (table IV). There was significant increase in Q_{max} relative to baseline in both the treatment groups at each interval (p < 0.001) (fig. 1). At the endpoint the alfuzosin group responded better than the tamsulosin group, though the difference between the two groups did not reach the level of significance (p = 0.453). Alfuzosin group experienced a steady decrease in IPSS from > 17 at baseline to < 14 at month 1 and to < 10 at the end month 2. The tamsulodin group also followed a similar pattern of decrease from a mean IPSS of 16.9 at baseline to < 9 at the end of month 2 (fig. 2). The difference between the two groups at the endpoint was significant (p = 0.015) (table II). The effects of alfuzosin and tamsulosin on blood pressure are summarized in table. At the endpoint there were significant reductions in all mean blood pressure variables in the alfuzosin group compared with baseline but not in patients treated with tamsulosin (p < 0.001). In the tamsulosin group the standing diastolic and supine diastolic blood pressures though decreased slightly in the 1st month of treatment, they again stabilized during 2nd month of treatment, while standing systolic and supine systolic blood pressures did not experience any change (figure 3-6). All the patients in both treatment groups exhibited an improvement of Q_{max} by ≥ 3 ml/s at the end of month 2 from baseline. However, improvement of total symptom score in terms of IPSS ≥ 25% from baseline was significantly higher in the alfuzosin group (88.9%) than that in the tamsulosin group (48.4%) (p < 0.001).

Discussion

The findings of the study demonstrated that both alfuzosin 10 mg and tamsulosin 0.4 mg as once-daily doses had reasonable efficacy in the treatment of lower urinary tract symptoms (LUTS) suggestive of benign hyperplasia of prostate (BPH). The urinary flow (in terms of Q_{max}) and urinary tract symptoms (in terms of IPSS) both improved from their baseline status. The mean postvoidal residual urine volume decreased dramatically from 87 and 115 ml to 62 and 58 ml in the alfuzosin and tamsulosin groups respectively. Roehrborn[6] in an attempt to examine the efficacy and safety of once daily formulation of alfuzosin (10 mg daily) in a pooled analysis of three parallel, randomized, double-blind placebo controlled 3-month studies of patients having LUTS with BPH demonstrated a significant decrease in the mean IPSS in the experimental group (6 ± 5.1) than that in the placebo group (4.2 ± 5.7) (p < 0.005). The peak flow rate (PFR) decreased by 2.3 ml/sec in the former group and by 1.1 ml/sec in the latter group (1 < 0.001). Buzelin[4] demonstrated significant increase in Q_{max} relative to baseline in both alfuzosina and tamsulosin groups with mean increase in Q_{max} was around 1.6 ml/s. However, they used alfuzosin in a dose of 2.5 mg thrice daily and measured improvements in symptoms in terms of Boyarsky score. The mean reduction in total symptom score at endpoint was 4.1 in the tamsulosin group and 3.8 in the alfuzosin group. In the present study the percentage of patients with a ≥ 3 ml/s improvement in Q_{max} was 100% in both the groups. However, a significantly higher percentage of patients in alfuzosin group experienced a decrease in total symptom scores of ≥25% from baseline. In the Buzelin's study a comparable percentage of patients in the two groups exhibited improvements at the endpoint of the study[4].

The indirect comparisons of the efficacy and tolerability of alfuzosin and tamsulosin using the data from the placebo-controlled studies for each drug suggest that both behave similarly clinically,[7] despite several differences in their in vitro pharmacology profile.[8] This conclusion is also supported by the results of a randomized, double-blind, direct comparative 12-week study, in which 256 patients with benign prostatic enlargements and lower urinary tract symptoms were treated with 2.5 mg alfuzosin three times daily or 0.4 mg tamsulosin once daily.[4] Similarly, a recent nonrandomized study comparing standard alfuzosin (2.5 mg three times daily), tamsulosin (0.4 mg once daily), and terazosin (5 mg once daily) treatment for 6 months reported that all three drugs caused similar improvements in the IPSS and urodynamic parameters of obstruction.[8]

It would be worthwhile to mention that an increased incidence of abnormal ejaculation relative to placebo has been reported in most studies with tamsulosin[9-11] but not in those with alfuzosin[4,12] although the present study did not find any patients in either group with abnormal ejaculation. It may be due to chance error because the present study worked on a smaller sample, while Buzelin[4] and other investigators worked on much larger sample size.

Thus, from a clinical viewpoint, alfuzosin and tamsulosin appear to be very similar in efficacy. The main difference between the two drugs is that tamsulosin had almost no effect in lowering the blood pressure. The standing

diastolic and supine diastolic blood pressures though decreased slightly in the 1st month of treatment, they again stabilized during 2nd month of treatment, while standing systolic and supine systolic blood pressures did not experience any change throughout the treatment period. There are several other practical advantages of using an α–1-adrenceptors without antihypertensive effects in the treatment of LUTS suggestive of BPH. Both hypertension and LUTS due to BPH are highly prevalent, age-related disorders. Population studies suggest that about half of the elderly men aged 65 or above 65 years may be hypertensive, similar to the proportion of elderly men who suffer from LUTS due to BPH.[13] Not surprisingly therefore, that a significant number of elderly men have both hypertension and LUTS suggestive of BPH.[9,13,14] Thus theoretically it would appear to be an attractive option to treat these patients with single pharmacological agent, i.e, an α-adrenoceptor antagonist with antihypertensive properties. However, about 30% of the patients with LUTS suggestive of BPH are already receiving some form antihypertensive treatment when they visit a urologist.[15] In such cases it is not desirable to interfere with their established antihypertensive therapy as this may lead to loss of blood-pressure control, require dose adjustment of the existing antihypertensive medication or provoke adverse events (e,g. orthostatic hypotension).

Monotherapy with α–1-adrenoceptor antagonists is, therefore, not the preferred first step in the treatment of most hypertensive patients. Finally, a1-adrenoceptor antagonists are not the first choice for hypertensive patients with coexisting cardiac disorders (e.g. angina pectoris and/or heart failure). Logically, patients with LUTS suggestive of BPH falling into categories, such as these, may benefit from an α–1-adrenoceptor antagonist without antihypertensive effect. The present study showed that tamsulosin (0.4 mg once daily) can provide this treatment option; when compared with the non-subtype-selective α–1-adrenoceptor antagonist alfuzosin (10 mg as once-daily), tamsulosin had comparable efficacy and tolerability in patients with LUTS suggestive of BPH. However, tamsulosin did not significantly reduce blood pressure (systolic and diastolic) as much as alfuzosin. Alfuzosin's effect on blood pressure and particularly the significant reduction from their baseline status is specially pronounced in elderly patients.[9] Although alfuzosin is generally well tolerated in normotensive men, elderly patients and those with hypertension have increased sensitively to vasodilatation.[16] Furthermore, the likelihood that treatment with alfuzosin may be discontinued, because (vasodilatory) adverse events are more marked in elderly (> 75 years) patients with LUTS suggestive of BPH having concomitant cardiovascular disease(s) and/or taking concomitant cardiovascular medication(s).[15] Because the therapeutic daily dose of alfuzosin in the treatment of hypertension is 10 - 20 mg, whereas the recommended dose in LUTS suggestive of BPH is 7.5 - 10 mg.[17]

The concomitant administration of non-subtype selective α–1-adrenoceptor antagonists with antihypertensive agents, particularly calcium antagonists is not recommended because of potentiation of the antihypertensive effects.[16] In contrast, in hypertensive patients whose blood pressure was controlled with an antihypertensive agent (e.g. nifedipine or enalapril), concomitant treatment with tamsulosin was shown not to induce clinically relevant additional blood pressure reduction.[18,19] This confirms that tamsulosin is a feasible treatment option for patients with LUTS suggestive of BPH who are normotensive or hypertensive but well controlled with conventional antihypertensives.

Table I. Comparison of baseline variables between groups (n = 67).

Baseline variables	Group		p-value#
	Alfuzosin (n=36)	Tamsulosin (n=31)	
IPSS	17.3±1.1	16.9±1.7	0.217
Q_{max} (ml/sec)	11.5±0.6	11.1±1.0	0.394
PVR	87.2±10.7	115.8±12.2	0.174
Standing systolic BP	148.9±6.9	135.7±11.5	< 0.001
Standing diastolic BP	97.0±5.2	85.0±6.1	< 0.001
Lying systolic BP	143.7±7.0	132.3±11.3	< 0.001
Lying diastolic BP	91.0±4.0	80.5±6.3	< 0.001

Figures in the parentheses denote corresponding percentage.
 # Data were analyzed using Student's t Test and level of significance was 0.05.

Alpha1-adrenoceptor antagonists were originally developed for the treatment of hypertension. As it was evident that α–1-adrenoceptor subtype is primarily present in the prostate and responsible for the contraction of its smooth muscles, research-eye shifted from treatment of hypertension with α–1-adrenoceptor antagonists to treatment of BPH causing LUTS with the same agents. Like previous studies, the present study also showed that tamsulosin (0.4 mg once-daily), when compared with the non-subtype-selective α–1-adrenoceptor antagonist alfuzosin (10 mg once-daily), had comparable efficacy and tolerability in patients with LUTS suggestive of BPH. However, the lack of a clinically significant reduction of blood pressure with

tamsulosin and its favourable efficacy/safety ratio may partly be the reason that the therapeutic dose of 0.4 mg once daily can be administered from the onset of therapy with no need for dose titration.

Table II. Comparison of outcome at month 1 between groups (n = 67).

Outcome measures	Group		p-value#
	Alfuzosin (n=36)	Tamsulosin (n=31)	
IPSS	13.58 ± 1.36	13.10 ± 2.04	0.249
Q_{max} (ml/sec)	13.08 ± 0.55	13.35 ± 0.88	0.144
PVR	74.64 ± 9.49	74.84 ± 12.81	0.942

Figures in the parentheses denote corresponding percentage.
 # Data were analyzed using Student's t-Test and level of significance was 0.05.

Table III. Comparison of outcome at month 2 between groups (n = 67).

Outcome at month 2	Group		p-value#
	Alfuzosin (n=36)	Tamsulosin (n=31)	
IPSS	9.81 ± 0.71	8.84 ± 2.00	0.015
Q_{max} (ml/sec)	14.83 ± 0.38	14.26 ± 1.24	0.453
PVR	62.50 ± 7.84	58.71 ± 6.58	0.035

Figures in the parentheses denote corresponding percentage.
 # Data were analyzed using Student's t-Test and level of significance was 0.05.

Table IV. Comparison of adverse effects between groups (n = 67)

Adverse effects	Group		p-value#
	Alfuzosin (n=36)	Tamsulosin (n=31)	
Postural hypotension	16 (44.4)	2 (6.5)	< 0.001
Dizziness	36 (100.0)	23 (74.2)	0.001
Tachycardia	2 (5.6)	22 (71.0)	< 0.001
Headache	21 (58.3)	26 (83.9)	0.023
Rhinitis	0 (0.0)	12 (38.7)	< 0.001
Asthenia	35 (97.2)	23 (74.2)	0.007
G1 tract upset	28 (77.8)	16 (51.6)	0.025

Figures in the parentheses denote corresponding percentage.
 # Data were analyzed using Chi-square (χ^2) or Fisher's Exact Test as applicable

Table V. Comparison of improvements between groups (n = 67)

Improvements	Group		p-value#
	Alfuzosin (n=36)	Tamsulosin (n=31)	
Q_{max} ≥ 3 ml/s from baseline	36(100.0)	31 (100.0)	----
IPSS ≥ 25% from baseline	32(88.9)	15 (48.4)	< 0.001

Figures in the parentheses denote corresponding %
 # Data were analyzed using Chi-square Test.

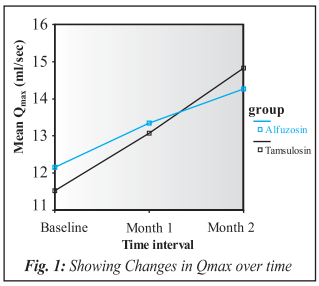

Fig. 1: *Showing Changes in Qmax over time*

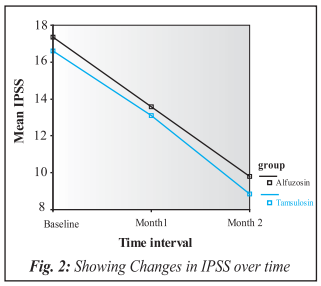

Fig. 2: *Showing Changes in IPSS over time*

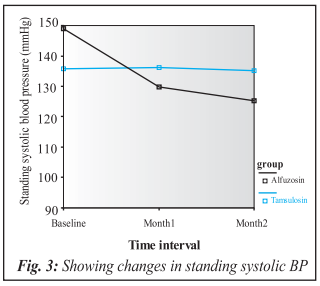

Fig. 3: *Showing changes in standing systolic BP*

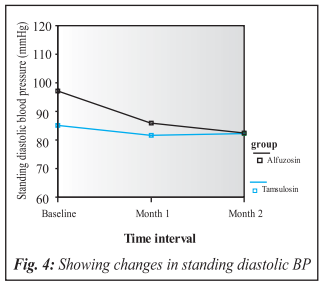

Fig. 4: *Showing changes in standing diastolic BP*

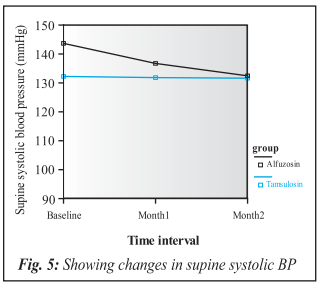

Fig. 5: *Showing changes in supine systolic BP*

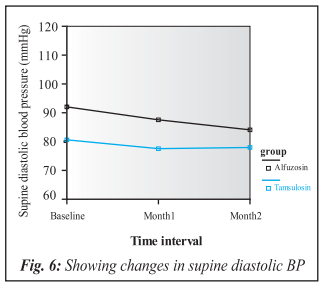

Fig. 6: *Showing changes in supine diastolic BP*

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